The interplay between glycaemia and cardiovascular disease

By

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Summary

Introduction

Numerous large clinical trials of cardiovascular risk lowering agents have been conducted in the hope of reducing the excess cardiovascular risk found in patients with diabetes mellitus. However, the relationship between glucose and cardiovascular disease remains complex and various areas require further study. Even in patients with diabetes, an individual's cardiovascular risk is highly variable depending on other clinical characteristics, the assumption that glucose is a continuous risk factor has often been based on weak evidence from relatively short studies, the effect of commonly used cardiovascular risk lowering agents often has unexpected effects on new-onset diabetes and statins have not yet been studied in detail, and whether glucose-lowering therapies actually reduce cardiovascular risk has remained a contentious issue despite the conduct of large clinical trials. Furthermore, the realisation that the combination of diabetes and chronic heart failure, a common complication of coronary disease, carries a particularly poor prognosis suggests that prediction of diabetes in this population may be clinically valuable.

Aims

I aimed to address the following different, though related, questions regarding glucose and cardiovascular disease:

1. Are anticipated cardiovascular event rates in diabetes endpoint trials actually achieved? Is it possible to easily identify patients with diabetes that are at particular risk of events (information that is crucial to investigators who wish to design clinical trials)?
2. Is fasting glucose concentration independently and convincingly associated with increased risk of cardiovascular events in those without diabetes?
3. Do statins, the most commonly prescribed medications worldwide, have any influence on the risk of developing diabetes?
4. If statins do indeed affect new-onset diabetes, is there any evidence of a dose-dependent effect?

5. How effectively can clinicians predict the development of diabetes in chronic heart failure using commonly recorded clinical information?
6. Does intensive glucose-lowering therapy reduce the risk of cardiovascular events in patients with diabetes?

Methods

To address these questions three approaches were used, namely (i) systematic review of previously published data from large cardiovascular endpoint trials conducted in patients with diabetes; (ii) analyses of existing datasets from two large clinical trials; (iii) meta-analyses of published and unpublished data from large clinical trials.

Results and interpretation

1. In a systematic review of 29 trials with 116,790 patients with diabetes, it was apparent that the majority of large cardiovascular endpoint trials conducted in patients with diabetes vastly overestimated the likely cardiovascular event rates in initial power calculations. Introduction of (i) previous history of cardiovascular disease and/or (ii) presence of proteinuria, as binary trial inclusion criteria, provides a simple and effective way to identify patients at high risk, something that is sought after for appropriate clinical trial power calculations.
2. In a population of 6,447 men without diabetes at baseline, impaired fasting glycaemia was not associated with increased risk of cardiovascular events over 15 years. Similarly, when baseline fasting glucose values <7.0mmol/L were split into quintiles, patients in the highest quintile were at similar risk of all vascular endpoints to those in the lowest. By contrast, impaired fasting glycaemia was a powerful risk factor for developing diabetes.
3. A meta-analysis of published and unpublished data from most large placebo- and standard care-controlled statin trials, which included data for 91,140 trial participants without diabetes at baseline, revealed that statin therapy is associated with a 9% higher risk for developing diabetes.

4. A subsequent meta-analysis of unpublished data from five large trials comparing intensive statin therapy with moderate dose therapy found that intensive statin therapy increases the risk of developing diabetes by 12% compared to moderate dosing, in keeping with a dose-dependent effect. While statin therapy remains effective at reducing cardiovascular risk it appears that patients on statin therapy, especially those on intensive regimens, should be considered for diabetes screening.
5. In an analysis of data for 1,620 patients with chronic heart failure and no diabetes at baseline studied for 2.8 years, the strongest predictors of new-onset diabetes were similar to those in the general population. In particular, the combination of HbA1c and body mass index provided a c-statistic of 0.79.
6. In a meta-analysis of published data for 33,040 patients with diabetes who participated in clinical trials comparing intensive glucose-lowering therapy with standard therapy, non-fatal myocardial infarctions were reduced by 17% on intensive therapy but no other cardiovascular endpoints were reduced. Death rates were similar in both groups.

Conclusion

While diabetes is associated with excess cardiovascular risk, risk varies considerably depending on other risk factors. Glucose is, at best, a weak risk factor in those without diabetes, and glucose-lowering in patients with diabetes has only yielded a modest reduction in non-fatal myocardial infarctions but not other events; by contrast, measures of glycaemia are powerful predictors of new-onset diabetes in patients with and without chronic heart failure. Finally, the relationship between glucose and vascular disease is further complicated by the fact that numerous medications designed to reduce cardiovascular risk appear to have surprising effects on the risk of developing diabetes.

Contents

Publications containing work undertaken in this thesis

- **Preiss D**, Sattar N, McMurray JJ. A systematic review of event rates in clinical trials in diabetes mellitus: the importance of quantifying baseline cardiovascular disease history and proteinuria and implications for clinical trial design. Am Heart J. 2011;161(1):210-219.
  See Chapter 2
- **Preiss D**, Welsh P, Murray HM, Shepherd J, Packard C, Macfarlane P et al. Fasting plasma glucose in non-diabetic participants and the risk for incident cardiovascular events, diabetes, and mortality: results from WOSCOPS 15-year follow-up. Eur.Heart J. 2010;31(10):1230-6.
  See Chapter 3
- Sattar N *, **Preiss D ***, Murray HM, Welsh P, Buckley BM, de Craen AJ et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010;375(9716):735-42.
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- **Preiss D**, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA. 2011;305(24):2556-64.
  See Chapter 5
- **Preiss D**, Zetterstrand S, McMurray JJ, Ostergren J, Michelson EL, Granger CB et al. Predictors of development of diabetes in patients with chronic heart failure in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program. Diabetes Care 2009;32(5):915-20.
  See Chapter 6
- Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, **Preiss D** et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet 2009;373(9677):1765-72.
  See Appendix

Invited Presentations to National and International Learned Societies for work undertaken in this thesis

- **European Association for the Study of Diabetes, Annual Conference – joint EASD / ESC symposium, Lisbon, Portugal**
  Lipid-lowering therapies and diabetes risk
  September 2011
- **American Diabetes Association, Annual Conference, San Diego, USA**
  Statin-associated diabetes: incidence, etiology and implications for practice
  June 2011
  Selected by the American Diabetes Association for inclusion in the official conference highlights publication, MD Conference Express
- **Diabetes UK Annual Conference, Hot Topics Session, London**
  Statins and Diabetes: new evidence
  March 2011
- **Diabetes UK Annual Conference, Hot Topics Session, Liverpool**
  Statins and Diabetes: a link?
  March 2010
- **FOCUS (ACB Annual Conference), Big Diseases Session, Glasgow**
  Metabolic Syndrome: collapsing under its own weight?
  May 2010

Seven other publications related to work in this thesis

- **Preiss D**, Sattar N, McMurray JJ. Event rates in trials of patients with type 2 diabetes. JAMA 2010;303(8):732-3 (letter)
- **Preiss D**, Sattar N. Reducing cardiovascular risk in type 2 diabetes mellitus. Medicine 2010;38(11):632-7 (book chapter, invited)
- **Preiss D**, Sattar N. Statins and the risk of new-onset diabetes: a review of recent evidence. Curr Opin Lipidol 2011;22(6):460-6 (review, invited)
- **Preiss D**, Seshasai SR, Ray K. Statin therapy dose and risk of new-onset diabetes. JAMA 2011;306(12):1326 (letter)
- Sattar N, Preiss D, Welsh P, Seshasai SR, Ray KK. Statins and risk of incident diabetes – Authors' reply. Lancet 2010;375:2141-2 (letter)
- **Preiss D**, Ray KK. Intensive glucose lowering treatment of type 2 diabetes. BMJ 2011;343:215-6 (editorial, invited)
- Ray KK, Seshasai SR, Erqou S, **Preiss D**, Sattar N. Intensive glucose control and cardiovascular outcomes – Authors' reply. Lancet 2009;374:524 (letter)

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me every opportunity in life and I hope that this thesis repays a small part of your generosity.

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Declaration

I declare that, except where explicit reference is made to the contribution of others (see below), that this dissertation is the result of my own work. Work in Chapters 1-6 has not been submitted for any other degree at the University of Glasgow or any other institution. Research contributions are listed below:

Chapter 2: I performed the literature search, data extraction, statistical analysis and manuscript writing. Professor McMurray assisted with the literature search.
Chapter 3: I led this project, guided the relevant statistical analyses and wrote the manuscript. Statistical analyses were provided by Ms Heather Murray, Robertson Centre for Biostatistics, University of Glasgow. Co-investigators provided comments on written drafts.
Chapters 4 and 5: I performed the literature searches, extracted published data, negotiated access to unpublished data, performed some of the statistical analyses and wrote the manuscripts. Professor Kausik Ray (St George's University of London) and Professor Sattar assisted with negotiating access to unpublished data. Dr Rao Seshasai (University of Cambridge) led the statistical analyses and was responsible for all meta-regression analyses and all analyses of statistical interactions. Co-investigators provided comments on written drafts.
Chapter 6: I led this project, guided the relevant analyses and wrote the manuscript. Statistical analyses were provided by Dr Sofia Zetterstrand and co-investigators provided comments on written drafts.
Appendix: My contributions consisted of providing literature searches, critical additions to and revisions of the manuscript and some statistical analyses. Professor Ray generated the hypothesis and led the project. Dr Seshasai was chiefly responsible for statistical analyses. Shanelle Wijesuriya, Rupa Sivakumaran and Sarah Nethercott assisted with literature searching. It should be highlighted that a full version of this work constitutes a formal chapter of Dr Seshasai's thesis (in preparation; University of Cambridge). It is included here with the permission of Dr Seshasai and Professor Ray because the subject is of particular relevance to my thesis and provides important background to the research undertaken.

David J Preiss

List of abbreviations used in the text

Note: Table abbreviations are listed along with tables

4S: Scandinavian Simvastatin Survival Study (trial)
ACCORD: Action to Control Cardiovascular Risk in Diabetes (trial)
ACE: angiotensin converting enzyme
ADA: American Diabetes Association
ADOPT: A Diabetes Outcome Progression Trial (trial)
ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (trial)
AFCAPS TexCAPS: AirForce/Texas Coronary Atherosclerosis Prevention Study (trial)
ALLHAT-LLT: Antihypertensive Lipid Lowering Heart Attack Trial – Lipid Lowering Therapy (trial)
ALT: alanine aminotransferase
ANOVA: analysis of variance
ARB: angiotensin receptor blocker
ARIC: Atherosclerosis Risk in Communities study
ASCOT-LLA: Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (trial)
A to Z: Aggrastat to Zocor
AUROC: area under the receiver operating characteristic curve
AusDIAB: Australian Diabetes, Obesity and Lifestyle study
BHF: British Heart Foundation
BMI: body mass index
CARE: Cholesterol And Recurrent Events Study (trial)
CHARM: Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (trial)
CI: confidence intervals
CORONA: Controlled Rosuvastatin Multinational Trial in Heart Failure (trial)
CTT: Cholesterol Treatment Trialists'
DECODE: Diabetes Epidemiology - Collaborative analysis of Diagnostic criteria in Europe
DEPCAT: social deprivation category

DREAM: Diabetes REduction Assessment with ramipril and rosiglitazone Medication (trial)

ERFC: Emerging Risk Factor Collaboration

FDA: Food and Drug Administration

FPG: fasting plasma glucose

GISSI: Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico- (trials)

HbA1c: Haemoglobin A1c

HDL: high density lipoprotein

HPS: Heart Protection Study (trial)

HR: hazard ratio

ICD: International Classification of Diseases

IDEAL: Incremental Decrease in End Points through Aggressive Lipid Lowering (trial)

IFG: impaired fasting glycaemia

IGT: impaired glucose tolerance

ISD: Information and Statistical Division

JUPITER: Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (trial)

LDL: low density lipoprotein

LIPID: Long-term Intervention with Pravastatin in Ischaemic Disease (trial)

LIPS: Lescol Intervention Prevention Study (trial)

LVEF: left ventricular ejection fraction

MEGA: Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (trial)

NCEP ATPIII: National Cholesterol Education Program Adult Treatment Panel III

NHS: National Health Service

NNT: numbers needed to treat

NYHA: New York Heart Association classification of heart failure symptoms

OGTT: oral glucose tolerance test

OR: odds ratio

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROactive: PROspective pioglitAzone Clinical Trial In macroVascular Events (trial)

PROSPER: Prospective Study of Pravastatin in the Elderly at Risk (trial)

PROVE-IT TIMI: Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction (trial)

Q: quintile

RECORD: Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (trial)

SD: standard deviation

SEARCH: Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (trial)

SPARCL: Stroke Prevention by Aggressive Reduction in Cholesterol Levels (trial)

TNT: Treating to New Targets (trial)

UGDP: University Group Diabetes Program (trial)

UKPDS: United Kingdom Prospective Diabetes Study (trial)

VADT: Veterans Affairs Diabetes Trial (trial)

WOSCOPS: West of Scotland Coronary Prevention Study (trial)

Chapter 1

1.1 Rationale for research conducted

Biomarkers are biological markers commonly used to indicate the presence of a specific disease, the risk of developing that disease, or response to therapy. The term most often refers to a protein present in the bloodstream which can be measured, but it may also refer to numerous other entities. The study of biomarkers tends to fall into three categories:

- *Association of a biomarker with the presence of or risk of developing disease*

When a biomarker is first described, initial research usually pursues statistical associations between the presence and/or concentration of the biomarker and the disease process in question. These data tend to be derived from observational studies, whether prospective, cross-sectional or retrospective. While demonstration of a statistical association between biomarker and disease development is an important initial step, such evidence does not necessarily equate to clinical utility. To add clinical benefit, it is necessary that a biomarker is not only associated with a disease, but that it meaningfully improves the ability to predict development of that disease. Consequently, studies of association are often coupled with or followed by studies of risk prediction.

- *Prediction of a disease or event using the biomarker*

Accurate prediction of disease presents the attractive possibility that those at risk of that disease can be targeted for screening and for preventative action to reduce this risk. Numerous risk prediction tools exist for cardiovascular disease, the leading cause of mortality in the western world. Examples include the Framingham Risk Score (1), QRISK2 (2) and ASSIGN (3). Other risk scores exist for type 2 diabetes, such as QDScore (4), though use of them in clinical practice remains limited. For a biomarker to be of clinical value it must be demonstrated that it meaningfully adds to risk prediction information yielded by such risk scores using established risk factor information. Such information has generally

been provided by showing that addition of the biomarker to a disease prediction model leads to an improvement in the model's area under the receiver operating curve (AUROC) or c-statistic. More recently, the bar has been raised such that now a biomarker must not only demonstrate the ability to improve this c-statistic, but also its ability to improve other derived statistics such as reclassification and discrimination indices (5). While an improvement in risk prediction is a valuable characteristic for a biomarker, proof of a causal link between it and a disease state addresses a different question of substantial importance but this is considerably more difficult to demonstrate. It is important to keep in mind that risk factors do not necessarily have to carry causal links with the disease in question to improve disease prediction.

- *Proving that a biomarker causes disease*

To prove a causal link between a putative risk factor (in this case biomarker) and a disease, Bradford Hill proposed the following nine criteria (6):

1. Strength of association: the stronger the association, the more likely that a causal relationship exists
2. Consistency of observation: an association should be replicated by different investigators
3. Specificity of the association: more accurate definition of the disease and more accurate measurement of the putative factor should strengthen observed associations
4. Temporality: exposure to the putative factor should precede the disease
5. Biological gradient: a dose-response relationship
6. Plausibility: the proposed causal relationship is consistent with other knowledge
7. Coherence
8. Experimentation: demonstration that a change in exposure to the putative causal factor leads to a change in clinical outcome.
9. Analogy

Criterion 8, 'experimentation', is probably the most important of the nine criteria in medical research and it demonstrates the need to conduct randomised controlled trials to properly establish causation. It is well established that the

randomised controlled trial is the gold standard approach to address whether therapeutic techniques which change biomarker levels in apparently beneficial ways actually lead to improvements in important clinical events. Another powerful statistical technique to assess a causal link between biomarker and disease which is expanding rapidly is the use of Mendelian randomisation (7).

Glucose, diabetes and cardiovascular disease

These considerations are relevant in the specific case of glucose, diabetes and cardiovascular disease and form the basis for this thesis. The relationship between circulating glucose concentrations and cardiovascular disease has long been of clinical interest. It is the association between diabetes mellitus, a condition defined by elevated concentrations of plasma glucose concentration under stipulated conditions, and cardiovascular disease that has received particular attention since it was noted that those with diabetes appear to be at particular risk of suffering cardiovascular events (8). This elevated cardiovascular risk in patients with diabetes has been confirmed in numerous observational studies (9;10) and has led to numerous trials of risk-lowering medicines such as antihypertensive agents, lipid modifying agents and antithrombotic agents with the aim of reducing this excess risk. Of particular relevance, large trials of glucose-lowering agents have been conducted in patients with diabetes based on the hypothesis that glucose itself is the causal agent which, at least partially, accounts for this elevated cardiovascular risk. Another possibility is that the noted association between diabetes and cardiovascular disease is explained by other confounding factors such as established cardiovascular risk factors (for example HDL-cholesterol) and possibly also other unmeasured factors.

Prior to the conduct of research contained in this thesis, it was apparent that while major efforts had been directed towards understanding the complex relationship between glycaemia and cardiovascular disease, certain key questions had either not previously been asked or, as yet, conclusively answered. I therefore wished to investigate a set of different, though linked, issues which fall within the overall theme of glycaemia and cardiovascular disease. In this Chapter I will describe the rationale that led to the research

conducted. The research areas are described in brief below and, importantly, all fall within the realm of large clinical trials.

One area of concern that became apparent during my reading through many major cardiovascular trials conducted in patients with diabetes was the difficulty researchers experienced when formulating power calculations. It appeared likely that although patients with diabetes are at elevated cardiovascular risk, it was being assumed that this additional risk was somewhat larger than is actually the case. The potential problem is that trials are likely to accrue fewer clinical events than anticipated, thereby leading to extensions of trials or, worse, to underpowered trial results (11). Given the expense incurred in conducting such trials and the huge importance of their findings to patient treatment and even financial strength of pharmaceutical companies, accurate prediction of cardiovascular event rates is hugely appealing and sought after. Of similar critical importance is the ability of trial designers to include in their trial inclusion criteria simple but effective characteristics to identify those patients who are at high risk of suffering cardiovascular risk i.e. those most likely to benefit from the treatment in question and, by extension, those who will allow investigators to obtain clinically useful, adequately powered and conclusive results. The importance of this point was further emphasised by a leading figure from one of the major international pharmaceutical companies who visited the BHF Glasgow Cardiovascular Research Centre in 2010 and made this very point while expressing frustration at the lack of a 'biomarker' that would provide this all-important information to allow improved trial design in diabetes. Review of data from large trials conducted in diabetes suggested the possibility that a simple and inexpensive solution may exist. Cardiovascular event rates in some trials of participants with diabetes and either proteinuria or existing cardiovascular disease appeared markedly elevated compared to when these two characteristics were absent. Indeed event rates in trials involving patients with diabetes but not proteinuria or cardiovascular disease appeared surprisingly low. While appreciating that overall cardiovascular risk depends on a multitude of variables, it seemed a plausible and practical idea that using either as binary inclusion criteria may be a useful approach for future trials. These thoughts led to work which was conducted over 2009-2010 and which is fully described in **Chapter 2**. In a systematic review of data from large cardiovascular endpoint

trials in patients with diabetes I wanted to examine (i) how accurate power calculations have tended to be in previously published studies; and (ii) what impact the use of either the presence of cardiovascular disease or proteinuria as inclusion criteria would have on event rates, and thereby power calculations, in clinical trials.

A second area where I perceived a need for additional data was in establishing what, if any, relationship exists between glucose levels and cardiovascular disease in patients without diabetes. While the study of diabetes has received major attention, consideration of a causal relationship between circulating glucose concentrations and incident cardiovascular events implies that such a continuous relationship should also exist in patients who do not have diabetes. At the time of writing, few large studies had examined this relationship using current diagnostic criteria for diabetes and many had focused on cardiovascular and all-cause mortality with less data available on cardiovascular morbidity (12). Given that diabetes requires considerable time after diagnosis to increase vascular risk (13), observational research in cohorts with intermediate categories of dysglycaemia (impaired fasting glycaemia, impaired glucose tolerance) seemed likely to have been to some extent limited by relatively short follow-up durations with the result that high quality data were required from longer studies. Few studies had also sought to simultaneously compare the strengths of associations between glucose levels and both incident cardiovascular disease and incident diabetes. I set out to investigate the associations between fasting glucose concentration, cardiovascular events and new-onset diabetes using a high quality dataset available after completion of a major statin trial in the west of Scotland in the 1990s (14). This dataset had the distinct advantage of post-trial follow-up using electronic data linkage which allowed patients to be followed for 15 years (15). This work, which was conducted during 2009-2010, is provided in **Chapter 3**.

The relationship between biomarker and disease process may be further complicated by the influence of other variables, often unsuspected. For example it has long been known that some medications aimed at reducing cardiovascular risk actually influence the risk of developing diabetes and glycaemic control in those with diabetes. Well known examples include thiazide diuretics and beta

blockers, anti-hypertensive agents both known to increase diabetes risk (16;17), and nicotinic acid (18), a lipid-modifying agent known to cause a deterioration in glycaemic control in those with diabetes. By contrast, angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (ARB) have been shown to reduce the risk of developing diabetes (19). Statins are the most prescribed medicines worldwide and this trend has accelerated in recent times such that as many as one in three adults over the age of 45 in the UK is currently on a statin. Atorvastatin and rosuvastatin are among the ten highest grossing medicines in the world. When any class of agents is so widely used, careful scrutiny of any detrimental effects is required as they may affect substantial numbers of people. By 2008 numerous large statin trials had published data on cardiovascular events (20), the majority confirming benefit in terms of cardiovascular risk reduction. Additional studies of potentially important side-effects had confirmed that statin therapy had no influence on the likelihood of developing cancer but that high-dose statin therapy in particular increased one's risk of developing a range of skeletal muscle pathologies ranging from mild myopathy and myalgia to the rare rhabdomyolysis (21). One issue which had not been examined was whether statin therapy had any influence on the risk of developing diabetes and the vast majority of major statin trial publications provided no relevant data. When one major trial selected new-onset diabetes as a specified secondary endpoint and observed a 25% increase (22), it was clear that there was a need for a systematic review of all available evidence to establish whether any effect does exist. Over 2008-2010, I co-led a collaborative project to collect as much published and unpublished data from large placebo- and standard care-controlled trials as possible. This work is described in detail in **Chapter 4**. Crucially, investigating the effect of statin therapy using data from randomised trials provided data of high quality and also immediately satisfied the majority of the Bradford Hill criteria.

The intriguing results of the research conducted in Chapter 4 to evaluate any effect of statin therapy on new-onset diabetes led to further collaborative research. The logical progression of the findings from placebo- and standard care-controlled trials was to seek data from those trials which had compared intensive-dose statin therapy to moderate dose therapy regarding new-onset diabetes. As before, numerous trials had been published in this area but very

little published information was available to address this issue. It again proved possible to form a new collaboration with the relevant trialists, pool unpublished trial data and thereby investigate the possibility of a dose-dependent effect of statin therapy on new-onset diabetes which would have been expected according to the Bradford Hill criteria. In addition, weaknesses present in the analysis of placebo- and standard care-controlled trials could be addressed, in particular the possibility of including not only data regarding new-onset diabetes but also cardiovascular events. This work was conducted over the course of 2009-2011 and is provided in **Chapter 5**. These two chapters, 4 and 5, between them contain the largest and highest quality data yet obtained and analysed to address the question of whether statin therapy affects new-onset diabetes.

A further point to consider when studying a link between biomarker and disease is that observed associations are likely to differ between various patient groups. For glucose and diabetes, one particularly important group to highlight is patients with chronic heart failure, a condition whose prevalence and incidence is increasing and which is expensive to treat. Most cases of chronic heart failure are attributable to coronary heart disease (23). Recent research has revealed the strong association between chronic heart failure and type 2 diabetes with a particularly high prevalence and incidence of diabetes in those with heart failure (24). Importantly, it also appears that patients with diabetes and chronic heart failure are at particular risk of morbidity, and that the risk of developing chronic heart failure is also elevated in patients with diabetes. Consequently, the study of the development of diabetes in chronic heart failure is increasingly considered very important. At the time of my research there were no published data assessing statistical prediction of new-onset diabetes in chronic heart failure. Suitable high quality data to address this question were available from a previously conducted trial of an angiotensin receptor antagonist. With the assistance of my co-supervisors I was able to obtain the necessary data and the subsequent work is detailed in **Chapter 6**.

Arguably the most important question when examining the relationship between biomarker and disease, in this case glucose and cardiovascular disease, is to establish whether interventions to lower glucose have any beneficial effect on cardiovascular outcomes. I had the opportunity to contribute substantially

towards a project led by colleagues at the University of Cambridge in which we pooled exiting data from large trials comparing intensive glucose lowering therapy with standard therapy in patients with type 2 diabetes. This work is included in the **Appendix**.

Each topic is presented separately with its own introduction, methods section, results and discussion. This partly reflects the fact that the majority of the data in this thesis have been published in peer-reviewed journals. Permission to reproduce these data was obtained in all cases and copies of the relevant certificates are included at the end of the thesis.

1.2 Aims of the thesis

Chapter 2

- To investigate whether event rates in cardiovascular endpoint trials conducted in patients with diabetes have been overestimated in pre-trial power calculations
- To examine cardiovascular event rates in trials including diabetic participants with and without baseline cardiovascular disease, or proteinuria, respectively to assess what impact the presence of either of these risk factors has on event rates.

Chapter 3

- To investigate the relationship between fasting plasma glucose and the risk of incident cardiovascular events, all-cause death and also the development of diabetes using an existing database from a large placebo-controlled statin trial

Chapter 4

- To investigate whether statin therapy increases the risk of developing diabetes using data from large placebo- and standard care-controlled trials

Chapter 5

- To examine the associations of intensive-dose statin therapy compared to moderate-dose therapy with the development of diabetes and the occurrence of major cardiovascular events, respectively, using data from large clinical trials

Chapter 6

- To investigate which commonly measured clinical and laboratory characteristics are associated with the development of diabetes in chronic heart failure

Data for intensive vs. standard glucose lowering in type 2 diabetes are available in the Appendix.

Chapter 2.

A systematic review of event rates in clinical trials in diabetes mellitus: the importance of quantifying baseline cardiovascular disease history and proteinuria and implications for clinical trial design

2.1 Introduction

Demonstration of the cardiovascular safety and efficacy of pharmacological treatments used in diabetes is an important clinical issue. The cardiovascular safety of treatments for diabetes was brought to the world's attention by a meta-analysis of trials using the thiazolidinedone, rosiglitazone, conducted by the Cleveland Clinic's Nissen and Wolski which was published in 2007 (25). In their manuscript, the authors combined cardiovascular endpoint data from 42 different trials and found that rosiglitazone therapy was associated with a 43% higher risk of myocardial infarction. The ensuing controversy initiated by that analysis highlighted the small-scale and short-term nature of many studies of new anti-diabetic drugs. In the rosiglitazone meta-analysis, only four of the 42 trials included more than 1000 patients and most lasted less than one year. This, along with the recruitment of relatively young diabetic subjects with little co-morbidity, meant that these studies individually accrued small numbers of cardiovascular events and lacked the statistical power to detect harm or benefit from the treatment being investigated.

These and additional trials in other disease areas (e.g. cyclooxygenase-2 inhibitors for the prevention of colonic adenomas (26), erythropoietin stimulating agents in chronic kidney disease (27), sibutramine and rimonabant for weight loss) led to the realisation that unexpected adverse cardiovascular outcomes on medications may only be detected in large clinical trials and that currently used surrogate measures of drug efficacy are not a reliable guide for establishing clinical cardiovascular benefit or safety.

The subsequent debate of these issues culminated in the release by the Food and Drug Administration (FDA) of guidance for the pharmaceutical industry on the evaluation of cardiovascular risk during the development of new therapies to

treat type 2 diabetes mellitus (28;29) in December 2008. Central to these new recommendations is the principle that trials must include a sufficient proportion of participants at high risk of cardiovascular events to ensure that an adequate number of end-points is obtained, thereby permitting a meaningful estimate of the effect of treatment. However, the FDA document provided little advice on which patients are likely to yield these high event rates and how to identify them. The guidance simply states that "patients with relatively advanced disease, elderly patients and patients with some degree of renal impairment" should be included. Importantly, the guidance does not suggest what size of effect inclusion of these groups of patients might have on event rates. In summary, large clinical trials of glucose-lowering and other potential cardiovascular risk modifying agents are needed in diabetes to properly evaluate their effects.

There are also examples of large and longer-term studies in patients with diabetes which have produced cardiovascular event rates well below those anticipated, leading to changes in primary endpoints during the running of the trial or to underpowered results.

I therefore reviewed large scale randomised clinical trials in participants with diabetes mellitus in order to evaluate achieved cardiovascular disease event rates. The first hypothesis was that event rates in diabetes outcome trials have been overestimated in pre-trial power calculations, driven in part by the questionable presumption that type 2 diabetes is a coronary heart disease 'risk equivalent' condition as was suggested by a previous high profile observational study (30). I also examined cardiovascular event rates in trials including diabetic participants with and without baseline cardiovascular disease, or proteinuria, respectively, both well established cardiovascular risk factors (31-33) and commonly used binary inclusion criteria in diabetes trials, to assess what impact the presence of either of these risk factors has on event rates.

2.2 Methods

I examined all-cause death and cardiovascular event rates in published randomised controlled trials in participants with diabetes mellitus, limited to trials where baseline history of structural cardiovascular disease and/or baseline proteinuria were either directly quoted or calculable from the data provided. These two risk factors were selected as they represent vascular end-organ damage and therefore, theoretically, will convey the overall impact of a combination of vascular risk factors in a simple way. This also reflects the recruitment process in clinical trials where simple criteria are selected which participants must satisfy to take part.

Data Sources and Searches

Studies of antihypertensive agents, lipid modifying agents, anti-platelet agents and glucose-lowering agents published between 1st January 1998 and 1st June 2010 that provided relevant information were gathered. An initial search was performed on 10th June 2009 and this was updated on 29th September 2010. I and my co-supervisor, Prof J McMurray, conducted separate searches of Medline and EMBASE using these criteria together with the terms 'diabetes mortality', 'diabetes cardiovascular', 'diabetes stroke', 'diabetes myocardial infarction', 'diabetes retinopathy', 'diabetes microalbuminuria', 'diabetes hypertension' and 'diabetes peripheral arterial disease' limited to randomised controlled trials in adults published in English. In some trials which included both diabetic and non-diabetic participants, data relating to diabetes were included in the primary publication whereas for other trials there were subsequent and separately published subgroup analyses with the necessary data.

Study Selection

For inclusion studies were required to: (a) include ≥1000 patients with diabetes, (b) report a follow-up period of ≥1 year and (c) provide data needed to calculate at least one of the four event rates listed below (see Data extraction and Quality Assessment). Both trials which enrolled only diabetic participants and trials with both diabetic and non-diabetic participants were included provided events in the

diabetic subgroup were available separately. Trials conducted specifically in patients with unrelated high risk conditions, namely heart failure, arrhythmia, dialysis, organ transplant or following a recent cardiovascular event (within 3 months of recruitment) were excluded. Twenty-nine trials (11;34-66) were eventually identified and are considered in this chapter. No trial recruited patients where presence of cardiovascular disease and proteinuria were either both required or both excluded at baseline.

Data extraction and Quality Assessment

I extracted baseline characteristic data and endpoint data from the selected published trials in tabular form and discrepancies were resolved by consensus with my co-supervisors. The four endpoints examined were (i) All-cause mortality, (ii) Cardiovascular mortality, (iii) Myocardial infarction (a composite of fatal and non-fatal events), and (iv) Stroke (fatal and non-fatal events). I also examined published power calculations for the selected trials, in which the primary endpoint consisted of death and/or major cardiovascular disease events, to assess how often predicted event rates are achieved in these trials.

Data Synthesis and Analysis

To assess how accurately primary endpoint (however defined in the individual trials) event rates were predicted in published power calculations, I divided achieved primary endpoint event rates from trials with anticipated event rates, thereby calculating how many obtained above or below expected rates. A ratio of 1.0 indicates that the actual event rate was equal to the predicted event rate, <1.0 indicates that the actual event rate was lower than the predicted event rate and >1.0 that the actual event rate was higher than the predicted event rate. Crude unadjusted event rates, expressed as events per 1000 patient years, were calculated for each study ([number of events/number of patients] X [1000/average follow-up in years (mean or median as available)]). I included all participants regardless of allocation to treatment group given that most trials compared two or more active treatments or treatment regimens though some trials did use placebo as control. Weighted mean event rates and weighted standard deviations (SD) were calculated according to trial stratification (see

below) as described by Bland and Kerry (67). Weighted mean event rates were calculated by dividing the total number of events in a specified category by patient-years of follow-up and expressing this per 1000 patient years. For estimating weighted SDs, the difference between the weighted sum of squares (calculated by adding the products of squared event rates and patient-years of follow-up from all trials in a specified category) and a correction term derived from the weighted mean was first calculated; this term, divided by degrees of freedom, provides weighted variance from which weighted SD follows.

Power calculations were performed using overall event rates for myocardial infarction plus stroke combined to allow comparison of the difference in patient numbers required in those with and without prior cardiovascular disease or proteinuria. A standard power equation was used to calculate numbers of participants needed per treatment arm (68):

$$n = 10.51\ [(R+1) - p2\ (R^2+1)]\ /\ p2\ (1-R)^2$$

n sample size for each group
p1 event rate in treatment group
p2 event rate in control group
R risk ratio (p1/p2)

Presentation of results

Trials were stratified according to the presence or absence of baseline cardiovascular disease and proteinuria respectively. Baseline cardiovascular disease was defined as objective evidence of coronary artery disease, peripheral arterial disease or cerebrovascular disease. For the purposes of this chapter, the term proteinuria reflects all categories of increased urinary protein excretion including microalbuminuria, macroalbuminuria and proteinuria.

(i) *History of cardiovascular disease at baseline:* In this category I selected trials where a history of cardiovascular disease was reported or calculable from baseline data. I divided trials into those where cardiovascular disease was (1)

present in all participants, (2) **present in some** but not all participants (referred to as 'Mixed' trials), or (3) **absent in all** participants.

(ii) *Proteinuria at baseline:* In this category I selected trials where proteinuria was required to be (1) **present in all** participants, (2) **present in some** but not all participants (referred to as 'Mixed' trials), or (3) **absent in all** participants.

2.3 Results

Of the 5758 manuscripts identified in the search criteria, I identified 159 relevant papers representing 29 trials (Figure 2.1). The 29 trials meeting the inclusion criteria included data on 116,790 diabetic participants with approximately 518,611 patient years of follow-up. Of these, 21 trials reported myocardial infarction numbers, 22 trials reported stroke numbers, 21 trials reported cardiovascular death numbers and 28 reported total mortality numbers. Baseline demographic data, clinical history, laboratory results and event rates are presented for those trials reporting baseline cardiovascular disease in Table 2.1 and for those trials reporting baseline proteinuria in Table 2.2. In 11 of the 29 trials, I was also able to compare the original published power calculations to actual achieved event rates based on clinical primary endpoints (i.e. death and/or cardiovascular disease events).

Predicted event rates are often overestimated in diabetes trials, leading to inaccurate power calculations

Of the 11 trials in diabetic participants which included death and/or cardiovascular disease events in their original primary endpoint power calculations, only one trial achieved an event rate in excess of what was predicted in the control arm. Only four trials achieved an event rate >75% the anticipated rate in the control arm (Figure 2.2). It therefore appears that initial power calculations often underestimate the numbers of patients that a trial will require as achieved endpoint rates tend to be somewhat lower than expected.

Baseline history of cardiovascular disease predicts very high event rates in diabetes whereas event rates are low with no history of cardiovascular disease

For all-cause death, the presence of cardiovascular disease at baseline was associated with three-fold higher death rate (Figure 2.3.1) compared to trials with no baseline cardiovascular disease (weighted mean rates 28.9 vs. 10.0 events/1000 patient years).
For cardiovascular disease death, the presence of cardiovascular disease at baseline was also associated with much higher event rates than when absent,

namely five-fold higher (Figure 2.3.2) (16.7 vs. 3.6 events/1000 patient years). For myocardial infarction and stroke, baseline cardiovascular disease was again associated with significantly higher event rates (four-fold [23.1 vs. 5.2 events/1000 patient years] and two-fold [12.1 vs. 5.4 events/1000 patient years], respectively) (Figure 2.3.3, 2.3.4). Summaries of event rates are provided in Table 2.3. Prevalence of proteinuria was low in trials of diabetic participants without baseline cardiovascular disease.

Baseline proteinuria predicts considerably higher event rates in diabetes whereas event rates are low with no baseline proteinuria

For all-cause death, baseline proteinuria was associated with a six-fold higher death rate than in its absence (Figure 2.3.1) (39.9 vs. 6.3 events/1000 patient years).
For cardiovascular disease death, the presence of baseline proteinuria was associated with 16-fold higher event rates than when absent (Figure 2.3.2) (18.7 vs. 1.2 events/1000 patient years).
There were insufficient data to compare the associations of the presence or absence of baseline proteinuria on stroke and myocardial infarction rates. Summaries of event rates are provided in Table 2.3. Specific definitions of proteinuria used in the various trials are provided in Table 2.4.

Observations from 'Mixed' trials

Event rates in 'Mixed' trials (reflecting intermediate levels of baseline cardiovascular disease and proteinuria) fell between the rates found in the other trials where baseline cardiovascular disease or proteinuria were either exclusion or inclusion criteria. Event rates varied considerably, typically four fold (Figure 2.3.1-4).

The impact of event rates on power calculations

Using combined total myocardial infarction plus stroke numbers as a theoretical composite primary endpoint, I calculated that trials with either baseline cardiovascular disease or proteinuria in all participants would have required in

the order of four-fold fewer participants than in the absence of these risk factors (Table 2.5).

Table 2.1. Baseline characteristics of trials in diabetic participants which reported cardiovascular disease prevalence.

	Study name	Features	Agent	N	Follow-up (yrs)	Age (yrs)	BMI (kg/m^2)	Any CVD (%)	HT (%)	Total / LDL-cholesterol (mmol/L)	HbA1c (%)	Proteinuria (%) *	MI/10^3 pt yrs (n)	Stroke/10^3 pt yrs (n)	CVD death/10^3 pt yrs (n)	Death/10^3 pt yrs (n)
ABSENT	CARDS (34)	CVD risk	statin	2838	3.9	62	29	0	84	5.4/3.0	7.8	17	8.5 (94) †	5.4 (60)	5.6 (62)	12.9 (143)
	JPAD (35)	No CVD	aspirin	2539	4.4	65	24	0	58	5.2/-	7.1	18	2.3 (26)	5.4 (60)	1.2 (13)	6.5 (72)
	PPP (36)	CVD risk	aspirin	1031	3.6	64	29	0	62	5.8/-	7.6	-	4 (15)	5.1 (19)	4.8 (18)	12.1 (45)
PRESENT	INVEST (37)	HT	various	6400	2.7	66	31	100	100	-/-	-	-	- (-)	- (-)	20.3 (351)	42 (725)
	PERSUADE (38)	CHD	ACEi	1502	4.3	62	-	100	39	-/-	-	-	20.7 (134)	6.3 (41)	16.6 (107)	25.7 (166)
	TNT (39)	CHD	statin	1501	4.9	63	30	100	71	4.5/2.5	7.4	-	23.9 (176) §	17.3 (127)	- (-)	21.1 (155)
	LIPID (40)	CHD	statin	1077	6	64	-	100	52	5.6/3.7	-	-	35.7 (231) ‡	13.5 (87)	- (-)	- (-)
	POPADAD (41)	PAD	aspirin	1276	6.7	60	29	100	-	5.5/3.1	8	-	17.0 (145)	10.2 (87)	9.1 (78)	22.8 (195)
	PROactive (42)	HbA1c ≥6.5%	glitazone	5238	2.9	62	31	100	76	4.8/2.9	7.8	44	- (-)	12.7 (193)	17.3 (263)	23.9 (363)
	DAVID (43)	PAD, DM >5yrs	anti-platelet	1209	2	64	28	100	57	-/-	-	-	14.1 (34)	10.8 (26)	14.1 (34)	19.9 (48)
MIXED TRIALS	FIELD (44)	Various, no statin	fibrate	9795	5	62	30	22	57	5.0/3.1	6.9	22	11.6 (568) ‡	6.8 (333)	5.5 (267)	13.9 (679)
	ACCORD (45)	HbA1c ≥7.5%, CVD risk	various	10251	3.5	62	32	35	85	4.7/2.7	8.1	-	12.6 (453)	4.1 (148)	6.4 (229)	12.8 (460)
	ADVANCE (46)	Various	ACEi/diuretic ; oral DM	11140	5	66	28	32	75	-/3.1	7.5	31	11.6 (647) ‡	8.7 (484)	9.7 (542)	18.5 (1031)
	ETDR (47)	Retinopathy	aspirin	3711	5.6	47	27	35	18	5.9/-	9.7	24	- (-)	- (-)	- (-)	34.0 (706)
	VADT (48)	HbA1c ≥7.5%	Oral DM	1791	5.6	60	31	40	72	4.7/2.8	9.4	51	14.2 (142)	6.4 (64)	7.3 (73)	19.6 (197)
	HOPE (49)	CVD risk	ACEi	3577	4.5	65	29	69	56	-/-	-	32	25.7 (414)	11.4 (184)	17.6 (284)	27.6 (444)
	HPS (50;51)	CVD risk	statin	5963	4.8	62	29	51	40	5.7/3.2	7.0 ||	-	- (-)	11.9 (342)	19.1 (546)	29 (830)
	LIFE (52)	HT, LVH	ARB or BB	1195	4.7	67	30	35	100	5.8/-	-	11.5	16.2 (91)	20.7 (116)	17.6 (99)	29.7 (167)
	ALLHAT (53)	HT, CVD risk	various	13101	4.9	67	31	36	100	-/-	-	-	22.3 (-)‡	11.5 (-)	- (-)	31.8 (-)

Footnote to Table 2.1

*: refers to proteinuria prevalence using trial specific definition; †: only includes MIs that were first cardiovascular event in any specific patient; ‡: Non-fatal MI plus coronary heart disease death; §: as in ‡ plus resuscitated cardiac arrest; ||: taken from a subset of 1087 patients;

Abbreviations: BMI: body mass index, SBP: systolic blood pressure, MI: myocardial infarction, CVD: cardiovascular disease, CHD: coronary heart disease, PAD: peripheral arterial disease, DM: diabetes mellitus, Oral DM: oral hypoglycaemic agent, HT: hypertension, ACEi: ACE inhibitor, ARB: angiotensin II receptor blocker, BB: Beta blocker, CCB: calcium channel blocker, LVH: left ventricular hypertrophy, normA: normoalbuminuria, microA: microalbuminuria

Table 2.2. Baseline characteristics of trials in diabetic participants which reported proteinuria prevalence

	Study name	Features	Agent	N	Follow-up (yrs)	Age	BMI	Any CVD %	HT %	Total / LDL -cholesterol	HbA1c (%)	Proteinuria (%) *	MI/10^3 pt yrs (n)	Stroke/10^3 pt yrs (n)	CVD death/10^3 pt yrs (n)	Death/10^3 pt yrs (n)
ABSENT	DIRECT (55)	Retinopathy, normA	ARB	1905	4.7	57	29	-	62	5.3/-	8.2	0	- (-)	- (-)	- (-)	8 (72)
	BENEDICT (56)	HT, normA	ACEi, CCB	1204	3.6	62	29	-	100	5.4/4.2	5.8	0	- (-)	- (-)	1.2 (5)	2.8 (12)
PRESENT	DIABHYCAR (57)	microA, proteinuria	ACEi	4912	4	65	29	25	56	-/-	7.8	100	7.1 (139)	11.9 (234)	18.0 (354)	33.5 (658)
	IDNT (58;59)	Proteinuria, HT	ARB, CCB	1590	3	59	31	29	100	-/-	8.2	100	25.8 (123)	14.5 (69)	21.4 (102)	43.4 (207)
	RENAAL (60)	Nephropathy	ARB	1513	3.4	60	30	-	93	5.9/3.7	8.5	100	22.9 (118)	- (-)	- (-)	60.9 (313)
MIXED TRIALS	ADOPT (61;62)	New DM	oral DM agent	4360	4	56	32	-	51	5.3/3.1	7.4	16	3.9 (68)	3 (52)	- (-)	5.5 (96)
	FIELD (44)	Various, no statin	fibrate	9795	5	62	30	22	57	5.0/3.1	6.9	22	11.6 (568) †	6.8 (333)	5.5 (267)	13.9 (679)
	RECORD (11)	HbA1c 7-9%	glitazone	4447	5.5	58	32	-	80	-/-	7.9	19	4.9 (120)	4.5 (109)	5.4 (131)	12 (293)
	ADVANCE (46)	Various	ACEi/diuretic; oral DM agent	11140	5	66	28	32	75	-/-	7.5	31	11.6 (647) †	8.7 (484)	9.7 (542)	18.5 (1031)
	ETDR (47)	Retinopathy	aspirin	3711	5.6	47	27	35	18	5.9/-	9.7	24	- (-)	- (-)	- (-)	34 (706)
	UKPDS (63;64)	New DM	various	3867	10	53	28	-	-	5.4/3.5	7.1	1.9	- (-)	- (-)	- (-)	18.2 (702)
	VADT (48)	HbA1c ≥7.5%	Oral DM agent	1791	5.6	60	31	40	72	4.7/2.8	9.4	51	14.2 (142)	6.4 (64)	7.3 (73)	19.6 (197)
	INSIGHT (65)	HT	CCB, diuretic	1302	3.5	66	-	-	100	-/-	-	6.4	- (-)	7.9 (36)	8.3 (38)	22.7 (103)
	HOPE (49)	CVD risk	ACEi	3577	4.5	65	29	69	56	-/-	-	32	25.7 (414)	11.4 (184)	17.6 (284)	27.6 (444)
	LIFE (52)	HT, LVH	ARB or BB	1195	4.7	67	30	35	100	5.8/-	-	11.5	16.2 (91)	20.7 (116)	17.6 (99)	29.7 (167)
	CHARISMA (66)	CVD risk	clopidogrel	6555	2.3	-	-	-	-	-/-	-	31	12.9 (194)	- (-)	16.2 (244)	24.3 (366)

*: refers to proteinuria prevalence using trial specific definition; †: Non-fatal myocardial infarction plus coronary heart disease death

Abbreviations: See Table 2.1

Table 2.3. Summary of event rates in diabetic trial participants stratified by the absence or presence of baseline cardiovascular disease and proteinuria

		All-cause death	CVD death	MI	Stroke
Event rates (events/1000 pt years) in trials stratified by baseline CVD prevalence					
No CVD	Weighted mean event rate (SD)	10.0 (3.7)	3.6 (2.6)	5.2 (3.5)	5.4 (0.2)
Mixed trials	Weighted mean event rate (SD)	22.6 (9.5)	10.2 (5.5)	15.6 (7.0)	9.0 (3.9)
All CVD	Weighted mean event rate (SD)	28.9 (9.6)	16.7 (4.3)	23.1 (7.9)	12.1 (3.5)
Event rates (events/1000 pt years) in trials stratified by baseline proteinuria prevalence					
No proteinuria	Weighted mean event rate (SD)	6.3 (3.4)	1.2 (-)	- (-)	- (-)
Mixed trials	Weighted mean event rate (SD)	18.6 (7.4)	9.3 (4.6)	11.6 (5.7)	7.5 (3.5)
All proteinuria	Weighted mean event rate (SD)	39.9 (12.7)	18.7 (1.8)	12.9 (10.0)	12.4 (1.4)

Abbreviations: CVD: cardiovascular disease; MI: myocardial infarction; SD: weighted standard deviation

Table 2.4. Definitions of proteinuria in trials as measured at baseline

Study	Urine parameter tested	Definition of abnormality
Diabetes Trials		
CARDS (34)	Albumin	Positive Micral test OR urine albumin/creatinine ratio ≥2.5mg/mmol OR urine albumin excretion ≥20ug/min
JPAD (35)	Protein	Urine protein ≥15mg/dL
PROactive (42)	Albumin	Positive Micral test
BENEDICT (56)	Albumin	Urine albumin ≥20ug/min
DIRECT (55)	Albumin	Urine albumin ≥20ug/min
DIABHYCAR (57)	Albumin and protein	Microalbuminuria: Urine albumin 20-200 mg/L Proteinuria: ≥200ug/L
IDNT (58;59)	Protein	≥900mg/d
RENAAL (60)	Albumin	Urine albumin creatinine ratio ≥300mg/g
ADOPT (61)	Albumin	Urine albumin creatinine ratio ≥3.4mg/mmol
FIELD (44)	Albumin	Microalbuminuria: urine albumin creatinine ratio 3.5-35mg/mmol Macroalbuminuria: urine albumin creatinine ratio >35mg/mmol
RECORD (11)	Albumin	Urine albumin creatinine ratio >2.5mg/mmol in men, >3.5mg/mmol in women
ADVANCE (46)	Albumin	Microalbuminuria: urine albumin creatinine ratio 30-300ug/mg Macroalbuminuria: urine albumin creatinine ratio >300ug/mg
VADT (48)	-	Not stated
ETDR (47)	Protein	Worse than 'none/trace' on urine dipstick
Other Trials (patients with and without diabetes)		
INSIGHT (65)	Protein	Urine protein ≥0.5g/d
HOPE (49)	Albumin	Urine albumin creatinine ratio ≥2mg/mmol
LIFE (52)	Albumin	Urine albumin creatinine ratio ≥33.9mg/mmol (≥300mg/g)
CHARISMA (66)	Albumin	Urine albumin ≥30ug/mL

