Beyond Ten-Year Risk: Novel Approaches to the Primary Prevention of Cardiovascular Disease

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MSc, BSc, BSc

Submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy

Health Economics and Health Technology Assessment (HEHTA)

Institute of Health and Wellbeing

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Author Declaration

I hereby declare that, with the exception of explicit referencing, this following research is my own work and has not been submitted for the award of a different degree at the University of Glasgow, or any other institution.

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2nd June 2019

Acknowledgements

I am incredibly grateful to my supervisors, Professor Andrew Briggs and Dr. Kathleen Boyd, for all the advice and support they have offered me during the last four years. ‘Research’ meetings over ales at Valhalla in Hell’s Kitchen, whiskies at the Òran Mór, and nutcrackers in the Virgin Islands have been particularly enjoyable. I would also like to thank Dr. Andrew Moran, who oversaw my work at Columbia University and wholeheartedly welcomed me into his team in New York. I am thankful to the Medical Research Council, who funded my PhD programme, and everyone at HEHTA who has helped me along the way.

I could not have made it through this programme without the constant backing of my friends and family. Throughout my studies, my mum and dad have provided valuable advice, timely visits, and frequent photos of Juno and Derry. I am thankful to Siobhán, Maya, Nisha, Dimitri, Tom One, and Lorenzo for their support. I am grateful also to Amanda, who has offered me endless encouragement which I shall gladly reciprocate in the coming years. Finally, I am thankful for the welcome distraction provided by friends in Glasgow, New York, and Johannesburg and Celtic Football Club.

"In Glasgow, 'how' means 'why?'

You do not ponder why; you demand HOW?"

Kevin Bridges

Papers and Presentations

Presentations

Long-Term Benefit Comparison of Absolute Risk Reduction versus Absolute Risk to Prioritize Statin Therapy, Poster Presentation, American Heart Association Epidemiology and Lifestyle Annual Meeting, New Orleans, USA, March 2018.

A Framework for the Cost-Effectiveness Analysis of Novel Biomarker Testing in Cardiovascular Disease, Podium Presentation, International Society for Pharmacoeconomics and Outcomes Research (ISPOR) European Congress, Glasgow, Scotland, November 2017. Winner: Award for Best Student Podium Presentation

Long-Term Benefits of LDL Lowering in Young Adulthood: A Computer Simulation Study, Poster Presentation, ISPOR European Congress, Glasgow, Scotland, November 2017

Cost-Effectiveness of Statin Prioritisation Based on Absolute Risk Reduction for Prevention of Cardiovascular Disease, ISPOR European Congress, Glasgow, Scotland, November 2017

Long-Term Benefits of Blood Pressure Lowering in Young Adulthood: A Computer Simulation Study, Poster Presentation, American Heart Association Epidemiology and Lifestyle Annual Meeting, Portland, USA, March 2017.

Signalling Demand: PCSK9 Inhibitors for Statin Intolerant Individuals, Poster Presentation, Society for Medical Decision Making (SMDM) North American Meeting, Vancouver, Canada, October 2016. Winner: Lee B. Lusted Student Prize

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Gray, Cindy M., Sally Wyke [et al., including Kohli-Lynch, C.N.]. *Long-Term Weight Loss Following a Randomised Controlled Trial of a Weight Management Programme for Men Delivered through Professional Football Clubs: The Football Fans in Training Follow-up Study.* Southampton (UK): NIHR Journals Library, 2018. PubMed, http://www.ncbi.nlm.nih.gov/books/NBK513426/. Accessed 17 Dec. 2018.

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Forthcoming Papers

Heterogeneity in Cost-Effectiveness Analysis, Oxford Research Encyclopedia of Economics and Finance (forthcoming 2019)
CN Kohli-Lynch[1,2], AH Briggs[1]

Lifetime Cost-Effectiveness of Benefit-Based Statin Treatment (under review)
CN Kohli-Lynch[1,2], BK Bellows[2], G Thanassoulis[3], Y Zhang[1], MJ Pletcher[4], E Vittinghoff[4], MJ Pencina[5], D Kazi[4], AD Sniderman[3], AE Moran[2]

Signalling Demand: PCSK9 Inhibitors for Statin Intolerant Individuals
CN Kohli-Lynch[1,2], AH Briggs[1], KA Boyd[1]

EU-MASCARA: Economic Evaluation of Novel Biomarkers for CVD
CN Kohli-Lynch[1,2], KA Boyd[1], AH Briggs[1], C Delles[6]

Novel Approaches to Preventive Statin Prioritisation in Scotland: Beyond Ten-Year Risk
CN Kohli-Lynch[1,2], KA Boyd[1], AH Briggs[1]

Mapping 10-Year Risk to Capacity-to-Benefit with the Scottish CVD Policy Model
CN Kohli-Lynch[1,2], AH Briggs[1], KA Boyd[1]

Economic Cost of Poor Calibration in 10-Year Risk Scores
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Abstract

In cost-effectiveness analysis, outcomes are typically averaged across large groups to represent a patient population. Implementation and reimbursement decisions based on such analyses often ignore considerable heterogeneity in cost-effectiveness between patients. While good practice guidance for economic evaluations suggest including subgroup analysis, in practice this is frequently overlooked or underutilised. This thesis shows that failing to adequately represent heterogeneity in decision-making leads to an inefficient distribution of healthcare resources. This theory is applied in a study of cholesterol-reducing medication for the primary prevention of cardiovascular disease (CVD).

Despite improvements in recent years, CVD remains a significant cause of mortality, morbidity, and health inequality around the world. Rates of the disease have begun to plateau in recent years and novel approaches to its prevention are required.

Cholesterol reduction for the primary prevention of cardiovascular disease is a clinical area where better reflection of heterogeneity in cost-effectiveness could significantly improve current practice. Statins are a widely prescribed cholesterol-reducing medication which have recently come off patent. This has led them to become cheaper and cost-effective in a large proportion of CVD-free populations in high-income countries. PCSK9 inhibitors are a more expensive and more effective cholesterol-reducing medication. For both treatments, decision-makers must establish which groups they will prioritise for treatment. Through epidemiologic and health economic analysis, this thesis aims to establish optimal approaches for prioritising patients for cholesterol-reducing therapy.

Preventive statin therapy is typically targeted at individuals estimated to have a high ten-year risk of developing CVD. However, individuals with the same ten-year risk may experience different outcomes from preventive treatment. The epidemiologic bases for three alternative approaches to the CVD prevention are discussed. These are: (i) continued use of ten-year risk scoring, (ii) novel decision mechanisms which incorporate ten-year risk, and (iii) direct use of decision-analytic models in clinical practice to guide treatment decisions.

Several treatment policies may be characterised by one of the aforementioned approaches to prevention. These include: lowering the risk threshold for treatment initiation, improving the discrimination of risk scores with novel biomarker testing, age-stratified risk thresholds,

absolute risk reduction-guided therapy, and outcome maximisation with decision-analytic models. Decision-analytic modelling was employed to assess the long-term effectiveness and cost-effectiveness of these policies. Additional analysis showed how decision-makers can signal demand for PCSK9 inhibitors and achieve welfare gains by reflecting heterogeneity in their decision-making.

This thesis demonstrates the importance of reflecting heterogeneity in cost-effectiveness. It shows that standard care regarding the primary prevention of CVD often ignores heterogeneity, leading to suboptimal decision-making. This holds true for long-established, inexpensive treatments like statin therapy and novel, expensive treatments like PCSK9 inhibitors.

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AB – Absolute benefit
ACC – American College of Cardiology
AHA – American Heart Association
AR – Absolute Risk
ARI – Absolute Risk Increase
ARIC – Atherosclerotic Risk in Communities [Study]
ARR – Absolute Risk Reduction
ASCVD – Atherosclerotic Cardiovascular Disease
AUROC – Area Under the Receiver Operating Curve
BHCKC - Belgian Health Care Knowledge Centre
BLUP – Best Linear Unbiased Predictor
BMI – Body Mass Index
CAD – Coronary Artery Disease
CARDIA – Cardiovascular Risk Development in young Adults [Study]
CBVD - Cerebrovascular Disease
CDC – Centers for Disease Control and Prevention
CG – Clinical Guideline
CHD - Coronary Heart Disease
CHS – Cardiovascular Health Study
CIS – Continuous Inpatient Stay
CPD – Cigarettes Per Day
CSR – Clinical Study Report
CTT - Cholesterol Treatment Trialists
CTTC - Cholesterol Treatment Trialists' Collaboration
CU – Columbia University
CVD – Cardiovascular Disease
DALY – Disability-Adjusted Life Year
DBP – Diastolic Blood Pressure
EMA – European Medicines Agency
EU – European Union
Ext. Dominated – Extendedly Dominated
FDA – [US] Food and Drug Administration
FLEMENGHO – FLEMish Study on ENvironment, Genes and Health Outcome
FOURIER – Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk [study]
GBD – Global Burden of Disease [Study]
GDG – Guideline Development Group
GP – General Practitioner
HDL-C – High-density Lipoprotein Cholesterol
Health ABC – Health, Aging, and Body Composition [study]

HEHTA – Health Economics and Health Technology Assessment
HRG - Healthcare Resource Group
HR-QoL – Health-Related Quality of Life
HS-CRP – High-Sensitivity C-Reactive Protein
ICD - International Statistical Classification of Disease & Health Related Problems
ICER – Incremental Cost-Effectiveness Ratio
IfCER – Institute for Clinical and Economic Review
IGT – Impaired Glucose Tolerance
IHD – Ischemic Heart Disease
INHB – Incremental Net Health Benefit
INMB – Incremental Net Monetary Benefit
IQWiG – Institute for Quality and Efficiency in Health Care
ISD – Information Services Division
JUPITER - Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin [study]
KU Leuven – Katholieke Universiteit Leuven
LDL-C – Low-Density Lipoprotein Cholesterol
LE – Life Expectancy
LYG – Life Years Gained
LYS – Life Years Saved
MACE – Major Adverse Cardiovascular Events
MASCARA – Markers for Sub-clinical Cardiovascular Risk Assessment
MEPS – Medical Expenditure Panel Survey
MESA – Multi-Ethnic Study of Atherosclerosis
NGT – Normal Glucose Tolerance
NHANES – National Health and Nutrition Examination Survey
NHB – Net Health Benefit
NHDS – National Hospital Discharge Survey
NHLBI – National Heart, Lung, and Blood Institute
NICE – National Institute for Health and Care Excellence
NKCHS – Norwegian Knowledge Centre for the Health Services
NNT – Number Needed to Treat
NorCaD – Norwegian Cardiovascular Disease [decision model]
NRI – Net Reclassification Improvement
OR – Odds Ratio
PCSK9 – Proprotein Convertase Subtilisin/Kexin type 9
PDF – Probability Density Function
PPICOSS – Perspective, Population, Intervention, Comparator, Outcome, Setting, Study Design
PSA – Probabilistic Sensitivity Analysis
PYLL – Potential Years of Life Lost
QALE – Quality-Adjusted Life Expectancy
QALY – Quality-Adjusted Life Year

RMSE – Root Mean Square Error
ROC – Receiver Operating Curve
RR – Relative Risk
RRR – Relative Risk Reduction
SAMS - Statin-Associated Muscle Symptoms
SBP – Systolic Blood Pressure
SF-12 – 12-Item Short Form Health Survey
SHeS – Scottish Health Survey
SHHEC – Scottish Heart Health Extended Cohort
SIGN – Scottish Intercollegiate Guidelines Network
SMC – Scottish Medicines Consortium
SMR – Scottish Morbidity Records
STOMP – Effects of STatins On Muscle Performance [study]
Str. Dominated – Strictly Dominated
STRIP – Special Turku Coronary Risk Factor Intervention Project
T2D – Type-2 Diabetes
TC – Total Cholesterol
TIA – Transient ischemic attack
TSA – Traditional Sensitivity Analysis
WHO – World Health Organisation
wNRI – Weighted Net Reclassification Improvement
WONDER – [CDC] Wide-ranging ONline Data for Epidemiologic Research
WOSCOPS – West Of Scotland COronary Prevention Study

Chapter 1
Introduction

In cost-effectiveness analysis, outcomes are often averaged across large groups of patients. Making implementation and reimbursement decisions based on such analysis may ignore considerable heterogeneity in cost-effectiveness between patients. This thesis shows that failing to represent such heterogeneity in decision-making leads to an inefficient distribution of constrained healthcare resources.

Cardiovascular disease (CVD) is a highly prevalent chronic health condition which is responsible for large amounts of mortality and morbidity worldwide (1). Prioritising patients for preventive interventions for CVD is important for policy-makers around the world (2). To target preventive treatment efficiently, it must be recognised that outcomes from such treatment often differ systematically between patient subgroups. Subgroups may be defined based on CVD risk factors which include age, sex, cholesterol, and blood pressure.

Despite improvements in recent years, cardiovascular disease remains a significant cause of mortality, morbidity, and health inequality around the world (3). As rates of the disease plateau, novel approaches to CVD prevention will be required.

Cholesterol reduction is a well-established means of reducing CVD risk (4,5). Clinical guidelines in high-income countries commonly recommend that high-risk patients are prioritised for statin, ezetimibe, or PCSK9 inhibitor therapy to reduce low-density lipoprotein cholesterol (LDL-C). Such treatments are often initiated based on a patient's 10-year risk of experiencing a primary CVD event (6). However, this approach to treatment prioritisation does not adequately reflect heterogeneity in the patient population. This leads to an inefficient distribution of healthcare resources. Cholesterol-reducing medication guidelines are analysed in this thesis to highlight the benefits that can be accrued by better representing heterogeneity in cost-effectiveness when determining which health care interventions to implement.

The purpose of this introductory chapter is to provide an orientation to the thesis. Four overarching objectives for the work are presented. This is followed by a description of the thesis structure.

1.1 Objectives

(i) Describe the health economic benefits associated with reflecting heterogeneity in cost-effectiveness analysis.

(ii) Apply the theory of heterogeneity in cost-effectiveness to the clinical area of CVD and its prevention.

(iii) Estimate the cost-effectiveness of novel policies to prioritise individuals for CVD prevention through cholesterol reduction. Pharmacologic intervention to reduce cholesterol forms a key part of guidelines for preventive intervention of CVD in most high-income countries. Without loss of generality, the prioritisation of cholesterol-reducing medication is utilised as a case study of the benefits associated with reflecting heterogeneity in cost-effectiveness analysis.

(iv) Produce policy recommendations based on findings from the novel approaches to CVD prevention explored in (iii).

1.2 Thesis Structure and Chapter Outline

The thesis is divided into four parts which each comprise of chapters. An overview of each part and each chapter is provided below.

Part 1: Reflecting Heterogeneity in Cost-Effectiveness Analysis

Part 1 of the thesis aims to describe the benefits associated with reflecting heterogeneity in cost-effectiveness from a theoretical standpoint. This provides a framework under which heterogeneity in cost-effectiveness of preventive therapy for CVD can be discussed throughout the remainder of the thesis.

Chapter 2 is the sole chapter included in Part 1. Traditional health economic decision rules are described. It is shown that they can be manipulated to derive optimal decision rules in the presence of heterogeneity in cost-effectiveness in a patient population. Optimal decision-making processes are described in two scenarios. The first scenario occurs when treatment cost is fixed and a decision-maker must determine which subgroups to treat. The second scenario occurs when treatment cost is not fixed. In this scenario, a decision-maker can signal demand for a treatment and ensure that an equilibrium between supply and demand is achieved whereby they achieve consumer surplus.

Part 2: Cardiovascular Disease Prevention

Part 2 provides a background to CVD and its prevention. Detailed descriptions of the health and economic consequences of the disease are provided. The epidemiologic basis for different approaches to CVD prevention and the importance of cholesterol-reduction, due to the integral role of LDL-C in atherogenesis, are described. The purpose of Part 2 is twofold: to demonstrate the applicability of the theory contained in Part 1 to the prevention of a highly prevalent disease and to develop specific policies which are analysed later in the thesis to inform policy recommendations.

Chapters 3 and 4 constitute Part 2 of the thesis. Chapter 3 describes CVD and approaches that can be adopted to reduce its incidence. The prevalence, incidence, and economic burden associated with the disease are discussed alongside different types of preventive intervention. Current guidelines regarding the prioritisation of patients for preventive intervention in high-income countries are reviewed. These guidelines typically recommend targeting treatment at patients with elevated 10-year risk of developing CVD.

Chapter 4 describes CVD epidemiology and aims to explain the existence of heterogeneity in outcome from preventive treatment for CVD. This helps to establish three broad approaches to prioritising patients for preventive intervention. Each approach attempts to address heterogeneity in cost-effectiveness. These are:

- 10-year risk scoring
- Novel decision mechanisms which incorporate 10-year risk
- Using decision models in clinical practice

Specific policies that adhere to one of these approaches to prioritisation are introduced.

Part 3: Cost-Effectiveness Analyses of Preventive Policies

Part 3 considers the cost-effectiveness of policies introduced earlier in the thesis. The first two chapters in Part 3 aim to set up proceeding analyses, introducing decision-analytic models that can be employed in the cost-effectiveness analysis of preventive interventions for CVD and detailing the clinical evidence for and against cholesterol-reducing treatments. Latter chapters describe cost-effectiveness analyses, set in Scotland and the U.S., which assess specified interventions.

Chapter 5 describes the rationale behind decision-analytic modelling and introduces two previously-published CVD policy models that will be employed in cost-effectiveness analyses of preventive interventions in later chapters. These are the Scotland-based Scottish CVD Policy Model (7,8) and the U.S.-based CVD Microsim Model (9).

Chapter 6 describes the evidence base regarding the efficacy, effectiveness, and safety of statin therapy. Statins are the most commonly prescribed cholesterol-reducing medication around the world (5) and many of the cost-effectiveness analyses included in the thesis relate to prioritising patients for this treatment.

Chapters 7 to 9 contain detailed descriptions of multiple cost-effectiveness analyses of statin prioritisation policies. Chapter 7 assesses the cost-effectiveness of two policies which involve continued use of 10-year risk scoring. The policies considered are reducing the risk threshold for statin initiation in Scotland and improving the discrimination of risk scores with novel biomarker testing. Chapter 8 assesses the cost-effectiveness of two policies which involve novel decision mechanisms that incorporate 10-year risk scoring. The policies considered are age-stratification of risk thresholds and the 'absolute risk reduction' approach to statin prioritisation. The latter targets treatment at patients based on a combinatory measure of their 10-year CVD risk and baseline LDL-C. Chapter 9 considers the cost-effectiveness of directly using decision models in clinical practice to maximise health outcomes.

Statins are cheap and relatively effective. Chapter 10 considers more expensive and more effective cholesterol-reducing medications. Analysis was conducted to establish a demand curve for PCSK9 inhibitor therapy for cholesterol reduction in patients with familial hypercholesterolaemia and statin intolerance or 'residual cholesterol risk' while receiving preventive statin therapy.

Part 4: Policy Recommendations, Further Research, and Conclusions

Part 4 aims to synthesise results from the thesis. It further aims to produce policy recommendations, provide concluding remarks, and recommend further research to increase understanding of heterogeneity in cost-effectiveness and its interaction with CVD prevention.

This part consists of Chapters 11 and 12. Chapter 11 synthesises and summarises cost-effectiveness results from Part 3. These recommendations relate to optimal statin prioritisation policies and signalling demand for PCSK9 inhibitors. Chapter 12 provides a summary of the research conducted throughout the thesis and highlights areas for further research.

Part 1

Reflecting Heterogeneity in Cost-Effectiveness Analysis

The objective of Part 1 is to describe the benefits associated with reflecting heterogeneity in cost-effectiveness. When decision-makers make reimbursement decisions based on cost-effectiveness results that have been averaged over a large population, they often ignore systematic variability in cost-effectiveness between patients. If one identifiable subgroup of patients is cost-effective to treat while another is not, making decisions based on costs and benefits averaged across the total population is suboptimal.

The following chapter describes forms of subgroup and heterogeneity in patient populations, discusses traditional decision rules employed in cost-effectiveness analysis, and shows how these can be adapted to account for heterogeneity. The theory discussed in Part 1 will be employed throughout the thesis. This theory guides and motivates the establishment of novel approaches for the primary prevention of CVD which better reflect heterogeneity in cost-effectiveness.

Chapter 2

Stratified Medicine, Heterogeneity, and Cost-Effectiveness

2.1 Purpose

Cost-effectiveness analysis of health care interventions aims to assess the value for money represented by a healthcare investment. This is generally achieved by dividing the costs associated with a treatment by accrued health benefits. Hence, a cost-per-unit of health associated with the treatment is derived. This type of analysis is an important tool for healthcare decision-makers who wish to maximise population health given a constrained and exogenously determined healthcare budget. However, costs and benefits associated with a treatment are often averaged across large groups of patients. This may ignore systematic variability in health and cost outcomes between identifiable patient subgroups.

This chapter will discuss stratified medicine and heterogeneity in patient populations. Furthermore, it will explain traditional cost-effectiveness decision rules and extend these rules to consider the impact of heterogeneity and stratification on cost-effectiveness.

2.2 Stratified Medicine

Definition

In recent decades, researchers have unravelled the genomic, epigenomic, and behavioural bases for many health conditions. It has therefore become increasingly feasible to stratify patient populations into risk- and benefit-based subgroups. These developments have been met with a clinical trend towards stratified medicine – described by the World Health Organisation as assessing "per population stratum" the benefit-risk profile of a health care intervention (10). Concurrently, researchers, healthcare institutions, funding bodies, and politicians have heralded an age of 'personalised' and 'precision' medicine, often promoting the idea that novel diagnostic technology can be employed to stratify populations and dictate patient treatment (11–20).

Variability in a dataset describes the extent to which data points are distributed around an average value. Heterogeneity in a patient population refers to variability in sociodemographic

and biological characteristics between patients. Subgroups are a set of patients defined by one or more of these characteristics. Heterogeneity in outcome specifically refers to variability in health and cost outcomes between individuals receiving the same treatment that can be explained by variability in the patient population. These definitions are listed in Table 2-1.

Patient outcomes may differ relatively or absolutely. Those receiving the same relative effect from a treatment will experience a treatment-related multiplicative alteration of their baseline health or cost outcome (e.g. 50% reduction in event probability, 20% increase in treatment costs). Those receiving the same absolute effect from a treatment will experience the same absolute change in outcome (e.g. one adverse event prevented, £100 additional costs incurred).

Term	Definition
Variability	Extent to which data points are distributed around an average value
Heterogeneity in population	Variability in sociodemographic and biological characteristics between patients
Heterogeneity in outcome	Variability in health and cost outcomes between individuals receiving the same treatment explained by heterogeneity in the population
Subgroup	Set of patients defined by one or more sociodemographic or biologic characteristic

Table 2-1: Definition of terms related to variability and heterogeneity

Forms of Subgroup and Heterogeneity

Interventions can produce heterogeneous outcomes due to a range of sociodemographic and biological factors. Sculpher (21) lists six forms of subgroup and heterogeneity: intervention-related factors, factors unrelated to intervention but related to health condition, factors unrelated to intervention and health condition, factors unrelated to the patient, preferences, and factors revealed over time. These forms of heterogeneity exist in all clinical areas, from chronic to acute conditions. The following section will describe these forms of subgroups and heterogeneity. These descriptions will be supplemented with examples from CVD.

1. **Intervention-related factors** are commonly considered in studies of clinical effectiveness. They characteristics typically indicate differential relative outcomes in

a population and can be referred to as treatment effect modifiers. Relative benefit is often quantified by hazard ratio or relative risk of adverse event (22).

Many examples of treatment effect modifiers exist in the clinical literature. An intervention-related factor which causes differential relative treatment effect in the prevention of CVD is LDL-C. Patients at high risk of experiencing a CVD event may be prescribed statins, an LDL-C reducing medication. Evidence suggests that statins produce a greater relative risk reduction for CVD in patients with higher baseline LDL-C (4). This is likely due to the strong positive relationship between LDL-C and CVD risk (23).

Intervention-related factors may also lead to systematic differences in costs. For example, dosage for some pharmacological interventions is determined by patient body mass index (BMI). This multiplicatively increases costs for patients based on BMI. Weight-based dosing is important for a range of medications including hydrocortisone for adrenal insufficiency, vancomycin for the treatment of bacterial infections, and aprotinin for use in cardiac surgery (24).

2. **Factors unrelated to an intervention effect but related to health condition** often alter absolute risk of adverse event. They may also cause differential pricing and preference valuation of clinical events.

Even when patients receive the same relative risk reduction from a treatment, absolute risk reduction may vary greatly. Consider two subgroups of a patient population in which the adverse event rate is 50% and 10%, respectively. Further consider a treatment which halves adverse event rates in all patient subgroups. While relative risk reduction is constant, the group with higher baseline risk will receive a much greater absolute risk reduction (25% versus 5%).

There are many examples of factors related to health condition but not treatment which affect patient outcomes. Based on the principles described above, risk stratification is often used to determine which patients should receive preventive treatment for CVD (25–28).

Sculpher notes that costs and quality of life valuations may also differ systematically based on observable patient characteristics. Evidence suggests that the direct medical cost of experiencing a stroke can vary between sexes and increases with age (29) and health state valuation is consistently lower for individuals with comorbid diabetes (30).

3. **Factors unrelated to both treatment effect and health condition** may affect patient outcomes.

   Age is an example of such a factor. Elderly individuals are typically at an increased risk of developing chronic diseases (e.g. CVD, chronic obstructive pulmonary disease, cancer) and experiencing adverse events (e.g. serious falls). These competing risks limit older individuals' capacity-to-benefit from interventions and, in turn, systematically alter the cost-effectiveness of treating them.

   Factors which alter risk of mortality are often unrelated to health condition and treatment effect but ultimately affect patient outcome. For example, though not necessarily correlated with surgery success, long-term survival after liver transplantation is significantly greater for younger individuals (31). Probability of non-CVD mortality increases with age and this competing risk can similarly limit an elderly individual's capacity-to-benefit from preventive treatment. However, the CVD example is complicated by the fact that age is an independent predictor of CVD risk, and therefore the competing risk of non-CVD mortality must be weighed against the increased risk of disease-related event (32).

4. **Factors unrelated to the patient** may affect health and cost outcomes. There is a multiplicity of such factors, including geographic location of treatment, treatment provider, or other environmental factors.

   Much research has been conducted which considers geographic- and provider-related sources of heterogeneity in patient outcome. An analysis of multinational clinical trials provides evidence that healthcare costs vary substantially between countries (33). Geue et al. have shown significant differentials exist between inpatient costs in rural and urban settings (34). Treatment success rate is also likely to vary based on physician characteristics. For example, research suggests that more experienced

surgeons have greater surgical success rates and their patients have better post-operative quality of life (35).

5. **Preferences** may lead to differential cost-effectiveness of health care interventions between patient subgroups. The health-related quality of life patients attribute to different treatments and health states often varies based on observable characteristics.

   An online survey of 1,000 U.S. residents found that the disutility attributable to regular pill-taking for CVD prevention varies greatly across the U.S. adult population (36). In a decision modelling study, Pandya et al. (37) showed that pill-taking disutility is a key determinant of the cost-effectiveness of preventive statin therapy. Additionally, studies have shown that individuals differentially value health states based on age (38).

6. **Factors revealed over time** may explain heterogeneity in cost-effectiveness. If these factors are observable, patients can be split into subgroups and a decision-maker can make differential decisions based on each group's respective outcomes.

   Treatment response is a factor which is revealed over time which may allow for differential decision-making. Some patients receiving statin therapy experience adverse effects including myalgia and loss of memory (39). These can often be avoided by changing dosage or choice of statin. Altering such treatment parameters can affect the patient's costs and health outcomes.

The types of heterogeneity and subgroup discussed may all be employed to stratify patient populations in cost-effectiveness analysis. The body responsible for health technology assessment and clinical guidelines for NHS England and NHS Wales is the National Institute for Health and Care Excellence (NICE). NICE discusses heterogeneity and subgroups in its reference case document (40), stating that "…it is important to consider how clinical- and cost-effectiveness may differ because of differing characteristics of patient population". Such heterogeneity, they note, should be analysed as part of a NICE health technology assessment. They also recognise that the use of a technology may be approved conditionally on the presence of a biomarker which predicts patient response to treatment. Indeed, the NICE Diagnostics Assessment Programme was set up in 2010 to evaluate the clinical- and cost-effectiveness of diagnostic technologies (41).

2.3 Cost-Effectiveness Analysis

Traditional Cost-Effectiveness Decision Rules

Cost-effectiveness analyses compare the costs and benefits associated with alternative treatment options. Employing cost-effectiveness analysis ensures that healthcare decision-makers receive acceptable value for money when investing in a health technology, accounting for the opportunity cost associated with displacing funds from the healthcare budget (42,43).

Standard health economic decision rules dictate that an intervention should be implemented over a relevant comparator if the incremental benefits from the intervention justify the incremental expenditure required to achieve these benefits (42). If incremental costs are negative and incremental benefits are positive, the treatment is considered 'cost-saving' and should be implemented. If the incremental costs are positive and the incremental benefits are negative, the treatment is 'dominated' and should not be implemented. When incremental costs and benefits are both positive or both negative, decision-makers must consider the treatment's incremental cost-effectiveness.

The measure typically adopted to represent health-related quality of life in cost-effectiveness analysis is the quality-adjusted life year (QALY). One QALY equals one year lived in full health (44,45) while zero QALYs is equivalent to death. Values between zero and one represent different health states, ranked in terms of preference by some population of interest. An individual's quality-adjusted life expectancy is equal to the product of the amount of time spent in different health states multiplied by the QALY value of these health states, summed over all the health states they experience in their life.

Disability-adjusted life years (DALYs) are an alternative metric which can be used to measure morbidity alongside longevity of life (46). They equal the sum of years of life lost from a health condition and years lived with disability weighted by a disability factor. One DALY equals one year of full health lost.

While they aim to capture similar health-related outcomes, QALYs and DALYs are not directly interchangeable. The DALY is primarily a measure of disease burden and may only be comparable with QALYs under the assumption that the quality of life associated with a

health condition is equivalent to the level of disability it confers (47). In practice, the preference-based nature of QALYs necessitates derivation through preference-elicitation from populations of interest while DALYs tend to be estimated through expert evaluation (48–50). Fundamentally, the decision rules which underpin cost-effectiveness analysis do not change dependent on whether QALYs or DALYs are being maximised.

The incremental cost-effectiveness ratio (ICER) is a metric which enables incremental comparison of the cost-effectiveness of health care interventions. The ICER of implementing a treatment over a comparator is equal to the treatment's incremental costs divided by incremental benefits, Equation (3-1). As QALYs are the most common health metric employed in cost-effectiveness analysis, ICERs usually represent the cost-per-QALY attributable to implementing a treatment.

$$\text{ICER} = \frac{\Delta C}{\Delta E}. \tag{3-1}$$

A decision-maker should implement an intervention over its comparator if they believe that the cost-per-QALY offered by the treatment represents acceptable value for money. Willingness-to-pay for a unitary increase in health benefit is represented by the decision-maker's cost-effectiveness threshold, λ. If incremental costs and benefits are both positive, the decision-maker should implement the treatment over its comparator if its ICER is below the cost-effectiveness threshold, as shown in Decision Rule 1A (43).

$$\text{Intervention funded if: } ICER = \frac{\Delta C}{\Delta E} < \lambda;\ \Delta C > 0, \Delta E > 0$$

Decision Rule 1A: Implementation of intervention with positive costs and positive effects based on ICER

If incremental costs and benefits are both negative, the decision-maker should implement the treatment over its comparator if its ICER is above the cost-effectiveness threshold, as shown in Decision Rule 1B. This is because the cost savings attributable to the intervention can be spent elsewhere in the budget to produce more health than is lost.

$$\text{Intervention funded if: } ICER = \frac{\Delta C}{\Delta E} > \lambda;\ \Delta C < 0, \Delta E < 0.$$

Decision Rule 1B: Implementation of intervention with negative costs and negative effects based on ICER

Incremental net monetary benefit (*INMB*) is an alternative measure of cost-effectiveness (51). Calculation of *INMB* requires converting incremental health benefits to costs to represent the

monetary value of these benefits. This is achieved by multiplying health benefits by the cost-effectiveness threshold. Next, the treatment's incremental costs are subtracted from this value, Equation (3-2). Notably, this measure does not require separate decision rules dependent on the sign of incremental costs or benefits. In addition, it is not a ratio of means and is therefore always defined and continuous.

$$INMB = \lambda * \Delta E - \Delta C. \tag{3-2}$$

A policy should be adopted over a comparator if it has an *INMB* greater than zero, as presented in Decision Rule 2. A welfare gain is achieved by implementing such a policy. When there are multiple interventions to choose between, the policy with the highest *INMB* should be implemented. In this situation, all policies must be compared incrementally to a common comparator.

$$\text{Intervention funded if: } INMB > 0.$$

Decision Rule 2: Implementation of intervention based on *INMB*

Incremental net health benefit (*INHB*) is a comparable measure to *INMB* (52). When calculating *INHB*, all incremental costs are represented by the health benefit value of these costs. This is achieved by dividing incremental costs by the cost-effectiveness threshold. Hence the costs represent the minimum amount of health that could be theoretically purchased elsewhere in the budget if the policy was not implemented. Similar to Decision Rule 2, a decision-maker should implement an intervention if *INHB* is greater than zero.

The incremental costs and effects attributable to implementing a health care intervention compared with a relevant comparator have been described by Weinstein and Stason (53). Constituents of incremental health and incremental cost are described in Equation (3-3) and Equation (3-4), respectively:

$$\Delta C = \Delta C_{Rx} + \Delta C_{se} + \Delta C_{morb} + \Delta C_{le} \tag{3-3}$$

$$\Delta E = \Delta E_{le} + \Delta E_{morb} + \Delta E_{se}. \tag{3-4}$$

ΔC refers to incremental change in costs, and consists of: direct treatment costs (*Rx*), cost increases attributable to treatment-related side effects (*se*), cost savings due to reduced morbidity (*morb*), and cost increases associated with extended life expectancy (*le*). ΔE refers to the incremental change in effect, typically measured by QALYs. Incremental effect consists of: increased benefits attributable to extension of life expectancy (*le*), increased

benefits due to reduced morbidity (*morb*), and reduced benefits due to treatment-related side effects (*se*).

One final measure to consider is *Treatment Value*. This is defined as the INMB excluding treatment costs, Equation (3-5).

$$Treatment\ Value = INMB + \Delta C_{Rx} = \lambda * \Delta E - (\Delta C_{se} + \Delta C_{morb} + \Delta C_{le}) \qquad (3\text{-}5)$$

It is possible to derive a decision rule for investing in health care interventions dependent on treatment cost. A decision-maker should invest in an intervention if the treatment value is greater than the direct treatment costs, shown below in Decision Rule 3. This rule makes it possible to determine the average cost-effective price at which a treatment becomes cost-effective.

Intervention funded if: $Treatment\ Value > \Delta C_{Rx}$

Decision Rule 3: Implementation of intervention based on Treatment Value

Perspective

Perspective should be considered when performing cost-effectiveness analysis. The health sector decision-maker and societal perspectives are the two perspectives most commonly applied in health technology assessment (54).

The health sector perspective accounts for all health gains (often represented by QALYs) in the population of interest, and all direct and indirect costs incurred by the health sector (40,54). This perspective aims to maximize health outcomes given an exogenously determined health sector budget.

Explicitly aiming to maximise health, with no direct attempt to affect other dimensions of social welfare, can be described as extra-welfarism. Extra-welfarists value health intrinsically and are willing to override individual preference to improve overall health in a population. This has been justified on the grounds that health is fundamental to an individual's "capacity to flourish" as a human being (55,56). Extra-welfarism closely mirrors Amartya Sen's 'capability approach' which stresses that utilitarian calculus ignores inequalities and oppression that limit the capability of some individuals to achieve "valuable functioning as a

part of living". The capability approach instead looks to equalise each person's capability to achieve happiness and fulfilment (57,58).

Some researchers and decision-makers prefer to employ the societal perspective. The societal perspective accounts for all direct medical, indirect medical, and indirect costs. This perspective aims to maximize social welfare, not just welfare derived from health. It assigns value to lost productivity and lost wages, for example. It therefore represents a utilitarian approach to prioritising public expenditure.

Some scholars argue that the societal perspective should be treated as a 'gold standard' for assessing health care interventions. The Second Panel on Cost-Effectiveness in Health and Medicine recommends in its reference case that the societal approach is adopted, acknowledging that this approach is best suited to a decision-maker who is concerned with the broad allocation of resources across a population (54). Drummond et al. also argue that healthcare decision-makers should be concerned with a broader array of outcomes than QALYs alone (42). A similar case is presented by Weatherly et al. (59). It is often difficult and time-consuming to conduct analyses from a societal perspective, however, and debate continues about the validity of welfarism versus extra-welfarism in determining which health care interventions are funded (42,54,60).

Despite recommendation to the contrary, the default perspective adopted in many cost-effectiveness analyses is that of a health sector decision-maker. A recent report suggests that decision-making bodies in most countries with established procedures for assessing the cost-effectiveness of health care interventions adopt the health sector perspective (61).

2.4 Stratified Cost-Effectiveness Analysis

At its core, stratified medicine aims to address heterogeneity in clinical outcomes. It recognises that average treatment outcomes often comprise of systematically different patient-level outcomes. Reflecting heterogeneous outcomes is arguably more important when conducting cost-effectiveness analysis. This is because cost-effectiveness results averaged across whole populations disregard heterogeneity related to both health and cost outcomes.

Benefits and costs of interventions are typically averaged across large patient groups in cost-effectiveness analyses. This leads to a situation in which heterogeneity may be overlooked in healthcare decision-making. Across populations, each constituent of incremental costs and incremental benefits may vary. For example, individuals with high levels of a biomarker may receive a greater relative risk reduction from a treatment and older individuals typically have worse health outcomes following acute illness (62–64).

If *INMB* can be reliably calculated at the individual- or subgroup- level, the decision to initiate treatment in the wider population can be separated into a set of mutually exclusive decisions. Dependent on willingness-to-pay, it is possible to establish 'limited use criteria' which avoid treating patients with *INMB* less than zero (65).

Likewise, if *Treatment Value* can be calculated at individual- or subgroup-level, decision-makers can establish the proportion of the patient population that should be eligible for treatment at a range of different prices. Performing this analysis and making decisions based on the results allows decision-makers to signal demand to healthcare providers.

Figure 2-1 demonstrates the health economic effect of disregarding heterogeneity of outcome on the cost-effectiveness plane. The figure presents a scenario in which two patient subgroups experience very different absolute health benefits from a treatment. Costs, however, are constant across the patient population. Subgroup A represents the average incremental outcomes attributable to the treatment in the total population (1 QALY gained), while Subgroups B and C represent outcomes in the population's two constituent subgroups (-2 and 3 QALYs gained, respectively). Costs are equal to £40,000 in each of the subgroups. A cost-effectiveness threshold of £30,000/QALY is represented by a dashed line on the graph.

If a decision-maker employs a cost-effectiveness threshold of £30,000/QALY, it is possible to determine whether Subgroups A, B, and C should be given treatment based on their position on the cost-effectiveness plane. When the decision to implement treatment is based on average treatment effects, the decision-maker would choose not to provide treatment to anyone in the population.

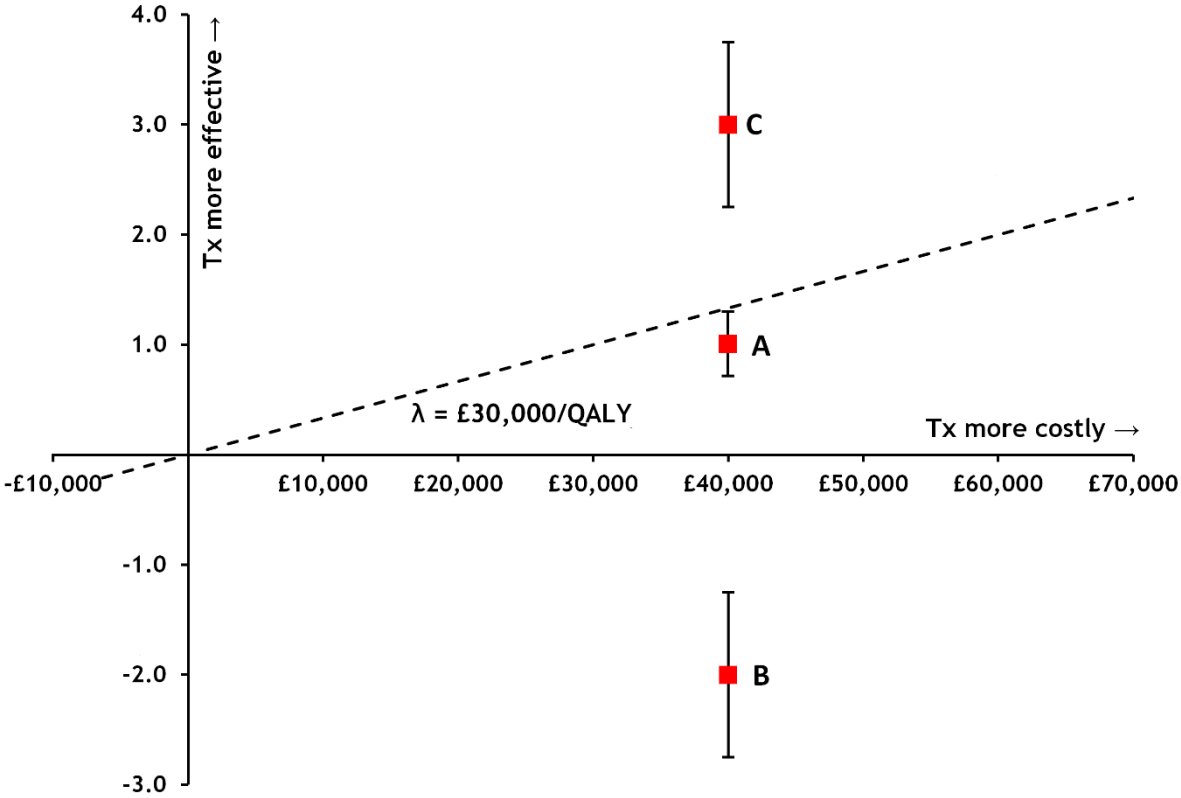


Figure 2-1: Differential treatment effects in subgroups, represented on the cost-effectiveness plane

Disaggregating the treatment effect leads to an alternative implementation decision. Treatment should be implemented in subgroups with positive costs and positive effects which lie above the dashed line on the cost-effectiveness plane. Treating Subgroup C, the patients who receive a positive health effect from treatment, represents acceptable value for money and should be implemented. The intervention should not be implemented in Subgroup B as these patients receive negative health benefits while incurring costs. Failure to recognise variability in treatment outcomes leads to inefficient and suboptimal decision-making as patients who are cost-effective to treat do not receive treatment.

2.4.1 Implementing Decision Rule 2: Stratified Cost-Effectiveness Analysis with Fixed Treatment-Related Costs

When the price of an intervention is fixed, stratified cost-effectiveness analysis can be employed to establish 'limited use criteria'. Limited use criteria restrict funding for interventions to those patient groups in which treatment is cost-effective.

Coyle et al. discuss the role of stratified cost-effectiveness in establishing limited use criteria for health care (65). They produce a mathematical framework which can be used to quantify the welfare gains achievable through the stratification of patient populations in cost-effectiveness analysis.

Let *i* be a discrete variable representing univariate subgroups of a patient population. These subgroups are mutually exclusive and when combined include every member of the patient population. Further, let $INMB_i$ represent the incremental net benefit of an intervention in group *i* and *INMB* represent the total net benefit in a population. The population-level *INMB* is equal to $INMB_i$ summed across all patient subgroups. We can define this relationship mathematically as follows:

$$INMB = \sum_i INMB_i.$$

It is possible that a subset of the subgroups will have an *INMB* less than zero. An efficient limited use criterion ensures that all subgroups with positive $INMB_i$ are treated, while those with negative $INMB_i$ remain untreated.

Let $INMB_{s(i)}$ be the total $INMB$ associated with only treating subgroups $i \epsilon s(i)$, where $s(i)$ is the subset of subgroups with $INMB_i$ greater than zero. We can define $INMB_{s(i)}$ as follows:

$$INMB_{s(i)} = \sum_i INMB_i \,, \forall i \; where \; INMB_i > \; 0.$$

It follows that, in all situations,

$$INMB_{s(i)} \geq INMB.$$

The net benefit gain from stratification, Δ_SINMB, is equal to the net benefit of treating only cost-effective subgroups subtracting the total net benefit in the population. Intuitively, this is equal to the negative sum of incremental net monetary benefit in all subgroups with negative $INMB_i$:

$$\Delta_S INMB = INMB_{s(i)} - INMB$$

$$= \; -\sum_i INMB_i, \forall i \; where \; INMB_i < \; 0.$$

Additional complexities can be added to this mathematical framework which better reflect the reality of stratification in clinical practice. The framework can be extended to the situation where more than one type of subgroup is used to stratify the patient population. Furthermore,

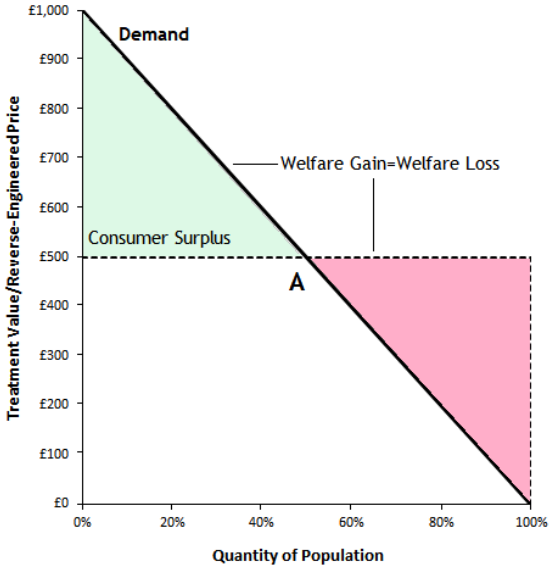
stratification of patients into subgroups may require additional costs. For example, it often requires additional testing and physician time to stratify patients into biomarker-related subgroups. These additional costs can be weighted into the $INMB_{\mathbf{i}}$ calculations.

2.4.2 Implementing Decision Rule 3: Signalling Demand with Stratified Cost-Effectiveness Analysis

Stratifying treatment decisions based on heterogeneity in cost-effectiveness allows decision-makers to signal demand to manufacturers (66,67). Decision-makers can establish a price at which an intervention becomes cost-effective in an entire patient population. Manufacturers respond to this decision mechanism by setting their price at the average cost-effective price. Implementing an intervention at the average cost-effective price for all individuals in a patient population leads to an *INMB* of zero.

Signalling demand is particularly relevant to situations with monopolist manufacturers and monopsonist decision-makers. Such a situation occurs when a manufacturer receives patent protection for a novel treatment and NICE must determine whether to recommend its use in the NHS (67).

If an intervention's treatment value can be established for every member of a population, then it is possible to determine the maximum price that one should pay for every individual. Consider a graph with $Treatment\ Value_i$ and proportion of patient population on its vertical and horizontal axes, respectively. Due to the relationship presented in Decision Rule 3, the vertical axis can alternatively and interchangeably be labelled as the maximum acceptable price of treatment for the decision-maker. This will hereafter be referred to as the patient's 'reverse-engineered price'. Having calculated reverse-engineered price for every individual in a population it is possible to plot these individuals on a graph in descending order with reverse-engineered price on the vertical axis, as shown by the black curves in Figures 2-2 and 2-3. The graph produced is a demand curve. This curve details the proportion of a patient population that a decision-maker is willing to provide treatment to at a range of prices.



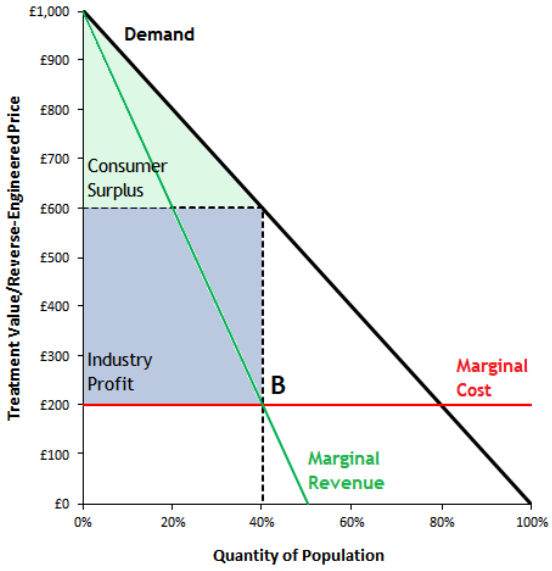


Figure 2-2 (left) and Figure 2-3 (right): Demand curves. Consumer's welfare loss equals welfare gain when average cost-effectiveness price adopted. Consumer realises surplus when reflecting heterogeneity in treatment decisions.

Figure 2-2 displays the scenario in which heterogeneity in cost-effectiveness exists in a population, but the decision-maker does not consider heterogeneity in their decision-making process. A manufacturer will set their price at the average cost-effectiveness price, plotted at Point A. This is the highest price the decision-maker is willing-to-pay for the treatment and it therefore maximises the provider's revenue (unit price multiplied by quantity sold). At this price, welfare gain is necessarily equal to welfare loss for the decision-maker.

Figure 2-3 displays the alternative situation in which heterogeneity is reflected in the decision-making process. It is assumed that differential pricing is not possible. From a decision-maker's perspective, they should choose to reimburse up to the least cost-effective individual with positive $INMB_i$ at a given price (plotted along the demand curve). Any individual that is more cost-effective to treat than this person will produce welfare gains for the decision-maker because the price is set below the level at which their $INMB_i$ is zero. A monopolist manufacturer will attempt to maximise profit. This occurs when marginal revenue is equal to the marginal cost of producing the intervention, shown at Point B.

In most cases, it will be difficult to establish a reverse-engineered price for every individual in a population. Moreover, a paradigm shift in health service decision-making would be necessary for cost-effectiveness decisions to be made at the level of individual patients. However, it is often possible to stratify populations into subgroups between which cost-effectiveness varies. This stratification can be based on risk score, age, biomarker levels, or

other relevant variables. In such analysis the demand curve would be discretised in the form of a step function.

2.5 Identifying Subgroups: Feasibility, Validity, and Equity

Clinical feasibility, statistical validity, and equity must be considered when reflecting heterogeneity in cost-effectiveness analysis. Decision-makers must determine whether subgroups identified can be operationalised in clinical practice, whether there is sufficient data to support stratified cost-effectiveness results, and whether stratification could lead to an inequitable distribution of healthcare resources (21).

Clinical feasibility should be a primary concern when conducting stratified cost-effectiveness analysis. Several patient characteristics may be routinely collected in clinical practice. These include patients' age, sex, family history of disease, and some clinical markers like blood cholesterol levels and blood pressure. It may require extra cost and effort to obtain other relevant patient characteristics. It is increasingly feasible to obtain genomic data from patients (68) and considerable research funding has been invested in identifying novel biomarkers for a range of health conditions. The additional costs incurred stratifying patients based on these characteristics must be accounted for in cost-effectiveness analyses.

Statistical validity is another key concern when addressing heterogeneity in cost-effectiveness analysis. When assessing cost-effectiveness in multiple subgroups, it is possible that researchers might identify relationships due to random error rather than the existence of a real relationship. This is referred to as the multiple testing problem in statistics (69). Techniques to correct for multiple testing in studies of clinical effectiveness have been discussed in the literature (70,71). Sculpher argues that these rules may be too imposing and "represent arbitrary hurdles for identifying meaningful subgroups for decision making". An alternative proposition is the pre-specification of subgroups for analysis alongside some hypothesised clinical or economic justification.

The uncertainty associated with subgrouping must be explored. In lieu of sufficient evidence from clinical trials, cost-effectiveness studies typically employ decision-analytic models to predict health and cost outcomes.

Uncertainty can be evaluated with decision-analytic models by altering model inputs and recording the effect that this has on estimated health and cost outcomes. Traditional sensitivity analysis (TSA) involves incrementally changing one or a set of model parameters. This approach can be used to assess the effect of key modelling assumptions on predicted outcomes. Probabilistic sensitivity analysis (PSA) involves assigning each parameter of interest a distribution instead of a fixed value. The model is run repeatedly, allowing parameters to vary according to their assigned distribution, and outcomes are recorded. The distribution of outcomes produced in PSA informs researchers of the scope of parametric uncertainty in the modelling process. Both TSA and PSA can be employed at the subgroup level to gain increased understanding of the inherent uncertainty in the decision-making process.

Consideration must be made regarding data limitation when undertaking stratified cost-effectiveness analysis. Meta-analysis of randomised controlled trial data should be treated as the gold standard for assessing the relationship between independent and dependent variables (72). Individual-level longitudinal data allows researchers to establish covariates which drive heterogeneity in cost-effectiveness outcomes in a population and to model covariate interactions. Cross-sectional datasets may also provide information on the baseline distribution of risk factors, costs, and morbidity in a population.

Subgrouping patient populations requires making inferences based on a smaller amount of data than in other cost-effectiveness studies. Uncertainty will therefore be greater in stratified cost-effectiveness analyses and it may be necessary to acquire more subgroup-level data. Espinoza et al. (73) provide a framework to estimate the expected value of acquiring further subgroup-related data when addressing heterogeneity in cost-effectiveness analysis. Applying the value of information framework (74), they show that the total expected value of perfect information (*tEVPI*) in a population which comprises of S mutually-exclusive subgroups is equal to the sum of each subgroup-specific EVPI ($EVPI_s$) weighted by the proportion of that subgroup in the population (w_s):

$$tEVPI = \sum_{s=1}^{S} EVPI_s w_s.$$

Equity is a final concern when implementing policies which reflect heterogeneity in cost-effectiveness. Making treatment decisions based on some patient characteristics may be deemed socially unacceptable. Stratifying populations based on sociodemographic characteristics like age, sex, race, and social class is likely to raise equity issues.

Alternatively, stratification by such characteristics may be considered socially acceptable if this stratification leads to a reduction in health inequalities (75). One approach to limit equity issues is for decision-making bodies to pre-specify acceptable characteristics with which to stratify patient populations.

2.6 QALYs and their Constrained Maximisation

Health economic analyses typically aim to influence policy in a manner that maximises QALYs in a population (40,42,55,59). It is worth questioning whether this is the correct maximand for decision-makers. Let 'correct' be defined by two necessary and sufficient dimensions first expressed by Williams (76). The correct way to prioritise treatment must be just, though this is an "essentially contested" concept, and must rest on some notion of consent from affected parties. Through consideration of these fundamental questions, it becomes clear that all healthcare decision-making is constrained, even for organisations like NICE who explicitly pursue cost-effective practice.

Is QALY Maximisation Just?

One reason that QALYs are seen to be just is that they represent an objective means to compare disparate health states. The benefit of using this metric to compare health-related utility across different health states and disease areas is well-established (77,78). Unlike biological health metrics (e.g. CVD events prevented, deterioration in CD4 count), QALYs can be compared across disease areas. Unlike life years gained and lives saved, they cardinally rank health state utility and therefore represent both longevity and quality of life in decision-making. While cardinal ranking of health state utility is difficult and controversial, it allows analysis to account for the intuitive fact that some health states are more desirable than others.

Some have argued that QALY maximisation in unjust. Harris imagines a world in which poor health is randomly distributed in a population. He argues that in such a world it is unjust to direct treatment away from those who suffer from diseases with high cost-per-QALY treatments (79). Two hypothetical patients who may receive a life-saving treatment are presented. The intervention will extend their lives by an equal amount of time (80). One patient is a 'victim of disaster' and has a low quality of life, while the other lives in full health. Under QALY maximisation, the fully healthy patient would receive treatment. The less

healthy patient appears to suffer ‘double jeopardy’ in this case: they experience a debilitating event and are punished for this by not receiving future treatment.

Cubbon argues that QALY maximisation is a just basis for allocating healthcare resources and takes issue with Harris’ critiques (78). He acknowledges QALY maximisation can discriminate against those less capable of deriving benefit from resources. Importantly, he notes this is only contingently true – it is not primarily because someone is ill that they are not treated. Rather, it is because someone else can gain more benefit given restricted healthcare resources. This discrimination loses its “sting” for Cubbon if those whose treatment is considered to have low cost-effectiveness are not systematically part of a clearly-defined and unchanging group. Lower value patients are a disparate group, he continues, and the conditions that constitute this group are continually changing.

The concept of ‘double jeopardy’ has been singled out for challenge in the literature. Singer et al. (81) highlight that more often than not health care aims to ameliorate a patient’s condition rather than save their life. There is much more scope to increase quality of life for a patient living at a QALY of 0.40 than a patient living at a QALY of 0.95. Hence, health resources are more likely to be directed towards the ill.

Rawles also questions unconstrained QALYs maximisation (82). He argues that life, life years, and suffering are distinct dimensions of the human experience that cannot be synthesised into a unitary metric. Harris echoes this critique of QALYs (79). Both researchers argue that life (of any quality) is undervalued in QALY formulation (83).

Cubbon notes that caring solely about life years or lives saved leads to irregular decision-making (78). If concerned only with saving lives, one may equally value saving a baby with short life expectancy to saving another who will live 70 more years. Intuitively this seems wrong. Health, in Cubbon’s view, is “sine qua non” for a range of human activity. In other words, its existence dictates one’s ability to appreciate their remaining life years.

Additional concerns have been raised with the use of QALYs in decision-making (76). Three distinct ethical concerns with QALYs raised are:

(i) The wrong population may be used to elicit preference for QALYs
(ii) Moving from individual to group values may be invalid.
(iii) QALY maximisation ignores interpersonal distribution of health gains.

Williams refutes the validity of the concerns raised above (76). With regards to preference elicitation, he notes that the way in which QALYs are derived allows for different views to be accepted. Originally clinicians' views were used to value health states, but the general public and patients can also inform valuation. Of the second concern, it is noted that some physicians may believe it unethical to replace the values of an individual patient with that of a larger group of patients. It follows that they should be able to provide care in a way which best suits their individual patient's desires. Williams counters: only in a purely private market (with no charity and no insurance) does a patient get everything they want. Pursing policies which maximise population-level QALYs simply increases transparency and accountability in areas where clinicians previously had "unchallenged private discretion".

Williams denies that the QALY approach to priority-setting must necessarily ignore interpersonal distribution of health (76). Nothing in the QALY approach requires that QALYs alone are maximised. In simple QALY maximisation, a value judgement is made that postulates that all QALYs gained are equal, regardless of who experiences them. This is described by Nord et al. (84) as the principle of "distributive neutrality". Williams notes that the principle of distributive neutrality can be defied and QALYs can be weighted by coefficients to represent a society's aversion to inequality.

Is QALY Maximisation Consented to by Affected Parties?

The second dimension necessary to define a correct maximand for health sector decision-makers is consent from affected parties. There are many parties affected by health sector decision-making. Anyone who may seek care in the health system is affected by a healthcare decision as no individual is certain of their future health status. Moreover, the decision to fund one programme (healthcare or otherwise) necessarily benefits some individuals and 'disbenefits' others through displaced funds (76).

QALY maximisation alone as the objective function of a health sector decision-maker is only justified if the general public subscribes to the principle of distributive neutrality. Decades of research, across many countries, suggests that individuals do not subscribe fully to the principle of distributive neutrality, that 'a QALY is a QALY is a QALY' (85) regardless of the characteristics of the person gaining health.

Empirical studies have long shown that individuals value QALY gains differently dependent on who receives them. There is considerable public and political support for the idea that QALY production in young children and parents should be valued at a higher rate than in the elderly (84,86–90). Initial and final health state may affect valuation of health gains. Research shows a tendency for individuals to prefer treatment in those that are very ill (91–94) and an aversion to treatments which leave a patient significantly disabled (94–96).

Evidence pertinent to preventive services shows that people may value QALYs differently dependent on how much health a patient gains. Choudhry et al. (97) found that individuals are more likely to support a large number of small health gains distributed across a large population rather than large health gains distributed across a smaller population, even when the total number of QALYs gained is equal. They additionally show that this decision reverts at very low levels of gain for the many.

Finally, individuals may value QALYs differently dependent on the socioeconomic status of patients who derive benefits. Dolan et al. reviewed literature to assess whether social value of health is affected by socioeconomic inequality. They showed widespread belief that health funds should be spent on reducing socioeconomic inequality in health while also increasing population health (98–104). This research additionally suggested that there may be a threshold of inequality that individuals are willing to accept.

As alluded to previously, weightings can be applied to QALYs in cost-effectiveness analyses to ensure that health gains are distributed to in a way that reflects a society's preference for health production in different patients. It appears that many candidate patient characteristics would need to be considered in a truly representative weighting process. Priority-setting based on weighted outcomes fundamentally accepts that QALYs are not the sole maximand of a health sector decision-maker.

QALY Maximisation and Health Sector Decision-Making

From the discussion above, it appears the QALYs should not necessarily be the sole maximand for a health sector decision-maker. However, in lieu of consensus regarding the distributive preferences of affected parties in a health system, cost-effectiveness analysis and the principle of distributive neutrality are likely the most valid mechanisms for priority-setting. It is roundly agreed that health gains should play an important role in determining

who receives treatment and valid weightings for patient characteristics have not been established.

In the NHS in England and Wales, the decision to implement new health technologies is assessed by NICE. Cost-effectiveness analyses and review of economic evaluations are conducted by NICE to determine whether an intervention is cost-effective at a willingness-to-pay threshold of £20,000-£30,000/QALY. In its Guide to the Methods of Technology Appraisal (40), NICE states that interventions with ICERs below £20,000/QALY should be appraised solely on their cost-effective. Interventions with ICERs above £20,000/QALY should account for additional factors including: innovative nature of the technology, whether the treatment extends life expectancy in patients near the end of their life, and 'non-health objectives'. Elsewhere the guide states that NICE committees "will take non-health objectives of the NHS into account by considering the extent to which society may be prepared to forego health gain in order to achieve other benefits that are not health related". NICE can therefore be thought of as generally pursuing QALY maximisation, somewhat constrained by other health- and non-health-related objectives.

In the Scottish NHS, the Scottish Medicines Consortium (SMC) is responsible for consulting local health boards about newly-licenced medicines and the Scottish Intercollegiate Guidelines Network (SIGN) is responsible for ensuring evidence-based clinical practice (105,106). Guidelines from the SMC and SIGN are more equivocal about the role of cost-effectiveness in decision-making. In its guidance to manufacturers on new product assessment, the SMC states that they do not have a fixed cost-effectiveness threshold with which they judge new submissions (107). The guidance continues, however, that the SMC takes note of NICE's cost-effectiveness thresholds and decision-making process for evaluating interventions. In its Guideline Developer's Handbook, SIGN is equally vague about the role of cost-effectiveness in its decision-making (108). It states that the incremental cost of a new intervention should be weighed against the benefits gained, but does not define a specific threshold for treatment implementation.

To different degrees, NICE, the SMC, and SIGN all support the principle of maximising health using cost-effectiveness analysis but are constrained in this maximisation. NICE explicitly states that its decisions may be shaped by additional measures of benefit. The equivocal language of the SMC and SIGN suggests that they too value non-QALY benefits in their decision-making.

Research supports the idea that health sector decision-makers in the U.K. do not solely aim to maximise QALYs. Shah et al. (109) looked at data from 51 impact assessments produced by the U.K. Department of Health in 2008 and 2009. They found that in only eight (15.6%) of the impact assessments, benefits were measured in terms of QALYs. Other benefits considered were patient and carer experience, patient and public empowerment, choice and access, equity and fairness, public trust and confidence, improved staff morale, and markets and structure. Some of these features may help the NHS to produce QALYs in the future, but the results certainly suggest that health expenditure in the U.K. does not aim solely to increase QALYs. Appleby et al. (110) similarly found that QALYs and cost-effectiveness are rarely mentioned in local government assessments of health expenditure.

It is useful to consider the role of a healthcare decision-maker in the U.K. as a QALY maximiser constrained by more than just costs. As Shah et al. (109) found, the decision-maker competes for resources with government-mandated health investments with disparate objectives. NICE guidelines contend that dimensions outwith simple QALY maximisation may be used to support rejection or reimbursement of an intervention. Mooney highlights that the very nature of NHS as it exists in Scotland, England, and Wales constrains QALY maximisation. The NHS was founded on the principle of equality of access: a system free at the point of service that meets the needs of everyone, based on clinical need rather than ability to pay (111). In its very structure, it assigns weight (and therefore distributes costs) to the production of health equity which need not align perfectly with QALY maximisation.

The role of cost-effectiveness analysis in the U.S. is more complicated. Some organisations that issue health care guidance aim to maximise health, or at least have general regard to the social welfare function of a patient population. The two most discussed U.S. guideline organisations in this thesis will be the American College of Cardiology (ACC) and the American Heart Association (AHA). Both claim that their objective is to maximise patient health and have discussed the role that cost-effectiveness analysis plays in this process (112–114). Neumann and Greenberg note that many other U.S. organisations also subscribe to some form of QALY maximising objective (115). Improving patient health is not the aim of all health sector decision-makers in the U.S., where profit-driven providers often offer more costly and worse services than their not-for-profit rivals (116–120).

2.7 Discounting in Health Economic Analysis

This thesis will regularly rely on the concept of discounting in health economic analysis. What follows is a short description of discounting, justifying its use in latter chapters.

Present health benefits and costs are often considered to be more important than those in the future. Cost-effectiveness analysis of health technologies can account for potential changes in the real value of benefits and costs through discounting. Decision-makers look to maximise health given an exogenous budget, acknowledging that costs incurred effectively amount to foregone health. By looking at the decision rules invoked by such maximisation it is possible to determine the rate at which health and costs should be discounted, respectively.

Discounting of future costs should not be considered as a simple reflection of individual preferences but instead as a means of accounting for real rates of return to investment, opportunity costs, and social time preference rates. For example, £1,000 today could be prudently invested to garner more real money in a year's time. Future costs should be weighted to account for the opportunity cost associated with paying for health in the present rather than the future. Moreover, if a society is expected to have increasing access to resources, current costs are more burdensome than those incurred in the future and discounting should be applied.

While discounting of costs is seen as intuitive and uncontroversial, the intuition for discounting of health benefits is less clear (121). This debate stems from the fact that health, unlike costs, cannot be invested in order to yield future gains. Hence the previous logic for cost discounting does not hold. It is important, however, to also consider time preference rates for health. Evidence suggests that it is natural for humans to prioritise current health and partially ignore future consequences (4,122,123). It may then be necessary to discount future health benefits associated with the introduction of new health technologies. The amount of health in period $t+1$ considered to be equivalent to one unit of health in period t is defined as the social time preference rate for health.

It is assumed that a health sector decision-maker has estimates of a few necessary variables when determining whether or not to implement a new health care intervention. These are listed below.

Δh_t – incremental health benefits in period t
Δc_t – incremental costs in period t
k_t – cost-effectiveness threshold in period t
r_h – social time preference rate for health

Under the assumption that all costs fall on a constrained budget, the expected foregone health in each period due to the additional costs of adopting the respective health technology can be represented by incurred costs divided by the cost-effectiveness threshold in each period ($\Delta c_t/k_t$). Health benefits and costs over two periods can then be represented as shown in Table 2-2 below, adapted from Claxton et al. (124). Note that the values in Period 2 are discounted to account for the social time preference rate for health.

Parameter	Time Period 1	Time Period 2
Health gained (present value)	Δh_1	$\frac{\Delta h_2}{(1+r_{h)}}$
Health foregone (present value)	$\frac{\Delta c_1}{k_1}$	$\frac{\Delta c_2}{k_2(1+r_{h)}}$

Table 2-2: Present value of health gained and health foregone over two time periods, adapted from Claxton et al. (text)

A decision-maker is expected to implement a new technology if the health gained is greater than health foregone over the total time period. As previously discussed, health gained minus health foregone can be described as incremental net health benefit. A decision-maker is expected to accept a new health technology if, and only if:

$$INHB = \left(\Delta h_1 + \frac{\Delta h_2}{(1+r_h)}\right) - \left(\frac{\Delta c_1}{k_1} + \frac{\Delta c_2}{k_2(1+r_h)}\right) > 0.$$

Note here that costs are simply a proxy for foregone health so health and costs should be discounted at the same rate. Importantly, however, this decision rule does not account for potential growths in the cost-effectiveness threshold. Such growth is common, and may be caused by changes to the health service's budget and cost of health care services and products. Claxton et al. show that differential discount rates should be employed for health benefits and costs if the cost-effectiveness threshold is projected to change (124).

The suggested discount rate for both health benefits and costs recommended by NICE is 3.5% (40). Paulden and Claxton argue that this value is set too high, and should be closer to 1.0-1.5% (125). In the U.S., the Second Panel on Cost-Effectiveness in Health and Medicine

recommends an equal discount rate of 3.0% (54). These values will be adopted as parameters for cost-effectiveness analyses in Chapters 7 to 10.

2.8 Chapter Summary

This chapter described stratified medicine, stratified cost-effectiveness analysis, and heterogeneity in cost-effectiveness. It showed that health services can achieve consumer surplus by reflecting heterogeneity in outcome in their decision-making.

Heterogeneity in cost-effectiveness will be an important consideration throughout this thesis. When selecting which subgroups of a population should receive a treatment, it is important to consider heterogeneity in expected health and cost outcomes. Epidemiology can help to establish patient subgroups that are most likely to benefit from a treatment. Chapter 4 discusses the epidemiology of CVD and the epidemiologic basis for novel approaches to its prevention. The remainder of the thesis then considers the relative cost-effectiveness of these novel approaches to prevention.

Part 2

Cardiovascular Disease Prevention

Part 2 provides an introduction to CVD and discusses approaches to its prevention. A particular focus is placed on linking this highly prevalent chronic health condition to the theory presented in Part 1 regarding heterogeneity in cost-effectiveness. Current clinical guidelines are discussed alongside the epidemiologic basis for alternative approaches to prevention.

Chapter 3 describes the prevalence and incidence of CVD in Scotland, England and Wales, the U.S., and the rest of the world. Theory regarding the prevention of CVD and current clinical guidelines are discussed. These guidelines typically recommend targeting treatment at patients with elevated 10-year CVD risk.

Chapter 4 presents the epidemiologic basis for three different approaches to CVD prevention. It describes the respective abilities of these approaches to reflect heterogeneity in cost-effectiveness and provides examples of policies which adopt each of these approaches to prevention. The three approaches discussed are:

- Continued use of 10-year risk scoring
- Novel decision mechanisms that incorporate 10-year risk scoring
- Use of decision-analytic models in the clinical process.

Chapter 3
Cardiovascular Disease

3.1 Purpose

This chapter aims to describe CVD and approaches that can be adopted to reduce its incidence. The prevalence, incidence, and economic burden associated with the disease in Scotland, England and Wales, the United States, and the rest of the world are discussed, respectively. A brief overview is provided of different forms of intervention that can be adopted to prevent CVD. Finally, guidelines regarding the prioritisation of patients for preventive intervention in high-income countries are detailed. These guidelines typically recommend targeting treatment at patients who have elevated 10-year risk of experiencing a primary CVD event. 'High-income' is defined according to the World Bank Atlas methodology, and therefore incorporates all countries with a gross national income (GNI) per capita greater than $12,056 in 2019 (126).

The purpose of this chapter is to introduce the clinical area of CVD. A primary objective of the thesis is to apply theory regarding heterogeneity in cost-effectiveness to CVD prevention.

3.2 Cardiovascular Disease

Definition

CVD is a term used to describe a range of diseases of the heart and blood circulatory system. The International Statistical Classification of Disease and Health Related Problems (ICD) indexes different forms of CVD. The conditions which constitute CVD can predominantly be described as either coronary heart disease (CHD) or cerebrovascular disease (CBVD), along with some less prevalent conditions (Table 3-1).

Coronary heart disease, also referred to as ischaemic heart disease (IHD) and coronary artery disease (CAD), is the most common type of CVD. It may manifest itself in the form of stable or unstable angina pectoris, myocardial infarction, or sudden cardiac arrest. These conditions generally stem from a similar physiological process called atherosclerosis (127).

Atherosclerosis is the build-up of fibro-fatty plaque on the walls of arteries, typically over many decades before the primary onset of a clinical event, as shown in Figure 3-1 (128). This build-up may lead to ischaemia (a restriction of blood flow) to the myocardium (the muscular tissue of the heart). Atherosclerotic build-up can be exacerbated or slowed down by a range of 'risk factors'. When myocardial oxygen demand is not met, an individual may experience chest pain or pressure (angina pectoris) and damage and death of heart tissue (myocardial infarction). Ischaemia can also cause the heart to pump irregularly which may ultimately result in cardiac arrest (129).

Cerebrovascular disease refers to conditions that arise when the flow of blood to the brain is restricted (130). An ischaemic stroke occurs when severe restriction of blood flow to the brain occurs, often caused by the dislodgement of a blood clot in an individual's arteries. This may lead to the damage and death of brain cells. Transient ischaemic attacks (TIAs) occur when there is a temporary restriction of blood flow to the brain. These events typically last less than an hour and are commonly referred to as 'mini-strokes'. Atherosclerosis is a key causal predictor of stroke risk (131,132).

ICD10 Codes	Condition
I20-25	Coronary Heart Disease
I60-69, G45	Cerebrovascular Disease
I00-16 I20-52 I70-99	Other: Acute rheumatic fever, chronic rheumatic fever, hypertensive diseases, pulmonary heart disease and diseases of pulmonary circulation, other forms of heart disease, diseases of arteries, arterioles, and capillaries, diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified, other and unspecified disorders of the circulatory system

Table 3-1: International Classification of Disease codes for CVD (text)

Less common constituent forms of CVD include pulmonary heart disease, acute rheumatic fever and chronic rheumatic heart disease, pericarditis, and myocarditis. The relationship between these conditions and modifiable risk factors is less established than CHD and CBVD, and they often develop following an initial CHD or CBVD event (133–135). Hence CVD prevention often focuses on reducing rates of CHD and CBVD.

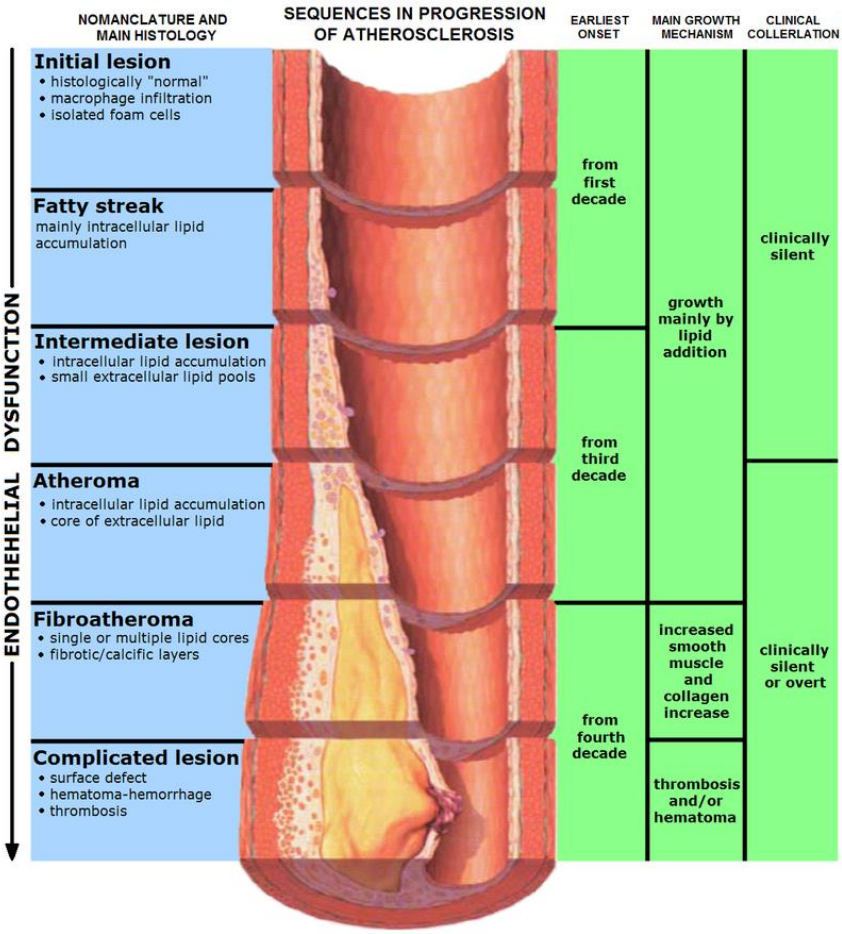


Figure 3-1: Timeline of atherosclerotic build-up (text)

Prevalence and Incidence

Advancements in health technology throughout the first half of the 20th century dramatically changed the medical landscape, extending population-level life expectancy and changing the types of diseases that cause mortality and morbidity in high-income countries.

In the early 1900s, leading recorded causes of mortality in Scotland, England and Wales, and the U.S. were respiratory conditions, infectious disease, and parasitic disease (136–138). Record keeping was poor at the time, however, and up to 50% of deaths were registered as ‘other’. Cancer and heart disease were common but not leading causes of mortality.

Since the start of the twentieth century, life expectancy in high-income countries has increased markedly. This, in turn, has altered the distribution of mortality and morbidity in these countries. Cutler, Deaton, and Lleras-Muney attribute the increase in life expectancy to knowledge, science, and technology (139). Enlightenment ideas of personal health and public administration resulted in individuals living a better quality of life, eating more nutritious

diets, and living in less squalor with better sanitation. Increased medical knowledge led to the spread of new health technologies (e.g. polio vaccines, oral rehydration therapy for diarrhea, vaccines, antibiotics) and practices were developed to combat illness (e.g. sanitary practice to prevent spread of germs).

As life expectancy increased, so too did the prevalence of chronic illnesses like cancer and CVD. Individuals began to live long enough to experience advanced atherosclerosis and the effects of unhealthy behaviour (including smoking, consumption of processed foods, and sedentary lifestyle) (140). Chronic conditions replaced infectious diseases as the major health concern for high-income populations. By 1950, age-adjusted rates of CHD and stroke mortality were 307 and 105 per 100,000, respectively (140). The mortality rate for CHD in the U.K. was around 200 per 100,000 in 1950, and peaked at 550 per 100,000 in 1970 (141).

In high-income countries, incidence rates of CVD have fallen in recent decades. O'Flaherty et al. note that CVD mortality rates fell by 50-80% in the U.S., U.K., and Western Europe in the latter half of the 20th century (142). Large decreases in CHD and CBVD mortality were observed across Western Europe. From 1980-2009, CHD mortality fell 67% and 66% to 87 and 38 per 100,000 for men and women, respectively. A similar reduction in CBVD mortality was observed during the same time period (143). From 1990-2013, age-adjusted cardiovascular mortality rates also decreased significantly in the U.S., from 376 to 274 per 100,000 (140).

Studies have attempted to quantify the contributors to falling rates of CVD in high-income countries. Changes in health behaviours alongside the development and improvement of primary and secondary health care interventions are largely responsible for this reduction in CVD mortality and morbidity (142). Hunink et al. estimated that around 54% of the decrease in CHD mortality in the U.S. in 1980-1990 could be attributed to reduction in risk factor levels while 43% was explained by improvements in treatment of chronic CHD (144). Similarly, Ford et al. found that 44% of the decrease in U.S. CHD mortality from 1980-2000 was explained by changes in risk factors, while 47% was explained by changes in treatment of chronic CHD (145). They additionally note that reduction in total cholesterol, systolic blood pressure, smoking, and physical inactivity accounted for 23%, 20%, 12%, and 5% of these reductions, respectively. A study set in the U.K. estimated that declines in CHD mortality from 1981-2000 were explained 58% by risk factor control and 42% by treatments (146). This study found that reduced levels of smoking had the greatest effect of all risk

factor-related disease reduction, followed by cholesterol and blood pressure control. A final study in 2012 estimated that half of the 6% reduction in CHD mortality observed in the U.K. between 2000-2007 was explained by improved treatment uptake (147).

Despite large improvements, it remains vital for health systems to fund preventive interventions for CVD. Rates of CVD in high-income countries have plateaued recently. Despite reductions in incidence, the condition remains a highly prevalent cause of morbidity, mortality, and economic burden in richer countries (140,148). Funding preventive interventions for CVD is also important in low- and middle-income countries. Rates of infectious disease are falling across the globe. As observed in high-income counterparts during the 20th century, low- and middle-income countries may soon experience an increase in chronic conditions like CVD as life expectancy increases (142).

Scotland, England, and Wales

CVD was responsible for around 160,000 deaths in the U.K. in 2015. Rates of the disease are disproportionately high in Scotland, where more than 15,000 people died of CVD in 2015 (149). With a population of approximately 5.4 million, Scotland represents around 8.2% of the total U.K. population while contributing 9.8% of CVD fatalities (150). In addition, the British Heart Foundation estimates that more than 7 million people in the U.K. currently live with CVD. Again, this rate is disproportionately high in Scotland, where 670,000 individuals are estimated to suffer from the condition (149).

There exists a strong socioeconomic deprivation gradient in CVD in the U.K. and Scotland. Hotchkiss et al. show that there is a strong socioeconomic gradient in unhealthy CVD risk factors in Scotland (151). These risk factors included smoking, insufficient fruit and vegetable consumption, excessive salt consumption, excessive alcohol consumption, diabetes, and hypertension.

Woodward, Brindle, and Tunstall-Pedoe have shown that the socioeconomic gradient in CVD persists when one controls for traditional risk factors like age, sex, diabetes, cholesterol, family history of CVD, chronic kidney disease, smoking, and blood pressure (152). Figure 3-2 shows the 2011-2015 standardised mortality rates for CHD in Scotland, provided by the Information Services Division of NHS National Services Scotland, disaggregated into three age-groups and an index of social deprivation (153). Individuals from more deprived areas

have a much greater rate of CHD mortality, and this is especially true for individuals aged less than 65 years old. Hippisley-Cox et al. have observed a similar relationship between social deprivation and CVD risk in England and Wales (154).