Table 2.5. Power calculations: how participant numbers are affected by baseline history of cardiovascular disease or proteinuria

	MI plus stroke (events/1000 pt years)	Participants required*
Trials stratified by baseline CVD prevalence		
No CVD	10.6	16985
Some CVD	24.6	6828
All CVD	35.2	4513
Trials stratified by baseline proteinuria prevalence		
No proteinuria	6.5†	28243†
Some proteinuria	19.1	9043
All proteinuria	25.3	6616

*: Assumptions for power calculations: (1) Primary endpoint is for total number of myocardial infarctions plus total number of strokes combined, with 90% power, alpha 0.05 and 5 year trial duration, assuming a 20% reduction in events in the active arm compared to the control arm; (2) each patient does not suffer more than one cardiovascular event

†: Combined event rate for trials with no baseline proteinuria estimated using correlation between death and total myocardial infarction and stroke combined across all trials

MI: myocardial infarction; CVD: cardiovascular disease

Figure 2.1. Flow diagram summarising the literature search to identify rates of mortality and cardiovascular endpoints in diabetic participants from large randomised controlled trials

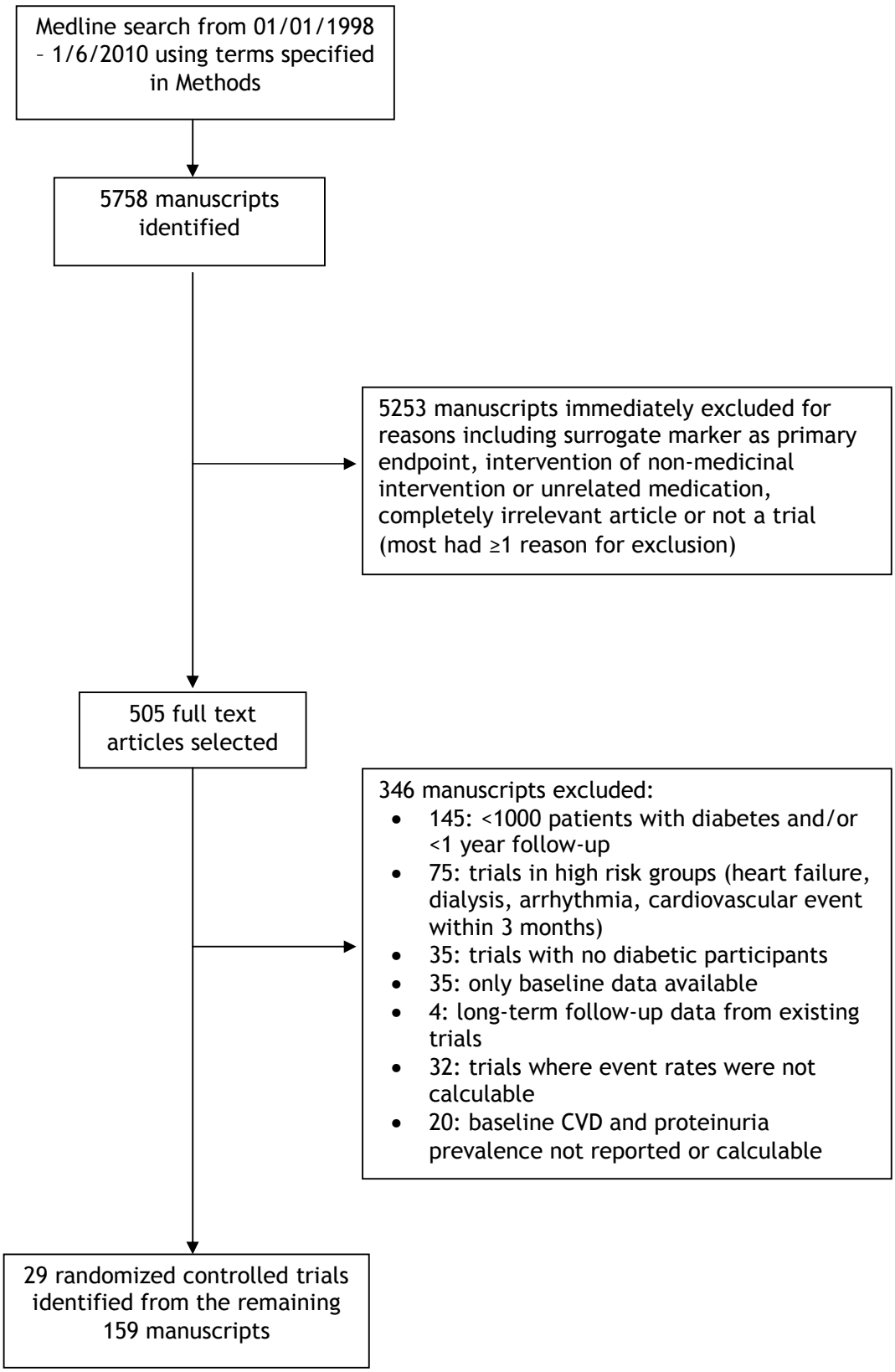
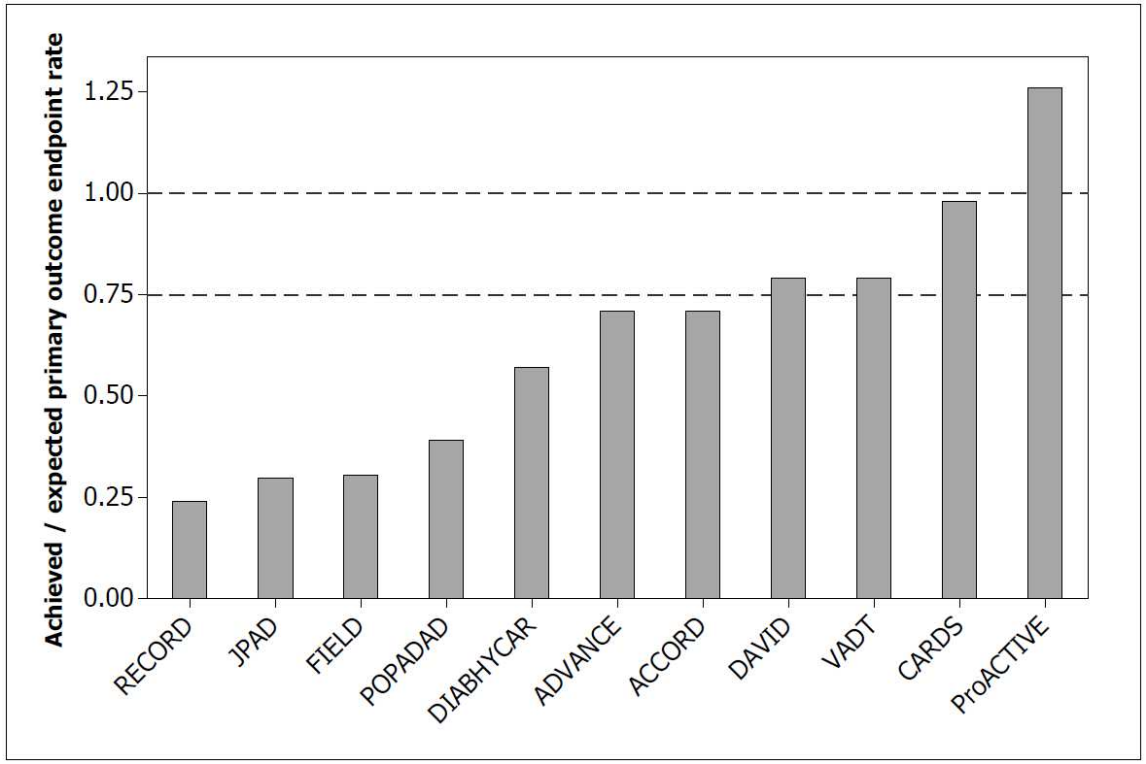


Figure 2.2. A comparison of anticipated and achieved primary endpoint event rates in the control arms of endpoint trials in diabetes



Footnote: Anticipated event rate in FIELD based on predicted 500 deaths in 8000 participants over 5 years (primary outcome measure was changed during the trial due to low event rate)

Figure 2.3. All-cause death (2.3.1), cardiovascular disease death (2.3.2), myocardial infarction (fatal and non-fatal) (2.3.3) and stroke (fatal and non-fatal) rates (2.3.4) in clinical trials of diabetic participants stratified by baseline prevalence of (i) history of cardiovascular disease, and (ii) proteinuria

Figure 2.3.1

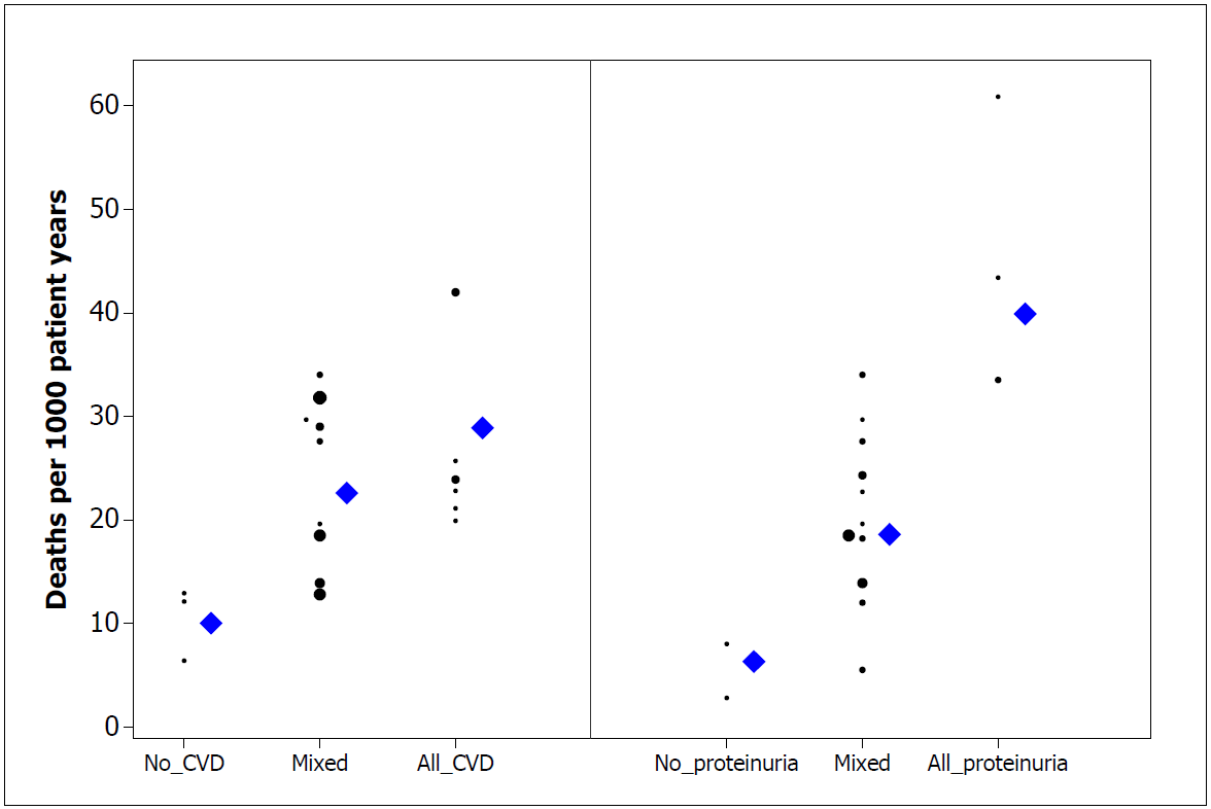


Figure 2.3.2

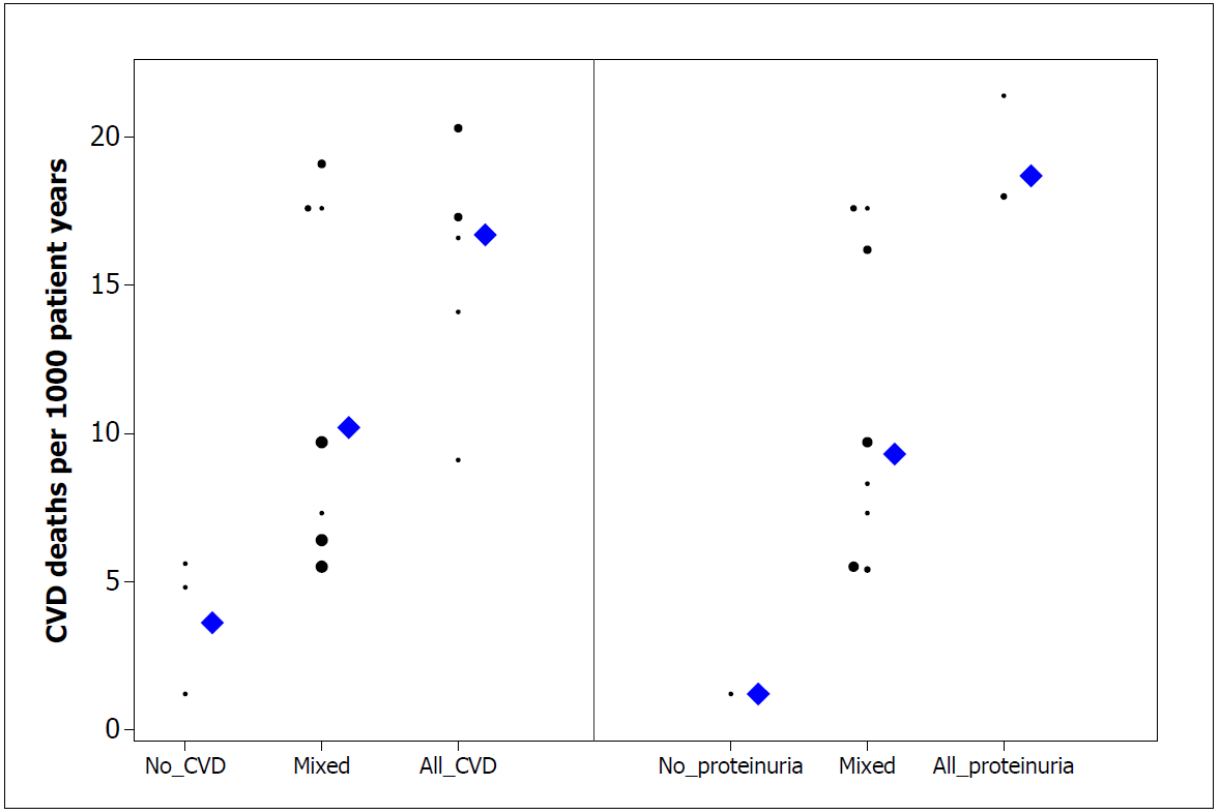

CVD deaths per 1000 patient years
0
5
10
15
20
No_CVD
Mixed
All_CVD
No_proteinuria
Mixed
All_proteinuria

Figure 2.3.3

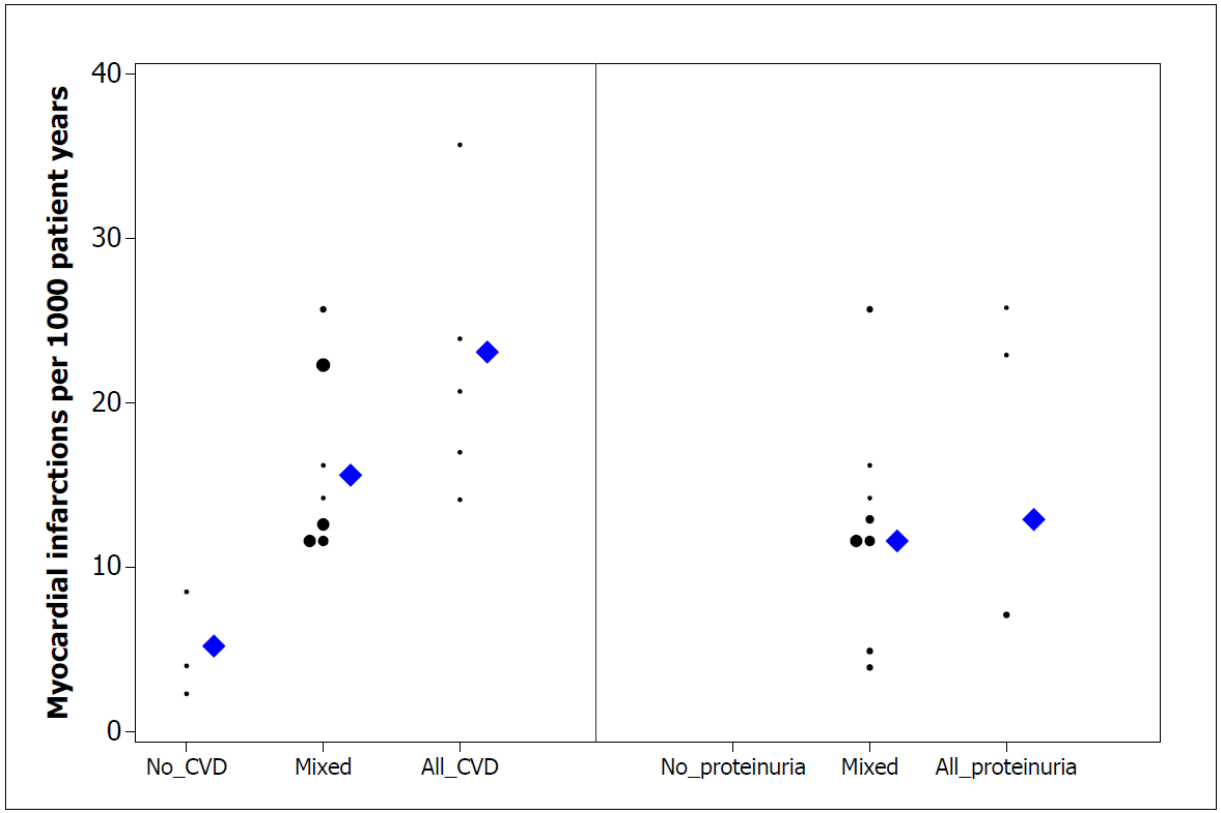
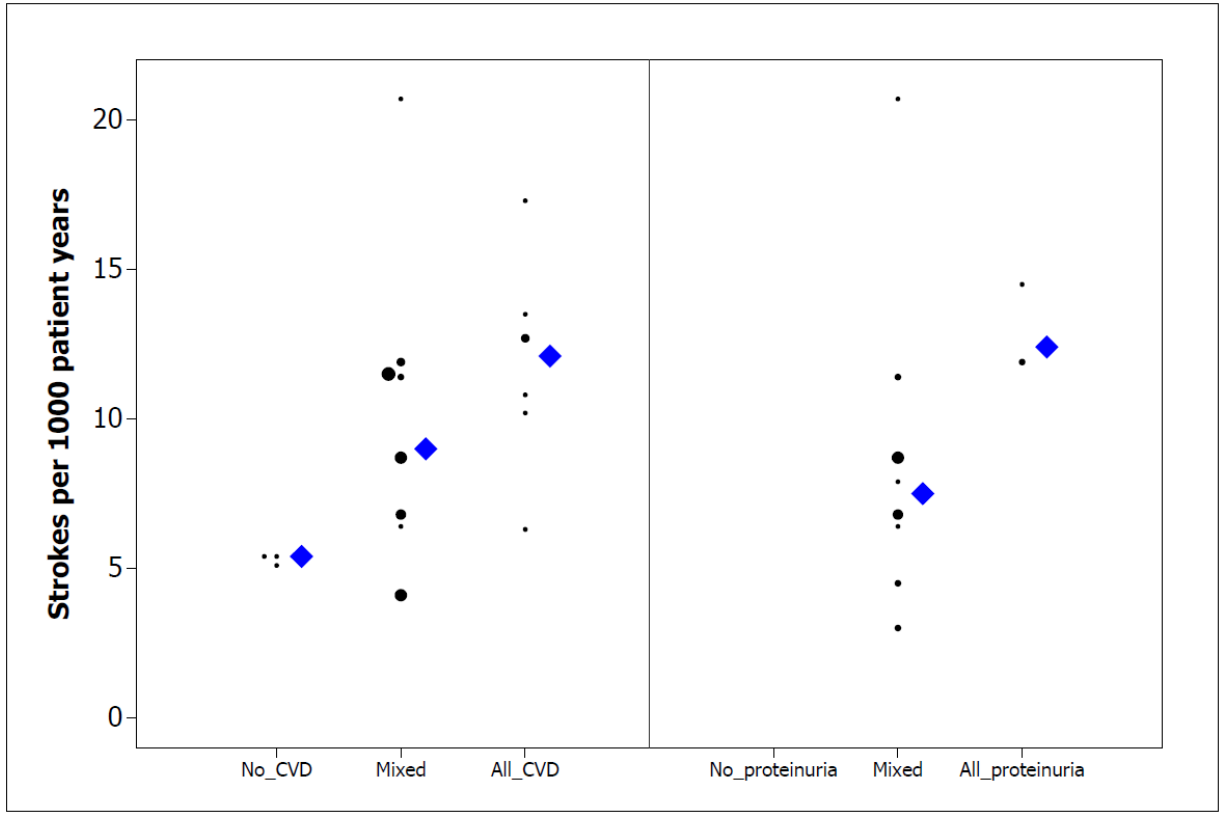

Myocardial infarctions per 1000 patient years
40
30
20
10
0
No_CVD
Mixed
All_CVD
No_proteinuria
Mixed
All_proteinuria

Figure 2.3.4



Footnote: dots represent individual trial event rates and are weighted according to trial participant numbers; diamonds represent weighted mean event rates

CVD: cardiovascular disease

2.4 Discussion

This analysis of mortality and cardiovascular event rates in diabetic participants in large clinical trials reveals three key messages. First, history of either cardiovascular disease or evidence of proteinuria at baseline in patients with diabetes is associated with substantially higher rates of death and cardiovascular disease events in trials compared to those with predominantly uncomplicated diabetes.

Second, event rates in patients with diabetes without cardiovascular disease or proteinuria are particularly low in absolute terms with significant implications for trial design in terms of required participant numbers. The mortality rates in the five trials which included participants with diabetes without a history of either cardiovascular disease or proteinuria, with a mean age of 57-65 years (34-36;55;56), ranged from only 3 to 13 deaths per 1000 patient years of follow-up. To place this in context, data from the Centers for Disease Control's National Center for Health Statistics show mortality rates in the general United States population of 9.3/1000 pt years for individuals in the age group 55-64 and 22.4/1000 pt years for subjects in age group 65-74 between 2002 and 2004. It is apparent that trials in diabetic participants with a low prevalence of cardiovascular disease and proteinuria will generate few endpoints and consequently either require huge participant numbers to achieve adequately powered results, or otherwise potentially lead to under-powered results. This is strongly at odds with the design of many clinical trials where the presence of uncomplicated diabetes is often assumed to carry a cardiovascular disease risk equivalent to non-diabetic subjects with underlying cardiovascular disease, probably based on existing cohort studies (30) though other larger studies have challenged this assumption (69).

Third, it is apparent that prediction of event rates in diabetes populations with heterogeneous combinations of risk factors is difficult, as evidenced by the regular overestimation of anticipated events in trial power calculations. It appears that if trial designers do not have information regarding the likely prevalence of baseline cardiovascular disease and proteinuria in their trial population, anticipated event rates will be difficult to predict accurately with

any degree of certainty. The consequences of the above observations for clinical trial design are significant. The symmetry between rates of mortality and cardiovascular disease endpoints for proteinuria and cardiovascular disease categories is also of interest.

Published FDA guidance (29) now states that for new diabetes medications 'concerns about cardiovascular risk should be more thoroughly addressed during drug development'. The guidance document highlights the need to conduct trials which obtain sufficient endpoints. However, apart from simply suggesting that patients with 'relatively advanced disease, elderly patients and patients with some degree of renal impairment' should be included in trials, no specific definitions of such patients are provided and the likely impact of including such patients in trials on event rates is not considered. The data presented here are therefore intended to guide those designing trials in diabetic populations, both for drug development and also for other pharmaceutical trials conducted in diabetic patients.

It is of course well established that microalbuminuria and history of cardiovascular disease are powerful risk factors for death and vascular events in diabetes (31-33), as again highlighted here. What is striking, however, is the substantial difference in event rates observed between trial populations with or predominantly without these risk factors and this difference is greater than expected based on existing cohort study data. One possibility which may partially explain these findings is the 'healthy participant effect' where trial volunteers represent a healthier cohort than may be expected in the general population. Whatever the explanation, it is apparent that simple extrapolation from cohort studies to predict event rates and calculate study power is problematic. It should be recognised that earlier trials in diabetes had far less access to large datasets on which to base their power calculations than is the case now. Also, the introduction of effective cardiovascular risk reducing agents such as statins has led to a significant reduction in cardiovascular morbidity in diabetes. Nonetheless, it appears that the majority of trials have based their power calculations on cohort studies, rather than previous trials. It may therefore be advisable to base power calculations on data from existing trials, as presented herein.

The potential for benefit from a pharmaceutical agent is also an important consideration when deciding on an appropriate trial population. As argued by Goldfine (28), those with advanced disease at high risk constitute an appropriate population if the likelihood of benefit is reasonable and the risk of harm low. However, these same individuals may also be at higher risk of and less able to tolerate adverse events. Careful consideration of preclinical data and mechanism of action are therefore warranted. Furthermore, evidence of benefit for an intervention in a specified group (e.g. patients with established coronary disease or microalbuminuria) may not necessarily be generalisable to all with diabetes and may require potentially narrower drug approval indications for therapies where benefit is sought. This is less likely to be an issue with newly developed glucose lowering agents where evidence of non-inferiority will often be the goal of a trial. Clearly, limiting trial inclusion criteria to only certain groups of patients will also reduce the numbers eligible to participate which itself may lengthen the recruitment period and increase the cost of screening.

The data presented in this chapter have strengths and weaknesses which should be highlighted. Firstly, clinical endpoints were adjudicated due to the nature of clinical trials, a major advantage over many cohort studies. Follow-up in some of the studies assumed the same follow-up for diabetic participants as in the total cohort (i.e. trials with diabetic and non-diabetic participants) but this was not explicitly stated in all cases. Furthermore, in five studies (39;40;44;46;53) I used data for non-fatal myocardial infarction combined with coronary heart disease death, rather than fatal myocardial infarction, to substitute for total myocardial infarction. Therefore, true myocardial infarction numbers will be lower than the numbers presented though the difference is likely to be small. Without availability of individual participant data, I could not properly address the association of baseline lipids, smoking, hypertension and indeed disease duration on event risks though body mass index (BMI) and age were generally comparable across trials. However, of these factors, only hypertension tends to be used as a specific inclusion criterion in trials and examination of trial event rates suggests that using a threshold blood pressure value as inclusion criteria would have a limited effect on accrued clinical events. Furthermore, while individual participant data can provide insights into risks associated with biomarkers under

specified conditions, it carries less advantages over summary data (as used here) when examining trial inclusion criteria which, by necessity, tend to be simple and few in number. Calculated event rates provided crude estimates only; in specific trials, true event rates may have been slightly different due to loss of patients to follow-up, and trials did not report all four specified endpoints with the effect that I used different numbers of trials and patients to calculate event rates. Furthermore, as discussed above, definitions of microalbuminuria and proteinuria varied between trials.

This summary and synthesis of event rates from existing data is intended to help inform the design of future cardiovascular disease trials in patients with diabetes. For evaluation of drug safety or efficacy, better selection of trial subjects will be economical in terms of limiting drug exposure and financial outlay, and potentially testing new therapies on those most likely to derive benefit. It is hoped that this analysis may aid sponsors and investigators wishing to comply with the FDA guidance.

These data were published in the American Heart Journal in 2011 (70).

Chapter 3.

Fasting plasma glucose in non-diabetic participants and the risk for incident cardiovascular events, diabetes, and mortality: results from the West of Scotland Coronary Prevention Study

3.1 Introduction

It is already conclusively established that diabetes mellitus is an independent risk factor for the development of cardiovascular events and death (71). Any relationship between fasting glucose levels in the non-diabetic range (<7.0mmol/L) and future cardiovascular disease has remained much debated. Some reports have claimed that elevated fasting plasma glucose (FPG) in the non-diabetic range is indeed associated with higher risk of cardiovascular disease while other reports have found more complex relationships. However, the quality of these data has often been variable. Methodological weaknesses of certain studies and meta-analyses have been (i) the inclusion of older studies with patients whose FPG levels would now be considered diagnostic of diabetes, (ii) that many studies have yielded few endpoints, and (iii) that statistical analysis has often failed to adjust for well established cardiovascular risk factors.

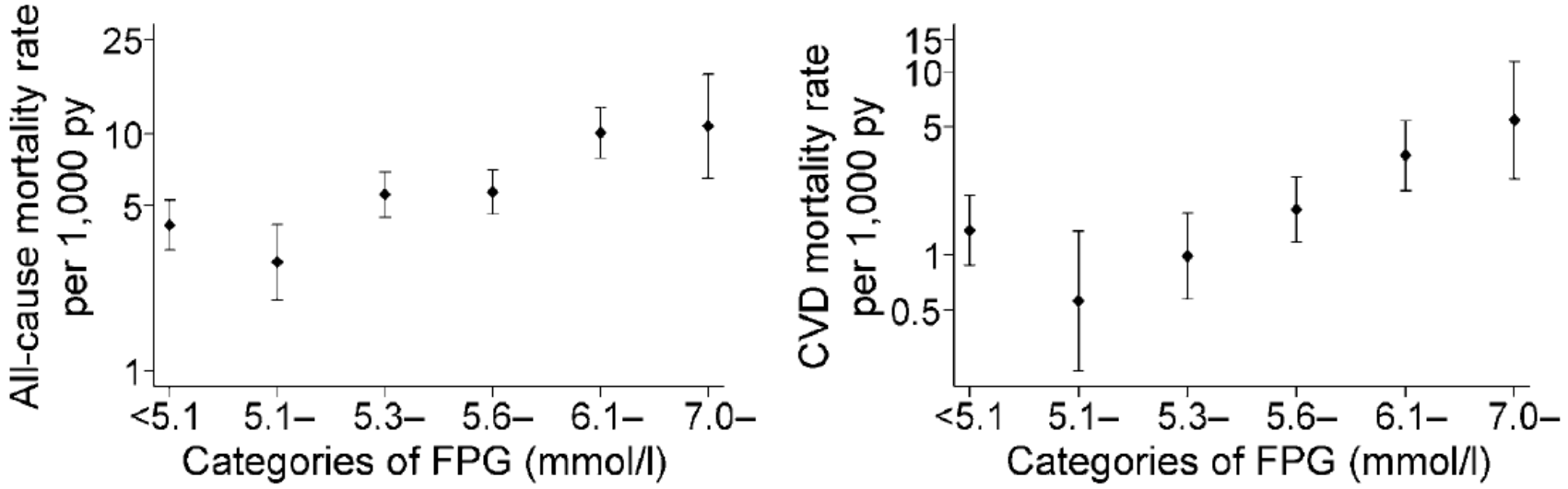
In a 2004 meta-analysis of 14 studies by Levitan et al (72), investigators reported a risk ratio of 1.27 for cardiovascular events when comparing the highest FPG category to the lowest in participants without diabetes. Further inspection of included studies reveals that seven of the 14 studies included patients with FPG ≥7.0mmol/L and only three of the remaining seven found any significant association between higher FPG and cardiovascular events. Other evidence has suggested that their may be a J-shaped relationship between FPG and coronary heart disease, with higher cardiovascular risk at both lower and higher FPG levels. Important studies include the Australian Diabetes, Obesity and Lifestyle study (AusDiab) (73) and the Diabetes Epidemiology - Collaborative analysis of Diagnostic criteria in Europe (DECODE) study (74) (see Figure 3.1). In addition, the meta-analysis of Levitan suggested a threshold effect with lowest cardiovascular risk at a FPG of 5.6mmol/L, though it should again be highlighted

that this analysis includes some patients who, by current criteria, would now be classified as having diabetes at baseline (see Figure 3.2); the possibility of a J-shaped relationship also suggests that reporting continuous associations between glucose and cardiovascular disease may be statistically erroneous. Two more recent data sets have found no relationship between non-diabetic FPG and cardiovascular disease, namely a study in Korean men (75) and another in British women (76).

Similar analyses have been conducted to evaluate any potential relationship between glycaemia and cardiovascular disease by comparing event rates in those with impaired fasting glycaemia (IFG) (FPG 6.1-6.9mmol/L) to those with normoglycaemia. A weak association was observed in a study of a Chinese cohort (77); furthermore, in the DECODE study, IFG was associated with a higher rate of all-cause death in men than in other non-diabetic men (hazard ratio [HR] 1.21) in age-adjusted analyses but there was no such relationship in women (12).

In an attempt to clarify the conflicting literature, I investigated the relationship between FPG and the risk of incident cardiovascular events, all-cause death and also the development of diabetes using an existing database from a large statin trial.

Figure 3.1. Unadjusted all-cause and cardiovascular mortality rates (95% CI) for fasting plasma glucose in individuals without previously diagnosed diabetes in the AusDiab study

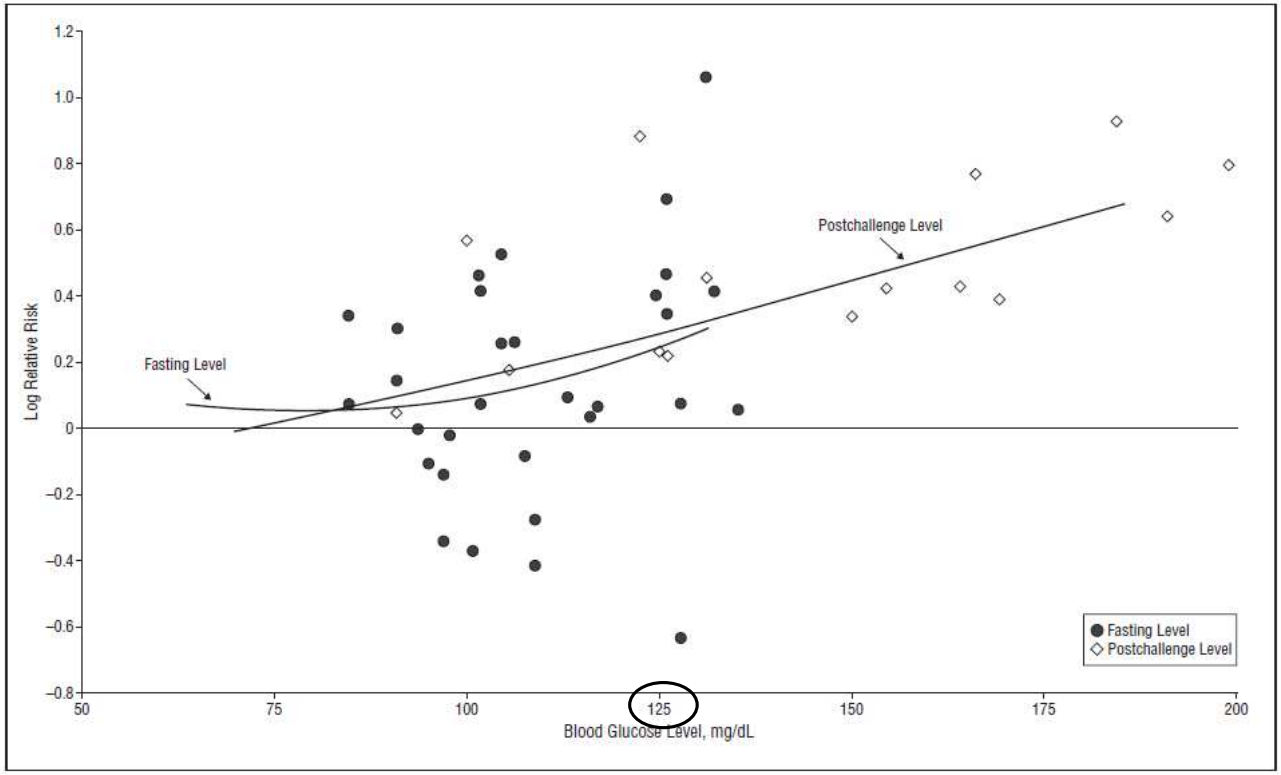


Footnote 1: Y axis in log scale

Footnote 2: Figure taken from Barr et al (73) and reproduced with the permission of Springer ©

FPG: fasting plasma glucose; CVD: cardiovascular disease

Figure 3.2. Dose-response relationship of cardiovascular disease with fasting and post-challenge blood glucose levels



Note that for studies with FPG below the diabetes threshold (<7mmol/L), cardiovascular risk is not clearly elevated, unlike for studies with FPG above the threshold

Taken from Levitan et al (72), copyright © 2004, American Medical Association; all rights reserved

3.2 Methods

Aims

The aim of this analysis was to investigate the relationships between FPG concentrations in the non-diabetic and diabetic range and both the occurrence of incident cardiovascular events and new-onset diabetes. This was achieved using the West of Scotland Coronary Prevention Study (WOSCOPS) database, details of which are provided below.

Background

WOSCOPS was the second large trial investigating the effect of statin therapy on cardiovascular endpoints to be published (14;15). WOSCOPS was designed to investigate the effect of pravastatin therapy, compared to placebo, on the composite endpoint of non-fatal myocardial infarction and coronary heart disease death. In the WOSCOPS analyses published to date, participants treated with pravastatin were at significantly lower risk of coronary events (14); furthermore, post trial follow-up for 15 years using computerised data demonstrated that patients treated with pravastatin in the original trial continued to be at lower risk of coronary events, in keeping with a 'legacy effect' of statin therapy (15).

Patients

In WOSCOPS, 6595 moderately hypercholesterolaemic men (serum low density lipoprotein [LDL]-cholesterol 4.5–6.0 mmol/L and triglycerides <6.0 mmol/L) with no history of myocardial infarction were randomised to pravastatin 40 mg daily or placebo and followed initially for an average of 4.9 years, with an additional follow-up to 15 years using linkage of computerised data held by National Health Service (NHS) Scotland, a technique previously shown to demonstrate good agreement with event adjudification by end-point committee (78). All subjects provided written informed consent for the original trial, and ethical approval was obtained for the trial (prior to the current requirement for online registration in a trial database). Men attended the screening clinic

(before randomisation to pravastatin or placebo) fasted and had blood samples taken for various analyses including plasma glucose. FPG measurements were carried out in quality-controlled NHS routine laboratories, and subsequent FPG measurements were made throughout the study every six months. A range of other physical and biochemical cardiovascular risk factors and other demographic variables was assessed and recorded at baseline.

Diagnoses of events

Specific diseases and events examined in the current analysis were as follows:

Diabetes mellitus. Baseline diabetes: Baseline diabetes was defined as either patients with FPG ≥7.0mmol/L or prior history of diabetes.
New-onset diabetes: Incident diabetes after baseline was defined as (i) two subsequent FPG measurements ≥7.0 mmol/L or (ii) commencement of hypoglycaemic agents during the study. Information regarding the development of diabetes was limited to the five years of the original trial and not to subsequent long-term (fifteen year) follow-up as was available for recording of cardiovascular events.

Cardiovascular endpoints and all-cause mortality. Follow-up of clinical cardiovascular events and mortality was based on linkage of records held by NHS Scotland and was conducted by Professor Ian Ford (Robertson Centre for Biostatistics, University of Glasgow). Using this method, follow-up data were available up to fifteen years for cardiovascular events and mortality. Personal identifiers for study participants were electronically linked to hospital discharge records (Scottish Morbidity Record 01) and General Register Office death records (held by the Information and Statistical Division [ISD] of NHS Scotland) by means of established record-linkage methods. Data on outcome events were extracted from the databases with the use of appropriate 'International Classification of Diseases' [ICD] codes (versions 9 and 10 – see definitions below). Approval for record linkage was given by the Privacy Advisory Committee at ISD, NHS Scotland.

Cardiovascular events were defined as:

1. Cardiovascular events: a composite of non-fatal cardiovascular events and fatal cardiovascular events (ICD 10: I00–I99);
2. Coronary events: a composite of non-fatal coronary events and coronary death (ICD 10: I20–I25 [ischaemic heart disease]);
3. stroke: a composite of non-fatal and fatal stroke (ICD 10: I60–I69 [cerebrovascular diseases]);
4. Coronary heart disease death;
5. All-cause mortality

Statistics

To examine the potential relationships between non-diabetic FPG and future cardiovascular events, coronary heart disease death, all-cause death, and new-onset diabetes, FPG for participants with no history or biochemical evidence of diabetes at baseline was divided into fifths (quintile 1 [Q1]–Q5), thereby allowing comparison of time to first event of interest by Cox proportional hazard models. Q2 was selected as referent based on previous analyses suggesting a possible J-shaped relationship between FPG and cardiovascular disease mortality (73;74). However, sensitivity analyses using Q1 as a referent were also performed. The HRs were adjusted for treatment and age in a minimally adjusted model and additionally for the following baseline covariates [treatment, age, cholesterol (high density lipoprotein [HDL]- and LDL-cholesterol), triglycerides, BMI, smoking status (current and ex-smoker), blood pressure (systolic and diastolic), hypertension, use of nitrate therapy, history of angina, social deprivation score (as analysed by deprivation category [DEPCAT], based on home post code), use of specific medications at baseline (aspirin, angiotensin converting enzyme [ACE]-inhibitors, ß-blockers, calcium channel blockers, diuretics, other antihypertensive agents)] in a fully adjusted model to better evaluate the importance of FPG for predicting future outcomes. Given the possible weighting of events by FPG close to the diabetes threshold (~7.0 mmol/L), the uppermost FPG quintile was further divided into fifths (Q5a–Q5e) for more detailed analysis. Analyses were also conducted for each treatment group (placebo and pravastatin) separately in further sensitivity analyses.

Cardiovascular disease risk was also assessed in those with baseline IFG using two definitions: (i) the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) (defined as FPG 6.1–6.9 mmol/L) (79), and (ii) the American Diabetes Association (ADA) definition (FPG 5.6–6.9 mmol/L) (80). Finally, cardiovascular event risk was studied in those with diabetes at baseline and in those who had developed diabetes during the 5 years of the original WOSCOPS trial over the subsequent ten years of follow-up.

Results are reported as number (percentage) of patients with events, HRs (95% confidence interval [CI]), and corresponding *p* values; *p* values were two-sided and $p<0.05$ was considered statistically significant. The validity of the proportional hazards assumption was assessed by testing the significance of interaction between glucose and the logarithm of time as a time-dependent covariate. All analyses were carried out using the statistical software SAS (version 9.1, SAS Institute, Cary, NC, USA).

Note

Professor Ian Ford and colleagues from the WOSCOPS steering committee provided access to the WOSCOPS database and Professor Ford was responsible for setting up the method for long-term follow-up of patients after WOSCOPS i.e. linkage of records held by NHS Scotland.

3.3 Results

Baseline characteristics of the cohort

Data were available for 6447 WOSCOPS participants with no history of diabetes at baseline and with FPG <7.0mmol/L. Baseline characteristics, split according to quintiles of baseline FPG, are provided in Table 3.1. The glucose cut-offs employed were ≤4.3mmol/L (Q1, n=1448), >4.3-4.6mmol/L (Q2, the referent, n=1657), >4.6-4.8mmol/L (Q3, n=1150), >4.8-5.1mmol/L (Q4, n=1116) and >5.1-6.9mmol/L (Q5, n=1076). The following continuous variables displayed small though statistically significant and apparently adverse changes across quintiles of higher FPG as analysed by ANOVA (unadjusted analyses): higher age, higher BMI, higher systolic blood pressure, higher diastolic blood pressure, higher total cholesterol and higher triglycerides. There was no difference in either LDL- or HDL-cholesterol across quintiles. With regard to categorical variables, the following variables were significantly different across increasing fasting glucose quintiles: there were fewer smokers, more patients with angina and hypertension, and more patients on nitrates. As described in the Methods, Q5 was also split into five subgroups, Q5a-Q5e for additional comparisons with Q2, the referent. Glucose cut-offs for these analyses were >5.1-5.2mmol/L (Q5a, n=223), >5.2-5.4mmol/L (Q5b, n=354), >5.4-5.5mmol/L (Q5c, n=95), >5.5-5.8mmol/L (Q5d, n=226) and >5.8-6.9mmol/L (Q5e, n=178).

Cardiovascular events and all-cause mortality over 15 years and diabetes over 5 years

Over fifteen years of follow-up, the numbers of cardiovascular and mortality events in the entire cohort (n=6447) were as follows:

- 2381 cardiovascular events
- 1474 coronary events
- 405 strokes
- 361 coronary heart disease deaths
- 1244 all-cause deaths

Over five years, there were 168 cases of new-onset diabetes in the cohort.

Risk of cardiovascular events and mortality according to glycaemic categories

Comparing risk of cardiovascular events and all-cause mortality across fifths of non-diabetic FPG by HR relative to Q2, none of the other quintiles (Q1, Q3-Q5) were at significantly increased or decreased risk of these events in age and treatment adjusted analyses (Model 1) (Table 3.2). In this minimally adjusted model, the HRs for cardiovascular events in Q1, Q3, Q4 and Q5 compared to Q2 were 1.05 (95% CI 0.94-1.19), 1.04 (95% CI 0.91-1.17), 1.06 (0.93-1.20) and 1.04 (0.92-1.18) respectively. HRs for all-cause mortality in Q1, Q3, Q4 and Q5 in the minimally adjusted model were 1.10 (0.94-1.30), 0.93 (0.78-1.11), 1.12 (0.94-1.32) and 1.05 (0.88-1.25) respectively. These findings were consistent after additionally adjusting for a range of diabetes and cardiovascular risk factors and potential confounders (Model 2), namely BMI, smoking, blood pressure, hypertension, cholesterol (HDL & LDL), triglycerides, use of nitrates, history of angina, social deprivation score (estimated from post code by DEPCAT) and various medications (aspirin, ACE-inhibitors, B-blockers, calcium channel blockers, diuretics). Most HRs were also somewhat attenuated in the fully adjusted model. The HRs for cardiovascular events in Q1, Q3, Q4 and Q5 compared to Q2 were 1.05 (0.94-1.19), 1.04 (0.91-1.17), 1.06 (0.93-1.20) and 1.04 (0.92-1.18) respectively for Model 2. Furthermore in model 2, HRs for all-cause mortality were 1.07 (0.90-1.25), 0.90 (0.75-1.07), 1.05 (0.88-1.24) and 0.96 (0.80-1.15).

Similarly, there was little evidence of higher risk of events in the five subgroups of Q5 (Table 3.3). In the minimally adjusted model, the HRs for cardiovascular events in Q5a, Q5b, Q5c, Q5d and Q5e compared to Q2 were 1.16 (0.93-1.44), 0.96 (0.79-1.16), 1.31 (0.96-1.80), 0.98 (0.78-1.25) and 1.21 (0.95-1.54) respectively. HRs for all-cause mortality in Q5a, Q5b, Q5c, Q5d and Q5e in the minimally adjusted model were 0.97 (0.70-1.34), 0.85 (0.65-1.13), 1.53 (1.02-2.30), 1.18 (0.87-1.60) and 1.25 (0.91-1.72) respectively. All-cause mortality in Q5c yielded the only statistically significant finding, quite likely a chance finding given the number of analyses conducted. Results were again attenuated after adjustment for potential confounders. The HRs for cardiovascular events in Q5a, Q5b, Q5c, Q5d and Q5e compared to Q2 were 1.01 (0.81-1.27), 0.86 (0.71-1.05), 1.10 (0.80-1.51), 0.87 (0.69-1.11) and 1.05 (0.82-1.35) respectively for Model 2.

Furthermore in model 2, HRs for all-cause mortality in these subgroups were 0.86 (0.62-1.19), 0.79 (0.60-1.04), 1.24 (0.82-1.87), 1.12 (0.82-1.52) and 1.11 (0.80-1.54).

All of these findings were consistently non-significant when Q1 was used as the referent (data not shown). Analysing risk of events using FPG as a continuous variable in fully adjusted models, HRs per 1mmol/L higher glucose for cardiovascular events (HR 0.95 [95%CI 0.88-1.04]), coronary events (HR 0.93 [95%CI 0.84-1.04]), strokes (HR 1.01 [95%CI 0.83-1.22] and coronary heart disease death (HR 0.90 [95%CI 0.73-1.11]) were also not found to be significant. However, as argued in the Methods section, analysis of glucose in a continuous fashion implies that risk is linear, an assumption which is unproven and unsupported by these findings.

Risk of cardiovascular events and mortality in participants with IFG

The risk of cardiovascular events and all-cause mortality was estimated in those who met two different criteria for IFG, namely that of NCEP ATPIII (defined as FPG 6.1-6.9mmol/L) and the ADA (defined as FPG 5.6-6.9mmol/L) (Table 3.4).