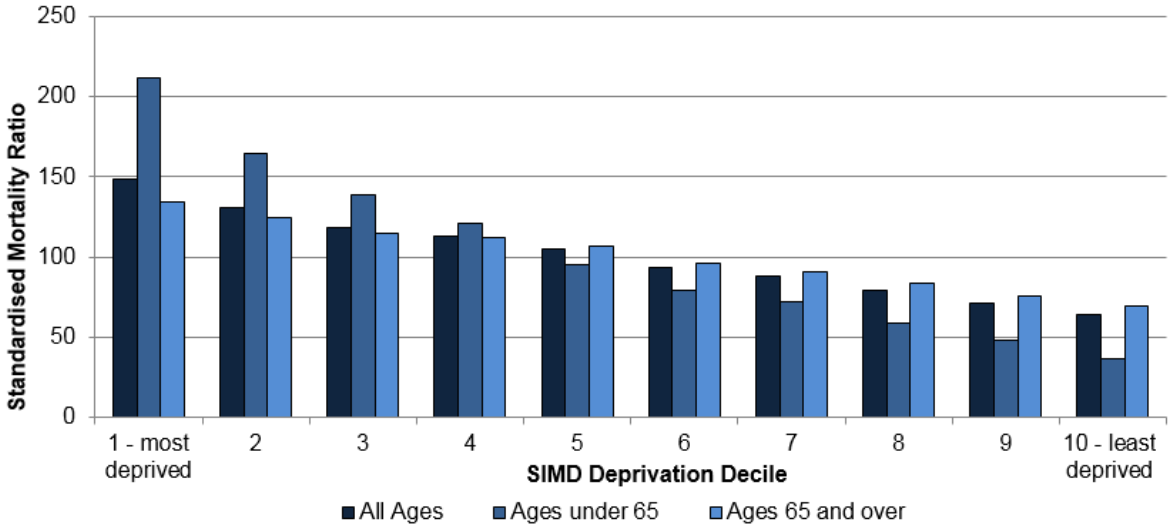


Figure 3-2: Standardised CHD Mortality Rate in Scotland for 2011-2015, Information Services Division NHS Scotland (text)

United States

The AHA estimates that CVD accounts for 835,000 deaths annually in the U.S., making it the nation's most common cause of death. In addition, it is estimated that some 92 million American adults currently live with chronic CVD (155).

Rates of CVD differ significantly amongst subgroups of the U.S. population. In 2009, the U.S. Center for Disease Control reported that non-Hispanic Black Americans have a 51.6% and 47.4% greater age-adjusted rate of CHD and stroke mortality compared to non-Hispanic Whites, respectively. It has also been shown that low socioeconomic status (defined by household income less than 150% of the federal poverty level) is a significant predictor of any CHD event and CHD mortality (156).

Figure 3-3 shows age-adjusted CVD mortality rates in the U.S. from 1969-2011, stratified by quintile of socioeconomic status (157). This analysis by Singh et al. showed both the secular trend of falling CVD mortality rates in the U.S. as well as the persistent socioeconomic disparity in the disease's mortality rate.

Predicting future incidence and prevalence of a health condition is a difficult process which entails inevitable uncertainty. Heidenreich et al. predict that there will be a substantial increase in CVD mortality in the U.S. by 2030. This study adopted cohort-component methodology which assumes changes in mortality rates are explained solely by assumptions regarding future births, deaths, and net migration (158). Pearson-Stuttard et al., on the other hand, employed a trend-based model which accounts for historical trends in CVD reduction (159). They predicted that CHD mortality would fall by 27% by 2030, while stroke mortality rates would remain constant.

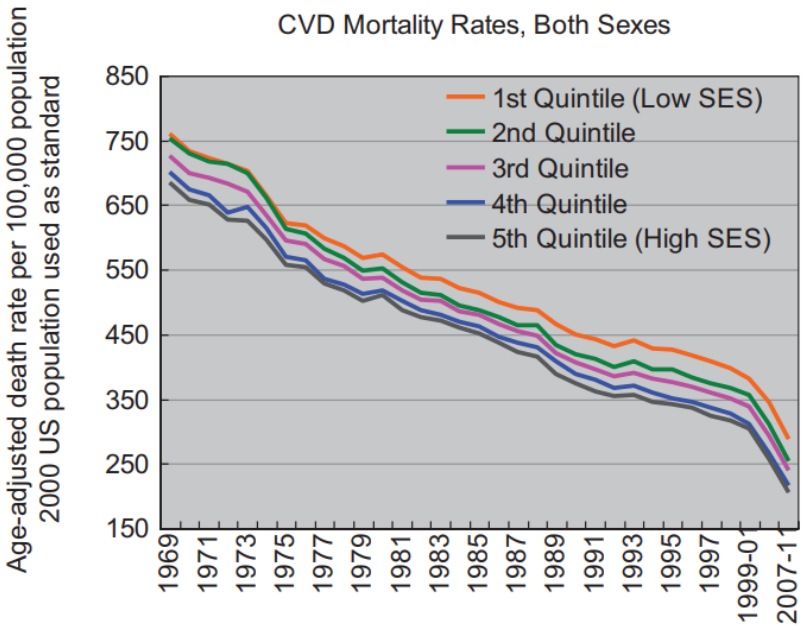


Figure 3-3: Age-standardised CVD Mortality Rate in U.S., 1969-2011, Singh et al. (text)

Europe and Rest of World

The Global Burden of Disease (GBD) Study has published detailed estimates of CVD incidence, prevalence, and incidence trends (1). This study estimated that CVD rates have decreased from 1990-2015 in almost all European countries. The gradient of decline has been much greater in Central and Western European countries. The study estimated that around 85 million individuals live with CVD in Europe, a number that has increased since 1990 despite falling incidence rates. This increase in prevalence is likely attributable to sociodemographic changes in the European population (e.g. aging populations) alongside increased obesity.

Age-standardised CVD mortality rates fell in all high-income countries and most middle-income countries between 1990-2015, however the GBD study notes that no significant change was observed in most of sub-Saharan Africa and countries across Oceania and Asia (1). In addition, Bangladesh and the Philippines experienced significant increases in age-standardised CVD mortality. The study also examined the relationship between a region's development (assigned using a combinatory measure of income per capita, education attainment, and fertility) and CVD mortality rates. They found that CVD mortality increases with the development index at low levels of development, but this trend reverts at higher levels of development, as shown in Figure 3-4 (1). This observation supports the hypothesis that rates of CVD increase (and will continue to increase) in less-developed countries as they become more successful at reducing rates of infectious disease, prolonging their population's life-expectancy.

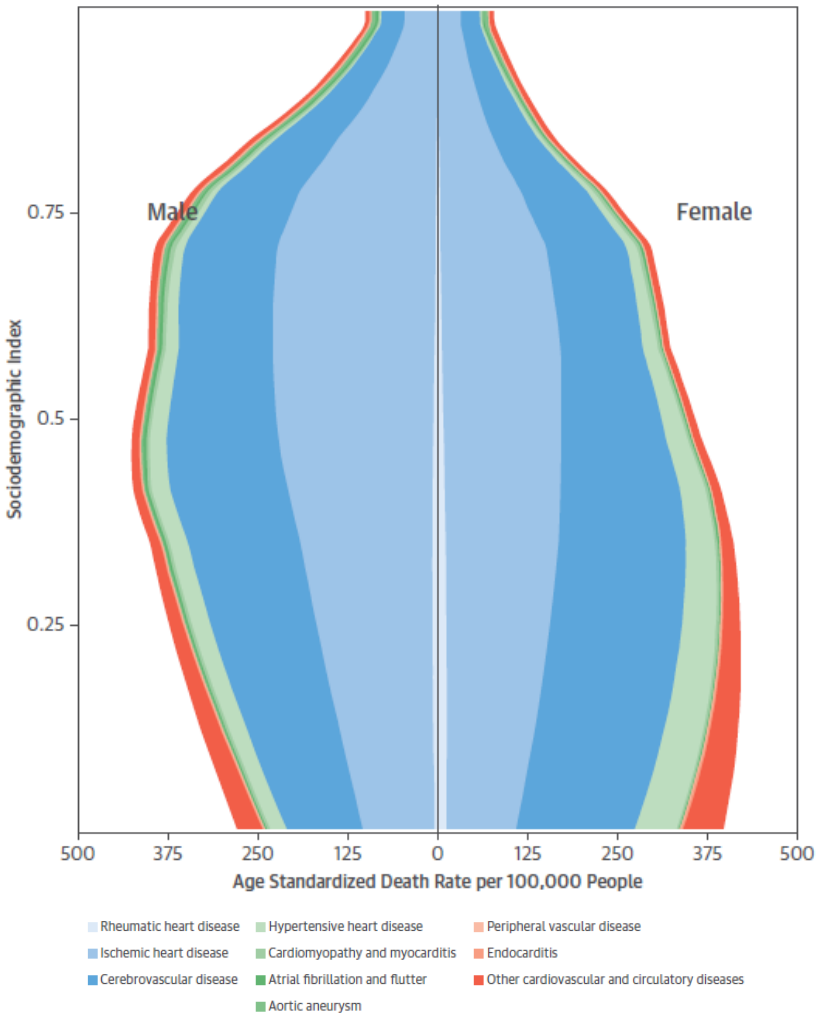


Figure 3-4: Age-standardised death rate for a range of cardiovascular conditions versus sociodemographic index for males and females, Roth et al. (text)

While this thesis will focus on CVD prevention in high-income countries, trends in the incidence and prevalence of the disease around the world should also be considered. The GBD analysis suggests that preventive strategy in high-income countries may become relevant to low- and middle-income countries in coming years as their health services and sociodemographic characteristics evolve. Indeed, one of the United Nations' Sustainable Development Goals is to achieve universal health coverage across the globe by 2030 (104). Implementing cost-effective interventions will help countries to achieve this goal.

3.3 Economic Burden of CVD

To estimate the total economic burden of a disease, researchers must account for primary, secondary, and tertiary healthcare costs alongside non-healthcare costs. Non-healthcare costs include informal care and years of lost work through mortality and incapacity.

The economic burden of CVD has been estimated in the U.K. and around Europe. In 2006, Luengo-Fernandez et al. performed a cost-of-illness analysis, considering the direct and indirect costs that CVD inflicts on the U.K. economy. It was estimated that the total economic burden of CVD in the U.K. in 2004 was £29.1 billion, of which the non-healthcare costs accounted for £11.7 billion (160). The same authors estimated the annual total economic burden and non-healthcare cost of CVD in the E.U. to be €168.8 billion and €64.2 billion, respectively (161).

In 2010, Heidenreich et al. performed cost-of-illness analysis for the AHA, estimating both the current and future economic burden of CVD (158). They estimated that in 2010, healthcare ("direct medical") and non-healthcare ("indirect") costs of CVD in the U.S. were $272.5 billion and $171.8 billion ($US 2008), respectively. By 2030 they predicted these costs will rise to $818.1 billion and $275.8 billion, respectively. The larger relative increase in healthcare costs was explained by the aging population in the U.S. and an upwards trend in per capita medical expenditure (159).

3.4 CVD Risk Factors

Increased etiological understanding of CVD has improved clinicians' ability to estimate the likelihood that a disease-free individual will experience a primary CVD event. Several risk scores have been developed since 1967, when Truett, Cornfield, and Kannel performed

multivariate discriminant function analysis to evaluate risk in the Framingham Heart Study (162). A recent systematic review (163) identified 363 multivariable models for the prediction of any future CVD outcome in an asymptomatic population since Truett et al.'s seminal paper.

While a range of variables have been considered in CVD risk estimation, Damen et al. note that most models include a similar set of covariates (163). Five key variables, age, sex, smoking, blood pressure, and blood cholesterol levels, appeared in 66% of the models identified in their systematic review. Other commonly included covariates were diabetes (52%) and BMI (29%). High levels of LDL-C are considered to increase CVD risk, while high levels of high-density lipoprotein cholesterol (HDL-C) are associated with reduced rates of CVD events (164). Both LDL-C and HDL-C are members of a group of biological substances called lipids. The term cholesterol and lipid are often used interchangeably in the discussion of CVD risk. Lipid is a broad term, however, which pertains to a wide range of biomolecules including fatty acids, vitamins, glycerides, and waxes (165).

3.5 Preventing CVD

Types of Prevention

There is a wide range of approaches and policies that can be adopted to prevent CVD. These are typically described by four categories: primordial, primary, secondary, and tertiary prevention.

Primordial prevention aims to stop the development of a disease's risk factors in early life. This is an important stage in the prevention of CVD. Even though atherosclerosis most often leads to CVD events which occur during adulthood, it has been established that atherosclerotic lesions develop in childhood (166).

The Special Turku Coronary Risk Factor Intervention Project (STRIP), conducted in Turku, Finland, provides an example of primordial prevention for CVD (167). Over 1,000 infants were randomised to receive an individualised dietary intervention versus standard care. By their mid-teenage years, individuals who received the intervention had lower levels of metabolic syndrome, high blood pressure, high blood glucose, and high waist circumference. While long-term follow-up is currently not available to show the effect of these reductions

on CVD risk, this primordial intervention should theoretically have arrested or delayed the development of atherosclerosis before its initial development.

Primary prevention aims to arrest the development of a disease before the occurrence of an incident event. This typically involves targeting unhealthy risk factors after they have developed. Preventive interventions for CVD usually take the form of legislative change, lifestyle advice, and pharmacological treatment. For example, the Soft Drinks Industry Levy was introduced in the U.K. in April 2018 (168). This is a tax on businesses which produce excessively sugary beverages, and aims to reduce obesity rates in the country (169). Pharmacologic forms of primary prevention include provision of cholesterol- and blood-pressure-reducing medication to patients to reduce atherosclerotic build-up and subclinical CVD (170).

Secondary prevention is employed to manage a condition. A key focus of such interventions is the correct diagnosis and management of patients who exhibit symptoms of a condition. Such interventions in CVD aim to slow down and prevent disease progression, improving patients' quality of life. Cholesterol-reducing medications are often prescribed for the secondary prevention of CVD. These aim to reduce LDL-C, and hence slow the continuation of atherosclerotic build-up that may lead to recurrent CVD events (171).

Finally, tertiary prevention is undertaken with the aim of reducing the level of morbidity experienced by individuals with symptomatic illness and preventing further disease-related deterioration. While secondary prevention aims to arrest further development of a disease, tertiary interventions simply aim to improve the quality of life, capability, and functioning of individuals with an established disease. Examples from CVD include stroke rehabilitation programmes and patient support groups to promote patient wellness and solidarity (172).

High-Risk vs. Population Approaches to Primary Prevention

This thesis will focus on the epidemiological basis, feasibility, and cost-effectiveness of different strategies for the primary prevention of CVD. All stages of prevention have contributed to the large reduction in CVD rates observed across high-income countries in recent decades. While there is increasing support for primordial prevention campaigns in the U.K. and U.S., the majority of preventive programs still focus on primary prevention.

Typically, such programs focus on risk factor reduction for CVD-free individuals aged 40 years and above (25,26,173,174).

In the seminal article *Sick Individuals and Sick Populations*, epidemiologist Geoffrey Rose set out two alternative approaches to primary prevention: the high-risk and population approaches (175). Building on previous analysis regarding CVD prevention (176), he showed that these different approaches to prevention could lead to very different population-level health outcomes. Sociologists, epidemiologists, and medical professionals have evaluated and critiqued these theories ever since.

As its name suggests, the high-risk approach to prevention focuses on a subset of a population predicted to be at high-risk of developing a condition. Rose describes this as the "traditional and natural medical approach to prevention" (175). A doctor may identify a patient as having high blood pressure. They will then intervene to reduce this individual's blood pressure, often through lifestyle modification or prescription of blood pressure-reducing medication. These preventive interventions will lead to reduced risk of illnesses associated with hypertension in future years.

Rose suggests that the benefits of the high-risk approach to prevention are the ease with which interventions can be tailored to patients' needs, the motivation of high-risk patients to improve their health, the motivation of physicians to improve the health of high-risk patients, and the favourable ratio of benefit to risk (or cost) associated with treating those most likely to develop a condition.

One issue with the high-risk approach to prevention is the difficulty associated with predicting CVD risk. This difficulty is demonstrated in Figure 3-5. The figure displays the distribution of estimated baseline risk in two subsets of the Scottish population derived from the Scottish Heart Health Extended Cohort (177). Risk was estimated using a statistical tool called the ASSIGN risk score which estimates an individual's probability of experiencing a primary CVD event within 10 years, dependent on traditional CVD risk factors (152,178). Individuals in the first subset, outlined in red, did not experience a CVD event within 10 years of baseline risk measurement. Underlying this distribution in green is the baseline risk distribution of individuals who experienced a CVD event within 10 years of risk prediction. A large number of events occurred in supposedly 'low-risk' individuals. As Rose puts it, "The painful truth is that for [an individual in the lowest cardiovascular risk group] in a

Western population, the commonest cause of death—by far—is coronary heart disease! Everyone, in fact, is a high-risk individual for this uniquely mass disease" (175).

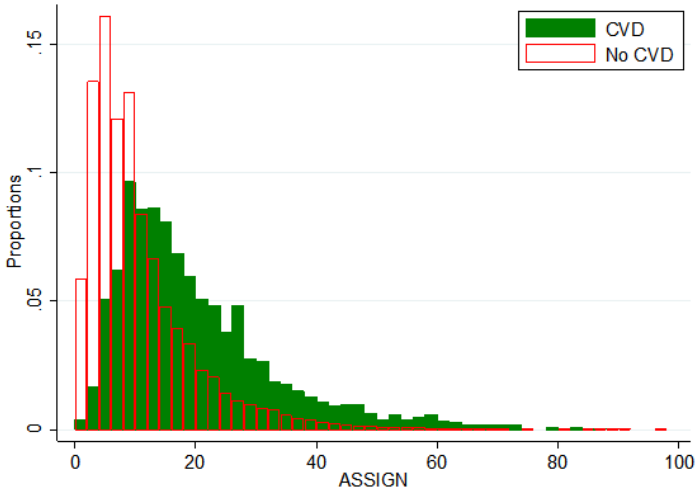


Figure 3-5: ASSIGN risk score distribution (whole population versus those who have event) in SHHEC

The population approach to primary prevention aims to lower average risk factor values in a population. This is typically achieved through 'public health' approaches to prevention including legislative changes and adoption of public health programmes. Examples of legislative changes are increased taxation or banning of unhealthy goods, regulation to improve environmental exposure of populations, subsidies for healthy produce, and mass media campaigns which promote healthy living. It is also possible to implement pharmacologic treatments using the population approach. For example, mass vaccination campaigns and public water fluoridation programmes adopt the population approach.

The key benefits of the population approach, according to Rose, are the radical nature of the intervention and the potential for large population-level gains. The radical nature of the intervention refers to the fact that the intervention aims to address the conditions that lead to high prevalence of a disease's underlying risk factors. This links directly to the next stated benefit. By moving population averages of risk factor levels to a healthier state, much greater benefit can be achieved than targeting a select group of individuals.

Limitations of the population approach are also discussed by Rose. Notably there is a 'prevention paradox' whereby larger population-level gains are achieved under the population approach, while smaller individual-level gains are achieved. This is because the gains are averaged over a much larger population. This directly leads to three other issues

with the population approach: due to low individual-level gains patients may have poor motivation to improve health, physicians may have poor motivation to treat patients, and the treatment may have unfavourable benefit-to-risk ratios.

Academics have long evaluated and critiqued Rose's high-risk and population approaches to prevention. Writing in the American Journal of Cardiology in 1985, Kottke et al. (179) estimated that lowering total serum cholesterol to 190 mg/dL and diastolic blood pressure to 80 mmHg for the top decile of CVD risk in the U.S. population would lead to a 33% reduction in CVD mortality in the U.S Alternatively, if population mean total serum cholesterol and diastolic blood pressure were lowered to these values, a 70% reduction in CVD mortality would be achieved. This argument disregards Rose's postulation that it is more difficult to motivate low-risk individuals to improve their health.

Barton et al. consider the cost-effectiveness of population interventions to reduce cholesterol and blood pressure in England and Wales (180). A worksheet-based model predicted life years lost, QALYs lost, and healthcare costs incurred for men and women aged 40-90 attributable to CVD. Relative risks were derived for blood pressure- and cholesterol-reducing interventions based on outcomes of previously enacted population health interventions. The life years gained, QALYs gained, and cost incurred associated with introducing such policies were then evaluated.

For blood pressure reduction, a salt reduction campaign was modelled. It was conservatively assumed that such a programme may achieve a population-wide 3g/day reduction in salt intake, based on studies of similar programmes in Japan, Finland, and other countries. Analysis of the U.K. survey data suggested that this dietary change would lead to a 2.5 mmHg reduction in mean population systolic blood pressure. Finally, based on the Framingham risk functions for the U.K., this blood pressure reduction was assumed to correspond to a 2% relative risk reduction for CVD events. Similar calculations were undertaken to predict that trans-fat levels could be reduced by around 0.5% of total dietary intake in the U.K., resulting in a population-level 6% relative risk reduction for fatal CVD events. Trans fats have been shown to increase LDL-C and reduce HDL-C, increasing CVD risk (181,182).

The salt reduction intervention was estimated to produce approximately 9,600 discounted life years and 131,000 discounted QALYs, leading to a discounted cost saving of £347 million over 10 years. The cholesterol reduction intervention was estimated to produce

approximately 571,000 discounted life years and 754,000 discounted QALYs, leading to discounted cost savings of £235 million over 10 years.

There are limitations with Barton et al.'s study: no intervention-related costs were applied and a short time horizon of ten years was adopted. The authors acknowledge these limitations. They note that the cost-savings imply that large amounts of money could be spent cost-effectively instituting the policies discussed. Moreover, they state that conservative modelling assumptions regarding prevention of recurrent events make their analysis "somewhat conservative" (180). It is also unclear how non-CVD costs were accounted for in the analysis. Any intervention that extends population life expectancy will certainly incur such costs which could be spent elsewhere by the health service. Nonetheless, this study shows that population interventions are likely to produce large health gains in a population through small average changes in risk factor levels and that these interventions may also be cost-effective.

Zulman et al. considered the relative benefits of the population and high-risk approaches using sex-specific Weibull regression models (183). They simulated a population of 10 million CVD-free Americans, applying four different treatment strategies: a population-based low-intensity intervention, a population-based medium-intensity intervention, a medium-intensity intervention for individuals in the top 25% of the population's LDL-C distribution, and medium-intensity treatment for individuals in the top 25% of the population's CVD risk distribution. The low-intensity population intervention was found to be comparable with the LDL-C-targeted intervention, leading to around 0.77 million events prevented over five years. The moderate-intensity population intervention was found to be comparable to risk-targeted intervention, leading to around 1.72 million events prevented. However, in both cases number needed to treat was much greater for population-based approaches. When a small risk of treatment-related adverse events was modelled, it was much more desirable to implement the targeted strategies.

The effect of population and high-risk strategies of prevention on health inequalities have long been discussed. Frohlich and Potvin (184) argue that effective population interventions can exacerbate health inequalities. They note that when a health care intervention is not specifically targeted at vulnerable populations, uptake and adherence of the intervention is usually greatest in higher socioeconomic status patients. Specific examples of this phenomenon are presented which relate to disparity in publicly provided cervical cancer

screening in Ontario, Canada and the U.S. (185), the inability of neonatal care programmes in Brazil to reach low-income mothers (186), and greater comprehension and uptake of health information campaigns regarding smoking by better educated individuals in Italy (187). Each of these examples highlights a specific mechanism through which population interventions may exacerbate health inequalities in a population.

Less socially deprived individuals are often better equipped to benefit from population health interventions. This may be due to better education as well as the apparent paradox that healthier patients often have better access to health services. The latter of these explanations has been described as the 'inverse care law'. The inverse care law was first theorised in a 1971 article by Julian Tudor Hart and states that availability of health care services tends to vary inversely with the need of the population receiving care (188). Richer, healthier populations have easy access to care while poorer, less healthy populations have limited access. Hart famously declared that the inverse care law "operates more completely where medical care is most exposed to market forces, and less so where such exposure is reduced" (188). This quotation highlights an important nuance to discussion regarding the population versus high-risk question. The capacity for a preventive strategy to reduce health inequalities is intrinsically linked to the health system and economic system in which it is implemented.

The tendency for population interventions to exacerbate health inequalities led Frohlich and Potvin to argue for a multidisciplinary 'vulnerable population' approach to prevention (184). They describe a vulnerable population as a group in society which is at a higher "risk of risks" due to shared social characteristics. Some examples of vulnerable populations in Canada are provided in the paper. These include First Nations peoples, people with low socioeconomic positions, and people with low levels of education. The key aims of the vulnerable population approach are to systematically lower mean risk factor values within vulnerable populations and to reduce intergenerational transmission of risk.

Studies have looked to compare the effect of population and high-risk strategies of care on health inequalities. Platt et al. (189) simulated primary prevention smoking cessation strategies using U.S. survey data. The high-risk population was defined as all smokers. The key outcomes recorded were: mean SBP in the population, standard deviation of SBP in the population, and the proportion of the population with hypertension. The high-risk primary prevention strategy assumed all smokers with SBP ≥130 mmHg would experience a blood pressure reduction equal to the mean difference between those who smoke and those who do

not in the dataset. The population strategy assumed 33% and 50% of smokers would stop smoking, causing a reduction in SBP. The high-risk strategy led to a greater reduction in population-level SBP than the population strategy, a greater reduction in population-level SBP variability, and fewer individuals suffering from hypertension. The authors note that the high-risk strategy led to a greater proportion of low-income individuals avoiding hypertension.

Kypridemos et al. (190) performed a simulation analysis of high-risk and population approaches to CVD prevention in England and Wales. They employed a microsimulation model of CVD to predict cardiovascular events and fatalities for five treatment scenarios. These were: baseline, universal screening and treatment of high-risk patients (patients with 10-year risk ≥10%, elevated cholesterol, or elevated SBP), targeted screening of only the two most deprived quintiles of the population and treatment of high-risk patients, population-wide interventions (a tax on high sugar beverages, mandatory food reformulation, increased fruit and vegetable consumption, and a public smoking cessation campaign), and a combination of universal screening and population-wide interventions. This analysis found that population interventions had a greater effect on CVD event reduction than the high-risk approach to prevention. In addition, it found that the combined population and high-risk strategy was the most successful at reducing health inequalities. A retrospective analysis of public health interventions introduced in the Netherlands between 1970-2010 produced similar findings (191). Both of these studies support the idea that high-risk strategies play an important role in prevention alongside population interventions.

3.6 Statins and Other Cholesterol-Reducing Medication

This thesis will focus on the cost-effectiveness of pharmacologic interventions which reduce cholesterol levels. These interventions were chosen as a case study to exhibit heterogeneity in cost-effectiveness because there is considerable equipoise regarding which individuals should receive them. For statins, this is because they recently came off patent. Prices have dropped substantially and more individuals are likely cost-effective to treat (192). Decision-makers must determine which of these individuals they are willing to extend treatment eligibility to. Prioritisation of patients for PCSK9 inhibitors is also an area of contention. This treatment received regulatory approval in recent years and is currently very expensive (193). Therefore, it is important to target treatment at patients with a high capacity-to-benefit.

Statins

Statins are a group of cholesterol-reducing medications. In biomedical literature they are often referred to as HMG-CoA reductase inhibitors. They have been shown to significantly reduce an individual's likelihood of developing CVD, and are recommended for the primary prevention of CVD in high-risk adults.

Links between cholesterol and CVD have long been established. As early as 1961, researchers working with data from the Framingham Heart Study established that, alongside high blood pressure, irregular heartbeat, and smoking, elevated cholesterol was a key risk factor for CVD (194).

Despite the established relationship between cholesterol and CVD, there was no treatment for cholesterol reduction with well-documented efficacy and tolerability before 1987 (195). At this time, cholesterol treatment was limited to dietary recommendations (reduced dietary saturated fat and cholesterol) which had high tolerability but low efficacy (196), bile-acid sequestrants which had moderate efficacy but low tolerability (197), fibrates which had moderate efficacy (198), and probucol, which was not routinely administered because it decreases HDL-C (or "good cholesterol") (199).

By the early 1970s, research had established that cholesterol was largely synthesised in human bodies by the liver with the aid of the enzyme HMG-CoA reductase (200). Around this time, biochemist Akira Endo began researching cholesterol-reducing drugs. His work led directly to the isolation of a fungi-derived compound which inhibited HMG-CoA reductase, ultimately resulting in the development of the class of drugs known as statins.

The first statin formulation to be approved for use by a regulatory authority was Merck & Co.'s lovastatin, marketed as Mevacor. Lovastatin received U.S. Food and Drug Administration (FDA) approval in 1987. A range of other similar formulations followed lovastatin to market in the following years, including simvastatin (1988), pravastatin (1991), fluvastatin (1994), atorvastatin (1997), cerivastatin (1998) and rosuvastatin (2003) (195,201,202).

Cholesterol control is now an integral part of many CVD prevention campaigns. Indeed, statins are one of the most commonly dispensed classes of drugs in most high-income

countries. In Scotland, England, and the U.S., atorvastatin and simvastatin frequently appear on lists of the ten most prescribed drugs (203–205).

Statin Patent Expiration

Merck & Co.'s patent for lovastatin expired in 2001. For around five years, lovastatin was subject to generic competition while other branded statins were not. This had little effect on sales of other branded statins, however, as lovastatin was clinically perceived as less effective than the later-released formulations (192).

Patent protection for most other statin formulations began to expire in the mid-2000s. Merck & Co.'s simvastatin, marketed as Zocor, was an early statin formulation which received approval for clinical use in the U.K. and U.S. Patent protection for Zocor expired in the U.K. and U.S in 2003 and 2006, respectively (206,207). Upon patent expiration, numerous companies began producing generic simvastatin. By 2005, these pills were less than 10% of the price of branded rivals. The annual cost per patient of simvastatin fell from more than £400 to £40 between 2003 and 2005 (206). A proportional reduction in the price of simvastatin occurred in the U.S. following Merck and Co.'s patent expiry in 2006 (208).

In recent years, patent protection for several other statins has expired. In 2011, Pfizer's patent protection for atorvastatin, marketed as Lipitor, expired in the U.S. (208). Lipitor's patent protection expired in the U.K. in 2012 (209). In 2016, the FDA approved the first generic version of rosuvastatin, which had previously been co-marketed by Shionogi & Co. and AstraZeneca under the brand name Crestor (210). Patent protection for rosuvastatin expired in the U.K. in December 2017 (211).

Simvastatin and atorvastatin are the two most prescribed statins in the U.S. and U.K. (208,212). In the U.K., moderate intensity formulations of these drugs can be purchased for £11 and £14 per patient per annum respectively (213). The average manufacturer prices of these drugs in the U.S. (as estimated for use in Medicaid reimbursement schedules) are $16 and $31 per patient per annum, respectively (214).

Given the recent expiration of rosuvastatin's U.K. patent protection and the tendency for drug costs to fall substantially in the years proceeding patent expiration, decision-makers on both

sides of the Atlantic might expect a further reduction in the weighted average price commonly paid for statins in their respective health systems.

Ezetimibe

While statins remain the most commonly prescribed pharmacologic treatment for cholesterol reduction, since 2000 two major pharmacologic alternatives to statin therapy have been developed: ezetimibe and PCSK9 inhibitors.

In the early 2000s, a cholesterol-reducing agent named ezetimibe was approved for use in the U.S. by the FDA (215) and in Europe through the mutual recognition procedure of the European Union following German authorisation (216).

Systematic reviews of ezetimibe studies have established that ezetimibe-statin combination therapy offers greater LDL-C reduction than statin monotherapy (217–220). Additionally, evidence shows that ezetimibe monotherapy significantly reduces LDL-C levels (220). However, this reduction is smaller than the effect that can be achieved by statin monotherapy in statin tolerant patients.

More recent analysis has shown that, alongside reducing LDL-C, ezetimibe (monotherapy versus placebo or ezetimibe plus some other lipid-lowering agent versus that agent alone) significantly reduces risk of myocardial infarction and stroke, without affecting risk of all-cause mortality, cardiovascular mortality, or cancer (221). A review of cost-effectiveness studies suggests that combination ezetimibe-statin treatment is cost-effective in select groups of high-risk patients (220).

PCSK9 Inhibitors

The second major class of new cholesterol-reducing agents are PCSK9 inhibitors. These are ‘fully human monoclonal antibodies’ which target the enzyme proprotein convertase subtilisin/kexin type 9 (PCSK9). This protein is produced in the liver and limits the ability of the body to remove serum LDL-C from circulation (222).

Alirocumab and evolocumab are two drugs which have been developed to inhibit the production of PCSK9 in the liver. They both received approval from the FDA and European

Medicines Agency (EMA) in 2015 (223–226). A review by the Institute for Clinical and Economic Review (IfCER) estimated that PCSK9 inhibitors have a much greater LDL-C-reducing effect than statins or ezetimibe (227), and results from the FOURIER trial show that they can reduce risk of CVD event substantially in an asymptomatic population (228). However, the IfCER report also stated that a large reduction in price will be necessary for PCSK9 inhibitors to be cost-effective for CVD prevention, even in high-risk statin intolerant individuals.

3.7 Risk Scoring

Asymptomatic patients are often prioritised for statin therapy and other preventive treatments for CVD based on their 10-year risk of experiencing a primary CVD event. Many risk scores have been developed to estimate an individual's 10-year risk of experiencing a primary CVD event.

Risk scores are developed using a branch of statistics called survival analysis (229). Survival analysis involves analysing data where the outcome of interest is time to some key event, often death or disease progression.

In CVD risk scores, the event of interest is a disease-free individual's primary CVD event. The definition of such events differs between risk scores, but are broadly similar, accounting for the most common CVD events one is likely to experience. Typically, these include: fatal and non-fatal myocardial infarctions, fatal and non-fatal strokes, and angina. Likelihood of experiencing one of these events is estimated based on a range of variables, known as 'risk factors'.

Framingham was the first risk score to be used in routine clinical practice. The equations that underpin this score were developed by Anderson et al. (230). The score was most recently updated for use in the U.S. population in 2008 (231). It includes age, sex, smoking status, systolic blood pressure (SBP), total cholesterol (TC), HDL-C, and diabetes as risk factors.

Another risk score commonly employed in clinical practice in the U.S. is the ACC/AHA Pooled Cohorts risk equation (232). This risk score is currently recommended for use by the ACC/AHA cholesterol treatment guidelines, which aim to reduce risk of CVD in asymptomatic adults (27,174). The events which comprise this score are 'hard'

atherosclerotic CVD events: myocardial infarction, fatal CHD, and non-fatal and fatal stroke. Other scores often employ broader definitions of CVD which include softer events including TIAs. Hence, an individual's risk will be lower when estimated with the ACC/AHA Pooled Cohorts equation compared to most other CVD risk scores.

While the Framingham equations have been validated extensively, they were developed using data from the U.S. For clinical practice in the U.K., there was considerable demand for a risk score derived from U.K. data. In recent years the QRISK, QRISK2, and QRISK3 scores have been developed in the U.K. (233–235). These scores were developed with Cox proportional hazard models, and were each developed with data from a group of more than one million patients across the U.K. QRISK accounts for several CVD risk factors including: age, sex, SBP, ratio of TC to HDL-C, family history of CVD, socioeconomic deprivation as measured by the Townsend deprivation score (236), smoking status, BMI, and use of hypertension treatment. QRISK2 contains the same variables as QRISK but also includes ethnicity, diagnosed type-2 diabetes, rheumatoid arthritis, renal disease, atrial fibrillation, and some interaction between traditional risk factors as covariates. QRISK3 again added new covariates to the risk score. These were: chronic kidney disease, SBP variability, migraine, corticosteroid use, systemic lupus erythematosus, atypical antipsychotic use, severe mental illness, and HIV/AIDS. Guidelines from NICE in 2014 recommend that QRISK2 alone is used to estimate risk of CVD in England and Wales (25).

The ASSIGN score was developed in Scotland by Woodward et al. (152). The ASSIGN risk factors were age, socioeconomic deprivation as measured by Scottish Index of Multiple Deprivation (237), SBP, TC, HDL-C, cigarettes per day (CPD), diabetes, and family history of CVD. Both ASSIGN and QRISK2 includes separate equations for men and women, allowing the magnitude of the association between risk factors and outcomes to differ between sexes.

ASSIGN was developed with data from the Scottish Heart Health Extended Cohort (SHHEC). SHHEC recruited approximately 16,000 men and women with no established CVD above the age of 35 from across Scotland in 1984-1987. Baseline risk factor information was recorded for a set of CVD risk factors. Subsequently, the dataset was linked to Scottish Morbidity Records (238) and death records (239). This allowed the clinical outcomes of survey participants to be recorded. SIGN recommends that the ASSIGN score be used to estimate CVD risk in Scotland as it was developed with a Scottish population and is the score

which most adequately describes the socioeconomic deprivation gradient in CVD incidence in Scotland (240).

While the risk scores employed vary, most high-income countries prioritise patients for preventive therapy like statins using 10-year risk scores. There are drawbacks to prioritisation based on 10-year risk alone. Ten years is a relatively short period of time over which to consider risk. This is especially true because CVD is a disease which develops over an extended period and often begins in childhood. It has therefore been argued by some researchers that 30-year or lifetime risk scores should be employed so that early causes of CVD risk can be addressed (241–243). Arguing that such scores would better reflect the benefit of preventive intervention in younger individuals, Ridker and Cook state, "by emphasizing so strongly the impact of aging in coronary risk prediction models, we inadvertently underemphasize those risk factors that are modifiable early in life and that can greatly alter long-term outcomes" (244).

The clinical utility of long-term scores has been largely disregarded (245). This is because most individuals are at high lifetime risk of experiencing a CVD event based on extensive nature of the disease. This makes inference from longer-term risk scores difficult (246). Later sections of this thesis will discuss the epidemiological basis for employing 10-year risk as a means of stratifying patient populations for preventive treatment in CVD, and alternative approaches to prioritisation.

3.8 Statin Guidelines

<u>England and Wales</u>

Several healthcare bodies have issued guidelines regarding the primary prevention of CVD. A key aspect of these guidelines is determining the subset of a CVD-free population that should be eligible to receive statin therapy.

NICE is responsible for publishing clinical practice guidelines, health technology assessment reports, guidance for social workers, and guidance for health promotion in the NHS in England and Wales.

NICE guidelines for statins for the primary prevention of CVD were published in 2008. NICE Clinical Guideline (CG) 67 defined individuals with no established CVD as being high-risk if they had a 10-year CVD risk score of 20% or greater (247). CG67 recommended that those patients classified as high-risk should receive intermediate-intensity statin therapy. No starting statin or preferred risk estimation tool was explicitly recommended by the guideline.

In 2014, NICE published a new guideline pertaining to the primary prevention of CVD (25). NICE Clinical Guideline 181 defines high-risk patients as individuals aged 40 and above with no established CVD and a 10-year risk score of 10% or greater, estimated using the QRISK2 risk estimation tool. The guideline additionally states that an individual should be considered high-risk if they have hypercholesterolaemia (defined as total cholesterol ≥7.5 mmol/L). CG181 states that high-risk patients are eligible to receive intermediate-intensity statin therapy (atorvastatin 20mg/day). It additionally states that prior to statin initiation, the benefits of lifestyle modification should be discussed, and statin initiation may be delayed until the patient has attempted to reduce their risk through lifestyle modification.

Reducing the threshold to 10% resulted in several million more people being eligible for statin therapy. Extensive analysis was completed in the development of this guideline using a Markov model which drew on work by Ward et al. (248). This analysis showed that transitioning to the 10% risk threshold was highly cost-effective.

NICE's decision to lower the risk threshold in England and Wales has been criticised. Opponents have warned against the dangers of mass-medication, and have pointed out that statins are known to have some adverse effects (249). Abramson et al. (250) argue that statins have little effect on populations with a 10-year risk lower than 10%. However, a meta-analysis of individual data from 27 randomised trials suggests this assertion is incorrect (251).

<u>Scotland</u>

SIGN is responsible for producing and disseminating guidelines for clinical practice in the Scottish NHS. It published Clinical Guideline 97, *Risk Estimation and the Prevention of Cardiovascular Disease*, in 2007 (240). CG97 recommended that individuals aged 40 and above with no established CVD and an ASSIGN risk score of 20% or greater should be considered 'high-risk'. Also considered in this category of risk are individuals with very

elevated levels of TC, individuals over the age of 40 with diabetes, and individuals with advanced levels of chronic kidney disease.

CG97 recommended several strategies for risk reduction in those who are judged to be at high-risk of developing CVD. The guideline states that overweight and obese individuals should be targeted with dietary interventions with the aim of reducing weight by at least 3kg. Furthermore, it recommends that high-risk individuals should be offered a regimen of intermediate-intensity statins (atorvastatin 20 mg/day) after a discussion with their clinician regarding the benefits and risks of the treatment. The guideline further states that the patient should be encouraged to reduce their cholesterol levels through lifestyle measures.

An update to CG67 was published in 2017 (26). No change was made to the way in which individuals are prioritised for preventive statin therapy. However, it was acknowledged that alternative approaches to 10-year risk scoring for statin prioritisation may lead to a more effective and cost-effective distribution of healthcare resources. The guideline specifically notes that age-stratified risk thresholds or reformulation of risk calculators could be implemented in the future in Scotland. It concludes that further economic analysis must be completed before SIGN can implement a novel approach to statin prioritisation. A key aim of this thesis is to produce such analysis. Indeed, work included in this thesis was referenced in the new guideline, and my thesis supervisors and I were acknowledged for contributing to ongoing work in risk estimation (26).

U.S. and Rest of the World

The ACC and AHA have issued joint guidelines for the management of cholesterol with statins in CVD-free individuals. Unlike NICE and SIGN, these are not public bodies but rather non-governmental, non-profit organisations. They state that initiation of statin therapy should be recommended for primary prevention patients with a 10-year ASCVD risk score greater than or equal to 7.5%, and should be considered for those with ‘borderline’ scores between 5.0-7.5% (27,174). These guidelines also stated that physicians should promote lifestyle measures to reduce cholesterol levels, regardless of the recommendation of pharmacological interventions. An update to ACC/AHA guidelines in 2018 recommended statins to borderline-risk patients with a variety of ‘risk-enhancing factors’ (174). These factors include family history of CVD, LDL-C ≥160 mg/dL, metabolic syndrome, chronic kidney disease, and other comorbidities. Finally, it is recommended that physicians promote

lifestyle measures to reduce LDL-C, regardless of the recommendation of pharmacological interventions.

Several healthcare bodies around the world have published similar guidance on statin eligibility. The 2016 European Guidelines on Cardiovascular Disease Prevention offers guidance based on 10-year risk of fatal CVD event. It states that high-risk individuals (5.0-10% risk, estimated using the SCORE European cardiovascular risk assessment model) should receive lifestyle advice and be considered for statin therapy. The guideline continues that for 'very high-risk' individuals (≥10% risk) statin therapy is more frequently required. It also notes, however, that individual circumstance should be considered in older patients, who often have a healthy profile of risk factors without statins, regardless of 10-year risk (173).

The 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidaemia for the Prevention of Cardiovascular Disease in the Adult recommends that individuals at 'intermediate risk' of CVD event (10-19% Framingham risk score) should be offered statins if they have any other individually elevated CVD risk factor, and all high-risk individuals (≥20% Framingham risk score) should be offered the treatment (28).

Guidelines issued by non-profit and governmental institutions in Australia, Singapore, New Zealand, Hong Kong, Japan, and many other high-income countries also recommend risk-based statin prioritisation (252–256).

Guideline Implementation and Regional Variation

National clinical guidelines are only useful insofar as they are able to influence clinical decision-making. Consistent decision-making across a health system is fundamental in maintaining equitable access to health care, a founding principle of the NHS.

The Scottish NHS is split into 14 geographically-based health boards. Health boards are prospectively funded through a resource allocation formula, accounting for demographic, geographic, and disease-related factors (257). This funding mechanism assigns health boards considerable scope to determine how resources are allocated in their locality. Such an arrangement allows health boards to address local health problems effectively but may undermine the influence of national clinical guidelines.

Many Scottish health boards have published guidelines related to preventive statin therapy in recent years (258–263). These guidelines tend to adhere to SIGN's recommendations regarding treatment for individuals with ASSIGN score ≥20%. Some notable exceptions exist. Clinicians adhering to NHS Lothian guidelines, for example, may consider statin treatment in individuals with ASSIGN score 10-20% (259). Audit Scotland has also shown that the type of statin prescribed to patients varies significantly across health boards (264). Such variation in practice may create a 'postcode lottery' whereby access to preventive therapy is not determined by need or capacity-to-benefit, but rather by geographic location.

Variation in the statin prescribing across the U.K. has been reported. Age-, sex-, and social deprivation-adjusted rates of statin initiation were greater in England and Wales than in Scotland during the period 2004-2012 (265). At this time, guidelines were relatively consistent between the countries of the U.K. Variations in practice have also been reported across English primary care practices (266,267), and practice-level variation in statin prescription has been observed in the U.S. (268).

Many approaches can be adopted to influence clinician behaviour and support wider implementation of clinical guidelines. Wettermark et al. (269) divide these strategies into four categories: education, engineering, economics, and enforcement. Education involves informing healthcare workers about best practice guidelines. Engineering involves organisational or managerial intervention, including institution of prescribing targets and micromanaged task delegation. Economic interventions include pay-for-performance schemes as well as co-payment mechanisms to align patient preference for treatments with clinical guidelines. Enforcement refers to imposition of legal regulations.

The impact of different approaches to guideline implementation have not been extensively studied (269,270). However, research from the U.K. suggests that concomitant prescription targets and pay-for-performance schemes have improved uptake of guidelines related to statin prescription (271–273). Retrospective analysis has shown that the benefits achieved from such schemes were maintained after their expiration (274). Time-limited campaigns to improve uptake of national clinical guidelines may affect long-term change on clinical practice and help ensure that guidelines are implemented effectively. This may help to reduce regional variation in clinical practice.

3.9 Statin Therapy: Cost-Effectiveness and Heterogeneity

This thesis will consider the cost-effectiveness of different approaches to the prioritisation of individuals for preventive statin therapy. As discussed in Chapter 2, representing heterogeneity in cost-effectiveness can result in welfare gains for decision-makers. What follows is a review of studies which synthesise results from cost-effectiveness analyses of statins. Patient-level drivers of cost-effectiveness are highlighted as these may be used to establish subgroups in which the treatment is likely most cost-effective.

Several reviews of the cost-effectiveness of statin therapy in primary prevention have been conducted. These have been primarily published as academic articles or as evidence alongside statin guidelines.

Morrison and Glassberg, 2003

In 2003, Morrison and Glassberg (275) examined the factors which determine cost-effectiveness of different statins. Four studies were identified which consider the cost-effectiveness of statins in the primary prevention of CVD, quantified by cost-per-life years saved (LYS). No studies of primary prevention considered cost-per-QALY. Data extraction methodology is not discussed.

There was considerable variability in the cost-effectiveness of statins in the studies reviewed. The incremental cost-per-LYS varied from $4,300 to $1,500,000. Groups of patients with multiple risk factors were typically more cost-effective to treat, as evidenced in Table 3-2, which presents data from Goldman et al. (276). It is also noted that statins are very cost-effective in “specific risk groups” including patients with heterozygous familial hypercholesterolaemia and type-2 diabetes.

This study has various limitations. The parameters of the individual studies considered are not discussed in much depth. While variability of cost-effectiveness within studies is explained, variability between studies is not. It is likely that study parameters (including time horizon, statin price, statin efficacy, and comparator) drives between-study heterogeneity in cost-effectiveness.

LDL-C (mmol/L)	Sex	HTN	Obese	Smoker	Cost-Per-LYS
≥7.8	F	-	-	-	130,000
6.5-7.7	M	-	-	-	93,000
≥7.8	M	-	-	-	58,000
≥7.8	M	+	-	-	28,000
≥7.8	M	+	+	-	17,000
≥7.8	M	+	+	+	15,000

HTN – hypertension

Table 3-2: Cost-per-LYS of preventive statin therapy for patient subgroups, from Goldman et al. (text)

Franco et al., 2005

In a 2005 review, Franco et al. synthesised literature on the cost-effectiveness of statins (277). This review sought to compare the cost-effectiveness of statin therapy versus no pharmacological treatment, quantified by incremental cost-per-LYS. The review identified 24 studies for review, which contained 216 ICERs. For each study, the following data were extracted: publication date, setting, annual drug costs, type of model, category of prevention, mean age at start of treatment, annual level of absolute CHD risk at start of treatment, time horizon, method of effect calculation, economics perspective, funding source, and cost-effectiveness ratio.

The authors first analysed the cost-effectiveness of statin therapy versus absolute CHD risk. This analysis found a high degree of variance between studies but a consensus that statins are cost-effective for individuals with absolute annual CHD risk greater than 4% and cost-ineffective below an annual risk of 1%. Multilevel linear regression analysis was then performed to estimate the effect of these variables on cost-effectiveness. In univariate analysis it was found that statins were significantly more cost-effective in secondary compared with primary prevention and at higher levels of risk when applying a two-sided p-value <0.005.

Secondary analysis considered interaction effects with absolute risk of CHD and other predictors. There was no significant difference between cost-effectiveness and source of funding in the univariate analysis. However, the secondary analysis showed that pharmaceutical industry-funded research was more likely to find that statins were cost-effective at low levels of risk. This could be explained by the fact that the patent for many different statins were soon due to expire in 2005. Anticipating loss of revenue attributable to

loss of market exclusivity, pharmaceutical companies likely desired to broaden the base of patients eligible to receive statin therapy.

One key limitation of this study was that it only included results for male populations. It was, therefore, unable to identify systematic differences in cost-effectiveness between men and women. Moreover, women tend to have lower absolute risk of CVD event than men. Omitting results of studies pertaining to women has the added effect of reducing the amount of data on low-risk populations. Three studies were also excluded from the review because they were cost-utility analyses and the study's main outcome was cost-per-LYS. Disregarding cost-utility ignores the fact that many CVD events are non-fatal, and the distribution of fatal and non-fatal events may differ between subgroups in a population.

Ward et al., 2007

Alongside NICE's 2007 guideline for the prevention of CVD, Ward et al. (248) conducted a review of statin cost-effectiveness studies. They specifically focused on the methodology of analyses set in the U.K. Several databases were searched for studies of statin cost-effectiveness, and titles and abstracts of identified studies were assessed by a review team. Initially 206 studies were identified by searches and 173 of these studies did not match inclusion criteria. Seven studies of primary prevention in the U.K. were identified. Studies included in the review were narratively reviewed, with particular emphasis placed on reporting the model structure and cost-effectiveness results.

Three of these studies estimated cost-effectiveness in male populations alone, one study employed a Markov model, one employed a decision tree, and three studies employed a 'life table approach'. The CVD risk of the population considered, time horizon of the study, mean age of participants in the study, CVD history of participants, and specific statin modelled varied extensively between studies. Central estimates of cost-effectiveness were presented in terms of cost-per-life year gained (LYG) in all studies. Lifetime cost-per-LYG ranged from £5,000-£13,000/LYG in high-risk and secondary prevention populations to £14,000-£30,000/LYG in low-risk populations.

Two non-U.K. studies regarding the cost-effectiveness of preventive statin therapy were identified. Johannesson and colleagues (278) estimated the optimal risk score cut-offs for treatment initiation in Swedish men and women, aged 35 and 70, at a range of cost-

effectiveness thresholds. It was found that lower treatment initiation thresholds were justified in younger men and women. This suggests that risk score alone is not an adequate determinant of statin cost-effectiveness. Van Hout and Simoons (279) analysed preventive statin therapy in a Dutch population. They similarly found that lower risk threshold should be employed for treatment initiation in younger individuals. Sensitivity analysis found that key drivers of statin cost-effectiveness are the price of treatment and relative risk reduction achieved by the therapy.

This study was limited by its scope. The authors focused on the modelling approaches taken in the studies they analysed. Heterogeneity in cost-effectiveness results is rarely discussed. The small number of studies identified for review is another limitation. Relaxing inclusion criteria would have allowed the authors to review a larger body of evidence.

Mitchell and Simpson, 2012

Mitchell and Simpson published a review of statin cost-effectiveness in the prevention of CVD in 2012 (280). This study specifically reviewed cost-effectiveness analyses of statins versus non-statin comparator for primary prevention published since 2000 and set in the U.S After the initial search, 365 studies were identified for further review. 100 studies were excluded from the analysis as they were published more than 10 years before the review was conducted, 154 were excluded from the analysis after title review, 42 were excluded due to a non-U.S. setting, and a further 27 were removed due to study design that did not meet inclusion criteria. Eventually, four studies were included in the review. Data on time horizon, CVD risk, ICER, LYG, and statin cost were collected from each of these studies.

Model parameters varied greatly between the reviewed studies. The time horizon employed ranged from five years to lifetime, the outcome measure employed varied between cost-per-QALY and cost-per-LYG, the annual cost of statin therapy ranged from $770 to $1,500, the age and risk factor profile of patient populations differed greatly, and the choice of non-statin treatment comparator varied between studies.

Running linear regression on the extracted data, ICERs were estimated at a range of drug prices for patients with Framingham risks scores of 5%, 10%, and 25%, respectively. As presented in Figure 3-6, the authors estimated that patients with a Framingham risk score of 10% and 5% would be cost-effective to treat at monthly statin prices of around $70/month

and $50/month, respectively, when employing a cost-effectiveness threshold of $50,000/QALY.

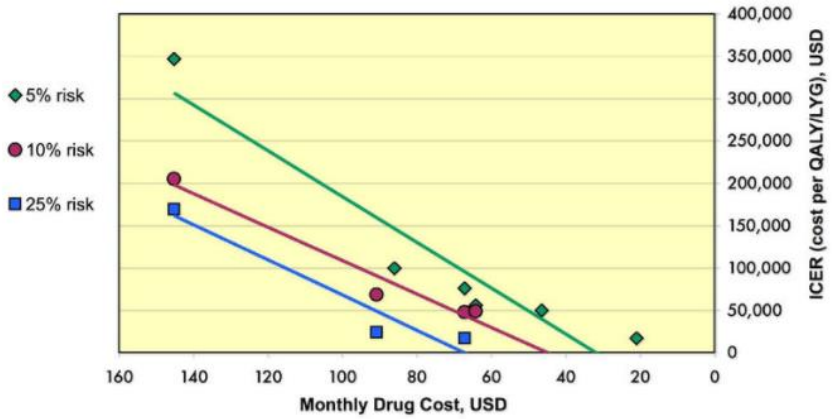


Figure 3-6: Monthly drug cost versus ICER for preventive statin therapy, stratified by 10-year CVD risk, Mitchell and Simpson (text)

Catalá-López et al., 2013

Catalá-López et al. (281) examined the potential for bias in cost-effectiveness analyses of statins for the primary prevention of CVD. They extracted data regarding quantitative cost-effectiveness outcomes (ICERs inflated to $US 2011), qualitative cost-effectiveness conclusions (favourable, unfavourable, neutral), source of funding (industry, non-profit, no funding/none disclosed), journal impact factor, and other study-level covariates for 43 identified cost-effectiveness analyses.

Fisher's exact tests were performed on 2x2 contingency tables to establish the relationship between qualitative conclusions and type of sponsorship and journal impact factor. They found that industry-sponsored studies were significantly more likely to report favourable results than others ($p < 0.001$), but no evidence of publication-based bias. Industry-sponsored studies found that the statin-based intervention of interest was cost-saving or had an ICER below $50,000/QALY more regularly than other studies (62% versus 22%, respectively; $p < 0.001$).

The methodology employed in this analysis did not allow for covariate adjustment. In addition, no further analysis considered drivers of cost-effectiveness in the included studies. Therefore, little information was provided regarding the cause of within- or between-study heterogeneity in cost-effectiveness.

Two limitations should be noted with regards to this study. Information on study funding was derived solely from the corresponding research article. It is possible that complete information on funding was not obtained. Furthermore, reviewers subjectively determined if a study's results were favourable, unfavourable, or neutral. The subjective nature of this classification was countered with guidance on the type of language that pertains to each of these categories and consensus was sought when reviewers were not in agreement. Nonetheless, the objectivity of the study's inputs may be questioned.

NICE, 2014

A review of statin cost-effectiveness was published alongside NICE's 2014 update to guidelines for the primary prevention of CVD (25). Four papers, pertaining to three studies comparing statin therapy to placebo in primary prevention were included in this review, with many of the studies discussed in previous reviews omitted because they had "very serious limitations" or because "more recent evidence was identified which was more applicable".

Two studies compared statins to placebo in an intermediate-risk CVD-free population, while the third study estimated the cost-effectiveness of preventive statin therapy versus placebo in patients with low LDL-C and elevated high-sensitivity C-reactive protein (hs-CRP) (248,282,283). All studies found statins were cost-effective, with the ICER ranging from cost-saving to £16,500/QALY.

A limitation regarding this study was the small number of studies included. This made it difficult to determine the drivers of cost-effectiveness between different studies. However, extensive reporting of sensitivity analysis results was included in the review. These results suggest potential drivers of heterogeneity in statin cost-effectiveness. Shorter duration of statin effectiveness, increased cost of statins, increased monitoring costs, reduced statin efficacy, increased treatment-related disutility, and reduced population CVD risk all led to reductions in cost-effectiveness.

Heterogeneity in Statin Cost-Effectiveness

This section summarised previously published systematic reviews which pertain to the cost-effectiveness of preventive statin therapy. These reviews showed considerable heterogeneity in the cost-effectiveness of statin therapy.

A number of potential drivers of cost-effectiveness were highlighted. It was shown across studies that 10-year risk of CVD is a key driver of the cost-effectiveness of preventive statin therapy. Other potential sources of heterogeneity in statin cost-effectiveness presented were: age of treatment initiation, cost of statin therapy, treatment efficacy, duration of treatment effectiveness, and treatment-related disutility.

3.10 Chapter Summary

Cardiovascular disease is a highly prevalent condition that leads to morbidity and mortality in low-, middle-, and high-income countries. It is often caused by atherosclerotic build-up in individuals' arteries, a process which commences at a young age. CVD has a high associated economic burden, and there is often a high socioeconomic gradient in the disease which exacerbates health inequalities within countries. Primary, secondary, and tertiary prevention of CVD can all be employed to halt the development of the disease, arrest its progression in patients with the condition, and improve sufferers' quality of life. Primary prevention often targets modifiable CVD risk factors like smoking, cholesterol, and SBP.

Most high-income countries employ risk-based statin prioritisation, regardless of health system. The degree to which clinical guidelines influence clinical practice may vary across these countries. By defining a group of patients as being 'high-risk', clinicians acknowledge heterogeneity in the CVD-free patient population. Preventive therapy may be more effective and cost-effective for high-risk subpopulations. However, reviews of statin cost-effectiveness suggested that other factors, like age of treatment initiation, may independently affect statin cost-effectiveness, Chapter 4 will discuss the epidemiologic basis for using 10-year risk to prioritise patients for preventive therapy for CVD. Further, it will discuss alternative approaches that clinicians could adopt that may better reflect heterogeneity in outcome from preventive treatment.

Chapter 4
Epidemiology and Prevention of Cardiovascular Disease

4.1 Purpose

The cost-effectiveness of an intervention can vary between patient subgroups for a variety of reasons. The importance of reflecting heterogeneity in cost-effectiveness analysis has been established. Current standard of care in CVD relies predominantly on prioritising individuals for preventive therapy based on 10-year risk scores. A review of cost-effectiveness analyses showed that 10-year risk is indeed one determinant of preventive statin therapy's cost-effectiveness. The purpose of this chapter is to establish the epidemiologic basis for a range of different approaches to CVD prevention.

This chapter will first present an illustrative example to show that individuals with the same 10-year risk score may experience different outcomes from preventive therapy for CVD. It will then proceed to discuss the epidemiological basis for alternative approaches to prevention which may better reflect heterogeneity in outcome. Three approaches which may better reflect heterogeneity in cost-effectiveness than standard of care are identified. These are: (i) continued use of 10-year risk scores, (ii) novel decision mechanisms which incorporate 10-year risk, and (iii) using decision models directly in clinical practice.

4.2 Illustrative Example

The following example aims to highlight issues inherent to 10-year CVD risk scoring. Risk factor profiles are presented for three hypothetical patients, each with a risk score of 10%. It is shown that these patients may experience very different outcomes attributable to preventive therapy.

Consider the three risk factor profiles presented in Table 4-1. Each of these hypothetical patients has a 10-year CVD risk of 10%, estimated with the ASSIGN risk score (152). This table demonstrates the importance of distinguishing between modifiable and non-modifiable risk factors. Modifiable risk factors, like LDL-C, HDL-C, SBP and CPD, can be intervened upon to reduce risk of disease. Non-modifiable risk factors, like age and sex, cannot be intervened upon.

Risk Factor	Patient A	Patient B	Patient C
Sex	Female	Female	Male
Age	50	50	70
SIMD	15.89	15.89	15.89
Family History	No	No	No
Diabetes	No	No	No
CPD	0	35	0
SBP (mmHg)	140	140	110
LDL-C (mmol/L)	8.7	4	4.5
HDL-C (mmol/L)	0.9	1.5	2
hs-CRP (mg/L)*	1	10	1
10-Year Risk**	10	10	10

*Not included in the ASSIGN risk score
**Estimated using the ASSIGN risk score

Table 4-1: Three different patients with ASSIGN score of 10%

Patient A and Patient B are both 50-year-old females with no family history of CVD. Risk of developing CVD increases with age, and is generally higher for men and for individuals with a family history of premature cardiovascular illness. Based solely on these non-modifiable risk factors, Patients A and B should be at a very low risk of developing CVD. However, they are at 10% 10-year risk driven by unhealthy levels of modifiable risk factors. Patient C, on the other hand, has a healthy modifiable risk factor profile but is male and aged 70 years. When risk is determined by a non-modifiable factor like age, capacity-to-benefit from preventive treatment is often diminished.

Even amongst individuals of the same age and CVD risk, the effect of preventive interventions may differ substantially. For example, strong evidence suggests that an individual's risk reduction from statin therapy is directly proportional to their LDL-C (251,284). Hence, Patient A will experience a greater absolute CVD risk reduction from statin therapy than Patient B, even though they have equal baseline risk.

Existing risk scores may also be incomplete. Most commonly-used 10-year risk scores contain a similar set of explanatory variables as those included in the ASSIGN Score. Research suggests that many independent risk factors for CVD are not included in risk scores. One such factor is hs-CRP. This biomarker has been shown to independently predict CVD risk when controlling for traditional risk factors (285,286). Though Patient A and Patient B have the same ASSIGN risk score, the former is likely at greater risk of developing CVD

event due to their increased hs-CRP. By identifying this risk through hs-CRP testing, it may be possible to better prioritise patients for statin therapy.

4.3 Heterogeneity in the Cost-Effectiveness of CVD Prevention

There are many forms of subgroup and heterogeneity relevant to CVD. The example above showed that patients with the same risk score may experience different outcomes attributable to the preventive CVD interventions. Failing to reflect such heterogeneity leads to suboptimal decision-making.

This thesis will consider three approaches to reflect heterogeneity in the cost-effectiveness of preventive interventions for CVD which theoretically improve upon standard of care:

1. Continued, but improved, use of 10-year risk scores.
2. Novel decision mechanisms which incorporate 10-year risk.
3. Using decision models directly in clinical practice.

What follows is a short epidemiological analysis of the basis for each of these approaches. Chapters 7, 8, and 9 will detail cost-effectiveness analyses of specific policies which adopt these approaches to prevention.

4.4 Continued Use of 10-Year Risk Scores

4.4.1 Theory Behind Current Practice

Continued use of 10-year risk scores is one approach to CVD prevention. The 2007 World Health Organisation (WHO) guidelines for assessment and management of cardiovascular risk discuss the basis for the "total risk approach" to prevention of CVD (287). It notes that the main biological process which contributes to CVD is atherosclerosis, and traditional risk factors work concurrently to increase the rate of atherosclerosis progression.

Atherosclerosis develops over a long period of time, and therefore disease state is difficult to define in CVD (166). Indeed, most individuals spend extended periods in a 'preclinical' state with extensive atherosclerotic build-up prior to experiencing a morbid CVD event (288). A multitude of studies have established a range of 'risk factors' which increase atherosclerosis, and these factors can be described as indicators of preclinical CVD (163,289).

The WHO guideline notes that risk factors "commonly coexist and act multiplicatively" (287). An individual with a unitary elevated factor might therefore be at lower total risk of developing CVD than an individual with a combination of moderately elevated factors. By combining the independent effect of many risk factors into a combinatory index, researchers have developed metrics which predict CVD risk better than focusing on individual factors. These indices most frequently take the form of 10-year CVD risk scores.

In addition to providing greater predictive validity than single variables, risk scores have the benefit of representing variables continuously. Many risk factors do not dichotomously affect risk, but rather have a continuous effect. LDL-C, for example, increases CVD risk in a continuous, direct relationship (4,290–292). An intervention commencement rule which aims to treat individuals with high LDL-C must necessarily set a cut-off at which treatment is initiated. For example, the AHA's 2013 definition of hyperlipidaemia is LDL-C ≥160 mg/dL (4.14 mmol/L) (27). A decision rule which only recommended statins for individuals with hyperlipidaemia ignores the potential benefit of the treatment in individuals with borderline hyperlipidaemia. Such a policy creates a false dichotomy which suggests that LDL-C does not affect risk below the threshold and drives risk above it. In contrast, a risk score dynamically reflects the incremental effect of increases in LDL-C on CVD risk.

Another argument commonly posited in support of 10-year risk scores for statin prioritisation relates to relative risk. The WHO and SIGN explicitly employ this argument in respective guideline documents (26,240,287) and both use statin therapy as an example. They argue that patients with elevated 10-year risk gain most from statin therapy. It is assumed that statins reduce relative risk of CVD equally across all patient subgroups. Those with higher absolute risk should therefore gain the greatest absolute risk reduction from treatment

To illustrate the point above, let us assume that the relative risk of CVD for a preventive therapy is 70% compared to no treatment. Additionally, assume that the therapy results in an equal relative risk versus no treatment across a population. Now consider two prospective patients, Patients X and Y, who have CVD risk scores of 50% and 10%, respectively. Absolute risk reduction attributable to this therapy is greater for Patient X, as shown in Table 4-2.

Sections 4.4.2 and 4.4.3 will discuss specific policies which retain 10-year risk scoring as the principal mechanism for statin prioritisation. These approaches attempt to counter issues with heterogeneity in cost-effectiveness of statin initiation based on 10-year risk alone without drastically changing current practice.

Patient	10-Year Risk (10YR)	Absolute Risk Reduction*
X	50%	15%
Y	10%	3%

*Absolute risk reduction = 10YR*0.3

Table 4-2: 10-year risk and absolute risk reduction, assumes equal relative risk of therapy for all patients

4.4.2 Policy: Lowering the Risk Threshold

Many statins have come off patent in recent years, leading to a drastic reduction in price. Therefore, many more individuals are now cost-effective to treat. In response, treatment guidelines have been updated which lower the threshold at which initiation of preventive statin is recommended (25,27).

Lowering the risk threshold will lead to more individuals who proceed to have events (cases) being treated. This occurs at the cost of treating more individuals who do not proceed to have events (non-cases). The statistical concepts of sensitivity and specificity help to illustrate this point.

<u>Sensitivity and Specificity</u>

In statistical terms, reducing the threshold at which a treatment is initiated increases the sensitivity of risk scoring. Sensitivity of a diagnostic tool, also referred to as its true positive rate, describes the ability of the score to correctly identify cases. It is therefore the probability of an individual being identified as high-risk given that they will proceed to have an event.

Mathematically, this can be represented as follows:

$$sensitivity = P('high\ risk'|event).$$

Reducing the CVD risk threshold treats all individuals prioritised for treatment under the previous threshold while expanding the subgroup of individuals who are eligible for treatment. Hence, the sensitivity of the new policy is necessarily equal to or greater than the

previous policy. As alluded to by Geoffrey Rose, many events occur in apparently 'low-risk' populations in a disease as highly prevalent as CVD (175) and we may expect a marked increase in sensitivity of a risk score as the threshold is reduced.

Notably, the conditional probability that defines sensitivity does not account for false negatives. A statistical counterpart to sensitivity is specificity, also referred to as the true negative rate. This term describes the probability of a non-case being identified as low-risk.

Specificity can be formulated mathematically as follows:

$$specificity = P('low\ risk'|no\ event).$$

Reducing the risk threshold leads to a reduction in the number of individuals classified as low-risk. Hence, specificity of the score using the reduced risk threshold is equal to or less than the previous policy.

<u>Policy Assessment</u>

Within the framework of 10-year risk scoring, choosing whether to reduce a risk threshold is a matter of weighing the benefits of increased sensitivity against the costs of reduced specificity. Increased sensitivity implies that more individuals who should be treated will be treated. Reduced specificity, on the other hand, implies that more individuals who should not be treated will be treated and hence will incur unnecessary costs and treatment-related disutility. Chapter 7 employs a decision-analytic model to perform such calculus.

4.4.3 Policy: Improving 10-Year Risk Scores

At the start of this chapter, it was shown that two individuals with the same risk score may be at very different CVD risk attributable to non-traditional risk factors. Patient B was likely at greater 10-year risk of CVD than Patient A as they had elevated hs-CRP. However, hs-CRP is not included in the ASSIGN risk score. Adding this biomarker as a covariate in an updated risk score would better reflect heterogeneity in risk.

Much research in CVD prevention has focused on improving the predictive validity of 10-year risk scores. By including additional covariates in risk scores, two individuals previously identified as identical risk may be reclassified. Improving 10-year risk scores allows decision-

makers to more confidently target treatment at patients who are likely to experience a CVD event within the next 10 years.

What follows is a short description of statistical methods typically employed to assess risk score improvement. The advantages and disadvantages of these methods are described, and the need for decision-analytic modelling is established.

Estimating the Statistical Validity of a Risk Score

Statistical techniques have been developed to assess the improvement that novel risk factors provide to risk prediction algorithms (293,294). The statistical validity of a risk score has traditionally been described in two ways: discrimination and calibration. Discrimination refers to the ability of a risk function to prospectively separate cases and non-cases into two distinct groups. Calibration, on the other hand, refers to how well a risk score predicts average risk in a population and subsets of this population.

Unless a risk score has perfect dichotomising predictive capability (correctly designating individuals as either 0% or 100% risk), perfect discrimination and calibration cannot be achieved simultaneously (295). Consider, for example, a risk score which designates one group of individuals as 5% risk and another as 95% risk. Presume that this risk score has perfect calibration; then 1 in 20 individuals in the lower risk group and 19 in 20 individuals in the higher risk group will experience an event. The fact that there are cases and non-cases in each risk group necessarily means that this score does not have perfect discrimination. On the other hand, presume that the score has perfect discrimination: all individuals in the lower risk group remain event-free while every individual in the higher risk group experiences an event. In this situation, the predicted and observed event rates in the risk groups are not correct, so the score is imperfectly calibrated.

Discrimination is the most important attribute when deciding who to treat with a risk score. When focusing on a 10-year time horizon, a physician wants to dichotomise a population into two groups: those who will have an event and those who will not. As long as a risk threshold can be defined which distinctly identifies these two groups, individuals' specific risk scores do not matter. This thesis aims to develop methodology which allows decision-makers to better specify which individuals should receive preventive interventions for CVD. Poorly calibrated risk scores may remain clinically useful if they highlight a group of individuals

who would benefit from treatment (296). Therefore, the discriminative ability of risk scores is of particular interest.

The importance of calibration should not be disregarded. Accurately predicting disease incidence and prevalence in a population relies on a score's calibration (297). If a health system planner wants to argue that more money should be invested in one disease are over another, they must know the future population-level incidence and prevalence of each disease. This requires good calibration of risk estimates.

Discrimination – Area under the Receiver Operating Curve Analysis

With regards to discrimination, the internal and external validation of risk scores is important. Internal validity refers to a risk score's ability to replicate results observed in the data used in its development. External validity refers to a score's ability to replicate results from datasets not used in its development.

Internal and external validation of risk scores can be described by area under the receiver operating curve (AUROC) analysis. The receiver operating curve (ROC) is a graphical representation of a risk score's sensitivity and specificity. It is constructed by plotting the score's sensitivity against the complement to its specificity (one minus specificity), as shown in Figure 4-1. A risk score which perfectly dichotomises cases and non-cases is referred to as 'perfect'. A perfect risk score is exemplified by the green curve in the figure. The threshold which dichotomises the patient population as such can be plotted on the ROC at point (0, 1).

The blue curve on Figure 4-1 plots a random risk score, also referred to as an 'uninformative' risk score. At all points on this curve sensitivity is equal to one minus specificity. This means that the probability of a case being identified as high-risk is always equal to the probability of a non-case being identified as high-risk. It follows that the ratio of cases estimated as high-risk to non-cases estimated as high-risk will always be equal to the ratio of cases to non-cases in the population. Therefore, the score provides no more information on a patient's risk than a completely random identification mechanism.

In the case of non-perfect informative risk scores, when the threshold is set such that all individuals are classified as high-risk the score has a sensitivity of one. This is because all cases are classified as high-risk. At the same time, the specificity of the score would be zero.

This is because the non-empty subset of non-cases is also classified as high-risk. Similarly, when the specificity is equal to one, the sensitivity is equal to zero. For a non-perfect score, we can plot sensitivity and one minus specificity for a continuous range of risk thresholds, as exemplified by the purple curve in Figure 4-1.

The c-statistic, or the AUROC, is an index employed in the quantitative comparison of ROCs. It is equal to the area between the ROC and the *x*-axis, and can range from 0.5 to 1. A perfect risk score has an AUROC of 1 and a random score has a value of 0.5. Hence, the closer a score is to a value of 1, the better its discrimination. If a score is less than 0.5, this implies systematic misspecification. Note, however, if the score consistently misspecifies individuals, then reclassifying all individuals to the opposite risk category will bring the score above 0.5.

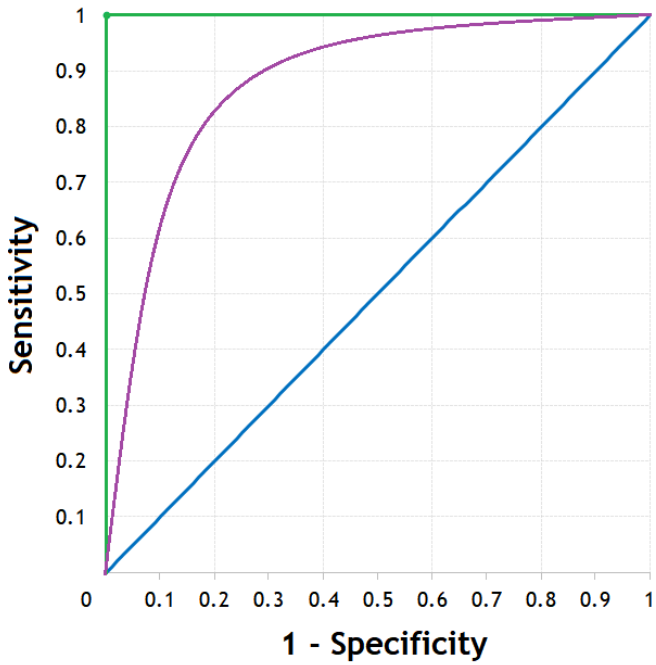


Figure 4-1: Receiver operating curve

A growing body of literature highlights the weakness of traditional measures of discrimination in highlighting the benefit of novel technology in risk assessment. The improvement offered by adding a new covariate to an existing risk score cannot be adequately described by AUROC analysis.

The law of diminishing returns makes it increasingly difficult for each additional risk factor added to a risk score to significantly improve the score's predictive ability. Intuitively, more of the explicable population-level uncertainty in outcome is described by each additional risk

factor. Hence, fewer individuals in a population will experience a notable change in their risk score attributable to each additional covariate included in a score. Most risk scores for CHD, stroke, and CVD have c-statistics of around 0.75-0.80 and a model based on age and sex alone can result in an c-statistic of 0.70 (298). Additionally, Wang et al. (299) have shown that the addition of an established CVD biomarker to traditional covariates in risk prediction models only increases the c-statistic from 0.76 to 0.77.

Reclassification Tables and Net Reclassification Indices

Increase in c-statistic does not fully capture the clinical benefit of adding new covariates to a risk score. A substantial proportion of a population is unlikely to be reclassified as high- or low-risk by including new covariates in a risk score. Nonetheless, the additional risk factor information may prove significant in reclassifying a subset of a total population. Specifically, the new risk factor may lead to considerable reclassification of intermediate-risk individuals (those whose traditional risk score is near the threshold for treatment initiation).

One methodological approach to address the shortcomings of AUROC analysis is the use of reclassification tables (300). Individuals in the population used to construct a risk score are split into separate risk-based categories (e.g. 0-10%, 10-20%, and >20% risk). The benefit of adding a new risk factor is evaluated by cross-tabulating individuals' categorisation for two risk scores: one which does not include the new risk factor and one which does. The researcher next assesses the proportion of the population that is reclassified with the new risk score, calculates the expected event rate in this reclassified population, and compares this to the observed event rate.

Reclassification tables are not particularly useful in evaluating updated risk scores. Simply calculating the proportion of individuals reclassified lacks information on the predictive benefits offered by such reclassification. Moreover, considering event rates in reclassified individuals is unlikely to produce a useful and objective measure of the improvement in the risk score. Such an approach considers all individuals reclassified collectively and therefore neglects the possibility of individual-level heterogeneity in the statistical benefit of the additional risk factor.

Pencina et al. highlight the issues with reclassification tables (293). They consider a hypothetical example where a new covariate is added to a 10-year risk score, and 100

individuals are reclassified ‘upwards’ from a 10-20% risk group to a >20% risk group. It is further considered that the observed event rate is 25% in this risk group. In this situation, despite the fact the reclassification table approach appears to support the use of the new covariate in risk scoring, 75% of the individuals reclassified should have stayed in the lower risk category.

Net reclassification improvement (*NRI*) is an alternative measure of a risk scores’ reclassification value proposed by Pencina et al. (293). Estimation of *NRI* is achieved by splitting reclassified individuals into two groups: those reclassified ‘upwards’ to a higher risk group and those reclassified ‘downwards’ to a lower risk group. As with sensitivity, specificity, and AUROC analysis, this approach requires one distinct ‘cut-off’ at which individuals are considered high-risk. *NRI* reflects the net improvement in classification of individuals who are reclassified upwards and the net improvement in individuals who are classified downwards. For individuals who are both reclassified and were observed to have experienced an event, the posterior probabilities of being reclassified upwards and downwards are computed, respectively. The latter is subsequently subtracted from the former, Equation (4-1). A similar calculation is performed for reclassified individuals who do not experience an event, Equation (4-2). Finally, these two values are subtracted from each other, Equation (4-3). Unlike reclassification tables, this index is able to concurrently consider the effect of updating a risk score in terms of sensitivity and specificity.

$$A = \mathrm{P(up|event)} - \mathrm{P(down|event)} \tag{4-1}$$
$$B = \mathrm{P(up|no\ event)} - \mathrm{P(down|no\ event)} \tag{4-2}$$
$$NRI = A - B \tag{4-3}$$

<u>Beyond NRI</u>

Greenland argues that *NRI* can provide decision-makers with misleading support for the implementation of an updated risk score. He points out that “predictive values, costs, and cut-points must be considered together to make well-informed decisions” (301). Pencina et al. responded by formulating an updated *NRI* index which details the incremental costs attributable to implementing the new risk score (302). The updated index is presented in Equation (4-4) and is referred to as the weighted NRI (*wNRI*).

$$\begin{aligned} wNRI = {} & S_1 * \big(P(event|up) * P(up) - P(event|down) * P(down)\big) \\ & + S_2 * (P(no\ event|down) * P(down) - P(no\ event|up) * P(up)) \end{aligned} \tag{4-4}$$

S_1 represents the savings from correct upwards reclassification and S_2 represents the savings from correct downwards reclassification. These values may be positive or negative. According to Pencina et al. (302), the new risk score should be adopted if the sum of the *wNRI* and population-level testing costs is negative. In other words, cost-savings are obtained attributable to the new testing and treating strategy. If the summed value of the *wNRI* and testing costs is positive, they suggest that the decision-maker must perform further formal cost-effectiveness analysis.

Extending the scope of *wNRI* to account for health outcomes could produce an index which better summarises the consequences of 'correct' and 'incorrect' treatment decisions. An updated weighted NRI score could replace the cost values in the *wNRI* equation (S_1 and S_2) with net monetary benefits attributable to treating or not treating cases and non-cases respectively. Such an index would combine both the incremental costs and incremental QALYs associated with reclassification. This would better quantify the consequences of reclassification. However, it would only highlight the benefit of adding a risk factor in an existing dataset with follow-up information available for all individuals. Such data are rarely available, especially for novel risk factors.

<u>Policy Assessment</u>

The statistical methods described above do not fully assess the cost-effectiveness of adding risk factors to an existing risk score. Decision-analytic modelling allows researchers to bypass restrictive data requirements and enables them to predict outcomes in a wide range of populations. Chapter 7 presents a framework that can be employed to assess the incremental costs and health benefits associated with updating risk scores with novel risk factor information.

4.4.4 Policy Analysis in Chapter 7

Chapter 7 will assess the cost-effectiveness of two policies that retain the central role of 10-year risk scores in statin prioritisation but attempt to improve upon current practice. It will consider the cost-effectiveness of:

- Lowering the risk thresholds for statin initiation in Scotland
- Improving the precision of current risk scores with novel biomarker data.

4.5 Novel Decision Mechanisms Which Incorporate 10-Year Risk

Novel approaches to prevention have been proposed which incorporate 10-year risk scoring. The aim of these approaches is to better reflect heterogeneity in patients with similar risk scores but different projected outcomes. Typically, such approaches involve treating according to 10-year risk while additionally stratifying treatment decisions by some other factor.

Age and LDL-C are two common factors with which 10-year risk-based decision-making may be additionally stratified. This stratification aims to correct for issues with the simple risk-based approach to prevention. These issues include neglecting competing risks, cumulative exposure, and heterogeneity in relative treatment effect.

4.5.1 Policy: Age-Stratified Risk Thresholds

Age-stratified risk thresholds are a decision mechanism which incorporate 10-year risk. This policy for prevention of CVD was introduced in Norway in 2009 (303). It requires setting separate treatment initiation thresholds for different age-groups. Effectiveness of statin prioritisation will likely improve if the threshold were reduced for younger age-groups and increased for the elderly.

Two key epidemiological factors support the implementation of age-stratified risk thresholds: competing risks and cumulative exposure to risk factors. Both of these factors contribute to the fact that treatment outcomes differ greatly between younger and older individuals.

The illustrative example at the start of this chapter showed individuals with drastically different risk profiles can have the same 10-year risk score. Patient C, for example, was a 70-year-old male with a healthy set of modifiable risk factors. Patient A and Patient B, on the other hand, were 50-year-old females with elevated levels of modifiable risk factors like TC and SBP. Patient C likely has less to gain from preventive therapy. This is partly because they are at high-risk of developing many fatal health conditions, regardless of treatment. Additionally, atherosclerosis is a cumulative process. Hence, slowing down its progression is likely to produce the greatest benefit at younger ages.

Competing Risks

The statistical methods used to estimate 10-year CVD risk typically ignore competing risks, limiting their utility. Competing risks are events that can occur prior to an event of interest, biasing statistical models of disease (304).

Estimation of 10-year risk involves applying survival analysis to longitudinal datasets. Survival analysis is a branch of statistics often employed in epidemiology. It involves statistically modelling the time it takes for a specific event of interest to occur and the effect of relevant covariates on time to event. In CVD, the event of interest is typically a primary CVD event. Relevant covariates included in risk scores include age, sex, cholesterol, smoking status, and blood pressure.

Andersen et al. (305) describe two key concepts central to survival analysis: risk and rate. Risk is defined as the proportion of individuals in a population who develop a condition in a specified period, say time zero through *t*. Equation (4-5) defines risk mathematically, with *D* representing the number of individuals with event from zero to *t*, and *N* representing the number of individuals in population of interest. Rate is defined as the number of individuals who develop a disease in a specific period divided by the amount of person-time at risk. Equation (4-6) defines rate mathematically with *Y* representing person-time at risk.

$$risk = \frac{D}{N} \tag{4-5}$$

$$rate = \frac{D}{Y} \tag{4-6}$$

The statistical counterparts of risk and rate are probability and hazard, respectively. Probability of an event occurring can be represented by the cumulative incidence function, *F(t)*. The value of this function is equal to the relative frequency of individuals with time to event less than *t*. The probability density function (PDF), *f(t)*, is central to the estimation of *F(t)*. In survival analysis, the PDF is interpreted as the probability that an event occurs at time *t*. *F(t)* is related to the PDF by the relationship presented in Equation (4-7). In the situation where data are complete, Equation (4-4) provides an unbiased estimate for *F(t)*. A similar measure that can be computed is the survival function, defined as the probability that an individual will survive beyond a given time and presented in Equation (4-8).

$$F(t) = \int_0^t f(t)dt \tag{4-7}$$

$$S(t) = 1 - F(t) \tag{4-8}$$

Hazard is represented by the hazard function, *h(t)*. The value of this function is equal to the instantaneous risk of event for an individual from time *t* to *t+d*, where *d* is a small interval of time. The hazard function represents the instantaneous probability of an event occurring at time *t*, *f(t)*, conditional on the probability that an individual had survived until time *t*, *S(t)*. Equation (4-9) presents the mathematical formulation of *h(t)*. This equation provides a reliable estimate of hazard when data are complete (304). Cumulative hazard, *H(t)*, is equal to the integral of the hazard function from time zero through *t*, Equation (4-10).

$$h(t) = \frac{f(t)}{S(t)} \tag{4-9}$$

$$H(t) = \int_0^t h(t)dt \tag{4-10}$$

When there are no competing risks, there is a one-to-one correspondence between survival and hazard. The proof for this relationship is shown in Figure 4-2. Consequently, models of the hazard function can be employed in simple survival analysis to estimate cumulative incidence of an event. This corollary is not true when competing risks are present.

$$h(t) = \frac{f(t)}{S(t)} = \frac{f(t)}{1 - F(t)} = \frac{F'(t)}{1 - F(t)}$$

$$= -\frac{\partial}{\partial t}\ln\big(1 - F(t)\big) = -\frac{\partial}{\partial t}\ln(S(t))$$

$$\therefore -\frac{\partial}{\partial t}\ln\big(S(t)\big) = h(t)$$

$$\Rightarrow -\ln\big(S(t)\big) = \int_0^t h(t)dt$$

$$\Rightarrow \ln\big(S(t)\big) = -H(t)$$

$$\Rightarrow S(t) = e^{-H(t)}$$

Figure 4-2: Proof of one-to-one relationship between *h(t)* and *S(t)*

Data limitations can affect the reliability of results derived from survival analysis. A dataset containing time to event or survival data for all individuals over a set period is desirable when building survival models. For a variety of reasons, such data may be unavailable. Individuals may become ‘lost to follow-up’. This means that, despite providing longitudinal data at some point, the individual is not followed up until the event of interest or through the end of the study. This may occur when the individual leaves the locality of the study, dies, or chooses to stop providing information to researchers. These individuals are described as ‘censored’.

If censoring is independent – meaning that it occurs completely at random and is not correlated with the dependent variable – a valid method for correction of survival models is to assume that the event rate for censored individuals is equal to that of the uncensored individuals (304). This will hereafter be described as naïve correction for censoring in survival analysis. Competing risk methodology is required to obtain unbiased estimates of hazard and survival when censoring is not independent.

Estimation of hazard and survival is complicated by the existence of competing risks. Competing risks lead individuals in a dataset to experience a censoring event before the event of interest. This censoring cannot always be treated as independent. The underlying mechanism that causes a competing event to occur often relates to the individual's risk of experiencing the event of interest. For example, Keurentjes et al. (306) estimate revision rates for patients receiving hip replacement surgery. They show that all-cause mortality is a competing risk for revision surgery, and patients who are at elevated risk of receiving revision surgery are also at a greater risk of all-cause mortality. Therefore, survival models which apply naïve correction methodology overstate probability of revision surgery.

Dealing with Competing Risks

Andersen et al. discuss the most appropriate methodology for competing risk survival analysis (305). Consider two competing events, A and B. In each interval of time t to $t+d$, individuals have the possibility of remaining event-free, experiencing Event A, or experiencing Event B. The cause-specific hazard of Event A is defined as $h_A(t)$, and is equal to the probability of experiencing Event A between time t and $t+d$. This value is a conditional probability, dependent on survival from both event types through time t. The cause-specific hazard of Event B is defined similarly as $h_B(t)$. Cumulative hazard of Event A, $H_A(t)$, is equal to the integral of $h_A(t)$ from time zero through t.

The survival function is computed differently in naïve and competing risk survival analyses. Survival relates to survival from both events in competing risk analysis. It is therefore calculated as follows:

$$S(t) = e^{-H_A(t)-H_B(t)}.$$

Now consider $F_A(t)$, the probability (cumulative incidence function) of Event A through time t. This is equal to the product of survival and cause-specific hazard, summed over all intervals between zero and t, Equation (4-11).

$$F_A(t) = \int_0^t f_A(t)dt = \int_0^t h_A(t) * S(t)dt = \int_0^t h_A(t) * e^{-H_A(t)-H_B(t)}dt \qquad (4\text{-}11)$$

Observing the functions which constitute Equation (4-11), there is no longer a one-to-one correspondence between cumulative incidence and cause-specific hazard. Incidence of a given event is now influenced by the rate of the competing event. Two major corollaries relate to this finding (305): naïve estimators of cumulative incidence are biased and the way in which a covariate affects cause-specific hazard may differ from the way in which it affects cumulative incidence.

The first corollary can be stated as follows: in the presence of competing risks, a naïve estimator of cumulative incidence (and therefore estimated probability of event) is biased. Volf provides a sports-based example of this situation (307). The time taken to score the first goal in a football match is the event of interest. A team may score the first goal, concede the first goal, or the game may end in a goalless draw. These are three mutually exclusive, competing endpoints. A naïve analysis will censor goalless draws and presume that the rate of games in which a team scores first in all games is the same as the rate at which they score first in games with goals. A football fan (or statistically-minded gambler) may be interested in estimating the probability that a team will score first in a game, given a range of covariates. A naïve analysis will overpredict this likelihood by disregarding the possibility of a goalless draw.

The second major corollary is: the way in which a covariate affects cause-specific hazard may differ from the way in which it affects cumulative incidence. Regarding the football example, consider if the covariates in the survival models included ‘number of defenders’. A team that defends well is less likely to concede a goal, increasing the likelihood of them scoring first and of a goalless draw. We therefore expect this variable to be positively correlated with the cause-specific hazard of scoring first and the cause-specific hazard of a goalless draw. Consider further that number of defenders is a stronger predictor of a team being involved in a goalless draw than of a team scoring first. If a team plays a formation with several defenders, the cumulative incidence of goalless draws may increase markedly. Because of the mutual exclusivity of considered events, this may lead to an overall reduction in the cumulative incidence of games where the team scores first. Hence, despite being positively associated with cause-specific hazard of scoring first, playing too many defenders likely leads to a reduction in the incidence of such events occurring.

Competing Risks as they Relate to CVD

Competing risks are particularly important when evaluating 10-year CVD risk scores. Applying the terminology from survival analysis literature, 10-year risk scores are estimates of cumulative incidence. They estimate probability of experiencing any primary CVD event within a 10-year period, moderated by a range of covariates. The methodology employed to estimate this probability can be described as naïve estimation. Individuals who leave the dataset due to non-CVD mortality are censored and it is assumed that they have a similar rate of disease to those who remain in the risk set (152,231,233–235,308).

As noted in the first corollary above, in the presence of competing risks, a naïve analysis provides biased estimations for event probability. This is true with CVD risk scores. Such scores disregard the fact that individuals may experience non-CVD mortality in the ten years following risk estimation. Therefore, risk of CVD will be overestimated by these scores. On a population level, utilising risk scores to predict future incidence of CVD in a large group of individuals will lead to overprediction. On the individual level, physicians who present risk scores to their patients will be providing misleading information.

Another key issue with 10-year risk scores relates to age. Age is a particularly dominant risk factor in CVD. This fact is reflected in the ASSIGN risk score algorithm which ascribes a 1.77 hazard ratio per 10-year increase in age for CVD development. In comparison, smoking an additional 10 cigarettes per day has an estimated hazard ratio of 1.22, and having a family history of CVD has a hazard ratio of 1.31 (152).

Figure 4-3 presents the significance of age in CVD risk scoring diagrammatically (309). This figure shows a set of CVD risk profiles and was built using the ASSIGN risk score. The numbers inside the cells are the specific risk score for that profile. Along the horizontal axis is patient's ratio of TC to HDL-C, and along the vertical axis is the patient's SBP. Each of these is positively associated with CVD risk, and therefore the healthiest health state is the bottom left hand corner of each profile.

Each profile set represents a different type of patient, based on their age and smoking status. The two profile sets on the left are for patients in the least socially deprived quintile of the Scottish population, and the highest deprived quintile is on the right. All risk profiles were

assigned the average family history (0.26) and diabetes (0.15) values from the Scottish Heart Health Extended Cohort, a study which representatively sampled the CVD-free adult Scottish population.

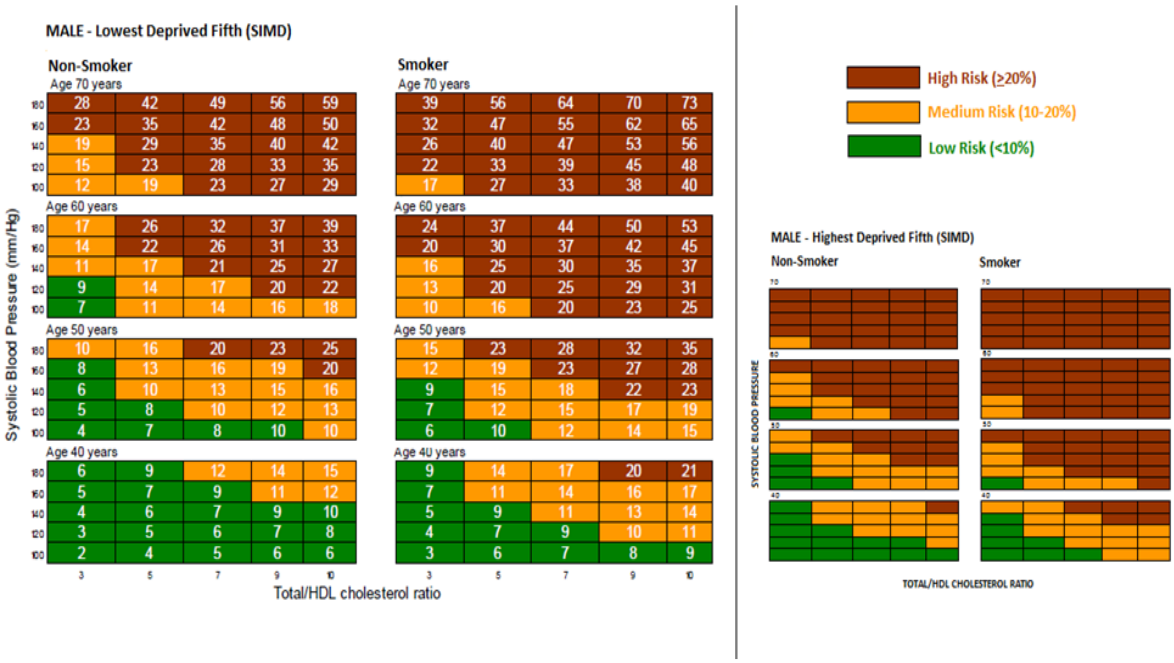


Figure 4-3: ASSIGN risk charts for Scottish males in the lowest and highest deprived quintiles according to Scottish Index of Multiple Deprivation, Lawson (text)

The profiles in Figure 4-3 show the strength of the age gradient in CVD risk. Red represents high-risk (≥20%), orange represents medium-risk (10-20%), and green represent low-risk (<10%). Notably, the majority of people above 60 years old are at high risk of developing CVD. While these risk charts are only for males, similar patterns occur in the charts for females.

Figure 4-4 shows the distribution of ASSIGN scores in the Scottish population. This graph was developed with data from the Scottish Health Survey (SHeS) 2011 (310). It presents a plot of age versus ASSIGN score for all CVD-free individuals aged 40 and above in the survey and clearly shows that 10-year risk increases with age.

The second corollary above stated that, in competing risks analyses, the way in which a covariate affects cause-specific hazard may differ from the way in which it affects cumulative incidence. This is true with regards to age and CVD risk. Age is positively associated with non-CVD mortality. This is because age is a risk factor generic to a range of chronic illnesses including chronic lower respiratory diseases, cancer, and dementia and Alzheimer's (311).

Alongside CVD, these diseases represent the leading causes of mortality in Scotland, England and Wales, and the U.S. (312–314). An elderly individual deemed to be at very high risk of CVD will often experience a fatal occurrence of one of these competing events before developing CVD. Therefore, increases in age will not necessarily lead to an increased incidence of CVD, as predicted with naïve estimations of 10-year risk.

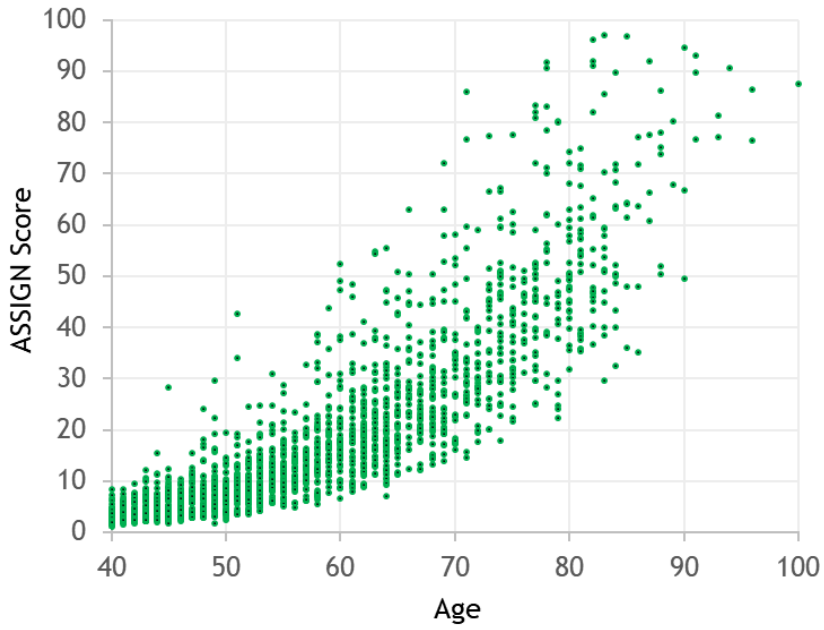


Figure 4-4: ASSIGN score versus age in the Scottish Health Survey 2011

Cumulative Exposure

A second argument in favour of the age-stratified risk threshold approach to prevention is that commencing treatment early in life reduces cumulative exposure to harmful risk factors. In turn, this should reduce atherosclerotic build-up and later life CVD risk.

Atherosclerosis is a cumulative process and extended exposure to modifiable risk factors increases CVD risk. The relationship between risk factor exposure and CVD risk was established in studies of long-term exposure to smoking. Cumulative exposure to smoking can be represented by pack-years, the number of cigarette packs smoked per day by an individual multiplied by the number of years they have smoked. A strong relationship between pack-years and cardiovascular risk has been identified in various studies (315–317). It has additionally been shown that years since quitting smoking is a significant predictor of CVD risk (318).

Early life exposure to many CVD risk factors including SBP, LDL-C, and triglycerides have also been shown to increase risk of atherosclerotic build-up in later life (319–323). These studies estimate the effect of risk factor exposure on atherosclerotic build-up rather than hard disease-related events. This is because extensive follow-up is required to link young adult exposure to events which often occur in later life. However, in an analysis of Framingham Offspring Study data, Vasan et al. have shown a significant effect of cumulative exposure to risk factors in middle-aged individuals on later life CVD events (324).

A breakthrough study published in 2017 showed that exposure to unhealthy risk factor levels in young adulthood significantly increases risk of experiencing a CVD event in later life (325). Pletcher et al. analysed data from 4,860 individuals who were enrolled in the longitudinal Framingham Offspring Study. These individuals attended an average of 6.3 in-person examinations. Age at first examination ranged from 20 to 70 years. Average length of follow-up was 24.5 years. Modifiable risk factor values, specifically LDL-C, HDL-C, diastolic blood pressure (DBP), and SBP, were imputed for every individual for each age from 20 to 70. This was achieved with a mixed modelling approach that fitted risk factor trajectories for every individual based on trends in the population.

Regression analysis was performed to estimate the effect of cumulative exposure to risk factors on later life CVD risk. Every individual's time weighted average LDL-C, HDL-C, DBP, and SBP between the ages of 20-39 was calculated. Cox proportional hazards models were then constructed to estimate the hazard ratio associated with these factors, adjusting for various traditional CVD risk factors. The dependent variable in these Cox models was any CHD event after age 40 and adjustment variables included current and cumulative later life values for the modifiable risk factors. Results showed that cumulative exposure to DBP and LDL-C in young adulthood significantly increased risk of CHD in later life (Figure 4-5). The relationship with SBP in young adulthood was less pronounced. The authors hypothesise that this was due to collinearity between individuals' SBP in early and later life.

Martin and Michos (326) argue that onetime assessment of cholesterol in adulthood likely leads to underestimation of its relationship with CHD. They note that in the Bogalusa Heart Study, two thirds of individuals in the highest quintile of non-HDL cholesterol and LDL-C during childhood ranked in the lowest two quintiles in adulthood. Hence, current levels of a risk factor were poor predictors for past exposure.

There are two implications of the results described above. First, two individuals with identical traditional risk factor profiles may be at very different risk of experiencing a CVD event, based on previous exposure. This implies that current risk scores do not adequately reflect heterogeneity in patient risk. Second, preventive interventions should commence as early as possible to reduce cumulative exposure.

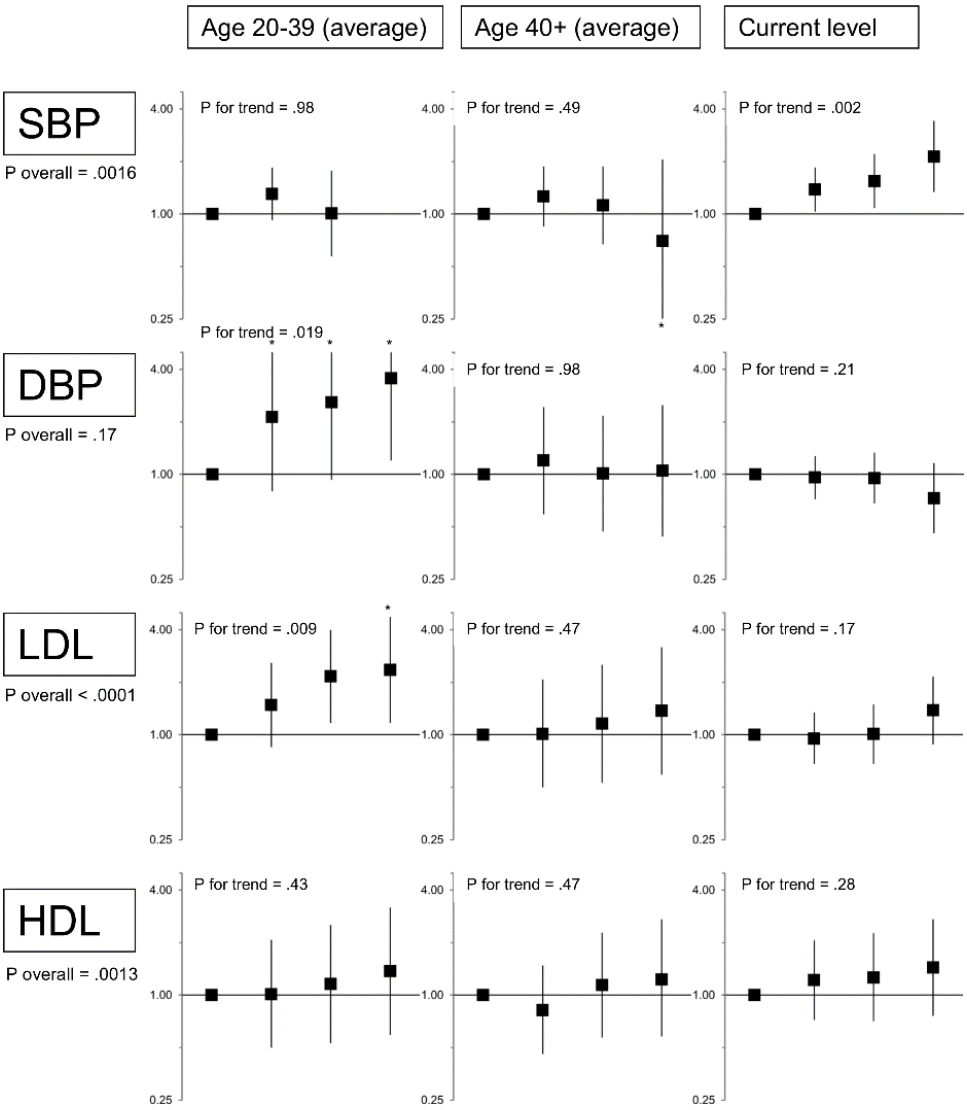


Figure 4-5: Adjusted hazard ratio for SBP, DBP, LDL-C, and HDL-C in Pletcher et al. (325). Categories: SBP - ≤120 (ref), 121-140, 141-160, >160 mmHg, DBP - ≤80 (ref), 81-90, 91-100, >100 mmHg, LDL-C - ≤100 (ref), 101-130, 131-160, >160 mg/dL, HDL-C - >65 (ref), 51-65, 36-50, ≤35 mg/dL. "P overall" refers to overall contribution of risk factor to the model.

Policy Assessment

Age-stratification of risk thresholds allows for better reflection of heterogeneity in patient risk and outcome. Reducing the risk threshold for younger individuals will allow treatment

to be targeted at individuals whose risk is driven by modifiable factors. Similarly, increasing the threshold for older individuals will lead to fewer healthy elderly individuals being treated. Due to competing risks, these individuals are less likely to experience the health benefits of preventive treatment. Moreover, commencing treatment in early life will limit individuals' cumulative exposure to risk factors which will reduce atherosclerotic build-up and CVD events in later life.

4.5.2 Policy: Absolute Risk Reduction-Based Prioritisation

The absolute risk reduction approach is a novel decision mechanism which incorporates 10-year risk. This policy requires prioritising individuals for preventive therapy based on the expected risk reduction they will achieve from treatment.

The basis for the absolute risk reduction approach to prevention is that risk factors can modify treatment effect. This violates the assumption that relative risk reduction for a treatment is equal across all subgroups of the population. With regards to preventive statin therapy for CVD, baseline LDL-C is a known treatment effect modifier.

In the presence of treatment effect modifiers, 10-year risk does not accurately predict treatment outcomes for patients with the same risk score. Two patients with the same risk score but different values of a treatment effect modifier will experience different relative risk reductions from a preventive treatment.

<u>LDL-C as a Treatment Effect Modifier</u>

Several major clinical trials have analysed the effect of statins on CVD risk (327–337). Established in 1994, the Cholesterol Treatment Trialists' Collaboration (CTTC) synthesises data from these trials (338). This has enabled powerful inference of statin effectiveness in patient subgroups.

A key finding from the CTTC is that relative risk reduction from statin therapy per mmol/L reduction in LDL-C is near constant (251). Further, it has been shown in large randomised controlled trials that statin efficacy, represented by reduction in LDL-C, is directly proportional to baseline LDL-C (339). Intermediate-intensity statins do not lead to a unitary reduction in LDL-C but rather a percentage reduction of around 29% (284). Combining these

two findings suggests that individuals with higher baseline LDL-C achieve greater absolute risk reduction attributable to statin therapy. Soran et al. (340) acknowledge this consequence. They show that the number needed to treat with statins to prevent one CVD event is often lower in low- and intermediate-risk individuals with high baseline LDL-C when compared with high-risk individuals with low baseline LDL-C.

Predicting Absolute Risk Reduction for Statins

Based on the theory presented above, Thanassoulis et al. developed an equation to predict 10-year absolute risk reduction (ARR_{10}) or 10-year absolute benefit (AB_{10}) attributable to statin therapy (341). This equation accounts for both absolute 10-year risk (AR_{10}) and baseline LDL-C, and presumes that statin therapy produces a 40% reduction in LDL-C.

Let $AR_{10,un}$ equal baseline untreated 10-year risk and *bLDL* equal baseline LDL-C. Furthermore, let $AR_{10,tr}$ equal treated 10-year risk, $S_{10,un}$ be untreated event-free survival, and $S_{10,tr}$ be treated event-free survival. The three latter terms are presented in Equations (4-12 to 4-14).

$$S_{10,un} = 1 - AR_{10,un} \tag{4-12}$$
$$S_{10,tr} = {S_{10,un}}^{x} \tag{4-13}$$
$$AR_{10,tr} = 1 - S_{10,tr} \tag{4-14}$$

If *HR* is the hazard ratio associated with a one mmol/L reduction in LDL-C, then the relative risk reduction experienced by an individual receiving statin therapy can be described by Equation (4-15).

$$x = HR^{bLDL*0.4} \tag{4-15}$$

It follows that the absolute risk reduction attributable to statin therapy can be described in terms of $AR_{10,un}$, x, and *bLDL*. This relationship is presented in Equation (4-16), which states that absolute CVD risk reduction attributable to statin therapy is equal to untreated risk minus treated risk. This is also equal to treated minus untreated event-free survival. The previous equations formalised the fact that statins reduce risk conditional on *bLDL* and therefore treated 10-year risk is dependent on *bLDL*. Hence absolute risk reduction is dependent on baseline LDL-C.

$$\begin{aligned} ARR_{10} &= AR_{10,un} - AR_{10,tr} \\ &= S_{10,tr} - S_{10,un} \\ &= {S_{10,un}}^{x} - S_{10,un} \end{aligned} \tag{4-16}$$

Thanassoulis et al. (341) consider the difference between the AR_{10} and the ARR_{10} approach to prevention. They obtained risk factor data for 2,134 individuals from National Health and Nutrition Examination Survey 2005-2010, representing 71.8 million Americans who are potentially eligible to receive statins for the primary prevention of CVD. AR_{10} was estimated for every individual using the ACC/AHA pooled cohorts 10-year risk score (342). They found that if the threshold for treatment initiation was not standard of care ($AR_{10} \geq 7.5\%$), but rather $ARR_{10} \geq 2.3\%$, 9.5 million lower-risk individuals would be prioritised for treatment who would achieve equal or greater benefit from statin therapy. The value 2.3% was selected as a prioritisation threshold because this was the minimum ARR_{10} in the group of individuals with $AR_{10} \geq 7.5\%$.

Policy Assessment

A full economic analysis of the absolute risk reduction approach to prevention has not yet been conducted. Thanassoulis et al. have established that this approach may lead to a large reduction in CVD events over a 10-year time horizon compared to standard of care. More extensive analysis should account for QALYs, costs, discounting, competing risks, and should employ a lifetime horizon.

4.5.3 Policy Analysis in Chapter 8

Chapter 8 will assess the cost-effectiveness of two alternatives to prioritisation based on 10-year risk alone for statin initiation. These approaches incorporate 10-year risk, but are stratified by age and LDL-C, respectively. They are:

- Age-stratified risk thresholds
- Absolute risk reduction.

4.6 Direct Use of Decision Models in Clinical Practice

4.6.1 Basic Concept

High-risk young adults generally gain more life years from treatment than elderly individuals. However, this is not necessarily true when the younger individual's risk is driven by smoking. Smokers of all ages are subject to significant fatal competing risks (343), and this drastically

limits their capacity-to-benefit from a preventive treatment. There clearly exists a complicated network of predictors and interactions that determine an individual's capacity-to-benefit from preventive therapy. It is therefore not surprising that defining a simple decision rule to prioritise patients for preventive treatment is very difficult.

As presented throughout this chapter, the 10-year risk scores used to prioritise patients for statin therapy in current practice do not capture heterogeneity in outcome effectively. In the presence of competing risks, missing variables, misspecified models, and non-linear treatment effects, it is very difficult to define a decision rule that maps any specific variable to an individual's capacity-to-benefit. Decision-analytic models allow researchers to synthesise data from multiple sources (344). Direct use of such models in clinical practice may allow clinicians to objectively weigh up the multitude of factors which should inform whether a patient is treated.

4.6.2 Policy: Treating Patients with Greatest Expected Life Year Gains

A decision-analytic model which predicts lifetime outcomes with perfect calibration would allow a decision-maker to assess who is likely to gain most from preventive therapy. This would require using a decision-analytic model in clinical practice to explicitly account for patient-level heterogeneity in outcome. The decision rule to commence treatment would not be based on a risk threshold. Rather, a decision-analytic model would be employed to predict an individual's absolute expected benefit from treatment. Those individuals that meet a minimum benefit threshold would receive treatment.

Decision-makers can employ decision-analytic models to maximise cost-effectiveness, life expectancy, or quality-adjusted life expectancy in a population. Treating patients with the lowest estimated cost-per-QALY attributable to treatment would maximise cost-effectiveness. Treating patients with the maximum estimated life years gains or QALY gains attributable to treatment would maximise life expectancy or quality-adjusted life expectancy, respectively.

<u>Maximising Health Outcomes with Decision Analytic Models</u>

Decision-analytic models, which will be discussed further in Chapter 5, predict health and cost outcomes in individuals based on a range of covariates. These models could be used in

clinical practice to determine which patients receive preventive treatment. This would allow physicians to target treatment at patients based on some expected outcomes. This could be an objective health outcome (e.g. expected life years or QALYs gained) or a marker of value (e.g. expected net health benefit from treatment).

In practice, a physician would use a decision model rather than a risk score to determine whether an individual receives treatment. Many physicians already use computer-based applications to access risk scores like ASSIGN, QRISK2, and the ACC/AHA ASCVD Risk Score (178,345,346).

Patient	ASSIGN Score	Statin Effect on Life Years	Treatment Eligibility	
			ASSIGN≥20	Life Year Maximisation
A	24	0.13	0.13	0.13
B	7	0.15	0.00	0.15
C	3	0.11	0.00	0.00
D	39	0.13	0.13	0.13
E	17	0.05	0.00	0.00
F	43	0.12	0.12	0.00
G	28	0.04	0.04	0.00
H	17	0.05	0.00	0.00
I	7	0.14	0.00	0.14
J	24	0.02	0.02	0.00
K	36	0.16	0.16	0.16
L	9	0.03	0.00	0.00
M	5	0.13	0.00	0.13
N	15	0.18	0.00	0.18
O	52	0.07	0.07	0.00
		Total LY gain:	0.67	1.02

Table 4-3: Example of risk scoring versus life expectancy maximisation to determine statin eligibility

Table 4-3 provides an example of how a decision model could be used to prioritise preventive statin therapy in Scotland. This table includes data for 15 patients from the Scottish Health Survey of 2011 (347). The first two columns show the patient's ID and ASSIGN score, respectively. Column three shows the life expectancy effect of statins on each patient, as predicted using the Scottish CVD Policy Model (7). Column four applies that effect to the patient if their assign score is above 20%. Hence, seven of the fifteen patients are highlighted grey and assigned the 'treated' change in life expectancy. Column five demonstrates an alternative approach: patients are prioritised based on their estimated capacity-to-benefit from treatment. The seven patients with the highest expected increase in life expectancy (life

year gain ≥0.13) are highlighted green and assigned an increase in life expectancy. Finally, in the bottom row, columns four and five are summed.

Even amongst this small cohort of potential patients, determining treatment eligibility with a decision-analytic model leads to a marked increase in health benefit. For this benefit to carry into actuality, it is necessary that the model predicts individual-level treatment benefit with an acceptable degree of discrimination and calibration

4.6.3 Policy Analysis in Chapter 9

Chapter 9 will assess the cost-effectiveness of using decision models in the clinical setting. Specifically, it will consider the cost-effectiveness of a statin initiation rule which aims to maximise life expectancy in a population.

4.7 Homogeneity in Cost-Effectiveness of Statin Therapy

Individuals evidently achieve different benefits from statin therapy based on sociodemographic and biological variables. However, statins are relatively low cost and have a small adverse effect profile (36,348). Collins et al. state that the large amount of evidence from randomised trials of statin therapy indicates that it is "unlikely that large absolute excesses in other serious adverse events still await discovery" (349). If individuals have a small chance of experiencing statin-related benefit, then all individuals in a population may soon be cost-effective to treat. While health outcomes attributable to treatment may differ in populations, there may be considerable homogeneity in cost-effectiveness of statin therapy.

In microsimulation analysis, Pandya et al. (37) found that with generic statin pricing the 10-year risk threshold for statin initiation could be reduced to less than 4% in the U.S., representing 65% of the CVD-free population aged 40 years and above. This cost-effectiveness was largely driven by drug price. In similar analyses Heller et al. found that implementing the ACC/AHA guideline would be cost-saving (350) and research by NICE found that the threshold for statin initiation in England and Wales could be reduced to 6% or lower and still be cost-effective (25). This suggests that much more than 65% of the CVD-free adult population would be cost-effective to treat.

Concerns over mass-medicalisation may limit the institution of statin prioritisation policies which treat large numbers of people. This is especially true because the expected absolute gains from preventive treatment are often small. There has been significant backlash from the clinical community following NICE's decision to reduce its threshold for treatment initiation from 20% to 10% in England and Wales (351). Uptake of the new guidelines has been low with around one fifth of individuals with risk scores between 10-19% receiving treatment (352). Clearly there has been a disconnect between those producing treatment guidelines based on cost-effectiveness analysis and clinicians concerned about overmedication of healthy individuals and polypharmacy in the elderly (353). Simple cost-effectiveness rules may not be sufficient in determining who should receive statin therapy, as guidelines based on cost-effectiveness may not be clinically acceptable.

Policy Assessment

Chapter 11 compares the policies discussed throughout this chapter. Primarily, it compares the cost-effectiveness of these strategies. Given the backlash to recent statin guidelines, it is also necessary to consider implicit constraints on prioritisation policies and alternative metrics to cost-effectiveness with which to assess these policies. This chapter compares strategies for CVD prevention constrained by treating a limited proportion of a population. It additionally considers the ability of alternative statin prioritisation policies to address health inequalities.

4.8 Chapter Summary

Outcomes attributable to preventive intervention in CVD may differ substantially between individuals. Even amongst individuals with the same 10-year risk score, there may be considerable heterogeneity in outcome associated with statin therapy. Three approaches were presented in this chapter which may better address heterogeneity in patient outcomes than current standard of care. These were: continue and updated use of 10-year risk scoring, novel decision mechanisms which incorporate 10-year risk alongside other important covariates, and direct utilisation of decision-analytic modelling in the clinical process.

Policies were presented which may be stratified into one of the three approaches to prevention discussed. Policies that involve continued and updated use of 10-year risk scores are lowering the threshold for treatment initiation and improving risk scores with novel risk factor

information. These policies would respectively allow decision-makers to increase the sensitivity of risk scoring and better target treatment at patients with elevated risk, respectively. Policies that involved novel decision mechanisms which incorporate 10-year risk alongside other important covariates were age-stratified risk thresholds and prioritisation based on statin absolute risk reduction. These policies address competing risks related to the age gradient in CVD risk, cumulative exposure to risk factors, and the existence of treatment effect modifiers, respectively. Finally using decision-analytic models in clinical practice would allow decision-makers to maximise health outcomes. The following chapters, contained within Part 3 of the thesis, will assess the cost-effectiveness of the policies described in this chapter.

Part 3

Cost-Effectiveness Analyses of Preventive Policies for CVD

Part 3 considers the cost-effectiveness of treatment prioritisation policies introduced in earlier chapters. Most of these analyses focus on the cost-effectiveness of prioritising patients for preventive statin therapy through different decision mechanisms. A final analysis shows how decision-makers can signal demand for more expensive cholesterol-reducing interventions in patients with statin intolerance or who require further cholesterol reduction while on statin therapy.

Chapters 5 and 6 set up the cost-effectiveness analyses. Chapter 5 describes two previously-published decision-analytic models that will be used throughout the remainder of Part 3 to assess the cost-effectiveness of different treatment policies. Despite being a commonly prescribed medication, there remains some controversy regarding statin therapy and perceived adverse effects. Chapter 6 discusses evidence regarding the safety, efficacy, and effectiveness of statin therapy.

Chapters 7 to 9 consist of a series of cost-effectiveness analyses of different prioritisation policies for preventive statin therapy. Chapter 7 considers two policies which involve continued use of 10-year risk scoring: reducing the risk threshold for treatment initiation and improving the discrimination of risk scores with novel biomarker testing. Chapter 8 considers two policies which involve novel decision mechanisms alongside 10-year risk scoring: age-stratified risk thresholds and the absolute risk reduction approach to statin prioritisation. Chapter 9 considers the cost-effectiveness of using decision models in clinical practice to maximise outcomes in the patient population.

Chapter 10 relates to PCSK9 inhibitors, a treatment which is more effective at reducing LDL-C than statin therapy and more expensive. This treatment may be useful for patients with high capacity-to-benefit from cholesterol reduction who require treatment supplemental to statin therapy or for patients who are statin intolerant. This chapter shows how decision-makers can signal demand for PCSK9 inhibitors by reflecting heterogeneity in their decision-making.

Chapter 5
Cardiovascular Disease Policy Models

5.1 Purpose

To maximise health outcomes given an exogenously determined healthcare budget, decision-makers must invest in cost-effective treatments. Decision-analytic models can be employed to estimate the cost-effectiveness of different treatments. These models allow researchers to systematically synthesise evidence regarding an intervention and estimate its health and cost consequences in a population of interest.

The purpose of this chapter is to describe the rationale behind policy modelling and to introduce existing models for CVD that can be employed in cost-effectiveness analyses throughout the remainder of thesis. Types of decision-analytic models and approaches for their validation and recalibration are described. The Scottish CVD Policy Model and the U.S.-based CVD Microsim Model are discussed, and these models are employed in epidemiologic analyses of CVD prevention.

5.2 Policy Models

Decision-analytic models are typically built with a specific research question in mind. For example, pharmaceutical companies often develop models which can be used to assess the cost-effectiveness of a specific product. Policy models adopt a more generic approach to disease modelling. They can be used in the assessment of multiple treatment options.

5.2.1 Types of Model

Decision models can take many forms, ranging from simple decision trees to complex state-transition models (354).

<u>Decision Tree Models</u>

Decision tree models are the simplest form of decision-analytic model. They involve constructing a probabilistic pathway that describes key stages in a patient's disease and

treatment history. They can be represented diagrammatically in a flowchart structure. Decision trees typically start with a square decision node. At this point in the flowchart, the initial treatment decision is made. Straight lines descend from the initial node representing patient pathways. Future events can be modelled with circular chance nodes (which assign a probability to future pathways in the model) and additional decision nodes. Finally, each pathway ends with a terminal node. Terminal nodes are assigned health and cost outcomes. The expected outcomes associated with different clinical decisions can hence be estimated by summing the probabilistically weighted outcomes of each terminal node, conditional on a set of clinical decisions.

Figure 5-1 presents a decision-tree employed by Bachman (355) in a cost-effectiveness analysis of community-based therapy for children with severe acute malnutrition in Zambia. The initial decision node determines whether individuals receive the care. Children receiving no care are stratified by HIV status, as this is a key determinant of mortality probability in untreated malnourished children. Those children who receive therapy may recover, die, be admitted to hospital, or default from care. Probability of mortality was lowest for children who received the intervention, followed by those who defaulted from care, while children admitted to hospital had the highest mortality rate.

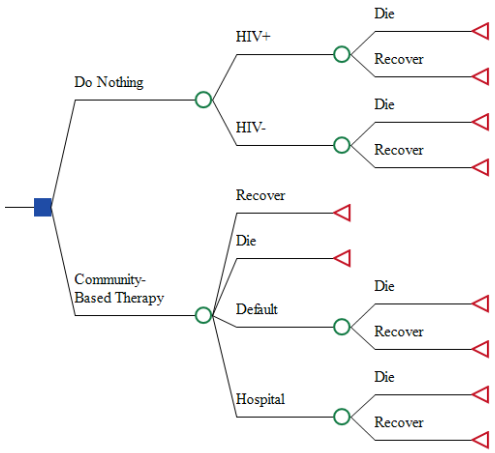


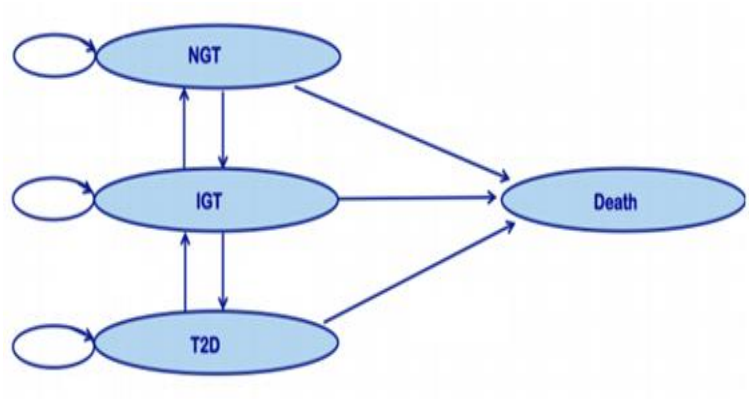
Figure 5-1: Decision tree model, Bachmann (text)

State-Transition Models

State-transition models are one of the most common types of decision-analytic model used in economic evaluations of health care interventions. Instead of modelling decision processes as a range of mutually exclusive pathways with terminal outcomes, state-transition models structure the process over a set of discrete time periods. These models are defined by a set of

mutually exclusive states (often determined by disease status). During each cycle one transition between states is possible, determined by an estimate of transition probability. Each state typically has an associated cost and measure of health. Transition between states may also be attributed health and cost outcomes.

The simplest form of state-transition model is a Markov cohort model. Figure 5-2 displays an example of a Markov cohort model that was employed in the cost-effectiveness analysis of interventions to prevent the onset of diabetes in high-risk individuals (356). Individuals or cohorts enter the model with normal glucose tolerance (NGT). They may then transition to a state of impaired glucose intolerance (IGT) based on a probability that is conditional on a set of risk factors. IGT is a predictor of an individual's risk of developing type-2 diabetes (T2D) (357). Next, individuals may transition from IGT to development of T2D. Individuals inhabiting all states are subject to the competing risk of death. An intervention which reduces development of T2D will reduce probability of state transition in the model.



NGT – normal glucose tolerance, IGT – impaired glucose tolerance, T2D – type-2 diabetes.

Figure 5-2: Markov cohort model, Neumann et al. (text)

To estimate health and cost outcomes for a cohort or individual, Markov models are 'run' for several cycles. The number of cycles employed in an analysis multiplied by the length of each cycle is referred to as the time horizon of the analysis. When comparing two treatment strategies, a time horizon should be employed which adequately captures all incremental disease-related outcomes (358).

Two key types of state-transition models exist: Markov cohort and microsimulation models. Markov cohort models simulate an entire cohort, distributing individuals deterministically across model states after each cycle based on state transition probabilities. The average length

of time spent in each state by the cohort is multiplied by health and cost valuations for the state. This allows for outcomes including life expectancy (LE), quality-adjusted life expectancy (QALE), and expected healthcare costs to be summed over the time horizon (359). Future health and cost outcomes can be discounted within the model structure.

Markov cohort models rely strictly on the Markovian assumption that state transitions occur in a 'memoryless' fashion. This means that once an individual enters a state in the model, their future transitions and outcomes are not dependent on their past disease history. Disease history includes both the time they have spent in their current state and the previous states they have occupied. With reference to Figure 5-2, an individual who has spent 10 cycles in the IGT state has the same probability of transition to T2D as an individual who has spent one year in the state, even if their risk factors are the same. Likewise, an individual who has spent their whole life with IGT would be at the same risk of transitioning to T2D as an individual who only recently developed IGT.

Complexity can be added to the structure of Markov models to reflect better disease processes. For example, additional 'tunnel' states can be added to models. All individuals in a state progress into a tunnel state after a specified number of cycles. However, including several tunnel states makes a model unwieldy.

Microsimulation is a more complex form of modelling. This process (also referred to as patient-level simulation) involves simulating a finite number of individuals. First-order Monte Carlo simulation is performed. This means that each transition between states is stochastically determined (as opposed to deterministically in the case of cohort models). The costs and QALYs accumulated in each discrete individual-level simulation are averaged to obtain population-level health and cost estimates. Essentially, each simulated individual's 'disease history' is tracked.

With its additional complexity, microsimulation offers some benefits over cohort modelling. NICE recently published a report which identified conditions under which microsimulation is preferable to a cohort modelling (360). These conditions include: model non-linearity with respect to heterogeneous patient characteristics, patient flow which is determined by time since last event (non-Markovian behaviour), and the desire to add additional modelling complexity in future analyses.

Discrete Event Simulation Models

Discrete event simulation is a further level of complexity that can be added to decision-analytic models. Unlike Markov models, discrete event simulation does not run cyclically. Instead individuals experience disease-related events based on probabilistic time-to-event distributions. At the time of each modelled event, the individual's accumulated costs and outcomes are estimated. In addition, their likelihood of future events is modified at this point. Extensive longitudinal cost and outcome data are often required to develop such a model.

Discrete event simulation represents an efficient means of modelling diseases with time varying event rates. Diseases defined by extensive periods of inactivity followed by rapid onset of numerous events, for example, cannot be efficiently modelled with state-transition models which cyclically estimate cumulative costs and outcomes. Discrete event simulation can also be performed without mutually exclusive branches and discrete states, increasing modelling flexibility (361).

The modelling process and derivation of time-to-event distributions required for discrete event simulation is generally considered less straightforward and more challenging than the construction of decision tree and state transition models (362).

5.2.2 Which Type of Model for CVD?

Albert Einstein may (or may not) have stated that "Everything should be as simple as it can be, but not simpler" (363). This principle holds true when constructing a model of CVD. A model should not be too complex that it requires an unobtainable amount of data to produce valid results. Simplistic model structures also aid in transparency as a wider audience may review and critique the model. Decision-makers who are not versed in decision-analytic modelling are more likely to accept results produced by a model which they understand. Nonetheless, considerable complexity is often required to model a disease and relevant treatments adequately.

Decision Tree, State-Transition, or Discrete Event Simulation?

Decision trees optimally represent processes with short time horizons and relatively few mutually exclusive pathways – otherwise a tree becomes 'bushy' and unwieldy.

Individuals may experience a range of different CVD events that lead to different health and cost outcomes. For example, a patient suffering an ischaemic stroke is likely to experience much greater chronic disease costs and quality of life decrements than a patient suffering from a myocardial infarction (364). Representing different disease states in a decision model can drastically increase the number of mutually-exclusive pathways in a decision tree. The time at which individuals experience a CVD event also matters. Individuals experiencing an event earlier in life have a much greater chance of full recovery and experience smaller reductions in quality of life (365).

CVD is a disease which can affect individuals at any time in the life. Moreover, exposure to risk factors can lead to events many years in the future. Hence a lengthy time horizon is required to capture all costs and effects attributable to a treatment. All the reasons listed suggest that a state-transition model should be used to optimally represent CVD.

Discrete event simulation models do not offer substantial benefits over state-transition models for CVD. The disease is defined by a limited set of health states and continually increasing risk. Hence the added complexity of event- and time-dependency in disease rates offered by discrete event simulation is not justified.

Markov Cohort or Microsimulation?

Under the assumption that state-transition models are the most efficient means of modelling CVD, it remains to establish whether cohort or microsimulation models should be preferred. The optimality of these model types is largely determined by the complexity of the decision problem.

Cohort models generally require more assumptions and hence less data to construct than microsimulation models. A key feature of Markov cohort models is the memoryless property: the assumption that any future disease-related transition in the model is not influenced by disease history. Previous exposure to risk factors and the individual's history of disease-related events are not important determinants of future outcome so data on these factors are not required to estimate transition probabilities. Cohort models also average health and cost outcomes across a large population. This is an unbiased means of predicting outcomes in a population under the assumption that there is a linear relationship between patient

characteristics and outcomes. However, in the event that this is not true, it is necessary to stratify analysis by subgroups in order to obtain unbiased estimates of outcomes (360). As with all statistical models, increased granularity of research question involves increased data requirement.

Microsimulation can offer considerable benefits in the modelling of CVD. It allows individual patient disease and covariate histories to be tracked. Microsimulation may also be employed as a means of dealing with the non-linear relationship between CVD risk factors and health outcomes. For example, an individual's likelihood of experiencing a secondary CVD event is much greater for older individuals with an unhealthy risk factor profile than for young healthy individuals (366,367). Microsimulation enables researchers to account for the combinatory effect of disease and risk factor histories on recurrent events.

CVD events have also been causally linked to a range of non-cardiovascular conditions. There is, for example, a growing understanding of the causal relationship between CVD and dementia (368). Developing a microsimulation model allows for easy adaptations of the model in the future, to answer increasingly complex research questions.

An additional benefit of microsimulation model relates to computing efficiency. Often a study requires estimating outcomes for a range of individuals from a representative cohort of a population. Running data for several thousand individuals through a cohort model can be very time-consuming: all potential outcomes must be considered and averaged for every individual. On the other hand, each 'run' of a microsimulation involves computing one disease history. Such time efficiency is particularly important when conducting computationally demanding processes like probabilistic sensitivity analysis.

5.2.3 Validating Models

The validity of an economic model can be established in numerous quantitative and qualitative ways. Qualitative inspection by experts can confirm that there is a sound basis for the model's structure and assumptions. Quantitative analysis helps to establish the internal validity, external validity, and cross validity of a model.

Internal validity is a measure of how accurately a model reproduces results from the data sources that contributed to its construction. The c-statistic is a statistical measure of the predictive accuracy for logistic regression models (369).

External validity refers to a model's ability to reproduce results from a dataset which did not contribute to its construction. External validation of a model requires a large individual-level, longitudinal dataset with sufficient follow-up. The model's predicted outcomes for an individual in that dataset are then compared with actuality.

5.2.4 Recalibrating Models

Recalibration is the process of systematically adjusting model inputs so that outputs generated are suitable in the population of interest (344). Suitability is typically measured by comparison with some external real-world dataset. For example, a model which aims to estimate the effect of different health care interventions on all-cause mortality in the Scottish population may be recalibrated to recent mortality rates provided by the Scottish Government.

5.3 CVD Policy Models

The need to choose between competing interventions for CVD has become an increasingly important issue for healthcare decision-makers in recent years. While rates of the disease have dropped significantly since the 1980s, CVD remains a leading cause of mortality in the U.K., U.S., and around the world.

Increased understanding of CVD's physiology and advancements in health technologies have led to the development of several novel interventions for CVD. These include: the development of new cholesterol-reducing medications, improved diagnosis of CVD risk, improved surgical outcomes, and support for population-based interventions. Policy models have been developed to assess the effectiveness and cost-effectiveness of these interventions.

For the purpose of this thesis, access was granted to two existing policy models: The Scottish CVD Policy Model (7,8,309) and the CVD Microsimulation Model (9). These were extensively redeveloped, modified, and employed for epidemiologic evaluation of CVD as well as cost-effectiveness analyses of multiple primary prevention policies. The first section

of this chapter will detail these two policy models. Next, epidemiological arguments from Chapter 4 will be evaluated using these models.

5.3.1 The Scottish CVD Policy Model

Background

Given the need for Scotland-specific analysis of CVD policy, in 2010 the Chief Scientist Office for Scotland funded research to develop the Scottish CVD Policy Model (309). The Scottish CVD Policy Model is a decision-analytic model that predicts LE, QALE, and cost outcomes for individuals based on their ASSIGN risk factors (7,8). It currently exists as two extensive Microsoft Excel documents, one for males and one for females.

Structure

Figure 5-3 shows a diagram of the model. Individuals enter CVD-free, and transition to one of four first event types throughout the course of their lives: non-fatal CHD, non-fatal CBVD, fatal CVD, or fatal non-CVD.

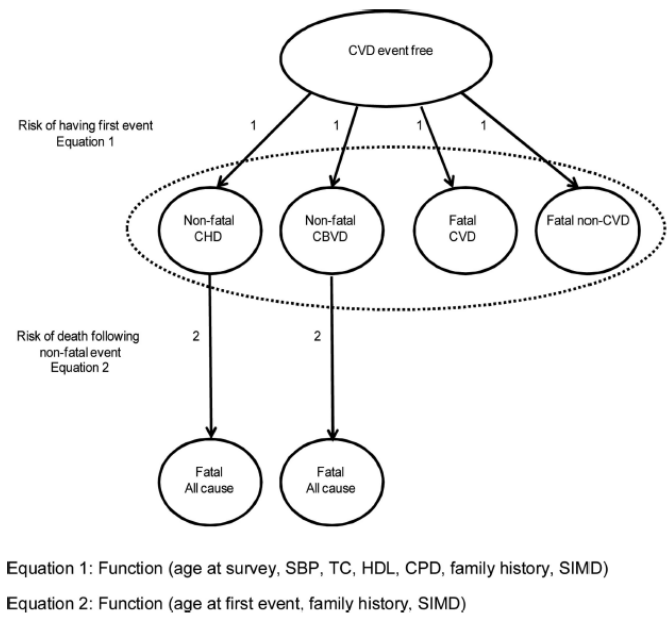


Figure 5-3: Structure of the Scottish CVD Policy Model

The model is particularly useful as it accounts for the competing risk of non-CVD death as a first event. This means it can account for the fact that age is a risk factor generic to a range of chronic illnesses. It also accounts for competing risks between different types of CVD

event. Risk factors may differentially increase risk of different CVD events. After the occurrence of a non-fatal first event, individuals progress to a final absorption state representing all-cause mortality.

Each state in the model has an assigned QALY value, sometimes disaggregated by patient characteristics. Individuals who have not experienced a primary CVD event are attributed a background health-related quality of life (HRQoL) value. These values are disaggregated by age and sex. Individuals inhabiting one of the two non-fatal chronic CVD states are assigned a decrement to this background HRQoL value, determined by the type of first event (CHD or CBVD). Within the chronic disease states, a proportion of individuals are assumed to experience further utility decrements attributable to secondary CVD events (disaggregated as myocardial infarctions, strokes, TIAs, heart failure, peripheral artery disease, and 'other' CVD events).

Costs are also assigned to all health states in the model. For individuals whose primary event is fatal, linear equations predict pre-event hospitalisation costs. These equations include age entering the model, SIMD, and family history of CVD as covariates. Similar equations predict pre-event health state costs for individuals whose primary event is non-fatal CHD or CBVD. Individuals inhabiting the chronic CVD states are attributed costs based on a linear equation that includes age at primary event, SIMD, and family history of CVD as covariates.

The sources and methodology used to derive health and cost estimates for each health state in the model are described later in this section.

Cohort Simulation

The Scottish CVD Policy Model can be employed in two ways. Primarily, it can produce individual-level outcome estimates for prospective patients based on their ASSIGN risk factors. In turn this can inform patient and physician decision-making.

Individual-level outcome estimates are obtained by inputting the individual's risk factor information into the model. These factors then dictate the probabilities that the individual will inhabit each model state each cycle of analysis. These factors also determine the cost and QALYs that an individual will accumulate in each state and cycle combination. The

individual's expected cost and QALYs are then summed over the time horizon of the analysis as follows:

$$E[c] = \sum_{t=0}^{h} \sum_{s} p_{s,t} * c_{s,t}$$
$$E[e] = \sum_{t=0}^{h} \sum_{s} p_{s,t} * e_{s,t} \ .$$

E[c] and *E[e]* refer to expected cost and expected health effects, respectively. These values are equal to the product of an individual's probability of inhabiting disease state, *s*, in cycle, *t*, summed over the time horizon of the analysis, *h*, and all disease states included in the model.

A further use of the model is to estimate population-level outcomes. In this situation, individual-level outcome estimation is computed as described above for a large number of individuals. The risk factor profiles for this analysis can be derived from large-scale cross-sectional surveys like the Scottish Health Survey (310). These outcomes can then be projected onto a wider population.

State Transition Probabilities: Data

Two types of state transitions exist in the model: transition to a primary event (fatal or non-fatal) and transition to the all-cause mortality state after a primary non-fatal event. Both of these transitions are determined by equations derived from competing risk survival analysis of a longitudinal dataset of Scottish adults.

All state transition probabilities in the model are derived from a dataset that linked baseline risk factor information in the Scottish Heart Health Extended Cohort (370–372) to a collection of routinely collected clinical data called the Scottish Morbidity Records (SMR) (238).

SHHEC is an extensive dataset that was used in the construction of the ASSIGN score. Baseline CVD risk factor information was recorded for 6,419 men and 6,618 women from 25 Scottish districts between 1986 and 1995. The risk factors collected as baseline were those previously described as the ASSIGN risk factors: age, sex, TC, HDL-C, SBP, FH, Diabetes, CPD, and SIMD.

The SMR is an electronic database maintained by the Scottish NHS' Information Services Division (ISD). This database records all hospitalized events that occur in the Scottish NHS,

detailing reason for admission, up to five secondary diagnoses, length of stay, and wait time. Health boards submit hospitalisation data to the ISD every 6 weeks, and audits of the SMR have found the data to be 99% complete (373–375).

SHHEC participants permitted their baseline data to be linked with the SMR via a unique NHS identification number. Linking these two datasets allows researchers to analyse the relationship between individuals' baseline characteristics and health outcomes. The most recent SHHEC-SMR linkages included data through 2006 and 2009, respectively. The 2006 linkage was employed in the development of the ASSIGN score and the 2009 linkage was employed in the development of the Scottish CVD Policy Model.

State Transition Probabilities: Analysis

A parametric competing risks approach was taken to estimate the probability of primary events. The competing risk approach provides an unbiased methodology for estimating event probability in the presence of competing events. This approach was discussed in Section 4.5.1. Primarily, it involves estimating cause-specific hazard functions for a set of mutually exclusive events. Probability of event-free survival can then be computed as a function of survival from all event types.

Cause-specific hazard reflects the probability that an individual will experience an event at a moment in time, conditional on the fact that they have not yet experienced a competing event. It can be estimated with parametric regression analysis. This analysis models the functional form of a population's cause-specific hazard based on some pre-defined statistical distribution.

The Gompertz distribution is a statistical distribution to which human survival data are often fitted. This model is named after actuarial scientist and mathematician Benjamin Gompertz, who postulated in an 1825 letter that human death rates increase exponentially with age (376). This model assumes an 'initial death rate' in humans, and assumes that as individuals age, their vulnerability to the causes of the initial death rate increases (377).

When performing Gompertz regression, the cause-specific hazard of an event type, k, is described by the function:

$$h_k(t) = \exp(xb) * \exp(\gamma t).$$

In this equation, *xb* is a linear predictor which modifies hazard rates for individuals based on *x*, a vector of covariates. The vector *b* consists of log hazard ratios for unitary increases in the covariates included in *x*. The term exp(γt) represents the underlying hazard rate in the population, with *t* representing time and *γ* being an ancillary parameter which defines the relationship between time and hazard in the population. Hence the term *exp(xb)* multiplicatively alters an individual's hazard rate dependent on their covariates.

Gompertz regression was performed on the SHHEC-SMR dataset to estimate cause-specific hazard functions for the four primary events in the model: non-fatal CHD, non-fatal CBVD, fatal CVD, and fatal non-CVD. In the model, survival and event probability for each cycle was then computed within the competing risk framework described in Chapter 4. The covariates included in these regression models were the ASSIGN variables. Results for the primary event regressions, developed by Lewsey et al. (7,309), are presented in Table 5-1.

Secondary transition rates out of the two non-fatal CVD states to all-cause mortality were also derived by performing Gompertz regression on the SHHEC-SMR dataset. Competing risks were not relevant as the analysis only considered the probability of transition to an absorption state with no competing events. The covariates employed in this regression were: age at first event, SIMD score, and family history of CVD. Results for the secondary event regressions, also developed by Lewsey et al. (7,309), are presented in Table 5-2.

Health-Related Quality of Life Inputs

HRQoL was assigned to disease states based on analysis of the Scottish Health Survey 2003 (378). The Scottish Health Survey is an annual cross-sectional, representative survey of determinants of health in the Scottish population. In 2003, 7,054 survey respondents aged 20 and above completed 12-item Short Form (SF-12) HRQoL questionnaires. These questionnaires can be used to generate QALYs (379).

The QALY values for respondents in SHeS 2003 were used to produce baseline QALY estimates for the adult Scottish population and to estimate utility decrements related to primary CHD and CBVD. Stratified baseline QALY values were calculated. Stratification was performed by 5-year age-groups and sex.

The utility decrements associated with a range of CVD events were estimated through a linear regression. The dependent variable in this regression was SF-12-derived QALY value and the independent variables were sex, age, and six CVD events. The estimated utility decrements for angina, myocardial infarction, irregular heartbeat, other heart condition, stroke, and intermittent claudication were 0.0891, 0.0403, 0.0499, 0.0336, 0.0938, and 0.0199, respectively. Within chronic disease states, an individual's HRQoL was estimated as their baseline QALY value minus the decrement associated with their primary event. In addition, a proportion of individuals in the chronic disease states were assumed to experience each of the CVD events described above. Hence, a weighted additional utility decrement was employed in both chronic disease states to reflect reduction in HRQoL associated with secondary events.

Cost Inputs

The SHHEC-SMR dataset was used to estimate lifetime hospitalisation costs in the model. Lifetime hospitalisation costs are a function of events experienced by an individual and overall length of stay. Together these two variables represent the patient's continuous inpatient stay (CIS).

Method 1 from Geue et al. (380) was employed to attribute cost of CIS to each hospitalisation episode observed in the SHHEC-SMR dataset. This effectively required assigning a healthcare resource group (HRG) (309) to each hospitalisation episode in the dataset with HRGv3.5 Grouper software (381), followed by attributing costs to these episodes from the English NHS tariff (382). Finally, it was necessary to estimate the overall cost of each CIS that involved more than one episode of care. Treating all episodes of care separately would lead to overestimation of costs, so an approach was adopted which established a dominant episode (and HRG) for all hospitalisations but which simultaneously accounted for other non-dominant episodes of care within this CIS. This was achieved by using a 'Spell Converter' software which designates episode of care dominance based on date of admission, date of discharge of final event, episode order, length of stay, and HRG.

Once lifetime hospitalisation costs were estimated for every individual in the SHHEC-SMR dataset, these data were employed in regression models to predict pre- and post-event hospitalisation costs in the model. Cubic splines were also included in the regression model to add a degree of non-linearity over time to the cost estimations. In addition, regressions

analyses of post-event costs were run for post-non-fatal CHD and post-non-fatal CBVD costs in men and women. The dependent variable in these equations was post-event costs. The same independent variables were employed as before with the exception of baseline age, which was replaced by age at first event. Finally, these regression equations were used to assigned pre- and post-event costs in the model.

Discrimination and Calibration

Internal and external validation of the model has been completed. These validation exercises have shown that the model has a good level of discrimination and calibration (309).

Internal validation of the functions that dictate state transition in the model was completed by means of AUROC analysis. The c-statistics for the primary risk functions for men and women are detailed in Tables 5-1 and 5-2. For primary events they range from 0.70-0.80, and for mortality post non-fatal CHD and CBVD they range from 0.65-0.68. C-statistics between 0.70 and 0.80 are considered to provide "acceptable" discrimination for models of CVD, according to Lloyd-Jones, and a score of 0.65 is described as performing "much better than random chance" (383).

The calibration of the model was assessed with data from the West Of Scotland COronary Prevention Study (WOSCOPS) (384). WOSCOPS was a placebo-controlled trial of pravastatin which enrolled hypercholesterolaemic men aged between 45 and 64 years, with an initial 5-year follow-up.

The baseline data of men in the placebo and treatment arms of WOSCOPS were inserted into the Scottish CVD Policy Model. Predicted cumulative incidence of non-fatal CHD, non-fatal CBVD, fatal CVD, and fatal non-CVD was recorded. These results were then visually compared to event rates in the WOSCOPS population. Figure 5-4 presents the results of this analysis for the placebo arm of the trial, and Figure 5-5 presents the results for the treatment arm.

Parameter	Hazard ratio: non-fatal CHD	Hazard ratio: non-fatal CBVD	Hazard ratio: CVD mortality	Hazard ratio: non-CVD mortality	Source
Men					
Age	1.05 (1.04, 1.05)	1.07 (1.06, 1.08)	1.10 (1.09, 1.11)	1.10 (1.09, 1.11)	SHHEC-SMR Dataset
SIMD	1.04 (1.01, 1.07)	1.10 (1.05, 1.15)	1.07 (1.03, 1.10)	1.10 (1.07, 1.13)	
Diabetes	1.93 (1.07, 2.76)	3.22 (1.94, 5.33)	2.37 (1.48, 3.81)	1.40 (0.84, 2.31)	
FH	1.50 (1.34, 1.69)	0.98 (0.79, 1.21)	1.18 (1.00, 1.39)	0.99 (0.85, 1.14)	
CPD	1.42 (1.34, 1.55)	1.61 (1.40, 1.86)	1.87 (1.67, 2.10)	1.84 (1.68, 2.02)	
SBP	1.08 (1.31, 1.11)	1.12 (1.08, 1.17)	1.16 (1.13, 1.20)	0.99 (0.95, 1.02)	
TC	1.29 (1.05, 1.35)	1.09 (1.00, 1.18)	1.13 (1.05, 1.21)	0.95 (0.90, 1.01)	
HDL-C	0.68 (1.23, 0.75)	0.94 (0.82, 1.07)	0.93 (0.83, 1.04)	1.21 (1.11, 1.32)	
c-statistic	0.70 (0.62, 0.71)	0.73 (0.71, 0.75)	0.77 (0.76, 0.79)	0.74 (0.72, 0.75)	
Women					
Age	1.06 (1.05, 1.07)	1.08 (1.07, 1.10)	1.11 (1.09, 1.12)	1.09 (1.08, 1.11)	SHHEC-SMR Dataset
SIMD	1.09 (1.06, 1.12)	1.14 (1.09, 1.19)	1.04 (1.00, 1.09)	1.08 (1.04, 1.11)	
Diabetes	2.07 (1.41, 3.03)	3.01 (1.81, 4.99)	3.14 (1.97, 5.00)	0.96 (0.51, 1.81)	
FH	1.68 (1.48, 1.90)	1.43 (1.16, 1.75)	1.27 (1.05, 1.53)	0.98 (0.85, 1.14)	
CPD	1.51 (1.34, 1.71)	1.71 (1.41, 2.08)	2.61 (2.24, 3.03)	2.14 (1.91, 2.41)	
SBP	1.06 (1.03, 1.10)	1.15 (1.09, 1.20)	1.19 (1.14, 1.24)	1.03 (0.99, 1.06)	
TC	1.21 (1.15, 1.27)	0.95 (0.86, 1.05)	1.06 (0.98, 1.15)	0.93 (0.87, 0.99)	
HDL-C	0.69 (0.63, 0.76)	0.84 (0.73, 0.97)	0.92 (0.81, 1.04)	0.98 (0.89, 1.07)	
c-statistic	0.74 (0.73, 0.75)	0.76 (0.73, 0.78)	0.80 (0.78, 0.82)	0.72 (0.70, 0.74)	

Table 5-1: Cause-specific hazards of primary events in the Scottish CVD Policy Model (text)

Parameter	Hazard ratio: mortality post-CHD	Hazard ratio: mortality post-CBVD	Source
Men			
Age at event	1.08 (1.07, 1.09)	1.07 (1.05, 1.09)	SHHEC-SMR Dataset
SIMD	1.14 (1.09, 1.19)	1.09 (1.03, 1.16)	
FH	0.97 (0.79, 1.18)	1.06 (0.77, 1.47)	
c-statistic	0.68 (0.65, 0.71)	0.65 (0.61, 0.69)	
Women			
Age at event	1.08 (1.06, 1.09)	1.07 (1.05, 1.09)	SHHEC-SMR Dataset
SIMD	1.08 (1.03, 1.13)	1.00 (0.93, 1.08)	
FH	0.75 (0.60, 0.95)	1.20 (0.86, 1.67)	
c-statistic	0.67 (0.63, 0.70)	0.66 (0.61, 0.71)	

Table 5-2: Cause-specific hazard of post-CVD mortality in the Scottish CVD Policy Model (text)

Figures 5-4 and 5-5 show that empirical data and simulation output were relatively close for the placebo and treatment arms of the trial. For patients who received placebo, non-fatal CBVD, fatal CVD, and fatal non-CVD events, predicted cumulative incidence generally fell within the confidence interval of observed results. However, the model systematically underpredicted incidence of non-fatal CHD. Results were more promising for the treatment arm of the trial. This suggests that the model is capable of assessing the impact of primary interventions on CVD incidence in the Scottish population. The lack of complete agreement between the model and external data, however, serves as a reminder that the model is not able to perfectly predict outcomes in the Scottish population and that it is necessary to explore uncertainty in any results that the model produces.

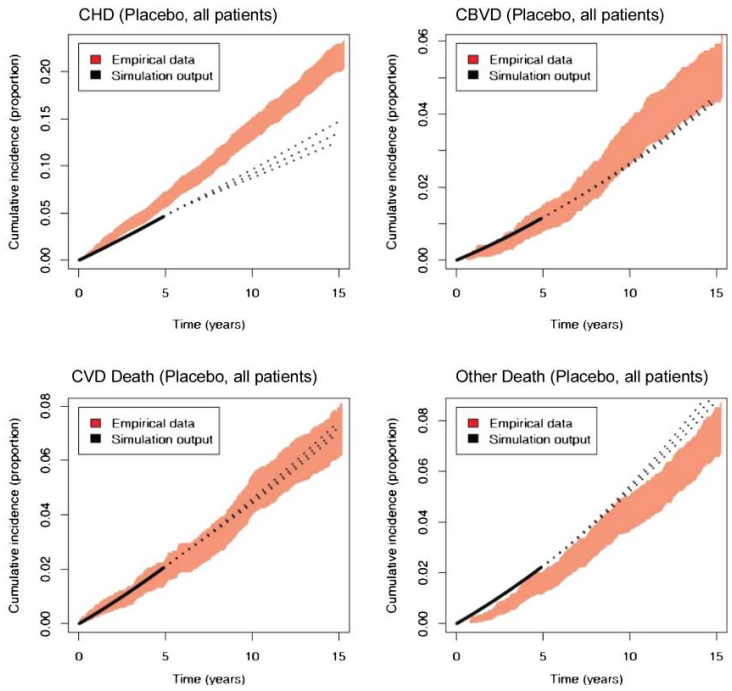


Figure 5-4: Predicted versus observed cumulative incidence of primary events in the placebo arm of the WOSCOPS trial, Lewsey et al. (text)

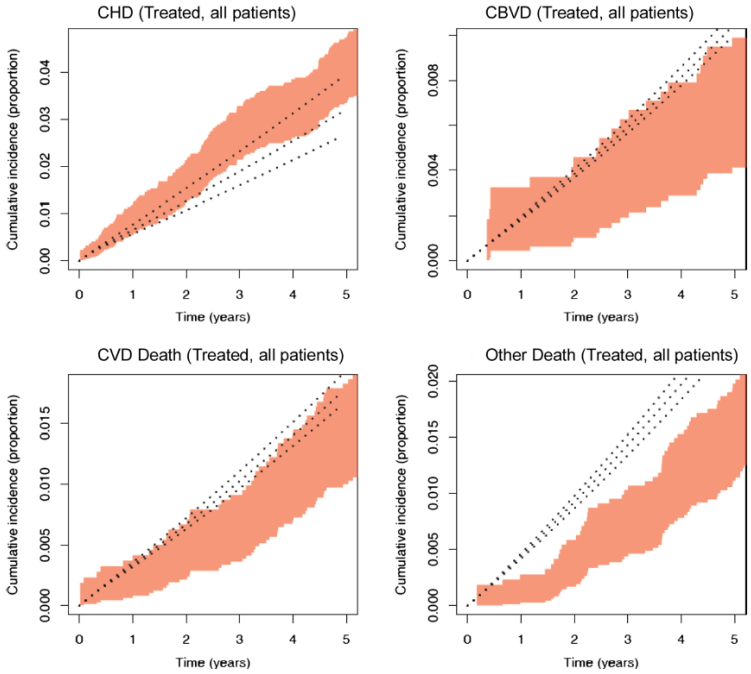


Figure 5-5: Predicted versus observed cumulative incidence of primary events in the treatment arm of the WOSCOPS trial, Lewsey et al. (text)

Recalibration

The Scottish CVD Policy Model was built with data that is becoming increasingly outdated. Event rates for CVD have followed a continuous downwards trajectory in Scotland since the mid-20th century (385). This reduction in event rate has been attributed to changes in biologic, demographic, and sociodemographic risk factors alongside improvements in health technology. This means that risk functions developed with data from the past likely overstate CVD incidence. Recalibration of the risk functions was performed to account for this.

Risk functions in the model were recalibrated in an attempt to replicate contemporary Scottish life tables. Recalibration was achieved by multiplying the linear predictor in the risk functions by a set of multiplicative factors and recording predicted LE for a range of risk profiles. Predicted LE was then compared with 2009 Scottish life tables (386). The multiplicative factor which produced the smallest root mean square error (RMSE) between model-predicted LE and life tables was employed in the model. This process was completed for the male and female models separately. Ultimately, recalibration led the RMSE to be reduced from 1.54 to 0.26 years

for men and from 2.05 to 0.89 years for women (7,309). For the purpose of this thesis, the recalibration process was completed with 2018 Scottish life tables (387).

5.4 CVD Microsimulation Model

Background

Motivated by the need to choose between competing interventions for CVD, Weinstein and colleagues published the CHD Policy Model in 1987 (388). This decision-analytic cohort simulation model was developed to forecast CHD incidence, prevalence, mortality, and cost in the U.S. population.

The original model was developed with FORTRAN software (389) and will hereafter be referred to as the 'FORTRAN model'. The FORTRAN model has been applied in many notable health technology assessments since its inception. It has been used to assess pharmacologic treatments and clinical guidelines in the U.S. (350,390–394), to analyse U.S. population interventions (395,396), and to predict future CVD incidence and prevalence in the U.S. population (397). The model has also been recalibrated and employed in analysis of CVD rates in Mexico, China, and Argentina (398–402).

Several changes have been made to the model over time. Originally developed to study epidemiology and policy related to CHD alone, the model now predicts the health and cost outcomes of interventions related to both CHD and stroke. It is therefore now referred to as the CVD Policy Model. Inputs have also been updated regularly, as has the software platform on which the model runs.

In 2014 the model was redeveloped to perform microsimulations (9). This new iteration of the model was developed using TreeAge software (403). Hereafter this new model will be referred to as the 'TreeAge Model' or the 'CVD Microsim Model'.

Structure

The CVD Microsim Model simulates CHD and stroke incidence and prevalence in the U.S. population aged 35 and greater. It is a microsimulation state-transition model, accepts a profile of CVD risk factors as inputs, and outputs health and cost outcomes for simulated individuals. State transitions are based on a range of data sources and statistical techniques, and the model's primary outputs are life years, QALYs, and healthcare costs.

Figure 5-6 shows the model structure. Individuals may enter a simulation before (State 1) or after (States 2-4) experiencing a primary CVD event. From the well state, they may transition to one of three non-fatal CVD states (CHD, Stroke, or Stroke + CHD), CVD mortality, or non-CVD mortality. After the occurrence of a primary CVD event, individuals transition to one of two absorption states, CVD mortality or non-CVD mortality.

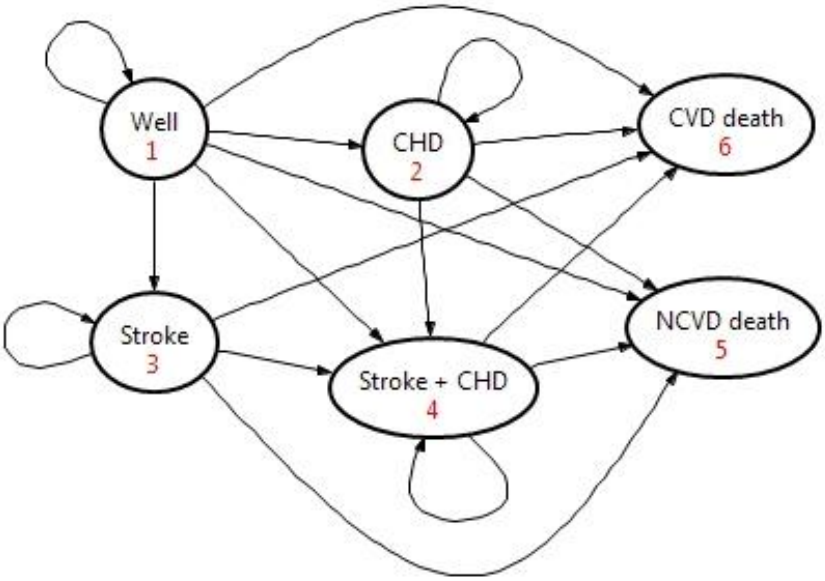


Figure 5-6: Structure of the CVD Microsim Model

Costs and QALYs are estimated according to an individual's pathway through the model. Each health state has an attributed health-related quality of life and cost. Additionally, in-cycle events

and interstate transitions have attributed costs. An individual's costs and QALYs over a pre-specified time horizon are estimated in accordance with costs and QALYs accumulated during their stochastic progression through the model.

An individual's health state is updated annually and rate of transition between states is determined by risk factor profile. Individuals entering chronic health states may experience further events. Following a stroke, for example, it is possible to experience a CHD or further stroke event within a cycle. Such events are explicitly modelled within the health states and determine an individual's cost and health outcomes as well as their disease history. In all years subsequent to an incident CVD event, individuals may experience CHD or stroke. Those who experience both CHD and stroke at any point in their lifetime transition to the Stroke + CHD state at the beginning of the model cycle following the second of these events.

Microsimulation

A large input dataset containing time-varying risk factor information for a group of individuals is required to run the model. This dataset should be representative of the population of interest for the given research question.

For each 'run' of the model, *N* risk profiles are selected from the input dataset. Each profile is inserted into the model and a pathway which an individual with that profile may progress through the model is predicted. Based on the individual's specific 'history' through the model, cost and health outcomes are estimated. After one run, TreeAge provides cumulative outcome information for the *N* microsimulations performed. This information allows cost-effectiveness and other decision-analytic metrics to be calculated for the population.

State Transition Probabilities: Data

The probability of transition between health states is determined using a range of data sources. Primary transitions are estimated with risk functions derived from analysis of a dataset which was constructed by pooling longitudinal data from several U.S. studies (Table 5-3). The

probability of subsequent transition between states was derived from a range of national and subnational health records (Table 5-4).

The dataset that informs primary transition within the model consists of data obtained from the NHLBI Pooled Cohorts Project at Columbia University. Hereafter, this dataset will be referred to as the CU-NHLBI Pooled Cohorts dataset. The six studies included in the CU-NHLBI Pooled Cohorts dataset are the: Atherosclerotic Risk in Communities (ARIC) Study, Cardiovascular Risk Development In young Adults (CARDIA) Study, Cardiovascular Health Study (CHS), Framingham Heart Study Offspring Cohort (FHS-O), Health, Aging, and Body Composition (Health ABC) Study, and the Multi-Ethnic Study of Atherosclerosis (MESA) (404–409). All studies periodically collected information on participants' CVD risk factors, and prospectively detailed incident CVD events.

There were several exclusion criteria for the dataset. Participants were excluded if they had known clinical CVD at baseline or had at no values recorded for BMI, CPD, SBP, DBP, LDL-C and HDL-C, diabetes, and use of lipid-lowering and anti-hypertensive medication. Missing values for BMI, CPD, SBP, DBP, LDL-C and HDL-C were imputed as the average of non-missing values for the participant. For other risk factors including diabetes, hypertension, and use of lipid-lowering and anti-hypertensive medication, missing values were imputed by last value carried forward. The final dataset for the primary risk function analysis comprised of 36,491 individuals from across the U.S., representing 731,241 life years of follow-up.

The source of probabilities which dictate transition out of chronic CVD were taken from national or subnational health records of individuals with chronic CVD. These are included in Table 5-4.

State Transition Probabilities: Analysis

Primary event rates were estimated using analysis by Dr. Yiyi Zhang at Columbia University and replicated similar analysis of the Framingham Heart Study that underpins the FORTRAN model. Primary transition within the model is determined based on logistic risk function which take the following form:

$$rate_{k,i} = \frac{\exp(\alpha + xb)}{1 + \exp(\alpha + xb)}.$$

In this equation, $rate_{k,i}$ denotes the annual probability of disease-free individual i experiencing primary CVD event k. The value α represents the underlying event rate for event k in the CU-NHLBI Pooled Cohorts population (or more specifically the intercept in the null model). The term x is a vector of CVD risk factors. The risk factors included in the base model are: age, SBP, LDL-C and HDL-C, CPD, body mass index (BMI), and diabetes. The term β is a vector of coefficients where each coefficient represents the additive increase in log odds of event k associated with a risk factor in x. Therefore, an individual's primary event risk is increased or decreased compared to the population average in accordance with their risk factor profile. Green and Symons have shown that the regression coefficients of the logistic model approximate to those of a proportional hazards model which has a constant underlying hazard rate (410). The pooled cohorts logistic risk equations are presented in Table 5-3.

Probability of secondary events in the model is not assigned with risk functions. Instead, a proportion of individuals with chronic CVD are assumed to experience further events annually. These secondary events include: recurrent CHD event within a year of a prior CHD occurrence, recurrent CHD event after a year of a prior CHD occurrence, stroke after CHD, CHD after stroke within 10 years, and CHD proceeding stroke after 10 years. Secondary event probabilities were stratified by age and sex and are presented in Table 5-4.

Following occurrence of all CHD and stroke events, a proportion of individuals (stratified by age and sex) are assumed to die within 30 days. These proportions were derived from 30-day case fatality rates from a combination of national and Californian data. The 30-day case fatality rate for CHD events differs between primary and recurrent CHD events. For stroke, 30-day case fatality rates were assumed to be equal for primary and secondary events. Values and sources for event and mortality rates are presented in Table 5-4.