- *NCEP ATP III definition*: the risk of all cardiovascular events was non-significantly elevated in those with IFG relative to those with lower FPG in the minimally adjusted Model 1. In the fully adjusted Model 2, all HRs were further attenuated towards 1.0. The HRs for cardiovascular disease and all-cause mortality in IFG were 1.14 (0.83-1.55) and 1.02 (0.66-1.60) respectively compared to non-diabetic participants without IFG (Model 2).

- *ADA criteria*: as with the NCEP ATP III criteria for IFG, HRs for clinical events were not significantly elevated compared to those with lower glucose values in either Model 1 or Model 2 though the point estimates were generally slightly lower for ADA criteria than NCEP ATP III. Event numbers were relatively low for stroke and coronary heart disease death for both sets of IFG criteria. The HRs for cardiovascular disease and all-cause mortality in IFG were 0.95 (0.78-1.15) and 1.01 (0.79-1.31) respectively compared to non-diabetic participants without IFG (Model 2).

Risk of cardiovascular events and mortality in participants with diabetes at baseline

In contrast with the above results which showed no significant elevation in the risk of cardiovascular events with increasing glucose in the non-diabetic range, risks of cardiovascular events (HR 1.32 [1.05-1.66], coronary events (HR 1.46 [1.10-1.92]) and all-cause mortality (HR 1.37 [1.02-1.83]) were significantly increased in Model 2 (fully adjusted model) in the 148 participants with diabetes at baseline compared to all subjects without diabetes at baseline. This provides external confidence in the findings from analyses in the WOSCOPS cohort. Those with diabetes at baseline had non-significantly elevated rates of coronary death (HR 1.47 [0.88-2.45]) though event numbers were lower for this analysis.

Risk of cardiovascular events and mortality in those who developed diabetes during the original WOSCOPS 5 year trial

Risks of cardiovascular events, coronary events and all-cause mortality were calculated from the end of the trial (at 5 years) over the subsequent 10 years in the 138 WOSCOPS participants who had developed diabetes but not suffered any coronary or cardiovascular events during the original trial (it should be noted that these are 138 patients from a total of 168 who developed diabetes during WOSCOPS; thirty were excluded from this analysis having suffered clinical events over the 5 years of the WOSCOPS trial – this step was necessary to avoid statistical complications). Risk of cardiovascular events (HR 1.29 [0.98-1.69]), coronary events (HR 1.36 [0.97-1.92]), stroke (HR 1.24 [0.67-2.29]), coronary heart disease death (HR 1.57 [0.82-3.00]) and all-cause mortality (HR 1.05 [0.71-1.56]) were non-significantly increased in these subjects.

The impact of randomisation to pravastatin or placebo on any relationship between glucose and cardiovascular events

There was no significant difference in the association of FPG with risk of endpoints by pravastatin/placebo randomisation, this despite the known effects of statin therapy on cardiovascular risk. P values for any interaction between

statin and placebo treated participants were as follows: all cardiovascular events, p=0.29; coronary events, p=0.75; strokes, p=0.99; coronary heart disease deaths, p=0.72; and all-cause mortality, p=0.69. There were only three specific statistically significant differences between the results for statin- and placebo-treated participants: Q3 yielded a borderline higher risk for cardiovascular events on placebo (HR 1.19 [1.00-1.14]), Q5a showed higher risk for cardiovascular events on placebo (HR 1.40 [1.03-1.89]) and Q5c showed higher risk of death on placebo (HR 1.93 [1.13-3.27]). Importantly, given the consistency of findings in the treatment arms, it was statistically defendable to combine the participants regardless of statin or placebo allocation (treatment is included in all adjustment models). For completeness, all results separated by treatment allocation are provided (Tables 3.5 and 3.6).

Risk of developing diabetes in those without diabetes at baseline

There were 168 cases of new-onset diabetes over the 5 years of the original WOSCOPS trial. The risk of new-onset diabetes over 5 years was estimated by quintiles of baseline FPG, the same as employed for the cardiovascular endpoint analyses. Risk of new-onset diabetes over the 5 years was compared with risk of cardiovascular events over 15 years across the glucose quintiles. As already described, higher FPG levels in the non-diabetic range were not associated with increased risk of cardiovascular events over 15 years. In contrast, there was a marked increase in the risk of developing diabetes in Q5 in Model 1 (age and treatment adjusted model) (HR 26.5 [95%CI 12.98-54.17]) compared to Q2. This association remained powerful in the fully adjusted Model 2 (HR 22.05 [95%CI 10.75-45.22]) which employed the same adjustments as for the cardiovascular analyses. Treatment allocation to placebo or pravastatin was not a relevant factor and no statistically significant interaction was found (Table 3.7).

As would be expected, both criteria for IFG, namely the NCEP ATPIII (HR 23.2 [95%CI 15.7-34.3]) and ADA criteria (HR 17.3 [95%CI 12.6-23.7]), demonstrated strongly elevated risks for developing diabetes compared to patients with normal FPG levels at baseline.

Figure 3.3 summarises the contrasting relative risks of developing diabetes and cardiovascular events according to FPG quintiles over five and fifteen years respectively.

Table 3.1. Baseline Characteristics split by quintiles of baseline fasting plasma glucose

	Quintiles of Glucose (mmol/L)					
	Q1 **≤ 4.3** **n=1448**	**Q2** **>4.3-4.6** **n=1657**	**Q3** **>4.6-4.8** **n=1150**	**Q4** **>4.8-5.1** **n=1116**	**Q5** **>5.1-6.9** **n=1076**	**Unadjusted p-value[1]**
Continuous variables [Mean (SD)]						
Age (years)	54.8 (5.5)	54.8 (5.6)	55.2 (5.5)	55.6 (5.6)	55.6 (5.3)	<0.0001
BMI (kg/m^2)	25.1 (2.9)	25.7 (3.0)	25.9 (3.1)	26.3 (3.3)	26.8 (3.3)	<0.0001
Systolic BP (mmHg)	132.9 (16.9)	134.0 (16.9)	135.9 (16.9)	137.1 (17.2)	138.5 (17.8)	<0.0001
Diastolic BP (mmHg)	82.6 (10.2)	83.2 (10.4)	84.0 (10.2)	85.0 (10.0)	85.5 (10.3)	<0.0001
Total Cholesterol (mmol/L)	6.96 (0.57)	6.99 (0.57)	7.03 (0.58)	7.07 (0.58)	7.13 (0.62)	<0.0001
HDL Cholesterol (mmol/L)	1.14 (0.25)	1.14 (0.25)	1.15 (0.24)	1.15 (0.24)	1.12 (0.24)	0.071
LDL Cholesterol (mmol/L)	4.96 (0.44)	4.95 (0.45)	4.96 (0.46)	4.97 (0.45)	4.98 (0.46)	0.38
Triglycerides (mmol/L)[2]	1.54 (1.48)	1.63 (1.49)	1.67 (1.48)	1.77 (1.49)	1.92 (1.48)	<0.0001
Categorical variables [n(%)]						
Current smoker	738 (51.0)	717 (43.3)	483 (42.0)	461 (41.3)	450 (41.8)	<0.0001
Nitrate use	19 (1.3)	21 (1.3)	22 (1.9)	36 (3.2)	33 (3.1)	0.0002
History of angina	61 (4.2)	66 (4.0)	52 (4.5)	64 (5.7)	84 (7.8)	<0.0001
History of hypertension	164 (11.3)	221 (13.3)	178 (15.5)	191 (17.1)	243 (22.6)	<0.0001

[1] Unadjusted p-value from ANOVA (continuous variable), chi-square test (categorical variable).

[2] Summary statistics for triglycerides based on geometric means.

BMI: body mass index; BP: blood pressure

Table 3.2. Associations of fasting plasma glucose by quintiles with cardiovascular endpoints and mortality over 15 years

		Q1		Q2	Q3		Q4		Q5		
Glucose (mmol/L)		≤4.3 (N=1448)		>4.3-4.6 (N=1657)	>4.6-4.8 (N=1150)		>4.8-5.1 (N=1116)		>5.1-6.9 (N=1076)		
		HR	(95%CI)	Referent	HR	(95%CI)	HR	(95%CI)	HR	(95%CI)	P-value
CVD events	**Events (%)**	**524 (36.2)**		**589 (35.6)**	**432 (37.6)**		**432 (38.7)**		**404 (37.6)**		
	Model l	1.05	0.94-1.19	1.0	1.04	0.91-1.17	1.06	0.93-1.20	1.04	0.92-1.18	0.44
	Model 2	1.04	0.92-1.17	1.0	1.01	0.89-1.15	1.00	0.89-1.14	0.95	0.83-1.08	0.25
CHD events	**Events (%)**	**331 (22.9)**		**362 (21.8)**	**264 (23.0)**		**265 (23.8)**		**252 (23.4)**		
	Model 1	1.08	0.93-1.26	1.0	1.03	0.88-1.21	1.06	0.90-1.24	1.05	0.89-1.24	0.47
	Model 2	1.07	0.92-1.25	1.0	1.01	0.86-1.19	0.98	0.83-1.15	0.93	0.79-1.10	0.19
Stroke	**Events (%)**	**88 (6.1)**		**87 (5.2)**	**82 (7.1)**		**75 (6.7)**		**73 (6.8)**		
	Model 1	1.18	0.88-1.59	1.0	1.30	0.96-1.76	1.22	0.89-1.66	1.25	0.91-1.71	0.39
	Model 2	1.13	0.84-1.53	1.0	1.21	0.89-1.64	1.12	0.82-1.53	1.05	0.77-1.45	0.95
CHD death	**Events (%)**	**77 (5.3)**		**95 (5.7)**	**62 (5.4)**		**69 (6.2)**		**58 (5.4)**		
	Model 1	0.97	0.72-1.32	1.0	0.89	0.65-1.23	0.98	0.72-1.34	0.85	0.61-1.18	0.86
	Model 2	0.93	0.69-1.26	1.0	0.85	0.62-1.18	0.90	0.66-1.23	0.74	0.53-1.03	0.33
All-cause mortality	**Events (%)**	**283 (19.5)**		**301 (18.2)**	**203 (17.6)**		**242 (21.7)**		**215 (20.0)**		
	Model 1	1.10	0.94-1.30	1.0	0.93	0.78-1.11	1.12	0.94-1.32	1.05	0.88-1.25	0.84
	Model 2	1.07	0.90-1.25	1.0	0.90	0.75-1.07	1.05	0.88-1.24	0.96	0.80-1.15	0.53

Model 1: adjusted for randomised treatment and age.

Model 2: Adjusted for BMI, smoking, BP, hypertension, cholesterol (HDL & LDL), triglycerides, nitrates use, history of angina, social deprivation score (DEPCAT), various medications (aspirin, ACE-inhibitors, B-blockers, calcium channel blockers, diuretics, other).

FPG: fasting plasma glucose; Q: quintile; HR: hazard ratio; CI: confidence interval; CVD: cardiovascular disease; CHD: coronary heart disease.

Table 3.3. Associations of fasting plasma glucose with cardiovascular events by quintiles of Q5 relative to Q2 over 15 years

		Q2	Q5a		Q5b		Q5c		Q5d		Q5e	
Glucose (mmol/L)		>4.3-4.6 N=1657	>5.1-5.2 N=223		>5.2-5.4 N=354		>5.4-5.5 N=95		>5.5-5.8 N=226		>5.8-6.9 N=178	
		Referent	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
CVD events	**Events (%)**	**589 (35.6)**	**90 (40.4)**		**124(35.0)**		**41 (43.2)**		**76 (33.6)**		**73 (41.0)**	
	Model l	1.0	1.16	0.93-1.44	0.96	0.79-1.16	1.31	0.96-1.80	0.98	0.78-1.25	1.21	0.95-1.54
	Model 2	1.0	1.01	0.81-1.27	0.86	0.71-1.05	1.10	0.80-1.51	0.87	0.69-1.11	1.05	0.82-1.35
CHD events	**Events (%)**	**362 (21.8)**	**48 (21.5)**		**85 (24.0)**		**25 (26.3)**		**47 (20.8)**		**47 (26.4)**	
	Model 1	1.0	0.98	0.73-1.33	1.08	0.85-1.37	1.30	0.86-1.94	1.00	0.74-1.36	1.25	0.92-1.69
	Model 2	1.0	0.84	0.62-1.14	0.95	0.74-1.20	1.07	0.71-1.61	0.87	0.64-1.18	1.02	0.75-1.38
Stroke	**Events (%)**	**87 (5.2)**	**19 (8.5)**		**17 (4.8)**		**7 (7.4)**		**14 (6.2)**		**16 (9.0)**	
	Model 1	1.0	1.57	0.96-2.58	0.84	0.50-1.42	1.49	0.69-3.23	1.20	0.68-2.11	1.65	0.97-2.81
	Model 2	1.0	1.27	0.77-2.10	0.74	0.44-1.26	1.06	0.49-2.30	1.06	0.60-1.87	1.39	0.81-2.38
CHD death	**Events (%)**	**95 (5.7)**	**9 (4.1)**		**19 (5.4)**		**4 (4.2)**		**11 (4.9)**		**15 (8.4)**	
	Model 1	1.0	0.68	0.34-1.34	0.88	0.54-1.44	0.77	0.28-2.10	0.87	0.47-1.63	1.38	0.80-2.38
	Model 2	1.0	0.52	0.26-1.03	0.73	0.44-1.20	0.55	0.20-1.50	0.78	0.42-1.47	1.08	0.62-1.88
All-cause mortality	**Events (%)**	**301 (18.2)**	**41 (18.4)**		**59 (16.7)**		**25 (26.3)**		**47 (20.8)**		**43 (24.2)**	
	Model 1	1.0	0.97	0.70-1.34	0.85	0.65-1.13	1.53	1.02-2.30	1.18	0.87-1.60	1.25	0.91-1.72
	Model 2	1.0	0.86	0.62-1.19	0.79	0.60-1.04	1.24	0.82-1.87	1.12	0.82-1.52	1.11	0.80-1.54

Model 1: adjusted for randomised treatment and age. *Model 2*: Adjusted for BMI, smoking, BP, hypertension, cholesterol (HDL & LDL), triglycerides, nitrates use, history of angina and social deprivation score (DEPCAT), various medications (aspirin, ACE-inhibitors, B-blockers, calcium channel blockers, diuretics, other).
FPG: fasting plasma glucose; Q: quintile; HR: hazard ratio; CI: confidence interval; CVD: cardiovascular disease; CHD: coronary heart disease.

Table 3.4. Hazard Ratio (95%CI) of cardiovascular endpoints and all-cause mortality among participants with impaired fasting glycaemia (two definitions) relative to normoglycaemia

		No diabetes with FPG ≤6.0mmol/L (N=6352)	Impaired fasting glucose: NCEP ATPIII (FPG 6.1-6.9mmol/L); N=95		No diabetes with FPG ≤5.5mmol/L N=6144	Impaired fasting glycaemia: ADA (FPG 5.6-6.9mmol/L); N=303	
		Referent	HR	95%CI	Referent	HR	95%CI
CVD events	**Events (%)**	**2341 (36.9)**	**40 (42.1)**		**2268 (36.9)**	**113 (37.3)**	
	Model l	1.0	1.25	(0.92-1.71)	1.0	1.05	(0.87-1.27)
	Model 2	1.0	1.14	(0.83-1.55)	1.0	0.95	(0.78-1.15)
CHD events	**Events (%)**	**1448 (22.8)**	**26 (27.4)**		**1402 (22.8)**	**72 (23.8)**	
	Model 1	1.0	1.27	(0.86-1.87)	1.0	1.07	(0.84-1.36)
	Model 2	1.0	1.09	(0.74-1.61)	1.0	0.93	(0.73-1.18)
Stroke	**Events (%)**	**397 (6.2)**	**8 (8.4)**		**381 (6.2)**	**24 (7.9)**	
	Model 1	1.0	1.39	(0.69-2.81)	1.0	1.29	(0.85-1.94)
	Model 2	1.0	1.25	(0.62-2.53)	1.0	1.17	(0.77-1.78)
CHD death	**Events (%)**	**353 (5.6)**	**8 (8.4)**		**342 (5.6)**	**19 (6.3)**	
	Model 1	1.0	1.55	(0.77-3.12)	1.0	1.12	(0.71-1.78)
	Model 2	1.0	1.34	(0.66-2.72)	1.0	1.00	(0.62-1.59)
All-cause mortality	**Events (%)**	**1224 (19.3)**	**20 (21.1)**		**1181 (19.2)**	**63 (20.8)**	
	Model 1	1.0	1.12	(0.72-1.75)	1.0	1.08	(0.84-1.39)
	Model 2	1.0	1.02	(0.66-1.60)	1.0	1.01	(0.79-1.31)

Model 1: adjusted for randomised treatment and age.

Model 2: In addition adjusted for BP, hypertension, cholesterol (HDL & LDL), triglycerides, nitrates use, history of angina, social deprivation score (DEPCAT), various medications (aspirin, ACE-inhibitors, B-blockers, calcium channel blockers, diuretics, other)

FPG: fasting plasma glucose; Q: quintile; HR: hazard ratio; CI: confidence interval; CVD: cardiovascular disease; CHD: coronary heart disease.

Table 3.5. Associations of fasting plasma glucose by quintiles with cardiovascular endpoints and mortality (over 15 yrs) according to randomised treatment group

Glucose (mmol/L)			Q1 ≤4.3 N=1448		Q2 >4.3-4.6 N=1657	Q3 >4.6-4.8 N=1150		Q4 >4.8-5.1 N=1116		Q5 >5.1-6.9 N=1076		P-value
			HR	(95%CI)	Referent	HR	(95%CI)	HR	(95%CI)	HR	(95%CI)	
CVD events		**Events (%)**	**524 (36.2)**		**589 (35.6)**	**432 (37.6)**		**432 (38.7)**		**404 (37.6)**		
	Pravastatin	Model l	0.99	0.84-1.18	1.0	0.89	0.74-1.07	0.96	0.80-1.16	0.99	0.82-1.19	0.98
		Model 2	1.03	0.87-1.22	1.0	0.89	0.74-1.07	0.90	0.75-1.09	0.89	0.74-1.08	0.23
	Placebo	Model 1	1.08	0.91-1.27	1.0	1.19	1.00-1.41	1.18	1.00-1.40	1.16	0.97-1.38	0.29
		Model 2	1.06	0.89-1.25	1.0	1.14	0.96-1.35	1.12	0.94-1.33	0.98	0.81-1.17	0.51
CHD events		**Events (%)**	**331 (22.9)**		**362 (21.8)**	**264 (23.0)**		**265 (23.8)**		**252 (23.4)**		
	Pravastatin	Model l	1.00	0.80-1.25	1.0	0.94	0.74-1.19	0.97	0.76-1.23	1.06	0.84-1.35	0.41
		Model 2	1.06	0.85-1.33	1.0	0.95	0.75-1.21	0.88	0.69-1.12	0.94	0.74-1.20	0.55
	Placebo	Model 1	1.12	0.91-1.36	1.0	1.12	0.91-1.39	1.17	0.94-1.44	1.11	0.89-1.38	0.82
		Model 2	1.10	0.90-1.35	1.0	1.08	0.87-1.34	1.09	0.88-1.35	0.90	0.72-1.13	0.13
Stroke		**Events (%)**	**88 (6.1)**		**87 (5.2)**	**82 (7.1)**		**75 (6.7)**		**73 (6.8)**		
	Pravastatin	Model l	1.15	0.75-1.76	1.0	1.17	0.75-1.83	1.16	0.74-1.81	1.17	0.75-1.83	0.91
		Model 2	1.12	0.73-1.74	1.0	1.16	0.74-1.81	1.08	0.69-1.70	0.95	0.60-1.50	0.37
	Placebo	Model 1	1.21	0.80-1.82	1.0	1.43	0.95-2.15	1.27	0.83-1.95	1.31	0.85-2.02	0.21
		Model 2	1.14	0.75-1.72	1.0	1.26	0.83-1.90	1.15	0.75-1.78	1.14	0.73-1.78	0.37
CHD death		**Events (%)**	**77 (5.3)**		**95 (5.7)**	**62 (5.4)**		**69 (6.2)**		**58 (5.4)**		
	Pravastatin	Model l	0.89	0.58-1.38	1.0	0.85	0.54-1.35	0.78	0.48-1.26	0.80	0.49-1.29	0.68
		Model 2	0.91	0.59-1.41	1.0	0.81	0.51-1.28	0.67	0.41-1.09	0.66	0.41-1.08	0.26
	Placebo	Model 1	0.99	0.66-1.51	1.0	0.95	0.61-1.48	1.25	0.83-1.88	1.02	0.66-1.60	0.55
		Model 2	0.96	0.63-1.45	1.0	0.92	0.59-1.43	1.14	0.75-1.73	0.79	0.50-1.26	0.70
All-cause mortality		**Events (%)**	**283 (19.5)**		**301 (18.2)**	**203 (17.6)**		**242 (21.7)**		**215 (20.0)**		
	Pravastatin	Model l	1.13	0.90-1.42	1.0	0.92	0.71-1.19	1.01	0.79-1.29	1.00	0.78-1.29	0.47
		Model 2	1.15	0.91-1.45	1.0	0.92	0.71-1.18	0.94	0.73-1.21	0.91	0.71-1.18	0.15
	Placebo	Model 1	1.06	0.84-1.34	1.0	0.94	0.73-1.20	1.23	0.97-1.55	1.12	0.88-1.44	0.32
		Model 2	1.00	0.80-1.27	1.0	0.90	0.70-1.16	1.16	0.92-1.47	1.02	0.80-1.31	0.59

Footnote to Table 3.5

Model 1: adjusted for age. *Model 2*: Additionally adjusted for BMI, smoking, BP, hypertension, cholesterol (HDL & LDL), triglycerides, nitrates use, history of angina and social deprivation score (DEPCAT), various medications (aspirin, ACE-inhibitors, B-blockers, calcium channel blockers, diuretics, other).

FPG: fasting plasma glucose; Q: quintile; HR: hazard ratio; CI: confidence interval; CVD: cardiovascular disease; CHD: coronary heart disease.

Table 3.6. Associations of fasting plasma glucose by fifths (Q5a-e) of the uppermost glucose quintile <7mmol/L with cardiovascular endpoints and mortality (over 15 yrs) according to randomised treatment group

Glucose (mmol/L)			Q2 >4.3-4.6 N=1657	Q5a >5.1-5.2 N=223		Q5b >5.2-5.4 N=354		Q5c >5.4-5.5 N=95		Q5d >5.5-5.8 N=226		Q5e >5.8-6.9 N=178	
			Referent	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
CVD events		**Events (%)**	**589 (35.6)**	**90 (40.4)**		**124 (35.0)**		**41 (43.2)**		**76 (33.6)**		**73 (41.0)**	
	Pravastatin	Model 1	1.0	0.95	0.68-1.32	0.87	0.65-1.16	1.21	0.79-1.87	0.95	0.67-1.35	1.21	0.86-1.71
		Model 2	1.0	0.84	0.61-1.17	0.80	0.60-1.07	1.00	0.64-1.54	0.91	0.64-1.30	1.07	0.75-1.52
	Placebo	Model 1	1.0	1.40	1.03-1.89	1.05	0.80-1.36	1.41	0.88-2.24	1.02	0.74-1.42	1.21	0.86-1.70
		Model 2	1.0	1.18	0.87-1.60	0.90	0.69-1.18	1.18	0.74-1.89	0.84	0.61-1.17	0.99	0.70-1.40
CHD events		**Events (%)**	**362 (21.8)**	**48 (21.5)**		**85 (24.0)**		**25 (26.3)**		**47 (20.8)**		**47 (26.4)**	
	Pravastatin	Model 1	1.0	0.90	0.58-1.41	0.93	0.65-1.35	1.62	0.97-2.70	0.94	0.59-1.49	1.41	0.92-2.16
		Model 2	1.0	0.78	0.50-1.22	0.84	0.58-1.23	1.31	0.78-2.20	0.90	0.56-1.43	1.20	0.78-1.86
	Placebo	Model 1	1.0	01.06	0.70-1.59	1.21	0.89-1.64	0.95	0.49-1.85	1.05	0.70-1.57	1.11	0.72-1.71
		Model 2	1.0	0.90	0.59-1.36	0.99	0.73-1.36	0.73	0.37-1.44	0.86	0.57-1.29	0.85	0.55-1.32
Stroke		**Events (%)**	**87 (5.2)**	**19 (8.5)**		**17 (4.8)**		**7 (7.4)**		**14 (6.2)**		**16 (9.0)**	
	Pravastatin	Model 1	1.0	1.69	0.87-3.28	0.97	0.49-1.93	0.83	0.20-3.42	0.89	0.35-2.25	1.40	0.63-3.11
		Model 2	1.0	1.37	0.70-2.69	0.81	0.41-1.64	0.55	0.13-2.29	0.82	0.32-2.08	1.06	0.47-2.39
	Placebo	Model 1	1.0	1.39	0.66-2.95	0.69	0.31-1.52	2.32	0.92-5.85	1.47	0.71-3.00	1.91	0.93-3.91
		Model 2	1.0	1.11	0.52-2.37	0.65	0.29-1.45	1.72	0.67-4.42	1.30	0.63-2.69	1.68	0.80-3.51
CHD death		**Events (%)**	**95 (5.7)**	**9 (4.1)**		**19 (5.4)**		**4 (4.2)**		**11 (4.9)**		**15 (8.4)**	
	Pravastatin	Model 1	1.0	0.69	0.27-1.72	0.82	0.40-1.67	0.37	0.05-2.65	0.66	0.24-1.84	1.28	0.58-2.83
		Model 2	1.0	0.52	0.20-1.33	0.69	0.33-1.41	0.26	0.04-1.92	0.64	0.23-1.79	1.07	0.48-2.83
	Placebo	Model 1	1.0	0.65	0.23-1.80	0.94	0.47-1.85	1.24	0.38-3.97	1.07	0.48-2.35	1.48	0.70-3.14
		Model 2	1.0	0.51	0.18-1.43	0.75	0.37-1.50	0.83	0.26-2.72	0.88	0.40-1.97	1.05	0.49-2.26
All-cause mortality		**Events (%)**	**301 (18.2)**	**41 (18.4)**		**59 (16.7)**		**25 (26.3)**		**47 (20.8)**		**43 (24.2)**	
	Pravastatin	Model 1	1.0	0.87	0.54-1.38	0.89	0.61-1.31	1.17	0.61-2.21	0.99	0.61-1.60	1.34	0.86-2.08
		Model 2	1.0	0.76	0.47-1.22	0.82	0.56-1.21	0.94	0.49-1.79	0.98	0.61-1.58	1.22	0.78-1.90
	Placebo	Model 1	1.0	1.08	0.68-1.70	0.82	0.55-1.22	1.93	1.13-3.27	1.35	0.90-2.02	1.16	0.72-1.84
		Model 2	1.0	0.99	0.62-1.57	0.76	0.51-1.15	1.59	0.93-2.74	1.23	0.82-1.85	1.03	0.64-1.65

Footnote to Table 3.6

Model 1: adjusted for age. *Model 2*: Additionally adjusted for BMI, smoking, BP, hypertension, cholesterol (HDL & LDL), triglycerides, nitrates use, history of angina and social deprivation score (DEPCAT), various medications (aspirin, ACE-inhibitors, B-blockers, calcium channel blockers, diuretics, other).

FPG: fasting plasma glucose; Q: quintile; HR: hazard ratio; CI: confidence interval; CVD: cardiovascular disease; CHD: coronary heart disease.

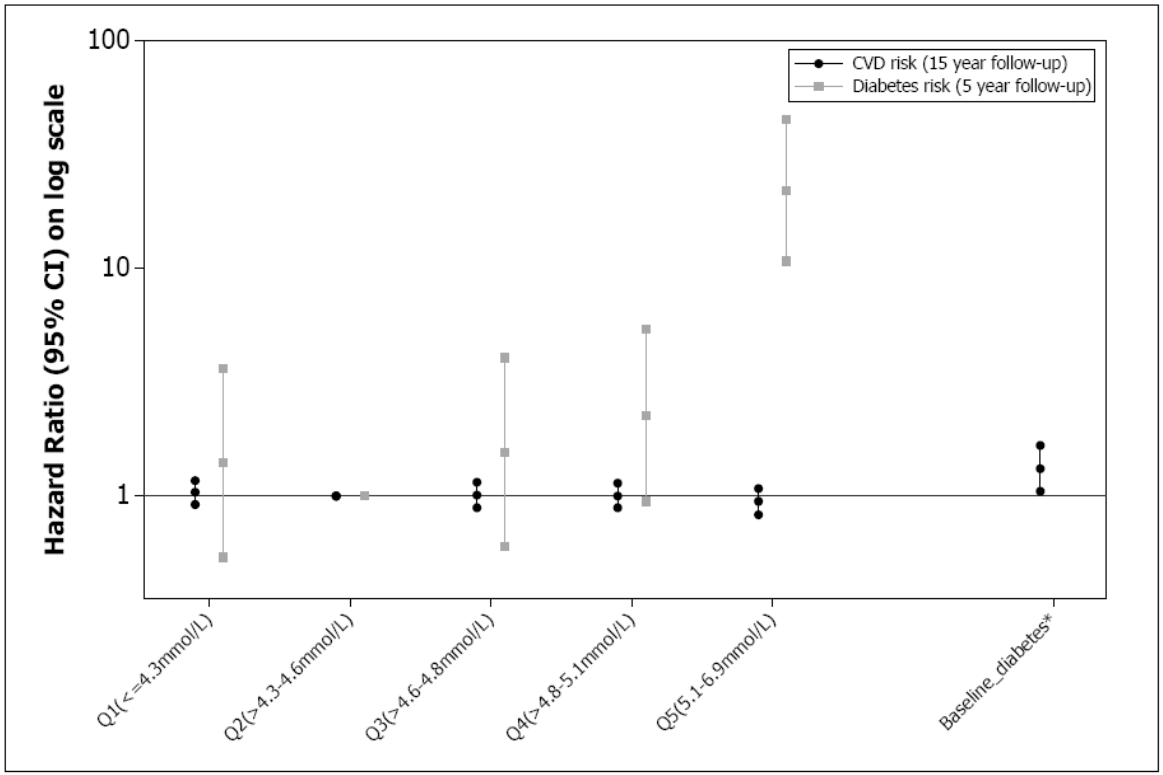
Table 3.7. Associations of fasting plasma glucose by quintiles with the development of diabetes (over 5 years) according to randomised treatment group

Glucose (mmol/L)			**Q1** ≤4.3 N=1448		**Q2** >4.3-4.6 N=1657	**Q3** >4.6-4.8 N=1150		**Q4** >4.8-5.1 N=1116		**Q5** >5.1-6.9 N=1076		
			HR	(95%CI)	Referent	HR	(95%CI)	HR	(95%CI)	HR	(95%CI)	P value
Incident diabetes		**Events (%)**	**9 (0.6%)**		**8 (0.5%)**	**9 (0.8%)**		**14 (1.3%)**		**128 (11.9%)**		
	Pravastatin	Model l	0.90	0.24-3.35	1.0	0.86	0.20-3.58	2.03	0.65-6.41	18.15	7.27-45.35	<0.0001
		Model 2	1.04	0.28-3.89	1.0	0.88	0.21-3.68	1.88	0.60-5.94	13.83	5.48-34.86	<0.0001
	Placebo	Model 1	1.89	0.45-7.91	1.0	2.85	0.71-11.39	3.30	0.85-12.78	40.05	12.62-127.13	<0.0001
		Model 2	2.00	0.48-8.42	1.0	2.92	0.73-11.70	3.21	0.83-12.47	35.06	10.97-112.07	<0.0001

Model 1: adjusted for age. *Model 2*: Additionally adjusted for BMI, smoking, BP, hypertension, cholesterol (HDL & LDL), triglycerides, nitrates use, history of angina and social deprivation score (DEPCAT), various medications (aspirin, ACE-inhibitors, B-blockers, calcium channel blockers, diuretics, other).

FPG: fasting plasma glucose; Q: quintile; HR: hazard ratio; CI: confidence interval; CVD: cardiovascular disease; CHD: coronary heart disease.

Figure 3.3. Risk of cardiovascular disease over 15 years compared to risk of diabetes over 5 years by baseline fasting plasma glucose levels in WOSCOPS (fully adjusted model)*



*note that Q1, Q3, Q4, Q5 data are all compared to referent Q2 (FPG >4.3-4.6mmol/L) whereas cardiovascular (CVD) risk for baseline diabetic patients is compared to all individuals without diabetes at baseline

3.4 Discussion

Analysis of the relationship between FPG and both cardiovascular events and all-cause mortality in western men in WOSCOPS demonstrated that FPG in the non-diabetes range was not associated with increased risk of cardiovascular events, coronary heart disease death, or all-cause mortality. As might have been expected, participants with a history of diabetes or biochemically confirmed new-onset diabetes at baseline were at increased risk of cardiovascular disease. In stark contrast to the lack of association of FPG with cardiovascular events and mortality in those without diabetes at baseline, there was a substantial and independent increase in the risk of new diabetes in participants in the highest quintile of FPG. These data demonstrate that an elevated FPG level in the non-diabetic range is a powerful risk marker for developing diabetes in the future but not for cardiovascular events over as long as 15 years of follow-up.

The relationships between various measures of glycaemia in individuals without diabetes and the development of cardiovascular disease have received much attention recently and led to important publications since the publication of these WOSCOPS results. The measures of glycaemia studied have included not only FPG but also post-prandial glucose and Haemoglobin A1c (HbA1c), a component of circulating haemoglobin which provides information on circulating glucose levels over the last two to three months. WOSCOPS did not include measurements of either HbA1c or post-challenge glucose. It is important to provide the context to the WOSCOPS results by also describing available data for post-prandial glucose and cardiovascular disease.

Post-prandial glucose: The best data available to assess any link between post-prandial glucose levels and subsequent cardiovascular events come from a manuscript combining results from both the population-based Reykjavik study (Iceland) and a linked meta-analysis of fifteen cohorts (81). The Reykjavik study had access to 1 hour post-prandial glucose levels, rather than the more typical 2 hour samples, but had the considerable advantages of considerable power (18,569 participants with 4,664 coronary events) and lengthy follow-up (23.5 years). The HR for coronary events in non-diabetic individuals was modest at 1.03 (1.01-1.05) per 1 mmol/L higher post-load glucose in analyses adjusted for

most established cardiovascular risk factors. In the linked meta-analysis of 15 cohorts with 12,652 coronary events in 102,382 participants, the HR for coronary events was slightly higher at 1.05 (1.03-1.07) per 1 mmol/l higher post-load glucose (81). There is therefore a significant but modest independent relationship between post-prandial glucose and risk of coronary heart disease.

HbA1c: In a separate meta-analysis of HbA1c data accompanying the Reykjavik study (81), 1% higher HbA1c was associated with 20% higher coronary risk in those without diabetes, an appreciably stronger relationship than has been observed for either fasting or post-prandial glucose. Also, in the Atherosclerosis Risk in Communities (ARIC) study, participants with no history of diabetes and with baseline HbA1c 5.5-5.9%, 6.0-6.4% and ≥6.5% had 23%, 78% and 95% higher risk of coronary events respectively than those with HbA1c 5.0-5.4% in a multivariable-adjusted model (82). The available evidence therefore suggests that HbA1c has a stronger relationship with subsequent vascular risk. Despite this stronger relationship, addition of HbA1c to algorithms predicting vascular risk appears to yield minimal improvement in predictive capability. Using the EPIC-Norfolk cohort, Simmons and colleagues addressed this question of risk prediction (83). Over 8.5 years in the 10,295 participants, AUROC for the Framingham risk score was not improved with addition of HbA1c for women (0.80 for Framingham analyses with and without HbA1c) and AUROC was only minimally improved for men (0.72 without HbA1c and 0.73 with HbA1c). Similarly, data from the ARIC study showed a statistically significant but limited improvement in the prediction of cardiovascular disease with the addition of HbA1c to multivariable prediction models (82). Addition of HbA1c to the ARIC prediction model led to a modest improvement in the net reclassification index for coronary heart disease prediction but for neither ischaemic stroke nor all-cause death. It also had little impact in models already containing conventional cardiovascular risk factors and FPG.

Fasting glucose: two large datasets have recently published data on fasting glucose and cardiovascular disease. Data from Sarwar et al's meta-analysis of 255,171 non-diabetic participants from 23 cohorts with 10,808 cases of coronary heart disease concluded that the relationship is of borderline significance (HR 1.06 [1.00–1.12] per 1 mmol/l higher fasting glucose). In recently published

Emerging Risk Factor Collaboration (ERFC) data (84), vascular risk was lowest in those with a FPG of 3.9-5.6mmol/L and a J-shaped relationship was evident. Those with FPG 5.6-6.1mmol/L were at 11% (HR 1.11 [1.04-1.18]) higher risk and those with FPG 6.1-7mmol/L at 17% higher risk (HR 1.17 [1.08-1.26]) in analyses adjusted for age, smoking status, BMI, and systolic blood pressure. In ERFC, addition of either FPG or IFG status to a vascular risk prediction model did not significantly improve risk prediction (84). ERFC results are summarised in Figure 3.4. Of note, very few studies in these large datasets have had follow-up durations as long as WOSCOPS.

Prior to publication of the ERFC meta-analyses and Reykjavik study with its meta-analysis, other studies investigating potential associations between FPG <7.0 mmol/L and incident cardiovascular events had produced variable results. The WOSCOPS results are in disagreement with meta-analyses of this earlier literature and many of the early studies (72). However, many of these earlier studies included patients who, by current definitions, had diabetes at baseline, and reporting of data may have been subject to some small study publication bias. A recent report in 652,901 Korean men, linked to national databases and followed up for 9 years, concluded that FPG had little if any association with the risk of subsequent myocardial infarction, and that the risk of ischaemic stroke was only clearly increased when FPG was ≥6.5 mmol/L (adjusted for classical risk factors) (75). This population of Asian men is dissimilar to western populations as seen by the rates of myocardial infarction and stroke (stroke rate is considerably higher in the Korean cohort); however, their results are broadly consistent with WOSCOPS.

It has long been known that the risk of both cardiovascular disease and mortality is higher in subjects with diabetes than in those without diabetes (84). This observation was confirmed in WOSCOPS, and the observed risk levels are of a similar magnitude to those recently reported in national Scottish record linkage studies (85). This lends external validity to the observations.

Wide appreciation of the association between diabetes and the risk of cardiovascular disease and mortality has prompted interest in the potential role of plasma glucose as a mediator of vascular disease. There are many theoretical

pathways for glucose (usually at very high concentrations) to mediate increased risk (e.g. inhibition of vascular smooth muscle cell apoptosis (86), stimulation of inflammation and oxidative stress, LDL oxidation, and increased thrombotic potential (87)). In addition, there has been intense interest in the use of intensive glucose-control therapy among people with diabetes to potentially reduce vascular risk. The relevant trials have produced mixed results with the exception of reductions in coronary events that were consistently observed in all trials (88). It is possible both in people with diabetes and those free from it that HbA1C and post-prandial glucose are better markers of cardiovascular risk than FPG. Based on the combined literature and new large meta-analytical data, however, even if the risk associations for these two markers are considerably stronger than for FPG, they are unlikely to add meaningfully to cardiovascular risk prediction (82;84).

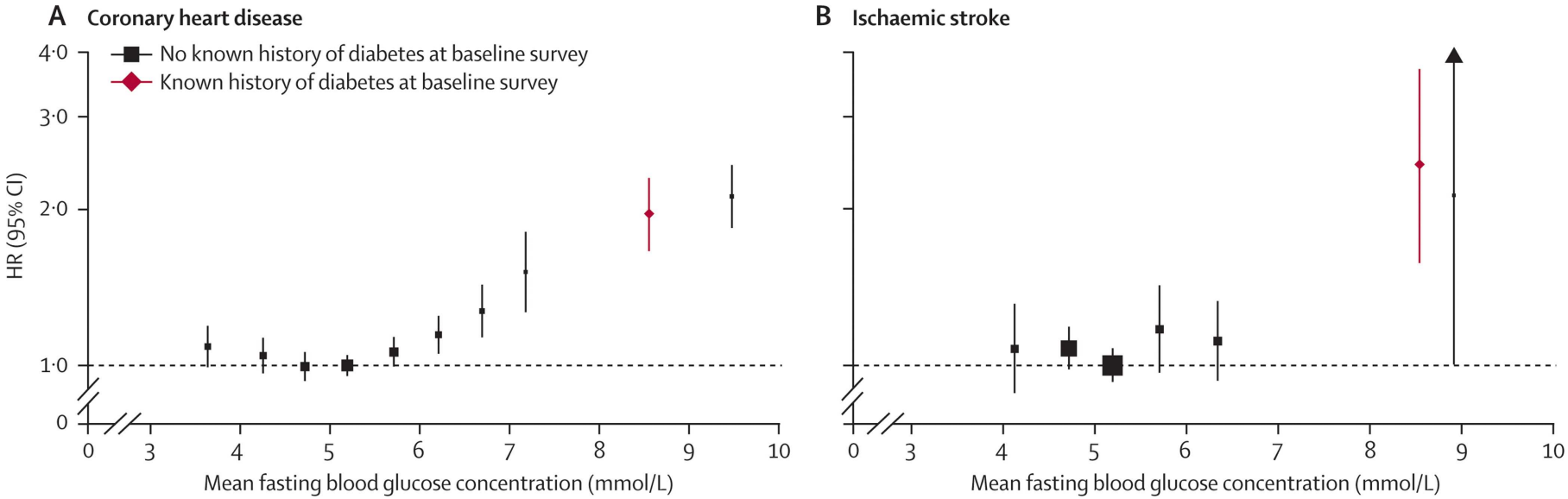
The WOSCOSPS analyses have numerous strengths, including the use of a well-characterised cohort without history of cardiovascular disease or diabetes, a fifteen year follow-up period allowing for study of any legacy effect by FPG, a standardised method for identifying the relevant clinical endpoints, and a large number of incident events thereby providing considerable power. Despite having only 5 years of follow-up for new-onset diabetes data, this was easily sufficient to demonstrate the clear contrast in the importance of elevated FPG for the development of cardiovascular disease and diabetes. It is also necessary to highlight some weaknesses in the data. Data were not available for women, only men, and although another group has recently reported broadly consistent results in cohorts of women (76), it is possible that vascular risk does increase in women at lower levels of FPG (89). The WOSCOPS database is taken from a statin trial conducted specifically in hypercholesterolaemic men with no history of myocardial infarction, implying that this patient group may not reflect the variation found in unselected populations; however, there was no clear interaction of statin allocation on associations of FPG with the risk of the various endpoints, baseline randomisation was adjusted for where required, and there is no established association between total cholesterol and glycaemia anyway. The WOSCOPS dataset may have lacked the necessary power to demonstrate a weak association between IFG and vascular events. Finally, although the WOSCOPS analyses may examine associations or lack thereof between glucose and

cardiovascular disease, causality cannot be proved or disproved in a prospective study of this nature. Regardless, it would appear that FPG levels in the non-diabetic range have either no relationship with the risk of subsequent cardiovascular events or possibly a very weak association at the upper end which, if incorporated into risk prediction algorithms, will not enhance risk prediction.

In conclusion, results from WOSCOPS investigating any link between FPG levels in the non-diabetic range and incident cardiovascular events and mortality suggest that no significant association exists in this white western male population. Consequently, the current FPG threshold for diagnosing diabetes therefore appropriately identifies western men at elevated risk of not only microvascular disease, but also cardiovascular disease.

The data provided in this chapter were published in the European Heart Journal in 2010 (90).

Figure 3.4. Hazard ratios for coronary heart disease and ischaemic stroke by baseline fasting blood glucose concentration in the Emerging Risk Factor Collaboration



Taken from Sarwar et al. (84) and reproduced with the permission of Elsevier ©

HR: hazard ratio; CI: confidence interval

Chapter 4.

Statins and risk of incident diabetes: a collaborative meta-analysis of randomised placebo- and standard care-controlled statin trials

4.1 Introduction

Statins are the most prescribed medications worldwide. In England, there were one million statin prescriptions per week in 2008 with an estimated third of the population aged >45yr on a statin (91). Statin therapy is effective for reducing the risk of cardiovascular events and its efficacy is related to a reduction in LDL-cholesterol levels (20). Statin therapy is also generally recognised as being safe and well tolerated apart from myalgia and myopathy. A recent article from a large British General Practitioner database has claimed that statin therapy increases the risk of developing a wide range of complications including, somewhat unexpectedly, cataracts and other side-effects (92). However, such analyses are clearly severely weakened by their design which compares patients receiving statins to those not on statins, inevitably very different populations, and the inability to account for all confounding factors including, for example, confounding by indication. The most powerful method to properly investigate the possibility of medication-induced side-effects is by examining datasets from large randomised trials and by performing meta-analyses of large randomised trials.

One issue that has received attention recently is the possibility that statin therapy may influence the chance of developing diabetes. Prior to 2010, only six large placebo- and standard care-controlled statin trials had published data on the development of diabetes with the result that definitive conclusions could not be drawn. This was demonstrated by a meta-analysis published in 2009 which included only this previously published data (93) (see Figure 4.1). While the possibility that statins may cause some patients to develop diabetes had not been seriously considered before 2008, the publication of the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) (22), a placebo-controlled trial of rosuvastatin in patients at apparently low cardiovascular risk, raised this issue. JUPITER included 17,802

adult patients, none with any history or biochemical evidence of diabetes (based on FPG concentrations), and followed them up for a median of 1.9 years until the study was prematurely discontinued when the trial met a pre-specified stopping rule due to cardiovascular benefit. However, analysis of the development of diabetes which was a prespecified secondary analysis revealed that 25% more cases of diabetes occurred in the rosuvastatin-treated arm. This was not expected by the investigators who had hypothesised that treatment with rosuvastatin may actually reduce future diabetes risk.

The hypothesis that statin therapy may influence diabetes risk was initially introduced by another statin trial, WOSCOPS, in which middle aged hypercholesterolaemic men with no history of myocardial infarction were randomised to pravastatin or placebo and followed up for 5 years (14). A publication of WOSCOPS data in 2001 found that pravastatin therapy was associated with a reduction in new-onset diabetes of 30% though event numbers were relatively small (94).

Of the other four trials which had previously published results on new-onset diabetes, none found any significant effect (50;95;96). Interestingly, three of the four yielded non-significant 15% higher risks for developing diabetes on statin therapy. Although the other trial, Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) (40), found a non-significant lower risk of diabetes on pravastatin, it is important to realise that this finding was based on only those patients who were normoglycaemic at baseline.

It is already well established that other commonly prescribed cardiovascular risk lowering agents can have an effect on the development of diabetes. On the one hand, thiazide diuretic therapy and beta-blockers are known to elevate diabetes risk (16;17) and nicotinic acid, an HDL-cholesterol raising agent, can also lead to a deterioration in glycaemic control in diabetes (18). Clearly this does not and should not mean that these agents are not prescribed where relevant, as their cardiovascular efficacy is well established. On the other hand, ACE-inhibitors and ARBs reduce the risk of future diabetes (19).

These mixed findings for statins and new-onset diabetes have led to calls for a systematic evaluation of the possible effect of statin therapy on new-onset diabetes (97). It is clearly of major public health importance to neither over-estimate clinical benefit nor under-estimate risk to patients. Consequently I, in conjunction with colleagues, planned a collaborative meta-analysis of large placebo-controlled and standard-care controlled statin trials to resolve this uncertainty.