Parameter	Description	Hazard Ratio (95% CI)	Beta Value (95% CI)	Distribution for PSA	Source
Risk function: Incident CHD event					
Age	Years*	1.109 (1.092, 1.127)	0.1036 (0.0880, 0.1193)	Beta	CU-NHLBI Pooled Cohorts Dataset
African American	Binary	0.842 (0.786, 0.901)	-0.1725 (-0.2410, -0.1039)	Beta	
Former smoker	Binary	1.201 (1.132, 1.275)	0.1835 (0.1240, 0.2430)	Beta	
Current Smoker	Binary	1.711 (1.525, 1.919)	0.5368 (0.4218, 0.6519)	Beta	
Cigarettes per day	-	1.006 (1.001, 1.010)	0.0055 (0.0008, 0.0102)	Beta	
Systolic blood pressure	mmHg	1.012 (1.010, 1.013)	0.0115 (0.0100, 0.0129)	Beta	
Diabetes	Binary	1.819 (1.699, 1.947)	0.5982 (0.5302, 0.6663)	Beta	
HDL-C	mg/dL	0.985 (0.983, 0.987)	-0.0151 (-0.0174, -0.0128)	Beta	
LDL-C	mg/dL	1.006 (1.005, 1.007)	0.0060 (0.0052, 0.0067)	Beta	
Age*LDL-C	-	1.000 (1.000, 1.000)	-0.0002 (-0.0002, -0.0001)	Beta	
Risk function: Incident stroke event					
Age	Years	1.147 (1.124, 1.171)	0.1372 (0.1170, 0.1575)	Beta	CU-NHLBI Pooled Cohorts Dataset
African American	Binary	1.539 (1.370, 1.729)	0.4312 (0.3147, 0.5478)	Beta	
Current Smoker	Binary	1.639 (1.376, 1.953)	0.4943 (0.3194, 0.6692)	Beta	
Cigarettes per day	-	1.009 (1.001, 1.017)	0.0089 (0.0010, 0.0167)	Beta	
Systolic blood pressure	mmHg	1.019 (1.017, 1.021)	0.0188 (0.0166, 0.0210)	Beta	
Diabetes	Binary	1.871 (1.680, 2.083)	0.6263 (0.5186, 0.7340)	Beta	
HDL-C	mg/dL	0.996 (0.992, 0.999)	-0.0045 (-0.0075, -0.0014)	Beta	

Parameter	Description	Hazard Ratio (95% CI)	Beta Value (95% CI)	Distribution for PSA	Source
LDL-C	mg/dL	1.002 (1.001, 1.003)	0.0018 (0.0006, 0.0030)	Beta	
Age*AA	-	0.977 (0.969, 0.985)	-0.0231 (-0.0316, -0.0147)	Beta	
Age*Current Smoker	-	0.991 (0.983, 0.999)	-0.0095 (-0.0176, -0.0014)	Beta	
Age*Diabetes	-	0.985 (0.978, 0.992)	-0.0149 (-0.0224, -0.0075)	Beta	
Risk function: Non-CVD mortality					
Age	Years	1.108 (1.100, 1.117)	0.1029 (0.0952, 0.1107)	Beta	CU-NHLBI Pooled Cohorts Dataset
African American	Binary	1.417 (1.326, 1.513)	0.3483 (0.2825, 0.4141)	Beta	
BMI	kg/m^2	0.991 (0.985, 0.996)	-0.0095 (-0.0149, -0.0042)	Beta	
Former smoker	Binary	1.280 (1.213, 1.352)	0.2472 (0.1931, 0.3012)	Beta	
Current Smoker	Binary	1.991 (1.803, 2.199)	0.6886 (0.5895, 0.7878)	Beta	
Cigarettes per day	-	1.019 (1.015, 1.023)	0.0192 (0.0152, 0.0232)	Beta	
Diabetes	Binary	1.526 (1.427, 1.632)	0.4224 (0.3553, 0.4895)	Beta	
Age*AA	-	0.988 (0.983, 0.993)	-0.0121 (-0.0166, -0.0075)	Beta	
Age*Diabetes	-	0.992 (0.987, 0.997)	-0.0080 (-0.0129, -0.0032)	Beta	

*Years centred around age 55

Table 5-3: CU-NHLBI Pooled cohorts logistic risk equations.

Parameter	Base Case Value	Distribution for PSA	Source
Following CHD event (annual probability)			
Recurrent* CHD event within 1 year of previous CHD even			
Men aged 40-44	3.53	Beta	(411–413,413,414)
Men aged 45-54	4.74	Beta	
Men aged 55-64	6.49	Beta	
Men aged 65-74	7.96	Beta	
Men aged 75+	12.8	Beta	
Women aged 40-44	2.26	Beta	
Women aged 45-54	3.96	Beta	
Women aged 55-64	4.98	Beta	
Women aged 65-74	8.29	Beta	
Women aged 75+	13.55	Beta	
Recurrent CHD event after 1 year of previous CHD event			
Men aged 40-44	1.22	Beta	(411–415)
Men aged 45-54	1.60	Beta	
Men aged 55-64	2.23	Beta	
Men aged 65-74	2.79	Beta	
Men aged 75+	4.53	Beta	
Women aged 40-44	0.96	Beta	
Women aged 45-54	1.25	Beta	
Women aged 55-64	1.63	Beta	
Women aged 65-74	2.72	Beta	
Women aged 75+	4.66	Beta	

Parameter	Base Case Value	Distribution for PSA	Source
Stroke after CHD			
Men aged 40-44	0.55	Beta	(416,417)
Men aged 45-54	0.55	Beta	
Men aged 55-64	0.79	Beta	
Men aged 65-74	0.83	Beta	
Men aged 75+	0.92	Beta	
Women aged 40-44	0.55	Beta	
Women aged 45-54	0.55	Beta	
Women aged 55-64	0.77	Beta	
Women aged 65-74	0.87	Beta	
Women aged 75+	0.89	Beta	
Following stroke event (annual probability)			
Recurrent stroke	3.60	Beta	(418)
CHD after stroke	2.50	Beta	(419)
CHD after stroke	2.20	Beta	(420)
30-day case fatality rates			
Incident CHD			
Men aged 40-44	9.37	Beta	(414,421–424)
Men aged 45-54	14.60	Beta	
Men aged 55-64	17.44	Beta	
Men aged 65-74	20.77	Beta	
Men aged 75-85	18.41	Beta	
Men aged 85+	78.18	Beta	

Parameter	Base Case Value	Distribution for PSA	Source
Women aged 40-44	7.08	Beta	
Women aged 45-54	9.83	Beta	
Women aged 55-64	13.16	Beta	
Women aged 65-74	17.97	Beta	
Women aged 75-84	14.97	Beta	
Women aged 85+	81.39	Beta	
Recurrent CHD			
Men aged 40-44	2.24	Beta	
Men aged 45-54	7.84	Beta	
Men aged 55-64	9.89	Beta	
Men aged 65-74	12.96	Beta	
Men aged 75-85	14.60	Beta	
Men aged 85+	27.16	Beta	(414,421–424)
Women aged 40-44	2.22	Beta	
Women aged 45-54	5.44	Beta	
Women aged 55-64	6.65	Beta	
Women aged 65-74	11.48	Beta	
Women aged 75-84	10.95	Beta	
Women aged 85+	75.79	Beta	
Any stroke			
Men aged 40-44	6.23	Beta	
Men aged 45-54	7.55	Beta	(425)
Men aged 55-64	8.95	Beta	

Parameter	Base Case Value	Distribution for PSA	Source
Men aged 65-74	13.88	Beta	
Men aged 75-85	21.20	Beta	
Men aged 85+	37.50	Beta	
Women aged 40-44	13.70	Beta	
Women aged 45-54	7.45	Beta	
Women aged 55-64	10.65	Beta	
Women aged 65-74	11.92	Beta	
Women aged 75-84	23.02	Beta	
Women aged 85+	46.50	Beta	
Other			
Maximum annual number of CVD events per cycle	2	n/a	Assumption

*Recurrent: any event following incident CVD event

Table 5-4: Probabilities for secondary events in CVD Microsim Model

Simulation Cohort

A longitudinal input dataset is required to run microsimulations with the CVD Microsim Model. The data inserted into the model come from the 1999-2014 iterations of the National Health and Nutrition Examination Survey (NHANES) (426). NHANES is a large-scale, nationwide survey of health and nutritional status amongst the non-incarcerated U.S. population. Participants were selected for inclusion in the survey using a complex, multistage probability sampling design. The probability sampling design allowed for oversampling of low-response demographics. Therefore, NHANES' population should adequately reflect the civilian, non-institutionalized U.S. population. De-identified individual-level NHANES data are publicly available.

Data regarding key CVD risk factors were obtained for all NHANES respondents aged 20-85 years. All participants responded to a health-related questionnaire in an interview component of the study. Additionally, height, weight, and blood pressure measurements were obtained by trained professionals for almost all NHANES participants. A subset of respondents was randomly assigned to contribute fasting blood test information.

Individuals were dropped from the dataset if they were below the age of 20 or reported a history of heart failure, angina, heart attack, or stroke. In order to perform microsimulations, complete risk factor information was needed for all individuals. Therefore, a large number of individuals with incomplete risk factor information were dropped from the dataset. Those missing lipid, BMI, and blood plasma glucose level information were censored.

In total, information for 82,091 NHANES individuals was obtained. Of these individuals, 67,269 were excluded, resulting in an input dataset of 14,822 individuals. Reasons for exclusion were: age <20 years (n=38,298), missing LDL-C data (n=25,595), existing CVD (n=1,964), and other missing data (n=1,412). Table 5-5 provides descriptive statistics of the included individuals.

Sampling weights were applied to all individuals who provided blood samples in the NHANES cohort. These weights help determine how demographically representative each individual is of the total U.S. non-incarcerated population. Eligibility for inclusion in a microsimulation is

determined by an individual's NHANES fasting blood weight. This methodology should create cohorts which are representative of the wider U.S. population

Risk Factor	Mean	Std. Dev.	Min	Max
Male (%)	47	50	0	1
Age	47.4	17.6	20	85
Diabetes (%)	12	32	0	1
Cigarettes per Day	2.4	5.6	0	53
SBP (mmHg)	122	12	93	199
DBP (mmHg)	70	6	33	110
LDL-C (mg/dL)	120	23	37	256
LDL-C (mmol/L)	3.09	0.6	0.9	6.6
HDL-C (mg/dL)	54	11	20	110
HDL-C (mmol/L)	1.4	0.3	0.5	2.9
BMI	28.4	5.8	14.2	57.2
ASCVD Risk Score (%)	7.6	11.7	0.0	90.0

Table 5-5: Descriptive statistics for NHANES 1999-2014 data

Sampling weights were applied to all individuals who provided blood samples in the NHANES cohort. These weights help determine how demographically representative each individual is of the total U.S. non-incarcerated population. Eligibility for inclusion in a microsimulation is determined by an individual's NHANES fasting blood weight. This methodology should create cohorts which are representative of the wider U.S. population

Making NHANES 'Longitudinal'

To carry out analysis with the TreeAge model a longitudinal table of input data is required. NHANES, however, is a cross-sectional dataset. Risk factor trajectories were therefore predicted for all individuals in the NHANES dataset.

It would have been possible to assume that included NHANES individuals' modifiable risk factors (lipids, blood pressure, and smoking status) did not change over time. However, such an assumption would likely bias results as it assumes no age-based trends in CVD risk factors. This assumption is unlikely to hold (427–429)

Statistical analysis was performed on the CU-NHLBI Pooled Cohorts dataset to predict individual-level time trends in CVD risk factors. This analysis developed predictive models for time varying CVD risk factors, obtaining best linear unbiased predictors (BLUPs) for time-varying covariates. These models were employed to forwards and backwards predict risk factor values for individuals, centred on their cross-sectional NHANES observations. The NHANES dataset was therefore rendered longitudinal. The methodology employed to make the NHANES dataset longitudinal is discussed in depth by Zhang et al. (427).

Health-Related Quality of Life Inputs

The default perspective adopted in the CVD Microsim Model is that of a health sector decision-maker. The analysis therefore accounts for all health gains in the population, and all direct and indirect medical costs. Details of the value and source of the model's HRQoL inputs are included in Table 5-6.

Quality of life and cost inputs were copied directly from the FORTRAN model's input tables. Each chronic disease health state has an attributed annual QALY penalty and corresponding cost. Every simulated individual accrues an age-specific background (non-CVD) healthcare cost. Additionally, all acute events in the model (e.g., hospitalizations, fatalities) have an associated acute (30-day) cost and QALY penalty. All outcome values are age-differentiated to account for age-based heterogeneity in costs and HRQoL.

The quality of life attributed to different health states in the model were obtained from a combination of data regarding CVD event rates in the U.S. (430,431) and utility weights derived from international analysis of the health-related quality of life associated with a range of disease (432). Treatment-related disutility can also be added to the model.

Parameter	Base Case Value	Distribution for PSA	Source
CHD			
Age 40-44	0.9348	Beta	(430–432)
Age 45-54	0.9374	Beta	
Age 55-64	0.9376	Beta	
Age 65-74	0.9372	Beta	
Age 75-84	0.9364	Beta	
Age 85+	0.9358	Beta	
Stroke			
All ages	0.8835	Beta	(430–432)
Acute (30-day) CHD			
Age 40-44	0.8970	Beta	(430–432)
Age 45-54	0.8862	Beta	
Age 55-64	0.8669	Beta	
Age 65-74	0.8351	Beta	
Age 75-84	0.7946	Beta	
Age 85+	0.6829	Beta	
Acute (30-day) stroke			
All ages	0.8662	Beta	(430–432)

Table 5-6: Chronic and acute utilities employed in CVD Microsimulation Model

Cost Inputs

A range of sources were used to estimate costs within the model. Details of the value and source of the model's cost inputs are included in Table 5-7.

Parameters	Base Case Value	Distribution for PSA	Source
Background health cost (USD 2010)			
Men aged 40-49	2,931	Gamma	(433)
Men aged 50-59	3,852	Gamma	
Men aged 60-69	5,133	Gamma	
Men aged 70-79	7,634	Gamma	
Men aged 80-89	11,552	Gamma	
Men aged 90+	22,145	Gamma	
Women aged 40-49	4,118	Gamma	
Women aged 50-59	5,588	Gamma	
Women aged 60-69	8,040	Gamma	
Women aged 70-79	9,872	Gamma	
Women aged 80-89	14,720	Gamma	
Women aged 90+	25,832	Gamma	
CHD first year (USD 2010)			
Aged 40-69	10,545	Gamma	(433)
Aged 70+	16,115	Gamma	
CHD subsequent years (USD 2010)			
Aged 40-89	2,154	Gamma	(433)
Aged 90+	3,386	Gamma	
Acute (30-day) CHD (USD 2010)			
Men aged 40-49	6,608	Gamma	(434,435)
Men aged 50-59	11,230	Gamma	
Men aged 60-69	16,250	Gamma	
Men aged 70-79	19,171	Gamma	
Men aged 80-89	20,000	Gamma	
Men aged 90+	20,861	Gamma	
Women aged 40-49	5,250	Gamma	
Women aged 50-59	7,050	Gamma	

Parameters	Base Case Value	Distribution for PSA	Source
Women aged 60-69	13,754	Gamma	
Women aged 70-79	17,567	Gamma	
Women aged 80-89	20,622	Gamma	
Women aged 90+	27,411	Gamma	
CHD Mortality (USD 2010)			
Men aged 40-49	51,012	Gamma	
Men aged 50-59	53,643	Gamma	
Men aged 60-69	58,324	Gamma	
Men aged 70-79	51,254	Gamma	
Men aged 80-89	43,277	Gamma	
Men aged 90+	36,923	Gamma	(434,435)
Women aged 40-49	51,334	Gamma	
Women aged 50-59	45,252	Gamma	
Women aged 60-69	54,958	Gamma	
Women aged 70-79	50,798	Gamma	
Women aged 80-89	43,410	Gamma	
Women aged 90+	36,763	Gamma	
Stroke first year (USD 2010)			
All ages	16,317	Gamma	(433)
Stroke subsequent years (USD 2010)			
All ages	4,534	Gamma	(433)
Acute (30-day) stroke (USD 2010)			
Men aged 40-49	20,792	Gamma	
Men aged 50-59	18,063	Gamma	
Men aged 60-69	16,865	Gamma	
Men aged 70-79	14,233	Gamma	
Men aged 80+	15,209	Gamma	(434,434)
Women aged 40-49	20,083	Gamma	
Women aged 50-59	17,353	Gamma	
Women aged 60-69	16,156	Gamma	
Women aged 70-79	13,524	Gamma	
Women aged 80+	14,500	Gamma	
Stroke Mortality (USD 2010)			
Men aged 40-49	25,696	Gamma	(434,435)

Parameters	Base Case Value	Distribution for PSA	Source
Men aged 50-59	23,890	Gamma	
Men aged 60-69	22,820	Gamma	
Men aged 70-79	20,468	Gamma	
Men aged 80+	21,340	Gamma	
Women aged 40-49	25,696	Gamma	
Women aged 50-59	23,256	Gamma	
Women aged 60-69	22,186	Gamma	
Women aged 70-79	19,834	Gamma	
Women aged 80+	20,706	Gamma	
Inflation factor			
$US 2010 to $US 2018	1.25213	n/a	(436)

Table 5-7: Costs employed in CVD Microsimulation Model

Costs for stroke hospitalization, CHD hospitalization, and acute stroke rehabilitation were estimated using Californian hospital data, deflated using cost-to-charge ratios and the ratio of U.S. national-to-Californian average costs (434,435). Outpatient costs incurred by patients with chronic CVD were estimated with pooled 1998-2008 Medical Expenditure Panel Survey (MEPS) data (433). Background costs were also estimated from MEPS. All costs were indexed to 2018 U.S. dollars using the medical component of the U.S. Consumer Price Index (436). All future costs and QALYs values are discounted at a rate of 3% in the model, in line with standard practice guidelines for the U.S. (54).

Discrimination, Calibration, and Recalibration

C-statistics were calculated for all logistic risk functions included in the microsimulation model. These values were 0.84, 0.85, and 0.87 for primary CHD, primary stroke, and non-CVD mortality, respectively. According to Lloyd-Jones, these c-statistic values indicate ‘excellent’ discriminative ability for these risk functions (383).

Validation of cardiovascular event rates in the CVD Microsimulation Model has not been directly undertaken. The model has instead been recalibrated to produce results similar to the extensively validated FORTRAN model. The traditional CVD Policy Model regularly

completes a series of quantitative validation exercises. The first validation exercise involved assessing the model's estimates for U.S.-wide stroke mortality, CHD mortality, and all-cause mortality against U.S. National Data for 2010. These model outcomes were within 1% of estimates from U.S. national vital statistics and the U.S. National Hospital Discharge Survey (NHDS) (392,393).

Figures 5-7 and 5-8 each show two graphs used in the recalibration of the male and female microsimulation models. On the vertical axes are incidence rates of CHD and stroke, respectively, and on the horizontal axes are the age of the simulated cohort. As mentioned previously, both simulations begin with a cohort of 40-year-old individuals. In each figure, the red and blue line represent rates derived from the FORTRAN and TreeAge models, respectively. FORTRAN output for a cohort appears step-wise because predictions are made for 10-year age categories, not by continuous (single-year) age. The black line represents the exponential trend observed in the step function produced by the FORTRAN model. These charts suggest that the TreeAge model is well calibrated, as the red and blue lines do not differ substantially.

Figure 5-9 shows two graphs which demonstrate the performance CVD Policy Model Microsimulation's cumulative mortality rates compared to Centers for Disease Control and Prevention's Wide-ranging ONline Data for Epidemiologic Research (CDC-WONDER) data, shown in red and blue, respectively. The vertical and horizontal axes represent all-cause mortality rate and age of cohort, respectively. By visual inspection, the model was judged to adequately reflect national-level U.S. all-cause mortality data.

5.5 Examples: Epidemiologic Studies Using CVD Policy Models

The following short studies provide examples of the Scottish CVD Policy Model and the CVD Microsimulation model. These models have been developed with the primary aim of performing cost-effectiveness analyses. However, they can be modified and intermediate outcomes (e.g. event rates, life expectancies) can be reported. This enables the models to address questions related to the epidemiologic concepts raised in Chapter 4.

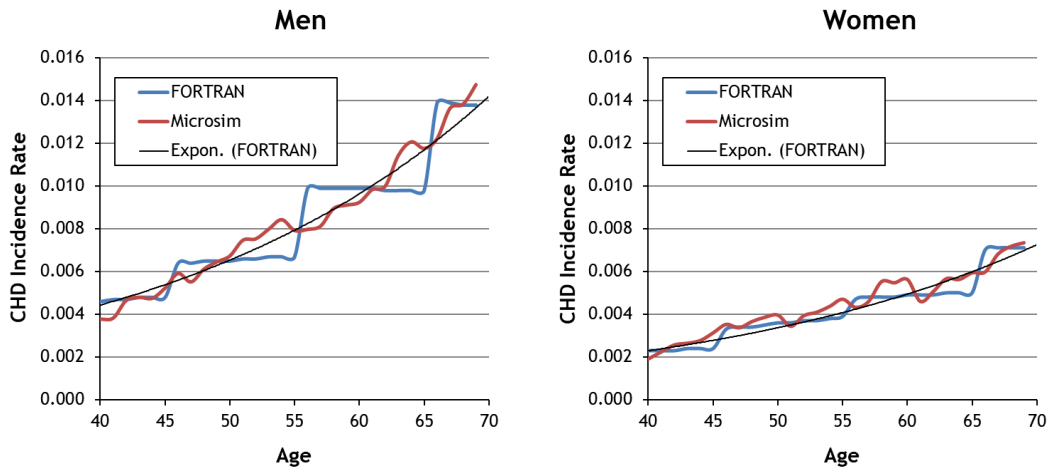


Figure 5-7: CHD incidence rate for men (left) and women (right) according to TreeAge and FORTRAN models

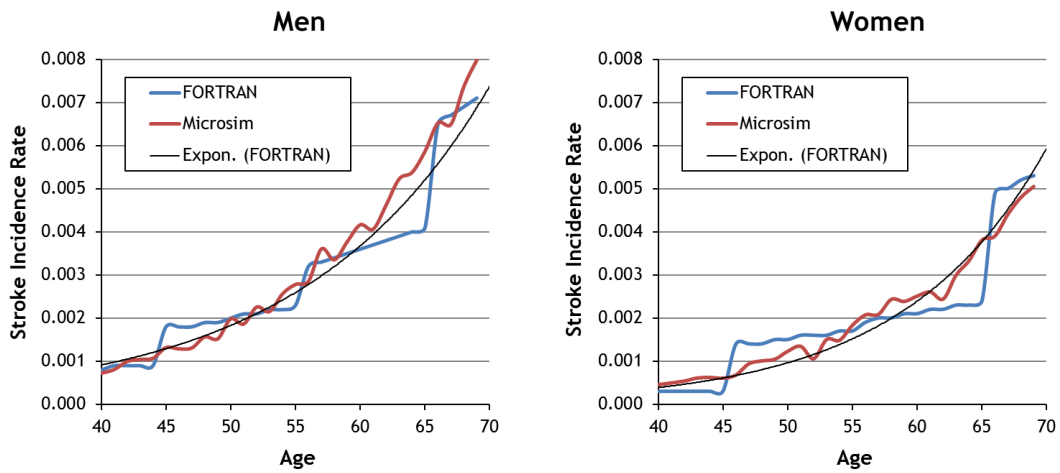


Figure 5-8: Stroke incidence rate for men (left) and women (right) according to TreeAge and FORTRAN models

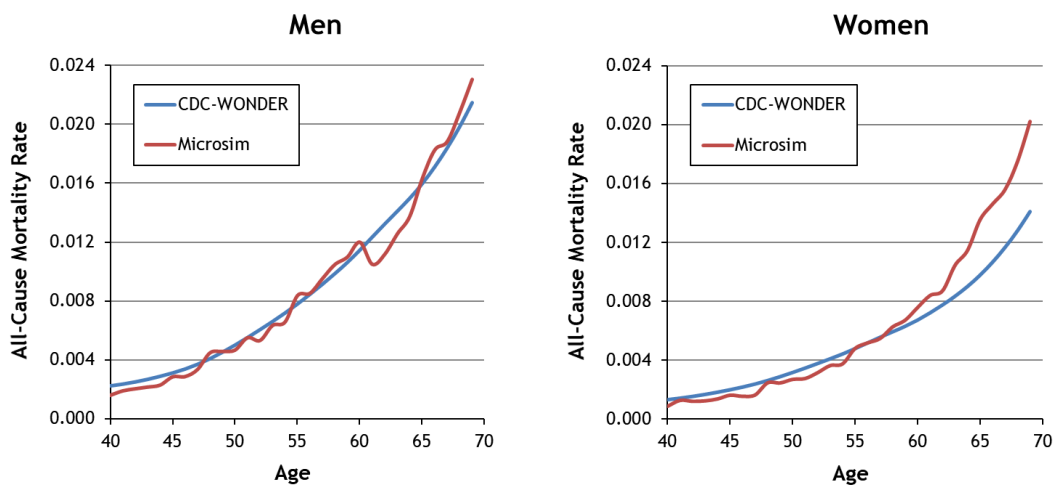


Figure 5-9: All-cause mortality rate for men (left) and women (right) according to TreeAge model and CDC-Wonder data

5.5.1 CVD Microsim Model: Cumulative Exposure to Risk Factors

As discussed in Section 4.5.1, cumulative exposure to CVD risk factors in young adulthood can lead to later life events. This is because atherosclerotic build-up develops over a lengthy period of time.

What follows is a description of two simulation studies which were performed to estimate the benefits associated with reducing cumulative exposure to CVD risk factors in young adulthood. These studies focused on the prevention of CVD in the U.S. using the CVD Microsim Model.

This work utilised risk functions developed by Pletcher et al. (325) which predicted CHD risk based on cumulative exposure to LDL-C and SBP, adjusted for traditional risk factors. Hence, CHD rather than CVD (CHD and stroke) outcomes were the primary outcome of concern.

Background

Hypercholesterolaemia and hypertension are highly prevalent during young adulthood in the U.S. population, but have low levels of awareness, treatment, and control. Based on the 2011-2012 U.S. NHANES, over six million young adults (18-39 years) have hypertension (7.3%) (437). Hypertension awareness (75%), treatment amongst those aware of their condition (50%) and control (40%) are all substantially lower in young adults compared with middle-aged adults (30-49 years) and older adults (≥60 years). Similarly, data from NHANES 2011-14 show that hypercholesterolaemia awareness is low in young adults (57%) (438).

Objective

The objective of this study was to quantify the opportunity cost associated with failing to control hypertension and hypercholesterolaemia in young adulthood. Opportunity cost is quantified in terms of later life CHD events that could have been prevented. The CVD Microsimulation was employed to estimate CHD outcomes.

Population, Intervention, Comparator, Outcome(s), Setting, Study Design (PICOSS)

Two separate analyses were performed: (i) analysis of hypertension control and (ii) analysis of hypercholesterolaemia control, both in young adulthood. The intervention and comparator for these studies did not aim to replicate the effects of a given treatment but rather a hypothetical scenario where elevated risk factors received a moderate level of control.

Population: The population of interest for the first analysis was any U.S. individual with DBP greater than 85 mmHg in young adulthood. The population of interest for the second analysis was any U.S. individual with LDL-C greater than 160 mg/dL (4.1 mmol/L) in young adulthood (aged 20-39).

Intervention: The intervention considered in the first analysis was a 5 mmHg reduction in DBP in young adults with DBP greater than 85 mmHg. The intervention considered in the second analysis was a 50 mg/dL (1.29 mmol/L) reduction in LDL-C in young adults with LDL-C greater than 160 mg/dL (4.14 mmol/L).

Comparator: The comparators for each of the analyses were no treatment and later life control of hypertension and hypercholesterolaemia, respectively. Later life was defined as 40 years of age and above. In the hypertension analysis, later life hypertension control was simulated by a 10 mmHg reduction in SBP. In the hypercholesterolaemia analysis, later life hypercholesterolaemia control was simulated by a 50 mg/dL reduction in LDL-C.

Outcomes: Later life CHD events prevented was the primary measure of outcome. These events were separated into primary and total events. Further reported were lifetime absolute CHD risk reduction, lifetime CHD relative risk, and person years of treatment.

Setting: Primary care in the U.S.

Study Design: Microsimulation.

Methodology

The CVD Microsim Model estimated individual-level CHD outcomes for individuals, dependent on risk factors exposures and accounting for competing risk of stroke or non-CVD mortality.

Cross-sectional CVD risk factor data were obtained from NHANES 1999-2010. The variables obtained were: age, sex, diabetes, LDL-C, HDL-C, smoking, SBP, DBP, BMI. Individuals were dropped from the dataset if they had heart failure or had experienced a CVD event. Forward and backwards trajectories were fitted using predictive equations, so a risk factor value was available for every individual from the ages 20-89.

NHANES data were obtained for 7,435 females and 6,439 males. In this population, 168 (2.3%) females and 619 (9.6%) males had elevated DBP in young adulthood. Additionally, 356 (4.8%) females and 494 (7.7%) males had elevated LDL-C in young adulthood. A cohort of 20,000 males and 20,000 females was produced using the NHANES dataset. This cohort was made representative of the U.S. population by selecting individuals from the original dataset for simulation based upon an NHANES-specific probability sampling weight.

Every individual in the cohort was simulated through the model from ages 20-70. From the age of 20 to 39, a time weighted average of DBP and LDL-C was estimated, and it was assumed that no CVD events would occur before the age of 40.

When this analysis was completed, the CU-NHLBI Pooled Cohorts dataset had not yet been fully cleaned. Risk functions that determine primary transition within the model were therefore taken from the Framingham Offspring Study (404). These risk functions take the same logistic form as the previously-discussed Pooled Cohort risk functions. However, they were updated to account for an individual's cumulative exposure to LDL-C and SBP between the ages of 20 and 39. Risk of first CHD event after age 40 was conditioned on both time-weighted average of early adult (ages 20-39) DBP and elevated DBP or SBP at age 40 and above. These new risk functions were derived from logistic regression analysis of the Framingham Offspring Study performed by Pletcher et al. (325).

The results from the Pletcher analysis are presented in Table 5-8. Increases in time-weighted average DBP (*dbptwa23)* and LDL-C *(ldltwa23)* were significantly associated with risk of CHD in later life.

Before simulation analysis was undertaken, risk functions were recalibrated to ensure that event rates observed in the model's runs were comparable to event rates produced by the FORTRAN CVD Policy Model.

Logistic Regression		Number of obs =	118971
Log pseudolikelihood = -2942.0756		Wald chi2(12) =	708.79
		Prob > chi2 =	0.00000
		Psuedo R2 =	0.1056

Covariate	Odds Ratio	Robust Std. Err.	Z	P>|Z|	[95% Conf. Interval]	
SBP (lvcf)	1.156026	0.063360	2.65	0.008	1.038281	1.287124
LDL-C (lvcf)	1.105461	0.066135	1.68	0.094	0.983151	1.242988
HDL-C (lvcf)	0.756097	0.048637	-4.35	0.000	0.666534	0.857694
LDL-C (twa)	1.428349	0.137747	3.70	0.000	1.182395	1.725574
DBP (twa)	1.253343	0.125270	2.26	0.024	1.030212	1.524803
Male	1.906012	0.227689	5.40	0.000	1.508143	2.408844
Diabetes	1.882810	0.225214	5.29	0.000	1.489324	2.380257
Smoker	2.603872	0.263688	9.45	0.000	2.135111	3.175549
BP Meds	1.906012	0.239475	5.67	0.000	1.565245	2.512759
Lipid Meds	0.814329	0.133595	-1.25	0.211	0.590412	1.123166
Age	1.053910	0.006974	7.93	0.000	1.040329	1.067668
Age^2	0.998715	0.000375	-3.43	0.001	0.997981	0.999450
Constant	0.000031	0.000022	-14.73	0.000	7.83E-06	0.000124

Table 5-8: Cox regression estimating effect of various covariates on risk of primary CHD event, accounting for young adulthood risk factor exposure. *lvcf* – last value carried forward, *twa* – time weighted average value aged 20-39

In the hypertension analysis, CHD outcomes were simulated in cohort of U.S. adults with DBP ≥85 mmHg any time in young adulthood in 3 scenarios: no treatment, later life SBP control alone, or early DBP control plus later life SBP control. In the hypercholesterolaemia analysis,

CHD outcomes were simulated in cohort of U.S. adults with LDL-C ≥160 mg/dL at any time in young adulthood in 3 scenarios: no treatment, later life LDL-C control alone, or early and later life LDL-C control.

Results

In the hypertension analysis, in a cohort of 20,000 males and 20,000 females with elevated DBP during young adulthood, treating DBP early in life led to large reductions in CHD events. Compared to waiting to treat DBP in later life, around 400 primary and 450 total CHD events could be averted by controlling DBP in early adulthood. Treating early life hypertension would result in around 290,000 extra years of treatment in the cohort compared to later life control. Results from the hypertension analysis are presented in Table 5-9. Absolute CHD risk reduction was 1.58% in the group treated in both early and later adulthood, and 0.92% in the group with later life treatment alone. Relative risk in those who received early adulthood treatment was 0.93, compared to 0.95 in the comparator arm.

In the hypercholesterolaemia analysis, early plus later adulthood treatment prevented approximately 1,900 and 2,800 additional primary and total CHD events in the cohort compared with later life treatment alone, respectively. More than 400,000 additional patient years of treatment would be required to achieve these benefits. Results from the hypercholesterolaemia analysis are presented in Table 5-10. Absolute CHD risk reduction was 11.85% in the group treated in both early and later adulthood, and 7.19% in the group with later life treatment alone. Relative risk in those who received early adulthood treatment was 0.65, compared to 0.78 for those who received later adulthood treatment alone.

Discussion and Limitations

This study showed that existing CVD policy models can be adapted to answer novel research questions. By altering the risk functions within this model and recalibrating these functions to contemporary event rates, it was possible to predict the benefits associated with early life intervention on modifiable risk factors.

This study highlights the benefit of early preventive intervention for CHD. In terms of preventable CHD events, there is a large opportunity cost associated with waiting to commence preventive blood pressure- and LDL-C-lowering treatment. The effect of intervening from age 20 onwards was investigated. While this may not be considered a viable, clinically feasible treatment strategy, the results presented suggest any reduction in the age at which treatment commences may improve health outcomes for individuals. Age-stratified risk thresholds for treatment initiation may help address this issue.

Monetary costs are notably missing from this analysis. The cost of treating and monitoring an individual from young adulthood until death may be large. Moreover, the cost of screening all young adults for elevated DBP and LDL-C is likely to be substantial. Further research should include a full health economic evaluation of the proposed intervention.

5.5.2 Scottish CVD Policy Model: Predicting Treatment-Related Health Outcomes

It is possible to predict the benefits associated with different treatment strategies using decision-analytic models. Moreover, the differential benefits associated with patient subgroups can be estimated. This can help guide research into which groups of patients should receive a treatment, and highlight issues with existing clinical practice.

Background

Lewsey et al. previously employed the Scottish CVD Policy Model to estimate life expectancy (LE) for a range of individuals in the Scottish population (7). Adapting their results, Figure 5-10 was developed to assess the benefit of preventive intervention in individuals with differing risk factor profiles. As with the risk charts presented in Chapter 4, each cell represents a distinct combination of risk factors. Diabetes and FH values were set to the SHHEC average.

The number within each box in Figure 5-10 represents the increase in quality-adjusted life years, discounted 3.5% annually, that an individual with this risk factor profile would experience if their SBP and TC to HDL-C ratio were reduced to 100 mmHg and 3, respectively. The boxes

Treatment Scenario *cohort of 20,000 men 20,00 women with DBP ≥85 mmHg between ages 20-39*	CHD Events Prevented		CHD Absolute Risk Reduction	CHD Relative Risk	Person Years of Treatment
	Primary	Total			
No treatment	0	0	0	1	0
Treat ≥ 40 years old Age 20-39: if DBP ≥85, no treatment Age ≥ 40: if SBP ≥140 or DBP≥ 90, treat BP <140/90	246	476	0.92%	0.95	525,000
Treat ≥ 20 years old Age 20-39: if DBP ≥85, treat to DBP <85 Age ≥ 40: if SBP ≥140 or DBP≥ 90, treat BP <140/90	630	926	1.58%	0.93	815,000

Table 5-9: CHD outcomes associated with different blood pressure control scenarios in a cohort of hypertensive young adults. All comparisons are with no treatment.

Treatment Scenario *cohort of 20,000 men 20,00 women with LDL-C ≥160 mmol/L between ages 20-39*	CHD Events Prevented		CHD Absolute Risk Reduction	CHD Relative Risk	Person Years of Treatment
	Primary	Total			
No treatment	0	0	0	1	0
Treat ≥ 40 years old Age 20-39: if DBP ≥85, no treatment Age ≥ 40: if SBP ≥140 or DBP≥ 90, treat BP <140/90	2,850	3,940	7.19%	0.78	944,000
Treat ≥ 20 years old Age 20-39: if DBP ≥85, treat to DBP <85 Age ≥ 40: if SBP ≥140 or DBP≥ 90, treat BP <140/90	4,740	6,770	11.85%	0.65	1,355,000

Table 5-10: CHD outcomes associated with different LDL cholesterol control scenarios in a cohort of hypercholesterolaemic young adults. All comparisons are with no treatment.

are colour-coded based on life years gained. Red represents life year gains less than 1 year, orange represents gains between 1-2 years, and green represents gains greater than 2 years. Results for women followed a similar pattern.

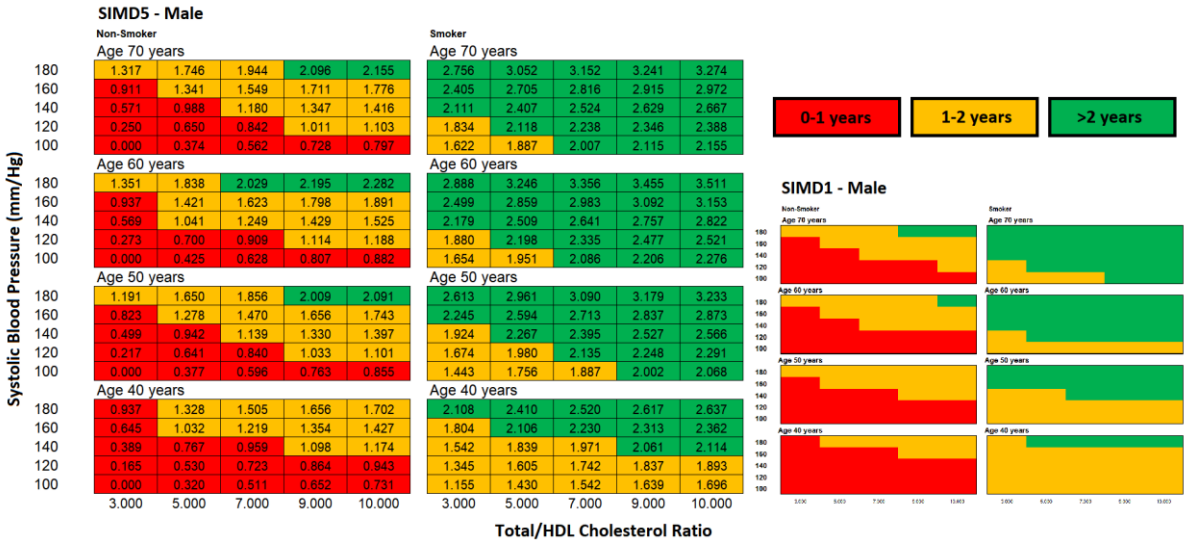


Figure 5-10: Discounted QALY gains from reducing SBP, TC:HDL-C ratio, and smoking in men in the least and most deprived SIMD quintiles, adapted from Lewsey et al. (text)

Figure 5-10 suggests that primary prevention is more effective at increasing QALE in individuals with unhealthy levels of modifiable risk factors like SBP, cholesterol, and cigarettes smoked per day. Conversely, ‘high-risk’ individuals whose risk is driven by a non-modifiable risk factor like age gain less from treatment. These results support the implementation of age-stratified risk threshold approach to prevention, as this would target treatment at individuals with unhealthy modifiable risk factor values within their age-group.

The analysis described predicts health gains associated with multifactorial interventions that return modifiable risk factors to healthy levels. In clinical practice no silver bullet treatment exists which will return every patient’s risk factors to the healthy levels assumed in the figures. Patterns in health gains associated with individual preventive policies may be different.

Objective

The objective of this analysis was to quantify the effect of a cholesterol-reducing intervention on discounted QALE for individuals with a range of CVD risk factor profiles.

PICOSS

Population: The population of interest was men living in Scotland aged 40, 50, 60, and 70 years with no established CVD. The effect of the intervention on individuals with a range of different CVD risk factors was assessed.

Intervention: The intervention considered was a 32% reduction in TC. This represents an upper estimate of the expected reduction in LDL-C achievable with intermediate-intensity statin therapy. No pill-taking decrement to quality of life and no treatment-related side effects (e.g. increase in risk of diabetes) were applied.

Comparator: The comparator for this analysis was no treatment.

Outcome: The outcome recorded was increase in discounted QALE attributable to the intervention.

Setting: Primary care in the Scottish NHS.

Study Design: Cohort simulation.

Methodology

Risk factors were inputted into the male version of the Scottish CVD Policy Model to estimate intervention-related benefits associated with LDL-C-reduction for individuals with a range of risk factor profiles.

Risk factor profiles were developed which varied by age (40, 50, 60, and 70), SBP (100, 120, 140, 160, and 180 mmHg), TC:HDL-C (4.5:1.5, 6.0:1.2, 6.3:0.9, 6.8:0.8, and 7.0:0.7 mmol/L),

SIMD (4.085 and 60.775), and cigarettes per day (0 and 20). Individual's diabetes and FH values were set to 1.49% and 26.3%, respectively, the average values in the SHHEC population. Given the range of dimensions considered, n=4*5*5*2*2=400 profiles were simulated. Discounted QALE was recorded for each profile. This value will be referred to as the 'baseline QALE' associated with each risk factor profile.

Next, each of the 400 profiles was re-simulated. However, in this simulation, TC was reduced by 32% at baseline. Again, discounted QALE was recorded for each individual. This value will be referred to as the 'treated QALE' associated with each risk factor profile. Finally, the difference between baseline and treated QALE was estimated for each risk factor. This was presented graphically, in a manner that would facilitate comparison with Figure 5-10.

<u>Results</u>

Cholesterol treatment was simulated for a range of male Scottish risk profiles. Figure 5-11 estimates discounted QALY gains attributable to a 32% TC reduction for a number of risk factor profiles. The gains are colour-coded whereby blue, red, orange, and green cells represent 0-0.15, 0.15-0.3, 0.3-0.45, and >0.45 discounted QALY gains, respectively.

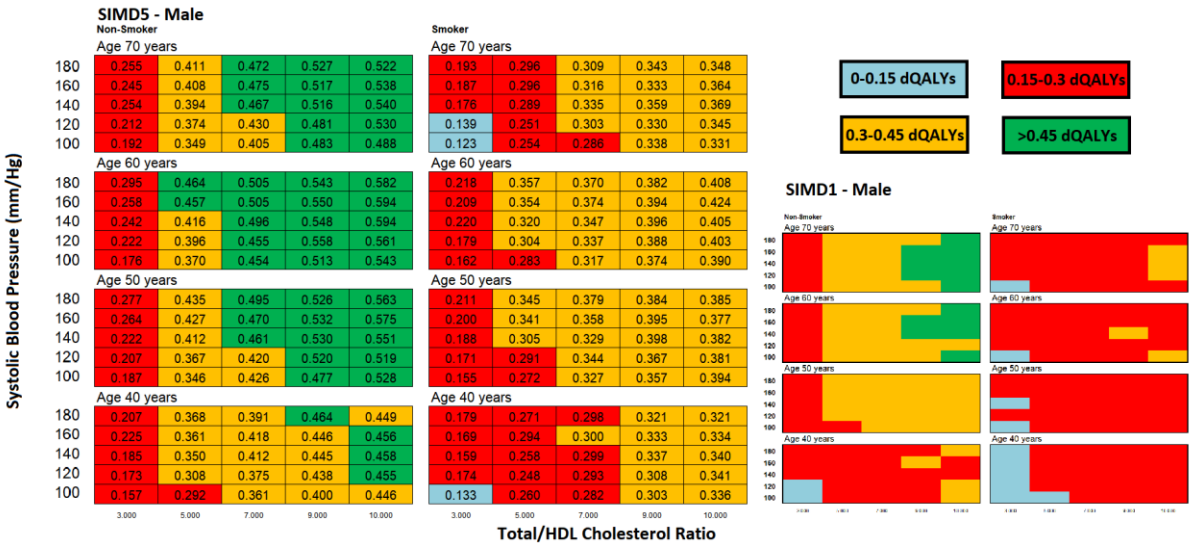


Figure 5-11: Discounted QALY gains from reducing TC by 32% in men in the least and most deprived SIMD quintiles

Discussion and Limitations

This study paints a more nuanced picture of capacity-to-benefit than the results presented in Figure 5-10. A more realistic simulation of univariate preventive intervention showed that it is difficult to define a function that maps 10-year risk to capacity-to-benefit from statin therapy.

Some relationships do emerge in Figure 5-11. Individuals with high levels of cholesterol achieve the most benefit from cholesterol reduction. However, unlike in Figure 5-10, non-smokers gain many more QALYs than smokers. Capacity-to-benefit is also highest in 50 and 60 year olds, suggesting a non-linear age-based trend. A corollary to these observations is that, even within age-groups, risk is not a singular predictor of capacity-to-benefit. The specific factors that drive risk matter.

The reason that 10-year risk is a poor predictor of capacity-to-benefit can be explained by a multiplicity of factors. Competing risks are an important consideration. Age, SBP, and smoking are strong predictors of non-CVD mortality. These factors increase CVD risk but also increase risk of a censoring event which may negate the need for CVD prevention. Optimal treatment strategies for patients depends on their individual profile of risk factors, not just the combinatory measure of 10-year risk.

Risk driven by modifiable risk factors may require alternative treatments alongside or in place of statin therapy. When an individual's risk is driven by smoking, a primary stage in prevention should be to address this risk factor. Reducing cigarettes smoked per day will reduce both the individual's risk of CVD and their risk of non-CVD mortality. Indeed, this analysis suggests that reducing smoking will likely improve their capacity-to-benefit from cholesterol reduction.

Shared decision-making (439) is an important tool for individuals with risk driven by non-modifiable risk factors. When an individual's risk is driven by age, alternative treatment options are limited. In this case, a physician and patient must discuss the potential benefits of treatment alongside the reality of the individual's life expectancy.

Ultimately, the only way to account for the multiplicity of factors that determine an individual's capacity-to-benefit from treatment is to directly employ decision-analytic models in the decision-making process. Such a policy is assessed in Chapter 9.

This study is limited by the simplicity of the intervention that was modelled and lack of sensitivity analysis. The study explicitly aimed to represent capacity-to-benefit from cholesterol-reducing treatment. Studies have shown a variety of small but significant side effects and disutilities associated with cholesterol-reducing treatments (36,440,441). This likely means the predicted QALY gains are overstated. The study also employs a combinatory index to capture the effect of TC and HDL-C on CVD risk. It would be clinically more useful to consider these risk factors separately. Finally, traditional and probabilistic sensitivity analysis were not completed. While the study quantifies variability in outcome related to patient characteristics, it does not reflect uncertainty related to model or treatment parameters.

5.6 Chapter Summary

This chapter has provided an introduction to policy models. Additionally, it has introduced, two existing CVD policy models which will be used throughout the remainder of this thesis to assess preventive interventions for cardiovascular disease. It was shown that these models can be updated with external data and can output intermediate outcomes to help answer questions regarding the benefits associated with preventive intervention.

The specific type of preventive intervention that will be modelled in later chapters are cholesterol-reducing medications. These are treated as a cornerstone of CVD prevention strategies in high-income countries. The principle cholesterol-reducing treatment that will be considered is statin therapy. The proceeding chapter will establish the validity of statins as an efficacious and safe preventive medicine. This will enable the thesis to proceed with cost-effectiveness analyses of statin prioritisation policies which aim to address heterogeneity in cost-effectiveness of the treatment.

Chapter 6
Statins

6.1 Purpose

Many of the cost-effectiveness analyses in the remainder of this thesis will focus on statins and their role in the primary prevention of CVD. Although widely prescribed in high-income countries, statins are a controversial treatment. It is therefore important to justify their use in clinical practice. It is particularly important to prove that statins are safe, effective, and maintain efficacy in low- and intermediate-risk populations. This chapter will explore the validity of such assumptions.

6.2 Efficacy of Statins in Low- and Intermediate-Risk Populations

Evidence in Favour

The efficacy of statin therapy for the primary prevention of CVD has been established in low- and intermediate-risk populations. In a 2011 meta-analysis, Tonelli et al. considered the efficacy of statin therapy in CVD-free intermediate-risk patients (442). Intermediate risk was defined as 10-year risk less than 20% and was estimated by extrapolating CVD event rates in the control arm of analysed trials. It was found that in intermediate-risk populations, statins reduced risk of all-cause mortality (relative risk [RR] 0.90, 95% confidence interval [CI] 0.84-0.97), non-fatal myocardial infarction (RR 0.64, 95% CI 0.49-0.84), and non-fatal stroke (RR 0.81, 95% CI 0.68-0.96). Similar results were reported by Navarese et al. in 2018 (339).

The Cholesterol Treatment Trialists' (CTT) collaborators also performed a meta-analysis of statin efficacy in low- and intermediate- risk populations (251). They considered the efficacy of statin therapy in five categories of 5-year major vascular risk: <5%, 5-10%, 10-20%, 20-30%, and >30%). Relative risk of major vascular event per 1.0 mmol/L LDL-C reduction was found to be consistent across risk groups, ranging from a relative risk of 0.62 (95% CI 0.47-0.81) to 0.79 (95% CI 0.74-0.84) in the lowest and highest risk groups, respectively. Individuals in the

lowest two risk categories also experienced clinically and statistically significant reductions in major coronary events and stroke.

Criticisms

There is some controversy surrounding the evidence in favour of statin efficacy. Abramson et al. critique the analyses mentioned in the two preceding paragraphs (250). They argue that there is no hard evidence that statins reduce all-cause mortality in low-risk individuals, the endpoints used to describe CVD in studies of statin efficacy are too broad, and that side effects have been understated. Furthermore, they point out that low-risk individuals achieve a small 10-year absolute risk reduction from statin therapy and therefore a greater number of individuals must be treated to prevent one adverse event in a low-risk population.

Other academics have expressed concern about the statistical methodology commonly applied to quantify statin benefits. Redberg and Katz (443) and Diamond and Ravnskov (444) argue that absolute rather than relative risk should be the measure employed to quantify benefit. Relative risk (RR) is equal to the ratio of event incidence in the treatment and control groups of a trial. Absolute risk reduction (ARR) is the absolute change in risk between arms. The number needed to treat to prevent an event in a population (NNT) is the inverse of ARR. Some argue that ARR better reflects a patient's capacity-to-benefit from preventive treatment as it highlights the fact that many people will gain nothing from treatment.

6.3 Safety of Statin Therapy

Evidence in Favour

Several side effects are commonly associated with statin therapy. These include: increased risk of diabetes, muscle pain (myalgia), muscle weakness (myopathy), cognitive dysfunction, and renal disorder. The evidence concerning such side effects overwhelmingly suggests that the benefits of the treatment outweigh the disadvantages.

Many randomised clinical trials have been completed to assess the safety and efficacy of statin therapy. Reimold et al. highlight that more than 170,000 people who take statins have been

studied with considerable follow-up, and posit that "statins have been studied more than nearly any other drug that people take" (445).

Meta-analyses largely confirm the safety profile of statin therapy. Finegold et al. considered the safety profile of statins in a 2014 meta-analysis which included data from 46,262 patients receiving statins for the primary prevention of CVD (446). Their study found that statins slightly increase an individual's risk of two adverse events: new diabetes diagnosis (absolute risk increase [ARI] 0.5%, 95% CI 0.1%-1.0%) and elevated enzyme levels which may lead to liver damage (ARI 0.4%, 95% CI 0.2%-0.6%). The study rejected the hypothesis that statins increase likelihood of myalgia (p-value 0.407), myopathy (p-value 0.905), renal disorder (p-value 0.092), and ten other commonly attributed side effects. Taylor et al. (447) found no evidence of serious harm caused by statin treatment.

Meta-analyses have also shown that statins have no deleterious effect on cognition. While the Finegold et al. study did not focus extensively on cognitive dysfunction, a separate meta-analysis by Swiger et al. examined the short- and long-term cognitive effects of statins in patients with no baseline cognitive dysfunction (448). This study rejected the hypothesis that statins affect short-term cognition (p-value 0.050). Moreover, analysis of long-term data found that statins may play a statistically and clinically significant role in reducing incident dementia (hazard ratio 0.71, 95% CI 0.61-0.82).

The link between statins and incident diabetes has been analysed in a meta-analysis of randomised controlled endpoint trials. Sattar et al. (440) found that statin therapy is associated with a statistically significant increase in incident diabetes (odds ratio 1.09; 95% CI 1.02–1.17). The authors of this study concluded that the increased risk of diabetes attributable to statins is offset by the treatment's benefits. This sentiment has been echoed by the ACC and AHA, the U.S. Preventive Services Task Force, the Royal College of General Practitioners in the U.K., the British Heart Foundation, and a wide range of clinical experts (349,449–452).

Criticism

Despite strong clinical trial evidence for their safety, statins remain a subject of considerable controversy. Dr. Ben Goldacre was co-author of a previously cited meta-analysis on statin safety

(446) but urges caution on its findings. He argues that the methodology used in this trial is correct but the analysed data were flawed (453). He states that public reporting of side effects in clinical trials is very poor.

Goldacre cites a study from Germany's cost-effectiveness agency, the Institute for Quality and Efficiency in Health Care (IQWiG) to support his claim of flawed data (454). Researchers at IQWiG obtained access to unpublished clinical study reports (CSRs) for a range of different treatments. These are documents produced by pharmaceutical companies which extensively detail the methodology and outcomes of clinical trials. CSRs are generally not made public though are provided to regulatory agencies like the FDA in the U.S. and the EMA in the E.U. The IQWiG study revealed that CSRs provided complete information on 84% of benefits and 87% of harms, while publicly available data only provided complete information on 35% of benefits and 43% of harms. A further 18% of benefits and 8% of harms were found to be 'reported partly' in the publicly available data.

Other researchers have questioned the reliability of evidence regarding statin safety. Yebyo et al. question whether the benefits of statins outweigh their harms over a 10-year time period, finding probability of net benefit is low when 10-year risk is low (455). In a cross-sectional analysis of 1999-2002 NHANES data, Buettner et al. (456) found that taking statins significantly increased risk of musculoskeletal pain. Abramson et al. argue that meta-analyses underestimate the risk of diabetes associated with statin therapy, noting that the increase in diabetes incidence observed in women taking statins in the JUPITER trial was more than five times the increase predicted by a 2012 CTT meta-analysis (250). Redberg and Katz (443) also discuss underreporting and misreporting of side effects in clinical trials, arguing that anecdotal evidence and results of a small clinical trial (457,458) suggest that statins may cause cognitive impairment. Including data from primary prevention trials, a preference study, and selected observational studies.

6.4 Response to Criticism of Statin Safety and Efficacy

It is important to ensure that statins are safe and efficacious in the patients for whom they are recommended. Placebo-controlled randomised clinical trials represent the gold standard for establishing these factors for a treatment. Meta-analyses of these trials suggest that statins are

safe and efficacious. Decision modelling techniques allow researchers to account for uncertainty inherent in these findings when assessing the cost-effectiveness of statins.

Efficacy

The benefits of statins are well-established. Greenhalgh provides a hierarchy for the reliability, validity, and generalisability of data (72). In descending order, this hierarchy consists of: systematic reviews and meta-analyses of randomised controlled trials, randomised controlled trials with definitive results, randomised controlled trials with non-definitive results, cohort studies, case-control studies, cross-sectional surveys, and case reports. Evidence from the multiple meta-analyses described above firmly suggests that statins are efficacious and safe in low- and intermediate-risk individuals.

Common criticisms of evidence regarding statin efficacy are: statins do not show improvement in all-cause mortality and relative risk overstates the benefits of statin therapy. With regards to all-cause mortality, it is true that a meta-analysis of relevant trials studies failed to show a statistically significant reduction in all-cause mortality attributable to statin therapy in CVD-free individuals (459). The results from this study, however, also show a strong relative risk for all-cause mortality which is marginally insignificant. Given existing debate regarding statistical significance (460–462), and the fact that average follow-up for individuals in this meta-analysis was 3.74 years, it is not surprising that it was difficult to establish a statistically significant relationship between the treatment and mortality - a rare event in CVD-free individuals. In addition, two separate contemporary analyses have shown a statistically significant effect of statins on all-cause mortality (251,442).

A further consideration must be made explicit: even if statins do not reduce all-cause mortality, they have been shown to reduce cardiovascular events. Such events are extremely debilitating and it is of societal interest to reduce rates of CVD.

The use of relative as opposed to absolute risk reduction in measuring statin efficacy must be considered. Redberg and Katz (443) and Diamond and Ravnskov (444) argue that the latter gives patients a better concept of their potential to benefit from treatment. Both articles note that statins have a high 10-year NNT to prevent one event for low-risk individuals. However, CVD

rates have dropped greatly in recent decades. Intuitively, as baseline event risk falls in a population, the NNT to prevent one event increases. As with all preventive interventions, the benefits accrued through treatment should be weighed against the costs of providing treatment to many people. Cost-effectiveness analysis explicitly undertakes such calculus.

Safety

Criticism regarding statin safety should be considered. Goldacre highlights the issue of trial reporting, while Abramson et al. and Redberg and Katz, and others question the interpretation and results of randomised clinical trials (250,443,453). Ultimately, statins are a widely studied treatment and their safety profile and benefit-harm ratio are well-established (463).

Goldacre's criticism of existing evidence for statin safety largely centres on clinical trial reporting. The IQWiG study cited (454) certainly provides evidence that the benefits and harms of pharmacological treatments are underreported in publicly-available resources. However, interpretation of this study could be more nuanced. The primary outcome measure employed in the study is completeness of outcome reporting. For a given treatment, some outcomes are less important than others and it is conceivable that publicly available resources deliberately document those outcomes considered to be clinically important. A larger proportion of studies were found to have incomplete reporting of benefits than harms. This suggests that selective reporting was employed, at least partly, to provide a concise summation of treatment outcomes rather than to conceal useful information. Furthermore, CSRs are made available to regulatory bodies. It is therefore likely that any serious adverse outcomes would be highlighted in approval documentation.

Abramson et al. (250) argue that the rate of statin-related myopathy experienced by individuals in clinical practice is much larger than the rate observed in clinical trials. The cite a cross-sectional study that shows statistically significant increase in 'musculoskeletal pain' experienced by individuals on statins (456). This study has some methodological limitations. Due to its cross-sectional nature, the study cannot account for the fact that patients can switch statins when they encounter side effects. Indeed, it has been shown that most patients who experience side effects can continue on the therapy without issue if they switch statin or dosage (464).

Both Abramson et al. (250) and Redberg and Katz (443) compare meta-analysis results to results from individual studies. With regards to diabetes risk, the former highlight that relative risk for development of diabetes was much greater for CVD-free women than the central estimate for increased diabetes risk produced by meta-analyses. This argument indeed highlights the need for better reflection of heterogeneity in treatment side effects in the literature. However, a post-hoc analysis of an individual trial provides much less reliable information than a meta-analysis. This is especially true for outcomes which have a very low prevalence like statin-induced diabetes. Redberg and Katz cite anecdotal evidence and one small trial which found statin-related side effects to be much greater than those observed in clinical trials. These sources provide useful information. However, meta-analyses provide much more reliable data than individual clinical trials, narrative reviews, or anecdotal evidence.

The Role of Decision-Analytic Modelling

The decision modelling process explicitly accounts for many of the issues raised by researchers who question evidence regarding statin safety and efficacy. Many researchers who are opposed to the expansion of statin eligibility for primary prevention argue that both the benefits and harms of statins must be considered. Of course, this is true. Decision-analytic modelling is a statistical methodology that was developed to perform such analysis.

Goldacre states that statins, and other preventive interventions, need "perfect information" because their benefits and disadvantages are often closely balanced (465). Perfect information will never be available for any treatment. However, it is important to consider the effect that modelling assumptions and the inherent uncertainty in their estimation have on health and cost outcomes. Traditional and probabilistic sensitivity analysis can be employed to do this.

6.5 Consequence of Statin Criticism in the Media

Despite the strong evidence in favour of the safety and efficacy of statins, they continue to be one of the most controversial treatments available to a widespread population. Some of this controversy is expressed in the clinical literature, as presented in Sections 6.2 and 6.3. Criticism

of statin policy is regularly presented in much less academically rigorous outlets including newspapers, websites, magazines, and television programmes (466).

It is possible that statins induce the nocebo effect, a phenomenon that occurs when patients anticipate side effects from a treatment. This anticipation manifests itself with the patient believing that they have experienced the expected side effect. Several researchers have attributed statin-induced muscle pains and other side effects to the nocebo effect (467–469). Indeed, a recent study found excess rates of adverse events in a trial of statin efficacy when patients and physicians were aware that statin therapy, and not placebo, was being administered (470). The authors suggested that this proved many of the side effects experienced by patients may not be causally linked to statins themselves, but rather to patient and physician perception of the treatment's side effect profile.

Additional consequences have been associated with continued adverse media coverage of statins. The ACC notes the strong relationship between adverse media coverage of statins and reduction in statin guideline uptake and adherence (471). Matthews et al. (472) performed an interrupted time series analysis of statin initiation and continuation. They analysed data collected in routine clinical practice in the U.K. to quantify the effect of an intense period of media criticism of the treatment on statin-taking behaviour. For the primary prevention population, they found no statistical difference in rates of statin initiation after such periods (odds ratio [OR] 0.99, 95% CI 0.87-1.13). However, they did find a significant proportion of those already taking statins stopped the treatment during these periods (OR 1.11, 95% CI 1.05-1.18). Intense media scrutiny of statin safety and efficacy, they conclude, could lead to an extra 2,000 CVD events in the U.K. over 10 years. Studies in Australia, Denmark, France, Turkey, and the Netherlands have also found a direct relationship between negative media attention and statin discontinuation (466,473–476).

6.6 Imperfect Evidence, Manufacturer Incentives, and Statins

Perfect evidence for the safety and efficacy of statin therapy will never exist. Researchers and decision-makers will always face data limitations. Given this reality and the low likelihood of further largescale statin trials, Goldacre is correct to argue that all available evidence regarding

statins should be made publicly available. Nonetheless, there is currently no great incentive for pharmaceutical companies to withhold information regarding statin safety and efficacy.

As a proponent of increased transparency in clinical trials, Goldacre founded the AllTrials campaign. The aim of AllTrials is to register all clinical trials, and subsequently report on the methodology and results of these trials. An intermediate step towards achieving this is the publication of each study's CSR. It is true that a large amount of medical research is unpublished. This was noted in the IQWIG study of CSRs versus publicly available resources (454). Pharmaceutical companies have a clear incentive to avoid publication of negative findings, even if doing so is detrimental to patient and population health. They may wish to suppress data on a treatment with regulatory approval but spurious efficacy, as demonstrated by Lee et al. (477). In addition, they may wish to avoid publishing negative results from trials of treatments discarded early in the development cycle (478).

Underreporting of trials may occur due to the nature of academic medicine. Journals are more likely to publish articles which show a clear effect of a treatment. Due to this publication bias, studies which show no statistical benefit or harm are largely underreported (479). Studies which show the largest effect size are over-reported and this may lead to bias in their favour.

An additional concern is that, without pre-specification of study methodology, pharmaceutical companies can benefit from the principle of multiple testing and undertake post-hoc analysis which favours their intervention. The incentive for pharmaceutical companies to apply a methodology which overstates the benefits or understates the harms of their intervention is clear. Constraints on publication, discussion, and analysis of data are common for researchers undertaking industry-funded clinical trials (480). Goldacre is correct to challenge the pharmaceutical industry and the way in which it withholds clinical trial data from researchers and decision-makers.

With regards to statins, it is unlikely that complete publication of trial methodology and outcomes would lead to a radical reassessment of the treatment's safety or efficacy. Statins are one of the most studied drugs in history. As the number of observations included in a meta-analysis increases, the confidence interval around effect estimates generally shrinks. Data on more than 180,000 patients, representing several hundred thousand life years of follow-up, are

included in statin treatment arms of recent meta-analyses (251). It is therefore unlikely that there will be a great change in point estimates for the treatment's benefits or harms.

Pharmaceutical companies may be jointly withholding important side effect information regarding statins, but this is unlikely. A sentiment often proved wrong in healthcare might well stand in the case of statins. Consider Adam Smith's famous quote about the invisible hand of the free market: "It is not from the benevolence of the butcher, the brewer, or the baker that we expect our dinner, but from their regard to their own interest" (481). The incentives for major pharmaceutical companies to shield side effect information is not clear now that all statin patents have expired. Regeneron, Sanofi, Amgen, and Merck & Co. are among the companies that currently have patent protection for non-statin cholesterol-reducing drugs including PCSK9 inhibitors and ezetimibe (215,223,224). The target demographic for these drugs is typically patients with statin intolerance. It is therefore in the interest of these companies to emphasise the rate of side effects attributable to statin therapy. Indeed, the U.S. National Library of Medicine's Clinical Trials database shows a large increase in trials focused on statin intolerance in recent years (482).

6.7 Chapter Summary

This chapter set out to justify the use of statins in primary CVD prevention. Widespread prescription of statins has been criticised in academic literature and other media. Critics have questioned the efficacy of statin therapy and have highlighted potential side effects associated with the treatment. Proceeding chapters in this thesis will analyse the cost-effectiveness of different decision mechanisms to prioritise patients for preventive statin therapy. It was therefore necessary to establish that statins are both efficacious and safe in primary prevention.

Questions regarding statin efficacy often centre around their ability to reduce all-cause mortality and the weakness of relative risk reduction as a measure of benefit. Meta-analyses suggest that statins do reduce all-cause mortality. Moreover, a treatment need not reduce mortality to improve population health. Concern regarding the use of absolute versus relative risk reduction in reporting of trial evidence is valid. However, as rates of CVD fall in high-income countries, continued reduction in CVD incidence will only occur if more intermediate- and low-risk

patients are treated. Decision-analytic modelling offers a systematic means of performing the calculus necessary to determine whether it is worthwhile treating more patients.

Concern regarding the safety of statins was also addressed. Meta-analysis evidence firmly supports the safety profile of statin therapy. However, statins are associated with a marginal increase in diabetes. Decision-analytic modelling can be employed to weigh this absolute risk increase for diabetes against the benefits provided by the treatment.

Prescribing statins to a large number of people will entail screening, treatment, and monitoring costs and some side effects. The following three chapters consist of a series of cost-effectiveness analyses. These analyses aim to establish the costs and health benefits associated with different approaches to prioritising patients for preventive statin therapy.

Chapter 7
Continued Use of 10-Year Risk Scores

7.1 Purpose

The following three chapters will discuss alternative approaches to the prioritisation of patients for preventive statin therapy. Cost-effectiveness analyses of different policies will be conducted. Each of these policies addresses heterogeneity in cost-effectiveness in the patient population to some extent, representing novel means of patient prioritisation.

Continued use of 10-year risk scores is one approach to the prevention of CVD. Risk scores are used to prioritise individuals for preventive therapy for CVD in a range of high-income countries. As these thresholds apply to all individuals, regardless of any other source of patient-level heterogeneity, hereafter this will be referred to as the 'blanket' risk threshold approach to prevention.

The purpose of this chapter is to analyse two policies which involve the continued use of 10-year risk scoring and aim to create more health than current standard of care. These policies are:

- Reducing the risk threshold (treating more individuals).
- Improving risk scores with novel biomarker data.

The epidemiologic bases for the two policies proposed were presented in Sections 4.4.2 and 4.4.3, respectively. Reducing the risk threshold will increase the sensitivity and reduce the specificity of the risk score. More cases and non-cases will be treated. Gaining novel biomarker data for will lead to an increase in testing costs but should target treatment at patients more likely to experience an event. Theoretically, both of these treatment strategies will improve population health outcomes but will lead to an increase in direct costs incurred by the healthcare system.

Sections 7.2 and 7.3 will discuss reducing the risk threshold and updating risk scores with novel biomarker data, respectively. They will relate these policy changes to heterogeneity in cost-

effectiveness analysis and estimate their cost-effectiveness in the setting of primary care in the Scottish NHS.

7.2 Cost-Effectiveness Analysis: Threshold Reduction in Scotland

7.2.1 Background

In recent years, several healthcare bodies have issued guidelines proposing a reduction in the blanket risk threshold at which individuals are prioritised for preventive CVD therapy (25,27,28,173). In turn, millions more CVD-free individuals have become eligible to receive statins. Moves towards threshold reduction have occurred largely because the price of statins has dropped dramatically. This has heralded in a new age of cheap and effective generic cholesterol-reducing therapy.

Analyses have been performed to estimate the cost-effectiveness of reducing the risk threshold for statin initiation in the U.S. and England and Wales (25,37,350). These analyses found that reducing the ACC/AHA Pooled Cohorts risk score threshold from 15% to 7.5% in the U.S. and QRISK2 risk threshold from 20% to 10% in England and Wales were cost-effective policies. No similar study has estimated the cost-effectiveness of reducing the threshold for statin initiation in Scotland.

7.2.2 Objective

The objective of this study was to estimate the cost-effectiveness of reducing the risk threshold for statin initiation in Scotland to 10%. Given that the focus of this study is to quantify the benefit of risk-based stratification, the comparator strategy was statins only for individuals with familial hypercholesterolaemia. This is a condition which SIGN and several other healthcare organisations recommend be treated with statin therapy.

7.2.3 PPICOSS

Population: The Scottish CVD-free population, aged 40 years and above.

Perspective: Scottish health sector decision-maker. All healthcare costs accrued by the Scottish NHS and health gains in treated patients are considered.

Intervention: Intermediate-intensity statin therapy (Atorvastatin 20mg/daily or similar). Two treatment prioritisation criteria are considered: (i) blanket 20% risk threshold and (ii) blanket 10% risk threshold.

Comparator: Statin therapy for individuals with familial hypercholesterolaemia.

Outcome: Lifetime cost-per-QALY, with both costs and QALYs discounted at 3.5% annually. Intermediate outcomes reported are: disaggregated healthcare costs, primary CVD events prevented, and CVD-free life years.

Setting: Primary care in the Scottish NHS.

Study Design: Cohort simulation.

7.2.4 Methodology

Scottish CVD Policy Model

The Scottish CVD Policy model was employed to estimate the cost-effectiveness of different methods of statin prioritisation. This decision-analytic model predicts life expectancy, quality-adjusted life expectancy, and cost outcomes for individuals based on their ASSIGN risk factors and was discussed in depth in Chapter 5.

Treatment Strategies

Three different treatment strategies were considered in the analysis. These were statin therapy initiation for individuals with familial hypercholesterolaemia, individuals with an ASSIGN score greater than 20% (ASSIGN 20), and individuals with an ASSIGN score greater than 10% (ASSIGN 10).

Statins for individuals with familial hypercholesterolaemia was included as a base case for the analysis as it was assumed that, regardless of risk threshold for statin initiation, these individuals would always receive statin therapy. Familial hypercholesterolaemia was defined as TC ≥7.5mmol/L and a family history of CVD or TC ≥8.0 mmol/L, as per SIGN's guideline for the primary prevention of CVD (26).

Scottish Health Survey and Census Data

All analysis was completed using a combination of the Scottish Health Survey 2011 (310) and the Scottish Census 2011 (483).

SHeS is a study of public health which was commissioned by the Scottish Government Health Directorates (484). It was conducted face-to-face with trained interviewers, contains information on many health indicators, and is principally focused on CVD. Values for all ASSIGN risk factors can be derived for all survey respondents from SHeS data. Access to SHeS database was available through the U.K. Data Service website (347).

The survey used a multi-stage stratified probability sampling design (485). Data were obtained from twenty-five strata. These divided Scotland into twenty-five distinct groups: the three island Health Boards (Orkney, Shetland, and Western Isles), along with 22 other groups constructed by dividing the remaining 11 Scottish Health Boards into data zones containing "deprived" and "non-deprived" populations. Areas were deemed to be deprived if they were in the top 15% of deprived areas according to SIMD. Stratification allowed for the oversampling of deprived areas. This was to ensure the survey gave a representative sample of the Scottish population, as response rates for surveys are typically lower in deprived areas.

SHeS 2011 consisted of two stages. All respondents completed an initial interview which obtained information on core topics including: household information, general health, general CVD, use of health services, lifestyle factors, economic activity, education, ethnic background, national identity and origin, family health background, and height and weight.

The second stage was a nurse interview, in which blood samples were obtained. A subsample of those interviewed in stage 1 was offered nurse interviews. These were important with regards to this analysis, as they obtained information on patients' cholesterol levels and blood pressure.

In total, 10,431 addresses were selected for initial sample. Interviews were conducted with 7,544 adults and the estimated response rate was approximately 56%. 4,644 of these adults were aged 40 and above and CVD free. Of those interviewed, 2,224 were eligible for a nurse visit, and 725 gave a blood sample. These low response rates are of some concern. However, the probability sampling approach accounted for the likelihood of non-response based on demographic predictors.

Additional data were needed to project results onto the Scottish population. The 2011 Scottish Census (483) provided information on the Scottish population, and the distribution of age-groups within it.

Multiple Imputation

A key issue with the SHeS data is the relatively small number of respondents for whom nurse interviews were performed. This means that data are sparse for three important modifiable risk factors: TC, HDL-C, and SBP.

Typically, one would carry out an analysis with the subset of respondents for whom blood samples were available when so many data are missing. However, the results from such an analysis would not be particularly useful. Despite the probabilistic sampling techniques employed by SHeS administrators to determine which individuals received a nurse interview, the small number of people with full risk factor profiles will likely lead to small sample bias.

The problem of small sample bias is exacerbated because this analysis was in part stratified by age-group. In the older age-groups, CVD was widespread. For example, CVD prevalence in the dataset for over 80s was 48%. Blood sample information was available for only 25 individuals older than 80 with no established CVD.

Almost complete information was available for respondent's age, sex, SIMD score, diabetes, and family history of CVD. Data on hours exercised per week was available for all of these individuals. Evidence suggests that exercise has strong relationships with TC, HDL-C, and SBP (486). For all individuals who were not offered a nurse visit and therefore did not have complete cholesterol or blood pressure data, SBP, TC, HDL-C was imputed using all available ASSIGN variables plus weekly hours of exercise as predictors.

It was determined that the best way to utilise the data available was to multiply impute missing SBP, TC, and HDL-C values for individuals who refused nurse visits (n=306) (487). Janssen et al. (488) show that imputing missing data is a more reliable means of obtaining unbiased estimates than removing variables with missing data or performing a complete case analysis in medical research. This result was validated even with 90% missing data in some variables, but strictly relied on the assumption that data were missing at random.

For the 306 individuals who refused a nurse visit, SBP, TC, and HDL-C, ten imputed risk profiles were created by with Stata 12.1 (489). Non-missing ASSIGN variables were employed in the imputation process along with the individual's weekly hours of exercise. During the simulation process, each of the ten imputed risk factor profiles was inputted into the model to simulate statin therapy, and the outcomes from these simulations were averaged to determine a central estimate of the treatment's effect on the individual's health and cost outcomes.

Descriptive statistics of the final dataset are displayed in Table 7-1. The descriptive statistics of the subset of the data for individuals who were offered but refused a nurse visit are included in Table 7-2. *FH*, *Diabetes*, and *Male* are binary variables. All other variables are continuous. Individual SIMD scores were not available in the dataset, instead SIMD quintiles were available and individuals were assigned the median SIMD of their recorded quintile.

Risk Factor	Obs	Mean	Std. Dev.	Min	Max
Male	4,644	0.42	0.49	0	1
Age	4,644	58.51	12.30	40	103
SIMD	4,644	19.51	13.39	5.18	45.62
Diabetes	4,644	0.07	0.25	0	1
FH	4,644	0.46	0.50	0	1
CPD	4,644	7	7.05	0	39
SBP (mmHg)	4,644	131	8.81	90	203
TC (mmol/L)	4,644	5.8	0.50	3.0	10.5
HDL-C (mmol/L)	4,644	1.5	0.22	0.6	3.3
ASSIGN Score	4,644	19.6	17.5	1.0	98.5

Table 7-1: Descriptive statistics of SHeS 2011 dataset

Risk Factor	Obs	Mean	Std. Dev.	Min	Max
Male	306	0.39	0.49	0	1
Age	306	60.44	12.92	40	103
SIMD	306	22.07	14.65	5.18	45.62
Diabetes	306	0.09	0.29	0	1
Family History	306	0.48	0.50	0	1
CPD	306	7	3.77	0	39
SBP (mmHg)	306	133	8.83	110	159
TC (mmol/L)	306	5.6	0.53	3.8	6.9
HDL-C (mmol/L)	306	1.5	0.23	0.9	2.0
ASSIGN Score	306	23.1	20.1	2.0	98.5

Table 7-2: Descriptive statistics of SHeS 2011 participants who refused a nurse visit; SBP, TC, and HDL-C multiply imputed

Simulation

The Scottish CVD Policy Model simulated the effect that giving statins to different groups of people. Two macros for Microsoft Excel were written using Microsoft Visual Basic (490). These are included in the appendix (A1). Macro One created a 'Do Nothing' scenario. This macro inserted the risk factor information for each individual from the dataset into the Scottish CVD Policy Model. It then recorded this individual's life expectancy, quality-adjusted life expectancy, and lifetime health costs, as determined by the model.

Macro Two simulated the impact of giving statins to everyone in the dataset. Again, it inserted each individual's risk factor information into the model systematically. However, this time several parameters were altered before outcomes were recorded, to simulate statin therapy.

Treatment Parameters

Parameters were altered in Macro Two to simulate the benefits, side effects, and cost of statin therapy. Intermediate-intensity statin therapy was simulated, in line with SIGN guidelines. The treatment simulated was Atorvastatin 20mg daily, again in accordance with SIGN guidelines. However, it was assumed that an individual could switch to a statin of similar potency if they experienced intolerance to the treatment.

Treatment effect on cholesterol levels: Baseline cholesterol values were altered for individuals to simulate the effect of statins of CVD risk factors. Meta-analysis evidence suggests that statins produce a 29% reduction in LDL-C and a smaller 20% reduction in triglycerides (37,284,491,492). Meta-analyses additionally show that intermediate-intensity statins increase HDL-C by approximately 4-7% (493).

The Scottish CVD Policy Model employs TC rather than LDL-C as a predictor of CVD risk. Moreover, SHeS 2011 only collected data on individual's TC and HDL-C due complexity in LDL-C measurement (494). According to Friedewald's equation, which has been extensively validated, LDL-C can be approximated by the following equation:

$$\mathrm{LDL} = \mathrm{TC} - \mathrm{HDL} - \left(\frac{\mathrm{triglycerides}}{\mathrm{k}}\right).$$

In this equation, k=5 when cholesterol is measured in mg/dL and k=2.17 when cholesterol is measured in mmol/L (495,496). Hence non-HDL cholesterol is predominantly a combination of LDL-C and triglycerides. Conservatively assuming that LDL-C accounts for 80% of total non-HDL cholesterol (284), the net effect of statins on non-HDL cholesterol was estimated to be 27.2% (80%*0.29+20%*0.20).

Side effects and treatment disutility: Statins are a relatively safe treatment with a well-established side effect profile (446). They have, however, been shown to increase absolute risk of developing diabetes by 0.39% and 0.5% in two meta-analyses (440,446). The larger of these

estimates was employed in the base case statin analysis by increasing risk of diabetes development for on-treatment patients.

An annual pill-taking disutility of 0.0011 QALYs was also applied. This value was derived from the willingness-to-pay to avoid daily pill-taking for CVD prevention in a cross-sectional cohort of 708 healthcare employees in Central North Carolina (497). As presented in Chapter 6, no meta-analysis provides statistically significant or positive point estimates for statin-induced myopathy. Therefore, no disutility or costs were applied for this perceived side effect.

Treatment costs: Statin costs were obtained from the British National Formulary (213). An annual cost of £13 was applied for every year on statin therapy, representing the annual NHS indicative price for generic Atorvastatin 20mg. Several cheaper intermediate-intensity generic statins are also available in case of the need for statin switching. It was, however, assumed that patients would not switch to a more expensive or most effective statin, namely higher doses of Atorvastatin or Rosuvastatin.

Risk assessment, monitoring, and side effect costs: Monitoring costs were also applied in the analysis. These costs were predominantly obtained from a cost-effectiveness analysis of risk thresholds for statin prioritisation included in NICE Clinical Guideline 181 (25).

The NICE analysis assumed that statin patients will have two additional general practitioner (GP) visits in years subsequent to treatment initiation when compared with individuals not receiving treatment. This represents a conservative assumption in terms of treatment cost-effectiveness, as one additional GP appointment was recommended by the NICE Guideline Development Group (GDG) (25). In this analysis it was assumed that all patients would attend one additional GP visit in subsequent years and one quarter of patients would have a further visit. This decision conservatively assumed resource use in excess of that suggested by the GDG, without overestimating the impact of costly GP appointments on the cost-effectiveness of statins.

Additional costs were added to each individual attributable to the small increase in diabetes expected in the statin-taking population. These costs were also obtained from NICE CG181 (25), and were weighted by the probability of statin-induced diabetes. These costs include the

annual cost of diabetes-related medication, four annual GP appointments, four annual nurse appointments, and a dietary management programme. These utilisation rates and costs are described in Table 7-3.

Resource	During Risk Assessment	Utilisation year 1	Utilisation year 2+	Price	Source
Appointments					(25)
Appointment to take blood sample (with healthcare assistant)	1	2	1	£6.46	
Appointment with nurse	1	0	0	£13.43	
Appointment with GP	0	2.25	1.25	£45.00	
Blood tests					
Total cholesterol	0	2	1	£1.00	
HDL cholesterol	0	2	1	£1.00	
Triglycerides	0	0	0	£1.00	
Combined lipid profile	1	0	0	£3.00	
Liver transaminase (ALT or AST)	1	2	1	£1.00	
Creatine kinase	0.1	0	0	£2.00	
HbA1c	1	1	1	£2.25	
Annual cost of early stage 2 diabetes					
4x500mg metformin, 1x10mg ramipril 1x10mg amlodipine all daily, 4xGP appointments yearly, 5x nurse appointments yearly, 1 diet management programme every 4 years				£314.33	(25)
Total costs					(25)
Annual monitoring cost, first year				£120.17	
Annual monitoring cost, subsequent years				£67.96	

Table 7-3: Monitoring price, utilisation, and cost of statin therapy in Scotland

Discounting: All costs and health benefits were discounted at a rate of 3.5% annually, the U.K. public service discount rate, as suggested by NICE (40).

Adherence: Adherence was not directly modelled but assumed to be reflected in the estimate for cholesterol modification. As all studies included in the meta-analyses to determine treatment parameters were conducted under the principle of 'intention to treat', it was assumed that

adherence was accounted for in the estimates of treatment effect. No costs, side effects, or treatment-related disutility values were modified by an adherence factor, representing a conservative assumption with regards to the cost-effectiveness of statin therapy.

Table 7-4 presents the range of treatment parameters employed in the simulation.

Parameter	Base Case Value	Distribution for PSA	Lower	Upper	Source
Change in cholesterol levels (%)					
Non-HDL cholesterol	-27.2	Beta	-15.0	-40.0	(284,491)
HDL cholesterol	+4.0	Beta	0.0	+9.0	(493)
Statin-induced diabetes, absolute risk increase (%)	+5.0	Log normal	+0.1	+1.0	(446)
Annual pill-taking disutility	0.0011	Beta	0.005	0	(497)
Annual treatment costs					
Atorvastatin 20mg/daily	£13.00	Gamma	£6.50	£19.50	(213)
Annual risk assessment, monitoring, and side effect costs					
Risk assessment	£26.34	Gamma	£19.76	£32.93	(25)
Monitoring, first year	£120.17	Gamma	£75.17	£165.17	
Monitoring, subsequent	£67.96	Gamma	£22.96	£112.96	
Weighted cost, type 2 diabetes treatment	£1.57	Gamma	-	-	

Table 7-4: Intermediate-intensity statin treatment parameters

Estimating Outcomes

Simulation results were stratified by prioritisation method. The policies considered were a blanket 20% risk threshold and blanket 10% risk threshold for prioritising preventive statin therapy, with statins for FH as a comparator.

Health and cost outcomes were estimated for individuals with a combination of the output from Macro 1 and Macro 2. If an individual met eligibility criteria, their outcome value was obtained from the output of Macro 2. Otherwise, outcomes were obtained from the output from Macro 1: their baseline outcomes. Gains in outcome i, for individual j, under prioritisation method k, $G_{i,j,k}$, was computed as follow:

$$G_{i,j,k} = O_{i,j,k} - O_{i,j,Baseline}$$
$$i \in \{LE, QALE, costs\}$$
$$j \in \{1,2,3, \dots ,4644\}$$
$$k \in \{Familial\ hypercholesterolaemia, 20\%\ threshold, 10\%\ threshold\}.$$

In these equations, $O_{i,j,k}$ represents the simulated value of outcome i for individual j under prioritisation method k, and $O_{i,j,Baseline}$ represents the simulated value of outcome i for individual j at baseline. Hence $G_{QALE,5,20\%\ threshold}$ is equal to the QALYs gained by individual number 5 under the 20% blanket threshold compared to receiving no treatment. If individual 5 has an ASSIGN score greater than 20%, they will receive treatment and this value will be non-zero. If individual 5 has an ASSIGN score less than 20%, $O_{QALE,5,20\%\ threshold}$ is equal to $O_{QALE,5,Baseline}$. They will receive no treatment effects and $G_{QALE,5,20\%\ threshold}$ will be equal to zero. More generally, for individuals who do not meet a prioritisation criterion k:

$$G_{i,j,k} = O_{i,j,k} - O_{i,j,Baseline} = 0.$$

The results were stratified by age-group to facilitate projection of results onto the Scottish population. The sum of outcome gains was calculated for each prioritisation method for individuals in 5-year age bands from 40 to 79 and individuals aged above 80 years. This value will be referred to as the sample outcome gain (*SG*). *SG* was calculated within each age-group as follows:

$$SG_{i,k,Age} = \sum_{j \in Age} G_{i,j,k}$$
$$Age \in \{40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80+\}.$$

Age refers to the subset of respondents in the dataset who fall into a given age-group. Hence, $SG_{costs,10\%\ threshold,55-59}$ is equal to the simulated sum of cost differentials attributable to a 10% risk threshold compared to no active treatment across all individuals aged 55-59 included in the SHeS sample.

Next, the average sample age-group outcome gain, $\overline{SG_{i,k,Age}}$, was estimated for strategy, k, in each age-group. This value was estimated as follows:

$$\overline{SG_{i,k,Age}} = \frac{SG_{i,k,Age}}{|Age|}$$

.

In the equation above, $|Age|$ represents the number of people in the SHeS dataset within the age-group Age. Hence, $\overline{SG_{LE,10\%\ risk\ threshold,80+}}$ equals the average life years gained under the 10% risk threshold compared to receiving no treatment for individuals aged 80 and above in the SHeS dataset.

Projecting Results

Data from the Scottish Census of 2011 was used to project the results onto the Scottish population (483). The objective of this analysis was to estimate the number of people who would be recommended statins and the outcome gains that would be achieved under each method of prioritisation.

The number of people in each age-group was obtained from the census data. As this study focused on statins for primary prevention of CVD, it was necessary to scale the number of people in each age-group down, to ensure the analysis related only to the CVD-free population. This was calculated by multiplying the number of people in each age-group according to the census by the percentage of CVD-free individuals in that age-group in the SHeS cohort. Table 7-5 presents the estimated Scottish population and Scottish CVD-free population for each age group employed in this analysis.

Age	Males	Female	Population	CVD-Free Population
40-44	191,440	203,258	394,698	387,199
45-49	200,319	210,610	410,929	394,903
50-54	184,198	191,629	375,827	355,532
55-59	162,197	168,694	330,891	307,729
60-64	164,725	171,797	336,522	297,149
65-69	124,671	136,527	261,198	223,585
70-74	100,691	119,903	220,594	178,019
75-79	76,818	101,296	178,114	134,120
80+	81,559	148,869	230,428	143,557
Sum	1,286,618	1,452,583	2,739,201	2,421,793

Table 7-5: Scottish Census population and estimated CVD-free populations, stratified by 5-year age-group

After obtaining the census-level age distributions, it was possible to estimate population-level absolute outcome gains in the different age-groups attributable to statin prioritisation strategies, denoted hereafter by $PG_{i,k,Age}$. Multiplying $\overline{SG_{i,k,Age}}$ by the number of people within the respective age-group in the Scottish population gave an estimate of the absolute outcome gains that would be achieved in age-group Age under prioritisation method k in the Scottish population. The number of people treated in each age-group was estimated by multiplying the percentage of people treated in the dataset by the number of CVD-free people in that age-group. This value will be denoted by $PT_{k,Age}$.

Finally, an estimate of the total outcome gains, $G_{i,k}$, and number of people treated for each prioritisation policy, $Treated_k$, was obtained. This was achieved by summing $PG_{i,k,Age}$ and $PT_{k,Age}$ across all the different age-groups:

$$G_{i,k} = \sum_{Age} PG_{i,k,Age}$$

$$Treated_k = \sum_{AGE} PT_{k,Age}.$$

Inflation

All chronic health and monitoring costs were inflated by 3.3%, accounting for annual inflation from 2014 to 2017. Values for the annual rate of inflation were derived from the U.K. Department of Health's Hospital and Community Health Services Pay and Price Inflation index (498). Costs in the model have not been updated since 2014, so this allowed the analysis to account for upwards trends in fees paid by the NHS to healthcare providers.

Cost-Effectiveness Analysis

Cost-effectiveness analysis was performed using traditional cost-effectiveness decision rules (43,354). Three policies were considered: treatment for familial hypercholesterolaemia, a 20% risk threshold, and a 10% risk threshold. These policies were ranked in terms of increasing health benefits. After accounting for the possibility of strict domination (a policy which incurs more costs and gains less health than a competitor), the ICER was estimated. Each policy was

incrementally compared to the next most expensive non-dominated policy. The possibility of extended domination was also considered at this point.

A willingness-to-pay threshold was defined for the cost-effectiveness analysis. The SMC and SIGN typically defer willingness-to-pay determination and cost-effectiveness analysis to NICE (499). A strategy was determined to be cost-effective if its ICER was below £20,000/QALY. This is the lower bound applied by NICE in their assessment of health technologies. The lower bound was selected for this analysis with consideration for analysis by researchers at the University of York which suggests that the willingness-to-pay threshold is presently set too high in the NHS (500)

Inequality

A final piece of analysis considered the consequences of different treatment strategies on health inequalities. Discounted QALY gains per 1,000 individuals were presented, disaggregated by SIMD quintile. The proportion of total QALYs gained by each SIMD quintile was also presented. A policy was considered progressive if more discounted QALYs were produced in the two most deprived compared to the two least deprived quintiles of the CVD-free Scottish population.

Sensitivity Analyses

One-way sensitivity analyses were undertaken to assess the impact of key modelling parameters on predicted cost-effectiveness outcomes. Table 7-4 describes the parameters and specific values altered in these analyses. Results from these sensitivity analyses were synthesised in a tornado diagram.

The parameters included in sensitivity analyses were: pill-taking disutility, non-HDL cholesterol reduction and HDL cholesterol increase, monitoring costs in the first year of treatment, monitoring costs in subsequent years of treatment, cost of risk assessment, and price of statins.

Few studies exist which estimate the disutility associated with daily pill-taking. Moreover, existing studies predict large and inconceivable ranges of potential disutility. For example, in an internet survey of disutility associated with daily pill-taking for cardiovascular prevention, Hutchins et al. (36) found that 62% of respondents would experience no disutility from pill-taking but 9% were willing to accept a 10% risk of immediate death to avoid daily pill-taking. It is very unlikely that such individuals would take statins if prescribed, and would therefore not encounter the costs or benefits of treatment. Sensitivity analyses considered the effect of nullifying and largely increasing the base case pill-taking disutility.

Properly defining monitoring costs in cost-effectiveness analyses of statin therapy is very important. As seen in Table 7-4, annual monitoring costs are indeed much more expensive than the therapy itself. Moreover, SIGN provides little guidance on patient monitoring. GP visits are the key driver of monitoring costs and are also an area of considerable uncertainty. Sensitivity analysis focused specifically on GP visits in first and subsequent years of treatment, considering the effect of increasing and reducing visits by one appointment per year, respectively.

Level of cholesterol modification was also varied in one-way sensitivity analyses. A relatively conservative estimate of the non-HDL cholesterol reducing effect of statins was applied in the base case analysis. Many studies have found non-HDL cholesterol reduction of more than 40% for intermediate-intensity statins (284). A 15% reduction was applied in a separate analysis, which conservatively reflects the non-HDL cholesterol reduction observed in trials of low-intensity statin therapy (284). The HDL-C-increasing effect of statins has been widely observed, but scholars debate the importance of HDL-C in cardiovascular prevention (501,502). Therefore, HDL-C increase was varied from zero to 9%, a central estimate of HDL-C increase from a meta-analysis of statins efficacy (493).

Probabilistic sensitivity analysis stochastically sampled Table 7-4 input distributions and Tables 5-1 and 5-2 risk factor hazard ratios in 500 independent iterations. The Microsoft Visual Basic code used for this analysis is included in the appendix (A2). Correlation between risk factor hazard ratios was accounted for through the Cholesky decomposition method (309,503). Using the cost and QALY results from probabilistic analyses, a cost-effectiveness acceptability curve was produced which shows the probability of each treatment strategy being the most cost-effective option for decision-makers at a range of willingness-to-pay thresholds.

7.2.5 Results

Demographics of Treated Patients

Table 7-6 provides descriptive statistics for the overall population and subpopulations treated under ASSIGN 20 and ASSIGN 10. It details the percentage of different age-groups treated under the different prioritisation strategies alongside the treated population's average risk factor values.

		Overall Population	ASSIGN 20	ASSIGN 10
Proportion of Age-Group Treated (%)	40-44	n/a	0	3
	45-49	n/a	2	14
	50-54	n/a	5	38
	55-59	n/a	15	74
	60-64	n/a	41	94
	65-69	n/a	75	100
	70-74	n/a	92	100
	75-79	n/a	100	100
	80+	n/a	100	100
Average Value	Male (%)	42	45	47
	SIMD	19.5	21.2	20.5
	Diabetes (%)	7	15	11
	FH (%)	46	68	62
	CPD	7	8	7
	SBP (mmHg)	131	134	133
	TC (mmol/L)	5.8	5.8	5.8
	HDL (mmol/L)	1.5	1.5	1.5

Table 7-6: Descriptive statistics of ASSIGN 20 and ASSIGN 10 treated populations

Compared to the general population, the treated populations include more men than women, have greater levels of social deprivation, and include a greater proportion of individuals with diabetes and family history of CVD. Risk factors levels are similar between the ASSIGN 20 and ASSIGN 10 subpopulations. However, more individuals aged 40-75 are treated under this strategy.

Base Case Cost-Effectiveness Analysis

Results for the base case cost-effectiveness analysis are presented in Table 7-7, with number treated, QALYs, and costs incremental to a policy which treats only familial hypercholesterolaemia. No strategy was strictly or extendedly dominated. These results are presented on the cost-effectiveness plane in Figure 7-1.

Policy	Number Treated	Discounted QALYs	Discounted Cost (£1000's)	ICER (£/QALY)
Familial Hyp.	*Reference*			
ASSIGN 20	794,000	92,300	636,000	6,900
ASSIGN 10	1,381,000	164,000	1,596,000	13,500

Table 7-7: Base-case cost-effectiveness results, ASSIGN 20 and ASSIGN 10

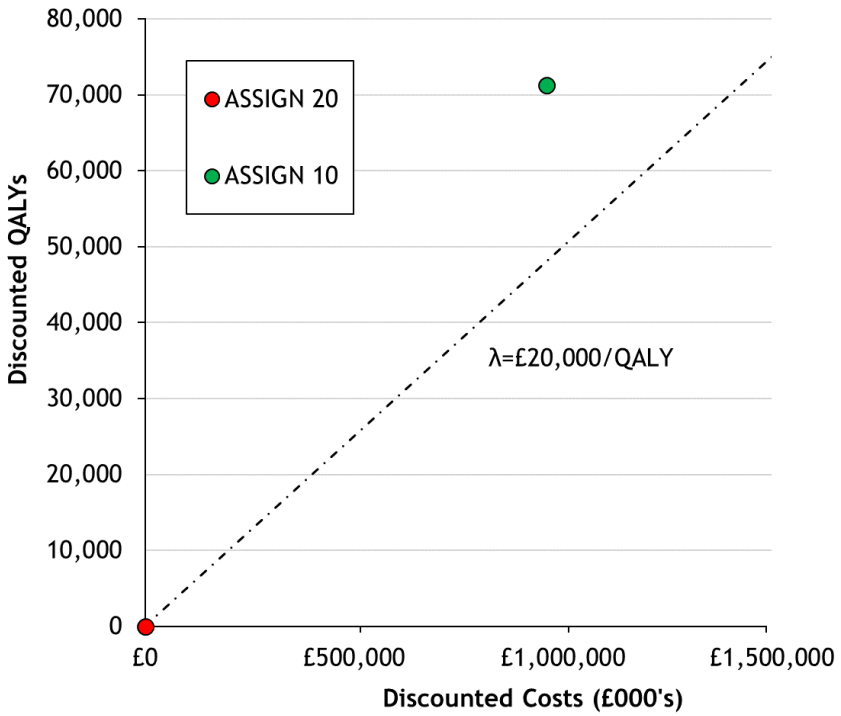


Figure 7-1: Base case cost-effectiveness plane, ASSIGN 20 and ASSIGN 10

The ASSIGN 20 strategy was estimated to treat around 794,000 individuals more than treatment for familial hypercholesterolaemia. The ICER of implementing ASSIGN 20 was estimated to be around £6,900/QALY. ASSIGN 10 required treating approximately 588,000 additional

individuals incremental to ASSIGN 20. The ICER of implementing ASSIGN 10 incremental to ASSIGN 20 was around £13,500/QALY. Therefore, with a willingness-to-pay threshold of £20,000/QALY, ASSIGN 10 is cost-effective and should be implemented.

Intermediate Outcomes

Tables 7-8 and 7-9 present intermediate outcomes for the base case. The former presents the primary CVD events prevented and life years gained estimated by the respective policies, and the latter presents an estimation of disaggregated costs.

Policy	Primary CVD Events Prevented	Life Years Gained
Familial Hyp.	*Reference*	
ASSIGN 20	27,000	170,000
ASSIGN 10	49,000	351,000

Table 7-8: Base case CVD events prevented and life years gained, ASSIGN 20 and ASSIGN 10

Incremental to statins for familial hypercholesterolaemia, ASSIGN 20 would prevent around 27,000 additional events, producing around 170,000 life years in the Scottish population. Incremental to ASSIGN 20, ASSIGN 10 would prevent around 22,000 additional events, producing around 181,000 additional life years in the Scottish population.

Policy	Disc. Costs (£1000's)			
	Non-CVD	CVD	Statin	Monitoring
Familial Hyp.	*Reference*			
ASSIGN 20	720,000	-718,000	84,000	550,000
ASSIGN 10	1,562,000	-1,322,000	190,000	1,166,000

Table 7-9: Base case disaggregated costs, ASSIGN 20 and ASSIGN 10

Both ASSIGN 20 and ASSIGN 10 lead to CVD-related cost savings compared to treating familial hypercholesterolaemia alone. These cost savings are likely attributable to prevention of CVD events. Statin costs represent around 7% of cost increases attributable to treatment for both ASSIGN 20 and ASSIGN 10. Monitoring and non-CVD costs represent around 38-40% and 53-55% of these costs, respectively.

Inequality Analysis

Results were disaggregated to estimate the effect of threshold reduction on health inequalities. Figure 7-2 shows the discounted QALY gains achieved per 1,000 individuals in the population, disaggregated by SIMD quintile. The darkest bars represent the most deprived quintile (SIMD5) while the lightest bars represent the least deprived quintile (SIMD1). In absolute terms, all SIMD quintiles gained more discounted QALYs under Blanket 10 than Blanket 20. Absolute health gains continuously increased with level of social deprivation.

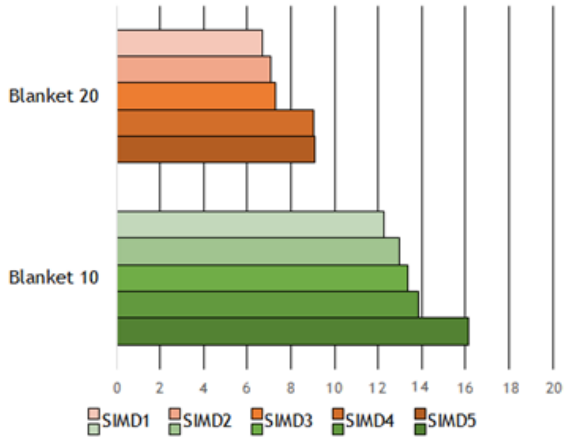


Figure 7-2: Discounted QALY gains for blanket risk threshold strategies per 1,000 individuals, disaggregated by SIMD quintile

The proportion of health gains achieved per quintile of social deprivation was also estimated. These results are displayed in Figure 7-3. The distribution of discounted QALY gains was similar for the two policies. Both policies were progressive: they led to a greater proportion of health gains being achieved in the two most deprived SIMD quintiles compared with the two least deprived quintiles.

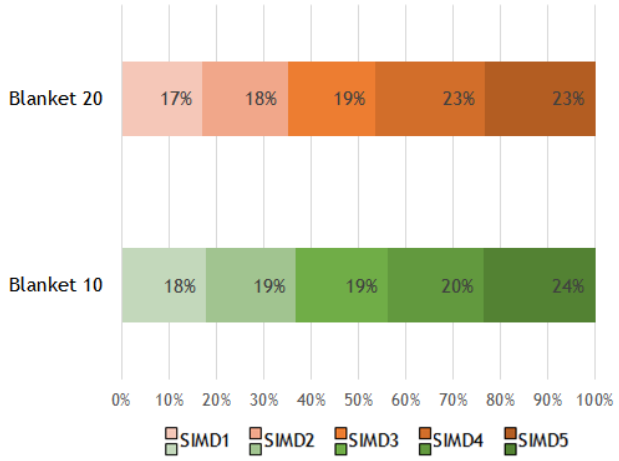


Figure 7-3: Proportion of discounted QALY gains achieved by different SIMD quintiles, blanket risk threshold strategies

Sensitivity Analyses

Figures 7-4 and 7-5 present the results of sensitivity analyses in the form of tornado diagrams. Tornado diagrams show the range of ICER estimates achieved by employing different parameter values in the decision modelling process, centred on the ICER estimated in the base case.

Figure 7-4 presents the different ICERs attributable to implementing ASSIGN 20 over statins only for familial hypercholesterolaemia. Figure 7-5 presents the ICERs of moving from ASSIGN 20 to ASSIGN 10. These charts show that there is considerably more uncertainty in deciding to move from ASSIGN 20 to ASSIGN 10 compared with instituting the ASSIGN 20 strategy. However, all sensitivity analyses produced ICERs less than £30,000/QALY for the transition from ASSIGN 20 to ASSIGN 10, suggesting the cost-effectiveness of extending statin eligibility is robust to changes in modelling assumptions.

The largest areas of uncertainty for Scottish decision-makers deciding whether to reduce the risk threshold for statin initiation are the non-HDL cholesterol-reducing effect of statins, pill-taking disutility, and monitoring costs in years subsequent to treatment initiation.

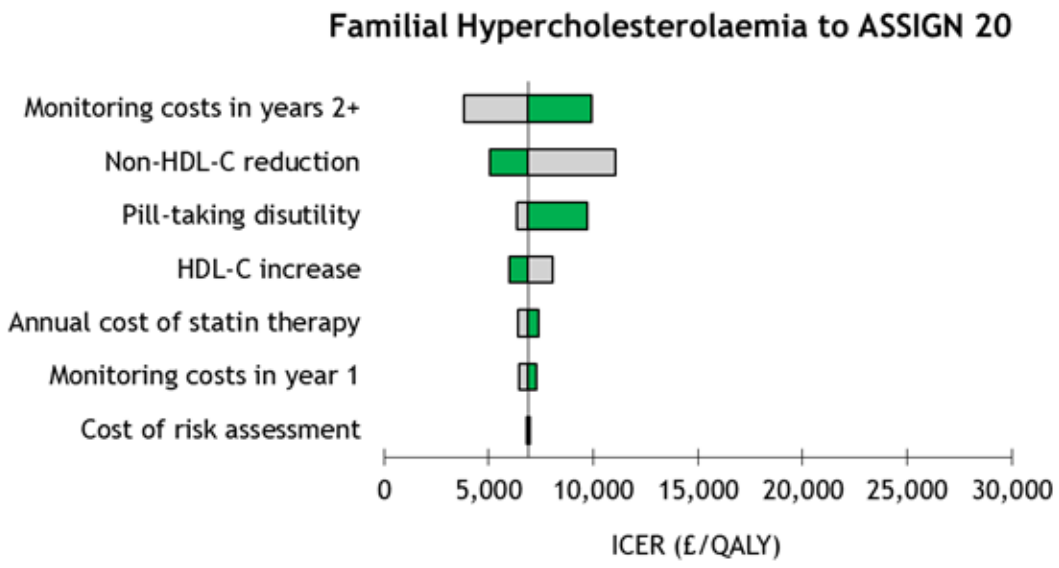


Figure 7-4: Tornado diagram, one-way sensitivity analysis of key parameters and their effect on ICER of implementing ASSIGN 20 over statins for only familial hypercholesterolaemia

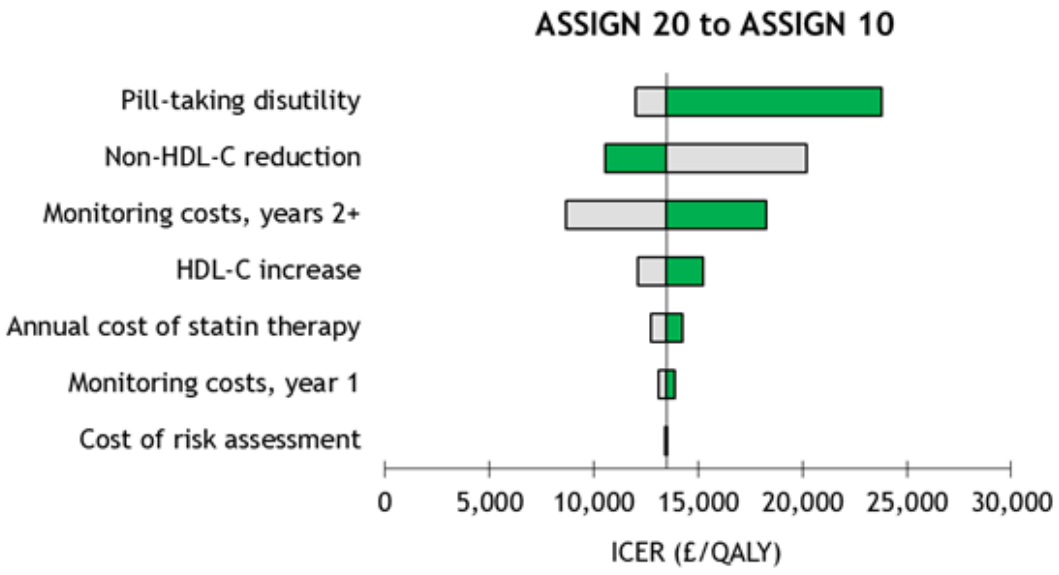


Figure 7-5: Tornado diagram, one-way sensitivity analysis of key parameters and their effect on ICER of implementing ASSIGN 10 over ASSIGN 20

Probabilistic sensitivity analysis provides more in-depth information regarding the total uncertainty inherent in the modelling process. Results from the PSA are presented in a cost-effectiveness acceptability curve in Figure 7-6. The red curve shows the proportion of simulations in which Blanket 20 was optimal at a range of cost-effectiveness thresholds and the

green curve represents Blanket 10. The black dashed line indicates a cost-effectiveness threshold of £20,000/QALY. At this threshold, Blanket 10 was optimal in 76% of simulations.

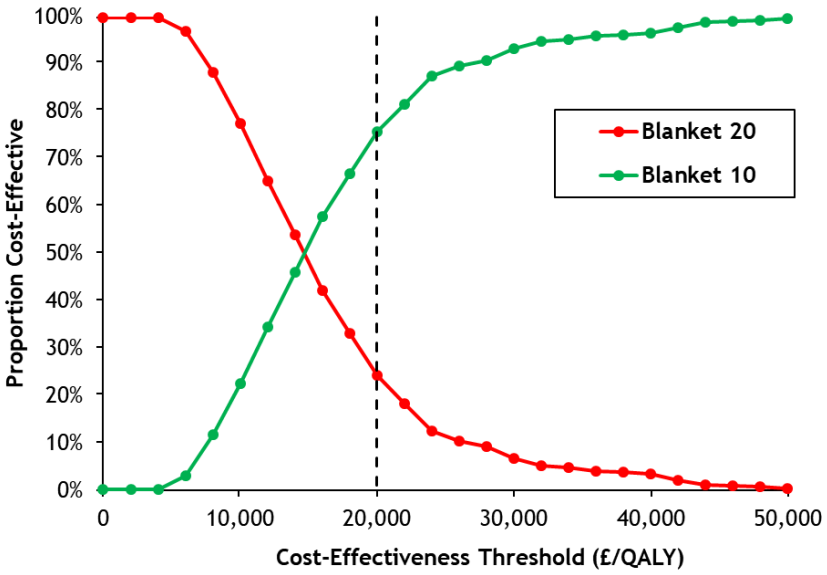


Figure 7-6: Cost-effectiveness acceptability curve, ASSIGN 20 versus ASSIGN 10

7.2.6 Discussion and Limitations

Discussion

Results from the preceding analysis suggest that reducing the ASSIGN risk threshold for statin initiation in Scotland to 10% would be cost-effective. Based on the willingness-to-pay threshold for NICE, the SMC, and SIGN, this policy should be enacted even under conservative modelling assumptions.

The disaggregated costs presented in Table 7-9 show that statins prescriptions contribute a small percentage of the costs attributable to increasing statin availability. The key drivers of increased costs are those associated with extended life expectancy and monitoring. The cost of non-CVD health care treatment cannot be altered with ease. However, this analysis highlights that reducing monitoring costs for statins could make the treatment much more cost-effectiveness and facilitate the expansion of treatment eligibility. This may be achieved through reducing GP appointments in years following treatment initiation and increasing the role of nurses, pharmacists, and other healthcare professionals in the monitoring process.

The sensitivity analysis regarding monitoring costs in years subsequent to treatment initiation produced important results. When lower monitoring costs were applied, the ICER of expanding treatment eligibility from those with familial hypercholesterolaemia to those with ASSIGN score ≥20% was around £3,800/QALY. Incrementally moving from ASSIGN 20 to ASSIGN 10 then produced an ICER of approximately £8,700/QALY. In this analysis it was assumed that patients would receive annual appointments with a healthcare assistant and have blood measurements recorded but that only 25% of patients would attend a GP appointment in years subsequent to treatment initiation. SIGN, NICE, and ACC/AHA guidelines do not explicitly specify a need for recurrent GP appointments in subsequent years of treatment. Therefore, the lower ICERs presented in this analysis may better represent the cost-effectiveness of expanding statin eligibility than base case estimates.

Throughout the rest of this thesis, alternative approaches to traditional risk scoring for statin prioritisation will be considered. While ASSIGN 10 is likely more cost-effective than ASSIGN 20, approaches which better represent patient-level heterogeneity in outcome may produce more health than a blanket risk threshold approach.

Limitations

While SHeS is an extensive survey which focuses on CVD in Scotland, it has many issues. Poor response rates are one issue that must be considered. It is possible that healthier people are more open to discussing the state of their health. This could introduce a bias in results, as the sample used for analysis may have been healthier than the general population. Consequently, the number of high-risk individuals in the Scottish population may have been underestimated.

Another notable issue with the SHeS dataset is the small number of individuals who completed the nurse interview. This resulted in the imputation of TC, HDL-C, and SBP values for many individuals, and multiple imputation of these values for 306 individuals who refused the nurse visit. Sterne et al. (504) note that multiple imputation can lead to biased results when a large amount of data are missing not completely at random.

It was necessary to make assumptions regarding some parameters in the model which may have biased results. No rate of adherence was applied in the analysis. The implicit assumption was that the effectiveness of the treatment would be similar to that observed in intention-to-treat analyses of clinical trials. In real-world clinical practice, as opposed to clinical trials, it is likely that there would be lower adherence to recommended treatment regimens, and some physicians would not follow guideline recommendations. Therefore, estimated population health benefits may be overstated. However, it can be assumed that patients who do not take the treatment will not incur the costs or the benefits associated with treatment. They will therefore not contribute to average incremental outcomes.

Some patients may fill their statin prescription but not consume the medication as scheduled (505). Table 7-9 showed that treatment monitoring and non-CVD costs accounted for a large proportion of cost increases associated with expanding statin eligibility. Hence, these patients will likely not incur the totality of incremental costs associated with statin therapy. Nonetheless they will achieve no health benefits from treatment while incurring costs. Results from this analysis will be significantly biased if this group represents a large proportion of the patient population. Non-compliance to preventive medication is poorly-defined in biomedical literature and data regarding the prevalence of different types of non-compliance are sparse (506,507). Further research should look to better explain non-compliance with statin therapy and its impact on cost-effectiveness.

7.3 Cost-Effectiveness Analysis: Updating Current Risk Scores

The following analysis will consider an alternative policy for preventive statin prioritisation which aims to better represent heterogeneity in decision-making while continuing to use 10-year risk scores to make treatment decisions. This policy is prioritisation of patients with an updated risk score. Specifically, risk scores can be updated by including additional covariates which better identify individuals at elevated risk of experiencing a CVD event.

Medical understanding of chronic diseases has advanced dramatically in recent decades. Such advancement can be attributed to many factors. These include: the exponential growth function of scientific knowledge, the availability of ‘big’ health data, increased computational power, new technology, and increased health research funding. Mannino and Buist note that

understanding of the combination of environmental and genetic factors along with comorbidities has drastically improved etiological understanding of COPD in recent years (508) and Beasley et al. (509) highlight the evolving role of novel factors in explaining asthma risk. In CVD, research led by Seidah and Boileau published in the early 2000s helped to establish the link between the PCSK9 gene in humans and familial hypercholesterolaemia (510). This work led directly to the development of a new class of drugs which inhibit PCSK9 with the aim of reducing LDL-C and CVD events.

With regards to prevention, increased understanding of a disease's risk factors and causes is clinically beneficial for two reasons: (i) it can help clinicians determine which asymptomatic individuals are at heightened risk of developing a disease, and (ii) new treatments can be developed which target the causes of a condition. This chapter will focus on the former. It will examine whether testing for novel CVD biomarkers will increase the cost-effectiveness of CVD risk diagnosis and subsequent treatment in the asymptomatic adult population.

Section 4.4.3 showed that adding a covariate to a risk score for CVD is unlikely to reclassify many patients. However, the greatest degree of clinical uncertainty for physicians will always exist in those patients with intermediate risk scores. Obtaining additional information on these patients can help to solidify the physician's treatment decision.

7.3.1 Background

<u>Cost-Effectiveness of Novel Biomarker Testing in CVD</u>

Several studies have addressed the cost-effectiveness of testing for novel CVD-related serum biomarkers in an asymptomatic population (283,511–514). Most have assessed the cost-effectiveness of screening for high-sensitivity C-reactive protein, a marker of inflammation. Estimates of the cost-effectiveness of hs-CRP testing have varied substantially, as have the structure of the economic evaluations.

The cost-effectiveness of novel serum biomarker screening for preventive CVD interventions was discussed at length in a systematic review produced by the Belgian Health Care Knowledge Centre (BHCKC) (515). Five papers were identified in this review. Of these papers, only one,

authored by Lee et al., compares hs-CRP testing to traditional risk scoring (511). The rest compare hs-CRP testing to prioritisation of individuals based on elevated lipid levels and, in some cases, the presence of additional risk factors.

The approach adopted in previous cost-effectiveness analyses likely biased their results. Omission of relevant comparators can bias ICER estimations, overstating the cost-effectiveness of expensive interventions (516). Given that most high-income countries employ 10-year risk scoring to prioritise individuals for primary CVD intervention, this approach should be treated as the primary comparator in any biomarker testing analysis.

The cost-effectiveness of hs-CRP screening compared to traditional risk scoring has not been established. Lee et al. (511) considered the cost-effectiveness of hs-CRP testing in U.S. adults deemed to be at intermediate- and low-risk of CVD according to the Framingham Risk Score. A lifetime horizon and a U.S. health sector perspective were adopted for the analysis. Risk scoring without hs-CRP screening was estimated to be more cost-effective than risk scoring with hs-CRP screening of intermediate-risk individuals. These findings relied on three assumptions: statins are safe to use over an extended time horizon, they will remain inexpensive, and they provide benefit to low-risk individuals with normal hs-CRP levels.

Novel Biomarkers for CVD

Large amounts of money and effort has been invested in identifying novel biomarkers for CVD in recent years. A 2017 systematic review identified at least 21 studies of novel biomarkers which may be involved in "pathophysiological processes" associated with cardiovascular disease (299). These include markers of myocardial necrosis (cTn, hs-cTn, H-FABP), cardiac inflammation (hs-CRP, GDF-15, fibrinogen, urinary acid), plaque instability (PAPP-A, MPO, MMPs), platelet activation (Lp-PLA2, sPLA2, sCD40L), neurohormonal activation (Copeptin, MR-proADM), and myocardial stress (NPs, ST2, ET-1, Gal-3, NRG-1, and MicroRNAs).

The European Union-funded Markers for Sub-clinical Cardiovascular Risk Assessment (EU-MASCARA) project is a collaborative effort by universities from 15 European countries that aims to improve understanding and diagnosis of sub-clinical CVD. This project involved the evaluation of numerous potential CVD biomarkers.

One novel biomarker for CVD which has been identified as part of the EU-MASCARA project is the 85-peptide urinary proteomic biomarker HF1 (517–519). HF1 is an established risk factor for left ventricular dysfunction (520). In recent years, researchers at KU Leuven in Belgium have shown that HF1 is also significant predictor of primary non-fatal CHD events, when controlling for traditional CVD risk factors (518). They have additionally shown that adding HF1 to 'basic' models of cardiovascular risk prediction leads to significant net reclassification improvement in CVD-free individuals [NRI: 63.8%, p-value <0.001].

7.3.2 Assessing Novel Biomarker Cost-Effectiveness: The Role of Decision Modelling

Section 4.4.3 discussed how traditional measures of statistical validity do not fully capture the costs and benefits of obtaining novel risk factor information from an individual. They often deliberately focus on epidemiologic 'event counting' and operate outside of the value system applied in health economic evaluation. Decision-analytic modelling, on the other hand, can be employed to assess the cost-effectiveness of introducing additional covariates to existing risk scores. Using decision models allows researchers to consider the long-term health and cost outcomes associated with preventive therapy in a range of individuals, accounting for heterogeneity in a way that other statistical techniques cannot.

Some researchers have argued against using decision-analytic models in the analysis of novel biomarkers. Vickers et al. (296) argue that decision-analytic techniques are often difficult to implement in the research of novel biomarkers and risk scoring. They state that such an approach is difficult to adopt due to lack of data. While this is true, the same can be said of any approach for evaluating novel risk factors. Indeed, a defining feature of research into novel therapies is lack of data availability.

Decision-analytic modelling enables the systematic combination of data from multiple sources. It therefore helps to overcome issues related to data availability. As with all studies, it is important to acknowledge and quantify the uncertainty inherent in the modelling process. Decision-analytic modellers have been proactive in developing methodology for the assessment of uncertainty (521).

Vickers et al. also argue that decision-analytic methodology is not of particular use in assessing novel risk scores as it requires dichotomising risk score results at a treatment initiation threshold (296). This is true of other methodologies developed to assess novel risk scores including the most widely used versions of NRI and wNRI. Moreover, health economic evaluations aim to assess implementable health policies. Such policies require a decision rule which allocates individuals to specific treatment strategies.

7.3.3 Objectives

The objective of this study was to develop a pragmatic methodological framework to assess the cost-effectiveness of novel biomarkers and their role in the primary prevention of CVD. This approach considers the inherent lack of data availability for such biomarkers.

A secondary objective was to apply the framework in the cost-effectiveness analysis of a novel biomarker for CVD. The novel biomarker analysed was the 85-peptide urinary proteomic biomarker HF1.

7.3.4 PPICOSS

Population: The Scottish CVD-free population, aged 40 years and above.

Perspective: Scottish health sector decision-maker. All healthcare costs accrued by the Scottish NHS and population-level health gains are considered.

Intervention: Intermediate-intensity statin therapy (Atorvastatin 20mg/daily). Two treatment prioritisation criteria are considered: (i) blanket 10% risk threshold measured with traditional ASSIGN score (treating n=B10 individuals), (ii) blanket 10% risk threshold measured with updated ASSIGN risk score, and (iii) blanket risk threshold measured with updated ASSIGN score setting threshold such that n≈B10 individuals treated.

Comparator: Statin therapy for individuals with familial hypercholesterolaemia.

Outcome: Lifetime cost-per-QALY, with both costs and QALYs discounted at 3.5% annually.

Setting: Primary care in the Scottish NHS.

Study Design: Cohort simulation.

7.3.5 Methodology

A Framework for the Cost-Effectiveness Analysis of Novel Biomarker Testing in CVD

A framework was established, defining a series of steps required to assess the cost-effectiveness of novel CVD biomarkers. This framework provides a roadmap of the analysis required to take (often limited) data regarding a potential CVD biomarker and predict the long-term cost-effectiveness of testing for this biomarker. The framework is predicated on the assumption that the researcher has access to data which can be analysed to predict the independent contribution of the biomarker to CVD risk.

The framework comprised of five steps. These were:

1. Estimate relationship between novel biomarker and risk of CVD, independent of any other relevant covariates.
2. Update an existing risk score to account for the novel biomarker.
3. Develop or update a decision-analytic model, using the novel biomarker information to inform CVD outcomes.
4. Define testing and treatment strategies.
5. Simulate the different strategies in a representative cohort of the population of interest.

Overview of Case Study

A case study was conducted which utilised the framework for cost-effectiveness analysis of novel biomarkers in CVD risk scoring. This case study examined the cost-effectiveness of testing for HF1 to prioritise patients for statin therapy in the Scottish NHS.

The Scottish CVD Policy Model (7,309) was adapted to compare population-level health and cost outcomes attributable to different prioritisation and treatment strategies in the Scottish

population. Both the model and the ASSIGN score were updated to include HF1 as an independent covariate. Next, the effect of different prioritisation and treatment combinations were simulated in a hypothetical cohort of the Scottish population and results were projected onto the Scottish population.

Step 1 - Estimating Relationship between HF1 and CVD Risk

Katholieke Universiteit (KU) Leuven, an EU-MASCARA research partner, provided access to the FLEMish Study on ENvironment, Genes and Health Outcome (FLEMENGHO) (518). FLEMENGHO recruited participants across Northern Belgium from 1985-2004. Individuals were contacted for follow-up examinations between 2005-2010. A sample of urinary proteomic data were obtained from study participants (520). At annual intervals until October 2014, information on individual's health status was obtained through the Belgian Population Registry and the Flemish Registry of Death Certificates.

In order to update risk scores and decision-analytic models with the novel biomarker data, competing risk regressions were run to estimate hazard ratios associated with HF1 and two clinical endpoints: non-fatal CHD and combined CVD events. The parametric regression model chosen was the Gompertz model as this was the model employed in the estimation of the risk functions which underlie the Scottish CVD Policy Model.

An attempt was made to control for all risk factors included in the Scottish CVD Policy Model (and ASSIGN score). This was carried out to ensure that the hazard ratios obtained for HF1 were as transferable as possible between the Scottish and Flemish populations.

It was not possible to include all covariates from the Scottish CVD Policy Model's cause-specific hazard functions. Baseline SIMD and FH values were not available in the FLEMENGHO dataset. The KU Leuven classification of social class was included as a covariate in the regressions. This is a rather limited and outdated index, which was developed at KU Leuven. It measures an individual's social class in accordance with the 'head' of their family's profession, ranked as: 0 – no profession, 1 – workers, housewives, and pensioners, 2 – middle class and small farmers, 3 – higher professions and big farmers. This score was specifically developed for the Belgian population. It was determined that using this local index would

maximise the potential for comparison between results derived from SHHEC and FLEMENGHO. Despite its limitations, it was assumed that the KU Leuven classification of social class would capture a similar effect to SIMD when controlling for all other ASSIGN risk factors for which data were available.

The impact of sex on CVD risk factors was accounted for differently in the FLEMENGHO and original SHHEC analysis. Regressions were run separately for men and women when deriving the ASSIGN score and constructing the Scottish CVD Policy Model. This allowed the magnitude of the association between the risk factors and outcomes to be different between the sexes. Due to the relatively small sample size and short follow-up of the FLEMENGHO dataset, sex was included as an independent covariate in the hazard function regressions; this approach was selected instead of modelling hazard functions for men and women separately. Hence it was assumed that the hazard ratio associated with HF1 and each of the respective endpoints did not differ between sexes.

Step 2 - Updating the ASSIGN Risk Score

The ASSIGN score was updated using data from the HF1 analysis. The score is calculated separately for men and women, but takes the same form for each sex:

$$ASSIGN = 100 * (1 - U^{B}). \quad \textbf{(7-1)}$$

In Equation (7-1), U represents the underlying 10-year survival rate from CVD in the SHHEC population for men and women respectively. B is a measure of the extent to which an individual's risk factor values differ from the SHHEC averages, accounting for the log hazard ratio associated with that risk factor and 10-year combined CVD events.

The ASSIGN score was updated using the hazard ratio obtained for HF1 from the cause-specific hazard regression for combined CVD events in the FLEMENGHO dataset. It was assumed that the updated ASSIGN score was the same as the traditional score for individuals with population mean HF1 scores and increased or decreased based on variation around this mean.

Step 3 - Updating the Scottish CVD Policy Model

Hazard ratios from the FLEMENGHO analysis were also used to update the Scottish CVD Policy Model. Transition to each primary event, k, in the Scottish CVD Policy Model is determined by cumulative incidence, linked to a cause-specific hazard function estimated using Gompertz regression. Each of these functions can be described by the following equation:

$$h_k(t) = exp(xb)\, exp(\gamma t). \tag{7-2}$$

In Equation 7-2, xb is the linear predictor from the regression, and γ is an ancillary parameter which specifies an underlying event rate in the population. Notably, the second half of this equation, $exp(\gamma t)$, should be unchanged by the addition of a new covariate to the model.

The linear predictor takes the form:

$$xb = \beta_{k,0} + \beta_{k,1}x_1 + \cdots + \beta_{k,n}x_n. \tag{7-3}$$

In Equation (7-3), x is a vector containing an individual's risk factor values, and b is a vector which defines log hazard ratios associated with these values and event k. Hence the cause-specific hazard for an individual for each event is either greater than or less than the population's underlying hazard based on the value of $exp(xb)$.

Equation (7-4) shows the example of the linear predictor with the n ASSIGN risk factors included as covariates. In order to account for hazard related to HF1, the linear predictor was updated to take the form:

$$\mathrm{xb}' = \beta_{\mathrm{k},0'} + \beta_{\mathrm{k},1}\mathrm{x}_1 + \cdots + \beta_{\mathrm{k,n}}\mathrm{x_n} + \beta_{\mathrm{k,HF}}\mathrm{x_{HF}}. \tag{7-4}$$

The key differences between Equations (7-3) and (7-4) are the inclusion of an HF1 log hazard ratio in the linear predictor and the updating of constant β_0 to $\beta_{0'}$ in Equation (7-4).

It was assumed that the cause-specific hazard for an individual with a mean HF1 score would be equal whether or not the covariate was included in the model. This hazard would then increase or decrease in accordance with hazard ratios associated with HF1 obtained from the Gompertz regressions run on the FLEMENGHO dataset. Substituting Equation (7-3) into (7-4) allows for the derivation of a linear predictor which accounts for HF. This is shown in Figure 7-7. It starts with the assumption that, at the average value of HF, $\overline{HF}$, in a population, P, cause-

specific hazard (and therefore the linear predictor) is equal for an individual, *i*, whether or not the covariate HF is included in the cause-specific hazard equation.

$$\forall i \in P, (HF = \overline{HF}) \rightarrow xb' = xb$$
$$\Rightarrow \beta_{k,0'} + \beta_{k,1}x_1 + \cdots + \beta_{k,n}x_n + \beta_{k,HF}\overline{HF} = \beta_0 + \beta_1 x_1 + \cdots + \beta_n x_n$$
$$\Rightarrow \beta_{0'} + \beta_{HF}\overline{HF} = \beta_0$$
$$\Rightarrow \beta_{0'} = \beta_0 - \beta_{HF}\overline{HF}$$

Now, substitute value for $\beta_{0'}$ into equation for *xb'*:

$$\Rightarrow xb' = \beta_{0'} + \beta_1 x_1 + \cdots + \beta_n x_n + \beta_{HF}\overline{HF}$$
$$= (\beta_0 - \beta_{HF}\overline{HF}) + \beta_1 x_1 + \cdots + \beta_n x_n + \beta_{HF}x_{HF}$$
$$= \beta_0 + \beta_1 x_1 + \cdots + \beta_n x_n + \beta_{HF}(x_{HF} - \overline{HF})$$

Figure 7-7: Defining linear predictor in biomarker model

In order to ensure outcomes were consistent for patients with average HF value in the simulated populations, event rates in the model were recalibrated. Recalibration was achieved by simulating individuals with mean risk factors profiles for a range of different age-, diabetes-, and sex-defined subgroups using hazard functions which contain HF1. Different multiplicative factors were systematically applied to the constant in the linear predictors for each primary event in the model. The root mean square error between non-fatal CBVD, fatal CVD, and fatal no-CVD primary event rates with and without HF1 included in the hazard ratios were then computed. The multiplicative factor which minimised the RMSE between these values was included in the updated version of the model.

Step 4 - Defining Testing and Treatment Strategies

The updated risk score, which accounts for an individual's HF1 value, will hereafter be referred to as $ASSIGN_{BIO}$. Four strategies for prioritising individuals for preventive statin therapy were considered. These were:

1. Treatment for familial hypercholesterolaemia.
2. The traditional ASSIGN score, with blanket risk threshold of 10%.
3. An updated $ASSIGN_{BIO}$ score, with blanket risk threshold of 10%.
4. The updated $ASSIGN_{BIO}$ score with a different blanket risk threshold dependent on the number of individuals treated under ASSIGN 10.

Strategy 1 was included because there is no clinical debate regarding the necessity of statins for people with very elevated LDL-C. Strategy 2 represents standard of care. Despite the fact that Scotland currently utilises a 20% risk threshold for treatment eligibility, guideline bodies in England and Wales and the U.S. have reduced their risk thresholds in recent years (25,27). Therefore, due to prevailing international guidelines, the 10% risk threshold employed in England and Wales was treated as the standard of care in this analysis.

Under Strategy 4, the $ASSIGN_{BIO}$ blanket risk threshold was permitted to deviate from 10%. A threshold was determined which would lead to an approximately equal number of people being treated under screening Strategy 3 and using the traditional ASSIGN 10 risk threshold. Keeping the number of people treated equal allowed for a more thorough investigation of the implications of using an updated risk score.

HF1 is unlikely to change treatment decisions in the vast majority of individuals. This is because additional risk factors in regression models offer diminishing returns in terms of predictive capability. It was therefore decided that, in testing strategies that employed the $ASSIGN_{BIO}$ risk score, HF1 testing would only occur in a group with intermediate risk that may potentially be reclassified due to the biomarker. The specific intermediate-risk group was defined using a Scottish dataset, based on the range of traditional ASSIGN scores of patients who were upwards or downwards reclassified when their risk was calculated with $ASSIGN_{BIO}$.

Step 5 - Simulation and Projection

The updated Scottish CVD Policy Model was used to simulate the effect that giving statins to different groups of people within this cohort would have on population life expectancy. Two Macros for Microsoft Excel were written using Microsoft Visual Basic and were explained in detail in Section 7.2.4.

The first macro created a base case. This macro inserted the risk factor information for each individual from the dataset into the Scottish CVD Policy Model. It then recorded this individual's health and cost outcomes, as determined by the model. The second macro estimated the impact of treating the patient with statin therapy for life.

Next, results were stratified by the prioritisation methods discussed, showing the incremental differences in health and cost outcomes for the individuals prioritised for treatment. Finally, these results were projected onto the Scottish population as a whole, using data from the Scottish Census of 2011, and employing the approach described in Section 7.2.4.

Simulation Parameters

The key parametric inputs for model costs and treatment effects were previously described in Table 7-4. The treatment provided to eligible patients was the same as the analysis in Section 7.2.

A cost of £419 for HF1 testing was applied for every individual who was judged to be eligible for urinary proteomic risk. Little evidence exists for the cost of urinary proteomic tests, and the HF1 test is provided by one laboratory, Mosaiques Diagnostics, which does not publicly disclose its price (522). The cost of HF1 testing in this analysis was therefore derived from a 2012 study of the cost-effectiveness of urinary proteomic testing for prostate cancer diagnosis (523) whose authors included several employees of Mosaiques Diagnostics. This study adopted a German health sector perspective, and reported the cost of a urinary proteomic test for prostate cancer as being €443. The value of €443 was inflated from EUR 2012 to EUR 2018, using European Commission data on inflation in the Euro area (524). The January 2018 exchange rate of EUR to GBP was then used to estimate the cost of testing in GBP 2018 (525).

One-way sensitivity analyses employed the upper and lower parameter values described in Table 7-4. The cost of HF1 testing was increased and decreased by 50% in this analysis.

Probabilistic sensitivity analysis stochastically sampled Table 7-4 input distributions, Tables 5-1 and 5-2 risk factor hazard ratios, and the hazard ratio associated with HF1 and non-fatal CHD in 500 independent iterations. Correlation between most risk factor hazard ratios was accounted for with the Cholesky decomposition method (309,503). However, the hazard ratio for HF1 was varied independently. Cost and QALY results from the probabilistic analyses were used to produce a cost-effectiveness acceptability curve.

Hypothetical Cohort

A hypothetical cohort of individuals from the Scottish population was created using data from the 2011 Scottish Health Survey (347). This was the same dataset employed for previously discussed analysis and therefore also included data for 4,644 CVD-free individuals. This dataset included values for all the Scottish CVD Policy Model and ASSIGN score inputs. Multiple imputation of variables was performed (487) for individuals who had missing variables and refused the nurse interview.

HF1 information was not available in the SHeS dataset. A value for HF1 was estimated for each individual. This estimation was derived by considering the covariance between HF1 and other variables in the dataset while allowing some random variation. Linear regression was performed on the FLEMENGHO dataset to determine the relationship between HF1 and other ASSIGN risk factors. HF1 values were assigned to each individual in accordance with the derived linear regression equation. The intercept of this equation was allowed to vary randomly for each individual. This produced a hypothetical cohort of individuals with complete ASSIGN and HF1 profiles.

Descriptive statistics for the hypothetical SHeS dataset are shown in Table 7-10.

Risk Factor	Obs	Mean	Std. Dev.	Min	Max
Male	4,644	0.42	0.49	0.00	1.00
Age	4,644	58.49	12.28	40.00	103.00
SIMD	4,644	20.11	14.47	5.21	48.89
Diabetes	4,644	0.07	0.25	0	1.00
Family History	4,644	0.45	0.50	0	1.00
CPD	4,644	7	7.05	0	39
SBP (mmHg)	4,644	131.12	8.58	89.50	202.50
TC (mmol/L)	4,644	5.78	0.48	3.20	10.50
HDL-C (mmol/L)	4,644	1.53	0.21	0.60	3.30
HF1	4,644	-0.94	0.48	-2.45	0.68
ASSIGN	4,644	20.23	18.71	0.77	99.69
ASSIGN Bio	4,644	21.43	21.16	0.61	99.98

Table 7-10: Descriptive statistics of hypothetical SHeS dataset, containing imputed HF1 values

7.3.6 Results

Relationship between HF1 and primary CVD outcomes

The hazard ratios associated with HF1 and five primary CVD outcomes were estimated using Gompertz regressions, performed on the FLEMENGHO dataset. The outcomes considered were non-fatal CHD and a combined CVD events. The Stata code used in this analysis is included in the appendix (A3).

As shown in Tables 7-11 and 7-12, HF1 was estimated to have a significant hazard ratio associated with non-fatal CHD and the combined CVD events. The predicted hazard ratios for HF1 and these outcomes were 1.69 and 1.48, respectively.

The hazard ratio associated with HF1 and three other outcomes were also estimated. These were non-fatal CBVD, fatal CVD, and fatal non-CVD events. It was assumed that HF1 had no effect on these outcomes, as there existed no published evidence suggesting this was the case. The effect of HF1 on these endpoints varied, and these risk models produced generally less reliable results, as shown in Tables 7-13 to 7-15.

No. of subjects = 570		Number of obs =	570
No. of failures = 25			
Time at risk = 2684.01			
		LR chi2(9) =	30.70
Log likelihood = -104.87		Prob > chi2 =	0.003

Covariate	Hazard Ratio	Std. Err.	Z	P>|Z|	[95% Conf.	Interval]
Age	1.067856	0.025436	2.76	0.006	1.019149	1.118892
Male	1.592539	0.722201	1.03	0.305	0.654754	3.873485
Social Status	1.150799	0.586987	0.28	0.783	0.423476	3.127310
HDL-C	1.518323	0.946809	0.67	0.503	0.447265	5.154228
TC	1.096418	0.269381	0.37	0.708	0.677396	1.774635
SBP	1.000397	0.012499	0.03	0.975	0.976198	1.025197
Diabetes	0.866543	0.701941	-0.18	0.860	0.177124	4.239392
CPD	1.048265	0.027452	1.80	0.072	0.995817	1.103475
HF1	1.686700	0.363188	2.43	0.015	1.105995	2.572306
Constant	0.000017	0.000038	-4.85	0.000	2.00E-07	0.001432
Gamma	0.355861	0.132823	2.68	0.007	9.55E-02	0.616190

Table 7-11: Gompertz regression analysis of FLEMENGHO, endpoint: non-fatal CHD

No. of subjects = 570 Number of obs = 570
No. of failures = 35
Time at risk = 2684.01
LR chi2(9) = 46.98
Log likelihood = -129.42 Prob > chi2 = 0.000

Covariate	Hazard Ratio	Std. Err.	Z	P>|Z|	[95% Conf. Interval]	
Age	1.083021	0.021692	3.98	0	1.041330	1.126381
Male	2.044032	0.775555	1.88	0.06	0.971676	4.299856
Social Status	0.864835	0.393940	-0.32	0.750	0.354163	2.111850
HDL-C	1.789390	0.921629	1.13	0.259	0.652066	4.910415
TC	1.234855	0.256811	1.01	0.310	0.821472	1.856263
SBP	0.990378	0.010475	-0.91	0.361	0.970058	1.011124
Diabetes	1.702969	0.983439	0.92	0.357	0.549099	5.281567
CPD	1.052059	0.023616	2.26	0.024	1.006776	1.099378
HF1	1.475500	0.269969	2.13	0.033	1.030853	2.111941
Constant	0.000016	0.000032	-5.68	0.000	3.60E-07	0.000731
Gamma	0.364783	0.112312	3.25	0.001	1.45E-01	0.584911

Table 7-12: Gompertz regression analysis of FLEMENGHO, endpoint: combined CVD

No. of subjects = 570 Number of obs = 570
No. of failures = 4
Time at risk = 2684.01
LR chi2(9) = 7.04
Log likelihood = -23.62 Prob > chi2 = 0.633

Covariate	Hazard Ratio	Std. Err.	Z	P>|Z|	[95% Conf. Interval]	
Age	1.090398	0.066605	1.42	0.157	0.967367	1.229077
Male	0.391354	0.503030	-0.73	0.465	0.031512	4.860357
Social Status	1.524187	1.849668	0.35	0.728	0.141276	16.444060
HDL-C	0.593889	1.029332	-0.30	0.764	0.019879	17.742450
TC	0.941828	0.610821	-0.09	0.926	0.264196	3.357510
SBP	0.930173	0.038300	-1.76	0.079	0.858056	1.008352
Diabetes	9.744097	14.500740	1.53	0.126	0.527255	180.078700
CPD	1.046633	0.068037	0.70	0.483	0.921428	1.188851
HF1	0.794405	0.474932	-0.38	0.700	0.246124	2.564070
Constant	0.132330	0.840595	-0.32	0.750	5.18E-07	33784.730
Gamma	-0.075865	0.340944	-0.22	0.824	-7.44E-01	0.592374

Table 7-13: Gompertz regression analysis of FLEMENGHO, endpoint: non-fatal CBVD

No. of subjects = 570 Number of obs = 570

No. of failures = 3

Time at risk = 2684.01

LR chi2(9) = 25.30

Log likelihood = -4.66 Prob > chi2 = 0.003

Covariate	Hazard Ratio	Std. Err.	Z	P>|Z|	[95% Conf. Interval]	
Age	1.432695	0.215155	2.390000	0.017000	1.067394	1.923017
Male	1.51E+11	8.59E+14	0.000000	0.996000	0.000000	.
Social Status	0.051866	0.290179	-0.530000	0.597000	0.000001	3000.2230
HDL-C	1.281408	2.363558	0.130000	0.893000	0.034486	47.613420
TC	7.867397	10.119860	1.600000	0.109000	0.632307	97.889060
SBP	0.998430	0.043429	-0.040000	0.971000	0.916839	1.087282
Diabetes	0.000000	0.000941	0.000000	0.999000	0.000000	.
CPD	1.350495	0.177687	2.280000	0.022000	1.043516	1.747780
HF1	0.342228	0.443316	-0.830000	0.408000	0.027020	4.334564
Constant	0.000000	0.000000	-0.010000	0.990000	0.000000	.
Gamma	1.862044	0.953737	1.95	0.051	-7.25E-03	3.731334

Table 7-14: Gompertz regression analysis of FLEMENGHO, endpoint: fatal CVD

No. of subjects = 570 Number of obs = 570

No. of failures = 10

Time at risk = 2684.01

LR chi2(9) = 23.26

Log likelihood = -37.24 Prob > chi2 = 0.006

Covariate	Hazard Ratio	Std. Err.	Z	P>|Z|	[95% Conf. Interval]	
Age	1.102375	0.039860	2.700000	0.007000	1.026954	1.183334
Male	0.317867	0.2779947	-1.310000	0.190000	0.057255	1.764715
Social Status	.5195993	.3943201	-0.860000	0.388000	0.117408	2.2995
HDL-C	0.156504	0.190903	-1.520000	0.128000	0.014330	1.709300
TC	0.945642	0.369294	-0.140000	0.886000	0.439859	2.033009
SBP	0.942947	0.025199	-2.200000	0.028000	0.894828	0.993653
Diabetes	10.249480	10.672890	2.230000	0.025000	1.331488	78.898170
CPD	1.070733	0.048053	1.520000	0.128000	0.980575	1.169180
HF1	0.470196	0.194878	-1.820000	0.069000	0.208684	1.059420
Constant	0.051990	0.213437	-0.720000	0.471000	0.000017	162.33130
Gamma	0.559165	0.196203	2.85	0.004	1.75E-01	0.943716

Table 7-15: Gompertz regression analysis of FLEMENGHO, endpoint: fatal non-CVD

The effects of HF1 on non-fatal CBVD, fatal CVD, and fatal non-CVD outcomes were not accounted for in further analysis. There was a relatively short follow-up time in the FLEMENGHO dataset, and a restricted number of individuals were included in the study. Therefore, a small number of non-fatal CBVD, fatal CVD, and fatal non-CVD events were observed (n=4, 3, and 10, respectively). The assumption that HF1 is not related with these outcomes may be considered conservative, especially for fatal CVD events. It is very likely that a risk factor which significantly and independently predicts non-fatal CHD risk in study with a relatively small number of participants and short time horizon will predict risk of fatal CVD in longer-term studies. This has been seen with TC, LDL-C, CPD, SBP, and other established CVD risk factors (152,231,233). Further research may identify such a relationship.

Constant Risk Threshold

Tables 7-16 and 7-17 describe the subpopulations reclassified above and below a risk score of 10% through introduction of the updated ASSIGN score, respectively. While all other risk factors are similar in the upwards classified group, HF1 is significantly higher (suggesting a higher risk of non-fatal CHD). Hence, the adapted ASSIGN score has successfully targeted individuals with a previously disregarded increased risk of CHD in the population.

The ASSIGN score range of upwards reclassified individuals is 9.30 to 9.90, while the ASSIGN score range of downwards reclassified individuals is 10.01 to 11.39 individuals. The age of reclassified individuals ranged from 43 to 64. These values can be employed to determine the individuals that should have their HF1 tested in the analysis. In this situation, a logical testing population would be individuals aged 40 to 65 with traditional ASSIGN score between 9.25 and 11.40. The Scottish Health Survey, combined with census data, can then be utilised to estimate the number of people in the Scottish population indicated for testing.

The ASSIGN and $ASSIGN_{BIO}$ scores from Scottish Health Survey dataset were projected onto the Scottish population by 5-year age group using census data. This made it possible to determine the distribution of each of these scores in the Scottish population. Hence, the number of people treated under each of the risk scores could be calculated.

Variable	Obs	Mean	Std. Dev.	Min	Max
Male	11	0.00	0.00	0	0
Age	11	58.73	6.83	46	64
SIMD	11	14.28	13.42	5.21	48.89
Diabetes	11	0	0	0	1
FH	11	0.09	0.30	0	1
CPD	11	2	4.96	0	14
SBP	11	128.98	2.06	124.39	131.44
TC	11	5.74	0.54	4.66	6.08
HDL	11	1.59	0.13	1.31	1.7
HF1	11	-0.95	0.27	-1.60	-0.64
ASSIGN	11	9.69	0.15	9.30	9.90
$ASSIGN_{BIO}$	11	10.21	0.17	10.02	10.57

Table 7-16: Characteristics of individuals 'upwards' reclassified above 10% risk

Variable	Obs	Mean	Std. Dev.	Min	Max
Male	77	0.61	0.49	0	1
Age	77	51.26	4.02	43	60
SIMD	77	21.74	15.12	5.21	48.89
Diabetes	77	0	0	0	0
FH	77	0.65	0.48	0	1
CPD	77	10	6.54	0	21
SBP	77	128.72	2.58	116	133.5
TC	77	5.68	0.36	5.00	7.60
HDL	77	1.51	0.26	1.1	3.1
HF	77	-1.11	0.32	-2.24	-0.44
ASSIGN	77	10.46	0.34	10.01	11.39
$ASSIGN_{BIO}$	77	9.46	0.45	8.15	9.99

Table 7-17: Characteristics of individuals 'downwards' reclassified below 10% risk

It was assumed reclassification would only occur in individuals aged 40-65 with traditional ASSIGN score between 9.25 and 11.40. Table 7-18 presents the estimated number of people eligible for treatment under each risk score and the estimated number of individuals who would require biomarker testing, given these criteria. Fewer individuals were estimated to be eligible for treatment with the $ASSIGN_{BIO}$ score. This suggests that the current ASSIGN score overpredicts risk in the population constructed for this analysis.

	N Tested	N Eligible for Treatment
ASSIGN 10	0	1,371,231
$ASSIGN_{BIO}$ 10	179,217	1,335,207

Table 7-18: Number eligible for testing and treatment under ASSIGN 10 and $ASSIGN_{BIO}$ 10

Table 7-19 displays the population-level outcomes associated with implementing biomarker testing and treating to the $ASSIGN_{BIO}$ score compared with using the traditional ASSIGN score. At a testing cost of £419, this policy would be dominated by current practice. $ASSIGN_{BIO}$ 10 would incur additional costs while leading to a reduction in QALYs, and is therefore said to be dominated and should not be implemented. Table 7-20 lists the disaggregated costs associated with this strategy.

Policy	Number Treated	Disc. QALE	Disc. Cost (£1000's)	ICER (£/QALY)
Familial Hyp.	*Reference*			
ASSIGN 10	1,371,231	176,000	1,508,000	8,600
$ASSIGN_{BIO}$ 10	1,335,207	173,000	1,522,000	Dominated

Table 7-19: Base case cost-effectiveness results, ASSIGN 10 and $ASSIGN_{BIO}$ 10

Policy	Discounted Costs (£1000's)				
	Non-CVD	CVD	Statin	Monitoring	Testing
Familial Hyp	*Reference*				
ASSIGN 10	1,375,000	-1,125,000	180,000	1,078,000	0
$ASSIGN_{BIO}$ 10	1,323,000	-1,087,000	173,000	1,037,000	75,000

Table 7-20: Base case disaggregated costs, ASSIGN 10 and $ASSIGN_{BIO}$ 10

While the $ASSIGN_{BIO}$ strategy is less cost-effective than current practice, the QALY gain per individual treated was greater in this group. This suggests that $ASSIGN_{BIO}$ was more effective at determining which individuals had the greatest capacity-to-benefit from treatment.

Constant Number Treated

The results above show that when a 10% risk threshold is employed, treating to the traditional ASSIGN score is more cost-effective than using $ASSIGN_{BIO}$ 10% This is driven by the fact that using an updated score would lead to less individuals receiving treatment. Restricting the use of statins is not advisable even in low-risk individuals. They are cheap and effective preventive interventions which are well tolerated by the vast majority of users.

$ASSIGN_{BIO}$ highlighted a group of patients with greater capacity-to-benefit than the traditional ASSIGN score. It was determined that a reasonable comparison between the traditional and

updated risk scores would consider them at differential 10-year risk thresholds. A value for $ASSIGN_{BIO}$ was calculated which would lead to similarly-sized population being eligible for preventive therapy. Analysis suggested that a score of 9.56% would lead to a similar number of individuals being prioritized for preventive therapy as ASSIGN 10. Cost-effectiveness analysis was therefore conducted to assess the comparative cost-effectiveness of ASSIGN 10 versus $ASSIGN_{BIO}$ 9.56.

Tables 7-21 and 7-22 describe the subpopulations reclassified to receive and not receive treatment through introduction of $ASSIGN_{BIO}$ 9.56, respectively. It was assumed reclassification would only occur in individuals aged 40-65 with traditional ASSIGN score between 8.90 and 11.40. Table 7-23 presents the estimated number of people eligible for treatment under each risk score and the estimated number of individuals who would require biomarker testing, given these criteria.

Table 7-24 presents population-level results from the differential threshold analysis. Treating to $ASSIGN_{BIO}$ 9.56 produces more than 300 discounted QALYs compared to ASSIGN 10, at a cost of around £93,000,000. The ICER of implementing this strategy is £230,000/QALY. This ICER is much greater than the cost-effectiveness threshold in most high-income countries and therefore HF1 testing should not be implemented.

Variable	Obs.	Mean	Std. Dev.	Min	Max
Male	36	0.25	0.44	0	1
Age	36	56.2	6.56	43	64
SIMD	36	16.97	14.89	5.21	48.89
Diabetes	36	0.11	0.32	0	1
FH	36	0.25	0.44	0	1
CPD	36	2	4.78	0	16
SBP	36	129	4	111	143
TC	36	5.7	0.46	4.4	6.5
HDL	36	1.5	0.22	1.0	1.8
HF	36	-1.01	0.28	-1.78	-0.45
ASSIGN	36	9.91	0.24	8.99	9.95
$ASSIGN_{BIO}$	36	9.68	0.23	9.57	10.57

Table 7-21: Characteristics of individuals reclassified upwards above $ASSIGN_{BIO}$ 9.56

Variable	Obs.	Mean	Std. Dev.	Min	Max
Male	35	0.68	0.47	0	1
Age	35	50.5	3.76	43	59
SIMD	35	20.33	13.53	5.21	48.89
Diabetes	35	0	0	0	0
FH	35	0.60	0.59	0	1
CPD	35	12	5.47	0	21
SBP	35	129	2	121	133
TC	35	5.7	0.48	5.0	7.6
HDL	35	1.5	0.34	1.1	3.1
HF	35	-1.13	0.39	-2.10	-0.31
ASSIGN	35	10.32	0.28	10.01	11.39
$ASSIGN_{BIO}$	35	9.08	0.35	8.15	9.56

Table 7-22: Characteristics of individuals reclassified downwards below $ASSIGN_{BIO}$ 9.56

	N Tested	N Eligible for Treatment
ASSIGN 10	0	1,371,231
$ASSIGN_{BIO}$ 9.56	215,660	1,371,261

Table 7-23: Number of individuals tested and eligible for treatment under ASSIGN 10 and $ASSIGN_{BIO}$ 9.56

Much of the total cost of this strategy is driven by the high cost of testing, as shown in Table 7-25. This suggests that urinary proteomic testing could be cost-effective if the cost of testing were to fall dramatically.

Policy	Number Treated	Disc. QALE	Disc. Cost (£1000's)	ICER (£/QALY)
Familial Hyp.	*Reference*			
ASSIGN 10	1,452,094	187,000	1,579,000	8,500
$ASSIGN_{BIO}$ 9.56	1,452,110	187,300	1,649,000	230,000

Table 7-24: Population-level outcomes for ASSIGN 10 and $ASSIGN_{BIO}$ 9.56

Policy	Discounted Costs (£1000's)				
	Non-CVD	CVD	Statin	Monitor'	Testing
Familial Hyp.	*Reference*				
ASSIGN 10	1,375,000	-1,125,000	180,000	1,078,000	0
$ASSIGN_{BIO}$ 9.56	1,371,000	-1,118,000	180,000	1,077,000	90,000

Table 7-25: Disaggregated costs for ASSIGN 10 and $ASSIGN_{BIO}$ 9.56

Figure 7-8 quantifies uncertainty related to the cost-effectiveness estimates for ASSIGN 10 compared to $ASSIGN_{BIO}$ 9.56. Figure 7-8 is a tornado diagram representing changes in the ICER of transitioning from ASSIGN 10 to $ASSIGN_{BIO}$ 9.56 associated with increasing and decreasing key parametric inputs in the modelling process. Results were most sensitive to changes in the cost of HF1 testing, follow by the effect of statins on cholesterol levels and the disutility associated with daily pill-taking.

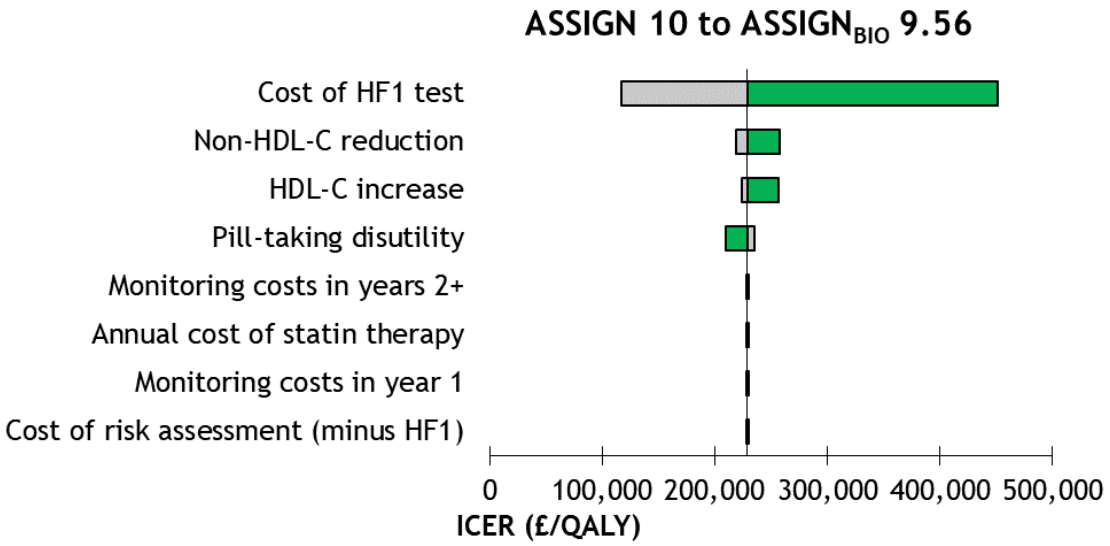


Figure 7-8: Tornado diagram, one-way sensitivity analysis of key parameters and their effect on ICER of $ASSIGN_{BIO}$ 9.56 versus ASSIGN 10

Figure 7-9 presents results from the probabilistic sensitivity analysis in a cost-effectiveness acceptability curve. The dashed line represents a cost-effectiveness threshold of £20,000/QALY. At this threshold, it is highly probable that ASSIGN 10 is the most cost-effective strategy for the decision-maker. As the threshold increases to very high levels, the proportion of iterations of the model that showed $ASSIGN_{BIO}$ 9.56 to be optimal grows. However, the majority of iterations do not favour this strategy until a threshold of approximately £250,000/QALY. This is well in advance of the threshold employed in all high-income countries. At very high thresholds ASSIGN 10 remained optimal in a significant proportion of iteration, suggesting considerable uncertainty in the ability of $ASSIGN_{BIO}$ 9.56 to increase QALYs in the population.

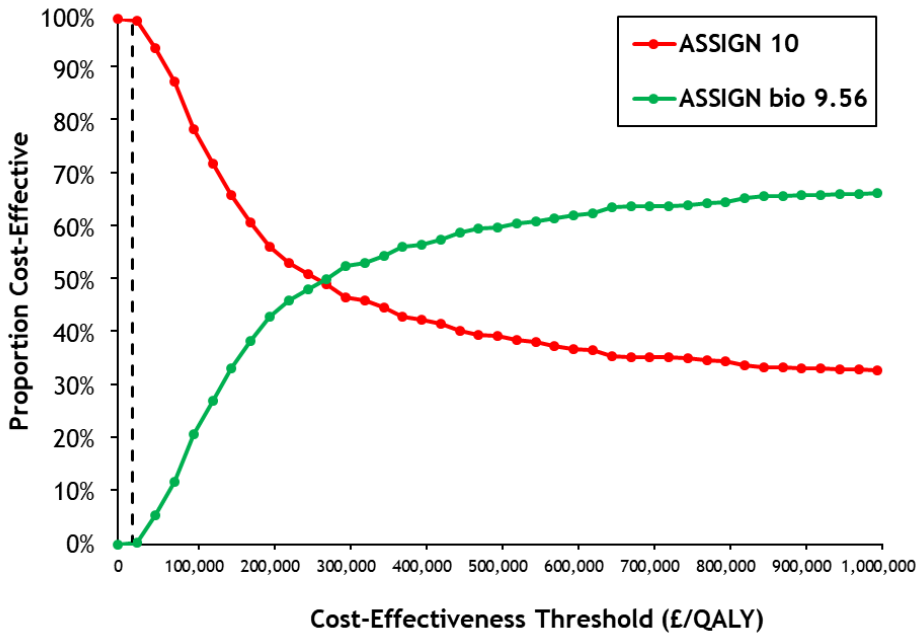


Figure 7-9: Cost-effectiveness acceptability curve, $ASSIGN_{BIO}$ 9.56 versus ASSIGN 10

Cost-Effective Test Pricing

It was possible to determine the cost-effectiveness of implementing the two strategies at a range of testing costs. Table 7-26 presents the costs at which the $ASSIGN_{BIO}$ 10 and $ASSIGN_{BIO}$ 9.56 strategies would be considered cost-effective compared to ASSIGN 10.

When comparing $ASSIGN_{BIO}$ 9.56 to ASSIGN 10, the price of testing was selected that brought the ICER below the willingness-to-pay threshold. Depending on the cost-effectiveness threshold adopted, an 89-94% reduction in HF1 testing costs (from £419) would be required to make $ASSIGN_{BIO}$ 9.56 more cost-effective than ASSIGN 10.

$ASSIGN_{BIO}$ 10 produces less QALYs than ASSIGN 10. Therefore, the maximum acceptable testing price should lead the ICER to be greater than the cost-effectiveness threshold, based on traditional health economic decision rules (43). This testing price ensures that adequate cost savings are achieved to justify the loss in QALYs. At a testing price of £18, HF1 testing would save more than £20,000 per QALY lost and the updated risk score is therefore cost-effective. However, at a testing price of zero, the ICER associated with implementing $ASSIGN_{BIO}$ 10 is

less than £25,000/QALY. Hence, no testing price exists at which $ASSIGN_{BIO}$ 10 should be implemented given a cost-effectiveness threshold ≥£25,000/QALY.

	Cost Effectiveness Threshold (£/QALY)		
	20,000	25,000	30,000
$ASSIGN_{BIO}$ 10	£18	DNE*	DNE
$ASSIGN_{BIO}$ 9.56	£26	£35	£44

*Does not exist

Table 7-26: Maximum acceptable testing price for different cost-effectiveness thresholds

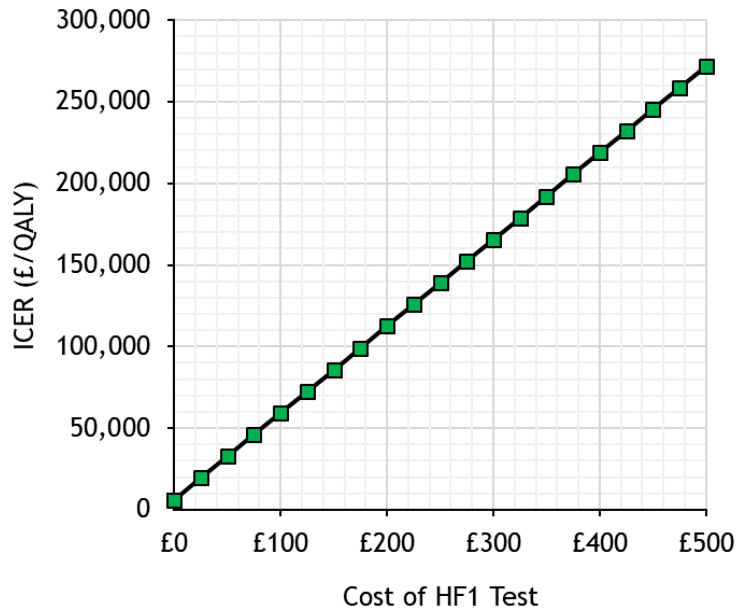


Figure 7-10: ICER and cost of HF1 test, $ASSIGN_{BIO}$ 9.56 versus ASSIGN 10

Figure 7-10 presents the ICER associated with transitioning from ASSIGN 10 to ASSIGNBIO 9.56 at a range of different test costs. As the cost of testing decreases, ASSIGNBIO becomes more cost-effective.

7.3.7 Discussion and Limitations

Discussion

Few reliable cost-effectiveness analyses of novel biomarker testing for CVD prevention have been conducted. A review of relevant literature highlighted deficiencies in previously published

cost-effectiveness analyses. In particular, the choice of comparator in the majority of identified articles failed to truly represent the decision problem under consideration. In most high-income countries, standard practice involves prioritising individuals for statins based on their 10-year risk of developing CVD. Omitting this intervention from cost-effectiveness analyses will produce biased results that overestimate the cost-effectiveness of biomarker testing.

Lee et al. (511) have assessed the cost-effectiveness of hs-CRP testing plus risk scoring with an adequate comparator. However, hs-CRP has been considered a viable biomarker for CVD for a long time. This research focused more specifically on novel biomarkers which inherently suffer from a lack of data availability. Hence, methods were developed which would allow the updating of a 10-year CVD risk score and a decision-analytic model without a comprehensive dataset with which all analysis could be performed.

The framework developed allows for the estimation of cost-effectiveness at a population level. AUROC, NRI, and wNRI analyses are limited by the fact that they can only assess the internal validity and significance of adding novel risk factors to traditional CVD risk scores. Estimating costs and health benefits with a decision-analytic model and a representative population dataset provides decision-makers with more policy-relevant information.

Using the framework developed to assess a urinary proteomic biomarker, it was established that testing prices for HF1 are currently too high. This is not surprising given that statin therapy is cheap and effective with a low side effect rate. Hence, the benefits outweigh the costs of initiating treatment in many untested patients and stratification is unnecessary.

Sensitivity analysis showed that a large reduction in price of test and a restricted testing strategy would lead HF1 testing to become cost-effective. Currently HF1 tests are produced and processed by one manufacturer with one laboratory. A large and consistent demand for this product might lead to an increase in test production. Economies of scale may then drive down the price of the test. As the NHS buyer's guide report for cholesterol measurement notes, "large-scale laboratory testing incurs minimal cost per test" (526). However, there is a large degree of unresolved uncertainty regarding the treatment's ability to improve population health.

An important distinction exists between diagnostic biomarkers and treatment effect modifiers. This modelling exercise assumed that HF1 was a diagnostic biomarker. Patients' HF1 levels did not modify the treatment's efficacy. Lee et al. (511) showed that if low hs-CRP reduces an individual's capacity-to-benefit from preventive therapy, then the cost-effectiveness of testing for hs-CRP increases. There is no area of literature which describes HF1 as a treatment effect modifier for preventive interventions in CVD.

Limitations

Uncertainty in the effect estimate of HF1 on CHD risk is a limitation to this analysis. One issue with novel biomarkers is lack of data. It is possible to obtain a 'statistically significant' estimate for the effect of HF1 on CHD risk with relatively little data. However, a low p-value is arguably not a sufficient marker of estimative precision (527). Univariate probabilistic sensitivity analysis would help to better quantify the effect of the relationship between HF and CVD risk on health economic outcomes. This would involve allowing the HF1 beta in the CHD risk equation to vary in some pre-assigned distribution, while all other variables were kept constant, and recording health and cost outcomes. Development of such methods for the quantification of uncertainty in novel biomarker testing cost-effectiveness was beyond the scope of this thesis, but should be addressed in further work.