Figure 4.1. Meta-analysis of the effect of statin therapy on the development of diabetes using only previously published data

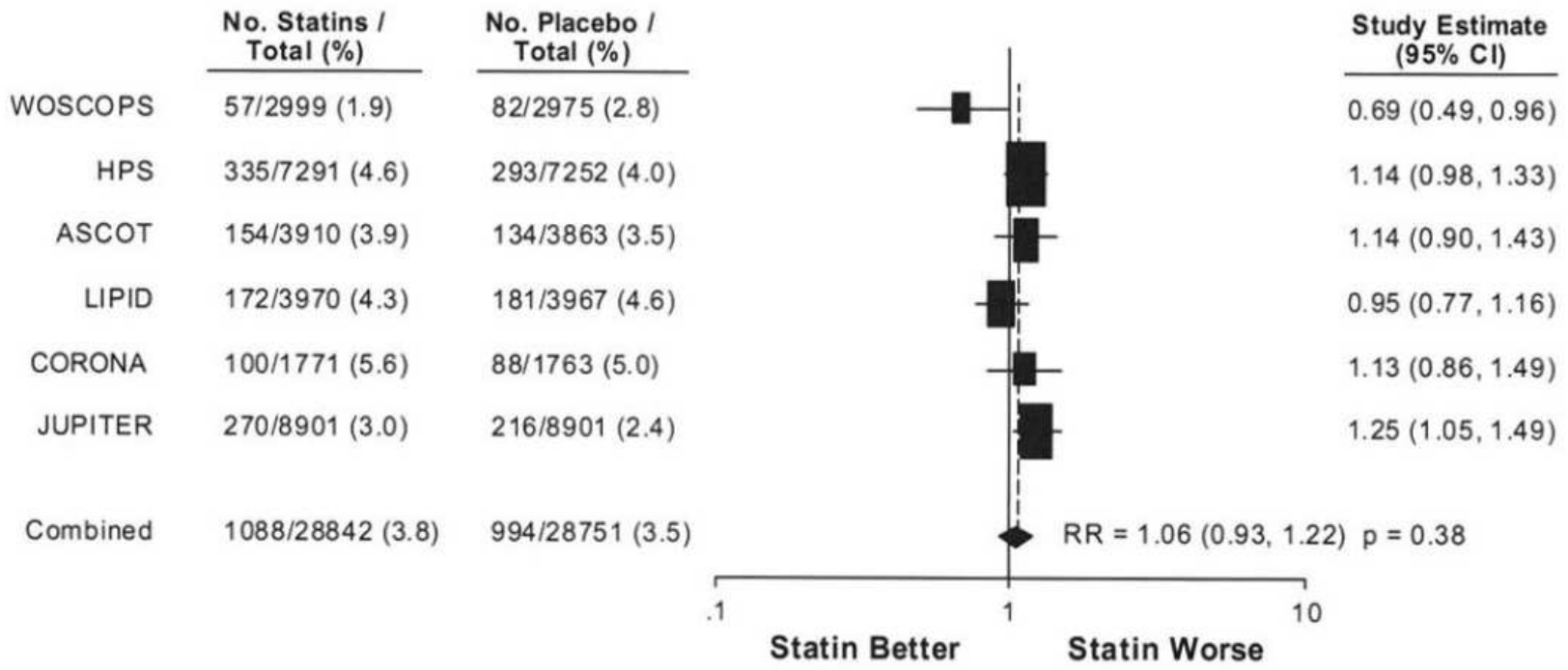


Figure taken from Rajpathak et al (93); reproduced with permission of the American Diabetes Association

CI: confidence interval

4.2 Methods

Aim of the analysis

The aim of this meta-analysis was to establish whether statin therapy has any impact on the development of diabetes. This was achieved by combining both published and unpublished data from large statin trials in a meta-analysis, the first to fully address this question.

Selection criteria for trials

I gathered data from all relevant large placebo-controlled and standard care-controlled endpoint trials that were specifically designed to evaluate the effect of statin therapy on cardiovascular events and/or mortality. Specifically, trials with >1000 patients and with follow-up longer than one year were sought, consistent with other large meta-analyses (20). Features which rendered trials unsuitable included inclusion of clinically unstable patients (defined as patients undergoing organ transplant or haemodialysis), trials in patients with pre-existing diabetes, trials of different statin doses and trials in which the primary outcome was a change in a surrogate marker of cardiovascular disease. Given the nature of the endpoint namely new-onset diabetes, which theoretically is partially subject to the frequency and nature of participant follow-up, trials also needed to follow up patients in both treatment arms identically.

Literature Search strategy

The literature study is summarised in the flow diagram (Figure 4.2). On January 8th 2009 I searched Medline, Embase and the Cochrane Central Register of Controlled Trials, from 1994 to 2009, to identify relevant trials. The start date of 1994 was chosen given that the first large scale statin trial, the Scandinavian Simvastatin Survival Study (4S), was published in 1994 (98). The word "statin" was used as title word and keyword for the search and the search was supplemented by using the names for specific statins: "rosuvastatin, "atorvastatin", "simvastatin", "pravastatin", "fluvastatin" and "lovastatin". Trials were limited to those including only adult patients and only those

published in English. Relevant data had previously been published in six trials, representing the minority of potentially relevant trials.

Data sources

Data searches revealed six statin trials which had previously published data on the development of diabetes stratified by randomised treatment (22;40;94-96;99). For these published trials, information regarding the number of non-diabetic patients at baseline was abstracted together with the number developing diabetes, baseline BMI, baseline age, baseline LDL-cholesterol and change in LDL-cholesterol during the trial.

As it was clear that the majority of large statin trials had not published data regarding development of diabetes, both Professor Naveed Sattar and I contacted investigators from nine additional statin trials with a Data Collection Sheet (see Figure 4.3) (98;100-107), requesting their participation in a collaborative meta-analysis (data from one trial, Prospective Study of Pravastatin in the Elderly at Risk [PROSPER] (108), was already made available by the Robertson Centre for Biostatistics, University of Glasgow). Investigators from six trials agreed to this request (98;100-104). For the remaining three trials from whom data were not received, one trial's investigators expressed a desire to collaborate but did not have access to the relevant data (Cholesterol And Recurrent Events Study [CARE]) (107), one trial's investigators declined the request though the data have subsequently been published (Stroke Prevention by Aggressive Reduction in Cholesterol Levels [SPARCL]) (105), and investigators from the third trial failed to issue a response (Lescol Intervention Prevention Study [LIPS]) (106). Questions in the Data Collection Sheet were about the number of participants at baseline without a history of diabetes, the number developing diabetes, the relative change in LDL-cholesterol during the trial (stratified by treatment arm), baseline BMI, age and the methods available to diagnose diabetes.

In accordance with recent Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (109;110), a checklist of PRISMA criteria was completed and is provided in Table 4.1.

Diagnostic criteria for new-onset diabetes

The various trials with unpublished data had access to slightly different methods for diagnosing diabetes, given that the trials were originally designed to assess cardiovascular benefit and not new-onset diabetes. The general diagnostic criteria for diabetes required that a participant must satisfy one or more of the following:

- Commencement of glucose lowering medication during the trial
- Adverse event report of new-onset diabetes during the trial
- Elevated FPG during the trial: at least one FPG result per patient was available for all trials with previously unpublished data but these were measured at different time intervals according to trial protocols. Therefore variable numbers of participants might be concluded as developing diabetes depending on the frequency of measurement and the requirement for either one or two elevated glucose values. In an attempt to approach expected rates of incident diabetes, it was stipulated that trials which measured FPG every six months (or more often) must use two FPG values ≥7.0mmol/L as a diagnostic criterion for diabetes, but that in trials where FPG was measured less frequently, one elevated glucose ≥7.0mmol/L was sufficient to confirm a diagnosis of diabetes. The rationale behind this approach was supported by data from the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) trial (100); using only a single elevated glucose value provided implausibly high diabetes rates. Using the approach described above, however, yielded diabetes incidence rates close to what would be expected normally.

Reanalysis of previously published data was carried out for WOSCOPS. A paper published in 2001 showed that pravastatin therapy in WOSCOPS was associated with significantly fewer cases of new-onset diabetes (94). However, this analysis employed non-standard diagnostic criteria for diabetes, namely the requirement that a follow-up FPG must be >2.0mmol/L higher than baseline FPG. In an attempt to standardise criteria, WOSCOPS data were reanalysed using standard

criteria as described above and the requirement for a >2.0mmol/L rise in FPG was dropped.

Quality assessment

An established tool (111) was used to independently evaluate the quality of each trial. Nine characteristics were assessed: randomisation, concealment of treatment allocation, similarity of groups at baseline, eligibility criteria, blinding of (i) outcome assessors (ii) patient and (iii) care provider to allocated treatment, point estimates, and intention-to-treat analysis thereby allowing each trial to be awarded a Delphi score of 0 (poorest quality) to 9 (highest quality). Disagreement was resolved through consensus and discussion with colleagues.

Statistics

Weighted mean follow-up duration was calculated for the combined dataset. Only three of the six trials with previously published data on incident diabetes had published the data as a HR. Consequently, it was necessary to adopt a standard approach across all the trials by calculating an odds ratio (OR) (with 95% CI) for developing diabetes on a statin. An overall OR was calculated for the pooled data using a random effects meta-analytical method which assumes that the true underlying effect varies between trials. This approach is more defendable than using a fixed effects meta-analysis which provides a less conservative estimate and potentially misleadingly narrow CIs. Statistical heterogeneity of results between trials was assessed with the I^2 statistic, derived from Cochran's Q [100 X (Q-df/Q)] (112), which provides a measure of the proportion of overall variation that is attributable to between-trial heterogeneity.

Meta-regression analyses were employed to investigate potential sources of heterogeneity between trial results i.e. to explain why trials might produce varying results, other than by chance. Factors that were investigated by meta-regression were baseline age, baseline BMI and change in LDL-cholesterol during the trial; these three factors were selected as they represent either diabetes

risk factors (age, BMI) or can provide insight into a dose-dependent effect of statin therapy (LDL-cholesterol change) and they were selected *a priori*. Due to the relatively small number of trials (n=13), it was not statistically defendable to analyse additional factors. To test for publication bias, a funnel plot was generated and the Egger test performed (113); however, these approaches were of limited use as almost all relevant data had been included.

Although five different statins were studies in the thirteen trials, it was deemed appropriate to combine their results based on homogeneity of effect (20) and the results eventually obtained. Individual statins were evaluated in sensitivity analyses. The following sensitivity analyses were also undertaken:

- Meta-analysis of only those trials which included measurement of FPG
- Meta-analysis of only placebo-controlled trials (i.e. excluding trials with a standard care group as control arm)
- Meta-analysis of all trials except JUPITER (22), the hypothesis-generating trial
- Meta-analysis of all trials except MEGA (100) which included only Japanese subjects
- Meta-analysis of trials of hydrophilic statins, namely pravastatin and rosuvastatin
- Meta-analysis of trials of lipophilic statins namely atorvastatin, simvastatin and lovastatin.

In an attempt to express the effect of statin therapy in absolute terms and to allow comparison to cardiovascular benefit, the number of patients developing diabetes per 1000 patient years on statin and control therapies was calculated.

Statistical software and Acknowledgement

Statistical analyses were carried out in conjunction with a colleague at the University of Cambridge, Dr Sreenivasa Rao Kondapally Seshasai. Both he and I performed the relevant meta-analyses and sensitivity analyses independently using different software packages. Dr Seshasai used Stata version 10.1 software while I employed Review Manager software. In the published article, figures

provided by Stata are included. Dr Seshasai was responsible for all the meta-regression analyses performed for this project and for all figures in the published manuscript.

Table 4.1. Checklist of PRISMA criteria

Section/Topic	Item	Checklist item	Is this item included in the text?
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	Yes
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	Yes
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	Yes
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design	Yes
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	Yes but not externally registered
Eligibility criteria	6	Specify study characteristics (such as length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	Yes
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	Yes

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Yes
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	Yes
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	Yes
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made	Yes
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	Yes: Delphi score
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	Yes
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	Yes
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	Yes. However, as much of the data were unpublished, the funnel plot is considered of lesser importance.
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	Yes

Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	Yes
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	Yes
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	Yes
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	Yes
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Yes
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	Yes though, as noted above, funnel plot of limited use as much of the data are unpublished
Additional analyses	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	Yes
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy	Yes

		makers)	
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	Yes
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	Yes
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	No external funding

Figure 4.2. Flow diagram of literature search to identify new-onset diabetes in large statin trials

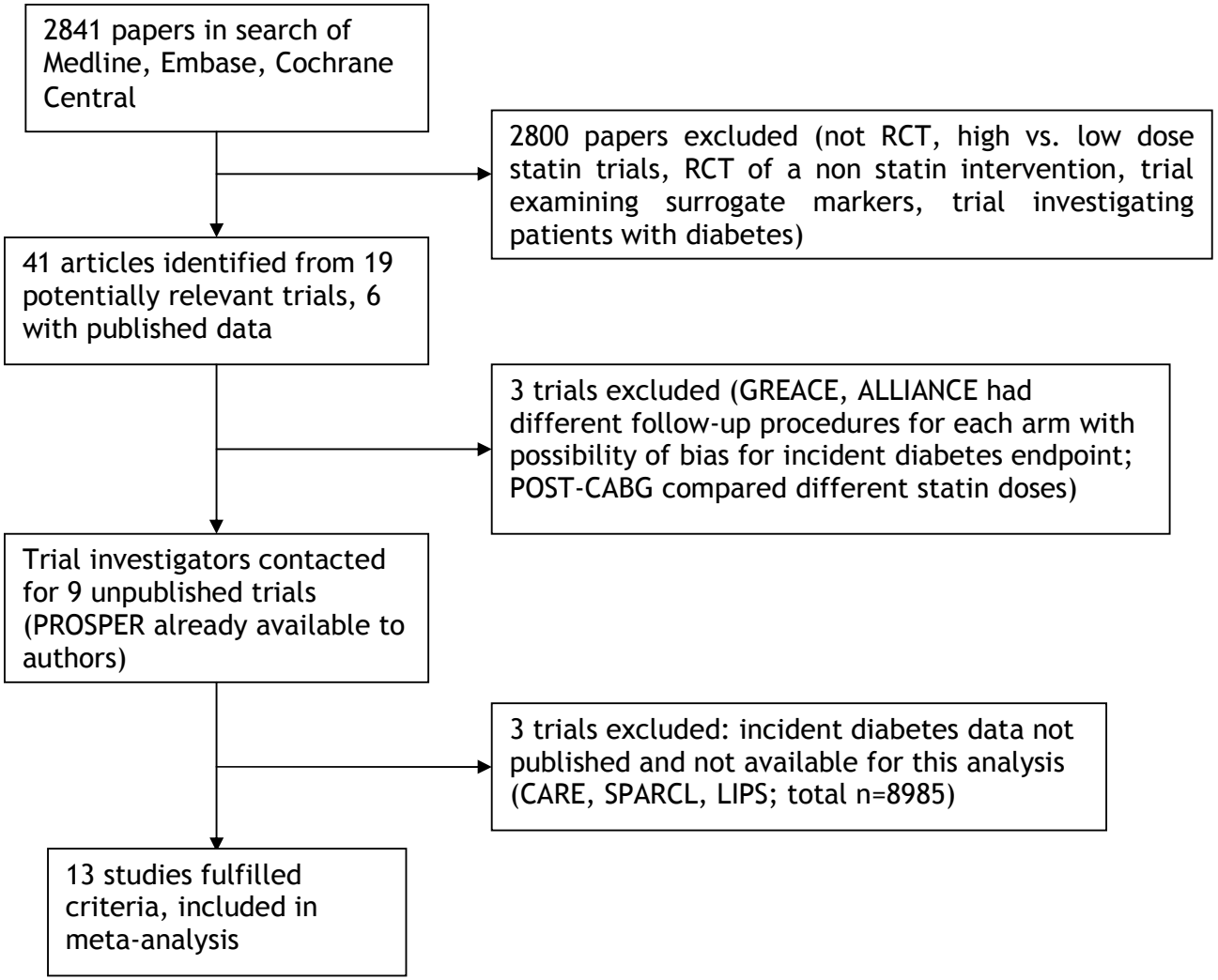


Figure 4.3. Formal Question Sheet used to request data from statin trials with unpublished data

From N Sattar, D Preiss and colleagues – WOSCOPS/PROSPER groups

Data request for statin-incident diabetes meta-analysis:

Dear colleague, thank you for considering our proposal to join the above meta-analysis. The following is a summary of the data required to enable us incorporate data from your trial into the meta-analysis.

1. Total number of non-DM subjects at baseline ___
    a. numbers allocated to placebo ___
    b. numbers allocated to Statin ___

2. Number developing diabetes in each group: placebo___ and statin ___

3. Methods of diagnosis of diabetes: which of the following used? (Please tick as appropriate)
    a. Physician reported ____
    b. Drugs or insulin ___
    c. Biochemistry ___ (criteria used?)

4. Mean age of all non-DM participants at baseline___

5. Mean BMI of all non-DM participants at baseline___

6. Mean LDL-cholesterol at:

    a. Baseline: placebo___ and statin ___
    b. End of study, or fixed time during study: placebo ___ and statin ___

4.3 Results

Data from 13 large statin trials were included in this meta-analysis. Trials were of high quality with a median Delphi score of 9 (range 6-9) (Table 4.2). The available data for patients with no history of diabetes at baseline in these trials are detailed in Table 4.3. Brief details of the trials which are relevant to this analysis are provided below.

The Trials

- Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA) (96): this placebo-controlled double-blinded randomised trial compared Atorvastatin 10mg daily to placebo in patients with hypertension and cardiovascular risk factors but no history of coronary heart disease

- Heart Protection Study (HPS) (99): this impressively large placebo controlled double blinded randomised statin trial compared simvastatin 40mg daily to placebo in patients with a history of cardiovascular disease

- JUPITER (22): this highly publicised placebo-controlled double-blinded randomised trial is the most recently published and compared rosuvastatin 20mg daily to placebo in patients with no history of cardiovascular disease

- WOSCOPS (94): in this placebo-controlled double-blinded trial, male participants with hypercholesteraemia and no history of myocardial infarction were randomised to pravastatin 40mg daily or placebo

- LIPID (40): participants with a history of myocardial infarction or unstable angina in the preceding three years were randomised to pravastatin 40mg daily or placebo in this controlled double-blinded trial

- Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) (95): this is one of only two previous large scale statin trials conducted in a heart failure cohort, specifically those with New York Heart Association (NYHA) functional classification of heart failure (classes II-IV) and aged >60; treatment arms were rosuvastatin 20mg daily or placebo in this double-blinded randomised trial

- PROSPER (108): in PROSPER, a placebo controlled double-blinded randomised trial, elderly patients (age 70-82 years) with previous cardiovascular disease or at high risk were randomised to pravastatin 40mg or placebo

- MEGA (100): this open-label trial was conducted in Japan and involved Japanese patients with no history of cardiovascular disease but with hypercholesteraemia who were randomised to pravastatin 10-20mg daily or no treatment

- AirForce/Texas Coronary Atherosclerosis Prevention Study (AFCAPS TexCAPS) (104): in this placebo-controlled double-blinded randomised trial, patients with no history of cardiovascular disease were treated with lovastatin 20-40mg or placebo

- 4S (98): this was the first large statin trial to be published; in this placebo-controlled double-blinded randomised trial, patients with a history of prior myocardial infarction or angina were treated with simvastatin 20-40mg or placebo

- Antihypertensive Lipid Lowering Heart Attack Trial – Lipid Lowering Therapy (ALLHAT-LLT) (101): this was an open-label trial comparing pravastatin 40mg daily to no treatment in patients with coronary heart disease or with cardiovascular risk factors

- Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI)–Heart Failure (GISSI-HF) (102): this was the second statin trial conducted in heart failure; patients with chronic heart failure (NYHA II-IV)

were randomised to rosuvastatin 10mg daily or placebo in a double-blinded trial

- GISSI-Prevenzione (103): this open-label trial compared treatment with pravastatin 20mg to no treatment in patients with a history of myocardial infarction in the previous six months; the trial was stopped before its planned end-date

General information

Results were available for 91,140 participants with approximately 364,560 patient years of follow-up. Data for average trial follow-up, for baseline age and BMI, the relative reduction in LDL-cholesterol reduction achieved, the frequency of FPG measurement, and the methods of diabetes diagnosis are provided in Table 4.3. The new cases of diabetes, specified for treatment arms in each trial, are provided in Table 4.4. As discussed in the methods sections, the incidence of diabetes provided confidence in the diagnostic measures that were used as trials with participants at theoretically highest risk for developing diabetes did demonstrate the highest incidences. Of the 13 trials only two, namely JUPITER and PROSPER, demonstrated individually significant associations between statin therapy and incident diabetes. In JUPITER, there was a 26% (4-51%) higher risk of diabetes on statin therapy and in PROSPER a 32% (3-69%) higher risk. The other trials had non-significant results with four giving an OR <1 and seven an OR >1.

Pooled results for statins and new-onset diabetes

In the combined cohort of 91,140 patients, 45,521 (49.9%) were treated with statins and 45,619 (50.1%) with control therapy. Over a weighted mean follow-up period of 4 years, 4,278 developed diabetes consisting of 2,226 (4.89% of the cohort) on statins and 2,052 (4.5%) on control therapy. This represents 174 additional cases of diabetes on statin therapy. Expressed in relative terms this equates to 9% (2-17%) higher risk of developing diabetes on statin therapy. Expressed in absolute terms, the additional 174 cases of diabetes on statin therapy can also be expressed as one extra case for every 255 (95%CI 150-852) patients treated for 4 years. Approximately 12.2 cases of diabetes were

diagnosed per 1000 patient years on statin therapy and 11.3 cases of diabetes occurred per 1000 patient years of control therapy. A forest plot of results is provided in Figure 4.4.

Individual statins

Five statins were studied in the 13 trials. Consequently, there were small numbers of studies conducted for any specific statin. For atorvastatin and lovastatin, only one trial was available and results were non-significant. For simvastatin, rosuvastatin and pravastatin, two trials, three trials and six trials were available respectively. Rosuvastatin was the only statin to individually demonstrate a statistically elevated risk of new-onset diabetes (18%). However, CI for all statins overlapped, suggesting that there is no clear difference between agents i.e. a class effect. A forest plot of results for the individual statins is provided in Figure 4.5.

Heart failure trials

When analysing only the two heart failure trials, namely CORONA and GISSI-HF, there were 22 more cases of diabetes in patients treated with rosuvastatin compared to placebo (325 vs. 303). The combined results did not reach statistical significance (OR 1.11 [0.94-1.31]) despite yielding low heterogeneity (I^2=0%), but this analysis lacked power with only 6,912 participants.

Funnel plot

A funnel plot was undertaken to investigate the possibility of publication bias (see Figure 4.6). It should be noted, however, that almost all published and unpublished data were eventually included which renders this analysis less helpful. Overall the data showed no evidence of publication bias either graphically or by the Egger test (p=0.144).

Sensitivity analyses

The following sensitivity analyses were conducted: (i) only placebo-controlled trials (MEGA, ALLHAT-LLT, GISSI-Prevenzione excluded), (ii) only trials which measured FPG post-randomisation, (iii) trials of lipophilic statins, (iv) trials of hydrophilic statins, (v) all trials except JUPITER, (vi) all trials except MEGA (vii) all trials using 99% CI. Results are provided in Table 4.5. While some of these analyses gave nominally non-significant results, all yielded similar ORs of 1.07-1.10 with overlapping CI.

Heterogeneity of results between studies

Heterogeneity, as assessed by the standard I^2 statistic, was low in the combined dataset (I^2=11%) which indicates that most variation between individual trial results was likely attributable to chance. As specified *a priori*, three variables were subjected to univariate meta-regression analyses in an attempt to explain any existing residual risk. These were (i) baseline age, (ii) baseline BMI, and (iii) the relative reduction in LDL-cholesterol. Figures of these analyses are provided (see Figure 4.7.1-3). Of these, only age demonstrated a significant interaction with higher risk of diabetes in trials with older patients (p=0.019). There was no clear evidence of a trend towards higher risk of diabetes in trials which achieved the biggest relative reduction in LDL-cholesterol (p=0.102). BMI did not appear to be an important factor in analyses including (p=0.177) and excluding MEGA (p=0.118).

Table 4.2. Delphi scores for trials included in meta-analysis

Parameter	A	B	C	D	E	F	G	H	I	Total
Trial										
ASCOT-LLA	1	1	1	1	1	1	1	1	1	9
HPS	1	1	1	1	1	1	1	1	1	9
JUPITER	1	1	1	1	1	1	1	1	1	9
WOSCOPS	1	1	1	1	1	1	1	1	1	9
LIPID	1	1	1	1	1	1	1	1	1	9
CORONA	1	1	1	1	1	1	1	1	1	9
PROSPER	1	1	1	1	1	1	1	1	1	9
MEGA	1	0	1	1	1	0	0	1	1	6
AFCAPS TexCAPS	1	1	1	1	1	1	1	1	1	9
4S	1	1	1	1	1	1	1	1	1	9
ALLHAT-LLT	1	0	1	1	1	0	0	1	1	6
GISSI-HF	1	1	1	1	1	1	1	1	1	9
GISSI Prevenzione	1	0	1	1	1	0	0	1	1	6

Delphi parameters (Yes = 1, No = 0)

A. Was a method of randomisation performed?

B. Was treatment allocation concealed?

C. Were randomised groups similar at baseline?

D. Were trial eligibility criteria specified?

E. Was the outcome assessor blinded?

F. Was the care provider blinded?

G. Was the patient blinded?

H. Were point estimates and measures of variability presented for primary outcome measures?

I. Did the analysis include an intention-to-treat analysis?

Table 4.3. Data for non-diabetic participants in thirteen placebo- and standard care-controlled statin trials that reported incident diabetes

	N (all)	N (non-DM patients)	Follow up (years)	Method of DM diagnosis	BMI (kg/m^2)	Age	Relative %LDL-C reduction	FPG after baseline
ASCOT-LLA (96)	10305	7773	3.3∫‡	(i) WHO 1999 criteria	28.6∫	63∫	34.8%∫ (12 month)	12 / 12
HPS (99)	20536	14573	5.0	(i) Physician reported (ii) Medication	27.2	65	29.4% (average in trial)	-
JUPITER (22)	17802	17802	1.9‡	(i) Physician reported	28.4‡	66‡	50% (12 months)	-
WOSCOPS (94)	6595	5974	4.8	(i) Two FPG ≥7.0mmol/L (ii) Medication	25.9	55	23.7% (12 months)	6 / 12
LIPID (40) †	9014	6997	6.0	(i) One FPG ≥7.0mmol/l (ii) Medication	-	62‡	25% (over 5 years)	12 / 12
CORONA (95)	5011	3534	2.7∫‡	(i) Physician reported	27∫	73∫	45.1%∫ (3 months)	-
PROSPER (108)	5804	5023	3.2	(i) One FPG >7.0mmol/L (ii) Medication	26.5	76	30.7% (12 months)	12 / 12
MEGA (100)	7832	6086	5.3	(i) Physician reported (ii) Medication (iii) Two FPG ≥7.0mmol/l	23.8	58.3	17.1% (12 months)	6 / 12
AFCAPS TexCAPS (104)	6605	6211	5.2∫	(i) Physician reported (ii) Medication (iii) One FPG ≥7.0mmol/l	27.0∫	58∫	26.7% (12 months)	12 / 12
4S (98)	4444	4242	5.4‡	(i) Physician reported (ii) Medication (iii) One FPG ≥7.0mmol/l	25.9	58.6	36.7% (12 months)	Study end
ALLHAT-LLT (101)	10355	6087	4.8∫	(i) One FPG ≥7.0mmol/L	29.0	66.4	18.1% (24 months)	24 / 12
GISSI HF (102)	4574	3378	3.9‡	(i) Two FPG ≥7.0mmol/l	26.7	67	34.9% (12 months)	1, 3, 6, 12 / 12 then 12 monthly
GISSI PREVENZIONE (103)	4271	3460	2.0‡	(i) One FPG ≥7.0mmol/L	26.3	59.3	11.5% (12 months)	6, 12 and 24 months
TOTAL	113148	91140	≈4.0	-	-	-	-	-

∫: data from total cohort (including diabetes at baseline), †: includes only subjects with normal fasting glycaemia at baseline, ‡: median.
DM: diabetes mellitus, CVD: cardiovascular disease, CHD: coronary heart disease, MI: myocardial infarction, NYHA: New York Heart Association, BMI: body mass index, FPG: fasting plasma glucose

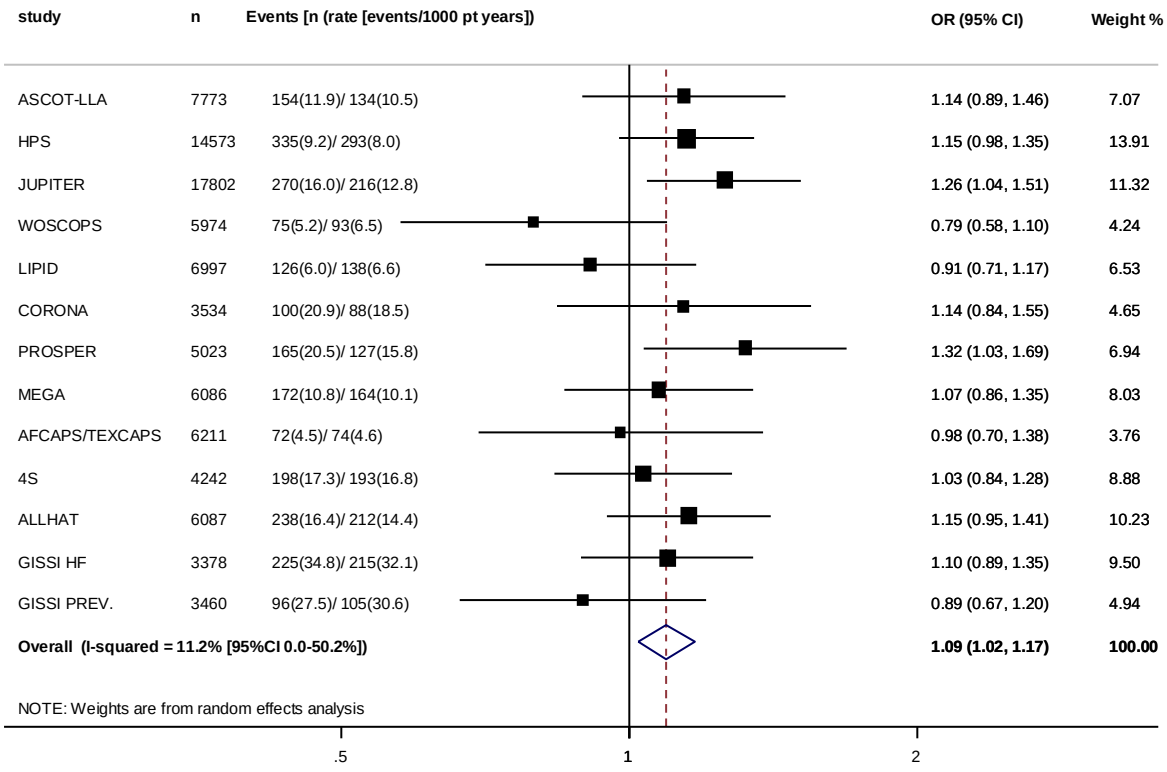
Table 4.4. Numbers of patients developing diabetes on statin and control therapy in thirteen randomised trials

	N (non-diabetic patients)	N on Statin	N on control	New diabetes cases	New diabetes on Statin	New diabetes on control
ASCOT-LLA	7773	3910	3863	288	154 (3.9%)	134 (3.5%)
HPS	14573	7291	7282	628	335 (4.6%)	293 (4.0%)
JUPITER	17802	8901	8901	486	270 (3.0%)	216 (2.4%)
WOSCOPS	5974	2999	2975	168	75 (2.5%)	93 (3.1%)
LIPID †	6997	3496	3501	264	126 (3.6%)	138 (3.9%)
CORONA	3534	1771	1763	188	100 (5.6%)	88 (5.0%)
PROSPER	5023	2510	2513	292	165 (6.6%)	127 (5.1%)
MEGA	6086	3013	3073	336	172 (5.7%)	164 (5.3%)
AFCAPS TexCAPS	6211	3094	3117	146	72 (2.3%)	74 (2.4%)
4S	4242	2116	2127	391	198 (9.4%)	193 (9.1%)
ALLHAT-LLT	6087	3017	3070	450	238 (7.9%)	212 (6.9%)
GISSI HF	3378	1660	1718	440	225 (13.6%)	215 (12.5%)
GISSI PREVENZIONE	3460	1743	1717	201	96 (5.5%)	105 (6.1%)
TOTAL	91140	45521	45619	4278	2226 (4.89%)	2052 (4.50%)

Table 4.5. Sensitivity analyses to further assess the relationship between statin therapy and new-onset diabetes

Specific Analysis	N	Odds ratio for developing diabetes (statin vs. control)	I^2 (heterogeneity)
Entire cohort (n=91140)	91140	1.09 (1.02-1.17)	11
Placebo-controlled trials (MEGA, ALLHAT-LLT, GISSI-Prevenzione excluded)	75507	1.10 (1.01-1.20)	21
Trials which measured FPG post-randomisation (HPS, CORONA excluded)	75033	1.07 (0.97-1.17)	32
Trials of lipophilic statins (HPS, ASCOT-LLA, 4S, AFCAPS TexCAPS)	32799	1.10 (0.99-1.22)	0
Trials of hydrophilic statins (WOSCOPS, ALLHAT-LLT, CORONA, PROSPER, MEGA, LIPID, JUPITER, GISSI-HF, GISSI Prevenzione)	58341	1.08 (0.98-1.20)	36
All trials except JUPITER	73338	1.08 (1.01-1.15)	1.5
All trials except MEGA	85054	1.09 (1.01-1.18)	18
All trials using 99% CI	91140	1.09 (1.00-1.19)	

Figure 4.4. Association between statin therapy and incident diabetes in 13 major cardiovascular trials



*Events per 1000 patient years; † Weights are from random-effects analysis; OR: odds ratio; CI: confidence interval

Figure 4.5. Associations between different statins and development of diabetes

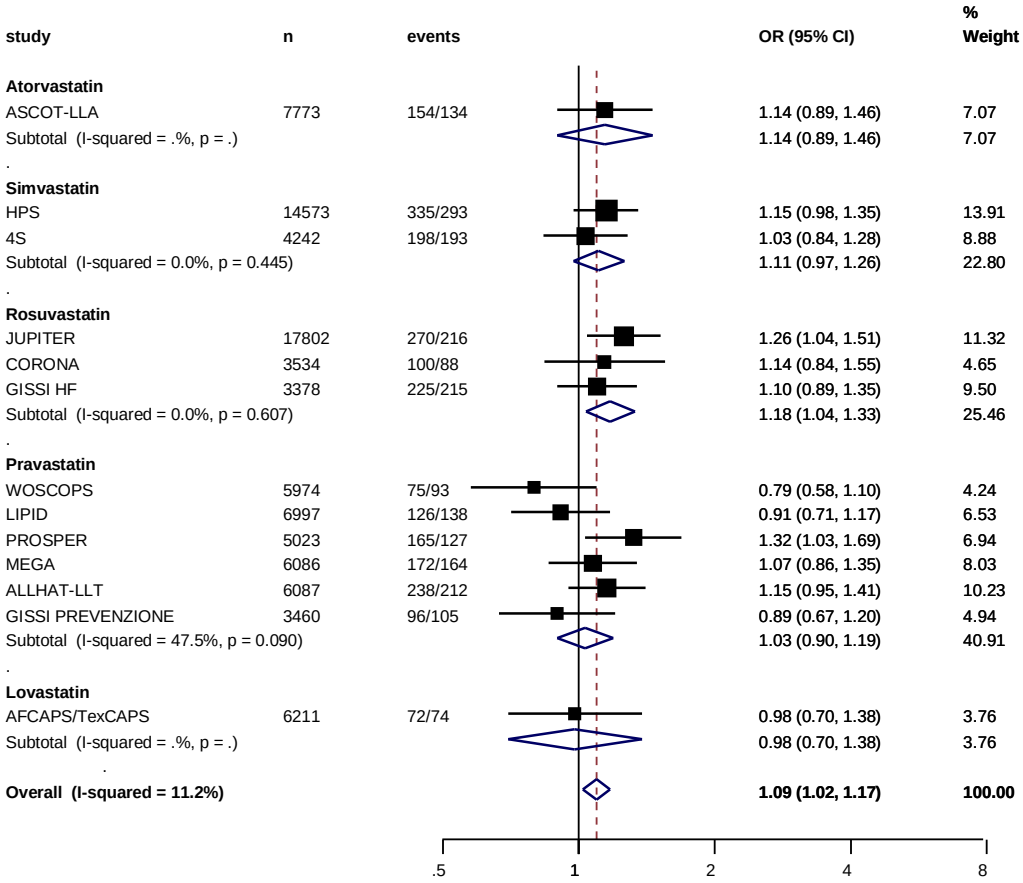


Figure 4.6. Funnel plot to assess the possibility of publication bias (limited to only those six trials with previously published data)

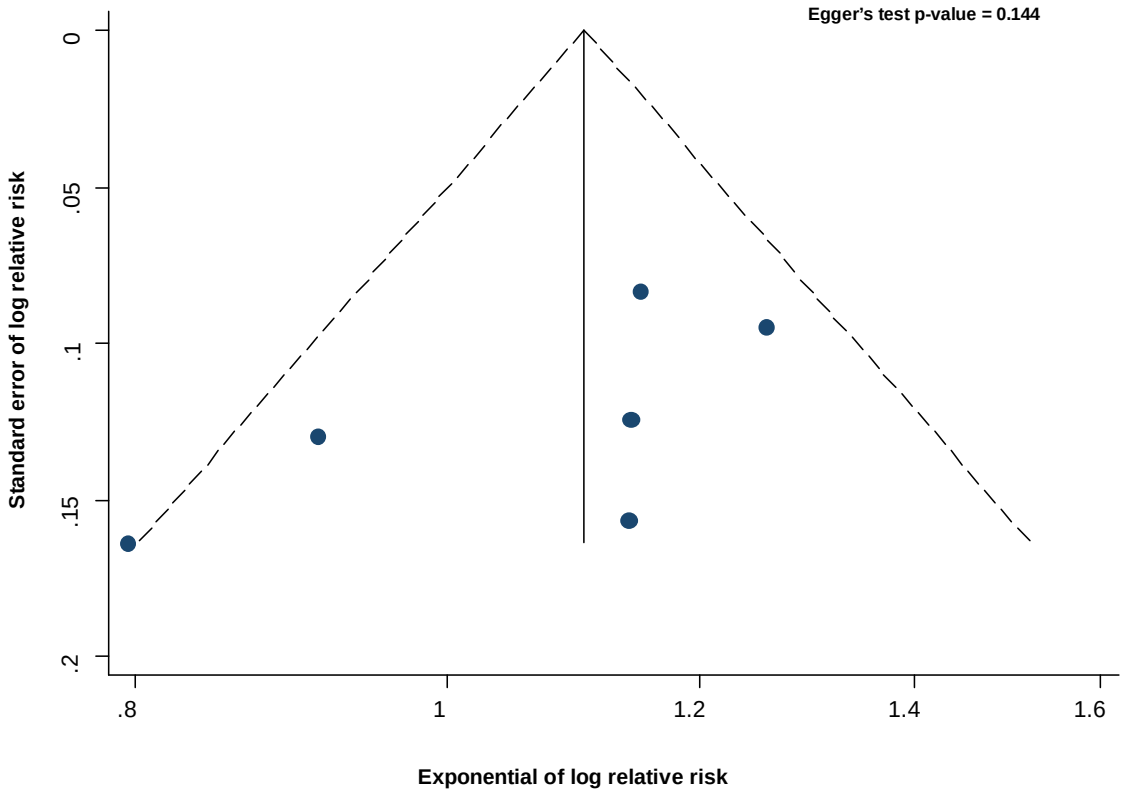
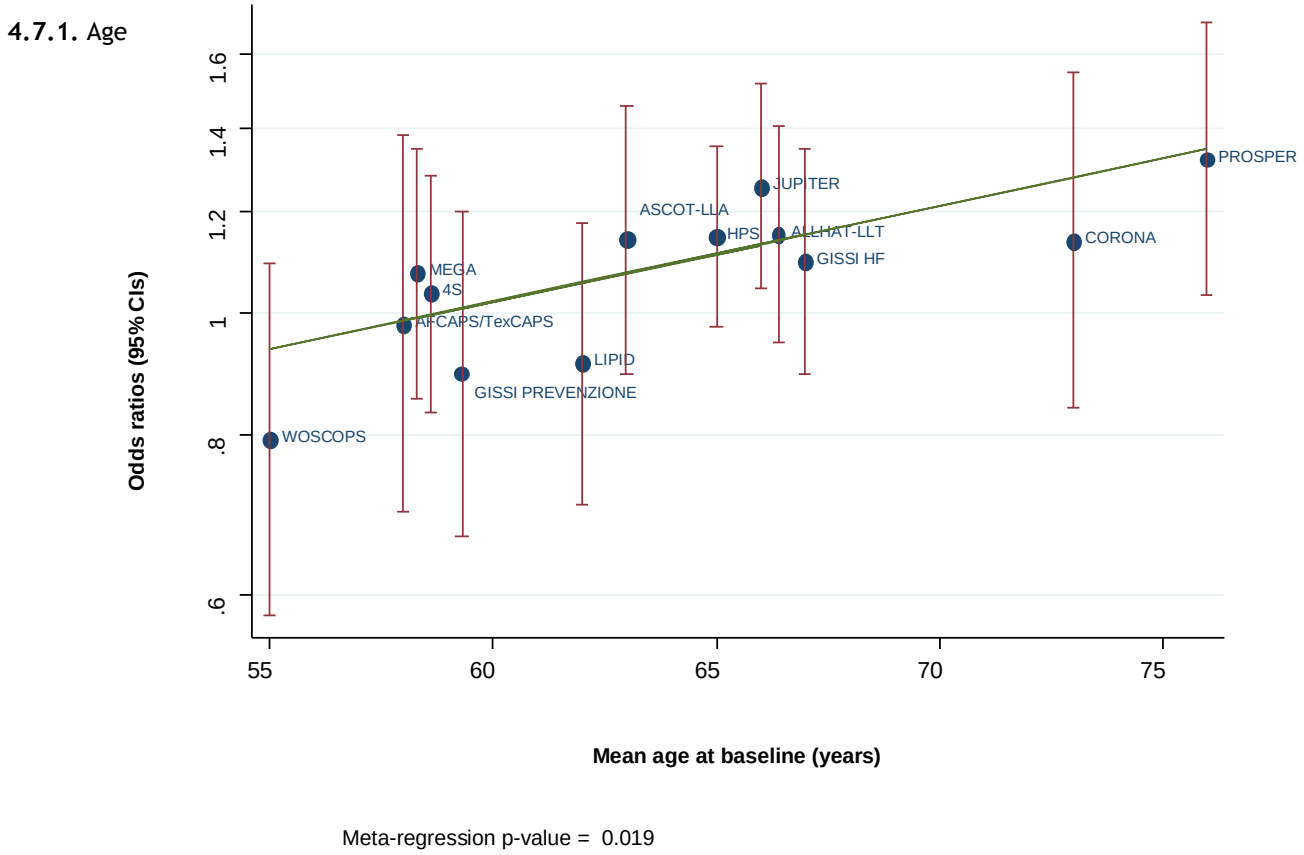
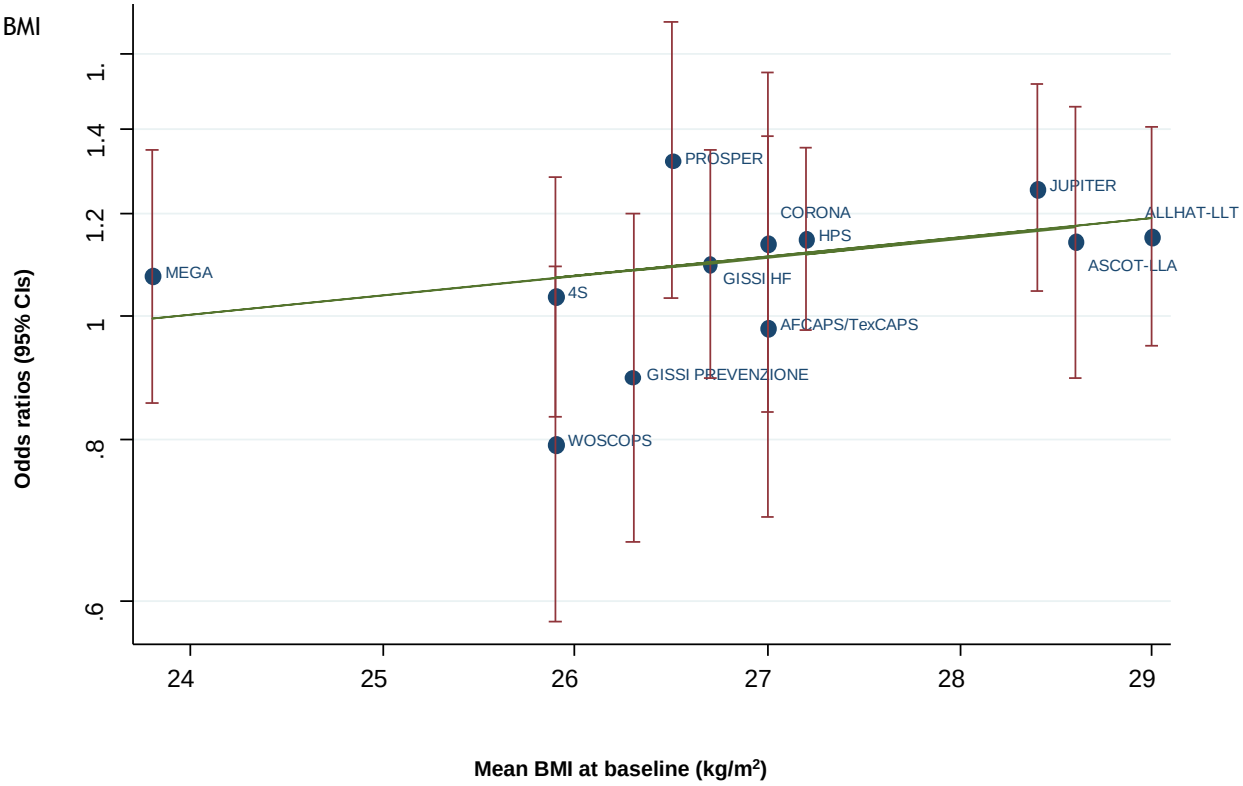


Figure 4.7.1-3. Meta-regression of (4.7.1) baseline age, (4.7.2) baseline BMI, and (4.7.3) on-treatment percentage reduction in LDL-cholesterol concentration for incident diabetes

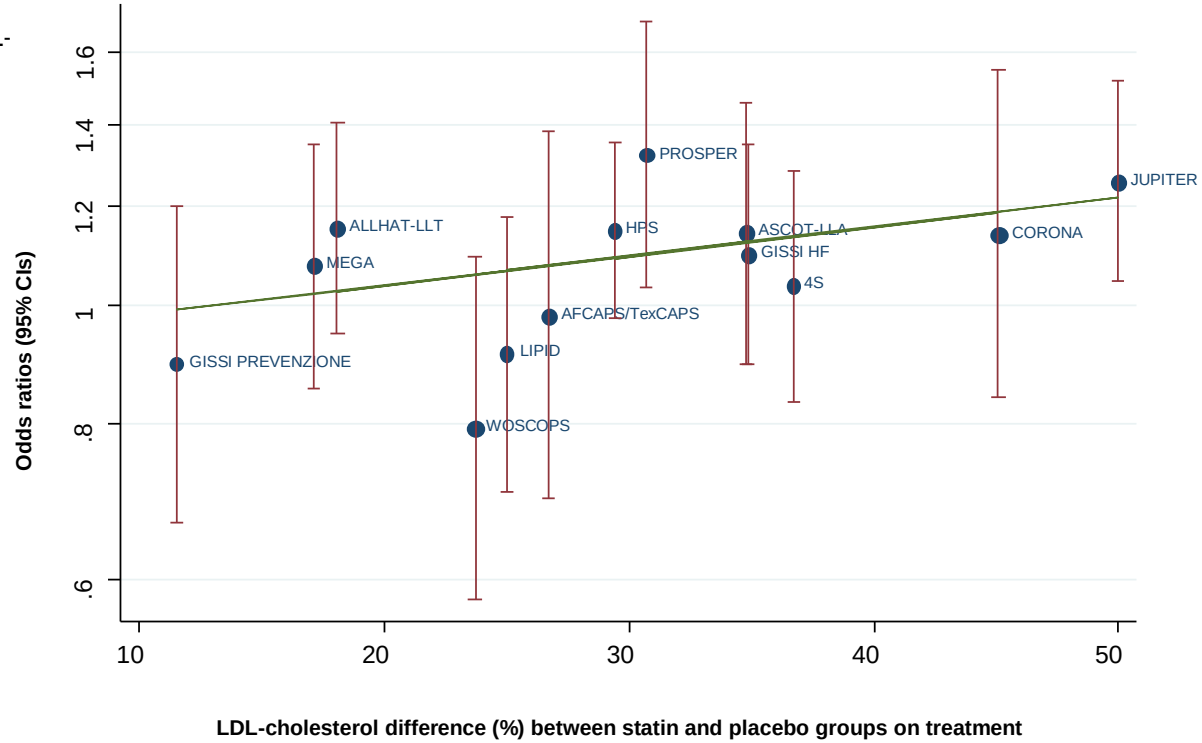


4.7.2. BMI



Meta-regression p-value = 0.177

4.7.3. % LDL-Cholesterol reduction



Meta-regression p-value = 0.102

4.4 Discussion

In this meta-analysis of the large statin trials it was possible to demonstrate that individuals assigned statin therapy were at slightly increased risk of developing diabetes compared with individuals assigned to either placebo or standard care. The risk of new-onset diabetes appeared higher in trials with older participants in a univariate meta-regression analysis. Results from the trials that included FPG measurements and were placebo-controlled were consistent with this novel finding. There was also no apparent difference between hydrophilic and lipophilic statins which both yielded similar association with diabetes risk.

These results do not definitively prove that statin therapy raises diabetes risk via a specific molecular mechanism, but clearly this possibility requires consideration. For example, in one study of the effects of various statins on the glucose-transporter-4, atorvastatin but not other statins appeared to have a detrimental effect on glucose metabolism (114). Conversely, genome-wide scans of type 2 diabetes have not identified an association with genes regulating LDL-cholesterol metabolism or 3-hydroxy-3-methylglutaryl-Co-A reductase, the pathway on which statins act to decrease circulating cholesterol (115;116). Myalgia and myopathy are relatively common side-effects on statin therapy and the possibility that exercise tolerance may be reduced in affected individuals, leading to weight gain and higher risk of developing diabetes, requires further examination. A modest 0.3kg relative weight gain was noted in rosuvastatin recipients compared to placebo recipients in JUPITER (117). While of interest, previous studies suggest that this minor difference cannot explain the 25% higher diabetes risk observed in JUPITER; for example, in both placebo- and metformin-treated participants in the Diabetes Prevention Program, risk of new-onset diabetes over 3.2 years was 11% higher per 1kg increase in weight (118). Another potential explanation for the link between new-onset diabetes and statin therapy is that there are residual confounding factors. These may plausibly include prolonged survival on statin treatment with increased opportunity to develop diabetes, or changing to a healthier lifestyle with resultant weight loss and lowered risk for incident diabetes after cardiovascular events, which are more likely in placebo than in statin treatment groups. Using ORs has the theoretical statistical disadvantage of not factoring in the element of time (i.e.

exact follow-up) which is dependent on compliance with medication and survival. HRs, which do not have the same weakness, were not available in all studies and could not be pooled in this analysis. Nonetheless, extrapolating directly from the Cholesterol Treatment Trialists' (CTT) meta-analysis (20), it can be calculated that for every 1000 patients surviving on statin therapy during trials completed prior to 2005, 984 patients were alive on control therapy, a difference of only 1.6% at the end of the trials. Furthermore, unlike this chapter's meta-analysis, CTT incorporated neither JUPITER (a trial with very few deaths) nor the heart failure trials (CORONA and GISSI-HF) in which death rates were very similar in both trial arms, as these trials were published subsequently. If these were included it would render this difference in survival even smaller. Furthermore, given that deaths occur throughout follow-up, it can be reasonably argued that the difference in total follow-up between statin and control recipients would be half i.e. 0.8%. Consequently, it is highly unlikely that longer follow-up or survival on statins can explain the findings of higher diabetes risk. This issue is examined further in Chapter 5.

A recent publication has also suggested that statin therapy may lead to a deterioration in glycaemia relatively quickly and that higher dose statin therapy has more of an effect (119). In this randomised, single-blind, placebo-controlled parallel study, 44 patients were allocated to placebo and 42, 44, 43, and 40 patients were given daily atorvastatin 10mg, 20mg, 40mg, and 80 mg respectively. Patients were studied over a period of two months. Treatment with atorvastatin 10mg, 20mg, 40mg, and 80mg led to significantly increased fasting plasma insulin levels compared to placebo (25%, 42%, 31%, and 45% increases respectively). Also, HbA1c levels were increased compared to placebo (2%, 5%, 5%, and 5% relative increase respectively on the respective increasing doses of atorvastatin). Finally, atorvastatin 10mg, 20mg, 40mg, and 80mg decreased insulin sensitivity (as estimated by Quantitative Insulin Sensitivity Check Index) by 1%, 3%, 3%, and 4% respectively compared to placebo (119). While this study found that statin therapy had a potentially detrimental impact on glycaemia in a relatively short timeframe, other short-term studies have yielded different conclusions. Three studies conducted in animals and humans suggested that statin therapy may actually have a beneficial impact on insulin sensitivity (120-122). Other studies have found no benefit (123-125). The quality of the study by

Koh is comparably higher than the other studies however, based on the number of participants and study of various statin doses. Nonetheless, this combination of findings suggests that the raised risk of incident diabetes with statins could represent a chance finding. However, such short-term studies are not necessarily informative about long-term risk and it is also important to consider that the heterogeneity of diabetes risks in the various randomised statin trials was low (I^2 11%).

To place these findings in a clinical context, it is best to provide results in absolute terms also, thereby allowing clinicians and patients to better assess the risk: benefit ratio of any new treatment. There were 174 additional cases of diabetes in the combined statin groups. However, this equates to only a small increase of diabetes in absolute terms. The risk appeared small compared to the putative reduction in vascular events. Using data from CTT's meta-analysis of statin trials with 71,370 non-diabetic participants (20), it was calculated that statin therapy led to a reduction in major coronary events (coronary heart disease death and non-fatal myocardial infarction) of 5·4 events per 255 patients treated for 4 years compared with control therapy for a 1 mmol/L reduction in LDL-cholesterol concentration. This composite coronary endpoint also does not take into account the likely benefits in terms of reducing strokes and coronary intervention and therefore the benefit of statin therapy would be expected to be even greater when accounting for these. Importantly, of the 13 trials in CTT with non-diabetic individuals, data are provided for incident diabetes in nine trials; therefore, the estimate of the risk: benefit described above could be slightly inaccurate. Nonetheless the comparison of risk: benefit in this way remains informative. Risk benefit considerations may also differ between specific groups of patients. For example, statin therapy has not shown cardiovascular benefit in two large trials of patients with heart failure (95;102), but risk of development of diabetes while on statins was similarly (in terms of point estimate), though non-significantly, increased in both trials. Therefore, the increase in diabetes may be of more importance in heart failure patients where diabetes is known to lead to poor clinical outcomes (126;127). Results suggest that clinical decision-making need not be changed for patients in whom statin therapy is recommended. It is also relevant to state that 'statin-induced' diabetes may not necessarily carry equivalent micro- and macrovascular risks

compared to the more usual development of diabetes (128). It was not possible to address this question with the available data.

The finding that statin therapy has an influence on both glycaemia (119) and on the development of diabetes (129) is not unusual in the area of cardiovascular prevention. It has previously been shown that numerous antihypertensive agents have contrasting effects on the development of diabetes. It is well established that both thiazides (16) and beta-blockers (17) have detrimental effects on new-onset diabetes. Nonetheless these agents remain important tools for cardiovascular risk reduction. On the other hand, inhibitors of the angiotensin system have consistently been shown to reduce the development of diabetes (19;130). While these agents are very well established, other lesser known medicines also require attention. Nicotinic acid is again being strongly promoted as an option for statin-intolerant patients despite knowledge that it also leads to higher glucose levels in patients with diabetes (18). It will be important in the future to appropriately select and monitor patients for new-onset diabetes based not only on known risk factors (family history of diabetes, high BMI) but also based on their prescribed medications.

Strengths and weaknesses of the analysis require consideration. The meta-analysis incorporated most of the available large statin trials, thereby providing great statistical power. The analysis was only missing data from three other trials (with 8985 participants without diabetes at baseline)—CARE, SPARCL, and LIPS. The meta-analysis could only be undertaken using summary data, rather than individual participant data. Furthermore, ORs were combined in the meta-analyses rather than HRs which were not available for all trials. However, the use of ORs tends to yield very similar results to HRs when event rates are low. Inevitably, methods for diagnosis of diabetes varied between the trials. In CORONA and HPS, diagnoses were based on physician reporting only, rather than on physician reporting and documented biochemical analyses which may be considered preferable. Exclusion of these two trials by analysis of the remaining eleven trials with biochemical analyses produced a null result (p=0·10) mainly due to the exclusion of the large number of events provided by HPS. Finally, to

estimate the total number of person-years of follow-up, it was assumed that the median approximated to the arithmetic mean in some cases, and in some trials baseline BMI, baseline age, change in LDL-cholesterol concentrations, and follow-up were taken from the entire cohort when data specific to non-diabetic patients were unavailable.

The variation in diagnostic methods may have contributed to the varying rates of developing diabetes between trials. However, the approach taken yielded diabetes incidences in keeping with what would be expected in the community, with the highest rates being observed in trials with patients known to be at high risk of developing diabetes. In particular either one or two glucose concentrations of 7·0 mmol/L were used as a diagnostic criterion, depending on the frequency of glucose measurement. Results obtained lend support to this pragmatic approach. The two trials with the lowest incidence of diabetes were AFCAPS TexCAPS and WOSCOPS, both primary-prevention trials with participants clearly at low diabetes risk (low BMIs compared with other primary prevention trials like ASCOT-LLA and JUPITER). The four trials with the highest diabetes incidence included participants known to be at high risk of developing diabetes. PROSPER recruited elderly participants (aged 70–82 years) with or at high risk of cardiovascular disease, GISSI Prevenzione recruited patients who had suffered a myocardial infarction within the last 6 months, and both GISSI HF and CORONA were conducted in patients with heart failure, a condition well-known to lead to high risk of developing diabetes.

Following a reanalysis of WOSCOPS data (decided prior to the analyses), this trial's risk of diabetes on pravastatin treatment was reported as non-significant, while a significantly reduced risk was reported in Circulation in 2001 (94). However, non-standard and unusual criteria were used for diagnosis of diabetes in this earlier publication. In particular, the 2001 paper included the requirement for a rise in FPG of 2.0 mmol/L or more during the trial from the baseline level before diabetes could be diagnosed. Standard criteria for diagnosis of diabetes were employed in a reanalysis of WOSCOPS, producing data that were easily compared with other trials. This had little impact on the overall results as use of 2001 WOSCOPS data would not have changed the overall findings. Only results for patients with normal FPG concentrations were

previously published for LIPID (40). The risk of developing diabetes on pravastatin in LIPID was non-significantly reduced (OR 0.91) but published data suggested slightly more cases of diabetes on pravastatin in those with IFG (9.2% of survivors on placebo and 9.7% of survivors on pravastatin developed diabetes). Data for those with IFG were requested from the LIPID investigators but none were available for this analysis. The true OR for diabetes risk in LIPID is thus likely to be somewhat closer to a value of 1.0.

The findings suggest that surveillance for dysglycaemia should be considered in patients receiving statin therapy. It is now also clear that the development of diabetes should be specified as a secondary endpoint in future large endpoint statin trials. If possible, reports of long-term follow-up in existing trials should also include incident diabetes to further investigate these findings.

This analysis could not conclusively answer the question of whether more intensive statin therapy carried a greater risk of developing diabetes than moderate dose therapy. To date, only two large statin trials conducted in primary or secondary prevention cohorts have compared an intensive statin regime with placebo, namely JUPITER (rosuvastatin 20mg vs. placebo) (22) and SPARCL (atorvastatin 80mg vs. placebo) (105). JUPITER has already been discussed in detail and results showed a 25% increase in new-onset diabetes on rosuvastatin; SPARCL was designed to assess the effect of statin therapy in patients with a prior stroke or transient ischaemic attack. Recently published results showed a 44% increase in new-onset diabetes on atorvastatin in SPARCL (131), suggesting that intensive statin regimes may indeed carry greater diabetes risk. While no relationship was noted between LDL-cholesterol lowering in the meta-analysis (129), it may be important to consider that this was only a univariate analysis, that diagnostic criteria for diabetes varied between trials, that baseline LDL-cholesterol levels varied between trial populations and that timings for cholesterol measurement differed between trials. This may have obscured any true relationship between strength of statin (LDL-cholesterol lowering) and new-onset diabetes. The LDL-cholesterol meta-regression also lacked SPARCL data which may have yielded a more convincing relationship with new-onset diabetes. The numbers of additional cases of diabetes in JUPITER and SPARCL are not trivial either. In JUPITER it can be estimated that there were 7

additional cases of new-onset diabetes for every 10 patients without diabetes at baseline protected from suffering a major cardiovascular event (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death). Likewise in SPARCL, there were approximately 9 additional cases of new-onset diabetes for every 10 patients protected from suffering a major cardiovascular event.

The possibility of a dose-dependent relationship between statin use and new-onset diabetes was examined in a further project and is fully described in Chapter 5.

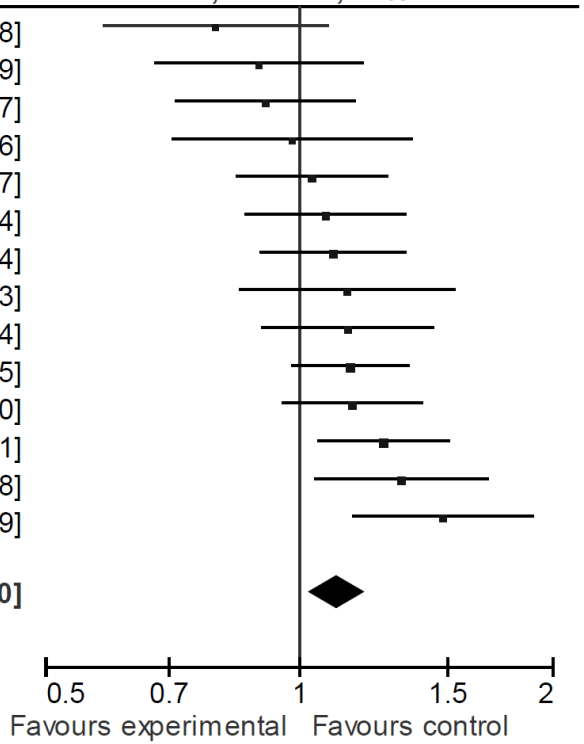
Data described in this chapter were published in the Lancet in 2010 (129). While data from SPARCL were not included in the published paper, I have subsequently pooled it with data from the other 13 trials. These updated pooled results show an increase in OR from 1.09 (13 trials) to 1.11 (14 trials) though there is a deterioration in I^2 from to 11% to 34% (see Figure 4.8).

Figure 4.8. Meta-analysis of new-onset diabetes in 14 large statin trials (including SPARCL)

Study or Subgroup	Statin Events	Statin Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
WOSCOPS	75	2999	93	2975	4.7%	0.79 [0.58, 1.08]
Gissi Prevenzione	96	1743	105	1717	5.3%	0.89 [0.67, 1.19]
LIPID	126	3496	138	3501	6.6%	0.91 [0.71, 1.17]
Afcaps Texcaps	72	3094	74	3117	4.3%	0.98 [0.71, 1.36]
4S	198	2116	193	2126	8.2%	1.03 [0.84, 1.27]
MEGA	172	3013	164	3073	7.6%	1.07 [0.86, 1.34]
GISSI HF	225	1660	215	1718	8.6%	1.10 [0.90, 1.34]
CORONA	100	1771	88	1763	5.0%	1.14 [0.85, 1.53]
ASCOT-LLA	154	3910	134	3863	6.9%	1.14 [0.90, 1.44]
HPS	335	7291	293	7282	10.9%	1.15 [0.98, 1.35]
ALLHAT	238	3017	212	3070	9.0%	1.15 [0.95, 1.40]
JUPITER	270	8901	216	8901	9.6%	1.26 [1.05, 1.51]
PROSPER	165	2510	127	2513	6.9%	1.32 [1.04, 1.68]
SPARCL	166	1905	115	1898	6.5%	1.48 [1.16, 1.89]
Total (95% CI)		**47426**		**47517**	**100.0%**	**1.11 [1.03, 1.20]**
Total events	2392		2167			

Heterogeneity: Tau² = 0.01; Chi² = 19.76, df = 13 (P = 0.10); I² = 34%

Test for overall effect: Z = 2.67 (P = 0.008)



Chapter 5.

Risk of incident diabetes on intensive compared to moderate dose statin therapy: a collaborative meta-analysis of randomised trials

5.1 Introduction

Statin therapy significantly reduces cardiovascular events among individuals with and without a history of diabetes compared with placebo (132;133). Intensive-dose statin therapy has also been shown to further reduce cardiovascular events compared to moderate-dose statin therapy (132;134;135) – see Figure 5.1. A recent meta-analysis of thirteen randomised placebo- and standard care-controlled trials involving 91,140 individuals, reported that among patients treated with statins, the risk of developing diabetes was 9% higher (95% CI 2-17%) over a 4 year period compared to patients randomised to placebo or standard care (129).

Recently, findings of three large endpoint trials comparing intensive to moderate-dose statin therapy have suggested an excess risk of incident diabetes among those treated with intensive statin regimens (131;136). However, two of these trials employed non-standard diagnostic criteria previously used to define incident diabetes (94). Additionally, published data from a fourth large clinical trial suggested the possibility of a deterioration in glucose control on intensive statin therapy (137), and a recent report of 220 hypercholesterolemic patients treated with placebo or different doses of atorvastatin and followed for only two months found that those on the highest dose developed greater insulin resistance, higher insulin levels, and higher HbA1c levels compared to those on the lowest dose or placebo (119), suggesting a potential dose effect.

While no significant relationship was observed between the extent of LDL-cholesterol lowering and new-onset diabetes in the meta-analysis of placebo- and standard care-controlled trials (129), most of those trials employed modest intensity statins and trial populations also differed greatly which may have obscured any meaningful association.

Confidence in the observed association between statin therapy and the development of diabetes would be enhanced by providing further large scale evidence of a dose-dependent association (129). Given the proven cardiovascular benefits of statins and the likely increasing use of intensive statin regimens, it is important to quantify any potential long-term risks to enable physicians and patients to make informed choices. Furthermore, it would be of value to investigate whether any specific group of patients is at higher risk of diabetes on intensive statin therapy than others. I therefore examined the associations of intensive-dose statin therapy compared to moderate-dose therapy with the development of diabetes and the occurrence of major cardiovascular events, respectively, by conducting a collaborative meta-analysis of published and unpublished data from relevant clinical trials.

Figure 5.1. The effect of intensive statin therapy compared to moderate dose statin therapy on the risk of myocardial infarction or coronary death

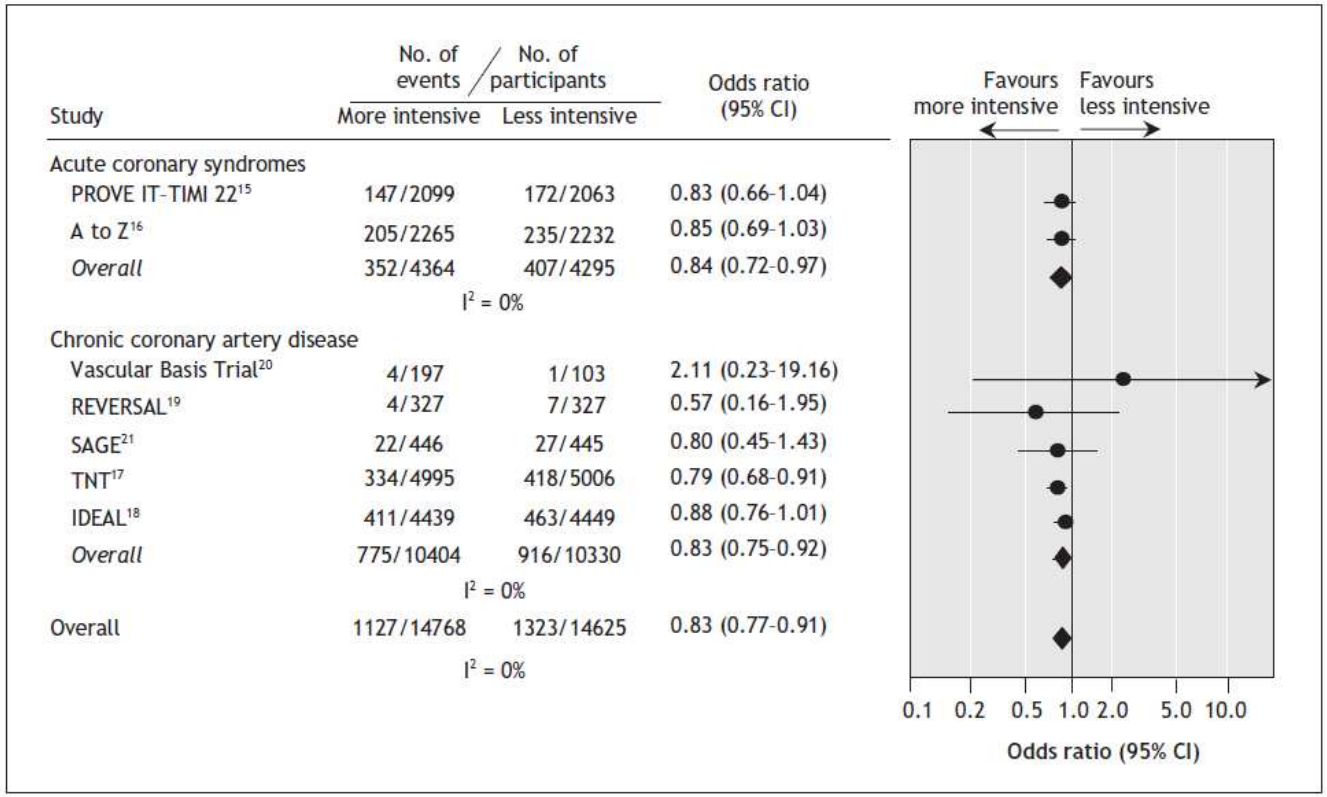


Figure taken from Josan et al (135). Copied under licence from the Canadian Medical Association and © Access Copyright. Further reproduction prohibited

5.2 Methods

Search strategy and selection criteria

Data were gathered from large randomised endpoint statin trials primarily designed to assess the effect of intensive-dose statin treatment compared to moderate-dose therapy on cardiovascular outcomes. Inclusion criteria included trials of 1000 or more participants exposed to statin therapy with a minimum mean follow-up of one year. The procedure for follow-up visits in both treatment arms was required to be identical to avoid bias in ascertainment of new-onset diabetes. I searched Medline, Embase and the Cochrane Central Register of Controlled Trials with the terms 'statin', 'HMG CoA reductase inhibitor' and names of individual statins as title words and keywords, and combined these with a search for the keywords 'intensive' or 'aggressive' to identify trials performed in adult patients (initial search date January 8th 2010, updated April 4th 2011; Figure 5.2) and published in English from 1st January 1996 until 31st March 2011. Abstracts and manuscripts were reviewed and discrepancies settled by consensus. Five trials were identified: the Treating to New Targets (TNT) trial (138), the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial (139), the Aggrastat to Zocor (A to Z) trial (140), the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction (PROVE-IT TIMI 22) trial (141) and the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) (136).

Data sources

Investigators from all five trials provided data for incident diabetes and major cardiovascular events according to a standard data query sheet (Figure 5.3). To ascertain whether any specific patient subgroups were at greater risk of developing diabetes on intensive statin therapy, data were collected on the key endpoints (see below) among those with BMI, HDL-cholesterol, triglycerides, age and FPG (where available) above and below the trial medians, as these factors are associated with diabetes risk. A PRISMA checklist was also completed (110).

Quality assessment

I used an established tool (111) to independently evaluate the quality of each trial. Nine characteristics were assessed: randomisation, concealment of treatment allocation, similarity of groups at baseline, eligibility criteria, blinding of (i) outcome assessors (ii) patient and (iii) care provider to allocated treatment, point estimates, and intention-to-treat analysis thereby allowing each trial to be awarded a Delphi score of 0 to 9. Disagreement was resolved through consensus and discussion.

Endpoints

New-onset diabetes: A patient was considered to have developed diabetes if (i) there was an adverse event report of newly diagnosed diabetes during the trial, or (ii) he/she commenced glucose lowering medication during the trial, or (iii) he/she had two FPG values ≥7.0mmol/L during the trial. For the two trials with data published using non-standard diabetes criteria (as in (iii) above but also requiring ≥2.0mmol/L increase in FPG from baseline) (131), a reanalysis of the data was performed using the standard diagnostic criteria but have also included a sensitivity analysis using these non-standard criteria previously employed in WOSCOPS (94).

Cardiovascular events: Data were also collected for a composite cardiovascular endpoint consisting of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary artery bypass surgery and percutaneous coronary intervention as well as data for specific cardiovascular events and all-cause mortality. For trials which recruited patients shortly after an acute coronary syndrome, the pre-specified trial definitions were used which included only those revascularisation procedures not linked to the pre-randomisation index event. These consisted of procedures performed >30 days after randomisation in PROVE IT-TIMI 22 and only ischaemia-driven procedures in A to Z.

Statistical analysis

To identify potential effects of intensive vs. moderate-dose statin therapy on incident diabetes and cardiovascular events, ORs and 95% CIs were calculated

from the available data for the number of patients who did not have diabetes at baseline and those who developed diabetes and cardiovascular events during follow-up. Study-specific ORs were pooled using a random-effects model meta-analysis to account for between-study heterogeneity which may have been introduced by differing methods for diagnosing diabetes available in the trials and different trial populations. Statistical heterogeneity across studies was quantified using the x^2 (or Cochran's Q statistic) and I^2 statistics, with a p-value >0.10 considered statistically non-significant. The I^2 statistic is derived from the Q statistic [(Q–df/Q)X100], and provides a measure of the proportion of the overall variation attributable to between-study heterogeneity (112). Although I obtained both published and unpublished information for the meta-analysis, the potential for publication bias was still assessed through formal testing namely the funnel plot and Egger's test. To evaluate the effect of statins across clinically relevant subgroups (see above), stratum-specific ORs were calculated for incident diabetes and major cardiovascular events and combined using random-effects meta-analysis. In exploratory analyses we compared results in patients with recent acute coronary syndrome to those with stable coronary heart disease, and also compared results for trials in which simvastatin 80mg and atorvastatin 80mg were the respective intensive regimens. All p-values were two-sided and $p<0.05$ was considered statistically significant. Analyses were conducted using Stata version 10.1 (College Station, Texas).

Table 5.1. Checklist of PRISMA criteria

Section/Topic	Item	Checklist item	Is this item included in the text?
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	Yes
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	Yes
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	Yes
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design	Yes
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	No
Eligibility criteria	6	Specify study characteristics (such as length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	Yes
Information	7	Describe all information sources (such as databases with dates of coverage, contact	Yes

sources		with study authors to identify additional studies) in the search and date last searched	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Yes
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	Yes
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	Yes
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made	Yes
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	Yes: Delphi score
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	Yes
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	Yes
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	Yes
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	Yes

Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	Yes
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	Yes
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	Yes
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	Yes
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Yes
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	Yes
Additional analyses	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression)	Yes
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	Yes
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	Yes

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	Yes
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	No external funding

Figure 5.2. Flow diagram summarising the literature search to identify intensive vs. moderate intensity randomised statin trials

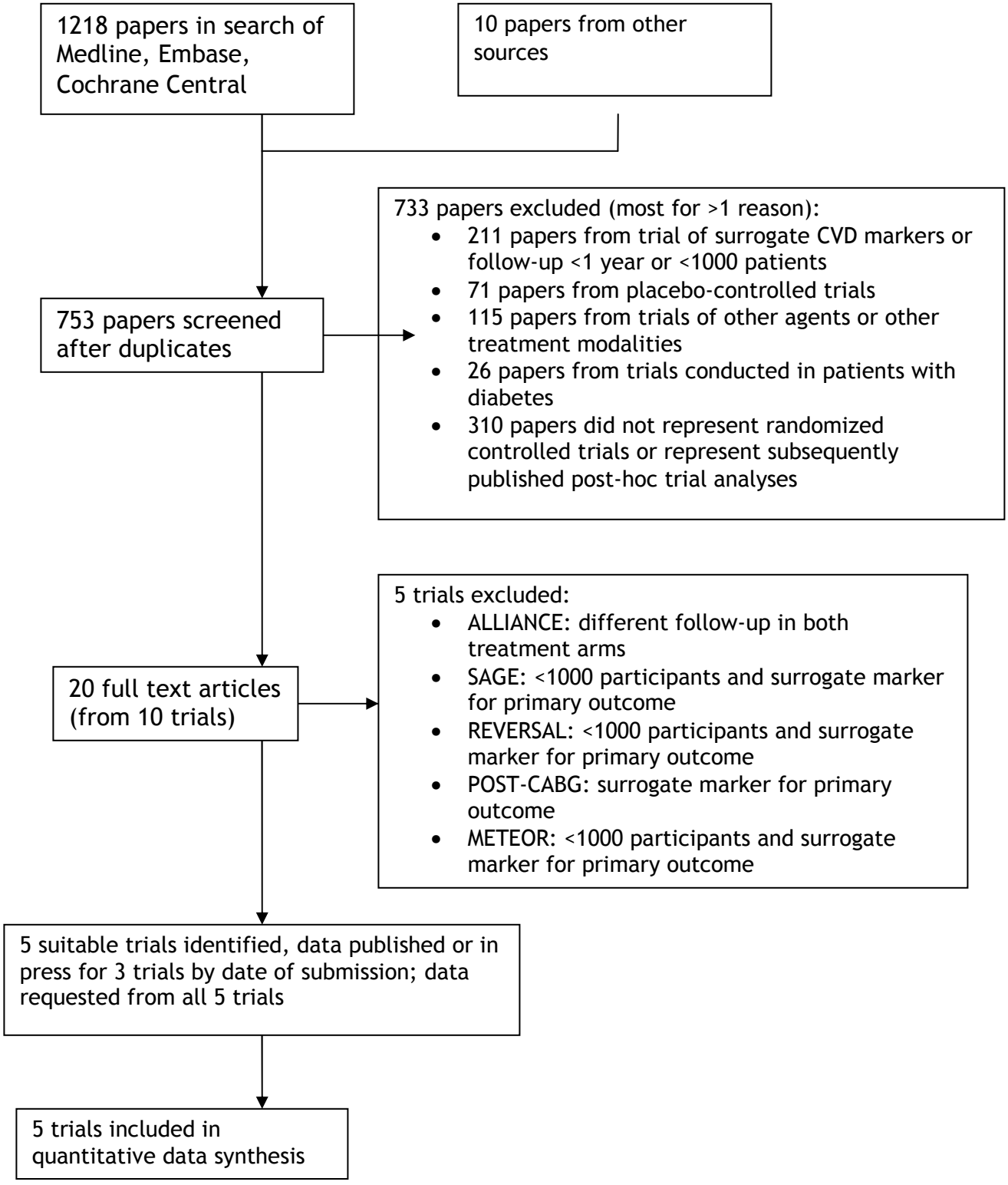


Figure 5.3. Data Collection Sheet used to request data from statin trials with unpublished data

Request for data from _____trial:
Meta-analysis of incident diabetes in intensive vs. standard dose statin trials

7. Total number of non-DM subjects at baseline ____
    a. Intensive statin ____
    b. Low dose statin ____

8. Baseline characteristics of all non-DM participants at baseline, where available
    a. Mean age (SD) yrs ____ (___)
    b. Mean BMI (SD) kg/m^2 ____ (___)
    c. Mean fasting glucose (SD) mmol/L ____ (___)
    d. Mean fasting or random HDL-c (SD) mmol/L ____ (___)
    e. Mean fasting or random Natural log [trigs] (SD), log mmol/L ____ (___)
    f. Number of male _____ and female _____ non-DM at baseline
    g. Number of current smokers _____ and not current smokers at baseline _____

9. Mean LDL-cholesterol (SD) at:
    a. Baseline:
        i. Intensive statin ___ (___)
        ii. Low dose statin ___ (___)
    b. End of study or fixed time during study
        i. Intensive statin ___ (___)
        ii. Low dose statin ___ (___)

10. Methods of diagnosis of diabetes – which of the following were used?
    a. Physician reported (i.e. Adverse Event) YES / NO
    b. Commencement of oral medication or insulin YES / NO
    c. Biochemistry (2 fasting glucose ≥7.0mmol/L) YES / NO

11. Number developing diabetes in each group:
    a. Intensive statin ___
    b. Low dose statin ___
    c. Hazard ratio for developing diabetes [high vs. low dose] (95%CI) ___ (___)

12. Number developing CVD events in each arm (*where CVD events includes the following:*
    CVD death, non-fatal MI, non-fatal stroke, coronary revascularisation [CABG, PCI])
    a. Intensive statin ___
    b. Standard/low dose statin ___
    c. Hazard ratio for CVD endpoints (high vs. low dose) [HR (95%CI)] ___ (___)

13. Interactions for incident diabetes endpoint:
    a. Dichotomous: Nr developing DM / n
        i. Baseline BMI
            1. > median high dose ___ / ___ low dose ___ / ___
            2. < median high dose ___ / ___ low dose ___ / ___
        ii. baseline fasting glucose (if available)
            1. > median high dose ___ / ___ low dose ___ / ___
            2. < median high dose ___ / ___ low dose ___ / ___
        iii. baseline HDL-c (fasting or random as available)
            1. > median high dose ___ / ___ low dose ___ / ___
            2. < median high dose ___ / ___ low dose ___ / ___
        iv. Baseline TGs
            1. > median high dose ___ / ___ low dose ___ / ___
            2. < median high dose ___ / ___ low dose ___ / ___
        v. baseline age
            1. > median high dose ___ / ___ low dose ___ / ___
            2. < median high dose ___ / ___ low dose ___ / ___
    b. Hazard ratios (95%CI) for developing DM: high vs. low dose
        i. Baseline BMI
            1. > median ___ (___)
            2. < median ___ (___)
        ii. baseline fasting glucose (if available)
            1. > median ___ (___)
            2. < median ___ (___)
        iii. baseline HDL-c (fasting or random as available)
            1. > median ___ (___)
            2. < median ___ (___)
        iv. Baseline TGs
            1. > median ___ (___)
            2. < median ___ (___)
        v. baseline age
            1. > median ___ (___)
            2. < median ___ (___)

14. Interactions for composite CVD endpoint (see point 6):
    a. Dichotomous: Nr developing composite CVD endpoint / n
        i. Baseline BMI
            1. > median high dose ___ / ___ low dose ___ / ___
            2. < median high dose ___ / ___ low dose ___ / ___
        ii. baseline fasting glucose (if available)
            1. > median high dose ___ / ___ low dose ___ / ___
            2. < median high dose ___ / ___ low dose ___ / ___
        iii. baseline HDL-c (fasting or random as available)
            1. > median high dose ___ / ___ low dose ___ / ___
            2. < median high dose ___ / ___ low dose ___ / ___
        iv. baseline TGs
            1. > median high dose ___ / ___ low dose ___ / ___
            2. < median high dose ___ / ___ low dose ___ / ___

v. baseline age
    1. > median high dose ___ / ___ low dose ___ / ___
    2. < median high dose ___ / ___ low dose ___ / ___

b. Hazard ratios (95%CI) for developing CVD endpoint: high vs. low dose
    i. Baseline BMI
        1. > median ___ (___)
        2. < median ___ (___)
    ii. baseline fasting glucose (if available)
        1. > median ___ (___)
        2. < median ___ (___)
    iii. baseline HDL-c (fasting or random as available)
        1. > median ___ (___)
        2. < median ___ (___)
    iv. baseline TGs
        1. > median ___ (___)
        2. < median ___ (___)
    v. baseline age
        1. > median ___ (___)
        2. < median ___ (___)

5.3 Results

The present analysis reports information from five randomised clinical trials providing data on 32,752 non-diabetic participants.

The trials

- PROVE-IT TIMI 22: this was a double blinded randomised controlled trial comparing the effect of atorvastatin 80mg to pravastatin 40mg in patients following an acute coronary syndrome

- A to Z: this was a double blinded randomised controlled trial comparing the effect of simvastatin 80mg to simvastatin 20mg in patients following an acute coronary syndrome

- TNT: this was a double blinded randomised controlled trial comparing the effect of atorvastatin 80mg to atorvastatin 10mg in patients with stable coronary heart disease

- IDEAL: this was an open-label blinded endpoint evaluation randomised controlled trial comparing atorvastatin 80mg to simvastatin 20mg or 40mg in patients who had previously suffered a myocardial infarction

- SEARCH: this was a double blinded randomised controlled trial comparing the effect of simvastatin 80mg to simvastatin 20mg in patients who had previously suffered a myocardial infarction

Of the 32,752 participants, 2,749 (8.4%) developed diabetes and 6,684 (20.4%) experienced a major cardiovascular event over a weighted mean follow-up of 4.9 years (weighted SD 1.9 years) (Table 5.2, Figure 5.4). Of the 2,749 diagnoses of diabetes, 2,059 (75%) were identified by non-biochemical methods (i.e. commencement of glucose-lowering medication or adverse event reporting), 219

(8%) by elevated FPG values in the trial, and 471 (17%) by more than one method. Trials were of high quality with a median Delphi score of 9 (range 6-9) (Table 5.3).

Intensive statin therapy and new-onset diabetes

TNT was the only trial to individually demonstrate a significantly increased risk for new-onset diabetes on intensive statin therapy compared to moderate dose therapy. All trials gave ORs for new-onset diabetes >1.0. In the combined dataset, there were 149 more cases of incident diabetes in participants assigned to intensive statin treatment than those receiving moderate therapy, OR 1.12 (95% CI 1.04-1.22) (Figure 5.4). In absolute terms there were 2.0 additional cases of diabetes per 1000 patient years among those receiving intensive statin therapy (18.9 [SD 5.2] cases per 1000 patient-years with high-dose statin treatment vs. 16.9 [SD 5.5] cases per 1000 patient-years with moderate-dose therapy) corresponding to a number needed to harm of 498 per year. There was no significant heterogeneity between trials for new-onset diabetes (x^2 for heterogeneity = 2.59, p=0.63; I^2=0% [95% CI 0-79%]). Likewise, there was no evidence of publication bias (p=0.54; Figure 5.5).

Intensive statin therapy and cardiovascular benefit

TNT and IDEAL individually demonstrated significantly reduced risks for experiencing cardiovascular events on intensive statin therapy compared to moderate dose therapy. In the combined dataset there were 416 fewer patients with cardiovascular events on intensive statin therapy, OR 0.84 (95% CI 0.75-0.94) (Figure 5.4). In absolute terms there were 6.5 fewer first major cardiovascular events per 1000 patient years among those receiving intensive statin therapy (44.5 [20.4] cases per 1000 patient-years with high-dose statin treatment and 51.0 [23.6] cases per 1000 patient-years with moderate-dose therapy) corresponding to a number needed to treat (NNT) of 155 to prevent one cardiovascular event per year. There was significant heterogeneity between trials for major cardiovascular events (x^2 for heterogeneity=15.04, p=0.005; I^2=74% [95% CI 36-90%]). However, there was no evidence of publication bias (p=0.70; Figure 5.5). ORs for specific components of the composite cardiovascular endpoint are provided in Table 5.4, showing similar

associations between intensive statin therapy and each cardiovascular endpoint component. Intensive-dose statin therapy was not associated with lower all-cause mortality compared to moderate-dose statin therapy (OR 0.93, 95% CI 0.81-1.05, 1318 cases/16408 patients on intensive therapy vs. 1360 cases/16342 patients on moderate dose). Intensive statin therapy was also not associated with lower rates of non-cardiovascular death as compared to moderate-dose statin therapy (OR 0.98, 95% CI 0.87-1.10, 559 cases/16408 patients on intensive therapy vs. 571 cases/16342 patients on moderate-dose). There was no significant heterogeneity between trials for all-cause mortality (x^2 for heterogeneity = 7.06, p=0.13; I^2=43% [95% CI 0-79%]) or for non-cardiovascular death (x^2 for heterogeneity = 3.41, p=0.49; I^2=0% [95% CI 0-79%]).

Subgroup analyses

Cardiovascular benefit was consistent across all subgroups of participants including those defined by age, HDL-cholesterol, triglycerides, BMI (assessed in 4 trials (136;138;139;141); n=29,036; 6,192 events) and FPG (assessed in 3 trials (138;139;141); n=16,352; 3,436 events) above and below the trial medians at baseline (Figure 5.6). The odds of developing diabetes among participants on intensive compared to moderate statin therapy was also similar for patients differing by age, HDL-cholesterol, BMI (2,626 events) and FPG (1,302 events) levels at baseline but was higher in those with triglyceride concentrations below the median compared to those with higher triglyceride levels. The trial specific medians of these variables are provided in Table 5.5.

Risk: benefit by statin type and trial population

The difference in relative LDL-cholesterol reduction between the more and less intensive statin arms was 12-15% in the 2 trials (n=14,301 (136;140)) that studied simvastatin 80 mg and 16-22% in the 3 trials (n=18,451 (138;139;141)) that studied atorvastatin 80 mg. The odds of developing diabetes was comparable with simvastatin 80 mg (OR 1.13, 95% CI 0.93-1.38; I^2=0%; 690 cases/7166 patients on simvastatin 80mg vs. 634 cases/7135 patients on moderate-dose) and atorvastatin

80 mg (OR 1.15, 95% CI 1.03-1.28; I^2=0%; 759 cases/9242 patients on atorvastatin 80 mg vs. 666 cases/9209 patients on moderate-dose) (p=0.56 for interaction) (Figure 5.7). In contrast, there was no significant cardiovascular benefit over moderate-dose therapy in the trials of simvastatin 80 mg (OR 0.95, 95% CI 0.88-1.03; I^2=0%; 1396 events/7166 patients on simvastatin 80mg vs. 1448 cases/7135 patients on moderate-dose) whereas there was for atorvastatin 80 mg (OR 0.78, 95% CI 0.73-0.85; I^2=14%; 1738 events/9242 patients on atorvastatin 80mg vs. 2102 events/9209 patients on moderate-dose) (p<0.001 for interaction). Three trials were conducted in stable coronary heart disease patients (n=25,853 (136;138;139)) and two in patients following a recent acute coronary syndrome (n=6,899 (140;141)). Intensive statin therapy was associated with higher odds of incident diabetes following acute coronary syndrome (OR 1.15, 95% CI 0.85-1.54; 166 cases/3475 patients on intensive therapy vs. 146 cases/3424 patients on moderate-dose) and in stable coronary heart disease (OR 1.12, 95% CI 1.03-1.22; 1283 cases/12933 patients on intensive therapy vs. 1154 cases/12920 patients on moderate-dose), while cardiovascular events were lower in both conditions (OR 0.86 [95% CI 0.76-0.98], 527 events/3475 patients vs. 589 events/3424 patients; and OR 0.83 [95% CI 0.70-0.98], 2607 events/12933 patients vs. 2961/12920 patients respectively) (Figure 5.8); there was no significant heterogeneity for these outcomes by study cohort.

Sensitivity analyses

In sensitivity analyses, the overall risk of developing diabetes (assessed in three trials (136;138;139)) and the reduction in cardiovascular events (assessed in five trials), calculated by combining trial-specific HRs, produced similar results to the primary analysis (Figure 5.9). Notably, the trial-specific ORs and HRs for new-onset diabetes were also very similar (Table 5.6). The risk of developing diabetes on intensive statin therapy using non-standard diagnostic criteria in two trials, namely TNT and IDEAL, was also qualitatively similar to the primary analysis where standard diagnostic criteria were used (OR 1.11, 95% CI 1.03-1.21) (Figure 5.10). Fixed-effects model meta-analysis produced similar trial-specific results and identical pooled results to random-effects model meta-analysis for new-onset diabetes when pooling data from the five trials (OR 1.12 [95% CI 1.04-1.22]. Finally,

risk of new-onset diabetes was also analysed using 99% CI as opposed to 95% CI. This yielded the following results: OR 1.12 (95% CI 1.01-1.25).