An additional limitation with this analysis relates to the approach adopted when establishing how many individuals should receive an HF1 test. Testing as small a subset of the population as possible will increase the probability that HF1 testing is cost-effective. ASSIGN score and age-based cut-offs for testing were derived by examining descriptive statistics of patients reclassified in the SHHEC cohort. While such work was beyond the scope of this analysis, further research should consider optimal strategies for patient testing.

The construction of the hypothetical cohort is a limitation of this study. The approach used to assign HF1 values to every individual in the SHES dataset ensures that a conceivable population was constructed for the simulation. However, it also limited the applicability of this study to the population of interest. A preferable option would have been to simulate individuals from a large cross-sectional dataset which includes information on the novel biomarker. In the case of HF1 and the Scottish population, such data were not available.

7.4 Chapter Summary

The purpose of this chapter was to analyse policies which involve the continued use of 10-year risk scoring but which aim to create more health than standard care. The cost-effectiveness of reducing the risk threshold for statin initiation in Scotland from 20% to 10% was estimated. Next, a framework was established for the cost-effectiveness analysis of risk scoring with novel biomarkers. This framework was employed in a case study of HF1, a urinary proteomic biomarker for CHD.

The framework developed for the cost-effectiveness analysis of novel CVD biomarkers was employed in the assessment of HF1. This analysis found that testing for HF1 would only be cost-effective if prices reduced dramatically and testing were restricted to a small group of individuals with intermediate risk. Nonetheless, if a cheap biomarker does exist which independently predicts CVD risk, there may be a clinical role for this marker in helping physicians discriminate between intermediate-risk patients.

Because statins are very cheap, have a relatively strong safety profile, and achieve benefit in low- and intermediate-risk patients, increasing the number of people receiving statins will be cost-effective in most cases. However, it is possible that a policy could be defined which treats the same number of individuals as ASSIGN 10 but leads to greater health outcomes in a population by better reflecting heterogeneity in cost-effectiveness of the treatment. Proceeding chapters will consider this possibility.

Chapter 8

Novel Decision Mechanisms Which Incorporate 10-Year Risk

8.1 Purpose

Chapter 4 showed that 10-year risk scoring is not necessarily the most effective way to establish which CVD-free individuals in a population have the highest capacity-to-benefit from preventive statin therapy. Individuals can experience different outcomes from the same treatment for a variety of reasons. Alternative treatment strategies which are not fully reliant 10-year risk which better represent heterogeneity in cost-effectiveness should be considered by decision-makers.

A conservative reformation of current practice may look to retain a role for 10-year risk scoring in prioritisation for preventive therapy while modulating treatment decisions along some other parameter. Age-stratification of risk thresholds and the absolute risk reduction approach to prevention are two alternative policies which could be employed to prioritize statin therapy. The purpose of this chapter is to estimate the cost-effectiveness of these two policies.

Section 8.2 considers the cost-effectiveness of age-stratified risk thresholds for statin prioritisation in Scotland. Section 8.3 considers the health benefits and cost-effectiveness of extending preventive statin therapy eligibility to U.S. adults with a combination of elevated 10-year risk and elevated baseline LDL-C.

8.2 Cost-Effectiveness Analysis: Age-Stratified Risk Thresholds

There is considerable variability in outcome for statin therapy between patients of different age-groups. Accounting for this variability should theoretically lead to population-level health gains.

Age-stratification of risk thresholds can be justified on the premise that younger individuals often gain more from preventive statin therapy. Younger individuals face fewer competing risks and restraining atherosclerotic build-up in young adulthood provides greater benefit than treating subclinical atherosclerotic CVD in later life. While the age distribution of individuals

prioritised for treatment under the age-stratified risk threshold approach will be different from current practice, risk will remain a key determinant of who receives statins within age-groups.

8.2.1 Background

Epidemiology and Simulation Analysis

Simulation analysis was presented in Chapter 5 that explored the epidemiology of CVD prevention. The results from this analysis showed that age is an independent predictor of capacity-to-benefit from preventive therapy for CVD, regardless of absolute risk. Section 5.5.1 showed that extended exposure to DBP and LDL-C in young adulthood is associated with increased risk of CHD, and addressing these risk factors early would lead to large reductions rates of CHD. Section 5.5.2 showed that younger individuals can achieve much more health benefits from preventive therapy than older individuals, even when they are at lower 10-year risk of experiencing a primary CVD event.

Current policy fails to account for the benefit offered by intervening on modifiable risk factors early in adulthood. Employing 10-year risk alone to determine an individual's eligibility to receive preventive therapy for CVD likely leads to a waste of health service resources. The age-stratified risk threshold approach to statin prioritisation is one policy which may lead to a more cost-effective distribution of resources.

The age-stratified risk threshold policy requires setting separate treatment initiation thresholds for different age-groups. Younger individuals with elevated modifiable risk factors but low 10-year risk are likely to gain most from such a policy. Therefore, age-stratification of risk thresholds will improve the effectiveness of statin prioritisation if the threshold is reduced for younger and increased for older people.

Age-Stratified Risk Thresholds in Norway

In 2009, Norway published and implemented its new guidelines for the prevention of CVD (303). The group of clinicians and academics tasked with developing these guidelines did not follow the European Society for Cardiology's guidelines which focus preventive efforts on

individuals with elevated 10-year risk. Instead, the new guidelines involved the implementation of age-stratified risk thresholds. These are described in guideline documents as 'age-differentiated' thresholds.

The guideline development process in Norway was threefold: a systematic review of clinical evidence for preventive interventions was conducted, cost-effectiveness analyses were reviewed and a CVD policy model was developed, and guidelines were produced by an interdisciplinary working group.

The systematic review of clinical literature was conducted by the Norwegian Knowledge Centre for the Health Services (NKCHS) and found that several treatments were effective for the prevention of CVD (528). High quality evidence was identified showing that blood pressure- and cholesterol-reducing medications reduce risk of disease-free individuals developing CVD. Amongst cholesterol-reducing medications, statins were assessed to have the strongest evidence base and efficacy.

Review of existing cost-effectiveness analyses and development of a Norwegian CVD policy model was also conducted by the NKCHS. This analysis found strong evidence in favour the cost-effectiveness of statins in individuals as young as 40 years old (529).

To estimate the benefits associated with age-stratified risk thresholds compared with blanket risk thresholds, a Markov model was developed (530). The Norwegian Cardiovascular Disease (NorCaD) Model was built with data on Norwegian CVD prevalence and healthcare costs. It predicts health and cost outcomes in the Norwegian population, moderated by the occurrence of CVD events.

Using the NorCaD model, researchers estimated the distribution of health gains in the Norwegian population associated with age-stratification of risk thresholds (303). They looked at the effect of a reduction in the recommended 5% blanket risk threshold for younger individuals (aged 40-49) and an increase for older individuals (aged 60-69).

Age-stratification of risk thresholds was estimated to reduce the number of individuals eligible for treatment by around 20% compared to the blanket threshold (198,100 versus 247,100). This

policy would lead to a disproportionately small 4% reduction in undiscounted life year gains (531,000 versus 539,000). Moreover, it would lead to a large increase in life expectancy for treated 40-49 year-olds and marginal reductions in life expectancy for treated individuals aged 60-69.

There were key limitations to this analysis. Primarily, this was not a cost-effectiveness analysis. Treating younger individuals with statins will require increased patient years of treatment and monitoring costs. Even if younger patients gain a lot of health from a preventive treatment, they are not necessarily cost-effective to treat. The analysis additionally did not account for health-related quality of life, but rather looked at the effect of interventions on life years. It therefore fails to account for the fact that CVD prevention can avert non-fatal events that lead to patient morbidity. Finally, future health benefits were not discounted. Section 2.7 established the validity and necessity of discounting in health technology assessment. Failing to discount future health benefits and costs ignores the opportunity cost associated with waiting to invest in an intervention and social time preference for health.

The Norwegian cardiovascular prevention guidelines group reviewed the NKCHS research, including the Norheim et al.'s novel analysis of age-stratified risk thresholds. In contrast to the 5% blanket risk threshold recommended by the European Cardiovascular Society, the guideline group determined that the new guidelines for cardiovascular prevention would involve age-stratification of risk thresholds. These thresholds were as follows:

- ≥1% for individuals aged 40-49
- ≥5% for individuals aged 50-59,
- ≥10% for individuals aged 60-69.

The guideline recommended that CVD risk is estimated using the NORRISK score (531) which was developed with Norwegian data. Unlike the ASSIGN, QRISK2, Framingham, and ACC/AHA ASCVD Risk Calculator, NORRISK estimates 10-year risk of cardiovascular mortality. This explains why these thresholds were generally lower than U.K. and U.S. thresholds for intervention which use risk scores which incorporate a broader range of clinical endpoints. Statin therapy was also indicated for patients with TC ≥8.0 mmol/L.

In 2017, new Norwegian guidelines for cardiovascular prevention were released (532). These guidelines retained the role of age-stratified risk thresholds in determining who receives statin therapy. The guideline did, however, make recommendations for treatment based on the NORRISK2 risk score (533). NORRISK2 estimates 10-year risk of both CVD mortality and morbidity, and therefore closer reflects risk scores like ASSIGN, QRISK2, and the ACC/AHA ASCVD Risk Calculator. The new thresholds for treatment initiation are as follows:

- ≥5% for individuals aged 45-54,
- ≥10% for individuals aged 55-64,
- ≥15% for individuals aged 65-74.

Norway's 2008 and 2017 guidelines both state that elderly patients should be treated on a case-by-case basis, considering "utility and risk" (532). Therefore, change in the upper age limit for treatment is not likely to greatly affect clinical practice. The new guidelines increased the age at which risk-based treatment is initiated. The guideline's authors note, however, that very few individuals aged 40-44 met the previous age-stratified threshold for treatment initiation. The new guideline additionally recommends treatment of all patients aged 70 and below with TC ≥7.0 mmol/L or LDL-C ≥5.0 mmol/L.

Further Evidence for Age-Stratified Risk Thresholds

Further research has been conducted which considers heterogeneity in outcome associated with CVD prevention driven by age. The results of these studies vary. Two studies support the implementation of age-stratification while one casts doubt on its capacity to produce long-term benefit when discounting is applied.

Ngalesoni et al. consider the health, cost, and equity outcomes associated with employing age-stratified risk thresholds to prioritise patients for preventive pharmacologic interventions for CVD (534). A Markov model simulated CVD outcomes in a closed, hypothetical cohort representative of the Tanzanian population. The cohort was assumed to have no history of MI or stroke at baseline. Compared to the WHO's recommended blanket risk threshold of 10%, they found that age-stratification of risk thresholds would lead to improvements in treated patients' life expectancy (1.7 years) and a more equitable distribution of health (0.02 reduction in Gini coefficient). Moreover, they found that these improvements in health and equity

outcomes could be achieved without a corresponding increase in healthcare expenditure. As with the previously-described analysis by Norheim et al. (303), a key limitation of this study was the fact that future health and cost outcomes were not discounted.

Navar-Boggan et al. (535) adopt a different approach to assessing the benefit of age-stratification of risk thresholds. Analysing data from the Framingham Offspring Study, they estimated the sensitivity and specificity of 10-year CVD risk scores for adults stratified into three age-groups. It was found that the ACC/AAH guideline-recommended threshold of 7.5% for statin initiation had low sensitivity for people aged 40-55 years. These values were 36% and 48% respectively. On the other hand, the 7.5% threshold would lead to drastic overtreatment of patients aged 66-75 years, with specificities of 17% and 3% in women and men, respectively. It is concluded that lowering the risk threshold for treatment initiation in younger adults to 5% while increasing it to 10-15% in older adults would significantly improve the predictive ability of risk scoring.

Not all analysis regarding age-stratification of risk thresholds has produced positive results. Liew et al. estimate potential years of life lost (PYLL) for patients in 5-year age-bands (536). PYLL is calculated as the life years gained from five years of total CVD risk elimination. Inasmuch, it represents the life years gained from a hypothetical, fully-effective but time-limited intervention. The effect of such an intervention was calculated separately with a simplistic age-based residual risk model and a Markov cohort model. PYLL and discounted PYLL are estimated in both analyses.

Liew et al.'s study addresses the lack of discounting in other modelling studies which consider age-stratified risk thresholds. Results show that undiscounted PYLL is much greater for younger individuals. However, when a 3.0% discount rate is applied, the age gradient in PYLL greatly reduces.

It is likely that Liew et al. understate the benefits associated with early prevention of atherosclerotic build-up in the arteries. They presume that the intervention stops producing benefits in patients after five years. In addition, patients are analysed based on age and risk score alone. The analysis may therefore fail to identify subgroups of patients that may gain from the

hypothetical treatment. As discussed in Chapter 4, the covariates that combine to produce a risk score often independently predict capacity-to-benefit from a given treatment.

No analysis of age-stratified risk thresholds has been conducted which specifically focuses on statin initiation in Scotland. Indeed, no such analysis has been conducted with regards to the rest of the U.K.

8.2.2 Objective

The objective of this analysis was to quantify the health and cost consequences associated with employing age-stratified risk thresholds to prioritise patients for preventive statin therapy in the Scottish NHS. This work aimed to build on previous analyses of age-stratified risk thresholds by performing a complete, discounted economic evaluation of the policy.

8.2.3 PPICOSS

Population: The Scottish CVD-free population, aged 40 years and above.

Perspective: Scottish health sector decision-maker. All healthcare costs accrued by the Scottish NHS and population-level health gains are considered.

Intervention: Intermediate-intensity statin therapy (Atorvastatin 20mg/daily). Four treatment prioritisation criteria are considered: (i) blanket 20% risk threshold (treating n=B20 individuals), (ii) blanket 10% risk threshold (treating n=B10 individuals), (iii) age-stratified risk threshold strategy (treating n≈B20 individuals), and (iv) age-stratified risk threshold strategy (treating n≈B10 individuals).

Comparator: Statin therapy for individuals with familial hypercholesterolaemia.

Outcome: Lifetime cost-per-QALY, with both costs and QALYs discounted at 3.5% annually. Intermediate outcomes reported are: disaggregated healthcare costs, primary CVD events prevented, and CVD-free life years.

Setting: Primary care in the Scottish NHS.

Study Design: Cohort simulation.

8.2.4 Methodology

The methodology adopted to estimate the cost-effectiveness of age-stratified risk thresholds was the same as the methodology employed to estimate the cost-effectiveness of risk threshold reduction in Chapter 7. This allowed for comparison between results in these chapters.

Scottish CVD Policy Model

The Scottish CVD Policy model was employed to estimate the cost-effectiveness of different methods of statin prioritisation. This model was discussed in depth in Chapter 5.

Treatment Strategies

The analysis aimed to compare absolute risk-based blanket 20% and blanket 10% risk threshold strategies to comparable age-stratified strategies. It was assumed that intermediate-intensity statin therapy would always be provided to individuals with familial hypercholesterolaemia (as defined according to SIGN's definition of elevated TC (≥7.5 mmol/L) and family history of premature CVD or TC ≥8.0 mmol/L.

The four remaining strategies considered were intermediate-intensity statins for: individuals with an ASSIGN score greater than 20% (treating n=*B20* individuals), individuals with an ASSIGN score greater than 10% (treating n=*B10* individuals), and individuals who met eligibility criteria based on age-stratified risk thresholds which treat *B20* and *B10* individuals, respectively.

The number treated in each case was kept approximately constant as this analysis aimed to estimate the cost-effectiveness of age-stratified risk thresholds. When comparing two strategies which treat different numbers of patients, it would be difficult to disaggregate the benefits accrued due to age-stratification and those accrued due to treating additional patients.

Defining Age-Stratified Risk Thresholds

Many combinations of age-groups and thresholds can be chosen when defining an age-stratified risk threshold requirement rule for statins. A systematic approach was adopted in this analysis.

Thresholds were changed per 5-year age group. Based on previously discussed assumptions, the threshold was reduced for younger and increased for older individuals. Two policies which would result in a similar number of people being treated to the two respective blanket thresholds were selected. These will hereafter be referred to as Age-Strat 20 (treating approximately B20 individuals) and Age-Strat 10 (treating approximately B10 individuals).

The process to determine age-stratified risk thresholds involved systematically lowering thresholds for younger individuals and increasing them for older individuals in a manner that led to a constant number of patients being treated. The specific age-stratified policies are shown in Table 8-1.

Age-Strat 20 would result in elderly individuals (aged ≥80 years) not receiving treatment. SIGN's guideline for CVD prevention states: "In the elderly, the decision to start statin therapy should be based on 10-year cardiovascular risk estimation, life expectancy, and quality of life. Age alone is not a contraindication to drug therapy" (26). Hence, it was generally presumed that older individuals receive treatment under standard of care.

	Statin Treatment Eligibility Thresholds			
Age	**ASSIGN 20**	**ASSIGN 10**	**Age-Strat 20**	**Age-Strat 10**
40-44	20%	10%	8.5%	7%
45-49	20%	10%	10%	8%
50-54	20%	10%	11%	9%
55-59	20%	10%	13%	10%
60-64	20%	10%	19%	12%
65-69	20%	10%	24%	18%
70-74	20%	10%	29%	25%
75-79	20%	10%	34%	30%
80+	20%	10%	n/a	45%

Table 8-1: Blanket and age-stratified risk thresholds policies

Scottish Health Survey, Census Data, and Multiple Imputation

As with the analyses in Chapter 7, all analysis was completed using a combination of the Scottish Health Survey 2011 and the Scottish Census 2011. The same dataset and imputation process was employed in this analysis as was employed in Section 7.2. The descriptive statistics for this dataset are described in Table 7-1.

Simulation

The Scottish CVD Policy Model simulated the effect of giving statins to different groups of people. The same approach to simulation was adopted as described in Section 7.2.4. This involved developing two Macros for Excel using Microsoft Visual Basic to estimate lifetime incremental health and cost outcomes attributable to intermediate-intensity statin therapy for all individuals in the dataset.

Treatment Parameters

The base case treatment parameters employed in this analysis were the same as the treatment parameters used to estimate cost-effectiveness of risk threshold reduction in Chapter 7. These parameters are presented in Table 7-4.

Estimating Outcomes and Projecting Results

Incremental costs and outcomes were simulated for all individuals in the SHeS dataset. The population was stratified by risk score, and only individuals meeting treatment criteria were assigned the incremental outcomes. Results were averaged across 5-year age-groups and projected onto the Scottish population with census data. Again, this process was described extensively in Chapter 7.

Cost-Effectiveness Analysis

Cost-effectiveness analysis was performed using traditional cost-effectiveness decision rules (43,354). A willingness-to-pay of £20,000/QALY was adopted for this analysis.

Sensitivity Analysis

One-way sensitivity analyses were undertaken to assess the impact of parametric assumptions on cost-effectiveness. The parameters included in sensitivity analyses were: pill-taking disutility, non-HDL cholesterol reduction and HDL cholesterol increase, monitoring costs in the first year of treatment, monitoring costs in subsequent years of treatment, cost of risk assessment, and price of statins.

Probabilistic sensitivity analysis stochastically sampled Table 7-4 input distributions and Tables 5-1 and 5-2 risk factor hazard ratios in 500 independent iterations. Correlation between risk factor hazard ratios was accounted for with the Cholesky decomposition method (309,503). Cost-effectiveness results from probabilistic analyses were used to produce a cost-effectiveness acceptability curve.

Inequality

A final piece of analysis considered the consequences of different treatment strategies on health inequalities. Discounted QALY gains per 1,000 individuals were presented, disaggregated by SIMD quintile. The proportion of total QALYs gained by each SIMD quintile was also presented.

8.2.5 Results

Demographics of Treated Patients

Table 8-2 provides descriptive statistics for the overall population and subpopulations treated under ASSIGN 20, Age-Strat 20, ASSIGN 10, and Age-Strat 10. It details the percentage of

different age-groups treated under the different prioritisation strategies alongside the treated population's average risk factor values.

		Overall Population	ASSIGN 20	Age-Strat 20	ASSIGN 10	Age-Strat 10
Proportion of Age-Group Treated (%)	40-44	n/a	0	5	3	12
	45-49	n/a	2	14	14	29
	50-54	n/a	5	30	38	49
	55-59	n/a	15	50	74	74
	60-64	n/a	41	45	94	86
	65-69	n/a	75	52	100	85
	70-74	n/a	92	65	100	80
	75-79	n/a	100	74	100	88
	80+	n/a	100	0	100	81
Average Value	Male (%)	42	45	53	47	51
	SIMD	19.5	21.2	23.5	20.5	21.4
	Diabetes (%)	7	15	17	11	11
	FH (%)	46	68	73	62	65
	CPD	7	8	10	7	7
	SBP (mmHg)	131	134	134	133	133
	TC (mmol/L)	5.8	5.8	5.8	5.8	5.8
	HDL (mmol/L)	1.5	1.5	1.5	1.5	1.5

Table 8-2: Descriptive statistics of treated populations for ASSIGN 20, Age-Strat 20, ASSIGN 10, and Age-Strat 10

As expected, a much larger proportion of young individuals were treated with age-stratified risk thresholds compared to the blankets approach. Age-stratification additionally increased the proportion of men and individuals with family history of CVD who were eligible for treatment. The average index of social deprivation for treatment eligible patients was marginally greater when age-stratified risk thresholds were applied, suggesting the treated population was from a more socially deprived background.

Base Case Cost-Effectiveness Analysis

The results from the base case cost-effectiveness analysis are presented in Table 8-3. These results are also shown on the cost-effectiveness plane in Figure 8-1 incremental to ASSIGN 20. Age-Strat 20 and Age-Strat 10 produced more discounted QALYs than their respective blanket threshold comparators.

Policy	Number Treated	Discounted QALYs	Discounted Cost (£1000's)	ICER (£/QALY)
Familial Hyp.	*Reference*			
ASSIGN 20	793,559	92,300	636,000	6,900
Age-Strat 20	793,596	99,500	882,000	Ext. Dominated
ASSIGN 10	1,381,059	164,000	1,596,000	13,500
Age-Strat 10	1,381,054	168,000	1,719,000	27,400

Ext. - extendedly

Table 8-3: Base case cost-effectiveness results, ASSIGN 20, Age-Strat 20, ASSIGN 10, Age-Strat 10

The additional health benefits offered by age-stratification of thresholds are purchased at a high cost. Age-Strat 20 is extendedly dominated by ASSIGN 10. The ICER associated with transitioning from ASSIGN 10 to Age-Strat 10 is around £27,400/QALY. This is in excess of the cost-effectiveness threshold adopted for this analysis. Therefore, given the policies considered and the base case assumptions, ASSIGN 10 is the optimal strategy for a decision-maker.

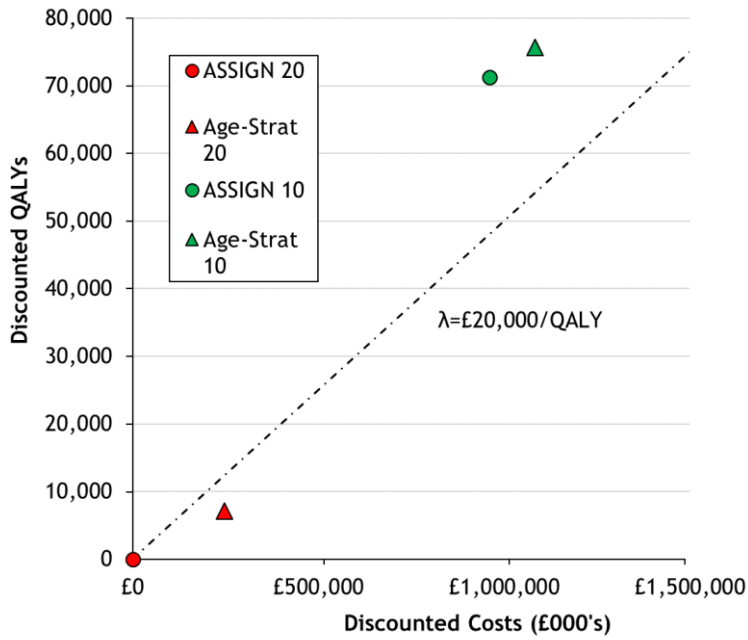


Figure 8-1: Base case cost-effectiveness plane, ASSIGN 20, Age-Strat 20, ASSIGN 10, and Age-Strat 10

Intermediate Outcomes

Tables 8-4 and 8-5 present intermediate outcomes from the base case analysis. The former presents the primary CVD events prevented and life years gained for the respective policies, and the latter presents their disaggregated costs.

Policy	Primary CVD Events Prevented	Life Years Gained
Familial Hyp.	*Reference*	
ASSIGN 20	27,000	170,000
Age-Strat 20	29,000	198,000
ASSIGN 10	49,000	351,000
Age-Strat 10	50,000	368,000

Table 8-4: Base case CVD events prevented and life years gained

Implementing age-stratified risk thresholds would prevent more than 1,500 primary CVD events when compared with ASSIGN 20. This would be achieved while treating the same number of individuals. In turn, this would lead to an approximately 28,000 additional undiscounted life years in the Scottish population. Implementing Age-Strat 10 over ASSIGN 10 would prevent approximately 1,200 additional primary CVD events, producing around 16,500 undiscounted life years.

Policy	Disc. Costs (£1000's)			
	Non-CVD	CVD	Statin	Monitoring
Familial Hyp.	*Reference*			
ASSIGN 20	720,000	-718,000	84,000	550,000
Age-Strat 20	986,000	-889,000	108,000	678,000
ASSIGN 10	1,562,000	-1,322,000	190,000	1,167,000
Age-Strat 10	1,707,000	-1,408,000	200,000	1,220,000

Table 8-5: Base case disaggregated costs

All strategies led to a decrease in CVD-related healthcare costs and increases in non-CVD-related healthcare costs. The age-stratified risk threshold strategies incurred greater non-CVD-related, statin, and monitoring costs than comparable blanket risk threshold strategies. This suggests that increased costs for age-stratified policies are incurred through extension of life

expectancy and associated costs, increased patient years of treatment, and an increased period of patient monitoring.

Inequality Analysis

Results were disaggregated to estimate the effect of threshold reduction on health inequalities. Figure 8-2 shows the discounted QALY gains achieved per 1,000 individuals in the population, disaggregated by SIMD quintile. In absolute terms, all SIMD quintiles achieved greater health gains under Age-Strat 10 when compared with Age-Strat 20. In both treatment scenarios, absolute health gains continuously increased with level of social deprivation.

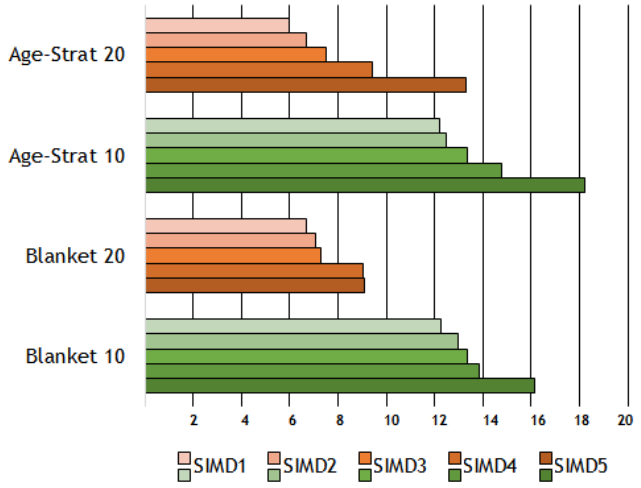


Figure 8-2: Discounted QALY gains for age-stratified and blanket risk threshold strategies per 1,000 individuals, disaggregated by SIMD quintile

The proportion of health gains achieved per quintile of social deprivation was also estimated and these results are presented in Figure 8-3. The distribution of discounted QALY gains was similar for both age-stratified risk threshold policies. The two most deprived quintiles of the Scottish population each achieved greater than 20% of all health gains. Both policies were progressive: they led to a greater proportion of health gains being achieved in the two most deprived SIMD quintiles compared with the two least deprived quintiles.

Age-Strat 20 was more progressive than Blanket 20. The two most deprived SIMD quintiles combined gained 53% of all health benefits under Age-Strat 20, compared to 30% of health

gains achieved by the two least deprived quintiles – a 23% difference. For Blanket 20 this difference was 11%. Age-Strat 10 was more progressive than Blanket 10. The difference in proportion of QALY gains between the two most deprived and least deprived quintiles for Age-Strat 10 and Blanket 10 were 12% and 7%, respectively.

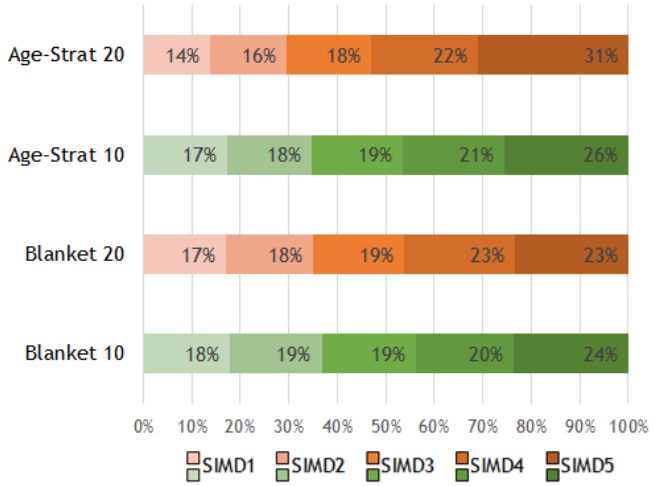


Figure 8-3: Proportion of discounted QALY gains achieved by different SIMD quintiles, age-stratified and blanket risk threshold strategies

Sensitivity Analyses

Results from the sensitivity analyses are presented in Figures 8-4 and 8-5. These tornado diagrams show the sensitivity of ICER estimates to univariate changes in model parameters. They present the ICERs associated with moving from ASSIGN 20 to Age-Strat 20 and ASSIGN 10 to Age-Strat 10, respectively. Age-Strat 20 remained extendedly dominated by ASSIGN 10 in all sensitivity analyses. The base case ICER of implementing Age-Strat 20 over ASSIGN 20 was approximately £34,700/QALY.

The three areas of greatest uncertainty highlighted by these analyses are pill-taking disutility, non-HDL cholesterol reduction, and monitoring costs. Pill-taking disutility and monitoring costs are particularly important when transitioning from a blanket threshold strategy to an age-stratified risk threshold strategy because the latter approach will involve treating a younger group of individuals. These younger individuals will receive the treatment for an extended period of time, accumulating costs and pill-taking utility decrements.

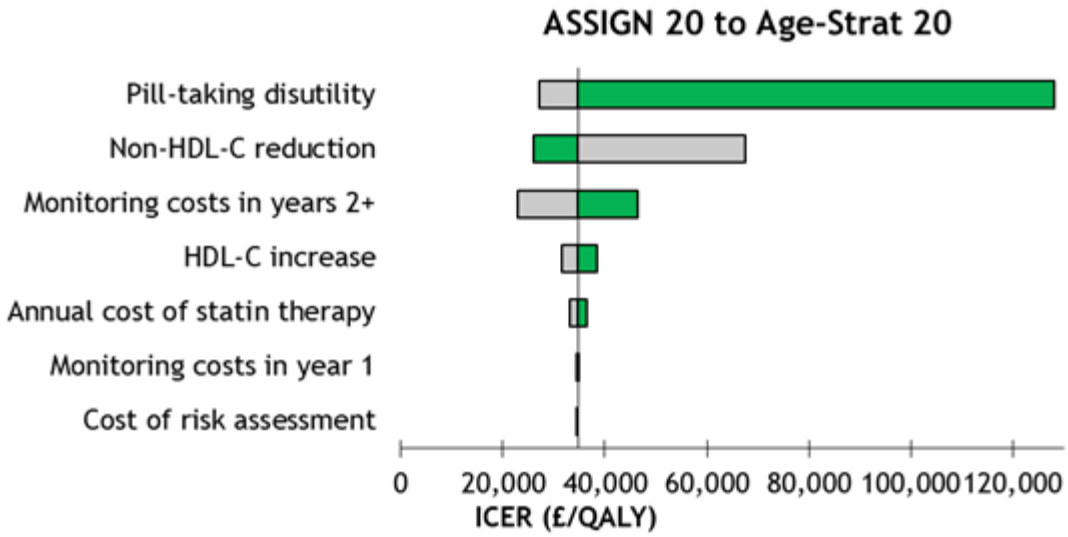


Figure 8-4: Tornado diagram, one-way sensitivity analysis of key parameters and their effect on ICER of implementing Age-Strat 20 over ASSIGN 20

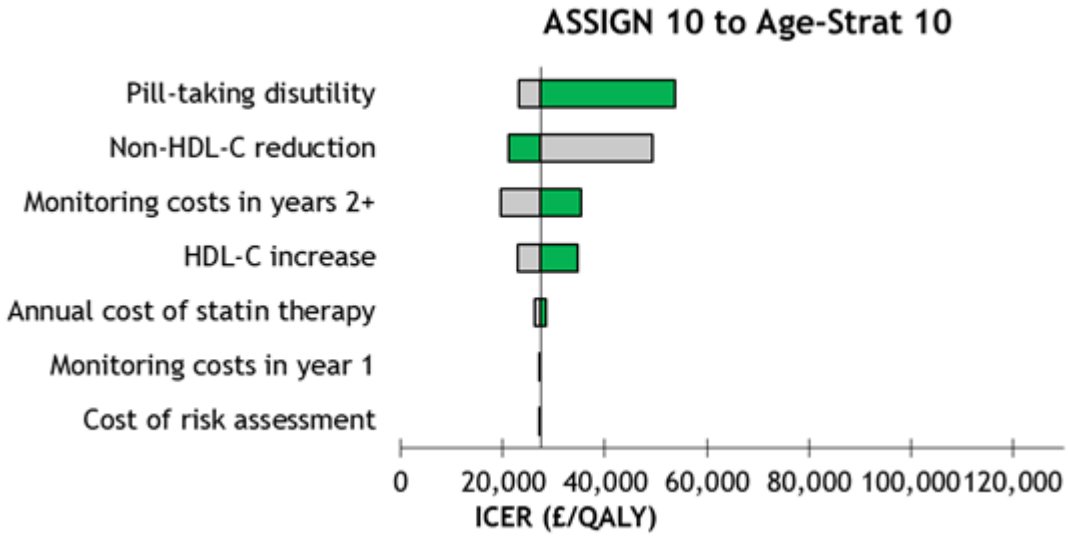


Figure 8-5: Tornado diagram, one-way sensitivity analysis of key parameters and their effect on ICER of implementing Age-Strat 10 over ASSIGN 10

Results from the PSA are presented in a cost-effectiveness acceptability curve in Figure 8-6. The red, black, blue, and green curves show the proportion of simulations in which Blanket 20, Age-Strat 20, Blanket 10, and Age-Strat 10 were optimal at a range of cost-effectiveness thresholds. The black dashed line indicates a cost-effectiveness threshold of £20,000/QALY. At this threshold, Age-Strat 10 was optimal in 45% of simulations. This analysis suggests some uncertainty regarding the cost-effective of Age-Strat 10, which may be the optimal treatment strategy.

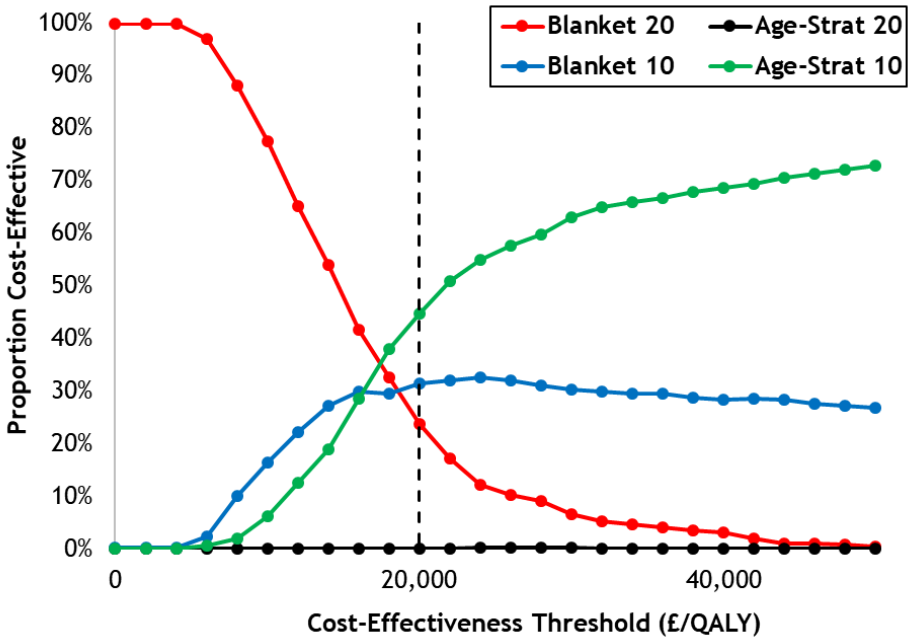


Figure 8-6: Cost-effectiveness acceptability curve, ASSIGN 20, Age-Strat 20, ASSIGN 10, and Age-Strat 10

8.2.6 Discussion and Limitations

Discussion

This analysis suggests that age-stratification of risk thresholds would produce considerable health benefits in the Scottish population. This result is in agreement with analyses by Norheim et al. (303) and Ngalesoni et al. (534) which emphasise the benefits offered by age-stratification of risk thresholds. It is not in line with results from Liew et al. (536) who predict that discounting of future health outcomes limits capacity-to-benefit from preventive treatment in younger individuals.

While the age-stratified approach to prevention leads to an increase in health outcomes, this improvement in population health was estimated to be too expensive for a Scottish NHS decision-maker. The ICER associated with transitioning from ASSIGN 20 to Age-Strat 20 and from ASSIGN 10 to Age-Strat 10 are both in excess of £20,000/QALY.

The ICER associated with transitioning from ASSIGN 10 to Age-Strat 10 is within the £20,000-30,000/QALY threshold range adopted by NICE in health technology assessment. However,

recent analysis suggests that the marginal cost of health production in the NHS is far below even £20,000/QALY (500). The optimality of ASSIGN 10 under base case assumptions may therefore be assumed robust.

Age-Strat 20 may be extendedly dominated by ASSIGN 10 due to the fact that statins are cheap and effective. Reducing the blanket risk threshold means that a large number of younger individuals with high capacity-to-benefit from treatment receive treatment. Nonetheless, it is surprising that the ICER associated with treating this group is lower than the ICER associated with Age-Strat 20. A possible explanation is that the blanket threshold approach treats a greater number of older individuals, who gain less from the treatment but have a higher tendency to be cost-saving.

Sensitivity analysis suggests that there may be a scenario in which the age-stratified approach to prevention would be the optimal choice for a Scottish NHS decision-maker. Two key factors which drive the high ICER for the age-stratified approach are cumulative pill-taking disutility and monitoring costs. Younger individuals are likely to spend longer receiving preventive treatment before the occurrence of a primary event and therefore accumulate much greater costs. Post-hoc analysis was performed to consider the circumstance in which ongoing monitoring costs and pill-taking disutility are completely nullified. In this situation, the ICER of instituting Age-Strat 10 would be around £13,500/QALY.

Limitations

Uptake and adherence are two aspects missing from this analysis. Clinical buy-in is important for preventive pharmacologic interventions. It is conceivable that medical providers look unfavourably on the concept treating elderly individuals with healthy risk factors. If this carries into clinical practice, then age-stratification may be a preferable strategy as it targets treatment at individuals who are unhealthy compared to their peers.

Further work should consider potential variation in uptake and adherence to statin recommendations, stratified by different patient populations. Value of implementation analysis may be performed to assess the costs and benefits of interventions aimed at improving these factors (537).

Another limitation of this analysis is the fact that the effect of cumulative exposure to LDL-C is not accounted for. As demonstrated in Chapter 4, lowering LDL-C at an early stage in life reduces atherosclerotic build-up and intervening early to stop this build-up can therefore have a large impact on later life CVD risk. This analysis, however, assumes that the relative risk reduction from statin therapy is not predicated on the age that an individual initiates treatment. This analysis therefore likely underestimates the benefit of statin therapy for younger individuals.

Further research could also focus on the cost-effectiveness analysis of reducing cumulative exposure to LDL-C. This analysis could consider the benefit of reducing the age at which annual risk assessment is currently recommended. This age limit is currently set at 40, but based on the cumulative exposure hypothesis, benefit can be accrued due to LDL-C-reduction at much earlier stages in life.

8.3 Cost-Effectiveness Analysis: Absolute Risk Reduction

A second policy which incorporates 10-year risk alongside some other covariate to prioritise statin therapy is the absolute risk reduction approach to prevention. Section 4.5.2 showed that baseline LDL-C is a predictor of absolute risk reduction from statin therapy. Individuals with higher baseline LDL-C may gain more health from LDL-C-reducing therapies than their peers. Employing a metric which accounts for both absolute 10-year risk and baseline LDL-C to determine who receives statins may lead to improvements in population-level health outcomes.

The following study considers the health benefits and cost-effectiveness of statin therapy in different subgroups of the U.S. CVD-free population. The population is stratified by baseline absolute risk and LDL-C. Health and cost outcomes associated with statin therapy are then estimated.

This study also considers the cost-effectiveness of a statin prioritisation policy based on both absolute risk and baseline LDL-C. Unlike the analysis of age-stratified risk thresholds, this analysis considers the cost-effectiveness of extending eligibility beyond current standard of care. There is considerable uncertainty in current U.S. guidelines regarding treatment of

individuals with risk scores between 5.0-7.5%. Rather than advocating a large change in clinical practice in the U.S., this study rather focuses on this area of existing uncertainty. Secondary analysis was conducted with the Scottish CVD Policy Model to enable comparison with other policies analysed in the thesis.

8.3.1 Background

The ACC and AHA have issued joint guidelines for the management of cholesterol with statins in CVD-free individuals. They recommend that primary prevention patients should be prescribed statin-therapy using a blanket risk threshold of 7.5%, estimated with the ACC/AHA ASCVD Risk Calculator. The guidelines additionally state that statins should be considered for CVD-free patients with 'borderline' risk scores between 5.0-7.5% (27). In 2018 guidelines, borderline-risk patients with a variety of 'risk-enhancing factors' were also recommended statins.

The blanket risk threshold approach to prevention is predicated on the assumption that treatments produce consistent benefit across heterogeneous patient subgroups. In other words, this approach assumes the relative risk associated with statins is equal in all subsets of the patient population, regardless of baseline LDL-C. If this assumption holds, then individuals with greater absolute risk will always achieve greater absolute risk reduction from the preventive treatment.

Several major clinical trials have analysed the effect of statins on CVD risk. Meta-analyses of data from more than 90,000 individuals, synthesizing more than 400,000 years of follow-up, has been conducted by the Cholesterol Treatment Trialists' collaboration (284,538). The large sample size of these studies has allowed for inference of statin effectiveness and the moderating impact of patients' covariates on effectiveness.

A key finding from the CTT meta-analysis was that an 'approximately linear relationship' exists between absolute reductions in LDL-C achieved by statin therapy and the proportional reductions in incidence of CVD (538). Further, it has been shown in large randomised controlled trials that statin efficacy, represented by reduction in LDL-C, is directly proportional to baseline LDL-C (339). Combining these two findings suggests that individuals with higher baseline LDL-C achieve greater absolute risk reduction attributable to statin therapy.

Navarese et al. performed meta-regression on longitudinal studies of cardiovascular health comprising of a combined 136,299 patients (339). Their study further supports the hypothesis that baseline LDL-C is a predictor of relative benefit from LDL-C-reducing therapy**.** The primary endpoint for this analysis was all-cause mortality. Multivariable meta-regression models found that every 40 mg/dL (1.03 mmol/L) increase in baseline LDL-C was associated with a relative risk of 0.91 (95% CI: 0.85-0.98) for all-cause mortality. This value was adjusted for magnitude of LDL-C reduction, baseline risk profile, type of cholesterol-reducing agent, and age. Secondary endpoints in the analysis included cardiovascular mortality and major adverse cardiovascular events (MACE) as clinical endpoints. The adjusted relative risk per 40 mg/dL increase in baseline LDL-C for these events were 0.88 (95% CI: 0.80-0.97) and 0.91 (95% CI: 0.85-0.98), respectively. Relative risks were similar for myocardial infarction and coronary revascularization. However, no significant effect was found on cerebrovascular outcomes.

Soran et al. (340) acknowledge the direct relationship between baseline LDL-C and CVD risk reduction from cholesterol-reducing therapy. They show that the number needed to treat with statins to prevent one CVD event is often lower in low- and intermediate-risk individuals with high baseline LDL-C compared with high-risk, low LDL-C individuals.

Based on the analysis presented above, Thanassoulis et al. developed an equation to predict 10-year absolute benefit (ARR_{10}), specifically 10-year absolute risk reduction, attributable to statin therapy (341). This equation accounts for both absolute 10-year risk (AR_{10}) and baseline LDL-C:

$$ARR_{10} = AR_{10,un} - AR_{10,tr}$$

In this equation $AR_{10,tr}$ and $AR_{10,un}$ represent treated and untreated absolute 10-year risk of CVD, respectively. $AR_{10,tr}$ is a product of both untreated risk and baseline LDL-C. Therefore, ARR_{10} is also a product of these factors. Thanassoulis et al. estimated that the minimum ARR_{10} expected in a population with $AR_{10} \geq 7.5\%$ is approximately 2.3%.

Previous studies estimated the potential health benefits associated with prioritizing patients for statin therapy based on ARR_{10} rather than AR_{10} (340,341,539). Each study found that adding statin treatment based on ARR_{10} to standard AR_{10}-based treatment would lead to considerable

health gains in the U.S. population. However, these studies all adopted a short, 10-year time horizon and did not consider the economic costs of statin treatment strategies.

8.3.2 Objective

The objective of this study was to establish the relationships between baseline 10-year risk, baseline LDL-C, and long-term benefits from preventive statin therapy. In addition, this study aimed to quantify the cost-effectiveness of extending preventive statin therapy eligibility based on ARR_{10} in the U.S. ARR_{10} was assumed to correspond directly with both AR_{10} and LDL-C. This stratified approach to statin eligibility expansion was compared to lowering the blanket risk threshold to 5.0%.

To appeal to a clinical audience, while also establishing the economic benefits associated with different strategies of prevention, both the clinical- and cost-effectiveness of changing standard of care were considered.

8.3.3 PPICOSS

Population: The U.S. CVD-free population, aged 40 years and above.

Perspective: Health sector decision-maker. All healthcare costs accrued and population-level health gains are considered.

Intervention: Intermediate-intensity statin therapy. In health benefit analysis, the discounted QALYs gained from statin treatment are considered, stratified by age of treatment initiation, sex, baseline risk, and baseline LDL-C. In population-level cost-effectiveness analysis, two treatment eligibility expansions to standard of care were considered:

(i) expanding treatment to individuals with the lowest ARR_{10} in the $AR_{10} \geq 7.5\%$ population ($ARR_{10} \geq 2.3\%$)

(ii) expanding treatment further to individuals with $AR_{10} \geq 5.0\%$.

Comparator: Intermediate-intensity statins for individuals with $AR_{10} \geq 7.5\%$ or diabetes, high-intensity statins for individuals with $AR_{10} \geq 7.5\%$ and diabetes or LDL-C $\geq$190 mg/dL.

Outcome: Health benefit analysis – long-term QALY gains from preventive statin therapy, discounted 3% annually. Health economic analysis – long-term cost-per-QALY associated with statin therapy, with both costs and QALYs discounted 3% annually.

Setting: Primary care in the U.S.

Study Design: Microsimulation.

8.3.4 Methodology

CVD Microsim Model

The Cardiovascular Disease (CVD) Microsimulation Model, which was discussed in Chapter 5, evaluated the cost-effectiveness of different statin prioritisation policies. Survival time, health-related quality of life, and healthcare costs are assigned to health states in the model (ASCVD-free, coronary heart disease, stroke, combined coronary heart disease and stroke, or dead)

Simulation Cohort

A cohort of U.S. adults aged 40 years at baseline was assembled by repeatedly sampling pooled 1999-2014 National Health and Nutrition Examination Surveys guided by survey sampling weights. Adult lifetime risk factor trajectories were selected to intersect with cohort members' cross-sectional NHANES characteristics. These trajectories were estimated in the CU-NHLBI Pooled Cohorts Study dataset to predict individual-level lifetime trends in CVD risk factors, conditioned on age, sex, race, body mass index, and other covariates.

ASCVD risk prediction and model validation

Risk functions for incident CHD, stroke, and non-cardiovascular mortality were estimated in the Columbia University NHLBI (CU-NHLBI) Pooled Cohorts dataset. C-statistics for these risk functions were 0.84, 0.85, and 0.87, respectively. The CVD Microsim Model was recalibrated to match outcomes from the previously published and extensively validated

FORTRAN model that shares the same input data. Simulation model predictions were also validated by comparing simulation output with cumulative CHD and stroke incidence from individual cohort studies and cumulative survival curves derived from U.S. life tables. Chapter 5 discusses the validation and recalibration process for the model in more depth.

Simulation Parameters

The main health outcome in lifetime statin treatment simulations was lifetime QALYs gained. Lifetime ASCVD events prevented was a secondary outcome. ASCVD and non-CVD healthcare costs were estimated for economic evaluations. Future QALYs and costs were discounted at a rate of 3% annually (54). Simulation parameters are shown in Table 8-6 and reflected current knowledge about the costs, benefits, and risks associated with statin therapy.

Intermediate-intensity statin therapy reduced baseline LDL-C by 29% and high-intensity statin therapy reduced baseline LDL-C by 43% (284). Individuals on statins experienced a slightly increased diabetes risk and incurred annual QALY decrements attributable to the inconvenience of daily pill-taking (440,497). A proportion of statin users may suffer from myalgias and other minor medication side effects. Meta-analysis evidence firmly rejects the hypothesis that persistent statin use induces such adverse effects and these were therefore not modelled (446). These effects were accounted for in the rate of medication discontinuation and rate of follow up office visits, but no disutility was assumed. In a sensitivity analysis, 4.7% and 0.006% of persistent statin users experienced mild and major adverse events (37).

Adherence to treatment (proportion persisting in taking statin beyond persistence observed in clinical trials) was assumed to be 67%, 53%, and 50% in the first, second, and subsequent years of treatment, respectively (540). These adherence factors attenuated LDL-C reduction, side effect risks, and treatment-related costs. Annual costs of medications and treatment monitoring were also included.

Parameter	Base Case	Distribution for PSA	Lower	Upper	Source
Statin LDL-C reduction (% change from baseline)					
Intermediate-intensity	29	Beta	14	38	(284)
High-intensity	43	Beta	39	46	(284)
RR per 1.0 mmol/L LDL-C reduction					
CHD	0.76	Beta	0.73	0.79	(251)
Stroke	0.85	Beta	0.80	0.89	(251)
Statin-induced diabetes, absolute risk increase (%)	0.50	Log normal	0.00	0.01	(440)
Pill-taking disutility	0.0011	Beta	0.0000	0.0055	(497)
Treatment adherence*					
Year 1	67%	Beta	50%	84%	(540)
Year 2	53%	Beta	40%	66%	(540)
Subsequent Years	50%	Beta	38%	63%	(540)
Statin costs					
Intermediate-intensity	$24.16	Gamma	$18.12	$30.20	(541)
High-intensity	$55.22	Gamma	$41.42	$69.03	(541)
Check-up and screening visit costs					
Check-up visit, on treatment	$77.19	Gamma	$57.89	$96.49	(542)
Screening visit, no treatment	$77.19	Gamma	$57.89	$96.49	(542)
Other costs					
Lipid panel test	$19.00	Gamma	$14.25	$23.75	(350)
Liver panel test	$1.17	Gamma	$0.88	$1.46	(350)
Weighted statin-induced diabetes cost	$7.75	Gamma	$5.81	$9.69	(350)
Annual number of visits					
Years between screening visits	5	ND**	4	6	(27)
Primary care check up on treatment (yearly or more)	1.25	Gamma	0	2.5	(27)
Discount Rates					
Health	3.00%	ND	6%	0	(54)
Costs	3.00%	ND	6%	0	(54)

*Adherence represents adherence rate beyond observed adherence in clinical trials, reduces LDL-C, treatment-related disutility and treatment-related costs in simulation. **No distributional assumptions in probabilistic sensitivity analysis.

Table 8-6: Simulation parameters for study of AR_{10} and ARR_{10}-based statin therapy

Health Outcomes Analysis

A health outcomes analysis evaluated the lifetime discounted QALYs gained from initiating preventive statin therapy in U.S adults without ASCVD at age 40, 50, or 60 years. Lifetime statin health outcomes were stratified by baseline AR_{10}, baseline LDL-C, sex, and age at treatment initiation.

Population Health Economic Analysis

Health economic analyses evaluated lifetime cost-effectiveness associated with prioritizing a range of ASCVD risk groups for preventive statin therapy. In all health economic analyses, a U.S. health sector perspective was adopted. Therefore, all formal healthcare costs were included in the analysis, regardless of payer (54).

Treatment groups included treat if $AR_{10} \geq 7.5\%$, (current standard of care; Group A); treat $ARR_{10} \geq 2.3\%$ but $AR_{10} < 7.5\%$ (Group B); and treat the remainder of $AR_{10} \geq 5.0\%$ (Group C). The ARR_{10} threshold of 2.3% represents the minimum expected benefit in individuals eligible for statins under the 2013 ACC/AHA guidelines (that is, the minimum expected ARR_{10} at the lowest AR_{10}) (341). The treatment groups are presented graphically in Figure 8-7, with each scatterplot point representing one-person year of treatment eligibility over the collective lifetime of the NHANES cohort and pie chart wedge areas representing the proportion of total person-years falling within the treatment group categories. Treatment strategies added these treatment groups sequentially and compared the outcomes associated with adding each new treatment group to the prior strategy incrementally: Group A was treated first, and then A+B, followed by A+B+C. Group A is currently strongly recommended for statin treatment in the 2013 ACC/AHA guideline. No specific guideline relates to Group B, but most of these individuals fall into the 5.0-7.4% AR_{10} range. Group C is a large group for which treatment initiation recommendations are unclear.

Following the ACC/AHA guidelines, in all treatment scenarios, patients with diabetes but $AR_{10} < 7.5\%$ were treated with intermediate-intensity statins (27). Similarly, in all treatment scenarios, patients with LDL-C ≥ 190 mg/dL and patients with diabetes and $AR_{10} \geq 7.5\%$ received high-

intensity statins. These groups were treated along with Group A and in all subsequent incremental strategies.

A new wave of individuals became statin treatment eligible every five years, based on these treatment strategies and determined by sex and dynamic changes in age and risk factor levels.

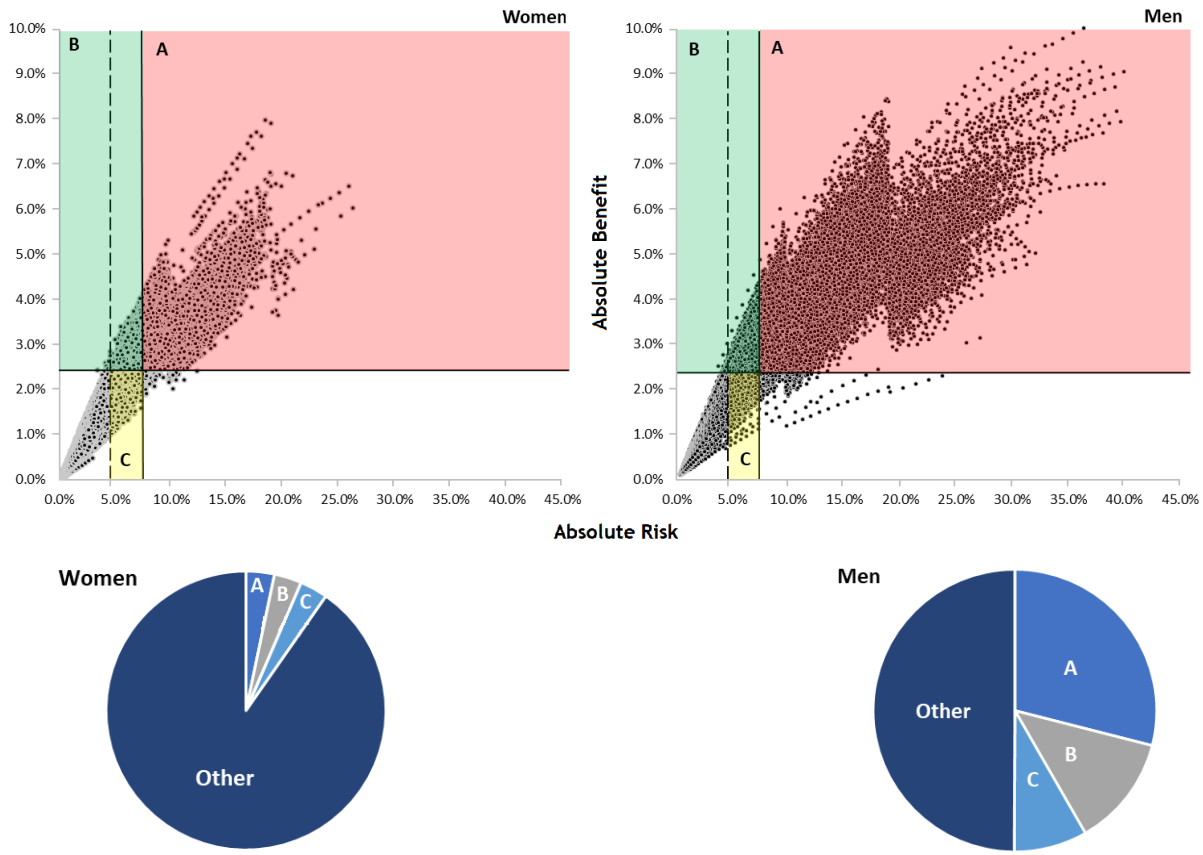


Figure 8-7: Treatment subgroups in population-level analysis. Each point represents estimated AR_{10} and ARR_{10} for one life year of an individual in NHANES 1999-2014. Underlying pie chart represents relative size of each treatment group.

<u>Stratified Health Economic Analysis</u>

Additional stratified analysis estimated ICERs associated with initiating statin therapy at age 40 in male and female subgroups of the U.S. population, according to combinations of baseline AR_{10} and ARR_{10}, each compared with no treatment. Statin treatment benefit was classified as very cost-effective (ICER <$10,000/QALY or cost-saving), moderately cost-effective (ICER ≥$10,000/QALY but <$50,000/QALY), borderline cost-effective (ICER ≥$50,000/QALY but <$150,000/QALY), or not cost-effective (ICER ≥$150,000/QALY) (543).

Sensitivity Analyses

Sensitivity analysis quantified uncertainty inherent in population-level cost-effectiveness modelling. One-way sensitivity analyses explored the results of the health economic analysis at upper and lower uncertainty bounds of treatment parameters described in Table 8-6.

Probabilistic sensitivity analyses stochastically sampled Table 8-6 input distributions in 500 independent iterations. Using the cost and QALY results from probabilistic analyses, a cost-effectiveness acceptability curve was produced to describe the probability of each treatment strategy being the most cost-effective option for decision-makers at a range of willingness-to-pay thresholds.

Secondary Analysis: Cost-Effectiveness of ARR in Scottish Population

The objective of this study was to estimate the health benefits and cost-effectiveness of prioritising patients with a combination of elevated LDL-C and 10-year risk for preventive statin therapy. This analysis adopted a U.S. health sector perspective, with the U.S-based CVD Microsim Model. Conducting the analysis from a U.S. perspective allowed for collaboration with U.S. researchers, leading to ongoing work on a research paper that aims to influence clinical practice in the U.S. However, the results cannot be compared to previous results in this thesis; CVD event risk, risk scores used in clinical practice, and costs of health services vary between Scotland and the U.S. A secondary analysis was therefore conducted using the Scottish CVD Policy Model to allow comparison of the costs and benefits associated with ARR compared to other prioritisation strategies considered in this thesis.

In the secondary analysis, population-level cost-effectiveness analysis was conducted from the perspective of a Scottish health sector decision-maker. The same methodology (e.g. estimation of Scottish population's risk factor distribution using SHeS 2011, treatment-related costs and effects, projection of results) was adopted as in Chapter 7 and Section 8.2**.** Two ARR strategies were defined which would treat approximately the same number of individuals as ASSIGN 20 and ASSIGN 10. Descriptive statistics of individuals treated, discounted QALYs, discounted

healthcare costs, CVD events prevented, and life years gained, were presented for each strategy. The SIMD-distribution of discounted QALY gains were also presented.

8.3.5 Results

Study cohort characteristics and outcomes without statin treatment

Characteristics of the simulation cohorts at ages 40 (baseline), 50, and 60 years in the scenario without statin treatment are shown in Table 8-7. In total, 1,000,000 individual ASCVD life histories were simulated (500,000 female) starting at age 40 until age 89 years. Without statin treatment, approximately 4.7% of the baseline cohort was projected to have an incident ASCVD event by age 50 years. An additional 7.5% was projected to experience incident ASCVD by age 60 years. AR_{10} increased with age, while mean LDL-C increased until age 50 years then decreased.

Health Outcomes Analysis

Across all age, AR_{10}, and sex categories, individuals with higher LDL-C consistently achieve greater lifetime health benefits from statin therapy, as shown in Figures 8-8 and 8-9. When assessed at age 40, the large majority of individuals had risk scores <5.0%; conversely, when assessed at age 60, data were too sparse for males and females with AR_{10} <5.0%.

At the same age at initiation, lifetime statin benefits increase directly and linearly with increasing AR_{10}. At any given AR_{10}, lifetime statin benefits are greater with higher baseline LDL-C. Indeed, high LDL-C, low-risk patients achieve greater lifetime statin benefit than high-risk, low LDL-C individuals. For example, 40 year-old males with LDL-C ≥160 mg/dL and AR_{10} <1% benefit similarly from statins as 50-year-old males with AR_{10} 15-20% and LDL-C 130-159 mg/dL. Similarly, 40-year-old females with AR_{10} <1% and LDL-C ≥160 mg/dL benefit as much from statin treatment as 60-year old females with AR_{10} 10-15% and LDL-C 130-159 mg/dL. Notably, women with low levels of LDL-C may experience negative QALYs from treatment, regardless of baseline AR_{10}. This is caused by the low levels of absolute risk reduction achieved in these populations and the existence of pill-taking disutility

	Females			Males			Total		
Simulation baseline age (years)	40	50	60	40	50	60	40	50	60
Characteristics									
N CVD-free	500,000	476,215	433,675	500,000	461,250	389,580	1,000,000	937,465	823,255
Cumulative mortality (%)	0.0	1.6	5.9	0.0	2.7	9.6	0.0	2.1	7.8
Cumulative CVD incidence (%)	0.0	3.5	8.7	0.0	5.9	15.6	0.0	4.7	12.2
African American (%)	11.5	11.4	11.2	10.5	10.5	9.9	11.0	10.9	10.6
Ten year ASCVD risk category (%)									
<2.5 %	92.0	79.1	3.8	75.0	49.5	0.0	83.5	64.5	2.0
2.5-4.9 %	6.8	17.2	64.8	18.5	32.6	0.1	12.7	24.7	34.2
5.0-7.4 %	0.8	2.5	18.2	4.9	12.1	16.2	2.9	7.2	17.2
>=7.5%	0.3	1.2	13.2	1.5	5.8	83.7	0.9	3.5	46.6
LDL cholesterol category (%)									
<100 mg/dL	17.6	14.4	16.9	11.3	10.8	18.7	14.5	12.6	17.7
100-129 mg/dL	50.0	51.9	55.7	45.0	49.0	57.4	47.5	50.4	56.5
130-159 mg/dL	28.1	28.6	23.0	35.5	33.2	20.9	31.8	30.8	22.0
>=160 mg/dL	4.3	5.2	4.4	8.1	7.1	2.9	6.2	6.1	3.7
Ten year ASCVD risk (mean)	0.9	1.9	4.8	2.0	3.4	11.6	1.5	2.6	8.0
LDL cholesterol (mean, mg/dL)	120.6	122.6	119.6	127.4	125.9	117.4	124.0	124.2	118.5
HDL cholesterol (mean, mg/dl)	58.0	59.7	60.9	46.8	47.1	48.2	52.4	53.5	54.9
Systolic blood pressure (mean, mmHg)	115.1	120.0	124.7	121.0	123.5	125.5	118.1	121.7	125.0
Active smoking (%)	18.9	18.1	16.9	26.4	25.0	22.7	22.6	21.5	19.6
Diabetes (%)	3.6	8.9	16.4	5.3	12.9	21.7	4.4	10.9	19.0

Table 8-7: Descriptive statistics of simulation cohort at ages 40, 50, and 60 years. Simulation starting at age 40. Data represents scenario with no statin treatment.

Policy	Years of Treatment Eligibility	CVD Events	CHD Events	CVD Free Years	Life Years	Discounted QALYs	Discounted Costs	ICER* ($/QALY)
Women								
Treat AR ≥7.5%	8,446,906	353,000	238,000	18,019,000	20,267,000	11,526,000	73,335,900,000	*Reference*
Add AR <7.5% but AB ≥2.5%	9,140,950	353,000	237,000	18,028,000	20,269,000	11,526,700	73,336,100,000	350
Add remainder AR ≥5.0%	10,014,973	352,000	236,000	18,038,000	20,271,000	11,527,100	73,340,300,000	7,700
Men								
Treat AR ≥7.5%	10,921,835	552,000	367,000	15,143,000	18,721,000	10,943,700	72,517,600,000	Str. Dom**
Add AR <7.5% but AB ≥2.5%	12,032,933	551,000	365,000	15,261,000	18,725,000	10,945,900	72,504,500,000	*Reference*
Add remainder AR ≥5.0%	12,868,559	550,000	365,000	15,285,000	18,727,000	10,946,800	72,505,400,000	1,000
Combined Women and Men								
Treat AR ≥7.5%	19,368,741	906,000	605,000	33,162,000	38,989,000	22,469,700	145,853,500,000	Str. Dom**
Add AR <7.5% but AB ≥2.5%	21,173,883	903,000	603,000	33,289,000	38,995,000	22,472,500	145,840,600,000	*Reference*
Add remainder AR ≥5.0%	22,883,532	902,000	601,000	33,323,000	38,998,000	22,474,000	145,845,700,000	3,400

*Incremental to prior most effective, non-dominated strategy **Strictly dominated

Table 8-8: Cost-effectiveness, person years of treatment, CHD events prevented, ASCVD events prevented, CVD-free years gained, and life years gained for three AR_{10} and ARR_{10}-based strategies for statin prioritization.

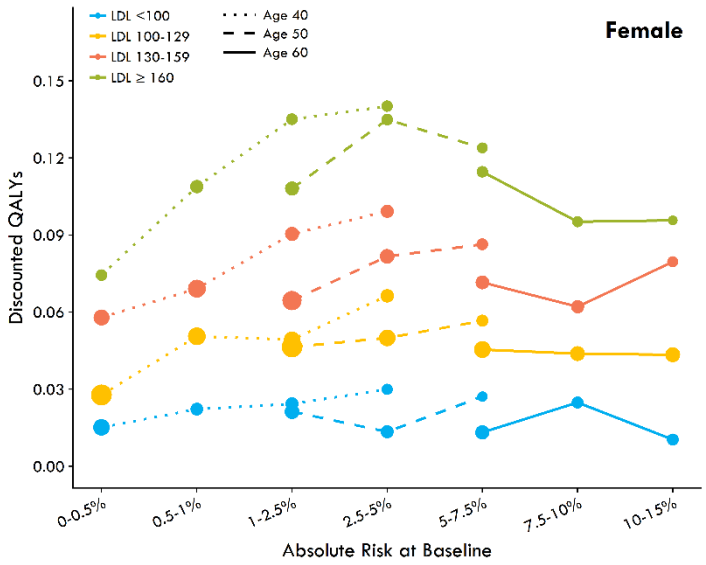


Figure 8-8: Average discounted QALY gains from statin therapy versus baseline AR_{10} for women, stratified by baseline LDL-C. Dotted line: statin therapy initiated at age 40, dashed line: statin therapy initiated at age 50, solid line: statin therapy initiated at age 60. Point size represents relative size of subgroup population.

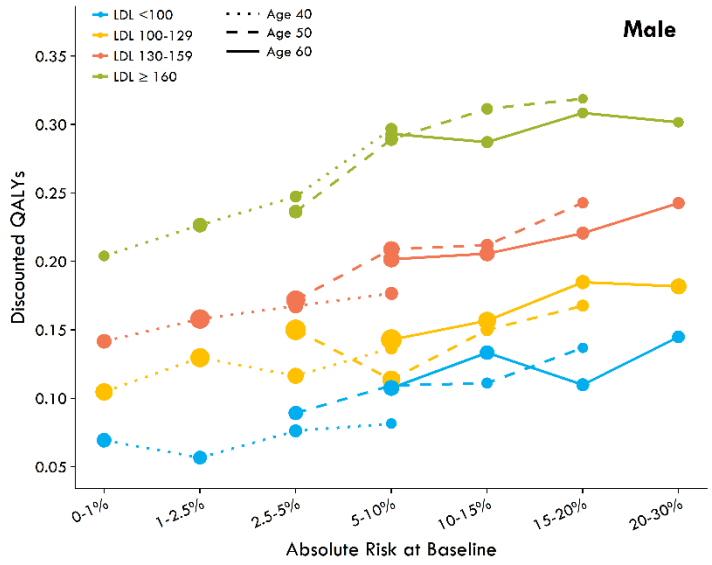


Figure 8-9: Average discounted QALY gains from statin therapy versus baseline AR_{10} for men, stratified by baseline LDL-C. Dotted line: statin therapy initiated at age 40, dashed line: statin therapy initiated at age 50, solid line: statin therapy initiated at age 60. Point size represents relative size of subgroup population.

Population Health Economic Analysis

In both the male and female simulations, large health gains were achieved by expanding statin eligibility. Statin therapy according to any strategy would prevent a larger number of CVD events in men, as shown in Table 8-8.

For women, the ICER associated with extending treatment eligibility to Group B was approximately $350/QALY. The ICER associated with further extending treatment eligibility by reducing the threshold for treatment initiation to 5% would be approximately $7,700/QALY.

For men, treating Group A only (current standard of care) was strictly dominated by treating Groups A+B. Adding men with ARR_{10} ≥2.3% but AR_{10} <7.5% to standard of care treatment would therefore gain health and save costs. The ICER for treating all individuals with AR_{10} ≥5% or ARR_{10} ≥2.3% (Groups A+B+C) compared with treating Groups A+B only was approximately $1,000/QALY.

Compared with current practice, men would gain approximately 78% of the lifetime QALYs, 71% of the life years, and 93% of the total CVD free years associated with adding ARR_{10} ≥2.3% but AR_{10}<7.5%, respectively. Men would also experience around 62% of the total person years of treatment.

When men and women were combined, extending treatment from standard of care to patients with ARR_{10} ≥2.3% was cost saving, and extending eligibility further to patients with AR_{10} ≥5% produced an ICER of $3,400/QALY. Given a willingness-to-pay threshold of $50,000/QALY, reducing the AR_{10} risk threshold to ≥5% while also treating all patients with ARR_{10} ≥2.3% was the optimal strategy. This finding was consistent in both the male and female subgroups.

Sensitivity Analysis

Figures 8-10 to 8-13 present results from the one-way sensitivity analysis in a tornado diagram. Figures 8-10 and 8-11 relate to the transition from treating Group A alone to treating Group A+B for men and women, respectively. Figure 8-12 and 8-13 relate to the transition from treating Group A+B compared to treating Group A+B+C.

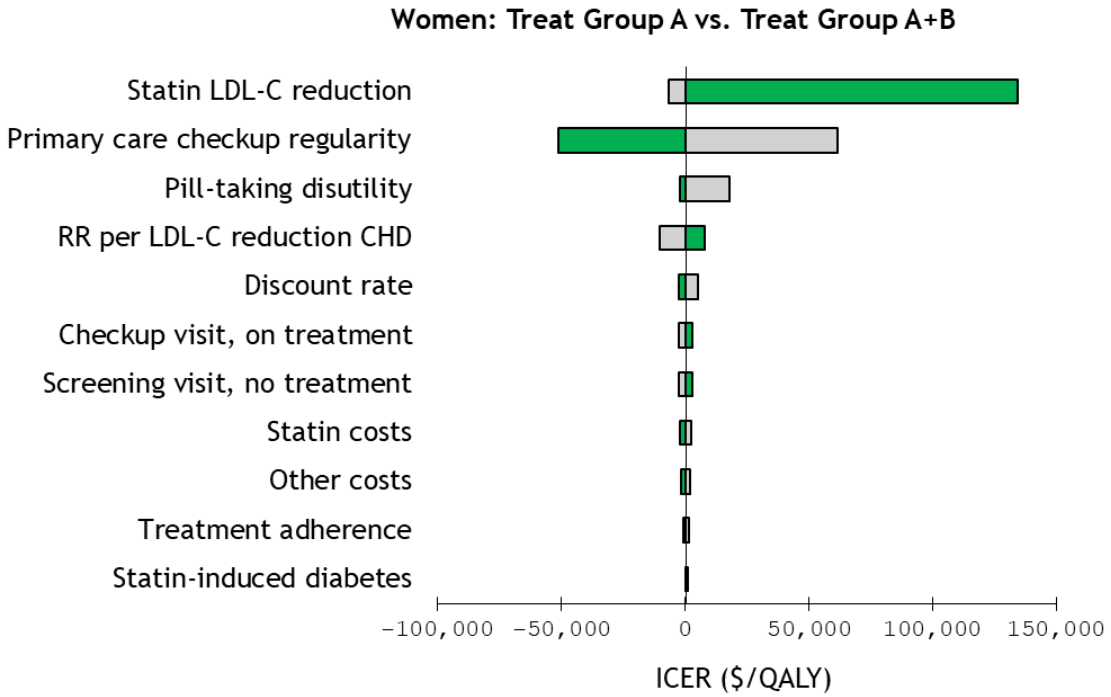


Figure 8-10: Tornado diagram representing ICER of treating women in Groups A+B compared to Group A alone

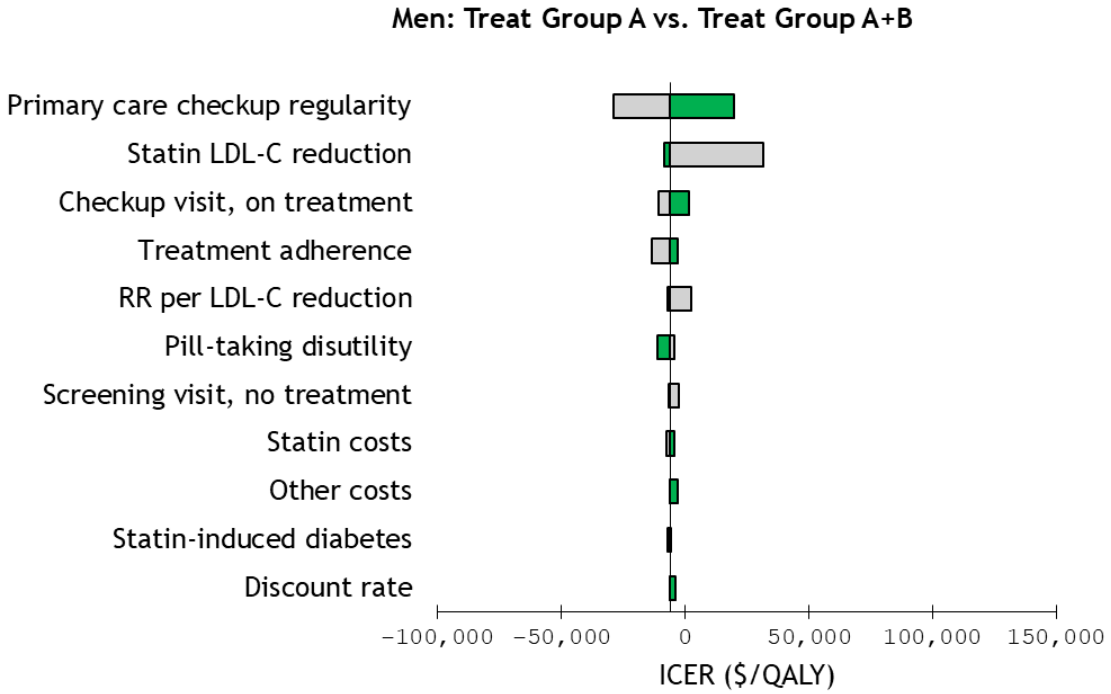
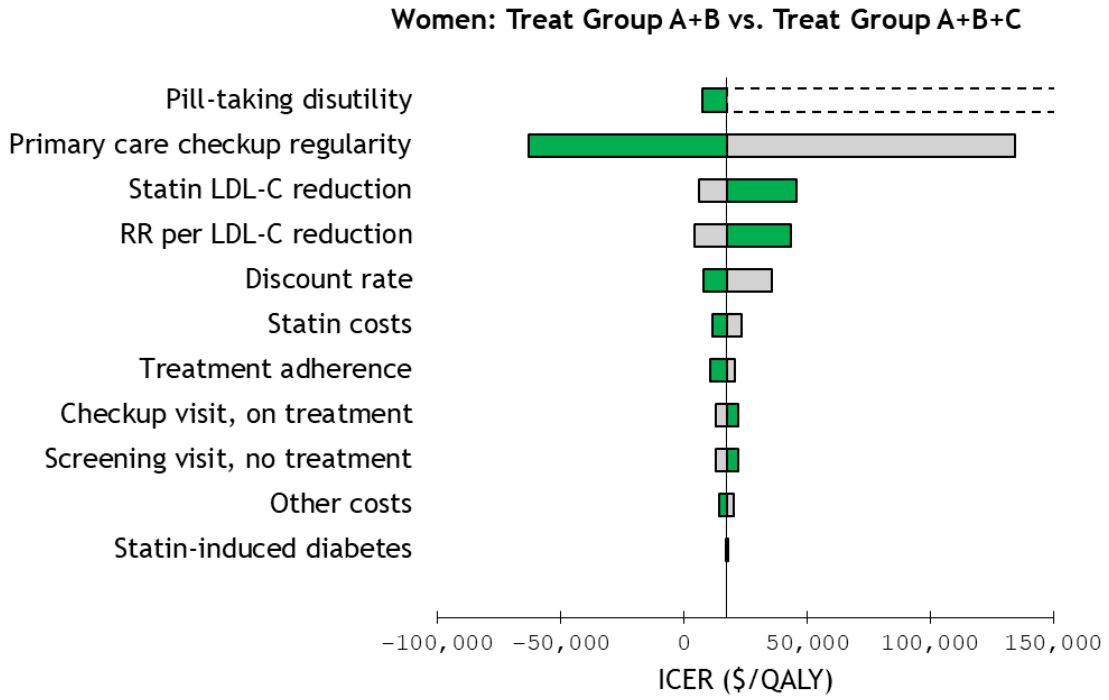


Figure 8-11: Tornado diagram representing ICER of treating men in Groups A+B compared to Group A alone



*Employing the upper estimate of pill-taking disutility led to the ARR10 approach being strictly dominated by no statin treatment

Figure 8-12: Tornado diagram representing ICER of treating women in Groups A+B+C compared to Group A+B.

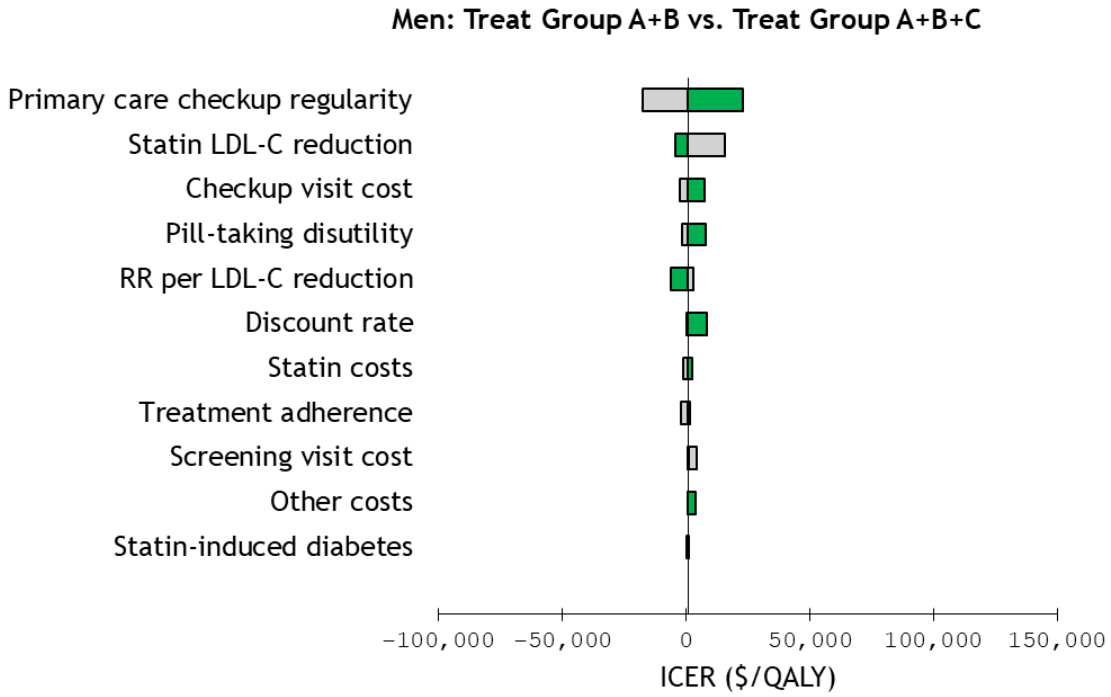


Figure 8-13: Tornado diagram representing ICER of treating men in Groups A+B+C compared to Group A+B

Uncertainty in the ICER estimate was greater for women than men, likely due to lower event rates in women. For both men and women, efficacy of statin therapy and regularity of on-treatment monitoring visits were strong determinants of cost-effectiveness. For women, higher pill-taking disutility led treatment of individuals with AR_{10} ≥7.5% or ARR_{10} ≥2.3% to be strictly dominated. At an annual pill-taking disutility of around 0.0033, the ICER for women fell below $50,000/QALY. An annual pill-taking disutility of 0.0033 for a 60-year-old with 20 years remaining life expectancy would amount to trading approximately 3.4 weeks of healthy life to avoid taking statins for the remaining lifetime.

Probabilistic sensitivity analysis results are presented in Figure 8-14 for women and Figure 8-15 for men. For men and women, at very low levels of willingness-to-pay (<$5,000/QALY), standard treatment has the highest probability of being cost-effective. As willing-to-pay increases, the probability that adding treatment of ARR_{10} ≥2.3% is optimal increases. However, if a decision-maker is willing to invest $10,000/QALY for men and $20,000/QALY for women, treating all AR_{10} ≥5.0% and ARR_{10} ≥2.3% becomes the most cost-effective strategy.