Table 5.2. Baseline data from five large endpoint trials comparing intensive to moderate dose statin therapy

	Patients without diabetes (baseline) / All patients	Trial patients	Intensive / moderate regimens	N intensive statin/ N moderate dose	Mean follow up (yr)	Methods of diagnosing diabetes	BMI (kg/m^2)	Age (yr)	HDL-c (mmol/L)	LDL-c (mmol/L)	Relative %LDL-c reduction ‡	Natural log (Trig mmol/L)	FPG (mmol/L)	FPG taken after baseline
PROVE IT-TIMI 22 (141)	3395/ 4162 (82%)	Recent acute coronary syndrome	Atorvastatin 80mg / Pravastatin 40mg	1707 / 1688	2.0 (0.6)	(i) Adverse event report (ii) DM medication (iii) Two FPG ≥7.0mmol/L	29 (5)	58 (11)	1.0 (0.3)	2.8 (0.8)	22%	0.57 (0.44)	5.8 (0.6) +	Not specified+
A to Z (140)	3504/ 4497 (78%)	Recent acute coronary syndrome	Simvastatin 40mg, Simvastatin 80mg / Placebo, Simvastatin 20mg	1768 / 1736	2.0 (1.5-2.0)*	(i) Adverse event report (ii) DM medication	-	60 (11)	1.0 (0.3)	2.9 (0.7)	15%	0.52 (0.39)	-	-
TNT (138) **	7595/ 10001 (76%)	Stable coronary heart disease	Atorvastatin 80mg / Atorvastatin 10mg	3798 / 3797	5.0 (0.5)	(i) Adverse event report (ii) Two FPG ≥7.0mmol/L (iii) DM medication	28 (4)	61 (9)	1.2 (0.3)	2.5 (0.5)	22%	0.41 (0.42)	5.4 (0.6)	Annual
IDEAL (139) **	7461/ 8888 (84%)	Previous myocardial infarction	Atorvastatin 80mg / Simvastatin 20mg/40mg	3737 / 3724	4.8 (4.4-5.0)*	(i) Adverse event report (ii) Two FPG ≥7.0mmol/L (iii) DM medication	27 (4)	62 (10)	1.2 (0.3)	3.2 (0.9)	16%	0.38 (0.44)	5.5 (0.6)	Final visit
SEARCH (136)	10797/ 12064 (89%)	Previous myocardial infarction	Simvastatin 80mg / Simvastatin 20mg	5398 / 5399	6.7 (1.4)	(i) Adverse event report	28 (4)	64 (9)	1.1 (0.4)†	25. (0.6)†	12%	0.48 (0.54)†	-	-
TOTAL	32752/ 39612 (83%)	-	-	16408 / 16344	4.9 (1.9) *	-	-	-			-			-

Continuous variables displayed as mean (SD) or median (IQR)
* Pooled mean (pooled SD) follow-up; † non-fasting; + 1315 FPG baseline results from the PROVE IT-TIMI 22 participants (equally distributed between treatment arms);
‡ calculated as [LDLc (intensive arm) – LDLc (moderate dose arm)] / LDLc (baseline); ** excludes patients with known diabetes mellitus and/or ≥FPG 7.0mmol/L at baseline
DM diabetes mellitus; FPG fasting plasma glucose; BMI: body mass index

Table 5.3. Delphi scores for trials included in meta-analysis

Parameter	A	B	C	D	E	F	G	H	I	Total
Trial										
PROVE-IT TIMI 22	1	1	1	1	1	1	1	1	1	9
A to Z	1	1	1	1	1	1	1	1	1	9
TNT	1	1	1	1	1	1	1	1	1	9
IDEAL	1	0	1	1	1	0	0	1	1	6
SEARCH	1	1	1	1	1	1	1	1	1	9

For definitions of parameters A-I please refer to Table 4.2

Table 5.4. Pooled event rates and odds ratios for individual components of the composite cardiovascular endpoint

Endpoints	Intensive regimen: Event rate (SD), expressed as events per 1000 patient years [Events / number of patients]	Moderate-dose: Event rate (SD), expressed as events per 1000 patient years [Events / number of patients]	Odds ratio (95%CI)	I^2 (95% CI)	Annual number needed to treat
Cardiovascular death	9.12 (4.78) [759 / 16408]	10.04 (5.85) [789 / 16342]	0.94 (0.83-1.07)	15% (0-82%)	1087
Non-fatal myocardial infarction	13.74 (8.45) [912 / 16408]	15.47 (8.54) [1041 / 16342]	0.87 (0.79-0.95)	0% (0-79%)	578
Non-fatal stroke *	4.74 (1.43) [394 / 16407]	5.39 (1.36) [436 / 16342]	0.90 (0.78-1.03)	0% (0-79%)	1538
Coronary revascularisation	27.92 (18.86) [1906 / 16407]	33.78 (21.45) [2326 / 16343]	0.80 (0.71-0.90)	63% (3-86%)	171

* includes fatal and non-fatal strokes from IDEAL (139)

Table 5.5. Trial-specific medians of five pre-specified predictors of diabetes

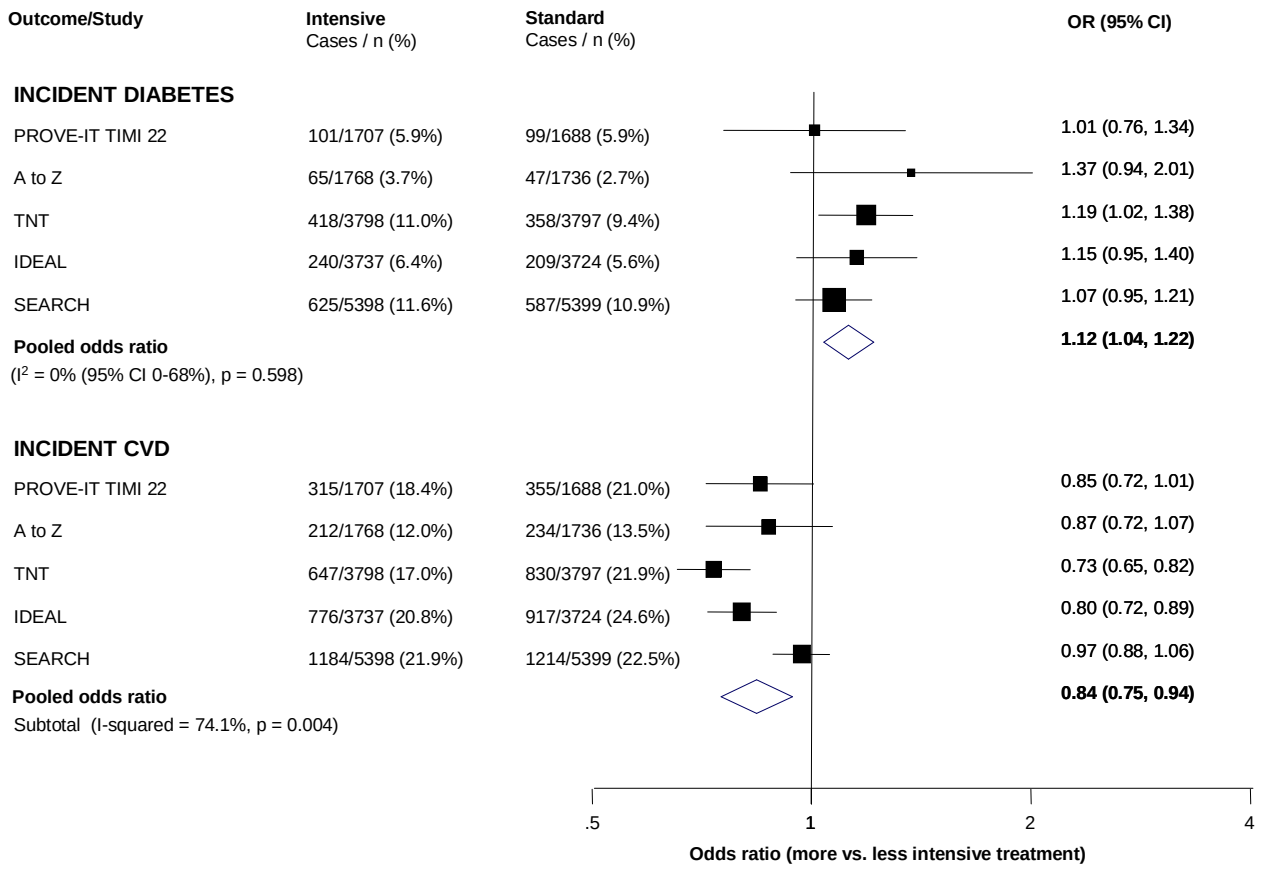
TRIALS	Age (years)	Body mass index (kg/m^2)	Fasting plasma glucose (mmol/L)	HDL-cholesterol (mmol/L)	Triglycerides (mmol/L)
PROVE-IT TIMI 22	57	28.2	5.4	1.0	1.7
A to Z	60	*	*	1.0	1.6
TNT	61	27.6	5.4	1.2	1.5
IDEAL	61	26.6	5.4	1.2	1.5
SEARCH	65	27.4	*	1.0	1.6

* not available

Table 5.6. Comparison of hazard ratios and odds ratios for new-onset diabetes in three trials

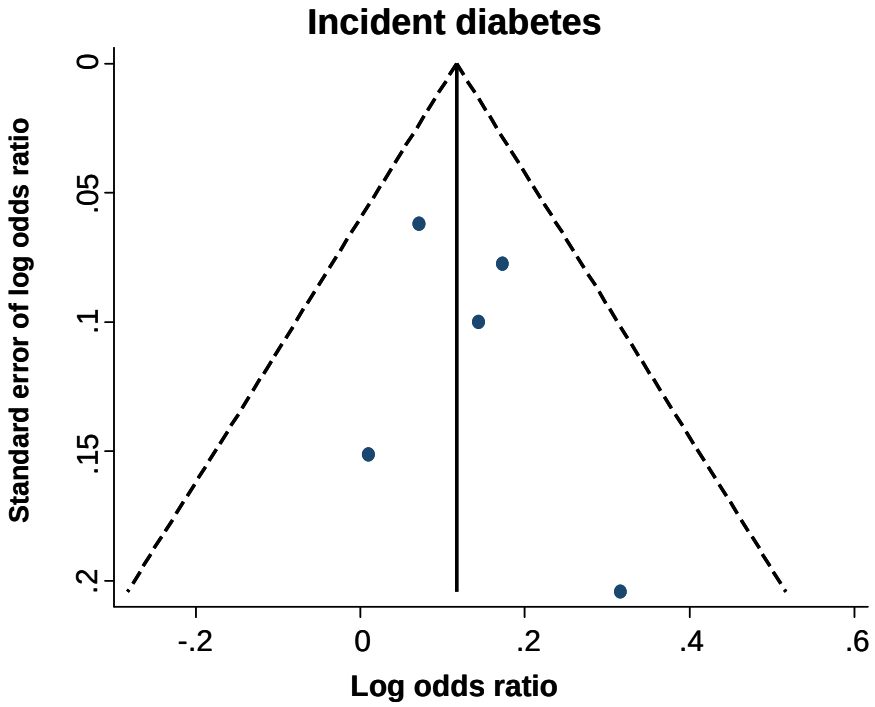
Trial	Hazard ratio (95% CI)	Odds ratio (95% CI)
TNT	1.18 (1.02-1.36)	1.19 (1.02-1.38)
IDEAL	1.16 (0.96-1.39)	1.15 (0.95-1.40)
SEARCH	1.07 (0.96-1.20)	1.07 (0.95-1.21)

Figure 5.4. Meta-analysis of new-onset diabetes and first major cardiovascular events in five large trials comparing intensive statin therapy to moderate dose therapy



OR: odds ratio; CI: confidence interval

Figure 5.5. Assessment of publication bias by funnel plot and Egger's test



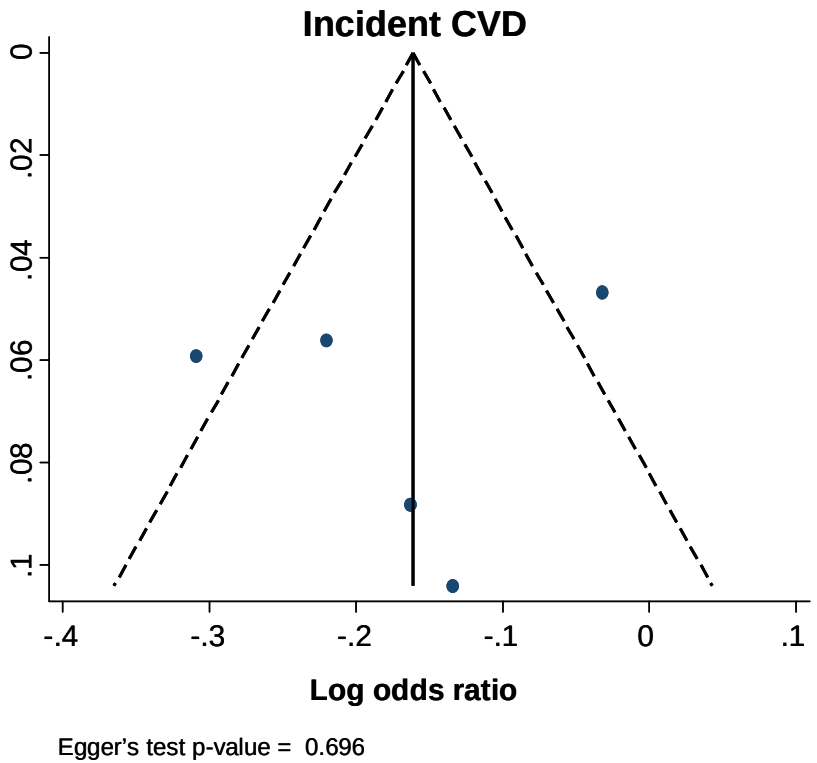
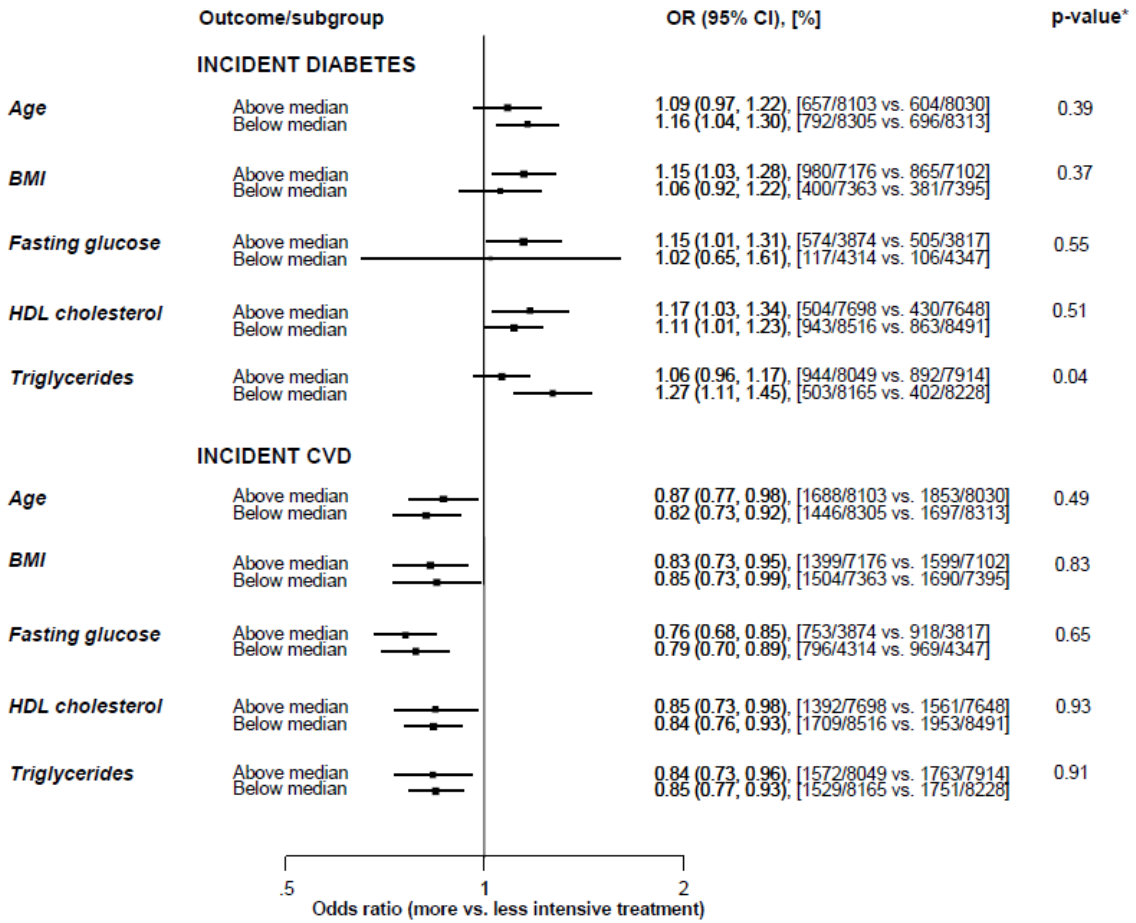


Figure 5.6. Subgroup analyses for new-onset diabetes and first major cardiovascular events



*Represents p-value for heterogeneity between groups

Figure 5.7. A comparison of new-onset diabetes and first major cardiovascular events in trials using atorvastatin 80mg and simvastatin 80mg as the respective intensive regimens

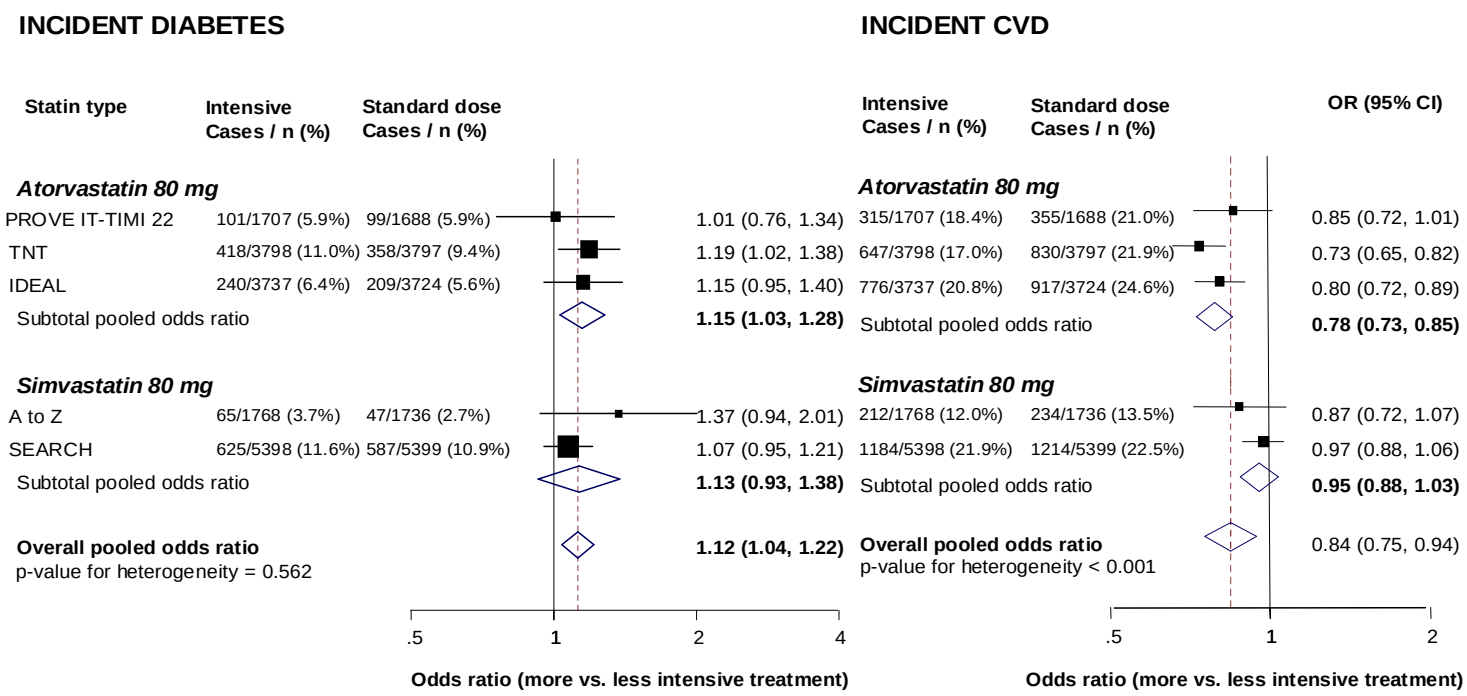


Figure 5.8. A comparison of new-onset diabetes and first major cardiovascular events in trials of patients following a recent acute coronary syndrome and patients with stable coronary heart disease

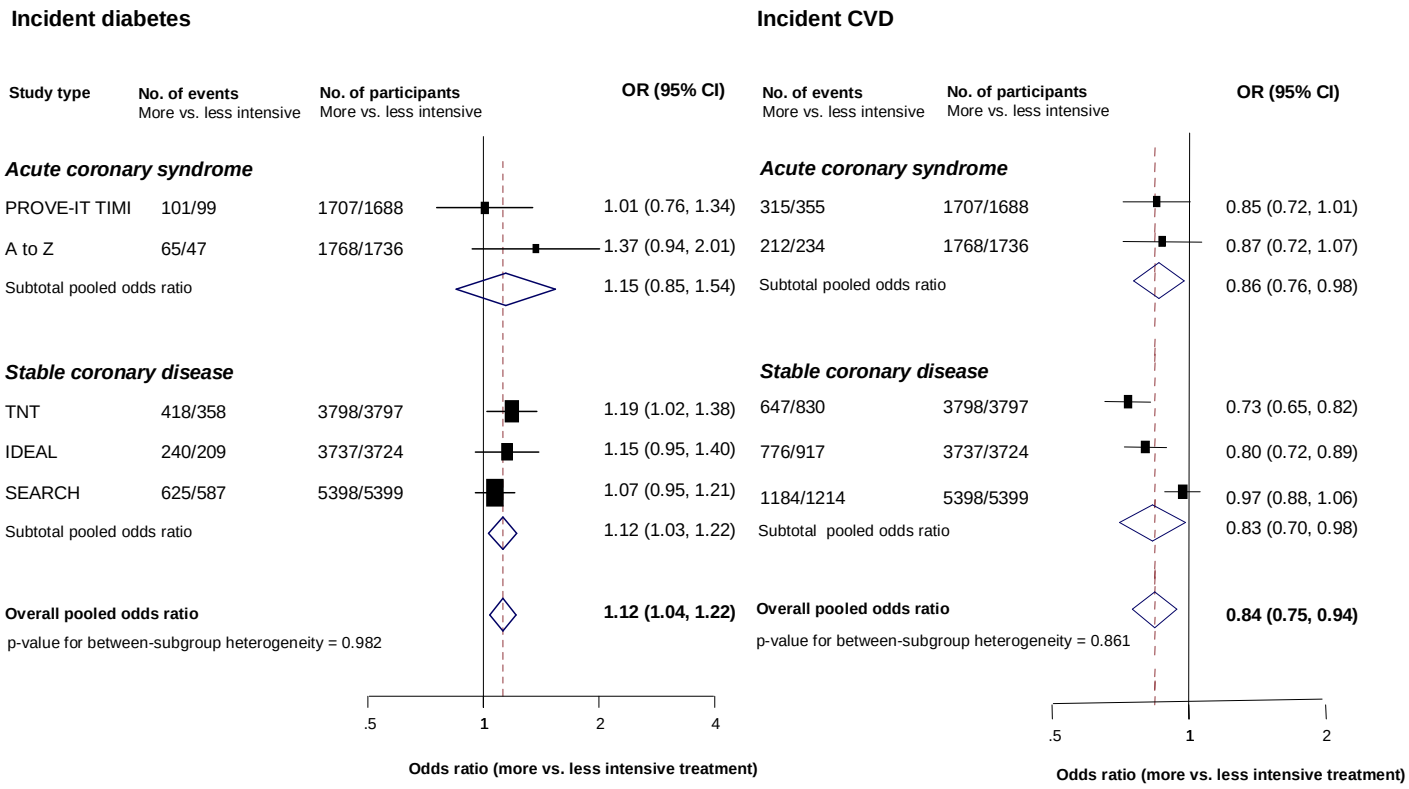
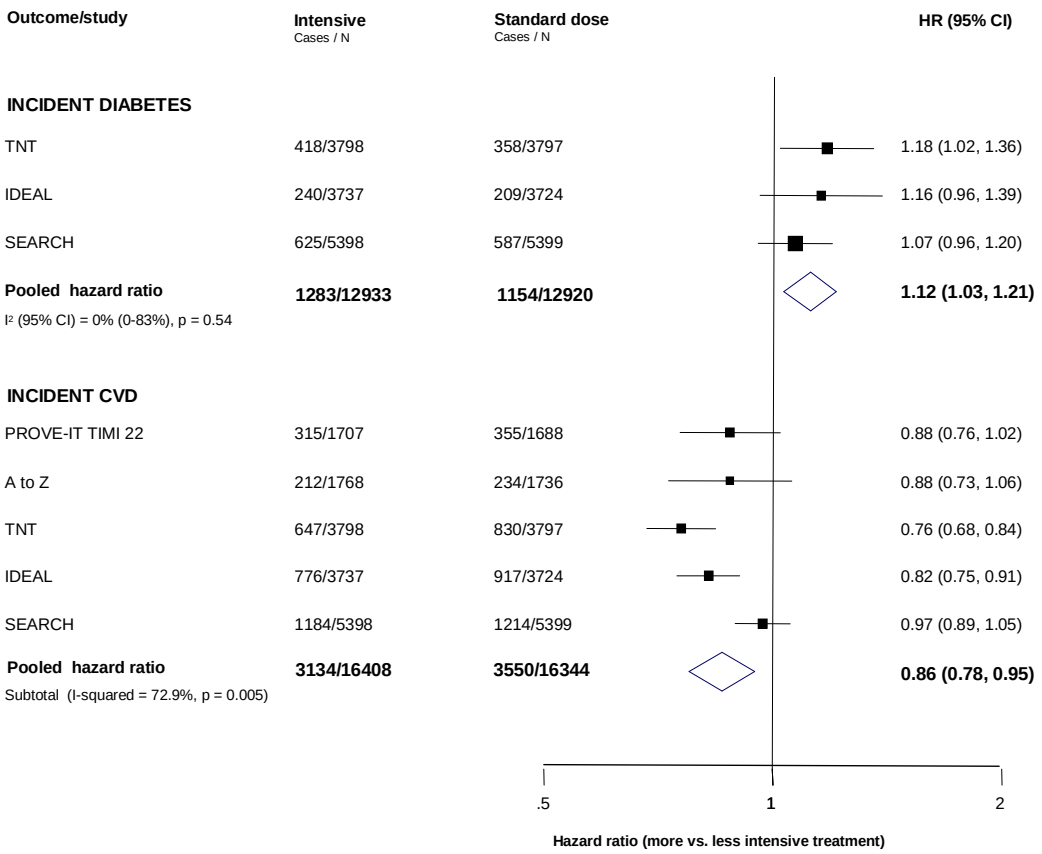
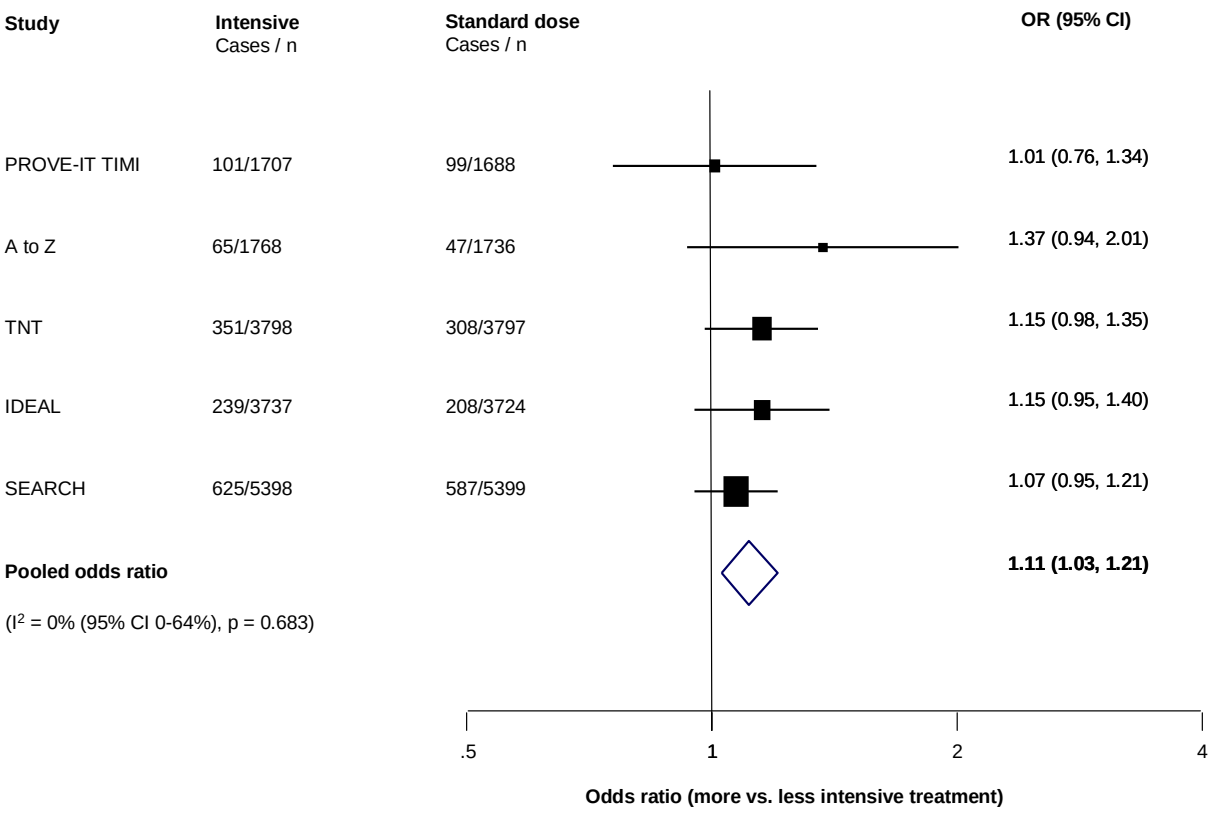


Figure 5.9. A sensitivity analysis using hazard ratios for new-onset diabetes and first major cardiovascular events



HR: hazard ratio

Figure 5.10. Meta-analysis of new-onset diabetes using non-standard diagnostic criteria in two trials



5.4 Discussion

This study demonstrates that use of intensive statin therapy compared with moderate-dose statin therapy was associated with a higher incidence of new-onset diabetes (OR 1.12). However, intensive statin therapy was associated with fewer major cardiovascular events (OR 0.84). In this combined trial population, although the risk of new-onset diabetes and the benefit of cardiovascular event reduction on intensive therapy were similar in relative terms, when expressed in absolute terms there was one additional case of diabetes for every 498 patients treated for one year compared to one fewer patient experiencing a cardiovascular event for every 155 patients treated for one year. The cardiovascular benefit described here may be a conservative estimate as three trials have demonstrated that intensive statin therapy also reduces multiple cardiovascular events if intensive statin therapy is continued (142-144). These findings complement the recent observation of excess risk of developing diabetes among statin-treated patients compared to those receiving placebo (129).

The benefits of statin therapy were consistent across all subgroups and for each component of the primary efficacy endpoint including cardiovascular death. Analyses of all-cause mortality were consistent with observations for cardiovascular death, although the generalisability of these findings to other populations is less clear as these depend upon the relative contributions of cardiovascular death (modified by statins) and non-cardiovascular deaths (non modifiable by statins) in those populations. For new-onset diabetes, however, there was some evidence that the odds of new-onset diabetes was higher among individuals with triglyceride concentrations below the median level of distribution on intensive statin treatment which, in the absence of a biologically plausible mechanism, may be a chance finding given the modest statistical significance in the context of multiple statistical tests. The higher incidence of new-onset diabetes and lower incidence of cardiovascular events was similar in patients following recent acute coronary syndrome and those with stable coronary disease. In the trials studied, whose control arms were different but comparable, the relative LDL-cholesterol reduction was greater in those that used atorvastatin 80 mg than in those that used simvastatin 80 mg (145).

Whereas the odds of developing diabetes was similar on both, there was a significantly lower odds of cardiovascular events in the trials with high-dose atorvastatin but not with high-dose simvastatin (132).

Important questions remain. First, a potential mechanism to explain the findings of a higher incidence of diabetes on statin therapy compared to placebo, and intensive statin therapy compared to moderate-dose therapy, has not been identified. Possibilities include a direct and off-target effect. For example, statins may influence muscle or liver insulin action directly, resulting in higher diabetes risk. Data from an animal model suggest that statin-induced myopathy is associated with the development of muscle insulin resistance, providing a potential mechanism (146). Second, it remains unclear whether statin therapy is associated with a generalised tendency for an increase in diabetes risk in many who take statins or whether there is a specific group of individuals at particular risk. Analysis of data from subgroups did not provide conclusive results. Third, although statin therapy is associated with a higher incidence of diabetes, to what extent this may carry with it the important associated long-term risks of developing microvascular disease is unknown. At present there are no large clinical studies that have examined the associations of statin therapy with microvascular disease. In contrast, fibrate therapy is associated with lower rates of microvascular complications (147;148). My colleagues and I hypothesise that given that cardiovascular risk from diabetes is modest in the first decade after diagnosis (13), and as the benefit of statin therapy increases over time and in absolute terms with increasing age (20), net cardiovascular benefit in high-risk individuals will still strongly favour statin therapy. Finally, it would be of interest to investigate the impact of intensive statin therapy on glycaemic control and treatment requirements in patients with established diabetes. One consideration to help quantify potential concerns is the establishment of a registry to examine these issues of long-term risk. These findings suggest that clinicians should be vigilant for the development of diabetes in patients on intensive statin therapy.

Strengths of this meta-analysis include the following: first, it was possible to include data from all the relevant clinical trials and thereby provide adequate power to detect potentially modest effects. Second, access to trial data allowed

relevant subgroup analyses. And third, it was possible to provide a direct comparison of the potential risk of new-onset diabetes with cardiovascular benefit thereby providing clinically useful information. Potential weaknesses include the following: first, different methods for diagnosing diabetes were available for the five trials and the trials were not designed to assess new-onset diabetes. However, the low heterogeneity in new-onset diabetes as well as the very similar sensitivity analysis using the non-standard criteria in two trials provides confidence in the results obtained. Second, analyses of incident diabetes were not pre-specified in the trial designs and only one trial (TNT) included regular measurement of FPG as a consequence. Because undiagnosed diabetes is relatively common (149), it is possible that the risk of incident diabetes in the trial participants may have been somewhat underestimated. Third, as all five trials specifically included participants with established coronary disease at high risk of future cardiovascular events rather than diabetes, these findings may not necessarily be generalisable to populations at higher risk of incident diabetes. Fourth, analyses were conducted without access to individual participant data.

It is strictly true to say that, by design, the two meta-analyses described in Chapters 5 and 6 cannot prove that statin therapy causes new-onset diabetes. However, due to the fact that they incorporate data from randomised trials and due to the fact that other studies have suggested deteriorations in glycaemia on statins, there are no other compelling explanations. The possibility of survival bias was already mentioned in Chapter 4. Another powerful argument against survival bias is that ORs (which do not factor in survival) and HRs (which do factor in survival time) were essentially identical for TNT, IDEAL and SEARCH and that pooled HRs for new-onset diabetes produced the same results as pooled ORs (1.12). Another suggestion has been that in some statin trials, patients may be aware of their treatment allocation despite double-blinding i.e. based on knowledge of their lipid results during trials. The argument is that such patients may be reassured by their improved lipid results which may lead them to adopt poorer lifestyles (less exercise and poor diet with concomitant weight rise) which increases risk of diabetes. Again, the small relative rise in weight in rosuvastatin recipients in JUPITER compared to placebo (0.3kg) (117) cannot explain a 25% increase in diabetes. A final suggestion has been that those

allocated to statins in trials may have experienced considerably more side-effects than those on placebo, leading them to seek medical attention and consequently increasing the chance of being screened for diabetes. However, side-effect profiles from JUPITER and SPARCL (22;105), trials with 25% and 44% increases in new-onset diabetes on statin, were very similar with the results that this cannot explain the observed increase in diabetes.

In conclusion, this meta-analysis extends earlier findings of an increased incidence of diabetes with statin therapy by providing evidence of a dose-dependent association.

The results provided in this chapter were published in JAMA in 2011 (150).

Chapter 6.

Predictors of development of diabetes in patients with chronic heart failure in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity program

6.1 Introduction

Diabetes and chronic heart failure are both common conditions and epidemiological studies have demonstrated that they often coexist (24). For example, while the prevalence of chronic heart failure in the general population is 1-4% (largely dependent on age), this rises to ~12% in patients with diabetes (151-153). Similarly, while the prevalence of diabetes is 4-7% in the general population, this rises to 6-25% in patients with known left ventricular systolic dysfunction and further to 12-30% in those with symptomatic heart failure (24). The prevalence of diabetes in clinical trial cohorts with heart failure has typically been 20-30% and, though one should be cautious in extrapolating these data to the general population, it is clear that diabetes occurs very commonly in heart failure. Diabetes is also a risk factor for developing heart failure (24;154).

While diabetes and heart failure commonly coexist as described, there is as yet no established explanation for why this occurs. One hypothesis requiring consideration is that the reactive hyperadrenergic state found in heart failure leads to an increase in the levels of circulating fatty acids which then leads to impaired glucose tolerance (IGT) and insulin resistance, possibly via free fatty acid-induced mitochondrial uncoupling (Figure 6.1) (155). Further data of interest come from a recent observational study in 15 patients with diabetes and severe heart failure who were treated with left ventricular assist devices. After 4 months there were marked reductions in FPG (8.8mmol/L to 5.8mmol/L), HbA1c (7.7% to 6.0%) and the need for glucose-lowering medication (six patients stopped medication) providing further support for a link between heart failure and diabetes (156).

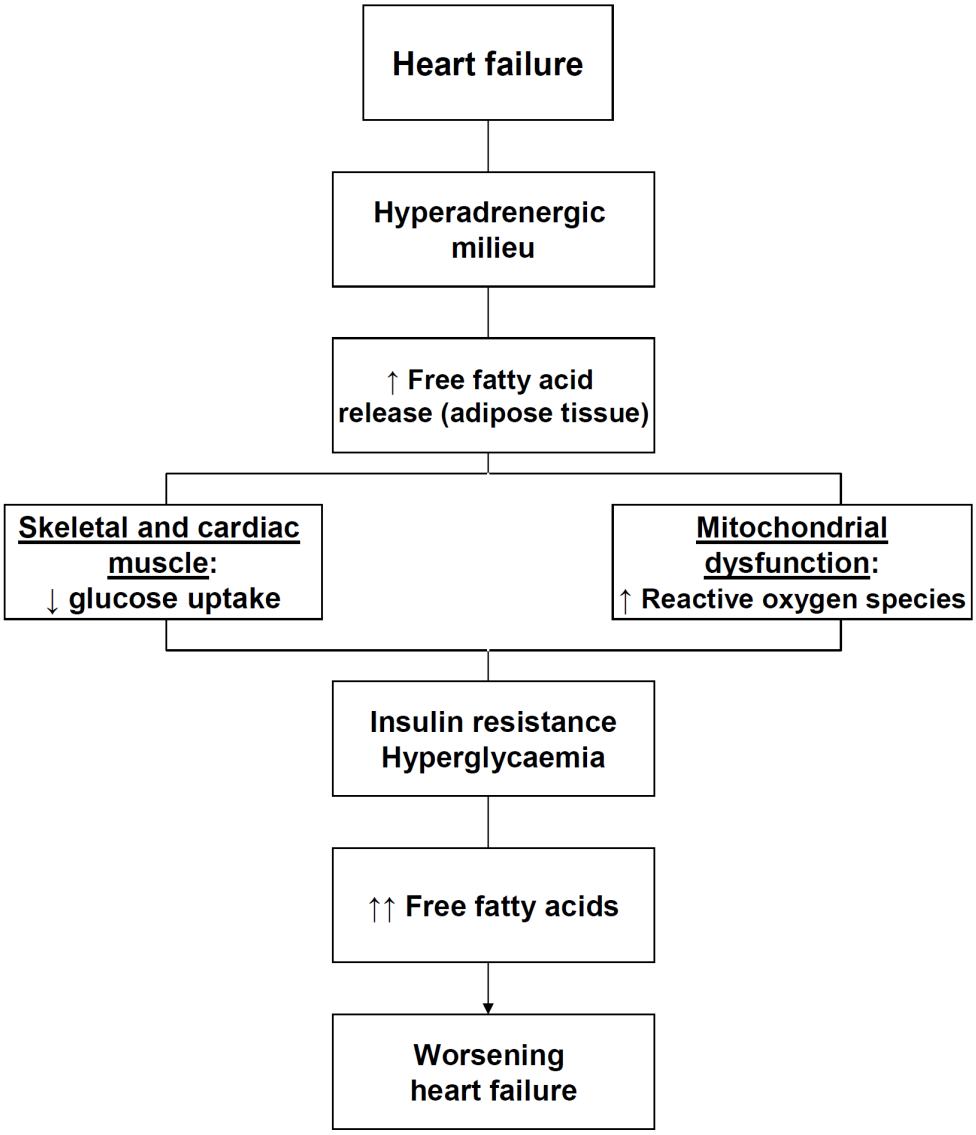
One advantage of recognising this link between diabetes and heart failure is that it provides an opportunity to screen for diabetes in a high risk group of patients.

There may be additional benefits however. Chronic heart failure patients with diabetes are also more likely to be hospitalised (126) and they suffer more complications including increased cardiovascular morbidity and mortality than patients with chronic heart failure alone (127). Consequently it is possible, though as yet unproven, that approaches to reduce progression to diabetes in chronic heart failure may benefit patients by allowing targeted preventative measures. To achieve this it is necessary to be able to predict new-onset diabetes in chronic heart failure but, to date, little work has been done in this area. By contrast, diabetes prediction algorithms are available for the general population.

Strong predictors of diabetes in the general population are well established. They include (i) measures of adiposity such as BMI, waist circumference, waist to hip ratio (157) – typically these measurements give univariate AUROC for developing diabetes of 0.66-0.73, (ii) dysglycaemia as demonstrated by abnormal fasting or post-load glucose levels (158), or elevated HbA1c (159;160) – typically these findings give an AUROC of 0.73-0.77, and (iii) combinations of measures of adiposity and dysglycaemia (161). These and other weaker predictors have been combined in risk algorithms such as the Cambridge Diabetes Risk Score which includes age, gender, BMI, family history of diabetes, smoking history and history of treatment with antihypertensive or steroid medications (AUROC 0.80) (162). Whether these same predictors may be useful in chronic heart failure to predict diabetes is unclear given the nature of the disease. For example, patients with heart failure are known to develop skeletal muscle atrophy (163) and this alteration in the usual balance between body fat and muscle plus potential effects on glucose handling by muscle in heart failure may theoretically alter the expected relationship between BMI and new-onset diabetes.

In summary, while data on the development of heart failure in patients with diabetes are widely available, there have been no data published regarding potential predictors of diabetes in patients with chronic heart failure. Using retrospective analysis of existing data from a large clinical trial conducted in patients with chronic heart failure, I investigated which characteristics were associated with development of diabetes.

Figure 6.1. In heart failure, increased free fatty acid release from adipose tissue inhibits muscular glucose uptake with resultant hyperglycaemia and insulin resistance



Adapted from Opie et al (155) and provided with the permission of Elsevier ©

6.2 Methods

Aims of the analysis

The aim was to identify risk factors for the development of diabetes in chronic heart failure and to assess the statistical predictive capabilities of any identified risk factors. This was undertaken using data from the previously conducted Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program.

Agreement for Data sharing with AstraZeneca

In 2008 a data analysis plan was submitted to AstraZeneca with the intention of carrying out the analyses described. This was approved by the CHARM steering committee and agreed with AstraZeneca (see Figure 6.2).

Background to CHARM

The CHARM program consisted of three parallel trials with complementary populations of patients with symptomatic chronic heart failure. The three patient groups were (i) patients with chronic heart failure and reduced left ventricular ejection fraction (LVEF) (≤0.40) already taking an ACE-inhibitor (the CHARM-Added trial) (164), (ii) patients with chronic heart failure and reduced LVEF (≤0.40) intolerant to ACE-inhibitor therapy (CHARM-Alternative trial) (165), and (iii) patients with chronic heart failure and preserved LVEF (>0.40) (CHARM-Preserved trial) (166). Results were also published for the combined cohort in the CHARM-Overall trial (167). The trial was completed in 2002. The current analyses from CHARM were post-hoc and were not prespecified.

CHARM patients: selection

In the combined cohort, 7601 patients, of whom 2163 had diabetes at baseline, were randomised to either candesartan or placebo and followed up for a median of 38 months. Candesartan therapy was titrated up incrementally to a maximum dose of 32mg daily or as much as tolerated. In CHARM, demographic data were

available for the majority of the combined cohort but laboratory data were only available for 2743 patients, 1021 (37%) with diabetes and 1722 (63%) with no history of diabetes, and these patients were recruited in North America. Therefore, in the analysis of predictors of the development of diabetes, only data from patients with complete datasets (including laboratory data) were analysed. Complete datasets (defined as containing all baseline clinical and demographic data, medications, blood results and randomisation data) were available for 1620 non-diabetic patients out of the 1722.

Diagnosis of diabetes in CHARM

Investigators were asked to report the occurrence of a new diagnosis of diabetes for all patients at the end of the CHARM trials. Fasting blood tests were not performed as part of the CHARM program, and formal tests for diabetes were not done. Details of diagnoses of diabetes (date of diagnosis, details of the criteria for diagnosis [whether based on FPG values ≥7.0mmol/L or post challenge glucose values of ≥11.1mmol/L or random glucose values ≥11.1mmol/L), any hypoglycaemic medication prescribed, and lifestyle modifications prescribed) during the study were documented on CHARM case report forms (Figure 6.3) at the closing study visit and the physician recording the data was required to make the relevant enquiries. Importantly therefore, although CHARM itself did not include biochemical methods to diagnose diabetes, it was able to report physician diagnosed diabetes rather than self-reported diabetes, and this has been shown to be a robust and standard method.

Available data in CHARM

Based on the knowledge that this was the first examination of predictors of diabetes in a large heart failure cohort, all available variables were considered potential predictors of diabetes and were therefore included in the analyses. The following data were available at baseline in CHARM:

- Demographics and medical history: age, gender, smoking status, medical history of myocardial infarction and hypertension, use of medications (ACE-inhibitors, B-blockers, diuretic therapy, nitrates, spironolactone,

digoxin, calcium channel blockers, lipid-lowering therapy, oral anticoagulants)

- Clinical measurements: BMI, systolic blood pressure, LVEF
- Symptomatic grading of heart failure: NYHA class II, III and IV (168)
- Laboratory biochemical analyses: HbA1c, electrolytes, serum creatinine, liver enzymes, full blood count and haematological data. All were carried out in central core laboratories using standard methods. HbA1c was measured on an automated high-performance liquid chromatography analyser (Bio-Rad Variant Analyser, GMI, Ramsey, MN) using a Diabetes Control and Complications Trial-aligned assay (169).
- Randomised treatment: placebo or candesartan allocation at baseline

Statistical analysis

With regard to baseline characteristics, continuous and normally distributed data are presented as mean (SD), continuous and skewed data as median (25^{th} centile, 75^{th} centile) and categorical data as number (percentage).

Univariate and multiple logistic regression analyses were carried out to identify those variables associated with the development of diabetes and these are expressed as ORs (95% CI). For attempting to identify independent predictors of diabetes, two methods of multivariate logistic regression were used: (i) multiple logistic regression including only those variables with a significant or borderline significant association with incident diabetes on univariate logistic regression (variables which demonstrated an association with diabetes and $p<0.10$ were included) and (ii), as an additional check (given the large number of parameters identified as potentially relevant), a forward-backward stepwise selection process was also performed and results were again expressed as ORs. The forward-backward selection procedure starts with estimating an intercept for the model, followed by a forward selection step. In this step the score x^2 statistic for each of the considered factors not yet included in the model is computed. If the effect with the largest statistic is significant at a prespecified entry significance level, the corresponding factor is added to the model. This is followed by a backward selection step. In this step, parameters for the complete model, as specified after the previous step, are estimated. The least significant

factor that does not meet a prespecified significance level is removed. The backward selection step is repeated until no factor is removed. The forward step is then repeated and followed by one or more backward elimination steps. The selection process terminates if no further factor can be added or if the factor just entered is the only factor removed in the subsequent backward elimination.

For the purpose of estimating the ability of variables to predict the development of diabetes, AUROC analysis was performed in a stepwise mode whereby AUROC was repeatedly estimated as independently predictive variables were added to the model. The more recently proposed tools of Net Reclassification Improvement and Integrated Discrimination Improvement, which are better suited to examining the effect of adding a new variable to an existing risk score, were not used.

Note

Given that the CHARM program was an industry funded study, data are held by AstraZeneca and not released in raw format.

Figure 6.2. Data request sent to and agreed with AstraZeneca

CHARM Analysis/Manuscript Proposal

Before completing this form, see attached instructions and example. Attach additional pages if necessary.
Send to xxx via fax and e-mail: .

Requester Name: Naveed Sattar / John McMurray / David Preiss

Address: University of Glasgow

EMAIL: nsattar@clinmed.gla.ac.uk

Title of Proposal: Predictors of incident diabetes in CHARM

_x_ Entire Population *-or-*
__ Subpopulation (Specify inclusion/exclusion criteria): All patients without diagnosis of T2DM at baseline

Comparison Groups comparisons of those developing vs. those not developing type 2 diabetes.

Background/Rationale

Due to rising obesity levels and an aging populaton, there is tremendous interest in identifying patients at elevated risk for type 2 diabetes. Many factors, both clinical and lab-based measures, have been identified as potential predictors. Amongst the most important 'traditional' predictors of diabetes risk in population studies of apparently healthy subjects are family history of diabetes, age, BMI (or some other measure of obesity), plasma triglyceride, and fasting glucose and blood pressure (the latter only in univariate analyses). More novel predictors of diabetes have been the subject of intense interest in recent years and our lab has contributed to such work by demonstrating elevated CRP (Freeman et al) and ALT (Sattar et al) predict type 2 diabetes independently of other measures. Such work has been widely replicated in other cohorts and it also makes biological sense since elevated liver function tests, esp. ALT and GGT are correlated to hepatic fat accumulation and thus enhanced hepatic insulin resistance and gluconeogenesis, whereas elevated inflammatory markers are linked to obesity and insulin resistance by multiple mechanisms. Many other groups (e.g. ARIC) have also demonstrated that other markers of inflammation (white cell count, Serum amyloid A or indeed low albumin) predict diabetes in the general population although the causality of this relationship remains uncertain in the low grade inflammation area. More crediable evidence suggests high grade inflammatory in conditions such as Rheumatoid Arthritis may be causatively linked to diabetes development and heart failure patients may fall into this category. However, such links have hitherto not been investigated. The CHARM study would seem an excellent study with which to determine predictors of development of type 2 diabetes in patients with chronic heart failure.

Recent relevant papers:

- Sattar N, Scherbakova O, Ford I, et al. Elevated alanine aminotransferase predicts new-onset type 2 diabetes independently of classical risk factors, metabolic syndrome, and C-reactive protein in the west of Scotland coronary prevention study. Diabetes. 2004 Nov;53(11):2855-60.
- Freeman DJ, Norrie J, Caslake MJ, Gaw A, Ford I, Lowe GD, O'Reilly DS, Packard CJ, Sattar N. C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. Diabetes. 2002 May;51(5):1596-600.
- Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. Circulation. 2003 Dec 16;108(24):2957-63.

Endpoints: Incident type 2 diabetes (as reported by investigators)

Hypotheses

Primary Question: How well do 'traditional' markers (BMI, triglyceride, low HDL-C, age, blood pressure, fasting (?) glucose, etc) predict risk of type 2 diabetes in patients with chronic heart failure without diabetes at baseline?

Secondary Question Do markers linked to inflammation (WCC, neutrophils percentage or similar) or abnormal liver function (ALT etc) or markers of disease severity predict risk for new-onset type 2 diabetes more strongly than traditional markers in this high risk population

CHARM analysis proposal form Naveed_John-1.doc

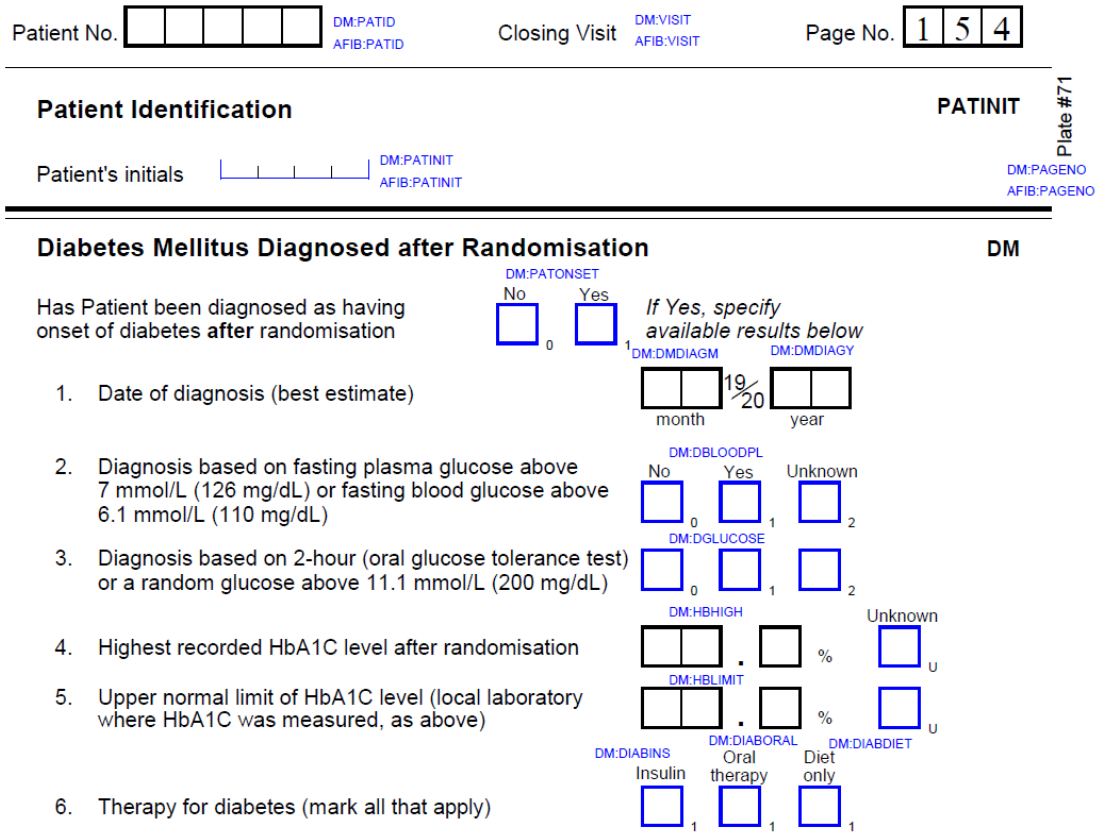
Tables / data analyses suggested

- Baseline characteristics of patients free from diabetes at baseline developing type 2 diabetes, and those not developing type 2 diabetes (with P-values for comparisons)
- Univariate predictors of type diabetes based on 1 SD change in each parameter or Y/N for categorical variable etc.
- Multivariate predictors: adjusting for case/control status, other drugs, beta-blockers, diuretics etc and gender
- We may also wish to examine whether predictors of diabetes are similar in active and placebo groups or examine for interaction where differences are apparent.

Decision: Revision Approved

Comments
Date

Figure 6.3. Section for reporting new-onset diabetes in the CHARM case report form



6.3 Results

Data for new-onset diabetes in the entire cohort and North American cohort in CHARM

In the entire CHARM cohort of 7601 participants randomised to treatment, 2163 (28.5% prevalence) were known to have diabetes at baseline. Of the 5438 participants with no known diabetes at baseline, 365 (6.7%) developed diabetes during CHARM, an incidence of 21 cases per 1000 patient years. In the North American cohort (n=2743) on whom the following results are based, 1021 (37.2% prevalence) were known to have diabetes at baseline. Of the remaining 1722 patients in North America who had blood samples analysed for general biochemistry, 1620 had full datasets at baseline including HbA1c results. Over the median follow-up period of 2.8 years, 126 (7.8%) of the 1620 initially non-diabetic North American participants developed diabetes reflecting an incidence of 27.8 cases per 1000 patient years.

The new diagnoses of diabetes were made as follows during CHARM:

- 78 (62%) diagnoses based on elevated FPG
- 7 diagnoses based on abnormal oral glucose tolerance tests (OGTTs)
- 5 diagnoses based on a combination of FPG and OGTT
- 36 cases did not have the method of diagnosis listed on the case report forms

Baseline Characteristics of CHARM participants

Baseline characteristics of the 1620 patients whose data are analysed in this chapter are provided in Table 6.1. Data are available both for the North American cohort combined and also separately for those who did (n=126) and did not (n=1494) develop diabetes during CHARM. The mean age of the North American cohort was 66.1 years and 67.3% were male. Other characteristics include the mean baseline BMI of 28.5kg/m^2, a mean LVEF of 0.38 and mean HbA1c of 6.3%. A history of hypertension was reported by 62% and 16% were current smokers. The majority were on beta-blocker and diuretic therapy and most were in NYHA class III. Half the participants were randomised to

candesartan and placebo respectively. Differences in the baseline characteristics between those who did and did not develop diabetes are dealt with in the following section.

Univariate associations of variables with new-onset diabetes in heart failure

Numerous parameters and variables measured at baseline showed significant positive associations with new-onset diabetes in univariate analyses (Table 6.2). Listed in order of decreasing significance (defined by the Wald Chi squared statistic) they are as follows: higher HbA1c (OR 2.30 per 1% increase), higher BMI (OR 1.10 per 1kg/m^2 increase), lower age (OR 0.97 per 1 year increase), use of diuretic therapy at baseline (OR 6.4), use of digoxin therapy at baseline (OR 1.77), lower serum creatinine concentration (OR 0.99 per 1umol/L increase), lower serum potassium concentration (OR 0.53 per 1mmol/L increase), lower red cell mean corpuscular volume (OR 0.96 per 1fL increase), higher red cell count (OR 1.53 per 1X10^{12}/L increase), use of beta-blocker therapy at baseline (OR 1.55), higher leukocyte count (OR 1.09 per 1X10^9/L increase), use of lipid-lowering therapy at baseline (OR 1.49), use of spironolactone therapy at baseline (OR 1.62), lower mean corpuscular haemoglobin (OR 0.92 per 1pg increase), higher serum alanine aminotransferase (ALT) concentration (OR 1.01 per 1U/L increase), and lower serum sodium concentration (OR 0.94 per 1mmol/L increase). Of these, higher HbA1c and higher BMI were comfortably the variables most strongly associated with new-onset diabetes. The data for HbA1c and BMI were also examined per SD change. For every one SD higher HbA1c and BMI, new-onset diabetes was 79% (OR 1.79 [1.54-2.08]) and 78% (OR 1.78 [1.53-2.09]) more likely, respectively.

The relationship between BMI and new-onset diabetes was studied after dividing participants into BMI quartiles (see Table 6.3) to assess the linearity of the relationship. It was clear that a strong linear relationship existed, allowing further analyses using BMI as a continuous measure. Those with BMI ≥28.0 kg/m^2 were 4.3 (2.8-6.6) times more likely to develop diabetes than those with lower BMI.

Independent predictors of new-onset diabetes in heart failure

Two approaches were taken to identify any independent predictors of new-onset diabetes in heart failure patients. First, all measures which demonstrated a significant or borderline significant relationship with the development of diabetes (as defined by $p<0.10$ in univariate analysis; 17 variables) were included in a logistic regression model. In the second approach, a forward-back stepwise selection method was employed (see Methods for full explanation).

In the first approach (using $p<0.10$), the following measures continued to demonstrate significant positive associations with new-onset diabetes (in decreasing order of significance): higher HbA1c (OR 2.20 per 1% increase), higher BMI (OR 1.09 per 1kg/m^2 increase), use of lipid-lowering therapy at baseline (OR 2.12), lower serum creatinine concentration (OR 0.99 per 1umol/L increase), use of diuretic therapy at baseline (OR 4.17), higher serum ALT concentration (OR 1.01 per 1U/L increase) and the use of digoxin at baseline (OR 1.73) (Table 6.2). As before, HbA1c and BMI demonstrated highly significant associations with new-onset diabetes.

In the second approach (stepwise selection), the measures which showed significant associations with the development of diabetes were much the same as in the above approach (Table 6.4). On this occasion, ORs are provided per SD difference in continuous measures. In decreasing order of significance the relevant measures were: higher HbA1c (OR 1.78 per 1SD increase), higher BMI (OR 1.64 per 1SD increase), use of lipid-lowering therapy at baseline (OR 2.05), lower serum creatinine concentration (OR 0.68 per 1SD increase), use of diuretic therapy at baseline (OR 4.81), the use of digoxin at baseline (OR 1.65), higher serum ALT concentration (OR 1.15 per 1SD increase) and younger age (OR 0.81 per 1SD increase). Expressed in another way, for every 1% higher HbA1c in this second multivariable model, the OR for developing diabetes was 2.28 (1.82-2.85) and for every 1kg/m^2 higher BMI, the OR for developing diabetes was 1.09 (1.05-1.12) (data not shown in tables).

The predictive capabilities of baseline variables for new-onset diabetes in heart failure

To assess the ability of the baseline variables to predict diabetes, factors significantly associated with incident diabetes in multivariable analyses were analysed by calculating AUROCs. In univariate predictive analysis, AUROC for HbA1c alone was 0.72 (Table 6.5). The optimal point for predicting new-onset diabetes was at an HbA1c of 6.5% which provided a sensitivity of 0.63 and a specificity of 0.70. AUROC for BMI in univariate analysis was 0.71. Using the optimal point for diabetes prediction, namely BMI 29.1kg/m^2, yielded a sensitivity of 0.73 and a specificity of 0.63. For all other factors, AUROCs were <0.63 and serum ALT performed the best.

In multivariate analysis, the combination of HbA1c and BMI provided an AUROC of 0.79 with a sensitivity of 0.73 and specificity of 0.72 for predicting future diabetes (Table 6.6). The addition of other elements, which were significantly associated with new-onset diabetes in multivariate logistic regression, improved the overall AUROC modestly to a maximum value of 0.82.

Table 6.1. Baseline characteristics of the 1,620 North American patients with full core laboratory datasets in CHARM with no medical history of diabetes at baseline, grouped by those who did and did not develop diabetes

	All participants	No diabetes during trials	Diabetes during trials
All patients	1,620 (100)	1,494 (92.2)	126 (7.8)
Age (years)	66.1 (12.1)	66.4 ± 12.0	61.5 ± 12.3
Sex (% male)	1090 (67.3))	1,008 (67.5)	82 (65.1)
BMI (kg/m^2)	28.5 (6)	28.2 ± 5.9	32.4 ± 6.2
Smoking habit			
Non-smoker	489 (30.2)	451 (30.2)	38 (30.2)
Previous smoker	877 (54.1)	804 (53.8)	73 (57.9)
Current smoker	254 (15.7)	239 (16.0)	15 (11.9)
Systolic blood pressure (mmHg)	127 ± 19	127 ± 19	130 ± 19
History of prior myocardial infarction	822 (50.7)	763 (51.1)	59 (46.8)
History of hypertension	1000 (61.7)	915 (61.2)	85 (67.5)
NYHA class			
II	645 (39.8)	600 (40.2)	45 (35.7)
III	938 (57.9)	860 (57.6)	78 (61.9)
IV	37 (2.3)	34 (2.3)	3 (2.4)
Left ventricular ejection fraction	0.38 ± 0.2	0.38 ± 0.2	0.36 ± 0.2
Drug therapy			
ACE-inhibitors	698 (43.1)	636 (42.6)	62 (49.2)
Beta-Blocker	871 (53.8)	791 (52.9)	80 (63.5)
Diuretic therapy	1357 (83.8)	1,235 (82.7)	122 (96.8)
Long-acting nitrates	405 (25.0)	380 (25.4)	25 (19.8)
Spironolactone	242 (14.9)	215 (14.4)	27 (21.4)
Digoxin	848 (52.3)	766 (51.3)	82 (65.1)
Calcium channel blocker	383 (23.6)	353 (23.6)	30 (23.8)
Lipid-lowering drug	739 (45.6)	670 (44.8)	69 (54.8)
Oral anticoagulant	520 (32.1)	484 (32.4)	36 (28.6)
Laboratory results			
HbA1C (%)	6.3 (0.7)	6.2 ± 0.7	6.8 ± 0.9
Creatinine (umol/L)	99 ± 34	100 ± 35	91 ± 26
Potassium (mmol/L)	4.4 ± 0.4	4.4 ± 0.4	4.3 ± 0.4
Sodium (mmol/L)	141 ± 3	141 ± 3	140 ± 3
ALT (units/L)	18 (13-25)	18 (13–25)	23 (16–33)
AST (units/L)	20 (16–25)	20 (16–25)	20 (17–26)
Alkaline phosphatase (units/L)	80 (65-97)	79 (65–97)	85.5 (69–106)
Bilirubin total (umol/L)	10.0 (6.8-13.7)	10.0 (6.8–13.7)	10.3 (8.0–12.0)
Bilirubin direct (umol/L)	2.0 (1.7–4.0)	2.0 (1.7–4.0)	2.0 (1.7–3.4)
Haemoglobin (mmol/L)	8.5 ± 1.0	8.5 ± 1.0	8.6 ± 0.8
Haematocrit (%)	41.2 ± 4.5	41.2 ± 4.6	41.5 ± 3.7
Red cell count ($10^{12}/L$)	4.5 ± 0.5	4.5 ± 0.5	4.6 ± 0.5
MCV (fL)	92.5 ± 5.9	92.6 ± 5.9	91.2 ± 5.3
MCH (pg)	30.9 ± 2.4	30.9 ± 2.4	30.5 ± 2.0
MCHC (mmol/L)	20.7 ± 0.7	20.7 ± 0.7	20.8 ± 0.7
White cell count ($10^9/L$)	7.2 ± 2.1	7.1 ± 2.1	7.6 ± 2.1
Eosinophils (%)	2.7 (1.7–4.1)	2.7 (1.7–4.1)	2.5 (1.6–3.4)
Lymphocytes (%)	25.8 ± 8.6	25.8 ± 8.6	26.8 ± 8.4
Basophils (%)	0.3 (0.2–0.5)	0.3 (0.2–0.5)	0.3 (0.2–0.6)
Neutrophils (%)	63.9 ± 9.5	63.9 ± 9.5	63.5 ± 9.5
Neutrophils band (%)	1 (0–3)	1 (0–3)	0.5 (0–1)
Monocytes (%)	6.7 ± 2.7	6.7 ± 2.7	6.6 ± 2.4
Treatment randomisation			
Candesartan	805 (49.7)	751 (50.3)	54 (42.9)

BMI: body mass index; NYHA: New York Heart Association; MCV: mean corpuscular volume; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; ALT: alanine-aminotransferase; AST: aspartate aminotransferase; mean (SD), n (%) or median (IQR)

Table 6.2. Baseline characteristics associated with the development of diabetes in CHARM as analysed by univariate and multiple logistic regression analyses

	Univariate logistic regression			Multiple logistic regression*		
	Wald Chi Sq	P value	OR (95%CI)	Wald Chi Sq	P value	OR (95%CI)
HbA1C (per %)	58.8	<0.0001	2.30 (1.86-2.84)	43.9	<0.0001	2.20 (1.74-2.78)
BMI (per kg/m^2)	52.7	<0.0001	1.10 (1.07-1.13)	24.7	<0.0001	1.09 (1.05-1.12)
Age (per year)	19	<0.0001	0.97 (0.96-0.98)	1.3	0.25	0.99 (0.97-1.01)
Diuretics at baseline (yes vs. no)	13.1	0.0003	6.39 (2.34-17.46)	6.9	0.008	4.17 (1.44-12.05)
Digoxin (yes vs. no)	8.7	0.003	1.77 (1.21-2.59)	5.9	0.016	1.73 (1.11-2.69)
Creatinine (per umol/L)	8.5	0.004	0.99 (0.98-1.00)	8.6	0.003	0.99 (0.98-1.00)
Potassium (per mmol/L)	8.2	0.004	0.53 (0.34-0.82)	3.3	0.07	0.63 (0.39-1.04)
MCV (per fL)	7.4	0.007	0.96 (0.93-0.99)	0.9	0.34	0.96 (0.89-1.04)
Red cell count (per 10^{12}/L)	5.7	0.02	1.53 (1.08-2.18)	0	0.97	1.01 (0.65-1.57)
Beta-Blocker (yes vs. no)	5.1	0.02	1.55 (1.06-2.25)	3.6	0.06	1.50 (0.99-2.27)
White cell count (per 10^9/L)	5.1	0.02	1.09 (1.01-1.18)	0.1	0.75	0.99 (0.90-1.08)
Lipid-lowering therapy (yes vs. no)	4.6	0.03	1.49 (1.03-2.15)	12.8	0.0003	2.12 (1.41-3.20)
Spironolactone (yes vs. no)	4.5	0.03	1.62 (1.04-2.54)	1.3	0.25	1.35 (0.81-2.23)
MCH (per pg)	4.4	0.04	0.92 (0.85-1.00)	0.2	0.64	1.04 (0.87-1.25)
ALT (per units/L)	4.3	0.04	1.01 (1.00-1.02)	6	0.015	1.01 (1.00-1.02)
Sodium (per mmol/L)	3.9	0.048	0.94 (0.89-1.00)	0.7	0.41	0.97 (0.91-1.04)
Eosinophils (per %)	3.9	0.049	0.91 (0.83-1.00)	2.5	0.12	0.91 (0.81-1.02)
Candesartan therapy (placebo vs. candesartan)	2.5	0.11	1.35 (0.93-1.95)	*	*	*
ACE-inhibitors (yes vs. no)	2.1	0.15	1.31 (0.91-1.88)	*	*	*
Bilirubin direct (per umol/L)	2	0.16	0.94 (0.86-1.03)	*	*	*
Long-acting nitrates (yes vs. no)	1.9	0.17	0.73 (0.46-1.14)	*	*	*
Systolic blood pressure (per mmHg)	1.9	0.17	1.01 (1.00-1.02)	*	*	*
Medical history: hypertension (yes vs. no)	1.9	0.17	1.31 (0.89-1.93)	*	*	*
Lymphocytes (per %)	1.6	0.21	1.01 (0.99-1.03)	*	*	*
Left ventricular Ejection fraction	1.5	0.22	0.48 (0.15-1.54)	*	*	*
MCHC (per mmol/L)	1.3	0.25	1.16 (0.90-1.48)	*	*	*

Basophils (per %)	1.2	0.27	1.32 (0.81–2.15)	*	*	*
Haemoglobin (per mmol/L)	1.2	0.28	1.11 (0.92–1.35)	*	*	*
NYHA (III or IV vs. I or II)	1	0.33	1.21 (0.83–1.76)	*	*	*
Medical history: prior myocardial infarction (yes vs. no)	0.8	0.36	0.84 (0.59–1.21)	*	*	*
Alkaline phosphatase (per units/L)	0.8	0.38	1.00 (1.00–1.01)	*	*	*
Oral anticoagulant therapy (yes vs. no)	0.8	0.38	0.84 (0.56–1.25)	*	*	*
Haematocrit (%)	0.7	0.41	1.02 (0.98–1.06)	*	*	*
AST (per units/L)	0.6	0.44	1.00 (1.00–1.01)	*	*	*
Bilirubin total (per umol/L)	0.6	0.44	0.99 (0.96–1.02)	*	*	*
Sex (female vs. male)	0.3	0.58	1.11 (0.76–1.63)	*	*	*
Neutrophils (per %)	0.3	0.6	1.00 (0.98–1.01)	*	*	*
Monocytes (per %)	0.1	0.73	0.99 (0.92–1.06)	*	*	*
Calcium channel blocker (yes vs. no)	0.002	0.96	1.01 (0.66–1.55)	*	*	*
Smoking habit (current or past vs. none)	0	0.99	1.00 (0.67–1.49)	*	*	*

*Only factors with $P < 0.10$ on univariate logistic regression were included in this multiple factor logistic regression.

For abbreviations see Table 6.1

Table 6.3. Diagnosis of new-onset diabetes according to BMI quartiles

BMI group	Developed diabetes during study	
	No	Yes
≤ 24.25 kg/m^2	400 (98.0%)	8 (2.0%)
24.25-27.70 kg/m^2	383 (95.3%)	19 (4.7%)
27.71-31.65 kg/m^2	368 (90.9%)	37 (9.1%)
>31.65 kg/m^2	343 (84.7%)	62 (15.3%)

BMI: body mass index

Table 6.4. Multiple logistic regression of baseline characteristics with stepwise selection of all effects predicting the development of diabetes in chronic heart failure

	Wald Chi sq	P	OR (95% CIs)
HbA1C	51.6	<0.0001	1.78 (1.52–2.08)
BMI	26.6	<0.0001	1.64 (1.36–1.98)
Lipid-lowering therapy	12.1	0.0005	2.05 (1.37–3.07)
Serum creatinine	9.7	0.0018	0.68 (0.54–0.87)
Diuretic therapy	8.6	0.0033	4.81 (1.69–13.69)
Digoxin therapy	5.2	0.0221	1.65 (1.08–2.54)
ALT (U/L)	4.9	0.0269	1.15 (1.02–1.31)
Age	3.9	0.0476	0.81 (0.65–1.00)

ORs are expressed per 1 SD change in age, BMI, ALT, HbA1C, and creatinine

Table 6.5. Receiver operating characteristic curve analysis for single factor logistic regression models predicting development of diabetes mellitus

Effect	**AUROC**
HbA1c	0.723
BMI	0.712
Digoxin (yes vs. no)	0.569
Lipid-lowering therapy (yes vs. no)	0.550
Creatinine (umol/L)	0.580
Diuretic therapy	0.571
ALT (U/L)	0.626
Age (years)	0.619

Table 6.6. Receiver operating characteristic curve analysis for the multiple logistic regression, with stepwise selection and addition of effects, predicting development of diabetes mellitus

Step	Effect entered	Effect removed	AUROC
1	HbA1c	-	0.723
2	+ BMI	-	0.788
3	+ Digoxin (yes vs. no)	-	0.800
4	+ Lipid-lowering therapy (yes vs. no)	-	0.802
5	+ Creatinine (umol/L)	-	0.809
6	+ Diuretic therapy	-	0.813
7	+ ALT (U/L)	-	0.816
8	+ Age (years)	-	0.816

6.4 Discussion

Analysis of data from the CHARM program confirmed the high prevalence and incidence of diabetes in patients with chronic heart failure. An estimated incidence of 21–28 cases per 1,000 patients per year (mean age 66 years) contrasts with the incidence of diabetes of 16.8 cases per 1,000 population per year (age 65–79 years) and 11.2 cases per 1,000 population per year (age 45–64 years) from the National Health and Nutrition Examination Survey in 2003 in which self-reporting of diabetes was used (170). Data available from 1,620 of these patients in CHARM, of who 126 developed diabetes, showed that the two most powerful independent predictors of diabetes in the program were HbA1C, a measure of dysglycaemia, and BMI. Both gave AUROCs very similar to those expected in the general population. Given the worse outcomes of chronic heart failure described in patients with diabetes (24), the ability to better identify individuals at risk of diabetes may allow the clinician to take steps (e.g. lifestyle improvement) to reduce this risk with resultant better clinical outcomes. In view of evidence that HbA1C is a predictor of cardiovascular death, hospitalisation, and total mortality in not only diabetic but also non-diabetic patients with chronic heart failure, its measurement in patients with chronic heart failure may have clinical potential, and future studies that include FPG will allow further assessment of this. This is on the background of emerging support for the use of HbA1C as part of a screening strategy for diabetes (171).

The independent associations of certain characteristics with the development of diabetes, namely use of lipid-lowering therapy, use of digoxin, and lower serum creatinine concentration, plus the strong association of diuretic use at baseline require further examination and explanation. With regard to baseline therapies, I have already confirmed the association between statin therapy and risk for incident diabetes in previous chapters (129;150), but these associations may also reflect confounding factors rather than any statin treatment effect. I am not aware of any data suggesting that digoxin therapy influences the development of diabetes. One possibility is that patients receiving both digoxin and diuretic therapies have more severe chronic heart failure requiring more intensive therapy, and, therefore, these are serving as proxies of heart failure severity. There is evidence that worse chronic heart failure predicts diabetes (172;173),

although, interestingly, neither NYHA status nor LVEF predicted new-onset diabetes in the present analysis. Further studies are needed to examine these issues. Furthermore, there are powerful data from the field of hypertension showing an increased incidence of diabetes on thiazide diuretic therapy relative to both placebo and other antihypertensive agents (174). The proportions of patients taking loop and thiazide diuretics in CHARM were not available. Those receiving multiple medications may have had blood samples for biochemical analyses taken more often outside the trial, thereby increasing the chance of detecting diabetes if FPG analyses were also performed. As shown in CHARM (167) and elsewhere, the use of ACE-inhibitors and ARBs leads to a rise in serum creatinine concentration, and so this finding may reflect confounding effects of treatments on diabetes risk rather than any direct association between renal function and diabetes risk. In addition, lower creatinine concentrations could partially reflect reduced muscle mass and thus a biologically plausible mechanism linking lower creatinine levels to elevated higher diabetes risk.

The increase in risk of diabetes per unit increase in serum ALT was admittedly modest and of uncertain clinical significance in this analysis; furthermore, elevation in serum ALT may occur as a result of hepatic congestion in heart failure. However, it should be recognised that the association between serum ALT and risk of diabetes concurs with findings in the general population. Serum ALT, a hepatocellular enzyme, is a reasonable marker of fat accumulation in the liver in non-alcoholic fatty liver disease (175). Non-alcoholic fatty liver disease is itself a condition strongly linked to insulin resistance, type 2 diabetes, and obesity. Serum ALT has previously been shown to predict diabetes in different populations, including hypercholesterolaemic men in Scotland (176) and a general population cohort in Japan (177), but to my knowledge this is the first evidence of any association in patients with chronic heart failure. This finding implies that liver fat is relevant to the pathogenesis of diabetes in patients with chronic heart failure, as it is in individuals without this condition.

The finding that younger age was an independent predictor of diabetes was unexpected. It may simply be that younger patients with heart failure have a longer survival time and consequently a greater chance to develop diabetes. An alternative explanation is that younger patients with chronic heart failure may

represent a slightly different phenotype with higher BMI and higher risk of diabetes compared with that of older patients. There are data to support this suggestion; in a substudy of 2,107 patients in CHARM, the prevalence of obesity (BMI ≥30 kg/m^2) was four times higher in patients with chronic heart failure aged <50 years than in patients aged ≥80 years (data not shown). Irrespective of the above findings, it should be noted that age did not significantly improve AUROC for prediction beyond other measures.

The strengths of the present analysis are the number of incident cases of diabetes and number of patients included in the program, together with excellent baseline phenotyping. There are also potential weaknesses that must be highlighted. Given that identifying predictors of diabetes was not a predetermined outcome of the CHARM program, these findings must be treated as post hoc. In addition, all data are limited to North American patients. Ideally, the diagnoses of diabetes would have been carried out uniformly under controlled circumstances in all patients, although pragmatic factors, as occurs in clinical practice, dictated otherwise. I cannot, therefore, exclude the possibility that patients with undiagnosed diabetes at baseline were included in the analysis. It would also have been preferable to measure and include FPG results and serum lipids, particularly serum triglycerides, but the patients were non-fasting and so these parameters were not available. Finally, potentially useful data such as family history of diabetes were not available. Nevertheless, the results provide the first comprehensive examination of predictors of diabetes in patients with chronic heart failure and provide a useful framework for further study.

In summary, the strongest predictors of development of diabetes in patients with chronic heart failure in the CHARM program were HbA1C and BMI, in line with prior observations in the general population. Other minor independent predictors of diabetes in part reflected disease severity or drug-associated diabetes risk, but their addition did not substantially improve prediction of diabetes. These findings suggest that simple predictors would serve well to identify those patients with chronic heart failure at elevated risk for developing type 2 diabetes. Identification of high-risk individuals may allow application of

approaches that reduce progression to diabetes in patients with heart failure and potentially result in better clinical outcomes.

Data included in this chapter were published in Diabetes Care in 2009 (178).

Appendix.

Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials

Please see the Acknowledgements and Declaration. This section is included as I made a significant contribution to the conduct of the project and because it provides an important back-drop to my theme of the interplay between glycaemia and cardiovascular disease. In particular, it should be noted that this work was led by Professor Kausik Ray and Dr Rao Seshasai, that Professor Ray wrote the first draft of the published paper and that Dr Seshasai was chiefly responsible for the statistical analyses.

A1. Introduction

Type 2 diabetes mellitus is a well established risk factor for cardiovascular disease. To date several observational studies have shown a positive correlation between measures of glycaemic control and both cardiovascular outcomes and microvascular disease independent of risk factors known to cluster with diabetes (179-181). As a result of such observations, randomised controlled trials have been conducted to assess whether more intensive control of glucose results in a reduction in long term clinical events and prolongs life compared to standard (less intensive) therapy. In contrast to the significant benefits demonstrated on microvascular outcomes (46;63), individually these trials have failed to show consistent beneficial effects on cardiovascular events (45;46;64;182).

Such inconsistent evidence has resulted in the American Heart Association, the American College of Cardiology and the ADA providing a conservative class IIb recommendation with level of evidence A (183) for the benefit of glycaemic control on cardiovascular disease. It is possible, however, that the relevant trials were individually underpowered to demonstrate clinical benefit particularly if event rates were lower than expected due to better control of risk factors, if duration of therapy was shorter than might be needed to observe a clinical benefit (184) or possibly if the differences in glycaemic control were

less than might be needed to show a significant benefit. To address such uncertainties we quantitatively assessed whether more intensive control of glucose among individuals with type 2 diabetes mellitus results in a reduction in cardiovascular events and is safe compared to less intensive therapy. This report presents data from a literature-based meta-analysis of published randomised controlled clinical trials whose goal was to assess the impact of differential glycaemic control on cardiovascular outcomes.

A2. Methods

Data sources

We searched MEDLINE, Cochrane Central and EMBASE databases for articles published in English from January 1970 to January 2009 using criteria ["glucose OR HbA1c"] AND ["Cardiovascular disease"] AND ["diabetes mellitus"] limited to randomised controlled trials. This initial search provided 2439 articles which were further screened for inclusion using titles, abstracts and/or full texts. We supplemented the electronic search by a hand search of reference lists of relevant publications including meta-analyses and reviews (Figure 7.1).

Study selection

Our predefined inclusion criteria for clinical trials were carefully considered and included all of the following: 1) randomisation of individuals with type 2 diabetes mellitus to a glucose lowering regimen vs. a control regimen (including placebo, usual care or less intensive glycaemic control) and which demonstrated a clinically significant difference in glycaemic control between treatment groups during follow up; 2) outcome trials which included cardiovascular events in the primary endpoint and which reported complete information on effect estimates or provided information in publications which would allow for effect estimates to be calculated for all of the following endpoints: non-fatal myocardial infarction, coronary heart disease events defined as fatal or non-fatal myocardial infarction, stroke and all-cause mortality; 3) trials conducted on stable individuals i.e. excluding studies of intensive glycaemic control in an acute hospital setting. Trials which met the above inclusion criteria were identified, with available information on cardiovascular outcomes and glycaemic control in principal publications, secondary publications and study web-sites.

Six trials initially screened were eventually excluded. One trial, A Diabetes Outcome Progression Trial (ADOPT), did not aim to assess cardiovascular outcomes in the primary endpoint (61), and another trial, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD), was not designed to compare intensive to moderate glucose-lowering

(185); also, only interim RECORD data on some of the outcomes of interest were available without information on HbA1c during follow up at the time of conducting this analysis. The Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial was excluded as this was conducted among individuals with IGT (186) and the University Group Diabetes Program (UGDP) trial was excluded as it had a mixture of subjects with both diabetes and IGT and did not provide information separately on those with diabetes or effect estimates for each outcome of interest in each treatment arm (187;188). Two further trials, STENO 2 and Kumamato, were excluded as the former tested multiple interventions and therefore did not purely assess intensive glucose control (189) and the latter did not report on the individual endpoints of interest but a composite endpoint of cardiovascular events which included peripheral vascular disease and angina (190). The search yielded five randomised controlled trials which fulfilled our important *a priori* study selection criteria. The five trials involving a total of 33,040 participants were: the United Kingdom Prospective Diabetes Study (UKPDS) which combines stratified data on the intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment (UKPDS 33) (63) and the effect of intensive blood-glucose control with metformin vs. placebo in overweight patients (UKPDS 34) (64), the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) (42;191;192), the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) (46), the Veterans Affairs Diabetes Trial (VADT) (48;193) and Action to Control Cardiovascular Risk in Diabetes trial (ACCORD) (45).

Data extraction

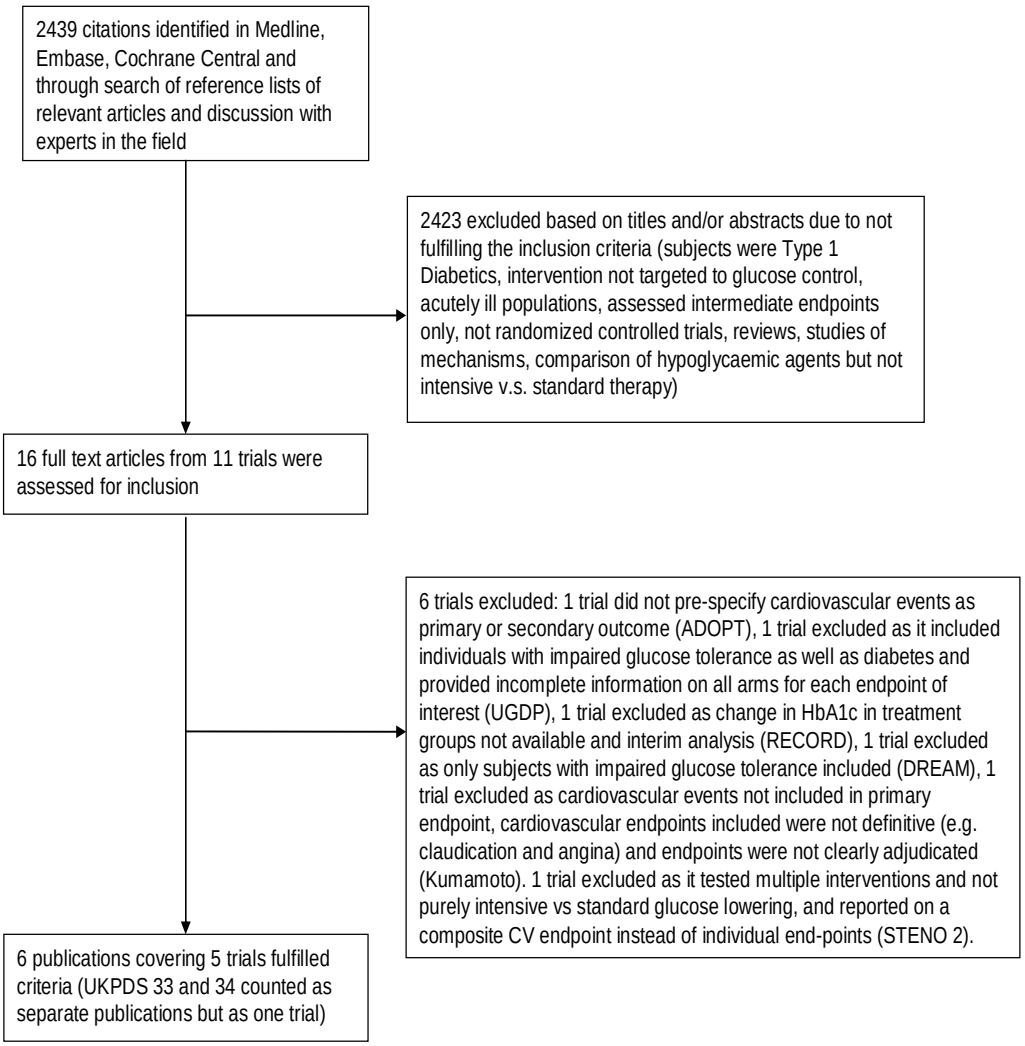
Together with three colleagues I abstracted information in duplicate using a standardised format from all relevant studies and where necessary, a fifth investigator, Professor Kausik Ray, adjudicated any discrepancies. Information was obtained on several baseline characteristics of the participants, on the absolute number of events (non-fatal myocardial infarction, coronary heart disease, stroke and all-cause mortality), and the event rates in each arm of randomisation. Where event rates could not be directly abstracted, they were calculated using published information on average follow-up duration and the

number of participants in each randomisation group. Information regarding HbA1c at baseline and during follow up was abstracted from the published reports. Follow-up duration was reported as a mean in PROactive and ACCORD and as a median in UKPDS, ADVANCE and VADT. For the purposes of approximation of the number of person years of follow up, the median in the latter 3 studies was assumed to approximate to the arithmetic mean.

Statistical analysis

While three out of five studies included in this meta-analysis provided information on HRs and CIs for each of the four main outcomes of interest, two of the studies did not but instead provided information on absolute numbers of events. Therefore, to standardise the reporting of our results, OR and 95% CIs were calculated from raw data from each trial. To assess the effect of more intensive vs. less intensive control of glucose on different outcomes, we conducted a random effects model meta-analysis which assumes that the true underlying effect varies between studies. Statistical heterogeneity across trials was assessed using the χ^2 (p value) and I^2 statistics, with a $p>0.1$ considered statistically non-significant. The I^2 statistic is derived from Cochran's Q i.e. χ^2 statistic [(Q – df/Q)*100] and provides a measure of the proportion of the overall variation that is attributable to between-study heterogeneity. In addition we assessed the likelihood of presence of publication bias using funnel plots and Egger test. To calculate the absolute rates of each endpoint of interest we divided the absolute number of events reported by the number of person years of follow up in the more vs. less intensive glucose control arms. Summary data for each endpoint were obtained by combining rates across studies using a random-effects model meta-analysis, as rates varied considerably between the studies. Other summary characteristics are presented as weighted means. For each analysis UKPDS 33 and 34 are combined using random effects or weighted means as appropriate and reported as UKPDS. As a sensitivity analysis, the main results (ORs) were compared with corresponding rate ratios in a random effects meta-analysis. All p values reported were two-sided and a p-value less than 0.05 was considered to be statistically significant. Analyses were performed using Stata version 10.1 (Stata Corp, College Station, Texas).

Figure A.1. Flow diagram of selection of studies for inclusion in present meta-analysis



A3. Results

Study population

Table A.1 reports the study design, baseline demographic characteristics, the duration of follow-up and the average HbA1c in the 5 studies included in this meta-analysis. The definitions of diabetes and eligibility criteria for each study are shown in Table A.2. Overall, there were 33,040 subjects in predominantly western populations who had diabetes on average for 8 years prior to enrolment. One study (UKPDS) enrolled subjects within the first year following diagnosis whereas the remaining 4 studies enrolled subjects with long-standing diabetes. Information on a prior history of macrovascular disease was available in 4 studies and ranged from 32% to 100% with one study (PROactive) mandating macrovascular disease in the eligibility criteria. The mean age of subjects in these five trials ranged from 53 to 66 years (weighted mean 62 years), with the proportion of women ranging from 3 to 42% (weighted mean 38 %). The average baseline LDL-cholesterol across studies was 3 mmol/L, the systolic blood pressure was 140 mmHg, and the baseline HbA1c was 7.8%. During an average follow-up of 4.95 years HbA1c was 0.9% lower in the more intensive treatment group compared to the less intensive group.

Event rates by differential glycaemic control

Table A.1 reports the definitions of the vascular endpoints used in the five trials. During approximately 163,000 person years of follow up, 1497 non-fatal myocardial infarctions, 2318 coronary events, 1127 fatal and non-fatal strokes and 2892 deaths from any cause were recorded. Table A.3 reports the event rates per 1000 person years of follow up in the more vs. less intensively treated populations in each trial. According to this combined data set there were 2.3 fewer myocardial infarctions or 2.9 fewer coronary events for every 200 more intensively treated patients for 5 years (1000 person years of follow up). The event rates for strokes and all-cause mortality were not statistically different between the two arms.

Effect of more intensive glucose control on risk reduction

Figures A.2 to A.5 show the effects of more vs. less intensive control of glucose on non-fatal myocardial infarctions, coronary events, stroke and death from any cause respectively. More intensive control of glucose significantly reduced non-fatal myocardial infarctions by 17% (OR 0.83, 95% CI 0.75-0.93) and coronary heart disease events by 15% (OR 0.85, 95% CI 0.77-0.93). There was no strong statistical evidence of heterogeneity in the effect estimate between studies for either non-fatal myocardial infarctions (I^2 = 0.0%, 95% CI 0.0 – 69.3%, p=0.61) or for coronary events (I^2 = 0.0%, 95% CI 0.0 – 52.7%, p=0.78). There was no significant effect of more intensive control of glucose on stroke OR 0.93, 95% CI 0.81-1.06) or on death from any cause (OR 1.02, 95% CI 0.87-1.19). While there was no significant heterogeneity observed for strokes (I^2 = 0.0%, 95% CI 0.0 – 62.0%, p=0.70) there was considerable heterogeneity across studies for the outcome of all-cause mortality (I^2 = 58.0%, 95% CI 0.0 – 84.4%, p=0.049). Rate ratios for more intensive vs. less intensive glycaemic control provided comparable results (Figure A.6). There was no strong evidence of publication bias from examination of funnel plots (Figure A.7). Overall there was no significant effect of intensive glucose lowering on heart failure (OR 1.08, 95% CI 0.90-1.31, I^2 = 62.9%), but considerable heterogeneity was observed across studies when separated by differential glitazones use, with the combination of the PROactive (100% glitazone use in the active arm) and ACCORD (92% glitazone use in the intensive treatment arm and 58% in the standard treatment arm) trials being associated with a significant excess risk of heart failure, but with no evidence of excess risk in the other three trials. (Figure A.8). Data on cardiovascular death and thus non-cardiovascular death were limited to 4 studies as the UKPDS study did not have data on this endpoint. In the 4 studies which allowed for comparison between the types of death reported, there were no significant differences between the intensity of glucose reduction and type of death (Figure A.9). The effect of intensive glucose reduction on myocardial infarctions, coronary heart disease events, stroke and heart failure in this restricted cohort were consistent with the main results (Figure A.9).

Effect of more intensive glucose control on hypoglycaemia and weight gain

Table A.4 reports the effects of more intensive glucose control on hypoglycaemia and weight gain. As expected the proportion of subjects who experienced any hypoglycaemic episode was greater in the more intensive treatment group compared with the less intensive group (weighted averages 38.1% vs. 28.6% more vs. less intensive groups respectively). Overall, severe hypoglycaemia was much less common and the proportion of subjects ranged from 0.7% to 8.5%. However, severe hypoglycaemia was almost twice as common in the more intensively treated group (weighted averages 2.3% vs. 1.2% of subjects, more vs. less intensive groups respectively). On average subjects receiving more intensive glycaemic control were 2.5 kg heavier at the end of study.

Table A.1. Baseline characteristics and treatment protocols of five clinical trials comparing different glucose lowering regimens among individuals with diabetes mellitus

Study	Location	Year	N	Mean age (yrs)	Duration since DM diagnosis (yrs)	% Males	% Smokers	% with CVD†	Mean SBP (mmHg)	Mean LDL (mmol / L)	Mean BMI (kg/m2)	Mean baseline HbA1c (%)	Treatment given	Average follow-up (yrs)	Total Person years of follow-up	Mean HbA1c over follow-up (Control)	Mean HbA1c over follow-up (Intensive)
UKPDS (63;64)	England 23 centres	1998	4620	53	< 1	59	30	NS*	136	3.53	28	7.1	Treatment with Sulfonylurea or insulin or metformin, target FPG <6mmol/l vs. control with standard diet, target FPG<15mmol/l	10.1	46,237	7.9	7.0
PROactive (42)	321 centres in 19 countries‡	2005	5238	62	8	66	14	100	143	2.90	31	7.9	Treatment with Pioglitazone PO 15-45mg (plus current medication) vs. control with current medication	2.9	15,059	7.6§	7.0§
ADVANCE (46)	215 centres in 20 countries±	2008	11,140	66	8	58	14	32	145	3.12	28	7.5	Treatment with gliclazide modified release PO 30-120mg +/- metformin, thiazolidinedione, glinide, acarbose or insulin, target HbA1c ≤ 6.5% vs. control with standard therapy per local guideline	5.0	55,700	7.3	6.8
VADT (48)	USA	2008	1791	60	12	97	17	40	132	2.78	31	9.4	Treatment with maximal dose metformin plus rosiglitazone (BMI>27) or glimepiride plus rosiglitazone (BMI<27) vs. control with half-dose of same	5.6	10,030	8.4	6.9
ACCORD (45)	USA & Canada	2008	10,251	62	10	61	14	35	136	2.71	32	8.3	Treatment with metformin, sulfonylurea, glinide, thiazolidinedione, acarbose, insulin or combination, target HbA1c <6% vs. control with standard therapy, target HbA1c 7-7.9%	3.5	35,879	7.5	6.4
Total / Average**	**-**	**-**	**33,040**	**62**	**8**	**62**	**16**	**-**	**140**	**3.00**	**30**	**7.8**	**-**	**4.95**	**162,905**	**7.5**	**6.6**

Table A.1 footnote

† CVD: Cardiovascular disease, includes MI, revascularisation procedure, stroke, peripheral arterial disease, etc. (defined differently across studies)
‡ Austria, Belgium, Denmark, Estonia, Finland, Czech Republic, France, Germany, Hungary, Italy, Latvia, Lithuania, Netherlands, , Norway, Poland, Slovakia, Sweden, Switzerland, UK
± Australia, Canada, China, Czech Republic, Estonia, France, Germany, Hungary, India, Ireland, Italy, Lithuania, Malaysia, Netherlands, New Zealand, Philippines, Poland, Russia, Slovakia, UK
§ For PROactive mean HbA1c level at end of follow-up was taken
* Excluded individual with current angina or heart failure, and those with more than major vascular event in the past or myocardial infarction in the previous year
** Pooled across studies weighting by study size.
FPG: Fasting plasma glucose; SBP: systolic blood pressure; CVD: cardiovascular disease; BMI: body mass index

Table A.2. Definitions of diabetes and clinical end-points used in clinical trials

	ACCORD	ADVANCE	PROactive	UKPDS*	VADT
Diabetes	Diagnosis of Type 2 DM defined according to the 1997 ADA criteria for 3 months or longer AND an HbA1c level ≥7.5%.	Eligibility relied on a diagnosis of Type 2 DM at age 30 years or older & pt is 55 years or older at entry, with the diagnosis made 10 or more years before entry. Specifically there were no entry criteria for HbA1c concentration or fasting blood glucose.	All pts diagnosed with type 2 DM. HbA1c above upper limit of normal i.e. local equivalent of 6.5% for a DCCT (Diabetes control & complications trial) traceable assay, despite existing treatments with diet alone or oral glucose lowering agents, with or without insulin.	Pts with new diagnosis referred within 2 weeks of first diagnosis of type 2 DM. Eligible pts had a fasting plasma glucose of <6.00mmol/L on two mornings 1-3 weeks apart.	All pts diagnosed with type 2 DM. Centrally measured HbA1c level >4sd above normal mean i.e. ≥7.5%. Or local HbA1c ≥8.3%.
Non-fatal MI	Prolonged ischaemic symptoms lasting >20 minutes and raised cardiac enzymes and/or serum CK-MB. Included Q-wave MIs, non Q-wave MIs, silent MIs, probable non Q-wave MIs, MI after cardiovascular invasive interventions, MI after coronary bypass graft surgery and MI after non-cardiovascular surgery.	ICD 9 code 410	Survived more than 24h after onset of symptoms, and in absence of PCI or CABG, had at least two of: symptoms suggestive of MI, ECG evidence of MI, raised serum cardiac markers; or after PCI or CABG patient had ECG evidence of MI. Included Silent MI (defined as new Q-waves on 2 contiguous leads or R-wave reduction in praecordial leads without a change in access deviation). Data refers to first event of that type.	WHO clinical criteria with ECG/enzyme changes or a new pathological Q-wave. ICD9 code 410.	First events of non-fatal MIs. Not further specified.
Stroke	Definite ischaemic stroke: CT or MRI within 14 days of onset of focal neurological deficit lasting more than 2 hours with evidence of brain infarction; no intraparenchymal haemorrhage, no significant blood in the subarachnoid space. Also included definite primary intracerebral haemorrhage, subarachnoid haemorrhage, stroke of unknown aetiology, non-fatal stroke after cardiovascular invasive interventions and non-fatal stroke post non-cardiovascular surgery.	Death due to cerebrovascular events and non-fatal stroke.	Acute focal neurological deficit lasting for longer than 24 hours or resulting in death within first 24 hours of symptoms. Data refers to a first event of that type.	Major strokes defined as signs or symptoms for 1 month or longer. Non-fatal strokes - ICD9 codes 430-434.9 and 436 and fatal strokes ICD9 codes 430-438.9	First events of strokes.
Total Coronary Heart Disease	Non-fatal MI and fatal MI.	Death due to coronary heart disease (incl. Sudden death) and non-fatal MI.	Non-fatal MI excluding silent MI plus cardiac mortality (fatal MIs plus death from other cardiac disease) Data refers to first event of that type.	Nonfatal MI (ICD9 code 10) + Fatal MI (ICD9 codes 410-414.9, 428-428.9)	First non-fatal MIs and fatal MIs.
Heart Failure	Congestive Heart Failure Death or hospitalisaion for Congestive Heart Failure (with documented clinical and radiological evidence)	Death due to heart failure, hospitalisation for heart failure, or worsening New York Heart Association class	Those requiring hospital admissions	Not associated by MI, with clinical symptoms confirmed by Kerley B lines, rales, raised JVP or 3rd heart sound ICD9 codes 411-428.1	New or worsening heart failure
Cardiovascular Mortality	Death from MI, heart failure, arrhythmia, invasive CV interventions, CV causes after non-CV surgery, stroke, unexpected death presumed to be from ischaemilc CV disease occurring within 24 hours after the onset of symptoms and death from other vascular diseases		Includes all cardiovascular deaths that occurred as a first event	ICD codes 430-438.9	Includes first events of Deaths from MI, Congestive heart failure, Coronary Revascularisation, Stroke, Cerebrorevascularisation, Complications of occlusions, peripheral revascularisation, sudden death and pulmonary embolus

* UKPDS 33 and 34 used the same criteria for defining endpoints

Table A.3. Event rates for various outcomes in five clinical trials included in a meta-analysis of more vs. less intensive glucose control †

Study	Non-fatal myocardial infarction		Coronary heart disease		Stroke		All-cause mortality	
	More Intensive	Less Intensive	More Intensive	Less Intensive	More Intensive	Less Intensive	More Intensive	Less Intensive
UKPDS (63;64)	7.2	9.1	12.8	16.7	4.5	5.0	16.2	19.5
PROactive (42) ** Ω	15.9	19.0	21.9	26.7	11.5	14.1	23.6	24.6
ADVANCE (46)	5.5	5.6	11.1	12.1	8.5	8.8	17.9	19.1
VADT (48)	12.8	15.5	15.4	17.9	5.6	7.2	20.4	18.9
ACCORD (45)	10.4	13.1	11.4	13.8	4.2	4.0	14.3	11.3
Combined Ψ	**10.0**	**12.3**	**14.3**	**17.2**	**6.8**	**7.7**	**18.3**	**18.6**

† Rates are given per 1000-person years

** Non-fatal strokes only

Ω CHD includes cardiac mortality

Ψ Combined rates were calculated by pooling study specific rates using random-effects model meta-analysis

NB. Where rates were not available for a specific endpoint in a given study the total person years in each study arm (which was used to calculate the event rates) was estimated using the average follow-up in each study

Table A.4. Numbers of adverse events in five clinical trials included in a meta-analysis of more vs. less intensive glucose control

Study	Any hypoglycaemic event [N patients (%)]		Serious hypoglycaemic event [N patients (%)]		Mean Weight gain (kg)		
	More Intensive	Less Intensive	More Intensive	Less Intensive	More intensive	Less Intensive	Difference
UKPDS	606 (19.8)	146 (9.4)	39 (1.3)	11 (0.7)	-	-	2.4
PROactive Δ	726 (27.9)	528 (20.1)	19 (0.7)	11 (0.4)	3.6	-0.4	4
ADVANCE Ω	2952 (53.0)	2116 (38.0)	150 (2.7)	81 (1.5)	-0.1	-1	0.9
VADT δ	1333 events (26.7)*	383 events (7.6)*	76 (8.5)	28 (3.1)	8.2	4.1	4.1
ACCORD^	830 events (4.6)*	261 events (1.5)*	538 events (3.0)*	179 events (1.0)*	3.5	0.4	3.1
Combined Ψ	**38.1**	**28.6**	**2.3**	**1.2**	**2.4**	**-0.1**	**2.5**