Stratified Health Economic Analysis

Figure 8-16 converts the health economic results into color-coded cost-effectiveness decision grids, ranking the cost-effectiveness (ICERs) of lifetime statin therapy at age 40 for a range of baseline AR_{10} and baseline LDL-C subgroups compared with no statin treatment. All combinations of AR_{10} and LDL-C are very or moderately cost-effective in men. In both men and women, cost-effectiveness increases with both higher AR_{10} and higher LDL-C.

Treating individuals with low AR_{10} and high LDL-C has a health economic value equivalent to treating individuals with high AR_{10} and low LDL-C. This principle is illustrated most strikingly in the similar lifetime cost-effectiveness of treating the highest AR_{10} men and women aged 40 years with LDL-C <100 mg/dL and the lowest AR_{10} men and women with LDL-C ≥160 mg/dL.

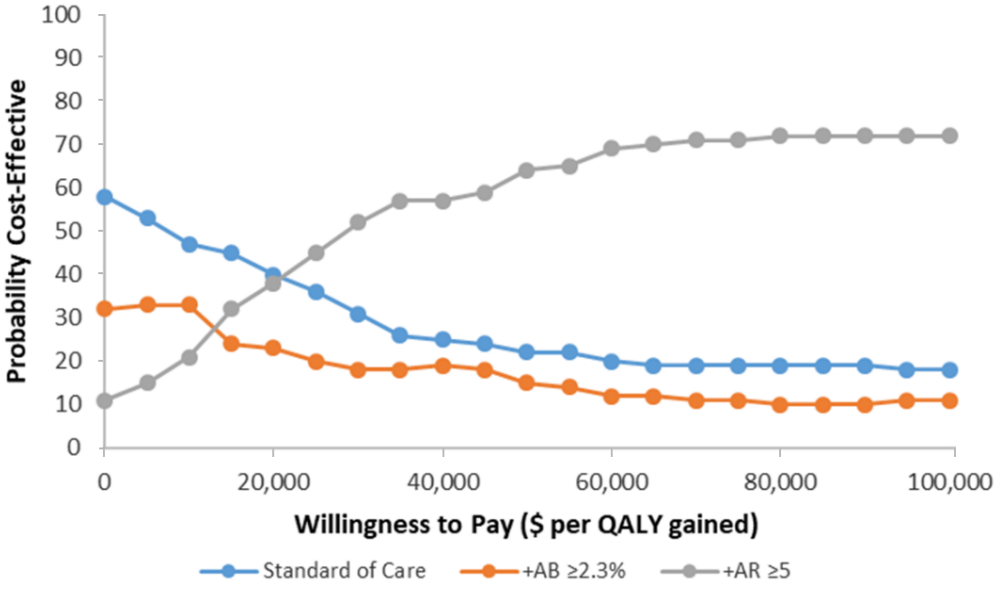


Figure 8-14: Cost-effectiveness acceptability curve for women

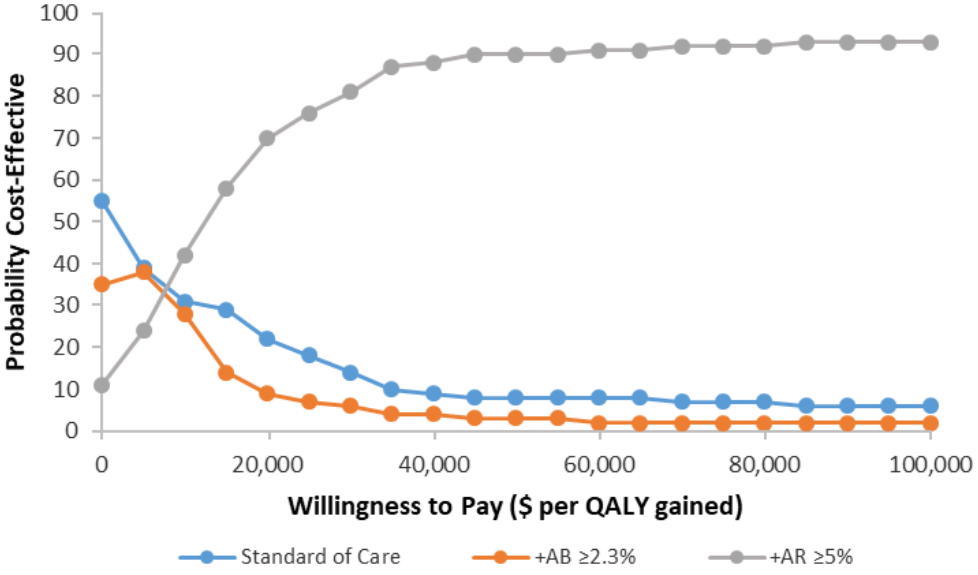


Figure 8-15: Cost-effectiveness acceptability curve for men

≥$150,000 per QALY	Not cost-effective
$50,000-100,000 per QALY	Borderline cost-effective
$10,000-50,000 per QALY	Moderately cost-effective
<10,000 per QALY (or cost-saving)	Very cost-effective

Women		Baseline LDL-C (mg/dl)			
		<100	100-129	130-159	>160
Baseline 10-Year Risk	0-1%	215,815	88,360	23,773	9,633
	1-2.5%	88,697	26,431	10,516	341
	2.5-5%	31,346	11,094	1,196	Cost Saving
	≥5%	4,729	608	Cost Saving	Cost Saving

Men		Baseline LDL-C			
		<100	100-129	130-159	>160
Baseline 10-Year Risk	0-1%	41,200	21,883	14,820	9,221
	1-2.5%	34,127	17,728	10,633	5,415
	2.5-5%	25,437	13,197	5,061	1,189
	≥5%	11,437	4,182	3,610	192

Figure 8-16: Cost-effectiveness grids showing ICERs associated with lifetime intermediate-intensity statin therapy (starting at age 40) for a range of AR_{10}- and LDL-C-defined subgroups. Results stratified by sex.

Secondary Analysis: Cost-Effectiveness of ARR in Scottish Population

Two absolute risk reduction-based prioritisation strategies were defined: ARR 20 which treats approximately the same number of individuals as ASSIGN 20 and ARR 10 which treats approximately the same number of individuals as ASSIGN 10. Individuals were treated under ARR 20 and ARR 10 if they were expected to achieve a minimum absolute risk reduction from treatment of 3.95% and 6.1%, respectively.

Table 8-9 presents the descriptive statistics for the cohort of individuals prioritised for statin therapy under blanket risk threshold policies, ARR policies, and age-stratified risk threshold policies, and statistics for the overall SHeS 2011 population. A greater proportion of older individuals were treated under the ARR approach to prioritisation compared to age-stratification of risk thresholds. Indeed, it appears that ARR strategies prioritise a similar group of patients for treatment as the blanket threshold strategies.

Cost-effectiveness results: Table 8-10 presents cost-effectiveness results for the ARR strategies compared to Blanket 20, Age-Strat 20, Blanket 10, and Age-Strat 10. Age-Strat 20 is extendedly dominated by Blanket 10. Blanket 20, ARR 20, Blanket 10, ARR 10, and Age-Strat 10 lead to consecutive increases in costs and QALYs. A decision-maker with a cost-effectiveness threshold of £20,000/QALY would choose to implement ARR 10.

		Overall Popula -tion	ASSIGN 20	Age-Strat 20	ARR 20	ASSIGN 10	Age-Strat 10	ARR 10
Proportion of Age-Group Treated (%)	40-44	n/a	0	5	0	3	12	2
	45-49	n/a	2	14	2	14	29	16
	50-54	n/a	5	30	6	38	49	39
	55-59	n/a	15	50	19	74	74	74
	60-64	n/a	41	45	45	94	86	93
	65-69	n/a	75	52	75	100	85	99
	70-74	n/a	92	65	89	100	80	99
	75-79	n/a	100	74	92	100	88	100
	80+	n/a	100	0	67	100	81	76
Average Value	Male (%)	42	45	53	47	47	51	47
	SIMD	19.5	21.2	23.5	20.6	20.5	21.4	20.4
	Diabetes (%)	7	15	17	13	11	11	10
	FH (%)	46	68	73	67	62	65	61
	CPD	7	8	10	8	7	7	7
	SBP (mmHg)	131	134	134	134	133	133	133
	TC (mmol/L)	5.8	5.8	5.8	5.9	5.8	5.8	5.8
	HDL (mmol/L)	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Table 8-9: Descriptive statistics of treated patients for Blanket, ARR, and Age-Strat policies

Policy	Number Treated	Discounted QALYs	Discounted Cost (£1000's)	ICER (£/QALY)
Familial Hyp.	*Reference*			
Blanket 20	793,559	92,300	636,000	6,900
ARR 20	793,762	96,300	687,000	12,900
Age-Strat 20	793,596	99,500	882,000	Ext. Dominated
Blanket 10	1,381,059	164,000	1,596,000	13,500
ARR 10	1,380,535	166,000	1,627,000	15,700
Age-Strat 10	1,381,054	168,000	1,719,000	36,500

Ext. – extendedly

Table 8-10: Base case cost-effectiveness analysis, Blanket, ARR, and Age-Strat policies

Intermediate outcomes: Primary CVD events prevented, life year gains, and the disaggregation of costs are presented in Tables 8-11 and 8-12. ARR policies prevent fewer events than Age-Strat policies and result in a smaller number of life year gains.

Policy	Primary CVD Events Prevented	Life Years Gained
Familial Hyp.	*Reference*	
Blanket 20	27,000	170,000
ARR 20	28,000	181,000
Age-Strat 20	29,000	198,000
Blanket 10	49,000	351,000
ARR 10	49,000	356,000
Age-Strat 10	50,000	368,000

Table 8-11: Intermediate Outcomes for Blanket, ARR, and Age-Strat policies

Policy	Disc. Costs (£1000's)			
	Non-CVD	CVD	Statin	Monitoring
Familial Hyp.	*Reference*			
Blanket 20	720,000	-718,000	84,000	550,000
ARR 20	776,000	-751,000	88,000	573,000
Age-Strat 20	986,000	-889,000	108,000	678,000
Blanket 10	1,562,000	-1,322,000	190,000	1,166,000
ARR 10	1,596,000	-1,337,000	192,000	1,176,000
Age-Strat 10	1,707,000	-1,408,000	200,000	1,220,000

Table 8-12: Disaggregated costs, Blanket, ARR, and Age-Strat policies

Probabilistic sensitivity analysis: Figure 8-17 presents results from a probabilistic sensitivity analysis in which risk function hazard ratios and key simulation parameters (Table 7-4) were sampled stochastically in 500 independent iterations. At a willingness-to-pay threshold of £20,000/QALY, ARR 10 was optimal in 70% of iterations.

Inequality Analysis: Results were disaggregated to estimate the effect of threshold reduction on health inequalities. Figure 8-18 shows the discounted QALY gains achieved per 1,000 individuals in the population, disaggregated by SIMD quintile. In absolute terms, all SIMD quintiles achieved greater health gains under ARR 10 than ARR 20. Absolute health gains continuously increased with level of social deprivation.

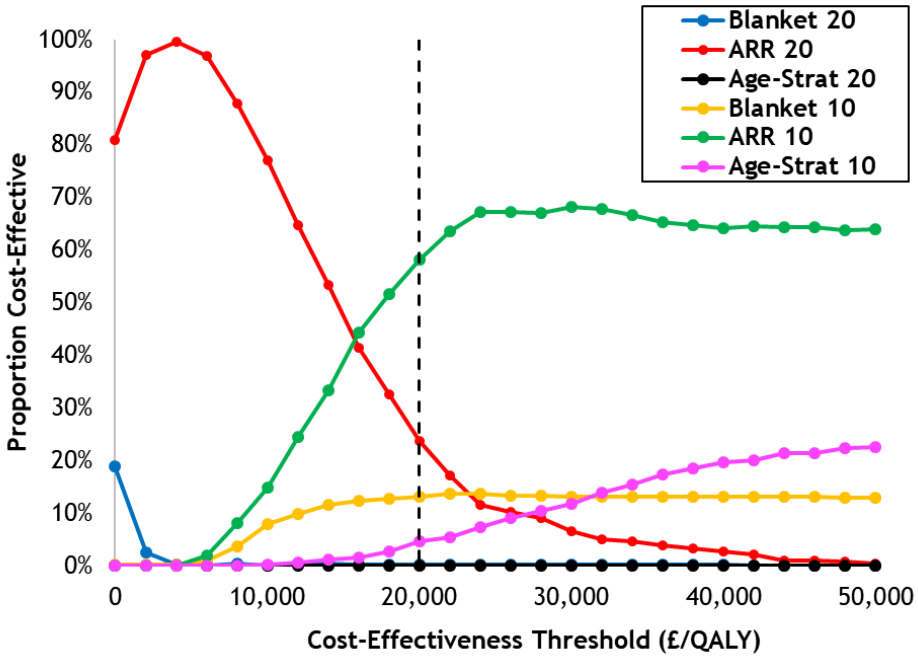


Figure 8-17: Cost-effectiveness acceptability curve, ASSIGN 20, Age-Strat 20, ARR 20, ASSIGN 10, Age-Strat 10, and ARR 10

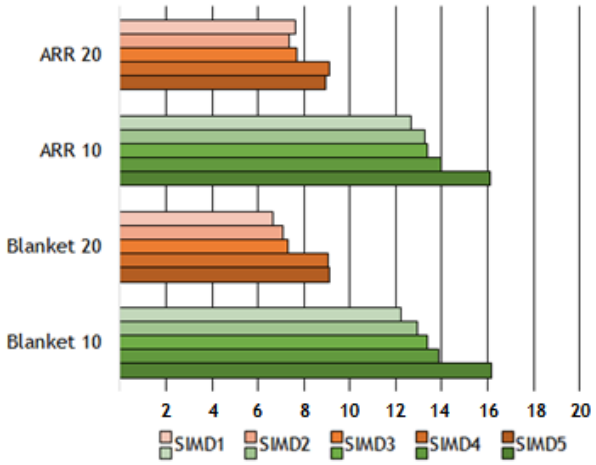


Figure 8-18: Discounted QALY gains for absolute risk reduction and blanket risk threshold strategies per 1,000 individuals, disaggregated by SIMD quintile

The proportion of health gains achieved per quintile of social deprivation was also estimated. These results are displayed in Figure 8-19. The distribution of discounted QALY gains was similar for the absolute risk reduction-based treatment strategies. Both policies were progressive: they led to a greater proportion of health gains being achieved in the two most deprived SIMD quintiles of the Scottish population compared with the two least deprived quintiles.

ARR 20 was less progressive than Blanket 20. The two most deprived SIMD quintiles combined gained 44% of all health benefits under Age-Strat 20, compared to 37% of health gains achieved by the two least deprived quintiles – a 7% difference. This difference was 11% for Blanket 20. ARR 10 was less progressive than Blanket 10. The difference in proportion of QALY gains between the two most deprived and least deprived quintiles for ARR 10 and Blanket 10 were 6% and 7%, respectively.

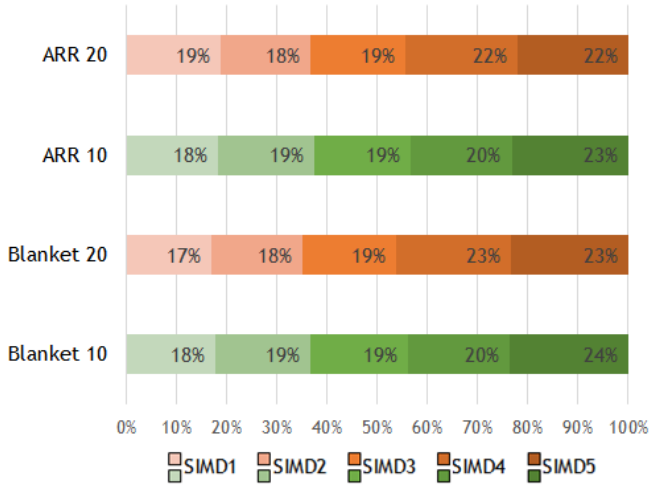


Figure 8-19: Proportion of discounted QALY gains achieved by different SIMD quintiles, absolute risk reduction and blanket risk threshold strategies

8.3.6 Discussion and Limitations

Discussion

Previous work has estimated the short-term (10-year) health benefits that could be achieved with ARR_{10}-based prioritisation for preventive statin therapy. This study builds on these studies, employing a much lengthier time horizon. This longer time horizon allowed for the capture of lifetime statin benefits in younger adults with elevated LDL-C. The CVD Microsimulation Model employed in the analysis also accounts for the competing risk of non-CVD mortality faced by older individuals. Additional strengths of this analysis include: representation of generic health outcomes (QALYs) which permit comparison between disease areas, estimations of the costs associated with different treatment strategies, and discounting of future outcomes.

The current paradigm in CVD prevention is based on absolute risk alone. This may be biased due to short-term perspective and a failure to account for covariates which modify treatment effect. The health benefit analysis here showed that the long-term, discounted benefits from statin therapy are greater for individuals with elevated baseline LDL-C. Indeed, LDL-C appears to be a stronger predictor of capacity-to-benefit from statin therapy than AR_{10} alone.

In the introduction of this study it was stated that the greatest degree of uncertainty in current U.S. guidelines relates to treatment decisions for individuals with an AR_{10} of 5.0-7.5%. The population-level cost-effectiveness analysis presented shows that it would be a cost-effective use of healthcare resources to treat individuals with AR_{10} <7.5% but ARR_{10} ≥2.3%. However, the highly cost-effective nature of statins suggests that adding treatment to all individual with AR_{10} ≥5.0% would also be cost-effective.

A secondary analysis, set in the Scottish NHS, considered the cost-effectiveness of ARR-based prioritisation compared to blanket and age-stratified risk thresholds. These results showed that implementing ARR to prescribe statins would lead to fewer discounted QALY gains in the Scottish population compared to equivalent age-stratified risk threshold policies. ARR-based policies likely reclassify a smaller group of intermediate-risk patients than age-stratification of risk thresholds, as exhibited in the descriptive statistics of treated patients. However, ARR-based prioritisation is less expensive than age-stratification of risk thresholds. Indeed, ARR 10 was the optimal strategy considered for decision-makers with a cost-effectiveness threshold of £20,000/QALY.

Limitations

This study assumed a direct association between baseline LDL-C and statin benefit (risk reduction is directly related to unit reduction in LDL-C) and did not account for statin effects independent of LDL-C change. Specifically, statin benefits were modelled based only on LDL-C change and not on alternative measures of statin efficacy like change in non-HDL cholesterol or Apo-E level. ASCVD prediction was based on “current” characteristics and not cumulative exposure history. Hence, this risk prediction may have underestimated the benefits of treating high LDL-C earlier in life, including before age 40.

Further research should consider the impact of changing the demographic profile of patients receiving statin therapy. Putting the onus of treatment on LDL-C alongside AR_{10} will likely result in the treated population being younger and less healthy. Changing the demographic profile of those treated may affect treatment uptake and adherence.

8.4 Chapter Summary

The purpose of this chapter was to analyse strategies which incorporate 10-year risk alongside another variable to determine who should receive preventive therapy for CVD. Age-stratified risk thresholds target treatment at individuals who are at heightened risk within their age-group due to unhealthy levels of modifiable risk factors. The absolute risk reduction approach to prevention targets treatment at patients with elevated levels of a treatment effect modifier. In the case of statins, this modifier is LDL-C. Each of these approaches aims to better reflect heterogeneity in treatment outcome between patients than a blanket risk threshold approach.

Individuals with the same 10-year risk score may experience very different outcomes from preventive therapy dependent on their age. Age-stratification of risk thresholds can be undertaken to prioritise treatment for a greater number of young, unhealthy individuals and fewer old, healthy individuals. Younger individuals face fewer competing risks and are therefore likely to gain more health from preventive therapy. The analysis in this chapter showed that age-stratification of risk thresholds leads to an improvement in overall population health. However, this strategy also requires regular monitoring of individuals from a young age. This regular monitoring, coupled with extended exposure to pill-taking disutility, leads age-stratification to have an ICER in excess of the cost-effectiveness threshold in the U.K. Innovative means of providing low cost patient monitoring would make age-stratification of risk threshold much more cost-effective.

Individuals with the same 10-year risk score but different levels of a treatment effect modifier may also experience different outcomes from preventive therapy. In the case of statin therapy, LDL-C is an important determinant of absolute CVD risk reduction. Analysis in this chapter showed that, when risk is kept constant, individuals with elevated LDL-C achieve greater health benefits from statin therapy. It was additionally shown that expanding current treatment

guidelines in the U.S. to include treatment for individuals with intermediate risk and elevated LDL-C would be cost-effective. Further expansion of treatment guidelines to all intermediate-risk patients would likely also be cost-effective. However, physicians may be inclined to prefer treatment strategies which focus on a subset of patients with an elevated level of a well-established CVD biomarker.

Age-stratified risk thresholds and the absolute risk reduction approach to statin prioritisation represent improvements upon current practice. They better reflect heterogeneity in patient outcome than simple 10-year risk scoring, potentially leading to welfare gains in the population. However, both policies modulate risk-based decision-making with one variable. Directly using decision models in clinical practice allows multiple drivers of heterogeneity in cost-effectiveness to be addressed concurrently. Chapter 9 includes a cost-effectiveness analysis of such a policy for statin prioritisation.

Chapter 9

Using Decision Models in Clinical Practice

9.1 Purpose

This thesis has so far considered two broad approaches to prioritising individuals for preventive statin therapy: continued use of 10-year risk scoring and reformulating treatment decisions based on 10-year risk score alongside some other determinant of benefit.

There are advantages and disadvantages to the approaches hitherto assessed. Analysis has shown that, compared to standard of care, reducing the risk threshold for treatment initiation, improving the validity of existing risk scores, and modulating risk-based treatment decisions with age- and LDL-C-stratification may all lead to cost-effective improvements in population health. However, none of these policies simultaneously address multiple causes of heterogeneity in cost-effectiveness of statin therapy.

In the presence of competing risks, missing variables, misspecified models, and non-linear treatment effects, it is difficult to define a decision rule that maps any specific variable to an individual's capacity-to-benefit from CVD prevention. As presented in Section 5.5.2, high-risk young adults generally gain more life years from treatment than elderly individuals. However, this is not necessarily true when the younger individual's risk is driven by smoking. Smokers of all ages are subject to significant fatal competing risks (343), and this drastically limits their capacity-to-benefit from preventive treatment.

There exists a complicated network of predictors and interactions that determine an individual's capacity-to-benefit from preventive therapy in CVD. It is therefore not surprising that defining a simple decision rule to prioritise patients for such treatment is very difficult. A final approach to statin prioritisation that will be considered is direct utilisation of decision-analytic models in clinical practice. Such an approach to prevention would necessitate a paradigm shift in clinical practice towards individual-level decision-making.

9.2 Cost-Effectiveness Analysis: Direct Use of Decision Models in Clinical Practice

9.2.1 Background

Decision-analytic models are tools which synthesise information regarding heath care interventions. They exist in many different forms including simple decision trees, Markov models, and discrete event simulation models. A distinguishing feature of these models which is pertinent to this chapter is that they predict absolute outcomes (e.g. life years, QALYs) as opposed to intermediate outcomes (e.g. risk reduction).

Decision-analytic models are commonly used in cost-effectiveness analysis. They can quantify long-term costs and effects associated with a treatment, projecting both beyond the time horizon of clinical trial evidence. Another use for decision-analytic models is in clinical practice. In this setting they can be used as tools for shared decision-making or to objectively guide physicians' decisions.

<u>Decision Models and Shared Decision-Making</u>

Decision-analytic models may be employed in clinical practice to help promote shared decision-making. In this setting they are often referred to as 'decision aids' or 'decision tools'. Shared decision-making is described by Barry and Edgman-Levitan (544) as a collaborative process between clinicians and patients. It aims to ensure that both health care recipient and provider have the same information regarding treatment options, allowing both to contribute to the final treatment decision. It may also help to increase patient adherence to treatment regimens as it better communicates to them potential benefits associated with the treatment (545).

Despite the benefits offered by decision-analytic models in shared decision-making, they have rarely been used to help patients and clinicians come to shared decisions in clinical practice (546,547). Some examples of decision-analytic models used as shared-decision making aids do exist, however.

Veloso's agent-based simulation model of multiple sclerosis was developed for use in shared decision-making (548). This model considers baseline characteristics of a patient suffering from

chronic multiple sclerosis. Using this information, if performs multiple simulations of the patient's potential 30-year disease progression. This progression can be altered by a list of treatment options. Alongside physicians, patients can observe the range of predicated outcomes and determine their preferred course of treatment. The model's developers concluded that it is a valuable and reliable prediction tool and could be used in clinical practice.

Nemes et al. (549) also developed a decision model for use in shared decision-making. Using stacked predictive models, their tool predicts 1-year health-related quality of life outcomes for patients receiving total hip replacements, dependent on a range of patient-level predictors. The authors conclude that such tools could be useful in clinical practice in the future. However, they also note that the predictive power of their model was not adequate for use in current clinical practice.

Decision-Analytic Models to Guide Clinical Practice

Decision-analytic models have also been developed to help physicians make objective decisions about treatment strategies in clinical practice. These models range across disease areas and involve differing degrees of modelling complexity.

Montgomery et al. evaluated the use of a decision tree as a decision-making aid in the treatment of hypertension (550,551). In a randomly-selected sample of U.K. patients, they employed a decision tree to determine whether a hypertensive patient was recommended blood pressure-reducing medication. This decision was based on the individual's preference for CVD aversion and their treatment-related disutility, both measured using standard gamble methodology. The decision analysis notified GPs that the patient should be treated if their expected utility from treatment exceeded that of no treatment. There was marked difference between the population prioritised for treatment using decision analysis and the population that would be recommended treatment based on conventional SBP- and risk-based guidelines. Heterogeneity in patient preference, it appears, is a strong determinant of capacity-to-benefit from treatment.

A decision tree was also developed by Bonner for use by mental health practitioners in clinical practice (552). They modelled complex 'dual diagnoses', where patients present to community-based mental health practitioners with two serious and concomitant mental health conditions. In

their case study, the patient group considered was patients with psychosis and a history of substance abuse. For patients with dual mental health diagnoses, there is a high level of uncertainty in treatment outcome, likelihood of delayed and incomplete recovery, and it is difficult to gauge rational patient preference.

A wide range of factors affect potential for recovery in patients with complex mental health conditions. It is therefore not clear whether a patient would be best served by hospitalization or community care. Bonner constructed a decision tree, for use in clinical practice, which would allow mental health practitioners to determine where a patient should be treated (552). This decision is contingent on the patient's probability of accepting treatment, their likelihood for mental state deterioration, and a utility weighting given to several potential outcomes.

As shown in the studies described above, using decision models to guide treatment decisions allows for complex, individual-level decision-making. It enables physicians to explicitly account for factors which limit capacity-to-benefit (e.g. high treatment-related disutility, old age, health state preference). If models can be developed with sufficient predictive capacity, then using decision models in clinical practice may be key to addressing heterogeneity of treatment-related outcome in a population.

Decision Models in Clinical Practice for Prevention of CVD

There is a clear and underexploited potential for decision analysis in the clinician's office. This role may be in shared decision-making or in guiding clinical practice. This chapter will focus on the latter, specifically analysing the role that decision models may play in guiding clinical practice in CVD.

Decision aids are particularly useful in clinical practice when there is considerable clinical equipoise (553,554). This is perhaps the case for statin therapy for the primary prevention of CVD. Statins are cheap and effective for almost all CVD-free individuals. However, clinicians appear unwilling to provide the treatment to all healthy adults (249). Clinical equipoise therefore exists in determining which subset of the CVD-free population should be prioritised to receive treatment.

Employing decision models to facilitate shared decision-making may increase adherence to treatment regimens, and help target treatment at those who experience the lowest levels of treatment-related disutility. Using decision models to determine objective guidelines for treatment initiation has the potential to more radically change clinical practice. Models like the Scottish CVD Policy Model can account for the array of factors which affect the risks and benefits associated with a treatment.

Decision models offer an explicit means of accounting for the range of factors which determine how much benefit a CVD-free patient is likely to achieve from preventive statin therapy. However, no previous study has considered the clinical utility of employing decision-analytic models to maximise health outcomes in a population and explicitly guide statin prioritisation decisions.

9.2.2 Objective

The objective of this analysis was to quantify the health and cost outcomes associated with employing decision-analytic models in clinical practice to prioritise patients for preventive statin therapy in the Scottish NHS. The analysis specifically focused on using decision-analytic models to prioritise treatment for patients expected to gain the greatest number of life years from statins.

9.2.3 PPICOSS

Population: The Scottish CVD-free population, aged 40 years and above.

Perspective: Scottish health sector decision-maker. All healthcare costs accrued by the Scottish NHS and population-level health gains are considered.

Intervention: Intermediate-intensity statin therapy (Atorvastatin 20mg/daily). Four treatment prioritisation criteria were considered: (i) blanket 20% risk threshold (treating n=*B20* individuals), (ii) blanket 10% risk threshold (treating n=*B10* individuals), (iii) life expectancy

maximisation (treating n≈*B20* individuals), and (iv) life expectancy maximisation (treating n≈*B10* individuals).

Comparator: Statin therapy only for individuals with familial hypercholesterolaemia.

Outcome: Lifetime cost-per-QALY, with both costs and QALYs discounted at 3.5% annually. Intermediate outcomes reported are: disaggregated healthcare costs, primary CVD events prevented, and CVD-free life years.

Setting: Primary care in the Scottish NHS.

Study Design: Cohort simulation.

9.2.4 Methodology

The methodology employed in this analysis was the same as the methodology employed to estimate the cost-effectiveness of risk threshold reduction and age-stratification of risk thresholds in previous chapters. This allowed for comparison between results in these chapters.

Scottish CVD Policy Model

The Scottish CVD Policy model was employed to estimate the cost-effectiveness of different methods of statin prioritisation. This model was discussed in depth in Chapter 5.

Treatment Strategies

The analysis aimed to compare absolute risk-based blanket 20% and blanket 10% risk threshold strategies to comparable life expectancy-maximising strategies which would be require using decision-analytic models in clinical practice. It was assumed that intermediate-intensity statin therapy would always be provided to individuals with familial hypercholesterolaemia (as defined according to SIGN's definition of elevated TC (≥7.5 mmol/L) and family history of premature CVD, or TC ≥8.0 mmol/L.

The four remaining strategies considered were statins for: individuals with an ASSIGN score greater than 20% (treating n≈*B20* individuals), individuals with an ASSIGN score greater than 10% (treating n≈*B10* individuals), the *B20* individuals expected to gain the most life years from statin therapy, and the *B10* individuals expected to gain the most life years from treatment. Expected benefit from treatment was estimated with the Scottish CVD Policy Model.

Defining Minimum Life Year Gains

Targeting treatment at patients who are expected to achieve the greatest life year gains from statins will hereafter be referred to as the 'life expectancy maximisation' approach to prevention.

Much like the blanket risk threshold approach to prevention requires setting a minimum risk score at which treatment is recommended, the life expectancy maximisation approach requires setting a minimum life year gain from statin therapy. The minimum life year gain can be set according to many different constraints. This analysis specifically aimed to constrain the number of individuals eligible to receive statins.

The number of people who would be treated at different life year gain thresholds were calculated by projecting simulated data from SHeS 2011 onto the Scottish population with census data. Life year gains from statin therapy were calculated for every individual in the SHeS dataset with the Scottish CVD Policy Model. The proportion of SHeS participants eligible for treatment at different life year gain-based thresholds were calculated by 5-year age-group. These proportions were then projected onto the CVD-free Scottish population using census data.

Scottish Health Survey, Census Data, and Multiple Imputation

As with analyses in Chapters 7 and 8, all analysis was completed using a combination of the Scottish Health Survey 2011 and the Scottish Census 2011. The same dataset and imputation process was employed in this analysis as was employed in Section 7.2.4. The descriptive statistics for this dataset are described in Table 7-1.

Simulation

The Scottish CVD Policy Model simulated the effect of giving statins to different groups of people. The same approach to simulation was adopted as described in Section 7.2.4. This involved developing two macros for Excel using Microsoft Visual Basic to estimate lifetime incremental health and cost outcomes attributable to intermediate-intensity statin therapy for all individuals in the dataset.

Treatment Parameters

The base case treatment parameters employed in this analysis were the same as the treatment parameters used to estimate cost-effectiveness of risk threshold reduction in Chapter 7. These parameters are presented in Table 7-4. They include a 27.2% reduction in non-HDL cholesterol attributable to statin therapy, an absolute risk of diabetes increase of 0.5% in the population, a 0.001 QALY decrement to account for pill-taking disutility, an annual cost of £13.00 for intermediate-intensity statin therapy, a £26.34 cost of initial risk assessment, a cost of £120.17 for monitoring in the first year of treatment, and a monitoring cost of £67.96 in subsequent years.

Estimating Outcomes and Projecting Results

Incremental costs and outcomes were simulated for all individuals in the SHeS dataset. The population was stratified by risk score and expected life years gained from treatment. Individuals meeting treatment criteria were assigned the incremental treatment-related outcomes. Results were averaged across 5-year age-groups and projected onto the Scottish population with census data. Again, this process was described extensively in Chapter 7.

Cost-Effectiveness Analysis

Cost-effectiveness analysis was performed using traditional cost-effectiveness decision rules (43,354). A strategy was determined to be cost-effective if its ICER was below £20,000/QALY.

Sensitivity Analysis

One-way sensitivity analyses were undertaken to assess the impact of parametric assumptions on estimated cost-effectiveness outcomes. Given that this study was subject to the same types of parametric uncertainty as analyses in Chapters 7 and 8, the same sensitivity analyses were performed. The parameters included in sensitivity analyses were: pill-taking disutility, non-HDL cholesterol reduction and HDL cholesterol increase, monitoring costs in the first year of treatment, monitoring costs in subsequent years of treatment, cost of risk assessment, and price of statins.

Probabilistic sensitivity analysis stochastically sampled Table 7-4 input distributions and risk factor hazard ratios from Tables 5-1 and 5-2 in 500 independent iterations. Correlation between risk factor hazard ratios was accounted for through the Cholesky decomposition method (309,503). Using the cost and QALY results from probabilistic analyses, a cost-effectiveness acceptability curve was produced which shows the probability of each treatment strategy being the most cost-effective option for decision-makers at a range of willingness-to-pay thresholds.

Secondary Analysis: Cost-Effectiveness of QALE-Maximisation

This analysis chose to maximise life expectancy. Discussion with stakeholders and the SIGN cardiovascular risk estimation guideline committee suggested that undiscounted life years gained was a logical outcome to maximise for clinicians. If a decision-maker truly wanted maximise population-level health outcomes in a population, they may instead wish to maximise discounted QALYs. A secondary analysis considered the health benefits and costs associated with employing the Scottish CVD Policy Model in clinical practice to maximise discounted quality-adjusted life expectancy (QALE) in the Scottish population.

In the secondary analysis, population-level cost-effectiveness analysis was conducted from the perspective of a Scottish health sector decision-maker. The same methodology was adopted as used to estimate the cost-effectiveness of LE-Max 10 and LE-Max 20. Two QALY-Max strategies were defined which would treat approximately the same number of individuals as ASSIGN 20 and ASSIGN 10. Descriptive statistics of individuals treated, discounted QALYs,

discounted healthcare costs, CVD events prevented, and life years gained, are presented for each strategy.

Inequality

A final piece of analysis considered the consequences of different treatment strategies on health inequalities. Discounted QALY gains per 1,000 individuals were presented, disaggregated by SIMD quintile. The proportion of total QALYs gained by each SIMD quintile was also presented. A policy was considered progressive if more discounted QALYs were produced in the two most deprived quintiles of the CVD-free Scottish population and regressive if more discounted QALYs were produced in the two least deprived quintiles of the population.

9.2.5 Results

Minimum Life Year Gains

Two treatment strategies were defined: Life Expectancy Maximisation 20 (LE-Max 20) which treats approximately the same number of individuals as ASSIGN 20 and Life Expectancy Maximisation 10 (LE-Max 10) which treats approximately the same number of individuals as ASSIGN 10.

The minimum life year gains to ensure LE-Max 20 treated the correct number of individuals was calculated to be 0.349. For LE-Max 10 this number was 0.212.

Demographics of Treated Patients

Table 9-1 provides descriptive statistics for the overall population and subpopulations treated under ASSIGN 20, LE-Max 20, ASSIGN 10, and LE-Max 10. It details the percentage of different age-groups treated under the different prioritisation strategies alongside the treated population's average risk factor values.

Implementing life expectancy maximisation would lead to large proportions of the CVD-free population aged 60 and below being treated. The vast majority of individuals prioritised for treatment under the LE-Max policies would be men. In addition, this population would be less socially deprived than the population treated under blanket risk thresholds, smoke less cigarettes per day, and have lower family history of CVD.

		Overall Population	ASSIGN 20	LE-Max 20	ASSIGN 10	LE-Max 10
Proportion of Age-Group Treated (%)	40-44	n/a	0	44	3	73
	45-49	n/a	2	39	14	68
	50-54	n/a	5	37	38	63
	55-59	n/a	15	38	74	60
	60-64	n/a	41	31	94	50
	65-69	n/a	75	32	100	51
	70-74	n/a	92	21	100	45
	75-79	n/a	100	17	100	38
	80+	n/a	100	4	100	24
Average Value	Male (%)	42	45	94	47	72
	SIMD	19.5	21.2	20.0	20.5	19.0
	Diabetes (%)	7	15	1	11	4
	FH (%)	46	68	35	62	32
	CPD	7	8	5	7	5
	SBP (mmHg)	131	134	131	133	130
	TC (mmol/L)	5.8	5.8	5.8	5.8	5.8
	HDL (mmol/L)	1.5	1.5	1.5	1.5	1.5

Table 9-1: Descriptive statistics of treated populations, ASSIGN and LE-Max policies

Base Case Cost-Effectiveness Analysis

The results from the base case cost-effectiveness analysis are presented in Table 9-2. These results are also shown on the cost-effectiveness plane in Figure 9-1**.** LE-Max 20 and LE-Max 10 produced many more QALYs than their respective blanket threshold comparators.

The additional health benefits offered by life-expectancy maximisation are purchased at a high cost. LE-Max 20 was dominated by ASSIGN 10. The ICER associated with transitioning from ASSIGN 10 to LE-Max 10 is around £29,900/QALY. This is in excess of the cost-effectiveness threshold adopted for this analysis. Therefore, given the policies considered and the base case assumptions, ASSIGN 10 is the optimal strategy for a decision-maker.

Policy	Number Treated	Discounted QALYs	Discounted Cost (£1000's)	ICER (£/QALY)
Familial Hyp.	*Reference*			
ASSIGN 20	793,559	92,300	636,000	6,900
LE-Max 20	793,387	141,000	1,597,000	Str. Dominated
ASSIGN 10	1,381,059	164,000	1,596,000	13,500
LE-Max 10	1,380,749	197,296	2,603,000	29,900

Str. – strictly

Table 9-2: Base case cost-effectiveness results, ASSIGN and LE-Max policies

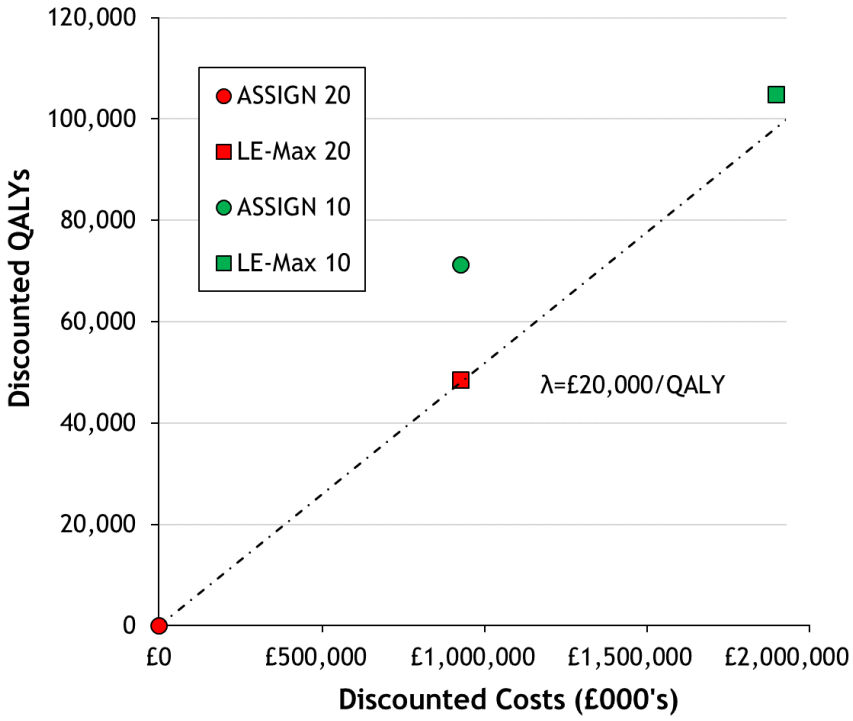


Figure 9-1: Base case cost-effectiveness plane, ASSIGN 20, LE-Max 20, ASSIGN 10, and LE-Max 10

Intermediate Outcomes

Tables 9-3 and 9-4 present intermediate outcomes from the base case analysis. The former presents the primary CVD events prevented and life years gained for the respective policies, and the latter presents their disaggregated costs.

Policy	Primary CVD Events Prevented	Life Years Gained
Familial Hyp.	*Reference*	
ASSIGN 20	27,000	170,000
LE-Max 20	35,000	398,000
ASSIGN 10	49,000	351,000
LE-Max 10	55,000	564,000

Table 9-3: Base case CVD events prevented and life years gained, ASSIGN and LE-Max policies

Maximising life expectancy using decision models to dictate clinical practice would prevent around 7,600 primary CVD events compared with ASSIGN 20. This would be achieved while treating the same number of individuals. In turn, this would lead to an approximately 227,700 additional life years in the Scottish population. Maximising life expectancy using decision models instead of ASSIGN 10 would prevent approximately 6,600 primary CVD events, producing around 212,400 undiscounted life years.

Policy	Disc. Costs (£1000's)			
	Non-CVD	CVD	Statin	Monitoring
Familial Hyp.	*Reference*			
ASSIGN 20	720,000	-718,000	84,000	550,000
LE-Max 20	1,487,000	-923,000	146,000	886,000
ASSIGN 10	1,562,000	-1,322,000	190,000	1,166,000
LE-Max 10	2,176,000	-1,388,000	262,000	1,552,000

Table 9-4: Base case disaggregated costs, ASSIGN and LE-Max policies

All strategies led to a decrease in CVD-related healthcare costs and increases in non-CVD-related healthcare costs. The life expectancy maximising strategies incurred greater non-CVD-related, statin, and monitoring costs than comparable blanket risk threshold strategies. This suggests that increased costs for age-stratified policies are incurred through extension of life expectancy- and treatment-related costs.

Sensitivity Analysis

Results from the sensitivity analyses are presented in Figures 9-2 and 9-3. These tornado diagrams show the sensitivity of ICER estimates to univariate changes in model parameters. Presented are the ICERs associated with moving from ASSIGN 20 to LE-Max 20 and ASSIGN 10 to LE-Max 10, respectively. The base case ICER of implementing LE-Max over ASSIGN 20 was approximately £19,800/QALY, however this was strictly dominated by ASSIGN 10.

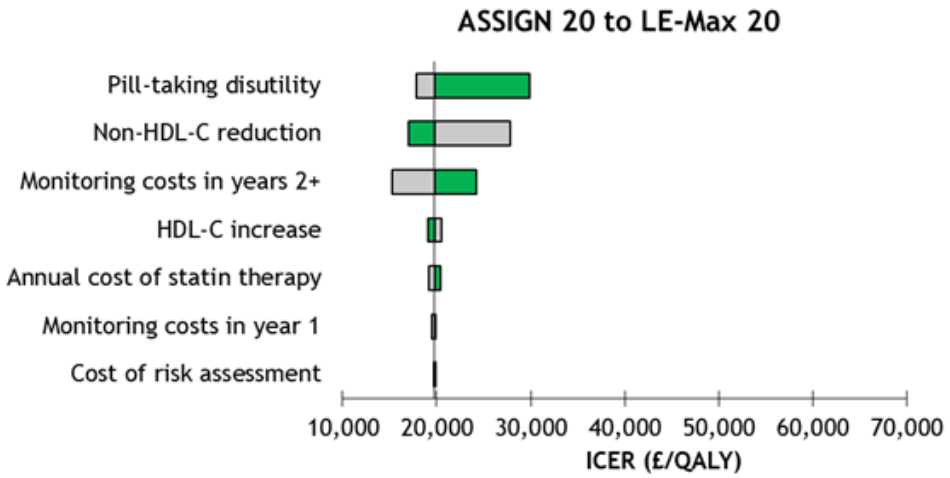


Figure 9-2: Tornado diagram, one-way sensitivity analysis of key parameters and their effect on ICER of implementing LE-Max 20 over ASSIGN 20

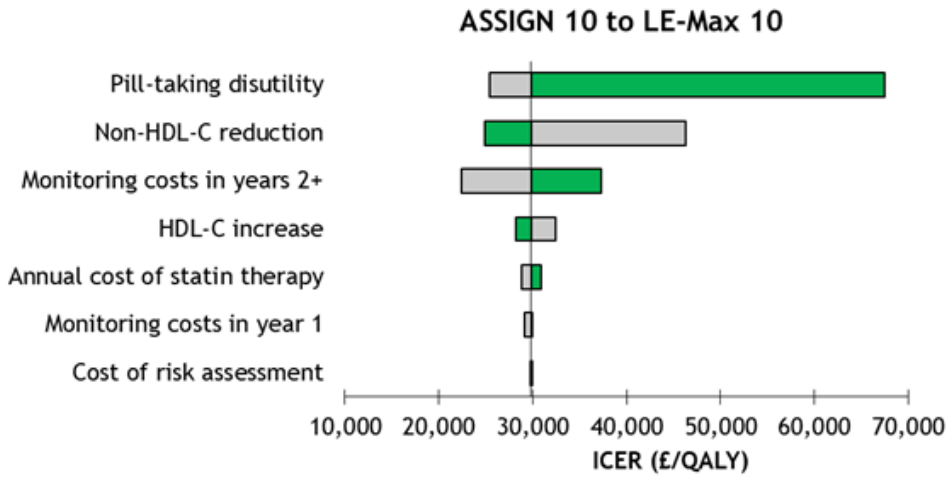


Figure 9-3: Tornado diagram, one-way sensitivity analysis of key parameters and their effect on ICER of implementing LE-Max 10 over ASSIGN 10

The key sources of uncertainty were pill-taking disutility, non-HDL cholesterol reduction, and monitoring costs in subsequent years. LE-Max 10 would only fall below the £20,000/QALY threshold compared to ASSIGN 10 if there were a large reduction in monitoring costs.

PSA was undertaken and the results are presented in a cost-effectiveness acceptability curve in Figure 9-4. The red, blue, green, and black curves show the proportion of simulations in which Blanket 20, LE-Max 20, Blanket 10, and LE-Max 10 were optimal at a range of cost-effectiveness thresholds. The black dashed line indicates a cost-effectiveness threshold of £20,000/QALY. At this threshold, Age-Strat 10 was optimal in around 50% of simulations. This suggests a considerable possibility that LE-Max 10 is the optimal treatment strategy.

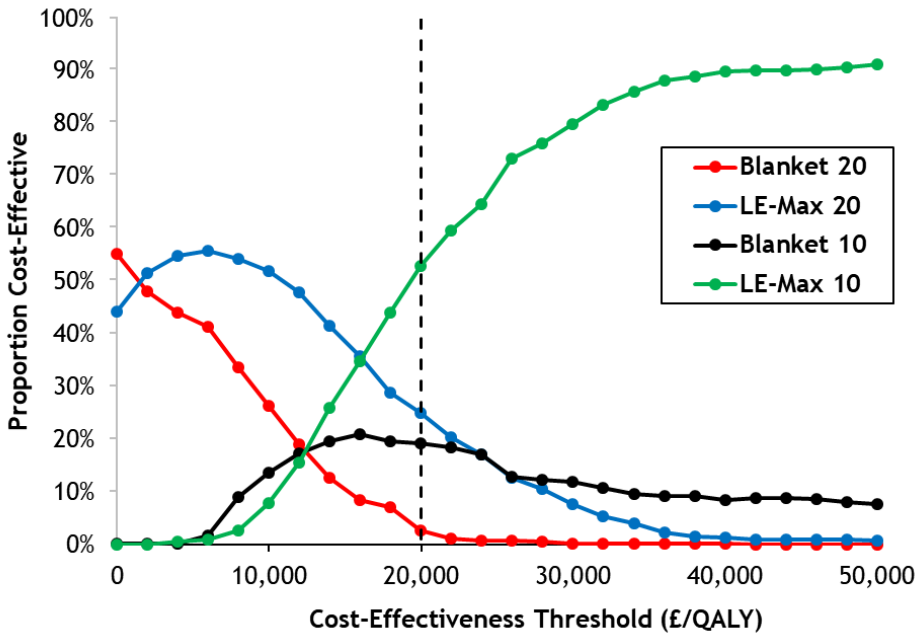


Figure 9-4: Cost-effectiveness acceptability curve, ASSIGN 20, LE-Max 20, ASSIGN 10, and LE-Max 10

Inequality Analysis

Results were disaggregated to estimate the effect of threshold reduction on health inequalities. Figure 9-5 shows the discounted QALY gains achieved per 1,000 individuals in the population, disaggregated by SIMD quintile. In absolute terms, all SIMD quintiles gained more discounted

QALYs under LE-Max 10 than LE-Max 20. For all policies, absolute health gains continuously increased with level of social deprivation.

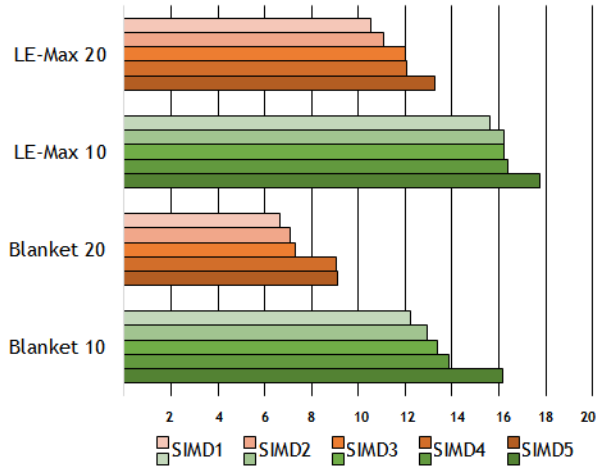


Figure 9-5: Discounted QALY gains for life expectancy maximisation and blanket risk threshold strategies per 1,000 individuals, disaggregated by SIMD quintile

The proportion of health gains achieved per quintile of social deprivation was estimated. These results are displayed in Figure 9-6. The SIMD distribution of discounted QALY gains was similar for LE-Max 20 and LE-Max 10. Both policies were progressive: they led to a greater proportion of health gains being achieved in the two most deprived SIMD quintiles compared with the two least deprived quintiles.

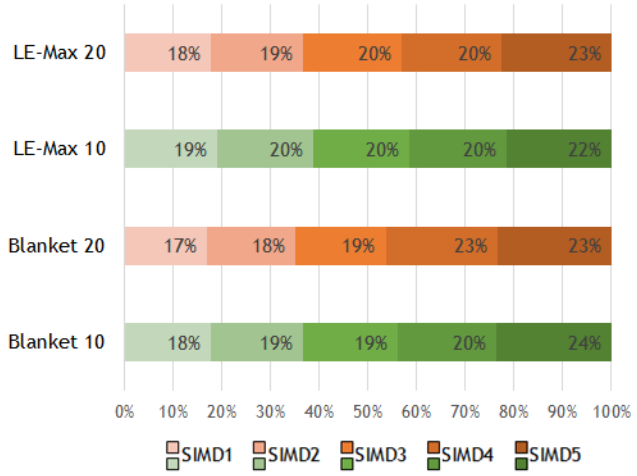


Figure 9-6: Proportion of discounted QALY gains achieved by different SIMD quintiles, life expectancy maximisation and blanket risk threshold strategies

LE-Max 20 was less progressive than LE-Max 10. The two most deprived SIMD quintiles combined gained 43% of all health benefits under LE-Max 20, compared to 37% of health gains achieved by the two least deprived quintiles – a difference of 6%. This difference was 11% for Blanket 20. LE-Max 10 was less progressive than Blanket 10. The difference in proportion of QALY gains between the two most and least deprived quintiles for LE-Max 10 and Blanket 10 were 3% and 7%, respectively.

Secondary Analysis: Cost-Effectiveness of QALE-Maximisation

Quality-adjusted life expectancy maximisation requires setting a minimum expected discounted QALY gain necessary for treatment eligibility. Two strategies were defined: Quality-Adjusted Life Expectancy Maximisation 20 (QALE-Max 20) which treats approximately the same number of individuals as ASSIGN 20, and Quality-Adjusted Life Expectancy Maximisation 10 (QALE-Max 10) which treats approximately the same number of individuals as ASSIGN 10. Individuals were treated under QALE-Max 20 and QALE-Max 10 if they were expected to achieve a minimum discounted QALY gain of 0.349 and 0.212, respectively.

Descriptive Statistics: Table 9-5 presents the descriptive statistics for the cohort of individuals prioritised for statin therapy under blanket risk threshold policies, LE-Max policies, QALE-Max policies, and respective statistics in the overall SHeS 2011 population. Both QALE-Max policies lead to a more equal distribution in the age of individuals prioritised for statins. However, equity concerns may be raised about these policies as men are much more likely to be prioritised under a QALE-Max strategy compared to blanket and life-expectancy maximisation policies.

Cost-effectiveness results: Table 9-6 presents cost-effectiveness results for the QALE-Max strategies compared to Blanket 20, LE-Max 20, Blanket 10, and LE-Max 10. LE-Max 20 and LE-Max 10 are strictly dominated by their QALY-maximising counterparts. In addition, Blanket 10 is extendedly dominated by QALE-Max 10. A decision-maker with a cost-effectiveness threshold of £20,000/QALY would choose to implement QALE-Max 10.

Intermediate outcomes: Primary CVD events prevented, life year gains, and the disaggregation of costs are presented in Tables 9-7 and 9-8. LE-Max policies prevent approximately the same number of CVD events as QALE-Max policies, but result in a greater number of life year gains.

		Overall Populat -ion	ASSIGN 20	LE-Max 20	QALE-Max 20	ASSIGN 10	LE-Max 10	QALE-Max 10
Proportion of Age-Group Treated (%)	40-44	n/a	0	44	14	3	73	37
	45-49	n/a	2	39	28	14	68	49
	50-54	n/a	5	37	37	38	63	54
	55-59	n/a	15	38	41	74	60	63
	60-64	n/a	41	31	37	94	50	65
	65-69	n/a	75	32	43	100	51	69
	70-74	n/a	92	21	37	100	45	68
	75-79	n/a	100	17	35	100	38	61
	80+	n/a	100	4	17	100	24	42
Average Value	Male (%)	42	45	94	99	47	72	73
	SIMD	19.5	21.2	20.0	20.2	20.5	19.0	20.2
	Diabetes (%)	7	15	1	5	11	4	8
	FH (%)	46	68	35	48	62	32	43
	CPD	7	8	5	6	7	5	5
	SBP (mmHg)	131	134	131	132	133	130	132
	TC (mmol/L)	5.8	5.8	5.8	5.8	5.8	5.8	5.8
	HDL (mmol/L)	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Table 9-5: Descriptive statistics of treated patients, ASSIGN and LE-Max policies

Policy	Number Treated	Discounted QALYs	Discounted Cost (£1000's)	ICER (£/QALY)
Familial Hyp.	*Reference*			
Blanket 20	793,559	92,300	636,000	6,900
LE-Max 20	793,387	141,000	1,597,000	Str. Dominated
QALE-Max 20	793,775	150,000	1,313,000	11,700
Blanket 10	1,381,059	164,000	1,596,000	Ext. Dominated
LE-Max 10	1,380,749	197,000	2,603,000	Str. Dominated
QALE-Max 10	1,381,122	206,000	2,306,000	17,700

Ext. – extendedly, Str. - strictly

Table 9-6: Base case cost-effectiveness analysis, ASSIGN and LE-Max policies

Policy	Primary CVD Events Prevented	Life Years Gained
Familial Hyp.	*Reference*	
Blanket 20	27,000	170,000
LE-Max 20	35,000	398,000
QALE-Max 20	35,000	376,000
Blanket 10	49,000	351,000
LE-Max 10	55,000	564,000
QALE-Max 10	55,000	535,000

Table 9-7: Intermediate outcomes, ASSIGN and LE-Max policies

Policy	Disc. Costs (£1000's)			
	Non-CVD	CVD	Statin	Monitoring
Familial Hyp.	*Reference*			
Blanket 20	720,000	-718,000	84,000	550,000
LE-Max 20	1,487,000	-923,000	146,000	886,000
QALE-Max 20	1,362,000	-955,000	126,000	779,000
Blanket 10	1,562,000	-1,322,000	190,000	1,166,000
LE-Max 10	2,176,000	-1,388,000	262,000	1,552,000
QALE-Max 10	2,130,000	-1,449,000	232,000	1,393,000

Table 9-8: Disaggregated costs, ASSIGN and LE-Max policies

Probabilistic sensitivity analysis: Figure 9-7 presents results from a probabilistic sensitivity analysis in which risk function hazard ratios and key simulation parameters (Table 7-4) were sampled stochastically in 500 independent iterations. At a willingness-to-pay threshold of £20,000/QALY, QALE-Max 10 was optimal in 70% of iterations and QALE-Max 20 was optimal in 28% of iterations.

Inequality analysis: Results were disaggregated to estimate the effect of threshold reduction on health inequalities. Figure 9-8 shows the discounted QALY gains achieved per 1,000 individuals in the population, disaggregated by SIMD quintile. In absolute terms, all SIMD quintiles gained more discounted QALYs under QALE-Max 10 than QALE-Max 20. For all policies, absolute health gains continuously increased with level of social deprivation.

The proportion of health gains achieved per quintile of social deprivation was also estimated. These results are displayed in Figure 9-9. The distribution of discounted QALY gains was similar for LE-Max 10, LE-Max 20, QALE-Max 10, and QALE-Max 20. Both policies were

progressive: they led to a greater proportion of health gains being achieved in the two most deprived SIMD quintiles compared with the two least deprived quintiles.

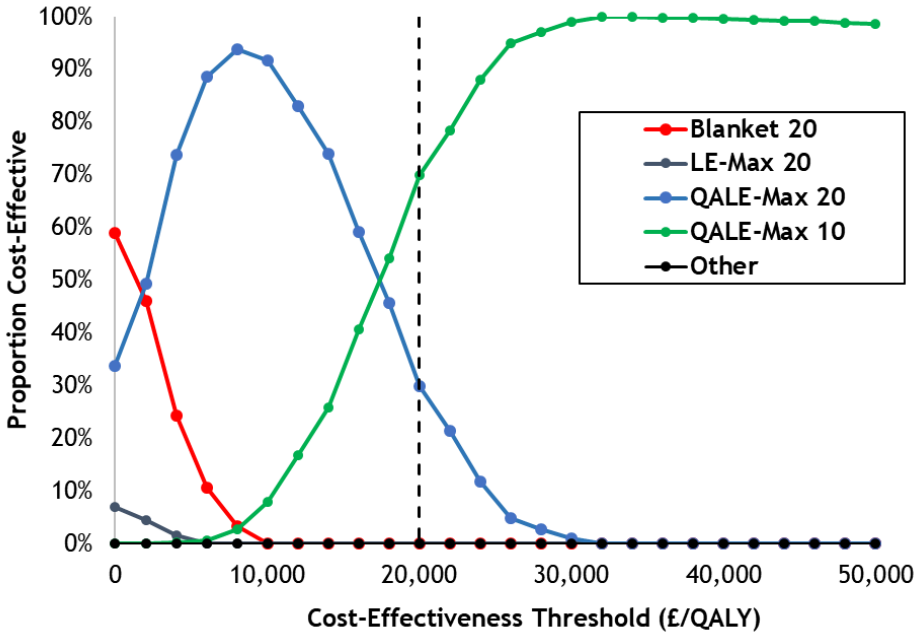


Figure 9-7: Cost-effectiveness acceptability curve, ASSIGN 20, LE-Max 20, QALE-Max 20, ASSIGN 10, LE-Max 10, and QALE-Max 10

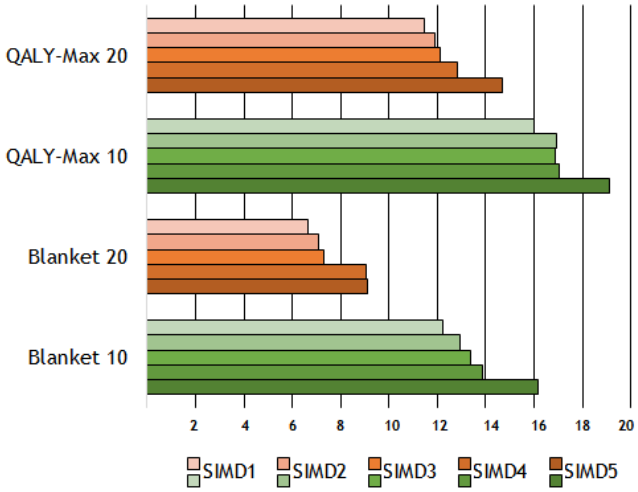


Figure 9-8: Discounted QALY gains for QALE Max and blanket risk threshold strategies per 1,000 individuals, disaggregated by SIMD quintile

QALE-Max 20 was less progressive than Blanket 20. The two most deprived SIMD quintiles combined gained 43% of all health benefits under QALE-Max 20, compared to 37% of health gains achieved by the two least deprived quintiles – a 6% difference. This difference was 11%

for Blanket 20. QALE-Max 10 was less progressive than Blanket 10. The difference in proportion of QALY gains between the two most and least deprived quintiles for QALE-Max 10 and Blanket 10 were 3% and 7% for these policies, respectively.

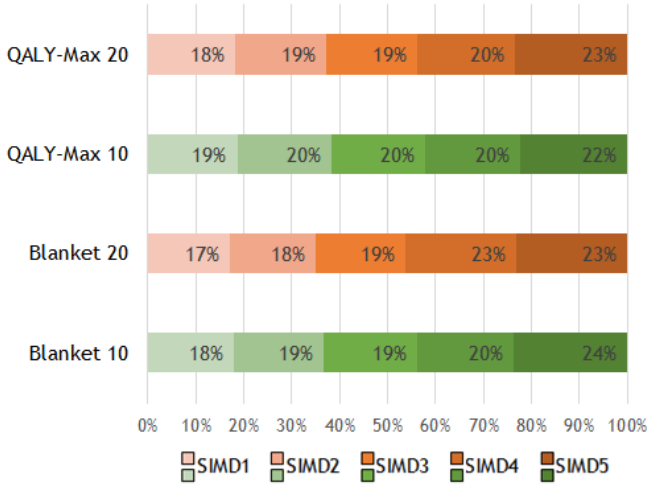


Figure 9-9: Proportion of discounted QALY gains achieved by different SIMD quintiles, QALE Max and blanket risk threshold strategies

9.2.8 Discussion and Limitations

This analysis considered the cost-effectiveness of using decision-analytic models in clinical practice to determine which individuals should receive preventive statin therapy. It showed that a large number of discounted QALYs and life years can be gained by treating the group of patients estimated to gain the most life years from treatment. However, this treatment strategy is likely to be costly and may involve societally unacceptable mass-medication of young and healthy individuals.

Compared to blanket risk thresholds, life expectancy maximisation leads to large increases in population health. Theoretically, if a decision model perfectly predicts patient-level outcomes, this approach to prevention should maximise life expectancy in a population, given a constraint on the number of individuals that can be treated. However, it was shown that the subpopulation eligible for treatment under LE-Max 20 and LE-Max 10 are expensive to treat. This is likely because they are young and will therefore require many years of on-treatment monitoring. In

order to make this treatment strategy cost-effective, it will be necessary to reduce monitoring costs.

Another key consideration related to the life expectancy maximisation approach to prevention is the societal acceptability of the policy. Table 9-5 showed that for CVD-free individuals aged 40-44 and 45-49, 73% and 68% would be treated under LE-Max 10, respectively. This is a large and likely very healthy proportion of the Scottish adult population. Moreover, a vast majority of patients treated under life expectancy maximisation would be men, and the treated population would be less socially deprived than those treated under the blanket risk threshold approach. Both of these factors may give rise to health equity concerns related to the policy of life expectancy maximisation.

Discussions were conducted with Scottish stakeholders and decision-makers when determining which treatment strategies should be analysed in this thesis. This involved attending several meetings of SIGN's Risk Estimation and the Prevention of Cardiovascular Disease guideline committee and presenting initial results from the analysis to Scotland's National Advisory Committee on Heart Disease. Based on feedback from these discussions, it was determined that life expectancy was most clinically comprehensible and acceptable outcome to maximise. Hence, the primary analysis in this chapter considered the cost-effectiveness of life expectancy maximisation. An alternative approach to prioritisation would be to maximise the clinical outcome most commonly considered in cost-effectiveness analyses, discounted QALYs.

A secondary analysis considered the cost-effectiveness of discounted QALY maximisation to prioritise statin therapy. Results from this analysis show that such an approach to prevention would be much more cost-effective than life expectancy maximisation. Indeed, these results showed that decision-makers applying a cost-effectiveness threshold of £20,000/QALY should implement QALY maximisation.

It is possible that QALY maximisation is not clinically feasible. This approach to prevention would disproportionately target treatment at men, which may be considered inequitable. Men are likely disproportionately prioritised for treatment because they are at higher risk of experiencing CVD and generally had higher total cholesterol levels than women in the SHeS 2011 cohort. It may also be explained by differentiation in the type of CVD events experienced

by men and women. Bots et al. (555) have shown that the men to women ratio is greater for CHD than stroke. The risk functions which underpin state transition in the Scottish CVD Policy Model assume that TC (a proxy for LDL-C in this analysis) has a greater effect on CHD than stroke for both men and women (7,309). A final reason that men likely gain more discounted QALYs from treatment than women typically experience CVD events later in life than men (556). Therefore, benefits accrue longer after treatment initiation for younger women than men and these benefits are valued less than more immediate benefits due to discounting.

9.3 Chapter Summary

Despite concerns about the feasibility of outcome maximisation to prioritise statin therapy, this analysis shows that using decision models to determine who should receive preventive interventions for CVD could produce large population-level improvements in health. These models reflect multiple dimensions of heterogeneity in cost-effectiveness, maximising outcomes.

Mass-medicalisation of the population prioritised for treatment with decision-analytic models may prove difficult. Efforts should perhaps be made to reduce cholesterol in this population through other means. Public health programmes aimed specifically at this population may be helpful. These may include health promotion campaigns and legislation that looks to reduce trans fats in food.

So far, this thesis has presented several approaches for prioritising patients for preventive statin therapy. This chapter showed the theoretical maximum benefit that can be achieved with this treatment. Patients often have residual risk when receiving preventive statin therapy. Moreover, a small but significant proportion of patients are statin intolerant. The following chapter will consider how best to treat patients who require further cholesterol reduction following initiation of statin therapy.

Chapter 10
Residual Risk and Statin Intolerance

10.1 Purpose

Statins are a cheap and effective means of reducing LDL-C and risk of CVD events. Because of this, researchers have noted that 'downward reclassification' of individuals with elevated levels of risk according to traditional risk scores is rarely warranted (557). Nonetheless, many patients treated with statins proceed to experience CVD-related morbidity and mortality. In the clinical literature, this has been referred to as the existence of 'residual risk' (558). In addition, some patients are statin intolerant.

This chapter will consider alternative cholesterol-reducing strategies to statin monotherapy that address the issues of residual risk and statin intolerance. Alternative cholesterol-reducing treatments are often expensive. Hence, this chapter will focus on patients with familial hypercholesterolaemia for whom novel treatments like PCSK9 inhibitors are most likely to be cost-effective. Representing heterogeneity in cost-effectiveness analyses may help healthcare decision-makers to signal demand for products like PCSK9 inhibitors and ensure that they are provided to the subset of the population that is cost-effective to treat.

10.2 Residual Risk

Ridker distinguishes between two forms of residual cardiovascular risk that statin-treated patients may experience (558). These are 'residual inflammatory risk' and 'residual cholesterol risk'.

Arterial inflammation occurs as a response to injuries incurred in the arteries. It likely plays an important role in atherogenesis and can precipitate future CVD events (559). Biomarkers including high-sensitivity C-reactive protein are indicators of the presence of arterial inflammation. Ongoing clinical trials have considered the potential use of anti-inflammatory medications (including low-dose methotrexate, colchicine, interleukin-1 inhibitors, and interleukin-6 inhibitors) in the treatment of residual inflammatory risk (560).

This chapter will not consider treatment for residual inflammatory risk as there is limited clinical understanding of the relationship between inflammation and CVD. The European Society of Cardiology noted in 2017, “For the inflammation hypothesis of cardiovascular disease to become widely accepted, further studies will be needed to show that anti-inflammatory agents have beneficial effects” (561).

Analysis in this chapter will focus on residual cholesterol risk, for which there are several established therapies. Residual cholesterol risk exists because statins do not produce enough LDL-C-reduction to completely minimize future risk of event. Remaining LDL-C continues to cause atherosclerotic build-up in the arteries which leads to CVD events.

Once a patient has achieved LDL-C reduction with a maximally tolerated intensity of statin monotherapy, alternative LDL-C-reducing therapies must be employed to address residual cholesterol risk. These therapies are typically prescribed on top of the patient’s existing statin regimen. This chapter will predominantly consider the role of PCSK9 inhibitors in addressing residual cholesterol risk.

Some CVD risk will remain even when all residual cholesterol risk is addressed for patients receiving statin therapy. Atherosclerosis commences at a young age. The atherosclerotic build-up that develops in childhood and young adulthood may be irreversible. Reith and Armitage note, “…residual risk following standard LDL-lowering treatment may be partly explained by treating late in the course of the [subclinical] disease” (562).

10.3 Statin Intolerance

Statin intolerance occurs when a patient is unable to continue taking prescribed statin therapy. This intolerance may be partial or complete. Partial intolerance occurs when a patient is able to switch to a lower dose or different type of statin and continue treatment. Complete intolerance, when a patient is cannot continue taking any type of statin at any dose, is a rare occurrence.

Patients may discontinue statins for several reasons. Meta-analysis evidence suggests that statins are a relatively safe treatment and that rates of commonly ascribed side effects have been shown

to be constant between treatment and control arms of randomised clinical trials (349,446,471,538). However, population-based studies have associated a range of side effects with statin treatment. Amongst these side effects are statin-associated muscle symptoms (SAMS). Other potential side effects highlighted by observational studies are: musculoskeletal complaints, gastro-internal discomfort, fatigue, increased liver enzymes, neuropathy, insomnia, and neurocognitive issues (563–566).

The vast majority of statin users who experience SAMS are able to switch to a different dosage or type of statin and continue treatment. Zhang et al. (567) investigated statin persistence following treatment discontinuation in a retrospective cohort study. They found that 92.2% of the 6,579 patients 'rechallenged' with statin after treatment discontinuation were still taking a statin 12 months after experiencing a statin-related adverse event.

The only prospective randomized analysis of the relationship between musculoskeletal issues and statin treatment comes from the Effects of Statins on Muscle Performance (STOMP) Study. STOMP was a double-blinded, placebo-controlled study which randomized 420 patients who had never been treated with statins to high-intensity statins (Atorvastatin 80mg daily) and placebo. Its primary outcome was rates of study-defined myalgia after 6 months. The prevalence of myalgia was 4.6% and 9.4% in the control and treatment arms of the trial, respectively. The difference in myalgia between the treatment groups was not judged to be significant (p-value 0.054) (568,569). Results from the STOMP study suggest that rates of statin-related muscle symptoms may be lower than reported in observational studies. However, this study had a low sample size. Therefore, its results do not rule out the possibility of a causal relationship between statins and muscle pain which leads to treatment disadherence and discontinuation.

10.4 Alternative Cholesterol-Reducing Therapies

Several therapies exist that can reduce LDL-C. Most prominent amongst these, in order of weighted between-group difference in achieved LDL-C-reduction in clinical trials, are: fibrates, ezetimibe, niacin, CETP inhibitors, diet, statins, bile acid sequestrants, ileal bypass, and PCSK9 inhibitors (4).

Analysis in this chapter will focus on PCSK9 inhibitors and their role in addressing residual cholesterol risk and statin intolerance. Bile acid sequestrants, ileal bypass, fibrates, and niacin are not recommended as first-in-line alternatives or supplements to statin therapy for patients with familial hypercholesterolaemia by NICE clinical guidelines or an expert consensus report from the ACC (25,570).

Both NICE and the ACC recommend that ezetimibe is 'considered' as a treatment for LDL-C reduction in individuals suffering from familial hypercholesterolaemia (570,571). Ezetimibe may be prescribed as a monotherapy for statin intolerant patients as well as supplemental to statins for some persistent statin patients who maintain elevated levels of LDL-C. Ezetimibe is less effective at reducing LDL-C than PCSK9 inhibitors, both as a monotherapy and as a supplemental treatment to statin therapy (227). NICE and the ACC both highlight that ezetimibe is costly and likely confers less benefit than PCSK9 inhibitors (25,570). The treatment has been available as a generic formulation in both the U.K. and U.S. since 2016, and has therefore seen a dramatic reduction in price (572,573).

PCSK9 Inhibitors

PCSK9 inhibitors are class of cholesterol-reducing medication. They are more expensive and significantly more effective at reducing LDL-C than statin monotherapy. Due to the causal relationship between LDL-C and atherosclerotic CVD, it has been predicted that PCSK9 inhibitors are more effective at reducing CVD risk in individuals compared to statin therapy (227).

Two PCSK9 inhibitors have been approved for use by the EMA and the FDA. Alirocumab (trade name Praluent) and evolocumab (trade name Repatha) received market-authorisation by the EMA in 2015 (225,226). These PCSK9 inhibitors are indicated in adults with familial hypercholesterolaemia either in combination with a maximally tolerated statin dose or as monotherapy in statin intolerant patients. Both treatments also received initial approval in the U.S. in 2015, with indication in similar populations (223,224).

Clinical trials have confirmed the efficacy of PCSK9 inhibitors. The landmark Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk

(FOURIER) outcomes trial aimed to assess whether addition of the evolocumab to intermediate- or high-intensity statin therapy reduces CVD risk. FOURIER was a randomized, double-blinded, placebo-controlled trial which followed 27,564 patients for a median duration of 2.2 years. Researchers found that addition of PCSK9 inhibitor treatment led to a significant reduction in their primary composite CVD endpoint (0.85; 95% CI: 0.79 to 0.92) (228). Secondary analysis of a 78-week randomized trial of alirocumab indicated a similar level of CVD risk reduction (574). In phase three trials, it has been shown that PCSK9 inhibitor monotherapy reduces LDL-C significantly more than alternative cholesterol-reducing therapies (575,576).

PCSK9 inhibitors are very expensive. The undiscounted annual price for PCSK9 inhibitors is approximately £4,500 in the U.K. and around $6,000 in the U.S. (reduced from $14,500 in late 2018) (577–579).The following analysis assesses the costs and benefits associated with PCSK9 inhibitors in two subsets of the Scottish population, and determines the proportion of these subpopulations that should receive the treatment at different price levels.

The SMC currently recommends that patients with familial hypercholesterolaemia and high levels of LDL-C after statin initiation or statin intolerance should be offered PCSK9 inhibitors. This guidance was based on a price reduction agreed under a 'patient access scheme' (580,581). Under such schemes, price of treatment is commercial in confidence and not available in the public domain. No novel cost-effectiveness analysis was undertaken when approving evolocumab or alirocumab in the Scottish NHS. Manufacturer submissions to the SMC, summarised in detailed advice documents, present cost-effectiveness estimates for the treatments in different subsets of the Scottish population with familial hypercholesterolaemia. However, these analyses found PCSK9 inhibitors to have very low ICERs, suggesting biased modelling or large price reductions. It is not clear which of these occurred. This lack of transparency gives the SMC considerable scope to implement cost-ineffective interventions when under pressure from patient groups and industry. Indeed, several interventions with dubious cost-effectiveness profiles have been approved for patients in the Scottish NHS in recent years (582–584).

NICE also approved PCSK9 inhibitors for primary prevention in some patients based on patient access scheme pricing, recommending the treatment is only provided to patients with primary

heterozygous familial hypercholesterolaemia with consistently high LDL-C following initiation of first-line cholesterol-reducing treatment (577,585).

10.5 Analysis: Signalling Demand for PCSK9 Inhibitors in the Scottish NHS

It was shown in Chapter 3 that reflecting heterogeneity in cost-effectiveness analysis can serve as a means of signalling demand to healthcare providers. A rational supplier will set their price such that the marginal revenue is equal to the marginal cost of production. Decision-makers then realise consumer surplus by only paying for the intervention for patients with incremental net health benefit attributable to treatment greater than zero (Figure 2-2).

The following section aims to establish demand curves for PCSK9 inhibitors in the Scottish NHS. This will be achieved by calculating individual-level cost-effectiveness for two hypothetical cohorts, representing Scottish populations with familial hypercholesterolaemia.

10.5.1 Background

There have been five studies of the cost-effectiveness of PCSK9 inhibitors for the primary prevention of CVD published in recent years that were not supported by industry. These resulted in publication of six peer-reviewed journal articles and three reports (227,392,392,577,578,586–589). All studies found that providing PCSK9 inhibitors at current prices to patients with familial hypercholesterolaemia is not cost-effective.

Kazi et al. estimated the cost-effectiveness of statins plus PCSK9 inhibitors compared to statin monotherapy in subgroups of the U.S. population with familial hypercholesterolaemia (392,578). This analysis was produced for a report on PCSK9 inhibitors published by the Institute for Clinical and Economic Review. PCSK9 inhibitor therapy was assumed to cost around $14,500 per year. From a health sector perspective, it was found that the ICER associated with statin + PCSK9 inhibitors in adults with heterozygous familial hypercholesterolaemia is around $504,000/QALY. A 68% reduction in the price of statins would be required to make the treatment cost-effective at a high cost-effectiveness threshold of $100,000/QALY.

An update to Kazi et al.'s analysis was published in 2017, which compared statins plus PCSK9 inhibitors to statins plus ezetimibe in the same population (193,227). This analysis found that the ICER was around $450,000/QALY and a 71% reduction in PCSK9 inhibitor price would be required for the treatment to be cost-effective at a threshold of $100,000/QALY. This updated analysis additionally found that the ICER associated with transitioning from statin monotherapy to statins plus ezetimibe was around $199,000/QALY, and hence this treatment option should not be considered a valid comparator.

Arrieta et al. simulated the cost-effectiveness of PCSK9 inhibitor therapy in FOURIER trial participants (586). The treatment was simulated incremental to current treatment, statin monotherapy for 70% of the population, and PCSK9 inhibitors were assumed to cost $14,000-$15,000 annually. Treatment effect was modelled by a 61% reduction in LDL-C, as observed in FOURIER, translated to relative risks via the Framingham CVD risk equations (231). The hypothetical cohort simulated in the analysis had an average TC of around 5.2 mmol/L. The paper does not state whether risk of event differed between patients with and without established CVD. However, amongst participants in the FOURIER trial, approximately 28.7% of participants had experienced CHD, CBVD, or peripheral artery disease (228). The cost-effectiveness analysis was conducted from the health sector perspective, and the calculated ICER associated with PCSK9 inhibitors was around $350,000/QALY. Sensitivity analysis found that the treatment would be cost-effective at an annual price of $4,250, given a threshold of $100,000/QALY. This would represent a 70% reduction in price of treatment.

An updated analysis was published by Arrieta et al. in 2017 (587). This analysis employed new data from the FOURIER trial to model treatment efficacy in the three years subsequent to treatment initiation. The analysis was conducted from the health sector decision-maker and private payer perspectives. From the health sector perspective, results were similar to the previously discussed study. PCSK9 inhibitors were not judged to be cost-effective in the FOURIER trial populations, with an ICER of around $338,000/QALY. A 62% reduction in price would be required for the treatment to be cost-effective at a threshold of $100,000/QALY. From the private payer perspective, PCSK9 inhibitors were estimated to produce a negative return on investment.

In 2017, Korman and Wisløff conducted a cost-effectiveness analysis of PCSK9 inhibitors for CVD prevention in high-risk subpopulations in Norway (589). PCSK9 inhibitors were assumed to cost around €7,800 per year. The CVD-free subpopulations analysed were patients with: diabetes, heterozygous familial hypercholesterolaemia, statin intolerance, and 'miscellaneous high-risk'. The estimated ICERs for these subpopulations were €94,000/QALY, €101,000/QALY, €139,000/QALY, and €213,000/QALY, respectively. Each of these ICERs is well in excess of the cost-effectiveness threshold of 600,000 NOK/QALY (€67,165/QALY) which is unofficially employed in health technology assessment in Norway.

The final cost-effectiveness analysis of PCSK9 inhibitors was conducted by NICE in its evaluation of alirocumab (577). This analysis applied an annual cost of £4,383 for the treatment. ICERs associated with implementation in primary prevention were: £37,000/QALY in the heterozygous familial hypercholesterolaemia population (LDL-C ≥3.5 mmol/L), £44,300 for 'high-risk' patients (LDL-C ≥2.5 mmol/L), and £34,000 for 'very high-risk' patients (LDL-C ≥2.5 mmol/L).

An additional three studies funded by industry have been published. These studies show PCSK9 inhibitors to be cost-effective or borderline cost-effective at current prices (590–592).

10.5.2 Objective

The objective of this study was to establish demand curves for PCSK9 inhibitors in two distinct patient populations:

(i) Patients with familial hypercholesterolaemia requiring residual cholesterol risk reduction supplemental to statin therapy.
(ii) Patients with familial hypercholesterolaemia requiring cholesterol-reduction who are statin intolerant.

10.5.3 PPICOSS

Populations: Scottish adults with no CVD and familial hypercholesterolaemia (TC ≥8.0 mmol/L). Separate analyses considered this population as two mutually exclusive subgroups: statin tolerant and statin intolerant patients.

Perspective: Scottish health sector decision-maker. All healthcare costs accrued by the Scottish NHS and population-level health gains are considered.

Intervention: PCSK9 inhibitors (treated as a class of therapy) for the primary prevention of CVD. In analysis of the statin tolerant population, PCSK9 inhibitors plus statin therapy was the intervention studied. In the analysis of the statin intolerant population, PCSK9 inhibitor monotherapy was the intervention studied.

Comparator: In statin tolerant patients, two potential comparators were considered: (i) statin monotherapy and (ii) ezetimibe plus statin therapy. In statin intolerant patients, two potential comparators were considered: (i) no active treatment and (ii) ezetimibe monotherapy.

Outcome: The outcome considered was a demand curve, which details the proportion of each subpopulation that a decision-maker should provide treatment to at a range of treatment costs. Intermediate outcomes that helped to establish this demand curve were: discounted healthcare costs and QALYs.

Setting: Primary care in the Scottish NHS.

Study Design: Cohort simulation.