*these values indicate number of events (instead of number of individuals) and values given in parentheses are event rates per 100 person-years; these values were not included in the calculation of the combined proportion

Δ Any hypoglycaemic episodes refer to those with symptoms compatible with hypoglycaemia. Serious episodes are those that required hospital admission

Ω Hypoglycaemia defined as blood glucose<2.8 mmol/l or the presence of typical signs and symptoms of hypoglycaemia without another apparent cause. Patients with transient dysfunction of the central nervous system, who were unable to treat themselves, requiring help from another person, were said to have serious hypoglycaemia. Also note that both treatment groups lost weight, expressed as negative weight gain

δ Any episodes are those hypoglycaemic episodes with symptoms, and serious episodes are life threatening, or those that cause hospitalisation, disability, death or incapacity

^ Any hypoglycaemic event refers to events requiring any form of assistance. Serious events are those that required medical assistance. For weight gain, numbers are mean weight gain for each group at 3 yrs of follow up

Figure A.2 Odds ratios showing effect of differential blood glucose control on non-fatal myocardial infarction

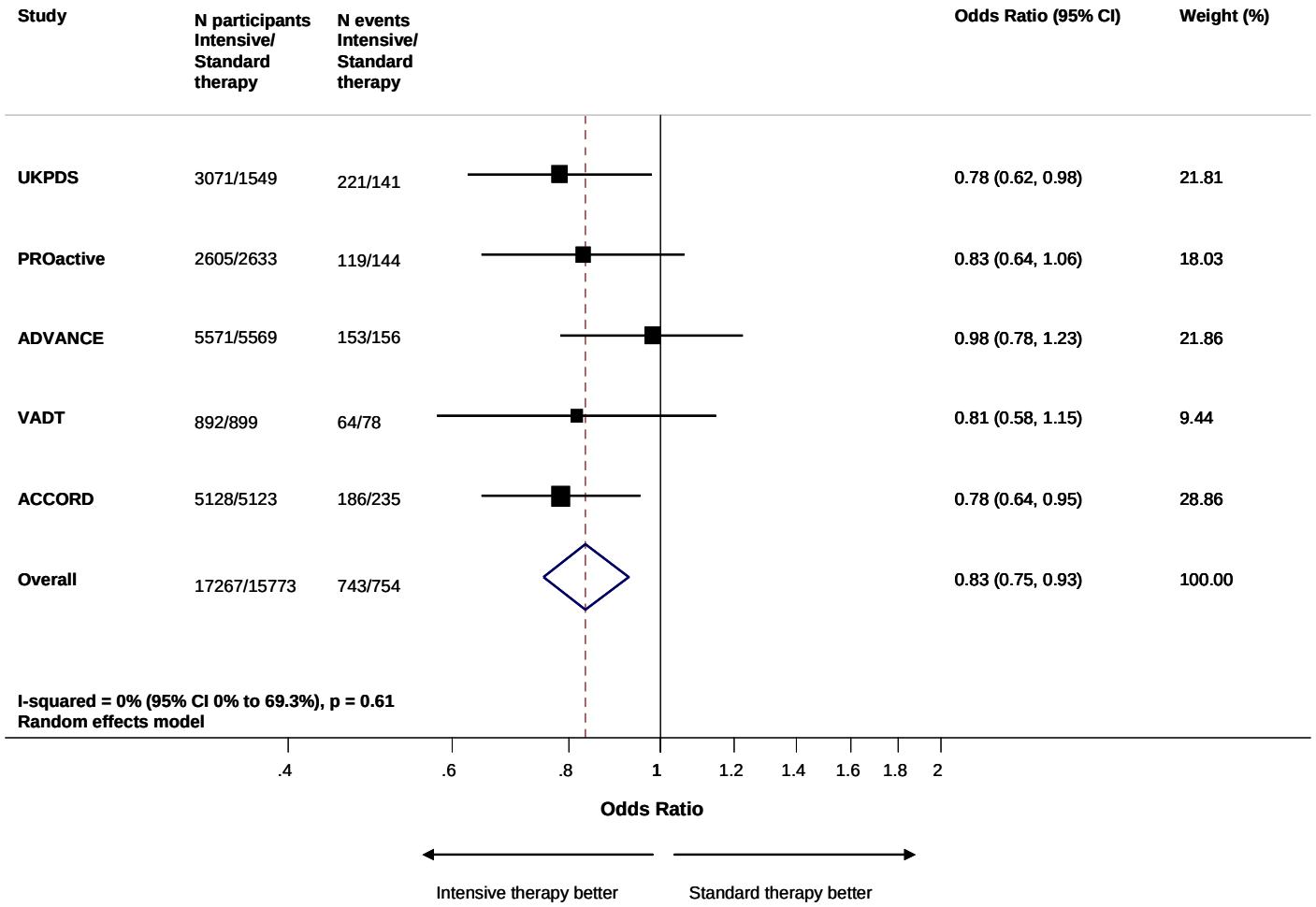
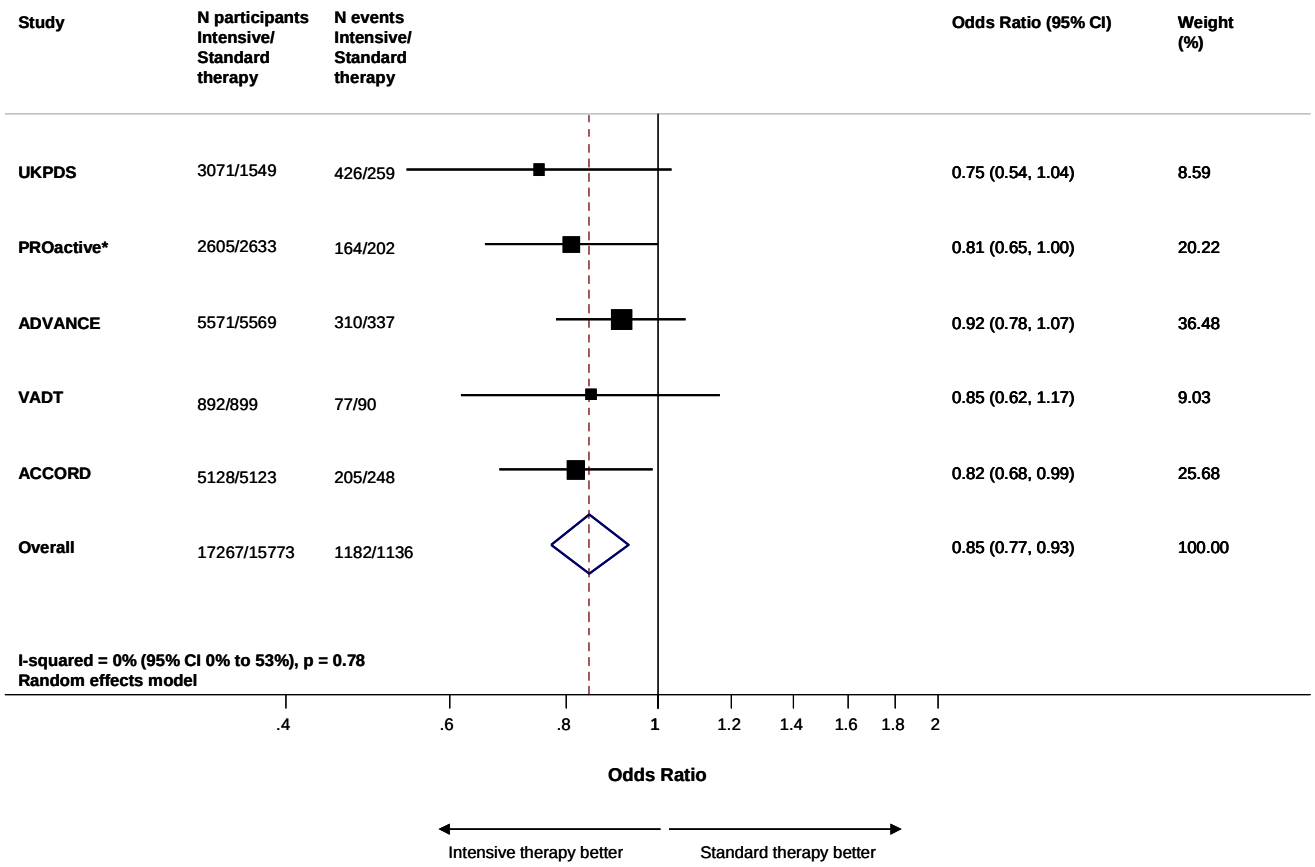
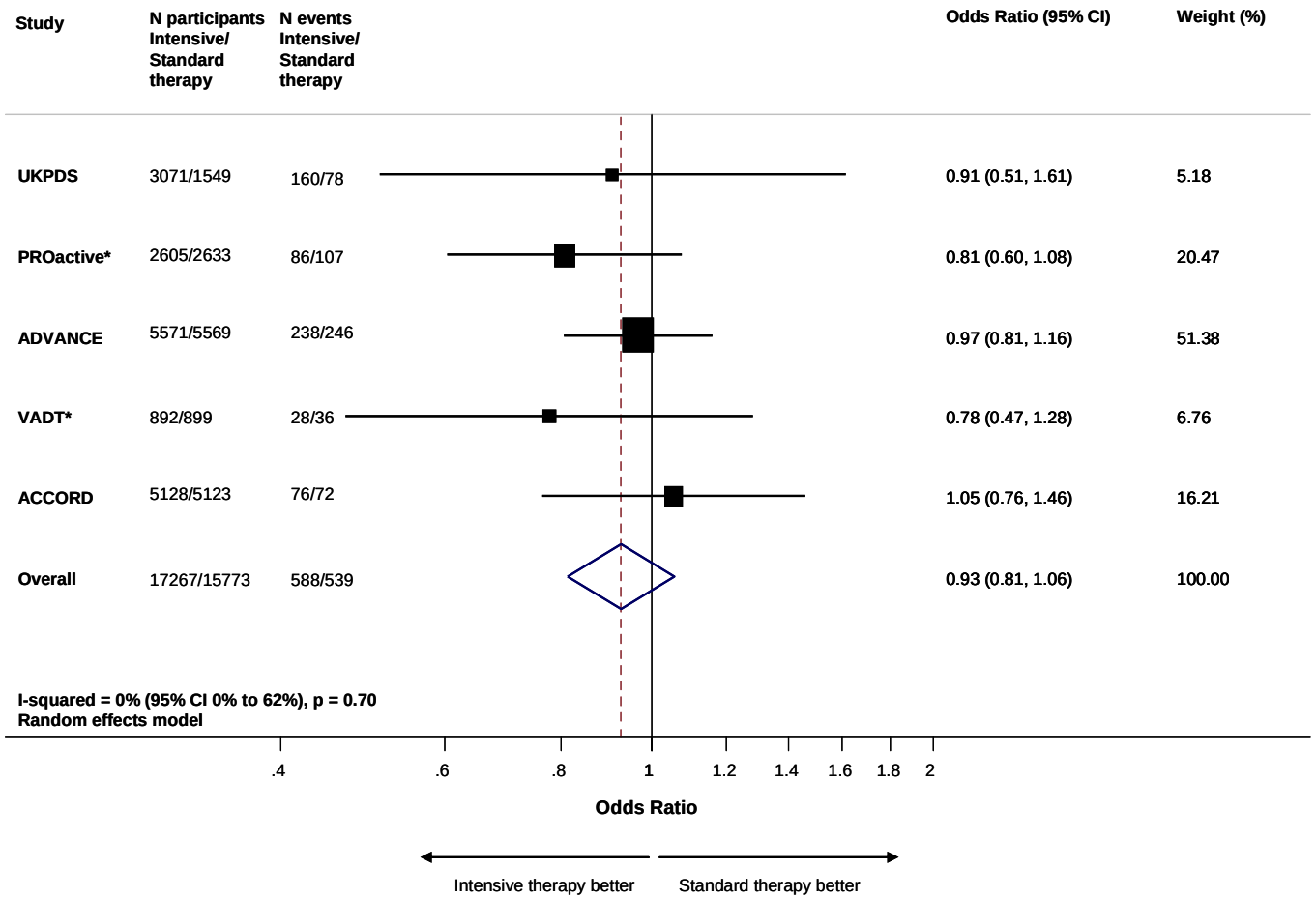


Figure A.3. Odds ratios showing effect of differential blood glucose control on coronary heart disease events



* Coronary heart disease events in PROactive included non-fatal myocardial infarction and death from all cardiac mortality

Figure A.4. Odds ratios showing effect of differential blood glucose control on stroke



* includes only non-fatal strokes

Figure A.5. Odds ratios showing effect of differential blood glucose control on all-cause mortality

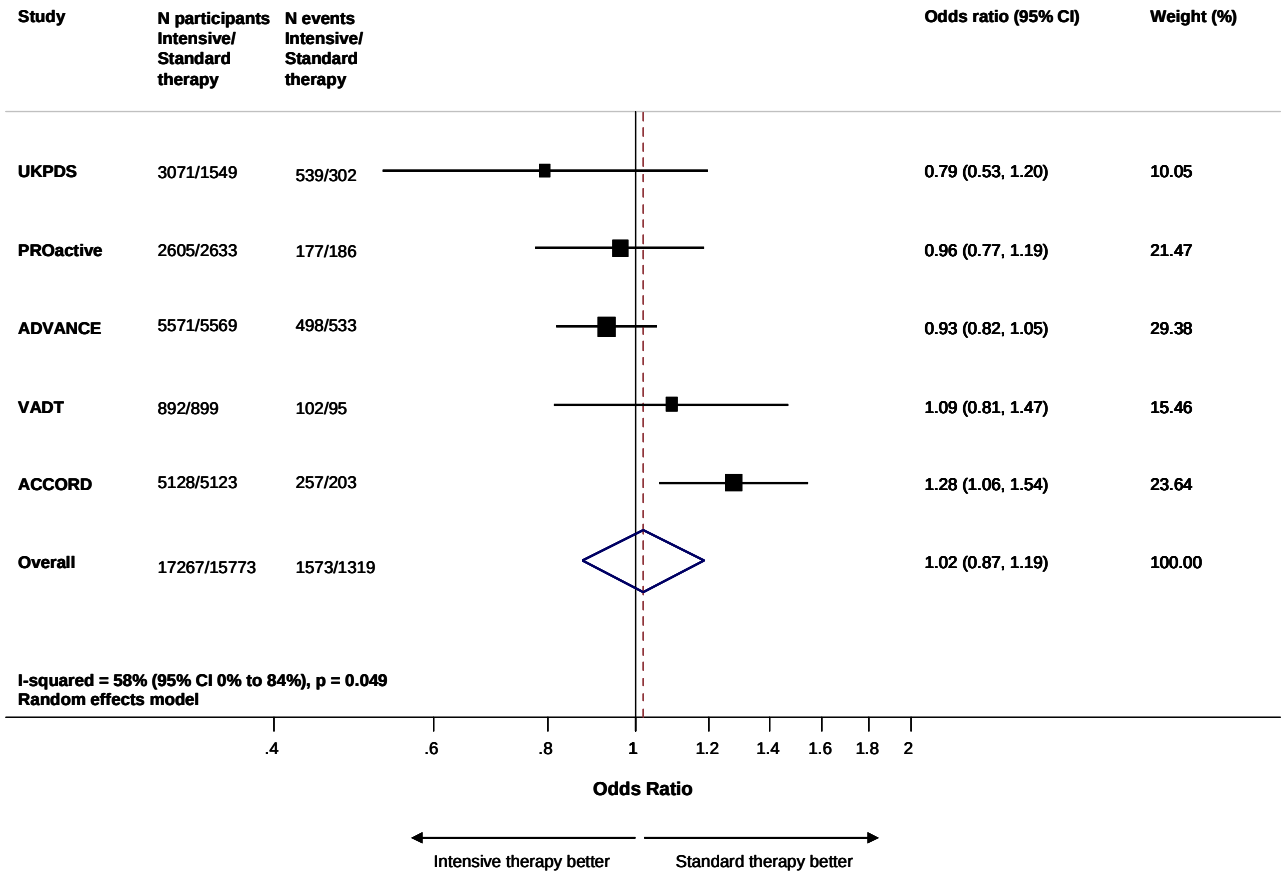
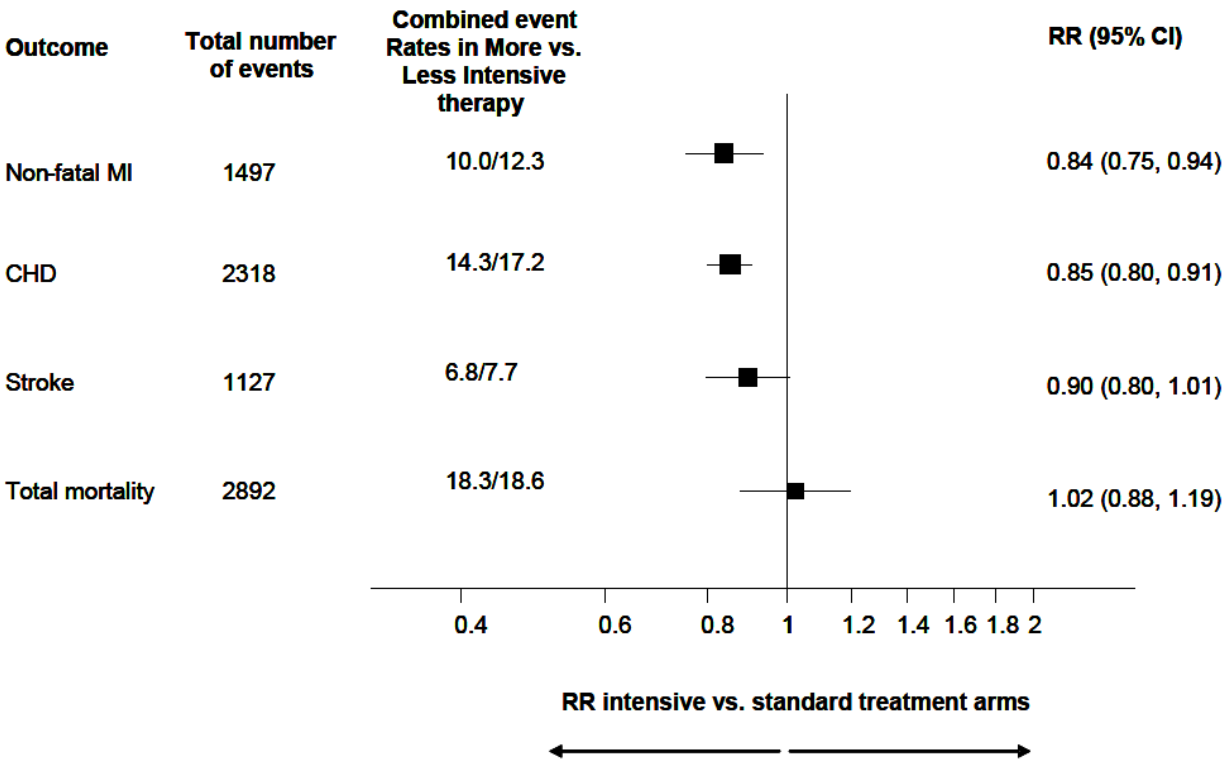


Figure A.6. Rate ratios showing effect of differential blood glucose control on various clinical outcomes



* Rates given per 1000 patient years

† Combined rates were calculated by pooling study specific rates using random-effects model meta-analysis

Figure A.7. Funnel plots of effect estimates for various clinical outcomes

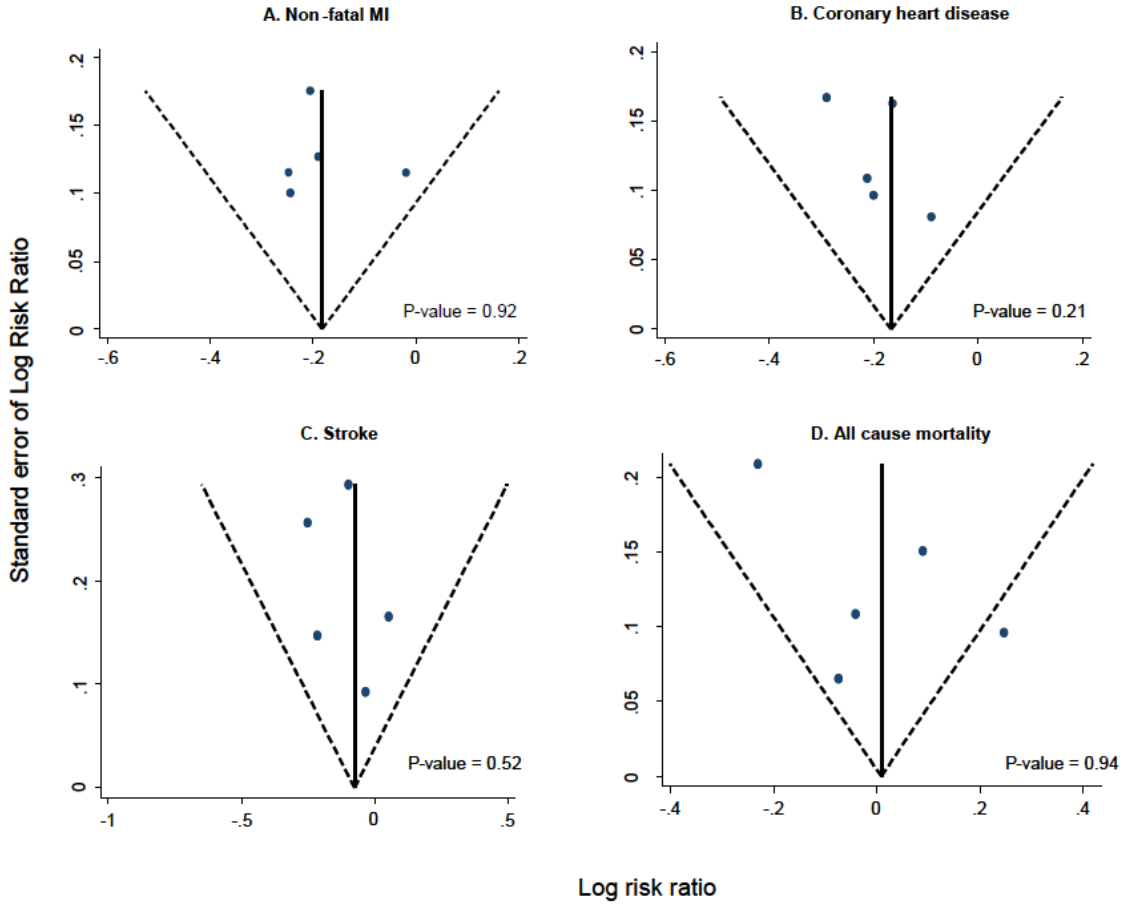


Figure A.8. Odds ratios showing effect of differential blood glucose control on heart failure

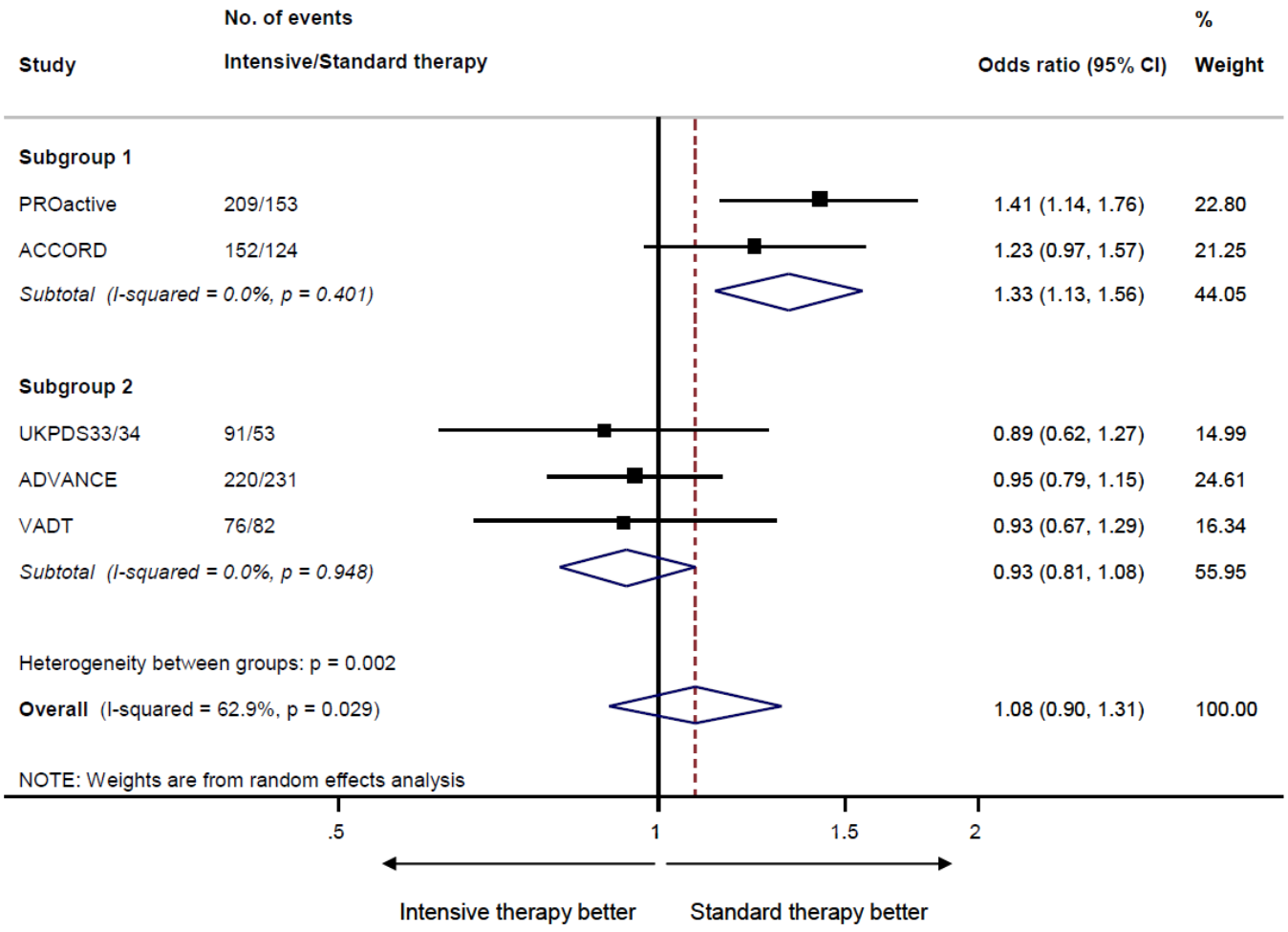
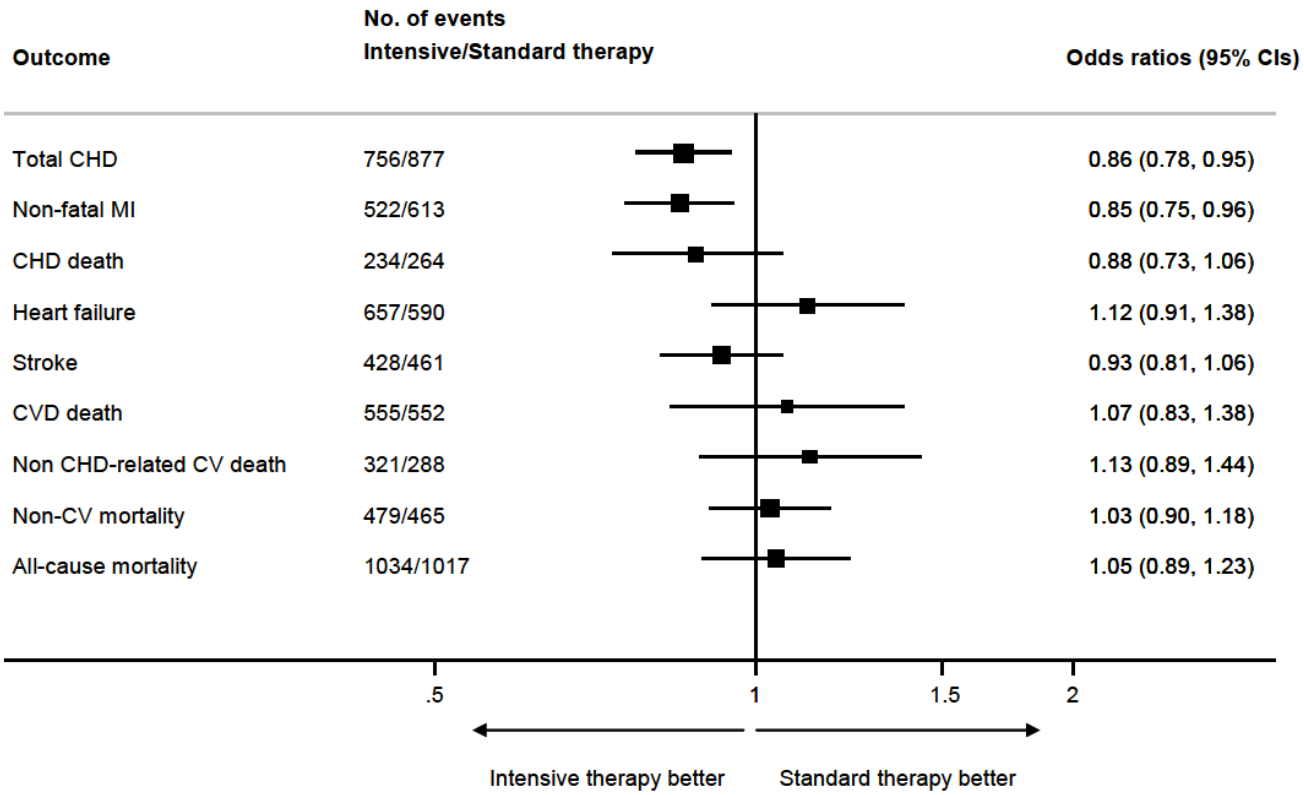


Figure A.9. Composite forest plot of clinical outcomes in studies with available information on these outcomes*



* List of contributing studies include: PROactive, ADVANCE, VADT & ACCORD

A4. Discussion

This literature-based meta-analysis, with carefully considered *a priori* inclusion criteria, identified five relevant clinical trials involving 33,040 participants with approximately 163,000 person-years of follow-up and reports information on 1497 non-fatal myocardial infarctions, 2318 coronary heart disease events, 1127 fatal and non-fatal strokes, and 2892 deaths from any cause. The summation of evidence from these trials demonstrated consistently that more intensive glycaemic control has cardiovascular benefit compared to less intensive therapy in type 2 diabetes. These data have demonstrated that over an average treatment period of approximately 5 years, a lowering in HbA1c of 0.9% resulted in a significant 17% reduction in the risk of non-fatal myocardial infarctions, a significant 15% reduction in coronary events, and a non-significant 7% trend towards a reduction in stroke, with no significant statistical heterogeneity observed across studies that varied considerably with respect to participant characteristics, baseline HbA1c levels and, more importantly, the hypoglycaemic regimens used. There was however no significant impact of more intensive glycaemic control on all-cause mortality with evidence of considerable heterogeneity across studies.

The UGDP study (194) in the early seventies of more intensive glycaemic control vs. usual care suggested an excess mortality with sulphonylureas compared with standard care but with potential benefits of insulin based regimens. This study was small and compared about 200 patients in each of the more intensively treated groups to a common control group. In contrast, the much larger UKPDS study, which compared more intensive to standard glycaemic control, failed to demonstrate cardiovascular benefit (63) although among a small subgroup of 753 overweight individuals randomised to metformin vs. usual care there was evidence of a clinical benefit favouring more intensive glucose control (64). Post hoc observational data from UKPDS suggested that for every 1% reduction in HbA1c there was a 14% reduction in risk of myocardial infarction (181) and more recently an extension of the initial randomised groups in the UKPDS study has demonstrated a reduction in myocardial infarction and death from any cause with both metformin and sulphonylurea-insulin regimens despite the fact that HbA1c levels were similar during the extension phase (184), suggesting that

these initial studies were underpowered to assess the impact of intensive therapy on cardiovascular outcomes.

Recently, two large studies have been conducted which despite significant differences in HbA1c have suggested that there may not be significant short-term benefits on macrovascular events (45;46). Furthermore the ACCORD trial (45) suggested that there may be an excess risk of death from any cause. An earlier meta-analysis (195) comprising data from UKPDS and two additional small studies (which recorded in total 60 additional cardiovascular events) (190;196) suggested that there was a 19% reduction in the combined endpoint of acute and non-acute cardiovascular events which included revascularisation. The absence of prior convincing data and possible harm has led consensus groups to provide a conservative level of endorsement (class IIb recommendation) for the cardiovascular benefits of more intensive glycaemic control (i.e. "usefulness and efficacy are less well established by evidence or opinion, with data derived from multiple randomised clinical trials or meta-analyses") (183). The present quantitative analysis of randomised controlled trials is the largest to date in terms of event numbers, and the combined data refute such assertions and provide reliable large-scale evidence of a consistent beneficial effect of more intensive control of glucose on non-fatal myocardial infarction and coronary events. Furthermore, overall there appears to be no increment in risk of all-cause mortality. Of note the risk reduction of 17% in myocardial infarction for a 0.9% difference in HbA1c is broadly consistent with observational data from the UKPDS study. Although there was a trend towards benefit for stroke, there were 372 fewer events compared to myocardial infarctions and thus less power to ascertain whether a significant benefit exists.

The implications and the context of these findings with regard to public health policy merit careful consideration in the context of the established benefits of intensive glucose control on microvascular disease. There is now well established evidence that among individuals with diabetes, statin therapy and more intensive blood pressure control reduce macrovascular events and, in contrast to the present findings, also reduce all-cause mortality by 9% and 27%, respectively (133;197-199). Despite the benefits of statin therapy and blood pressure control individuals with diabetes remain at elevated risk of vascular

events with even higher absolute rates observed among those with diabetes and existing cardiovascular disease. This suggests that further interventions to safely reduce vascular risk are needed. The present analysis demonstrates that within this combined dataset with an average mortality rate of 18.6 per 1000 person years of follow up (control group weighted mean), approximately 2 myocardial infarctions or 3 coronary events are prevented for about every 200 individuals who achieve a further 0.9% reduction in HbA1c over 5 years (from a baseline HbA1c of 7.84%). These correspond to NNT over 5 years of 87 and 69 respectively. These figures are considerably more modest than comparable figures per mmol/L LDL-cholesterol reduction or for a 4 mmHg lower BP (8.2 and 12.5 cardiovascular events prevented) (133;199). Given the burden of vascular risk among individuals with diabetes, a global approach to vascular risk involving multiple interventions including stricter glycaemic control appears to be warranted.

As always, for any given therapy there is also the potential for harm. As expected, more intensive glucose control was associated with a relative 2.5 kg increase in weight and nearly a doubling in severe hypoglycaemic episodes. General inspection of the published data would indicate that the two studies (ACCORD and VADT) with increased mortalities had i) the longest diabetes durations at baseline of 10 and 11.5 years, ii) highest HbA1c at baseline, iii) greater weight gains in the intensive groups (other than PROactive), and iv) incurred more than a doubling in the measured rates of serious hypoglycaemic events, whereas other trials had less than a doubling of such events. These data potentially indicate that the higher mortality risk in ACCORD and VADT could be potentially linked to both hypoglycaemia and greater weight gain. In addition, the ACCORD study had a significantly higher risk of cardiovascular death and non-coronary cardiovascular deaths. Several interesting features of the treatment strategies used in ACCORD also merit careful consideration in light of the proposed adverse side effects of hypoglycaemia on vascular deaths. In ACCORD, a target HbA1c below 6% was achieved *rapidly* among the intensively-treated individuals through early and aggressive use of insulin including, where necessary, the use of bolus doses. Additionally, a greater proportion of subjects within the intensively-treated group received rosiglitazone at the end of follow-up (91%) compared with those receiving standard treatment (58%) (25). In

contrast, in ADVANCE, an HbA1c target of ≤6.5% was achieved much more slowly, with much less use of insulin and often with longer acting preparations. In addition to pharmacological interventions, participants were encouraged to adopt a favourable lifestyle and were closely monitored for outcomes and adverse events. While the data presented in our meta-analysis cannot substantiate or refute such mechanistic associations, a practical clinical approach may be to lower HbA1c steadily with care taken to avoid severe hypoglycaemia. Furthermore, it may be appropriate to aim for less stringent glycaemia targets in patients with more advanced disease (longer duration and higher baseline HBA1c) (200).

Limitations

The present study has some potential limitations which should be considered. First, meta-analysis remains retrospective research that is influenced by the methodological rigour of the included studies, the degree of comprehensiveness of search strategies and the possibility of publication bias. We tried to minimise the likelihood of bias by developing a detailed protocol *a priori*, by performing a meticulous search of published and unpublished studies, and by using explicit criteria for study selection, data extraction and analysis. Therefore some notable studies were not eligible for our meta-analysis for legitimate reasons. We believe we have been robust in our approach and that the resultant evidence is more applicable as a result. Second, as in other meta-analyses, these results should be interpreted with caution as individual studies varied considerably with respect to the demographic characteristics of the participants, the duration of follow-up and the pharmacological interventions used to control glucose in the intensively treated groups. Therefore this study can only provide information on whether more intensive control of glucose is safe and effective at reducing macrovascular events compared to less intensive therapy, rather than providing evidence of superiority or harm of any particular glucose lowering regimen. This being said, we did not observe any statistically significant heterogeneity across studies with respect to effects of glucose reduction on non-fatal myocardial infarctions, coronary events or strokes. Such data together with the vastly differing ancillary metabolic effects of differing glucose regimens (metformin, sulphonylureas, insulin, glitazones etc) included in the five trials, suggests their

common action to lower glucose must be at least partially responsible for the observed vascular risk benefits. Although there was no effect on all-cause mortality, significant heterogeneity was observed across studies which could not be further clarified without access to individual participant data. Third, there were not sufficient data to analyse the effects of intensive glycaemic control within various subgroups. Such analyses are more informative when done using individual participant data and similar approaches are also needed to determine whether there is a significant correlation between the magnitude of HbA1c lowering and cardiovascular events and all-cause mortality. Therefore, the present findings will help encourage the establishment of the collective pooling and harmonising of individual participant data analogous to that of blood pressure and cholesterol which have proved highly informative. Fourth, we used ORs rather than HRs (which were only available in a proportion of studies) to maximise the published information that was available. In sensitivity analyses we conducted random effects meta-analyses using rate ratios which provided effect estimates of similar magnitude to the ORs presented. With respect to the calculation of rates, the median number of person years of follow up in 3 studies was assumed to approximate the arithmetic mean in the 2 other studies. In variables with a skewed distribution such as follow-up time, the median is usually not a good approximation of the mean.

Conclusion

In this meta-analysis, based on aggregate data on 33,040 men and women from five clinical trials yielding approximately 163,000 person-years of follow-up, we observed that a 0.9% further reduction in HbA1c reduced non-fatal myocardial infarctions by 17% and coronary events by 15% with no excess risk of death among individuals with type 2 diabetes mellitus. Our findings provide reassurance about the efficacy of glycaemic control for vascular risk reduction. However, the lack of clear benefit on all-cause mortality with glycaemia reduction, compared to strong evidence for such a benefit with lipid-lowering and blood pressure reduction, reinforces the critical importance of the latter modalities to reduce cardiovascular disease and all-cause death in individuals with diabetes. Future studies are required to assess the optimum methods for achieving better control of glycaemia and to assess whether guidelines should

recommend a specific reduction in HbA1c or a specific reduction in HbA1c or different target levels of control in different populations.

This manuscript was published in the Lancet in 2009 (88).

Conclusions and future work

In my thesis I have explored various aspects of the complex relationship between glycaemia and cardiovascular disease. Below I have listed the main conclusions from each chapter together with areas where future work should be directed:

Chapter 2: *A systematic review of event rates in clinical trials in diabetes mellitus: the importance of quantifying baseline cardiovascular disease history and proteinuria and implications for clinical trial design*

Cardiovascular endpoint event rates in trials of patients with diabetes are often much lower than anticipated in pre-trial power calculations and it is clear that basing pre-trial power calculations on population data is problematic. Consequently, there is a need in trials to have simple and robust inclusion criteria which identify patients with diabetes who are at particularly high risk of cardiovascular events. Data from large trials convincingly demonstrate that patients with known cardiovascular disease and/or proteinuria are at substantially higher risk than those without these features; while this is to be expected, the magnitude of the difference in risk is surprising and it is apparent that those with uncomplicated diabetes actually have a low absolute cardiovascular event rate. These points are highly relevant as indicated by recent guidance regarding glucose-lowering therapies released by the FDA (29). Following release of meta-analysis results suggesting that rosiglitazone may actually increase the risk of cardiovascular events (25), the FDA recognised the fact that demonstrating improvement in a surrogate marker (i.e. HbA1c) on a medication does not guarantee patient safety and that large randomised clinical trials are required to establish safety. Numerous glucose-lowering agents have recently been released or are under development. Each will be required to demonstrate cardiovascular safety in a large trial. It is therefore hoped that the data provided from this analysis may assist those designing such trials. As I did not have access to individual participant data in my analysis, it was not possible to analyse the impact of various risk factors in a multivariable fashion or in subgroups. This would require agreement from trialists to contribute trial data and analysis would require highly specialised statisticians, along the lines of the ERFC based at the University of Cambridge. Nevertheless, such a project could be of even greater benefit to those planning trials of not only glucose-lowering

agents but all cardiovascular agents in those with diabetes. Newer biomarkers such as NTproBNP and troponin may also provide incremental information, facilitating identification of patients with diabetes at high risk of events.

Chapter 3: *Fasting plasma glucose in non-diabetic participants and the risk for incident cardiovascular events, diabetes, and mortality: results from the West of Scotland Coronary Prevention Study*

FPG in the non-diabetic range has little, if any, association with the risk of cardiovascular events. Certainly it appears that adding FPG results to existing risk prediction equations would be highly unlikely to yield any substantial improvement. By contrast, higher FPG levels in the non-diabetic range carry markedly elevated risks for developing diabetes. These contrasting risks for cardiovascular events and new-onset diabetes have been demonstrated in previous large clinical trials of glucose-lowering strategies. For example, in the Diabetes Prevention Program (201), both lifestyle modification therapy and metformin therapy were able to greatly reduce the risk of developing diabetes. Fewer trials have been conducted to assess the effect of glucose-lowering in patients with IGT and IFG. In the largest clinical trial to date (n=9,306 patients with IGT), nateglinide therapy did not reduce cardiovascular events compared to placebo (HR 0.94 95%CI 0.82-1.09) (202) though post-challenge glucose concentrations were actually higher in the nateglinide recipients. This does not necessarily mean that no glucose-lowering agents will be valuable in non-diabetic patients. I am currently involved in a meta-analysis where we are collecting published and unpublished data for trials of glucose-lowering therapies in individuals with IFG and IGT which will be pooled to assess any cardiovascular benefits. One possibility is that beneficial effects may take substantial amounts of time to develop. Also, some agents are known to have pleiotropic effects. For example, metformin therapy leads to weight loss and moderate reductions in serum cholesterol even in statin users (203). I am also currently investigating the effect of metformin on change in carotid intima media thickness (a surrogate marker of cardiovascular disease) in patients with existing coronary heart disease but not diabetes in a placebo-controlled randomised clinical trial, the Carotid Atherosclerosis:MEtformin for insulin ResistAnce (CAMERA) study (204). In addition, UK researchers have proposed a

large clinical endpoint trial of metformin in patients without diabetes, the Glucose Lowering In Non-diabeTic hyperglycaemia (GLINT) study.

Chapters 4 and 5: *Statins and risk of incident diabetes: a collaborative meta-analysis of randomised placebo- and standard care-controlled statin trials; Risk of incident diabetes on intensive compared to moderate dose statin therapy: a collaborative meta-analysis of randomised trials*

The use of statin therapy is associated with an increased risk of developing diabetes compared to placebo, and intensive statin therapy is associated with a further risk of new-onset diabetes compared to moderate dose therapy. While the benefits of cardiovascular risk reduction certainly outweigh this newly identified risk when treating patients according to established guidelines, the risk is not trivial as demonstrated by the finding that intensive statin therapy leads to one additional case of new-onset diabetes for every three patients protected from a cardiovascular event (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation). The key question is now to identify the explanation for this increase in diabetes. As discussed in chapters 4 and 5, there are data from animal models to support the hypothesis that statin therapy leads to peripheral (skeletal muscle, adipose tissue) insulin resistance. Further studies on animal models are required together with suitably powered and designed insulin clamp studies in humans to establish the culprit organ / organs and molecular pathways. Second, it would be of value to determine whether this increase in new-onset diabetes actually leads to the increased risk of microvascular and macrovascular disease associated with diabetes. Given the apparent modest effect of statins on new-onset diabetes plus the time taken for such complications to occur, this matter may be impossible to address. Third, it would be of interest to study whether the use of statins leads to a long term increase in diabetes risk, and what the influence of statin withdrawal is. Fourth, further studies of existing data should examine whether statin therapy has any detrimental effect on glucose control or the need for glucose-lowering therapy in those with known diabetes. And fifth, further study should be directed towards identifying any subgroup of statin recipients at particular risk. I am in the process of applying for Fellowship funding to investigate these areas. Of interest, the ongoing placebo-controlled

J-PREDICT study is specifically designed to evaluate the impact of pitavastatin therapy on the development of diabetes in 1,240 participants with IGT.

Chapter 6: *Predictors of development of diabetes in patients with chronic heart failure in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity program*

The prevalence of diabetes in patients with chronic heart failure is high and the strongest statistical predictors of diabetes are BMI and HbA1c, similar to the general population. Since publication of the data in this chapter, other studies of observational data have been published. Given the apparent link between heart failure morbidity and diabetes (24), one area of particular interest is the use of glucose-lowering agents in those with heart failure. Use of metformin in patients with chronic heart failure has long been contra-indicated. However, observational data reveal that metformin is actually used quite frequently in heart failure patients and that this may even be beneficial (205;206). Various trials should be considered. One is the use of metformin in patients with existing diabetes and heart failure to assess its impact on cardiovascular events and all-cause death. Another option is the use of metformin in patients with heart failure alone to assess not only cardiovascular benefit but also any effect on new-onset diabetes. To date researchers at the University of Dundee have led the way in this area and they are currently conducting the TAYSIDE trial (207) which, it is hoped, will lead to the conduct of a large clinical trial of metformin in heart failure. I am also currently involved in an analysis of the EMPHASIS-HF database, in which patients with chronic heart failure were recruited, to assess the effect of the mineralocorticoid antagonist, eplerenone, on new-onset diabetes.

Appendix: *Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials*

Intensive glucose-therapy reduces the risk of non-fatal myocardial infarction but not other cardiovascular events in patients with type 2 diabetes. The clinical application of glucose-lowering remains highly controversial following publication of the relevant trials and subsequent analyses. The key issues are the effects of intensive glucose-lowering on all-cause mortality and

cardiovascular mortality and these remain unresolved. Crucially, we do not yet understand the reasons for increased mortality on intensive-glucose lowering noted in two trials, nor do we know with confidence in which, if any, subgroups of patients clinicians should target or avoid intensive glucose-lowering though more recent data do suggest that those with no existing cardiovascular disease are most likely to derive cardiovascular benefit (208). Further clinical trials are required to address these uncertainties. Numerous large clinical trials are already underway to assess the cardiovascular safety of glucose-lowering agents in patients with diabetes and IGT. These include trials of gliptin therapy (TECOS [sitagliptin], SAVOR-TIMI 53 [saxagliptin], EXAMINE [alogliptin]), glucagon-like peptide-1 analogues (EXSCEL [exenatide], LEADER [liraglutide], ELIXA [lixisenatide], T-emerge 8 [taspoglutide]), and other agents (ORIGIN [insulin glargine], ACE [acarbose], ALECARDIO [aleglitazar]). Given the close relationship between diabetes and chronic heart failure, a sensible addition to the usual cardiovascular endpoints of these trials such as cardiovascular death, myocardial infarction and stroke, would be the development of heart failure. One important consideration to keep in mind, according to some experts in this area, is to avoid a 'glucocentric' approach to cardiovascular risk reduction in patients with diabetes (209). This is supported by the clinical evidence where intensive-glucose lowering, which is challenging for clinician and patient, has produced only modest benefit on non-fatal myocardial infarction unlike cholesterol- and blood pressure-lowering strategies which have demonstrated far greater clinical benefits (133;199).

In summary, it is clear that the relationship between cardiovascular disease, glycaemia and diabetes is complex. While cardiovascular disease and diabetes often coexist in patients and while patients without either condition may often be at elevated risk of developing both, risk factors for these differ substantially. Indeed, risk factors common to both cardiovascular disease and diabetes vary substantially in their contributions to risk of developing each. Consequently, treatments that target any particular risk factor may have the expected effect on one condition but little, or even an unexpected, effect on the other.

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