10.5.4 Methodology

<u>Scottish CVD Policy Model</u>

The Scottish CVD Policy model was employed to estimate the cost-effectiveness of different methods of statin prioritisation. Intermediate outcomes, including weighted probability of remaining alive and CVD-free in each model state was also estimated. The model was discussed in depth in Chapter 5.

Simulation Cohort

As there does not exist a large cross-sectional dataset of CVD risk factor information for Scottish adults with familial hypercholesterolaemia, a hypothetical cohort was constructed for this analysis. This cohort was constructed using the Scottish Health Survey 2011 dataset employed in previous analyses in this thesis.

The SHeS 2011 dataset includes cross-sectional risk factor information on 4,644 CVD-free Scottish adults (aged 40 and above). Some respondents to the survey were offered a nurse visit, in which blood samples were taken. This dataset can be split into three subsets: individuals who have complete ASSIGN risk factor information, individuals who were not offered a nurse interview so have incomplete risk factor information, and individuals who refused a nurse interview so have incomplete risk factor information. For all risk factors except TC, missing values were imputed for patients who were not offered a nurse interview and multiply imputed for the 306 individuals who were offered a nurse interview and refused. The assumption underlying this process is that censoring of missing risk factor information was only informative for individuals who refused the nurse interview and it was necessary to account for uncertainty caused by this informative censoring.

Patients with familial hypercholesterolaemia were the focus of this analysis. This condition is defined by SIGN as a TC ≥8.0 mmol/L (26). For patients with a family history of CVD, this threshold is lowered to 7.5 mmol/L. The analysis focused on patients with elevated TC alone as they were assumed have a higher likelihood of being cost-effective to treat.

The majority of individuals included in the SHeS dataset were not hypercholesterolaemic. Extremely high levels of TC and LDL-C are most commonly caused by genetic factors and the condition can occur in a heterogeneous group of individuals (593). Hence, an individual's non-cholesterol risk factors are weak predictors of hypercholesterolaemia. This implies that, aside from cholesterol levels, the distribution of CVD risk factors are not significantly different between the hypercholesterolaemic and general population in Scotland. It was therefore determined that data from the SHeS 2011 dataset could be used to construct a hypothetical cohort of patients.

Each individual in the SHeS 2011 dataset was randomly assigned a TC value equal to or greater than 8.0 mmol/L. This value was randomly allocated from the distribution of TC values of patients with familial hypercholesterolaemia in the unaltered dataset. Hence, a dataset was constructed representing a hypothetical cohort of 4,644 Scottish adults with TC ≥8.0 mmol/L providing full ASSIGN risk factor information for each individual.

The hypothetical cohort of patients was employed in two separate analyses. In one analysis it was assumed that each individual in the cohort was statin tolerant. In a second analysis it was assumed that each individual in the cohort was statin intolerant. Hence, a further assumption of this study was that ASSIGN risk factors are not predictive of statin tolerance. Treatment strategies and comparators differed in these two analyses.

Approach to Analysis

The analysis aimed to derive demand curves for PCSK9 inhibitors in two distinct Scottish populations: adults with familial hypercholesterolaemia who are statin tolerant and statin intolerant, respectively.

The first stage in the analysis was establishing the optimal comparator to PCSK9 inhibitors in each population. Guidelines for PCSK9 inhibitors and ezetimibe in clinical practice in Scotland are vague and there is a lack of cost-effectiveness analysis underpinning these guidelines (26,240). In patients who do not achieve adequate cholesterol lowering through statins alone, SIGN states that ezetimibe and PCSK9 inhibitors 'may be considered' (26). Hence, the optimal comparator is not clear.

The average benefits and costs of relevant comparators in the 4,644-individual cohort were estimated using the Scottish CVD Policy Model. For statin intolerant patients, the comparators considered were: no active treatment, statin monotherapy, ezetimibe plus statin therapy, and PCSK9 inhibitor plus statin therapy. For statin intolerant patients, the comparators considered were: no active treatment, ezetimibe monotherapy, and statin monotherapy. Traditional health economic decision rules (42,43) were employed to select the valid comparator in each population, employing a cost-effectiveness threshold of £20,000/QALY.

Based on previous cost-effectiveness analyses and the high price of PCSK9 inhibitor therapy, it was hypothesised that this therapy would have an ICER well in excess of £20,000/QALY in both populations.

The next stage in the analysis was to construct the demand curves for PCSK9 inhibitors in the two populations. This was achieved in 4 steps:

1. Estimation of discounted costs and QALYs associated with chosen comparator and PCSK9 inhibitors for each individual in the cohort.
2. Establishment of *Treatment Value* (*INMB* disregarding direct treatment costs) of PCSK9 inhibitors for each individual in the cohort.
3. Calculation of annual cost of PCSK9 inhibitor therapy at which each patient's treatment-related costs would equal their *Treatment Value*. This is the maximum annual price, or reverse-engineered price, a decision-maker should pay for PCSK9 inhibitors, given their cost-effectiveness threshold.
4. Plotting maximum annual price of treatment in descending order on a graph, creating the demand curve.

Choosing Valid Comparator

Several comparators exist for residual cholesterol risk reduction in patients with familial hypercholesterolaemia. As explained in the introductory section of this chapter, statins and ezetimibe are the two most relevant comparators according to clinical guidelines.

To establish a demand curve for a treatment, it must be possible to compare this treatment to a unitary comparator. Preferably, this comparator will represent standard of care. Given the lack of cost-effectiveness analysis underpinning existing guidelines for the provision of ezetimibe in the Scottish NHS, the optimal comparator and standard of care may not align. Statin tolerant patients may receive no active treatment, statin monotherapy, or statins plus ezetimibe. Statin intolerant patients may receive no active treatment or ezetimibe monotherapy.

Cost-effectiveness analyses were conducted to establish the cost-effectiveness frontier for addressing residual cholesterol risk in statin tolerant and statin intolerant Scottish patients. In both populations, the optimal treatment strategy (non-dominated with an ICER less than

£20,000/QALY) was chosen as the valid comparator for PCSK9 inhibitors in the demand curve analysis.

Input Parameters

The key parametric inputs for the treatment-related costs and effects are described in Table 10-1. These relate to statin therapy, ezetimibe, and PCSK9 inhibitors.

All statin-related modelling inputs were previously described in Chapter 7 (Table 7-4). The LDL-C-lowering and HDL-C-increasing effect of statin therapy were derived from meta-analyses of preventive statin therapy (284,493). This meta-analysis informed treatment parameters in previous studies of statins in this thesis. Side effects and treatment-related disutilities were derived from a range of sources. Statins were assumed to increase risk of diabetes, and were also associated with a small annual pill-taking disutility

Compared with statin therapy, there is less information regarding the efficacy and safety of ezetimibe and PCSK9 inhibitors. This is because they are newer treatments which have been studied in fewer clinical trials with shorter follow-up. The LDL-C-lowering effect of ezetimibe monotherapy, ezetimibe plus statin therapy, PCSK9 inhibitor monotherapy, and PCSK9 inhibitors plus statin therapy were derived from a recent meta-analysis conducted by IfCER in the U.S. (578). In all treatment scenarios, LDL-C reduction was translated to a reduction in non-HDL cholesterol using Friedewald's equation (495,496), as in analyses in Chapters 7,8, and 9, assuming the treatments only affected LDL-C. Based on a previously-conducted cost-effectiveness analysis, it was assumed that adverse injection-site reactions would occur in a proportion of patients receiving these injections and this would lead to patient disutility and increased costs (392).

Parameter	Base Case Value	Source
Change in cholesterol levels		
HDL-C increase (statin monotherapy)	+4.0%	(493)
LDL-C decrease (statin monotherapy)	-29.0%	(284)
LDL-C decrease (ezetimibe monotherapy)	-18.6%	(578)
LDL-C decrease (PCSK9 inhibitor monotherapy)	-53.7%	(578)
LDL-C decrease (statin plus ezetimibe)	-45.7%	(578)
LDL-C decrease (statin plus PCSK9 inhibitor)	-75.3%	(578)
Non-HDL cholesterol (Statin monotherapy)	-27.2%	(495,496)
Non-HDL cholesterol (ezetimibe monotherapy)	-14.9%	(495,496)
Non-HDL cholesterol (PCSK9 inhibitor monotherapy)	-42.9%	(495,496)
Non-HDL cholesterol (statin plus ezetimibe)	-36.6%	(495,496)
Non-HDL cholesterol (statin plus PCSK9 inhibitor)	-60.2%	(495,496)
Side effects and disutility		
Statin-induced diabetes, increase in absolute risk	5.0%	(440)
Annual pill-taking disutility (statins)	0.0011	(497)
Annual disutility (PCSK9 inhibitors)	0.0003	(392)
Treatment costs		
Annual price Atorvastatin 20mg/daily	£13.00	(213)
Annual price statin plus ezetimibe	£506.74	(594)
Annual price ezetimibe	£342.03	(594)
Annual price statin plus PCSK9 inhibitor	£4,408.30	(594)
Annual price PCSK9 inhibitor	£4,395.30	(594)
Risk assessment, monitoring, and side effect costs*		
Risk assessment	£26.34	(25)
Monitoring, first year (statins)	£120.17	(25)
Monitoring, subsequent years (statins)	£67.96	(25)
Annual cost of early type 2 diabetes treatment	£314.33	(25)

Table 10-1: Efficacy, side effects, disutility, and costs associated with statins, ezetimibe, and PCSK9 inhibitors. *Assumed to be equal across treatment strategies

Producing Demand Curves

Once a valid comparator was selected, the four steps described above were completed to produce the demand curve. Recall from Chapter 2 that *Treatment Value* is defined as the net monetary benefit of a treatment excluding its direct treatment-related costs but accounting for costs of side-effects, disease-related morbidity, and life-expectancy. The metric *Treatment Value* will be

key in establishing the demand curve for the two populations of interest in this analysis. Screening and annual monitoring costs may also be accounted for, when relevant. The four steps listed above were undertaken to establish a demand curve.

Step 1: Estimation of costs and QALYS associated with comparator and PCSK9 inhibitors

The first step towards producing PCSK9 inhibitors demand curves was estimating lifetime costs, QALYs, and weighted, discounted CVD-free life years associated with PCSK9 inhibitors and their comparator. These values were estimated for every individual in the cohort. In the analysis of statin tolerant patients, the PCSK9 inhibitor strategy is always considered as a supplement to statin therapy. For statin intolerant patients it refers to PCSK9 inhibitor monotherapy. The role of CVD-free life years in producing the demand curve will be discussed in Step 3.

The Scottish CVD Policy Model was employed to estimate outcomes of interest using the simulation parameters listed above. Macros for Microsoft Excel were produced to conduct the analysis.

For the comparator, all healthcare costs incremental to no active treatment were accounted for. These were: non-CVD-related healthcare costs, CVD-related healthcare costs, medication costs, and monitoring costs. Health benefits incremental to no active treatment included all QALY gains incurred from reduced CVD events alongside losses incurred due to treatment-related side effects and disutility.

For PCSK9 inhibitors, incremental to no active treatment the healthcare costs accounted for included non-CVD-related healthcare costs, CVD-related healthcare costs, and monitoring costs. The cost of the PCSK9 inhibitor medication was not accounted for. Health benefits in the analysis included all QALY gains incurred from reduced CVD events alongside losses incurred due to treatment-related side effects and disutility.

Step 2: Establishing Treatment Value of PCSK9 inhibitors for each individual in cohort.

The next step in producing the demand curve was to estimate *Treatment Value* of PCSK9 inhibitors versus the comparator for every individual in the cohort. All of the constituents of the *Treatment Value* equation were computed in Step 1.

Let ΔC equal the cost of PCSK9 inhibitors, excluding the cost of medication, incremental to the total cost of the comparator. This incremental cost can be split into four categories: ΔC_{se}, incremental costs incurred due to side effects, ΔC_{morb}, incremental costs saved due reduced CVD-related morbidity, ΔC_{le}, incremental costs incurred due to increased life expectancy, and $\Delta C_{monitor}$, incremental costs incurred due screening and check-up costs. Further, let ΔE represent the incremental QALYs associated with PCSK9 inhibitors versus the chosen comparator, ΔC_{Rx} represent the incremental medication costs associated with PCSK9 inhibitors, and λ represent the decision-maker's cost-effectiveness threshold. *Treatment Value* for individual *i* can be estimated with the following equation:

$$Treatment\ Value_i = INMB + \Delta C_{Rx} \quad (10\text{-}1)$$
$$= \lambda * \Delta E_i - (\Delta C_{se,i} + \Delta C_{morb,i} + \Delta C_{le,i} + \Delta C_{monitor,i}). \quad (10\text{-}2)$$

<u>Step 3: Calculating reverse-engineered price for PCSK9 inhibitor therapy for each individual</u>

The next step was to establish the annual cost of PCSK9 inhibitors that would result in each individual's incremental net monetary benefit to equal zero. This value represents the maximum price a decision-maker should be willing to pay for medication for patient *i*, given their cost-effectiveness threshold. This will be referred to as the reverse-engineered price hereafter. Rearranging Equation (10-1), it can be shown that this value occurs when the patient's total treatment-related costs equal *Treatment Value*.

$$Treatment\ Value_i = INMB + \Delta C_{Rx,i}$$
$$\Rightarrow INMB = Treatment\ Value_i - \Delta C_{Rx,i}$$
$$\Rightarrow INMB = 0, \text{if and only if } Treatment\ Value_i = \Delta C_{Rx,i}.$$

The following calculations describe the computational process required to estimate the annual price of treatment which ensures that ΔC_{Rx} is equal *Treatment Value* for individual *i*. Let:

t = cycle (years) after treatment initiation,
h = time horizon of analysis,
$Treatment\ Value_i$ = net present value of $Treatment\ Value$ for patient i,
$p_{t,i}$ = probability that patient i is CVD-free and alive at time t,
d_r = discount rate (assumed equal for health and cost outcomes),
x = annual cost of PCSK9 inhibitor medication,
$E(C_{comp,i})$ = expected lifetime costs of comparator for patient i,
$E(C_{Rx,i})$ = expected lifetime costs of PCSK9 inhibitor for patient i.

The cost of PCSK9 inhibitor medication is only considered while the patient is CVD-free. It is assumed patients will receive the same treatment after a primary CVD event. Then, by definition,

$$\mathrm{E}\left(C_{Rx,i}\right) = p_{1,i} * x + \frac{p_{2,i}}{(1+d_r)} * x + \frac{p_{2,i}}{(1+d_r)^2} * x + \cdots + \frac{p_{h,i}}{(1+d_r)^{h-1}} * x$$

$$\Rightarrow \sum_{t=1}^{h} \frac{p_{t,i}}{(1+d_r)^{t-1}} * x = x * \sum_{t=1}^{h} \frac{p_{t,i}}{(1+d_r)^{t-1}}.$$

We require a value of x such that,

$$\Delta C_{Rx} = E\left(C_{Rx,i}\right) - E(C_{comp,i}) = Treatment\ Value_i,$$

$$\Rightarrow x * \sum_{t=1}^{h} \frac{p_{t,i}}{(1+d_r)^{t-1}} - E(C_{comp,i}) = Treatment\ Value_i$$

$$\therefore x = \frac{Treatment\ Value_i + E(C_{comp,i})}{\sum_{t=1}^{h} \frac{p_{t,i}}{(1+d_r)^{t-1}}}.$$

The value on the denominator in this final equation is the sum of the weighted probabilities that an individual was CVD-free and alive at each stage in the analysis, accounting for the discounting of future life years. It was possible to obtain this value as output from the Scottish CVD Policy Model as it represents an intermediate step necessary for computing the model's primary outcomes. Hence it was possible to establish a value x_i such that the *INMB* associated with PCSK9 inhibitors compared to standard of care was equal to zero for each individual in the dataset. This value is the reverse-engineered price: the maximum annual price a decision-maker should be willing to pay to give patient *i* the intervention instead of the comparator.

<u>Step 4: Plotting demand curve</u>

The final step in producing the demand curve was to plot each individual's value of x_i against the percentile of x values they represent in the population. Any point on the curve shows the proportion of the population that a decision-maker would choose to provide PCSK9 inhibitors to at a fixed annual price of treatment.

Secondary Analysis

The analysis described so far aims to compute the optimal value of x_i for every individual in the population. It is unlikely that such computation would be completed in clinical practice. However, a demand curve can be discretized into a step function, where x_i is established for a set of subgroups of a population. Producing such a curve would allow decision-makers to recommend differential treatment strategies for different subgroups of a population.

Secondary analysis aimed to establish subgroups of the populations that were significantly more likely to be cost-effective to treat at high medication prices. Linear regression was performed to highlight drivers of cost-effectiveness. Reverse-engineered price was the dependent variable in these regression analyses and the ASSIGN risk factors were included as predictors.

10.5.5 Results

Hypothetical Cohort Descriptive Statistics

Table 10-2 describes the descriptive statistics for the hypothetical cohort of individuals with familial hypercholesterolaemia employed in the analysis. TC ranged from 8.0 to 10.5 mmol/L.

Risk Factor	Obs	Mean	Std. Dev.	Min	Max
Male	4,644	0.42	0.49	0	1
Age	4,644	58.51	12.30	40	103
SIMD	4,644	19.51	13.39	5.18	45.62
Diabetes	4,644	0.07	0.25	0	1
FH	4,644	0.46	0.50	0	1
CPD	4,644	7	7.05	0	39
SBP (mmHg)	4,644	131	8.81	90	203
TC (mmol/L)	4,644	8.3	0.54	8.0	10.5
HDL-C (mmol/L)	4,644	1.5	0.22	0.6	3.3
ASSIGN Score	4,644	19.6	17.5	1.0	98.5

Table 10-2: Descriptive statistics of hypothetical Scottish cohort with familial hypercholesterolaemia

Choosing Valid Comparators

Tables 10-3 and 10-4 display cost-effectiveness outcomes of different treatment strategies for statin tolerant individuals. Statin therapy, statins plus ezetimibe, and statins plus PCSK9 inhibitors incrementally increase costs and QALYs compared to no active treatment, respectively.

Policy	Discounted QALYs		Discounted Costs (£1000's)		
	Disease-Related	Disutility	Health Care	Treatment	Monitoring
Do Nothing	*Reference*				
Statin therapy	984	67	2,040	796	4,630
Statins + Ezetimibe	1,200	19	2,590	31,400	4,670
Statins + PCSK9i	1,940	19	4,880	283,000	4,830

Table 10-3: Disaggregated costs and QALYs for statin tolerant population

Policy	Discounted QALYs	Discounted Costs (£000's)	ICER (£/QALY)
Do Nothing	*Reference*		
Statin monotherapy	917	7,460	8,100
Statins + Ezetimibe	1,190	38,600	116,400
Statins + PCSK9i	1,920	293,000	344,600

Table 10-4: Cost-effectiveness results for statin tolerant population

Employing a cost-effectiveness threshold of £20,000/QALY, statin monotherapy is the optimal treatment strategy for statin tolerant individuals. In the demand curve analysis, statin monotherapy was therefore considered to be the valid comparator to PCSK9 inhibitors.

Tables 10-5 and 10-6 display the cost-effectiveness outcomes of different treatment strategies for statin intolerant individuals. Ezetimibe monotherapy and PCSK9 inhibitor monotherapy incrementally increase costs and QALYs compared to no active treatment.

Employing a cost-effectiveness threshold of £20,000/QALY, no treatment is the optimal treatment strategy for statin intolerant individuals. In the demand curve analysis, statin monotherapy was therefore considered to be the valid comparator to no active treatment.

Policy	Discounted QALYs		Discounted Costs (£1000's)		
	Disease-Related	Disutility	Disease-Related	Health Care	Monitoring
Do Nothing	*Reference*				
Ezetimibe*	493	18	878	31,700	4,500
PCSK9i	1,410	19	3,170	275,000	4,720

*Monotherapy

Table 10-5: Disaggregated costs and QALYs for statin intolerant population

Policy	Discounted QALYs	Discounted Costs (£000's)	ICER (£/QALY)
Do Nothing	*Reference*		
Ezetimibe	475	37,100	78,000
Statins + PCSK9i	1,390	283,000	269,800

*Monotherapy

Table 10-6: Cost-effectiveness results for statin intolerant population

Demand Curves

The demand curve for PCSK9 inhibitor therapy for the statin tolerant population with familial hypercholesterolaemia is presented in Figure 10-1. The key result is presented in the green curve, which represents demand for the treatment given a cost-effectiveness threshold of £20,000/QALY. The red curves represent demand at thresholds of £10,000/QALY and £30,000/QALY, respectively.

The median reverse-engineered annual treatment price in the population was £250. At an annual PCSK9 inhibitor price of £519, the decision-maker would provide the therapy to 25% of the population. At an annual PCSK9 inhibitor price of £827, the decision-maker would provide the therapy to 10% of the population. At the current listed price for PCSK9 inhibitors in the Scottish NHS, not one individual in the hypothetical cohort would be cost-effective to treat.

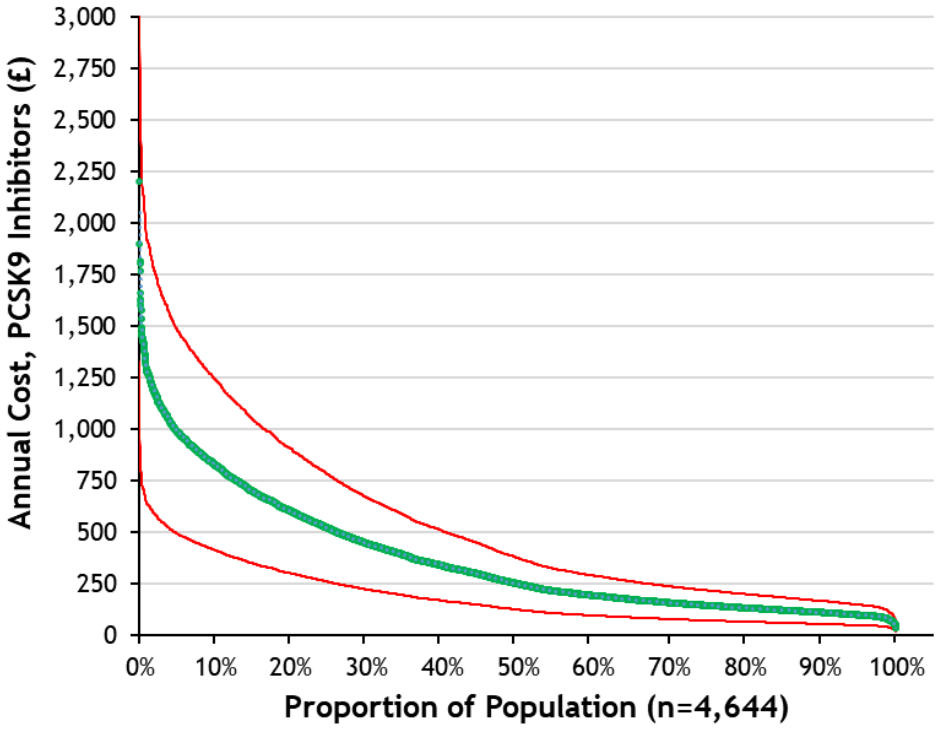


Figure 10-1: Demand curve for PCSK9 inhibitors versus statin therapy in hypothetical cohort of CVD-free statin tolerant adults with familial hypercholesterolaemia

The demand curve for PCSK9 inhibitor therapy for the statin intolerant population is presented in Figure 10-2. In this curve the key result is presented in the black curve, which represents demand for the treatment given a cost-effectiveness threshold of £20,000/QALY while the red curves represent demand at thresholds of £10,000/QALY and £30,000/QALY, respectively.

The median reverse-engineered price in the population was £393. At an annual PCSK9 inhibitor price of £710, the decision-maker would provide the therapy to 25% of the population. At an annual PCSK9 inhibitor price of £1,152, the decision-maker would provide the therapy to 10% of the population. At the current listed price for PCSK9 inhibitors in the Scottish NHS, not one individuals in the cohort would be cost-effective to treat

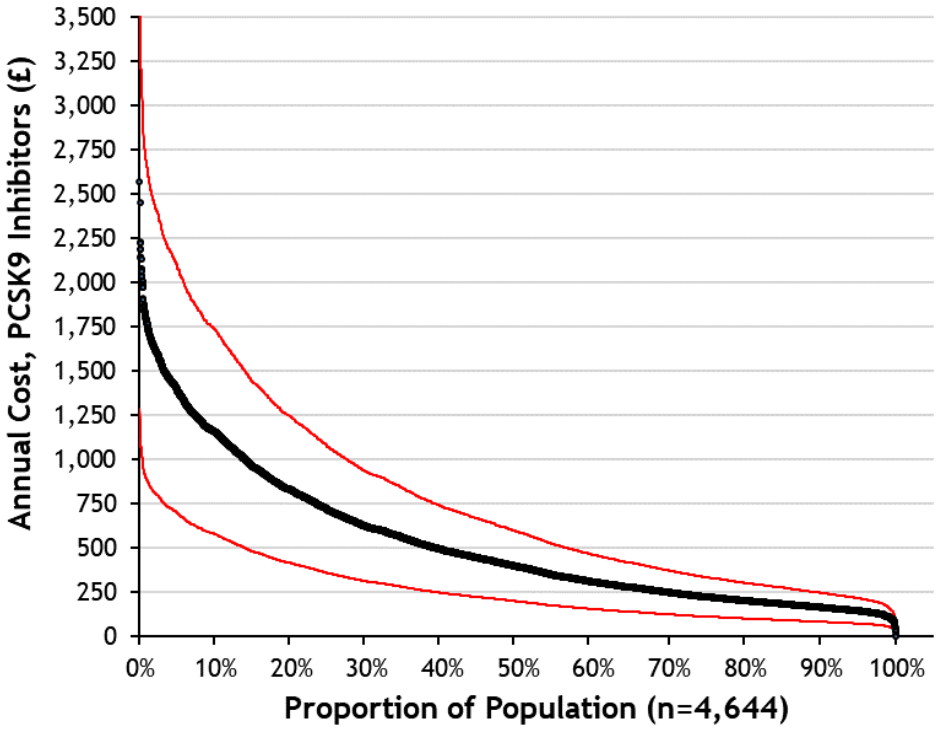


Figure 10-2: Demand curve for PCSK9 inhibitors versus statin therapy in hypothetical cohort of CVD-free statin intolerant adults with familial hypercholesterolaemia

Secondary Analysis

Linear regression was conducted using results for both populations. These tests aimed to establish the factors which influenced individual-level maximum price of treatment in statin tolerant and intolerant individuals with familial hypercholesterolaemia. The dependent variable in each linear regression was reverse-engineered price of treatment. The independent variables were the ASSIGN variables. Results from the linear regression analysis are presented in Tables 10-7 and 10-8.

This linear regression model presented in Tables 10-7 and 10-8 represents a meta-model. Their respective adjusted r-squared terms of around 85% suggest that these models could be used successfully to predict reverse-engineered price for PCSK9 inhibitors in a cohort of statin tolerant and statin intolerant Scottish adults with familial hypercholesterolaemia. Hypothesis testing regarding the effect of different covariates on reverse-engineered price cannot be conducted reliably with a meta-model. However, results from these linear regressions show that the Scottish CVD Policy Model predicts several factors may be drivers of reverse-engineered

price. *Male*, *Age*, and *TC* are all strongly positively correlated with reverse-engineered price according to the model.

Number of obs =		4644	R-squared	=	0.8517
F(9,4634)	=	2956.34	Adj R-squared	=	0.85
Prob > F	=	0.0000	Root MSE	=	115.060

Covariate	Coef.	Std. Err.	t	P>|t|	[95% Conf. Interval]	
Male	468.0	3.5	134.9	0.000	461.0	475.0
Age	10.7	0.145	73.4	0.000	10.4	11.0
SIMD	1.7	0.1	13.1	0.000	1.4	1.9
Diabetes	75.0	6.8	11.1	0.000	61.7	88.3
FH	8.2	3.6	2.3	0.021	1.3	15.2
CPD	-2.4	0.2	-9.9	0.000	-2.8	-1.9
SBP	1.6	0.2	8.1	0.000	1.2	2.0
TC	65.9	3.2	20.8	0.000	59.7	72.1
HDL-C	-125.0	8.0	-15.7	0.000	-141.0	-109.0
Constant	-1060.0	39.7	-26.6	0.000	-1130.0	-978.0

Table 10-7: Linear regression analysis with reverse-engineered price of PCSK9 inhibitor therapy for statin tolerant individuals as dependent variable and ASSIGN risk factors as predictors

Number of obs =		4644	R-squared	=	0.8559
F(9,4634)	=	30.58.10	Adj R-squared	=	0.86
Prob > F	=	0.0000	Root MSE	=	153.700

Covariate	Coef.	Std. Err.	t	P>|t|	[95% Conf. Interval]	
Male	616.0	0.4	132.9	0.000	607.0	625.0
Age	16.6	0.2	85.2	0.000	16.2	17.0
SIMD	3.1	0.2	18.2	0.000	2.8	3.4
Diabetes	16.4	9.1	1.8	0.070	-1.3	34.2
FH	-13.9	4.7	-2.9	0.003	-23.2	-4.6
CPD	-5.8	0.3	-18.0	0.000	-6.4	-5.2
SBP	1.4	0.3	5.5	0.000	0.9	2.0
TC	88.5	4.2	20.9	0.000	80.2	96.8
HDL-C	-139.0	10.7	-13.0	0.000	-160.0	-118.0
Constant	-1450.0	53.0	-27.3	0.000	-1550.0	-1340.0

Table 10-8: Linear regression analysis with reverse-engineered price of PCSK9 inhibitor therapy for statin intolerant individuals as dependent variable and ASSIGN risk factors as predictors

10.5.6 Discussion and Limitations

Discussion

Demand curves were produced which show the portion of two Scottish populations with familial hypercholesterolaemia that should be treated with PCSK9 inhibitors at a range of annual treatment prices. Undertaking this analysis can signal demand for PCSK9 inhibitors to manufacturers, helping dictate their pricing strategy.

A rationally-acting monopolist manufacturer would choose to reduce their price in response to these results. Otherwise they would risk wasting their exclusivity period gaining less revenue than could otherwise be achieved if price were set at the point where marginal revenue equals marginal cost.

Recent developments in PCSK9 inhibitor pricing suggests that manufacturers are aware of the need to reduce their price to find some equilibrium with demand for the product. In 2018, Amgen drastically reduced the price of Repatha and Regeneron and Sanofi have similarly reduced the price of Praluent (595–597). It is likely that this decision was taken in direct response to cost-effectiveness analyses which showed that large reductions in the treatment price was necessary to justify expansive use of PCSK9 inhibitors in CVD prevention (193,392,578,586). The companies appear to have been rewarded for this decision with broader recommendations for PCSK9 inhibitor therapy in the 2018 ACC/AHA guidelines for cholesterol management (174).

There is considerable heterogeneity in cost-effectiveness of PCSK9 inhibitors, even within the hypercholesterolaemic population. While no individual in either population was cost-effective to treat at the current price of PCSK9 inhibitors in Scotland, high annual medication costs (in excess of £800 per year) may be justified in some subgroups of the population. This analysis showed that a decision-maker should be willing to pay more for PCSK9 inhibitors for statin intolerant patients. Intuitively this makes sense as a cheaper, yet less effective, alternatives exist for cholesterol control in the statin tolerant population.

Annemans et al. have suggested that PCSK9 inhibitor therapy should be targeted at patients with high risk and high LDL-C, much like the absolute risk reduction approach to prevention discussed in Section 8.3 (598). Results from this analysis support this suggestion. Elderly patients, those with the highest levels of total cholesterol, and those with greater ASSIGN risk scores were deemed to be the most likely to be cost-effective to treat.

Limitations

As with all modelling studies, assumptions were required to undertake this analysis. These assumptions may limit the applicability of a study to the real world. Two key assumptions that could limit this analysis relate to the construction of a hypothetical cohort and the price of comparators.

The low prevalence of familial hypercholesterolaemia in the Scotland means that it would be difficult to obtain risk factor information from enough individuals suffering from the condition to construct a truly representative cohort for the analysis. Due to lack of data availability, a hypothetical cohort was constructed for this analysis. The risk factors in this cohort were mostly taken from a cross-sectional survey of the Scottish population. Values for TC, however, were assumed to be in excess of 8.0 mmol/L. This was to reflect the TC of individuals with familial hypercholesterolaemia. The analysis therefore relies on the assumption that risk factors are distributed evenly amongst individuals in Scotland with and without familial hypercholesterolaemia. Further research should be conducted, perhaps supplemented with data from outside Scotland, to establish the validity of this assumption.

Another assumption in this analysis relates to the price of comparators. The demand curve for PCSK9 inhibitors considers the proportion of the hypercholesterolaemic population treated at varying treatment prices. It was assumed, however, that the price of statins and ezetimibe were static. The high cost of ezetimibe resulted in it being excluded from analyses due to extended dominance. In reality, manufacturers of ezetimibe could reduce the price of their treatment in response to a reduction in the price of PCSK9 inhibitors. Inasmuch, this analysis just provides a framework for signalling demand for PCSK9 inhibitors. Further analysis should consider demand for PCSK9 inhibitors as a function of the price of relevant comparators. Treatment price

for comparators will tend towards the marginal cost of production and become relatively static after their patent expires (599).

This study looked at incremental cost-effectiveness in the hypothetical cohort constructed for the analysis, but did not estimate absolute costs or health benefits at a population level. To establish population-level outcomes, a better understanding of the prevalence of statin tolerant and statin intolerant familial hypercholesterolaemia is required. Given the apparently low prevalence of the condition – around 1% in the Scottish Health Survey 2011 (347) – a very large study would be required to reliably estimate the prevalence of the condition.

10.6 Chapter Summary

The majority of this thesis has focused on heterogeneity in cost-effectiveness with specific regard to the prioritisation of patients for preventive statin therapy. After initiation of this treatment, some patients have residual cholesterol risk and others are deemed to be statin intolerant. This chapter aimed to establish how best to prioritise patients for expensive treatments that offer additional cholesterol reduction.

Reflecting heterogeneity in decision-making would allow for a more cost-effective distribution of PCSK9 inhibitors in the Scottish population. PCSK9 inhibitors are much more expensive than statins. Therefore, stratifying patients into cost-effective subgroups is even more important for this treatment as it is necessary to avoid the large cost consequences associated with incorrect treatment decisions.

More generally, this chapter showed that reflecting heterogeneity in cost-effectiveness in a population allows decision-makers to signal demand for a treatment. The theoretical underpinnings of demand signalling were discussed in Section 2.4.2. Willingness to treat different proportions of a population dependent on treatment price ensures that decision-makers are able to achieve welfare gains when investing in a health care intervention.

In the case of PCSK9 inhibitors, making decisions based on the results of this analysis would likely force manufacturers to lower prices. The analysis in this chapter confirms results from the

literature that show PCSK9 inhibitors are currently too expensive, even in very high-risk subsets of the familial hypercholesterolaemic population (193,227,392,577,578,586–588). If decision-makers abide by traditional health economic decision rules, they should not provide PCSK9 inhibitors to any of their population unless considerable price reductions are agreed upon.

In 2018, the manufacturers of PCSK9 inhibitors drastically reduced the price of treatment in the U.S. (595,596). Given this price reduction, it is now the role of decision-makers to ensure that the treatment is targeted at cost-effective subgroups of patients in the U.S.

There has been less transparency in Scotland, England and Wales, where the treatment has been approved on patient access schemes (577,580,581,585). This chapter showed that a significant reduction in price would need to have been negotiated with manufacturers by the SMC for the treatment to be cost-effective for any individuals in Scotland. This is also true for NICE.

Part 4

Policy Recommendations, Further Research, and Conclusions

Part 4 aims to synthesise results from the thesis, produce policy recommendations, suggest further research, and provide concluding remarks.

Chapter 11 provides policy recommendations based on the analyses in Part 3. Results from cost-effectiveness analyses are synthesised to define optimal strategies for preventive statin therapy prioritisation. Optimal treatment decisions are presented for several scenarios, dependent on constraints that may be placed upon a decision-maker. Recommendations are also provided regarding the approach decision-makers should adopt to signal demand for PCSK9 inhibitors.

Chapter 12 summarises the research contained within the thesis and highlights areas for further research. Four areas that require further research are highlighted. These are: parametric inputs for statin cost-effectiveness analyses, validity of novel CVD biomarkers, long-term safety and efficacy of PCSK9 inhibitor therapy, and optimal objective functions for healthcare decision-makers.

Chapter 11
Policy Recommendations

11.1 Purpose

Several approaches for the primary prevention of CVD have been analysed throughout this thesis. It has been shown that population-level health gains can be achieved by looking beyond 10-year risk when prioritising patients for preventive therapy. However, the policies discussed have not yet been collectively compared with each other.

The purpose of this chapter is to compare and contrast the approaches to prevention heretofore discussed. Decision-makers who wish to maximise health outcomes given an exogenously determined healthcare budget should invest in cost-effective treatment strategies. However, health sector decision-makers can have multiple objectives. Concomitant objectives can include the reduction of health inequalities, improvement of social welfare, as well as more nefarious aims like profit-maximisation.

This chapter compares policies for statin prioritisation, selecting optimal treatment decisions for policymakers. It shows that these decisions may be constrained by societal preference regarding distribution of resources and distribution of health outcomes. Finally, a series of policy recommendations are produced, based on the analysis conducted in this thesis.

11.2 Maximising QALYs in CVD Prevention

This thesis has considered the costs and QALYs associated with several policies for prioritising patients for preventive statin therapy. These policies were split into three categories: policies which retain the role of 10-year risk scoring in decision-making, policies which prioritise treatment based on 10-year risk scoring alongside some other covariate, and policies which maximise outcomes through direct utilisation of decision models in clinical practice. Policies have been compared using traditional health economic decision rules within these categories. The aim of this section is to compare all policies simultaneously.

The policies that have been considered can be separated into two groups. One group treats the same number of individuals as current guidelines in Scotland (prioritisation for familial hypercholesterolaemia and individuals with ASSIGN score ≥20%). The second group treats the same number of individuals as a policy which extends treatment to all individuals with ASSIGN score ≥10%. Several decision mechanisms for patient prioritisation have been considered. These include prioritisation based on: blanket risk thresholds, updated $ASSIGN_{BIO}$ blanket risk thresholds, absolute risk reduction, age-stratified risk thresholds, life expectancy maximisation, and quality-adjusted life expectancy maximisation.

$ASSIGN_{BIO}$ will not be included as a comparator. Assessment of the novel biomarker HF1 was completed as a case study rather than a genuine proposal for change in clinical practice. To assess whether a novel biomarker should be used to prioritise patients for preventive interventions in CVD, it is necessary to include a range of candidate biomarkers (and biomarker combinations) in the analysis. The population-level health gains associated with this strategy were small in comparison to the other policies considered as reclassification occurred in a small proportion of the total Scottish population. Probabilistic sensitivity analysis showed a large amount of uncertainty regarding the ability of HF1 testing to improve population health. Finally, the benefit of biomarker testing is not contingent on the use of a blanket risk threshold policy. Reclassifying patients based on biomarker values may prove equally as beneficial when combined with other policies discussed.

Table 11-1 shows the discounted costs, discounted QALYs, and ICERs associated with several policies. The optimal policy for decision-makers with a threshold of £20,000/QALY is marked with an asterisk. These strategies are plotted on a cost-effectiveness plane in Figure 11-1 and uncertainty regarding these results are represented in a cost-effectiveness acceptability curve in Figure 11-2. Employing a cost-effectiveness threshold of £20,000/QALY, QALE-Max 10 should be implemented. The demographics of patient prioritised for treatment under different policies are presented in Table 11-2.

Policy	Number Treated	Discounted QALYs	Discounted Cost (£1000's)	ICER (£/QALY)
Familial Hyp.		*Reference*		
Blanket 20	793,559	92,300	636,000	6,900
ARR 20	793,762	96,300	687,000	Extendedly
Age-Strat 20	793,596	99,500	882,000	Extendedly
LE-Max 20	793,387	141,000	1,597,000	Str. Dominated
QALE-Max 20	793,775	150,000	1,313,000	11,700
Blanket 10	1,381,059	164,000	1,596,430	Ext. Dominated
ARR 10	1,380,535	166,000	1,627,000	Ext. Dominated
Age-Strat 10	1,381,054	168,000	1,719,000	Ext. Dominated
LE-Max 10	1,380,749	197,000	2,603,000	Str. Dominated
QALE-Max 10	1,381,122	206,000	2,306,000	17,700*

*Optimal policy with λ=£20,000/QALY. Ext. – extendedly, Str. – strictly

Table 11-1: Costs, QALYs, and ICERs for various statin prioritisation policies

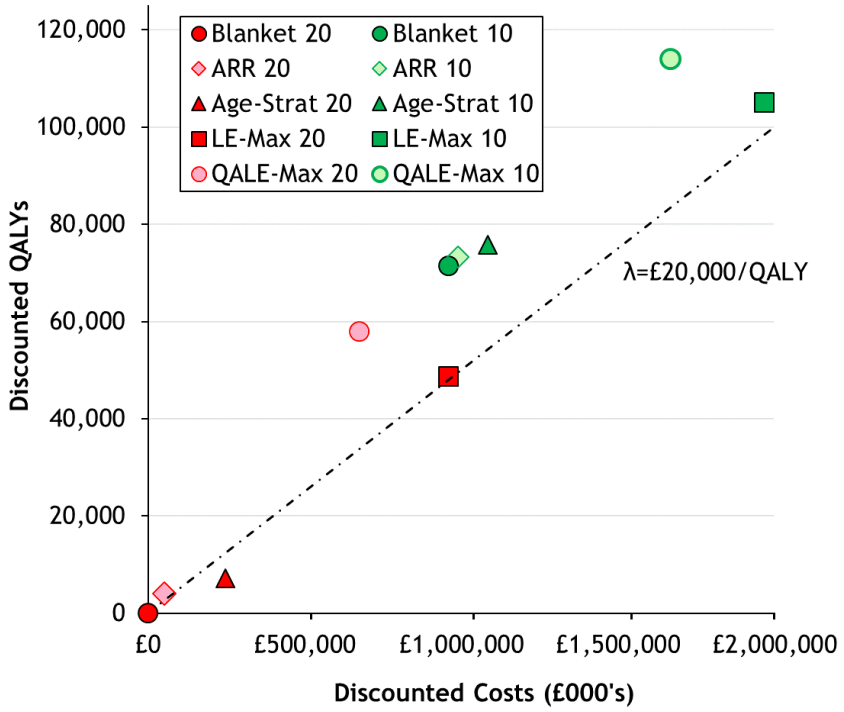


Figure 11-1: Cost-effectiveness plane, all policies

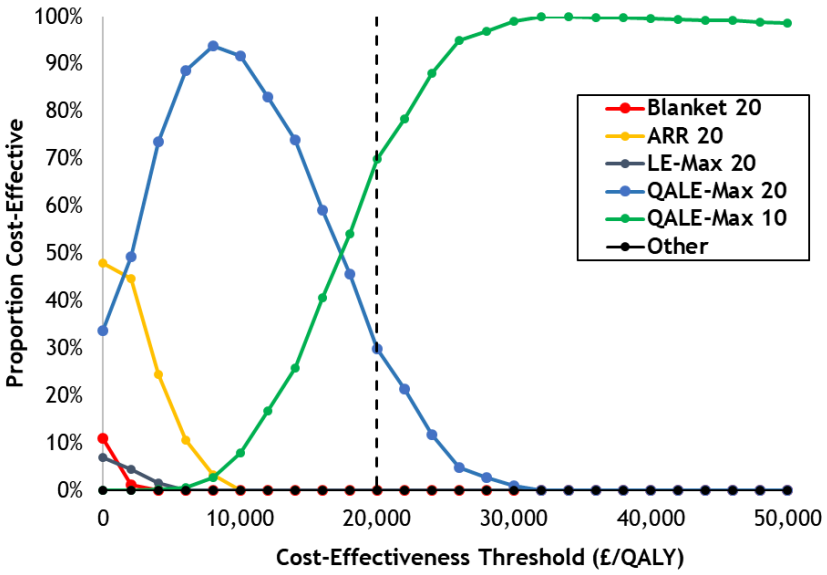


Figure 11-2: Cost-effectiveness acceptability curve, all policies

Instituting Constraints

No policy is worth introducing if it does not garner clinical and societal buy-in. If a clinician does not agree with a treatment guideline they are unlikely to implement it (600,601). As the general public funds the NHS in the U.K., societal values may also constrain which policies are deemed acceptable and should be implemented. These considerations represent constraints on the decision-maker, limiting the policies that can be implemented.

It is beyond the scope of this thesis to establish the constraints that clinicians, patients, and the general public are likely to place on preventive statin policy. Rather, two examples of the types of constraints that may be placed on policy-makers are considered. These examples were retrospectively derived from results presented in Table 11-2 and health inequality analysis conducted alongside the cost-effectiveness analyses throughout the thesis. The first constraint aims to establish equality in access to preventive statin therapy between men and women. The second constraint looks to maximise equality in outcome across quintiles of socioeconomic deprivation.

Constraint 1: Equality of Access

The sex distribution of patients prioritised for treatment must be approximately equal.

Examining Table 11-2, a clear inequality stands out between treated patient groups. The policies which prioritise treatment based on outcome maximisation disproportionately provide treatment to men. Reasons for this result are discussed in Section 9.2. These included distribution of TC between men and women, likely age of first event, and differentials between the type of CVD event men and women are likely to experience. If clinicians (or society) believe such an imbalance in treatment prioritisation is inequitable, LE-Max 10, LE-Max 20, QALE-Max 10, and QALE-Max 20 may be excluded from consideration for implementation.

Under Constraint 1, ARR 10 emerges as the optimal policy for the decision-maker, as shown in Table 11-3. Age-Strat 10 is undominated so remains on the cost-effectiveness frontier, but has an ICER too high to justify implementation. Results from sensitivity analyses presented in Chapter 8 (Figure 8-5) suggest that Age-Strat 10 may be cost-effective if a policy could be defined which limits monitoring costs in years subsequent to treatment initiation.

Notably, more than 40,000 QALYs are lost across the population when Constraint 1 is implemented compared to the optimal policy under unconstrained decision-making. Indeed, the potential welfare losses are even greater when one accounts for the fact that these QALYs would be purchased well below the decision-maker's cost-effectiveness threshold.

		Overall Population	ASSIGN 20	Age-Strat 20	ARR 20	LE-Max 20	QALE-Max 20	ASSIGN 10	Age-Strat 10	ARR 10	LE-Max 10	QALE-Max 10
Proportion of Age-Group Treated (%)	40-44	n/a	0	5	0	44	14	3	12	2	73	37
	45-49	n/a	2	14	2	39	28	14	29	16	68	49
	50-54	n/a	5	30	6	37	37	38	49	39	63	54
	55-59	n/a	15	50	19	38	41	74	74	74	60	63
	60-64	n/a	41	45	45	31	37	94	86	93	50	65
	65-69	n/a	75	52	75	32	43	100	85	99	51	69
	70-74	n/a	92	65	89	21	37	100	80	99	45	68
	75-79	n/a	100	74	92	17	35	100	88	100	38	61
	80+	n/a	100	0	67	4	17	100	81	76	24	42
Average Value	Male (%)	42	45	53	47	94	99	47	51	47	72	73
	SIMD	19.5	21.2	23.5	20.6	20.0	20.2	20.5	21.4	20.4	19.0	20.2
	Diabetes (%)	7	15	17	13	1	5	11	11	10	4	8
	FH (%)	46	68	73	67	35	48	62	65	61	32	43
	CPD	7	8	10	8	5	6	7	7	7	5	5
	SBP (mmHg)	131	134	134	134	131	132	133	133	133	130	132
	TC (mmol/L)	5.8	5.8	5.8	5.9	5.8	5.8	5.8	5.8	5.8	5.8	5.8
	HDL (mmol/L)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Table 11-2: Descriptive statistics of individuals prioritised for treatment under different policies

Policy	Number Treated	Discounted QALYs	Discounted Cost (£1000's)	ICER (£/QALY)
Familial Hyp.		*Reference*		
Blanket 20	793,559	92,300	636,000	6,900
ARR 20	793,762	96,300	687,000	12,900
Age-Strat 20	793,596	99,500	882,000	Ext. Dominated
LE-Max 20	793,387	141,000	1,597,000	Excluded
QALE-Max 20	793,775	150,000	1,313,000	Excluded
Blanket 10	1,381,059	164,000	1,596,000	13,500
ARR 10	1,380,535	166,000	1,627,000	15,700*
Age-Strat 10	1,381,054	168,000	1,719,000	36,500
LE-Max 10	1,380,749	197,000	2,603,000	Excluded
QALE-Max 10	1,381,122	206,000	2,306,000	Excluded

*Optimal policy with λ=£20,000/QALY. Ext. – extendedly

Table 11-3: Cost-effectiveness under Constraint 1

Constraint 2: Equality of Outcome

The implemented policy should not lead to an increase in health inequality in the Scottish population.

Increased SIMD is a significant risk factor for fatal and non-fatal CVD events (152,309,602) and all-cause mortality (603). Moreover, an inverse relationship exists between SIMD and life expectancy (7). It can therefore be presumed that, if no treatment were enacted, health would be distributed unequally in favour of less socially deprived individuals in Scotland.

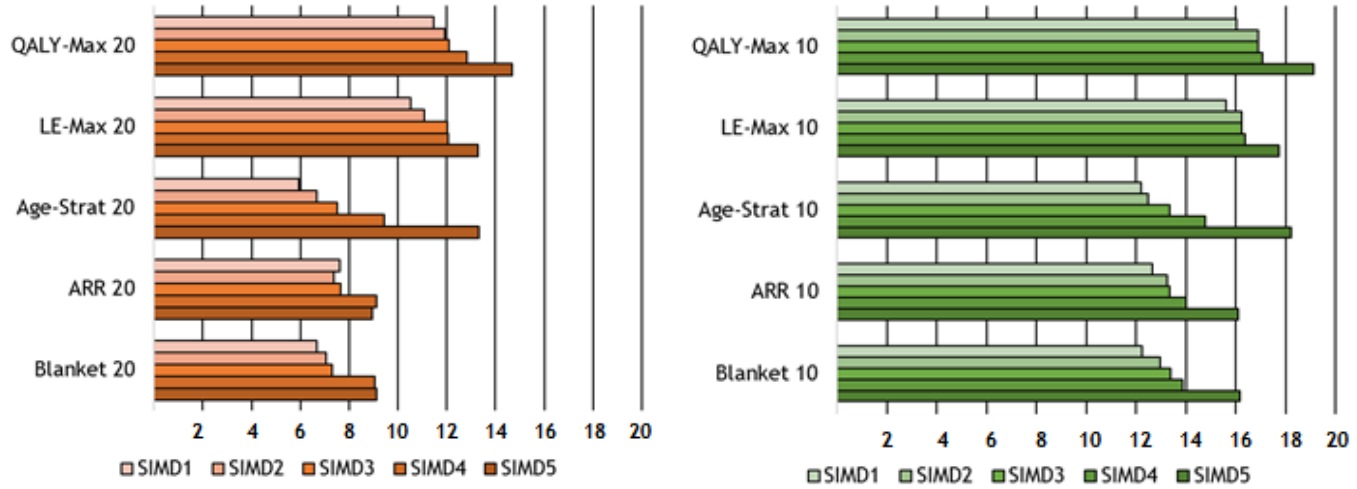
The following analysis will treat statins for familial hypercholesterolaemia as status quo. This is despite the fact that SIGN currently recommends statins are initiated in all individuals with ASSIGN score greater than 20% (26). This decision was made to ensure that current practice is treated with as much scrutiny as other policies. If Blanket 20 is not cost-effective it should not be implemented. Similarly, in this example if it does not adhere to the constraints placed upon the decision-maker it should not be implemented.

Figure 11-3 shows discounted QALY gains for different statin prioritisation policies per 1,000 individuals in the population, stratified by SIMD quintiles. Each number is incremental to a policy of only treating individuals with familial hypercholesterolaemia. Figure 11-4 shows the proportion of total health gains realised by each SIMD quintile.

All of the policies considered would produce health gains in each SIMD quintile. Moreover, individuals in the two most deprived quintiles achieve more of the total QALY gains than those in the two least deprived quintiles for each policy. Hence, if any of the policies considered were implemented, they would reduce the social deprivation gradient in health compared to treatment for familial hypercholesterolaemia alone.

Given the fact that no policy considered will increase health inequality, Constraint 2 does not lead to the exclusion of any of the treatment strategies for a decision-maker. Direct utilisation of decision models in clinical practice to maximise quality-adjusted life expectancy in a population, QALE-Max 10, is the optimal treatment strategy.

Social deprivation is strongly associated with CVD risk and CVD risk factors (152,234,604). This likely explains why each policy is progressive compared to status quo. Policies which target treatment at individuals with high CVD risk, elevated risk factors, and a combination of these are likely to disproportionately treat more socially deprived patients. Constraints regarding health inequality may be of more interest to decision-makers in disease areas that disproportionately affect the less socially deprived.



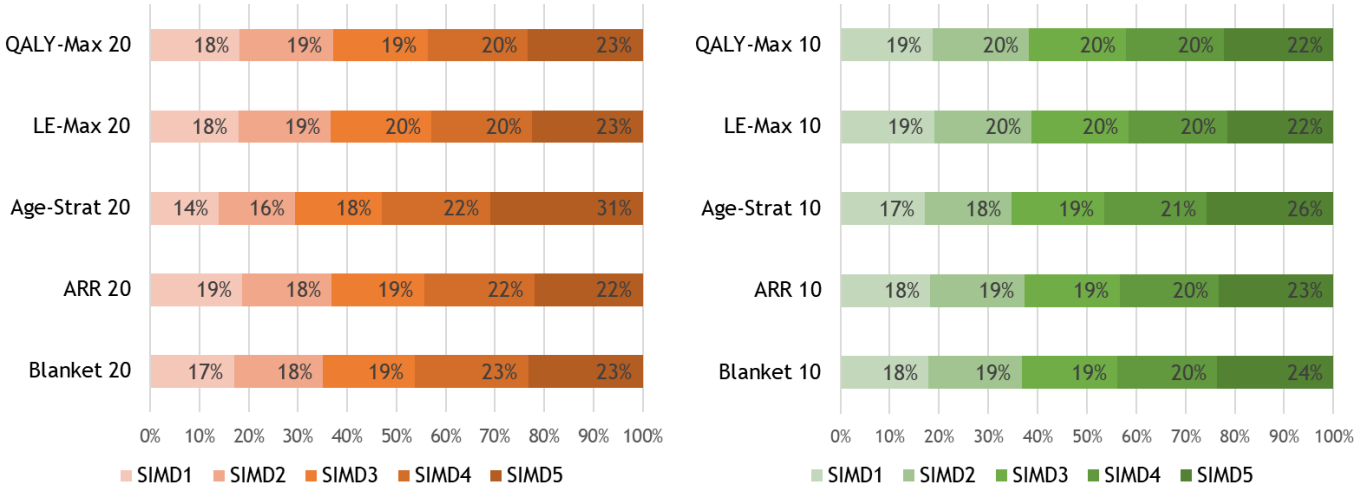


Figure 11-3 (top): Discounted QALY gains for all policies per 1,000 individuals
Figure 11-4 (bottom): Proportion of discounted QALY gains achieved by different SIMD quintiles

11.3 Policy Recommendations

Most healthcare decision-makers are constrained in their ability to maximise QALYs. NICE is perhaps the decision-making body tasked most explicitly with QALY maximisation in the world, having explicitly stated its willingness-to-pay for QALYs since its inception in 1999 (605). Even NICE does not treat the QALY as its sole maximand and include other (explicit and implicit) criteria in their decisions. On a personal note, working alongside the committee tasked with updating SIGN's guidelines for risk estimation and CVD prevention, it was clear that some (potentially cost-effective) policies would not be considered due to 'clinical infeasibility.' Decision-makers clearly face many political, ethical, logistical, and clinical constraints when implementing interventions.

It is not the task of a health economist to dictate what is clinically acceptable and feasible to healthcare practitioners. A health economist can (and should) inform decision-makers of the efficiency losses associated with treatment constraints. It was necessary to present results from the analysis in this thesis contingent on decision-making constraints. Policy recommendations are presented contingent on constraints that could be placed upon the decision-maker.

Two existing policies are relevant to recommendations that may emerge from this thesis: SIGN guidance regarding statin prioritisation (26) and SMC policy regarding the use of PCSK9 inhibitors in familial hypercholesterolaemic patients with residual cholesterol risk while on statin therapy or those with statin intolerance (580,581).

Guidelines regarding preventive statin therapy were published by SIGN in 2017 (26). These guidelines retained the role of 10-year risk scoring in determining who should receive treatment. They state that statins should be offered to patients with familial hypercholesterolaemia and those with an ASSIGN score greater than or equal to 20%. The guideline additionally recommended that alternative approaches to statin prioritisation be considered in a guideline update when new evidence emerges.

The SMC has approved the use of PCSK9 inhibitors for a select group of patients with familial hypercholesterolaemia (580,581). The cost-effectiveness of this decision is unclear, however,

as it was agreed under a patient access scheme in which a discount on the list price is agreed and kept confidential. Therefore, the price paid for the treatment was not disclosed to the public. While it is likely that the discounted price has made PCSK9 inhibitors more cost-effective, given the confidential nature of current SMC guidance on the use of PCSK9 inhibitors, it is useful to provide recommendation on their use in Scotland.

Below are five policy recommendations for SIGN and the SMC, derived from analysis contained within this thesis:

1. Statin eligibility should be expanded in Scotland. Analysis in this thesis consistently showed that, regardless of the specific decision mechanism implemented, it would be cost-effective expand treatment eligibility to more individuals. This could be achieved by reducing the blanket risk threshold or instituting a novel policy which treats more people than standard care.

2. If a decision-maker faces no constraints on who should be prioritised for treatment, direct utilisation of decision models in clinical practice to maximise discounted QALYs should be implemented.

3. If outcome maximisation is rejected as a means of prioritising statin therapy, the absolute risk reduction approach to prevention should be implemented. This would maintain a role for risk scoring in the decision-making process, but would increase health gains in the population by targeting treatment at patients with elevated cholesterol levels.

4. Reducing the monitoring costs for patients receiving statins would significantly increase the cost-effectiveness of statin therapy. In the case of recommendation number three above, such cost reduction would likely result in age-stratification of risk thresholds becoming the optimal treatment strategy.

5. The SMC should conduct its own subgroup-level cost-effectiveness analysis when considering which patients with familial hypercholesterolaemia should receive PCSK9 inhibitors. This will increase transparency in Scottish NHS decision-making and reduce reliance on manufacturer submissions. By representing heterogeneity in patient cost-effectiveness and determining the proportion of patients that will be treated at different price points, the SMC can signal demand to pharmaceutical companies and ensure that they spend their limited health resources efficiently.

Chapter 12
Conclusions and Further Research

This thesis has described several approaches and policies for the primary prevention of CVD. Moreover, it has assessed a range of novel approaches to prioritise patients for preventive therapy for CVD.

Standard of care in most high-income countries involves prioritising disease-free patients for preventive treatment like statin therapy, based on an assessment of their 10-year risk. One issue with this approach is that patients with the same risk score can experience vastly different outcomes from preventive treatment. By adopting treatment strategies which look beyond 10-year risk, decision-makers can acknowledge and incorporate patient heterogeneity in their decision-making which can lead to improved population-level outcomes. Reflecting heterogeneity allows for differential decisions to be made regarding treatment for different subgroups of a population and leads to a more efficient distribution of limited health care resources.

12.1 Heterogeneity in Cost-Effectiveness Analysis

Chapter 2 highlighted the benefits that can be achieved when decision-makers reflect heterogeneity in cost-effectiveness in their decision-making processes. Two ways that decision-makers can use knowledge on heterogeneity in cost-effectiveness were presented.

Firstly, when the cost of a treatment is fixed, stratified decision-making can be used to make differential treatment decisions for patient groups with different cost-effectiveness. Central estimates of cost-effectiveness, which average costs and benefits over a large population, ignore the fact that outcomes can vary systematically between patient subgroups. Some of these subgroups may be cost-effective to treat while others are not. In such a situation, cost-effectiveness analysis based on central estimates of costs and QALYs inevitably lead to suboptimal decision-making. If subgroup analysis is applied resources are invested more efficiently, treating patients who gain more health from an intervention and avoiding spending money on those who do not benefit sufficiently to justify expenditure.

Secondly, when treatment price is not set, decision-makers can signal demand for a treatment based on heterogeneity in cost-effectiveness. By estimating the maximum price that they are willing to pay for an intervention, defined for all relevant subgroups in a population, the decision-maker can then signal their demand to providers. Reimbursing providers based on this approach leads to population-level welfare gains.

12.2 Epidemiology and Prevention of CVD

Chapter 4 discussed the epidemiological basis for heterogeneous outcomes in CVD-free patients receiving statins. It focused on the fact that patients with the same 10-year risk, estimated with one of the many CVD risk scores, may experience different outcomes from preventive treatment. This chapter was split into three sections which reflected changes that could be made to policies currently employed for CVD prevention in high-income countries.

The chapter first discussed the epidemiological basis for continued use of 10-year risk to prioritise patients for preventive statin therapy. It was shown that, under the assumption of equal risk reduction from a treatment across subgroups, patients with higher absolute risk receive the greatest risk reduction. Methods were discussed for the validation and improvement of 10-year risk scores, which may help to better prioritise patients for treatment.

One alternative approach to the continued use of 10-year risk scoring is to use CVD risk alongside some other covariate to prioritise patients for treatment. Specifically, decision-makers could use age or LDL-C to modulate risk-based decision-making.

The principle of age-stratified risk thresholds was discussed at length. It was shown that traditional risk scores are ‘naïve’ estimators of event risk and ignore the presence of competing risks. This leads to a treatment prioritisation system whereby older individuals have a higher CVD risk score, but may experience fewer benefits from treatment due to their concurrent risk of non-CVD mortality. Hence, resources may achieve greater benefit when targeted at younger patients with an unhealthy profile of modifiable risk factors.

The epidemiological basis for the absolute risk reduction approach to statin prioritisation was also considered. The LDL-C reduction achieved with statin therapy is generally proportional to an individual's baseline LDL-C. Each unitary decrease in LDL-C is associated with an approximately fixed relative risk of developing CVD. It follows that absolute risk reduction from statins is a function of both baseline risk and baseline LDL-C.

Finally, the direct utilisation of decision-analytic modelling in the clinical process was considered. Decision models synthesise data from a range of sources in order to predict long-term outcomes associated with a treatment. They can account for competing risks, differential treatment effect in patients, discounting of outcomes, and other factors. They represent a means of systematically addressing multiple drivers of heterogeneity in patient outcome simultaneously.

12.3 Cost-Effectiveness Analyses of Statin Prioritisation Policies

Analyses were conducted in Chapters 7 to 9 to assess the cost-effectiveness of several policies for prioritising patients for preventive statin therapy. These policies were thematically categorised in the same way as the epidemiology section: continued use of 10-year risk, novel decision mechanisms which incorporate 10-year risk, and direct use of decision-analytic models in the clinical process to maximise health outcomes. Each policy considered aims to address heterogeneity in cost-effectiveness of preventive therapy for CVD to some extent. Inasmuch, the analyses conducted in Chapters 7, 8, and 9 represented a case study for the health economic theory presented in Chapter 2.

Chapter 7 assessed two policies for statin prioritisation which maintain the role of 10-year risk scoring in clinical decision-making. First, the cost-effectiveness of reducing the risk threshold for treatment initiation in Scotland from 20% to 10% was analysed. Increasing the number of people eligible to receive statins was shown to be cost-effective, driven by the treatment's low price and robust safety profile. The cost-effectiveness of risk threshold reduction in Scotland has not previously been analysed and this research could help inform pending updates to SIGN's guidelines on preventive statin therapy (26). Second, a framework was developed to assess the cost-effectiveness of including novel biomarkers in risk scoring algorithms. This

framework was employed to assess the cost-effectiveness of testing for the urinary proteomic biomarker HF1 in clinical practice.

Chapter 8 assessed two policies for statin prioritisation which involve novel decision mechanisms which incorporate 10-year risk scoring. These policies were age-stratified risk thresholds and absolute risk reduction. Large health gains were achieved by targeting treating at younger patients. Lesser gains were achieved through absolute risk reduction. Previous cost-effectiveness analyses of age-stratified risk thresholds have been conducted (303,534). However, these analyses were not conducted in accordance with best practice guidelines for decision modelling. They failed to account for health-related quality of life and did not discount future health and cost outcomes. No previous long-term cost-effectiveness analysis has been conducted regarding the absolute risk reduction approach to CVD prevention. Hence, this novel analysis may inform future research and clinical decision-making.

Chapter 9 considered the cost-effectiveness of using decision-analytic models directly in clinical practice to determine which individuals should receive statins. It showed that a large number of discounted QALYs and life years can be gained by treating the group of patients estimated to gain the most life years or discounted QALYs from treatment. Maximising discounted QALYs produced the most health of all treatment strategies considered and was reasonably cost-effective. Both outcome-maximising policies led to resource allocation that may be societally unacceptable, targeting treating at large numbers of younger individuals and disproportionately treating men.

Chapter 11 compared all of the policies evaluated in Chapters 7 to 9, producing policy recommendations based on the results. It was shown that expanding treatment eligibility is undoubtedly cost-effective, but the prioritisation mechanism that a decision-maker should employ may vary based on implementation constraints. A decision-maker who aims to maximise health in a population should implement the QALY maximisation policy evaluated in Chapter 9.

The outcome-maximisation policies could be considered clinically or societally unacceptable by some decision-makers due to the distribution of patients prioritised for treatment. In this

case, absolute risk reduction would be the optimal treatment strategy for decision-makers, offering a small but cost-effective modification of the blanket risk threshold approach.

12.4 Signalling Demand for PCSK9 Inhibitors

Assessing heterogeneity in cost-effectiveness and using these results to guide individual- or subgroup-level treatment decisions was discussed in Chapter 2. Conducting such analysis signals demand for health care interventions to providers regarding acceptable costs for the treatments. Demand curves were constructed in Chapter 10 for PCSK9 inhibitors for the primary prevention of CVD in patients with familial hypercholesterolaemia.

Considerable price reductions would be required to ensure that even a small proportion of the Scottish population with familial hypercholesterolaemia would be cost-effective to treat with PCSK9 inhibitors. Indeed, at current prices, not one individual in a hypothetical cohort of more than 4,500 patients was deemed eligible for treatment. Similar analysis has been conducted regarding the cost-effectiveness of PCSK9 inhibitors in high-risk subgroups of the CVD-free population (193,392,578,586,588). However, none of these studies explicitly approached the decision problem from the perspective of a decision-maker aiming to signal demand for a treatment.

12.5 Further Research

A variety of analyses have been conducted regarding the epidemiology of CVD and the cost-effectiveness of CVD prevention. All analyses have limitations and further research can always be conducted to improve validity of results. Through conducting analysis for this thesis, four broad categories of further research emerged that would be useful for researchers and decision-makers. These are research specific to: cost-effectiveness analysis of statins, novel biomarkers for CVD, PCSK9 inhibitors, and, more broadly, the objective of health sector decision-makers in the U.K. and U.S.

Cost-Effectiveness Analyses of Statins

Inputs for several parameters included in cost-effectiveness analyses of statins have been under-studied. One study (350) was identified which details adherence of patients to statin therapy and no literature was identified pertaining to health practitioners' adherence to clinical recommendations for statin prioritisation. Another variable for which limited research was identified was pill-taking disutility. Two online surveys, conducted by the same research group, were identified (36,497). In these studies, pill-taking disutility varied greatly within the population and differed based on the preference-elicitation approach adopted. More research should be conducted on this parameter to inform updates of existing analyses and future analyses.

More information on each of these covariates would allow for more accurate estimation of statin cost-effectiveness in all of the analyses in this thesis. Sensitivity analyses showed that adherence has little effect on cost-effectiveness outcomes. This is likely because individuals who stop taking a treatment did not accrue treatment-related benefits or costs in the analyses. Pill-taking disutility, on the other hand, has a large effect on cost-effectiveness outcomes.

There is one key aspect of statin benefit may not have been adequately modelled in the statin cost-effectiveness analyses in this thesis. It was shown in Chapter 4 that cumulative exposure to LDL-C in young adulthood increases later life risk of CVD. This occurs because LDL-C continuously contributes to the atherosclerotic build-up in the arteries. Cost-effectiveness analyses in the thesis assumed that statins affect instantaneous risk of CVD, but did not account for benefits accrued due to a reduction in cumulative risk factor exposure. Further research should consider whether the way statin efficacy is modelled could be improved by accounting for cumulative exposure. Further research should also consider the cost-effectiveness of reducing cumulative exposure to statins from a young age. This could be achieved by reducing the age at which CVD risk screening is initiated.

Biomarkers

A framework was established for the cost-effectiveness analysis of novel CVD biomarker testing. This framework explicitly accounted for the fact that data are often sparse for novel

biomarkers. Hence, further research would help establish the validity of novel CVD biomarkers, including HF1, as candidates for inclusion in CVD risk screening procedures.

Analysis presented in Chapter 7 (Tables 7-11 to 7-15) showed a large degree of uncertainty in the independent effect of HF1 on CVD risk. It was established that HF1 is a significant independent predictor of non-fatal CHD. However, limited event data and short follow-up time made it impossible to predict the effect of HF1 on risk of other important outcomes like non-fatal CBVD, fatal CVD, and fatal non-CVD events. As follow-up time increases for the ongoing FLEMENGHO study, more information will be available regarding these relationships. Repeat analysis on an updated dataset would help validate results regarding the cost-effectiveness of HF1 testing.

Further research should also compare the cost-effectiveness of adding a range of different risk factors to CVD risk scoring algorithms. Even if HF1 were available at a price which justified implementation when compared to traditional risk scoring, it is possible that testing for alternative novel risk factors would offer better value for money to decision-makers. Indeed, several biomarkers that may be cheaper to procure than HF1 information have been shown to independently predict CVD risk (515,606–608).

PCSK9 Inhibitors

In Chapter 10, analysis of PCSK9 inhibitors was conducted in a hypothetical cohort of Scottish individuals with familial hypercholesterolaemia. This is because no dataset exists with extensive CVD risk factor information on patients with familial hypercholesterolaemia in Scotland. It was assumed that the hypothetical cohort of patients would have a similar distribution of CVD risk factors to the general population. However, if the risk factor distributions of this patient population systematically differ from CVD-free participants in the Scottish Health Survey 2011, then the demand curves for PCSK9 inhibitors may be biased. Further research should establish the risk factor profile of the hypercholesterolaemic population in Scotland.

Objective Function of Health Service Decision-Makers

Chapter 11 produced policy recommendations for statin prioritisation based on results from this thesis. These recommendations came with a caveat: the optimal strategy for a decision-maker is determined by more than just financial constraints or efficiency goals. It is possible that implementation of a policy which increases health inequality would not be implementable for a health sector decision-maker. There may also be a degree of aversion to policies which disproportionately target treatment at one specific group of patients. Further research into societal aversion to different statin prioritisation policies is required to establish a definitive optimal treatment strategy.

12.6 Conclusion

The objectives of this thesis included describing the health economics benefits associated with reflecting heterogeneity in cost-effectiveness in healthcare decision-making and applying this theory to the prevention of cardiovascular disease. Optimal decision rules in the presence of heterogeneity in cost-effectiveness were defined, the epidemiologic basis for heterogeneity in outcome from preventive therapies for CVD were presented, and cost-effectiveness analyses of specific policies which address heterogeneity were conducted.

Despite improvements in recent years, cardiovascular disease remains a significant cause of mortality, morbidity, and health inequality around the world. As rates of the disease plateau, novel approaches to CVD prevention will be required.

‘Personalised’ and ‘precision’ medicine have long been considered the future of health service provision in high-income countries (11,12,14,15,601). Granulating treatment decisions often invokes the use of new and expensive diagnostic technology. This thesis accepts that novel approaches should be adopted which better reflect patient heterogeneity than current practice. It also argues, however, that better reflection of heterogeneity is not dependent on costly new technology. Rather, reformulation of patient prioritisation based on better use of existing information should be employed to improve population health.

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Appendix

A1. Microsoft Visual Basic code which simulates statin therapy using the Scottish CVD Policy Model

```
Sub Statins_BASEandSTATIN()
'
' Statins_Statins Macro
'

'''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''BASE PART
Application.DisplayAlerts = False

Dim Index
Dim Trials
Index = 0

Application.StatusBar = True
Windows("Scottish CVD Policy Model - Men.xls"). _
      Activate
Trials = Worksheets("40+ NO CVD DATA").Cells(1, "A").Value

Windows("Scottish CVD Policy Model - Women.xls"). _
      Activate
   Sheets("Female - Parameters").Range("G14") = 0

Windows("Scottish CVD Policy Model - Men.xls"). _
      Activate
   Sheets("Male - Parameters").Range("G14") = 0

Application.ScreenUpdating = False
Application.Calculation = xlCalculationManual

Do
   Sheets("40+ NO CVD DATA").Select
   Range("C6").Select
   ActiveCell.Offset(Index, 0).Range("A1").Select

   ''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''MEN'''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''
   If ActiveCell.Value = 1 Then

   Range("D6").Select
   ActiveCell.Offset(Index, 0).Range("A1:I1").Select
   Application.CutCopyMode = False
   Selection.Copy
```

```
    Sheets("Male - Parameters").Select
    Range("E9:M9").Select
    Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone,
    SkipBlanks _
        :=False, Transpose:=False

    Calculate

    Range("G4:P4").Select
    Application.CutCopyMode = False
    Selection.Copy

    ''''''''''''''''''''''''''''''''''''''''''WOMEN''''''''''''''''''''''''''''''''''''''''''''''''''''''''
    Else

    Range("D6").Select
    ActiveCell.Offset(Index, 0).Range("A1:I1").Select
    Application.CutCopyMode = False
    Selection.Copy

    Windows("Scottish CVD Policy Model - Women.xls"). _
        Activate
    Sheets("Female - Parameters").Select
    Range("E9:M9").Select
    Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone,
    SkipBlanks _
        :=False, Transpose:=False

    Calculate

    Range("G4:P4").Select
    Application.CutCopyMode = False
    Selection.Copy

    End If

'Pastes output
Windows("Scottish CVD Policy Model - Men.xls"). _
        Activate
Sheets("RESULTS").Select
Range("B5").Select
ActiveCell.Offset(Index, 0).Range("A1").Select
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
    :=False, Transpose:=False
'End of selecting and pasting output

    Index = Index + 1
```

```
''''Hopefully a status bar

Application.StatusBar = "Statins Progress: " & Index & " of " & Trials & ": " &
   Format(Index / Trials, "Percent")
       DoEvents

Loop While Index < Trials

Application.ScreenUpdating = True
Application.Calculation = xlCalculationAutomatic
Application.StatusBar = False

''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''STATIN PART

Dim IndexA
Dim TrialsA
IndexA = 0
Windows("Scottish CVD Policy Model - Men.xls"). _
       Activate
TrialsA = Worksheets("40+ NO CVD DATA").Cells(1, "A").Value

Windows("Scottish CVD Policy Model - Women.xls"). _
       Activate
   Sheets("Female - Parameters").Range("G14") = 1

Windows("Scottish CVD Policy Model - Men.xls"). _
       Activate
   Sheets("Male - Parameters").Range("G14") = 1

Application.ScreenUpdating = False
Application.Calculation = xlCalculationManual

Do
   Sheets("40+ NO CVD DATA").Select
   Range("C6").Select
   ActiveCell.Offset(IndexA, 0).Range("A1").Select

   ''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''MEN'''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''
   If ActiveCell.Value = 1 Then

   Range("D6").Select
   ActiveCell.Offset(IndexA, 0).Range("A1:I1").Select
   Application.CutCopyMode = False
   Selection.Copy

   Sheets("Male - Parameters").Select
   Range("E9:M9").Select
```

```
    Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone,
    SkipBlanks _
        :=False, Transpose:=False

    Calculate

    Range("G4:P4").Select
    Application.CutCopyMode = False
    Selection.Copy

    """""""""""""""""""""""WOMEN"""""""""""""""""""""""""""""
    Else

    Range("D6").Select
    ActiveCell.Offset(IndexA, 0).Range("A1:I1").Select
    Application.CutCopyMode = False
    Selection.Copy

    Windows("Scottish CVD Policy Model - Women.xls"). _
        Activate
    Sheets("Female - Parameters").Range("E9:M9").Select
    Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone,
    SkipBlanks _
        :=False, Transpose:=False

    Calculate

    Range("G4:P4").Select
    Application.CutCopyMode = False
    Selection.Copy

    End If

'Pastes output
Windows("Scottish CVD Policy Model - Men.xls"). _
        Activate
Sheets("RESULTS").Select
Range("O5").Select
ActiveCell.Offset(IndexA, 0).Range("A1").Select
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
    :=False, Transpose:=False
'End of selecting and pasting output

    IndexA = IndexA + 1

""Hopefully a status bar
```

```
Application.StatusBar = "Statins Progress: " & IndexA & " of " & TrialsA & ": " &
   Format(IndexA / TrialsA, "Percent")
      DoEvents

Loop While IndexA < TrialsA

Application.ScreenUpdating = True
Application.Calculation = xlCalculationAutomatic
Application.StatusBar = False
Application.DisplayAlerts = True

End Sub
```

A2. Microsoft Visual Basic code which performs probabilistic sensitivity analysis using the Scottish CVD Policy Model

```
Sub runPSA()
'
' runPSA Macro

Dim PSA_Index
Dim PSA_Trials
PSA_Index = 1
PSA_Trials = 100

Do
   'Copy coefficients to Men's model
   Windows("CoefficientsMen F.xlsx").Activate
   Range("B3:B67").Select
   Selection.Offset(0, PSA_Index).Select
   Selection.Copy
   Windows("Scottish CVD Policy Model - Men.xls").Activate
   Range("E21").Select
   Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone,
SkipBlanks_:=False, Transpose:=False

   'Copy coefficients to Women's model
   Windows("CoefficientsWomen F.xlsx").Activate
   Range("C3:C67").Select
   Selection.Offset(0, PSA_Index).Select
   Selection.Copy
   Windows("Scottish CVD Policy Model - Women.xls").Activate
   Range("E21").Select
   Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone,
SkipBlanks_:=False, Transpose:=False

   'Copy other PSA variables into women's model
   Application.CutCopyMode = False
   Calculate
   Calculate
   Calculate
   Range("N19:N21").Select
   Selection.Copy
   Range("L25").Select
   Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone,
SkipBlanks_:=False, Transpose:=False

      :=False, Transpose:=False
   Range("L25:L27").Select
   Selection.Copy
```

```
    'Copy other PSA variables into men's model
    Windows("Scottish CVD Policy Model - Men.xls").Activate
    Range("L25").Select
    Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone,
SkipBlanks_:=False, Transpose:=False

    Range("A1").Select

    'Runs Base_and_Statin macro
    Call Statins_BASEandSTATIN

    'Save results
    Sheets("RESULTS").Select
    Sheets("RESULTS").Copy
    ActiveWorkbook.SaveAs Filename:= _
        "C:\Users\cnk2112\Desktop\PSA\Results F\Results" & PSA_Index & ".xlsx",
FileFormat:= _
        xlOpenXMLWorkbook, CreateBackup:=False
    ActiveWindow.Close
    Sheets("Male - Parameters").Select
    Range("A1").Select

    PSA_Index = PSA_Index + 1

Loop While PSA_Index < PSA_Trials

End Sub
```

A3. Stata code which performed Gompertz regression on FLEMENGHO dataset

```
//PREPARING THE DATASET
//Can install via File>Install>Excel...

set more off
clear all

cd "C:\Users\ciara\Desktop\Columbia PC - Desktop\Chapter 6 - 10-Year Risk
Scores\Novel Biomarkers Scores\Older\Analysis Folder\FLEMENGHO"
ssc install carryforward
ssc install stcompet

//Import (if not done so already)
import excel "UrinaryProteomics.xls", sheet("g") firstrow

//Drop people younger than 30
drop if age<35

//Drop people with history of CVD
drop if hcv2==1
summarize

//Drop if missing cholesterol data
drop if missing(tchol)
drop if missing(HCHOL)

//Generate variables
//Sex (Male 1, Female 0)
gen sex=0
replace sex=1 if SEX==1
BMI
gen bmi=bw/bh/bh

//Preparing Data for Competing Risks Analysis
ssc install carryforward
ssc install stcompet

//Create necessary event variables
//Non-fatal CHD
gen nonfatalCHD=0
replace nonfatalCHD=1 if nfcar2==1
gen timenonfatalCHD=tnfcar2

//Non-fatal CBVD
gen nonfatalCBVD=0
replace nonfatalCBVD=1 if nfcbv==1
```

```
gen timenonfatalCBVD=tnfcbv

//Fatal CVD
gen fatalCVD=0
replace fatalCVD=1 if fcv==1
gen timefatalCVD=fudf

//Fatal non-CVD
gen fatalNonCVD=0
replace fatalNonCVD=1 if fncv==1
replace fatalNonCVD=1 if frf==1
gen timefatalNonCVD=fudf

//Combined
gen combinedCVD=0
replace combinedCVD=1 if nonfatalCHD==1
replace combinedCVD=1 if nonfatalCBVD==1
replace combinedCVD=1 if fatalCVD==1

//Generate time and status variables
//time
egen time=rowmin(timenonfatalCHD timenonfatalCBV timefatalCVD
timefatalNonCVD)

//event type
gen
status=0+1*(nonfatalCHD==1)+2*(nonfatalCBVD==1)+3*(fatalCVD==1)+4*(fatalNo
nCVD==1)
gen status2=0+1*(combinedCVD==1)
label define stat 0 "censored" 1 "Non-fatal CCHD" 2 "Non-fatal CBVD" 3 "Fatal
CVD" 4 "Fatal Non-CVD"
label values status stat

//Carrying out regressions
stset time, failure(status==1) scale(365.25) id(cpnbrx)
streg age sex sock HCHOL tchol sbp hdm qcsmk HF, d(gom)
matrix list e(V)
//translate @Results nonfatalCHD.txt

stset time, failure(status==2) scale(365.25) id(cpnbrx)
streg age sex sock HCHOL tchol sbp hdm qcsmk HF, d(gom)
matrix list e(V)
//translate @Results nonfatalCBVD.txt

stset time, failure(status==3) scale(365.25) id(cpnbrx)
streg age sex sock HCHOL tchol sbp hdm qcsmk HF, d(gom)
matrix list e(V)
//translate @Results fatalCVD.txt
```

```
stset time, failure(status==4) scale(365.25) id(cpnbrx)
streg age sex sock HCHOL tchol sbp hdm qcsmk HF, d(gom)
matrix list e(V)
//translate @Results fatalNonCVD.txt

stset time, failure(status2==1) scale(365.25) id(cpnbrx)
streg age sex sock HCHOL tchol sbp hdm qcsmk HF, d(gom)
matrix list e(V)
//translate @Results combinedCVD.txt
```