



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

CARDIOVASCULAR IMAGING TO GUIDE PRIMARY PREVENTION

Citation for published version:

Meah, MN, Dweck, M & Newby, D 2020, 'CARDIOVASCULAR IMAGING TO GUIDE PRIMARY PREVENTION', *Heart*. <https://doi.org/10.1136/heartjnl-2019-316217>

Digital Object Identifier (DOI):

[10.1136/heartjnl-2019-316217](https://doi.org/10.1136/heartjnl-2019-316217)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Heart

Publisher Rights Statement:

this is the authors accepted manuscript

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



CARDIOVASCULAR IMAGING TO GUIDE PRIMARY PREVENTION

AUTHORS:

Dr Mohammed N Meah (MB ChB), Dr Marc R Dweck (PhD), Professor David E Newby (DSc)

British Heart Foundation Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, United Kingdom

Corresponding Author:

Professor David Newby, Room SU.314, Chancellor's Building, University of Edinburgh, 49

Little France Crescent, Edinburgh, EH16 4SB

Tel: +44 131 242 6515

Email: d.e.newby@ed.ac.uk

LEARNING OBJECTIVES

1. Review the history and evidence behind risk prediction scores
2. Assess the current evidence base for the use of imaging to guide primary prevention
3. Consider the impact of imaging on clinical outcomes.

Word Count: 3476

INTRODUCTION

Coronary heart disease is the commonest cause of death across the world. The World Health Organisation estimates it accounts for nearly a third of all global deaths each year and since 1990, more people have died from cardiovascular disease than any other cause.¹ So how can we prevent this inexorable tide of cardiovascular morbidity and mortality?

The concept of primary prevention is rooted in history with the old adage “prevention is better than cure” being attributed to Desiderius Erasmus, the 15th century Dutch philosopher. Prevention of cardiovascular diseases, such as myocardial infarction and stroke, is a major goal of the medical community and is embodied in current international guidelines. Indeed, the use of cardiovascular risk scores to identify individuals at risk is the current standard of care across the world.²⁻⁶ The rationale for this practice is to select those individuals at greatest risk to maximise the cost-effectiveness of treatment, without recommending therapy in the entire population. This is especially important given that the majority of cardiovascular events are unheralded, and the prognosis in those suffering myocardial infarctions without preceding symptoms of angina is worse.⁷ However, there is considerable debate surrounding whether this is something that risk scores can accurately do. In an area of practice that requires significant improvement, this article aims to look at whether cardiovascular imaging can be used to optimise the process of primary prevention.

The Birth of Risk Scores

Although many different risk scores are used throughout the world, the Framingham score is perhaps the most famous. Inspired by the death of President Roosevelt in 1945 and on the back of a pandemic of the then “untreatable” cardiovascular disease, the United States of America established the National Heart, Lung and Blood Institute

whose primary aim was to conduct an epidemiological study of heart disease.⁸ The Framingham Heart Study was credited with identifying the importance of blood pressure control in the battle to prevent heart disease. It also popularised the term 'risk factor', the articulation of which led to the development of cardiovascular risk scores.⁹ Armed with the knowledge of risk factors such as systolic hypertension and hyperlipidaemia, studies in a primary prevention setting were conducted and confirmed the therapeutic and prognostic efficacy of treatment.¹⁰ For example, in the case of lipid control in asymptomatic hypercholesterolaemic men, the West of Scotland Coronary Prevention Study (WOSCOPS)¹¹ demonstrated pravastatin reduced the rates of coronary heart disease death or non-fatal myocardial infarction. As a result of these effective therapies, interventions were focused on identifying those at risk of adverse cardiovascular events in an attempt to prevent them from occurring in the first place. Although individual risk factors are widely recognised and accepted, the nuance of how much risk is required before a treatment should be initiated has since remained a controversial topic. Over the years, many epidemiological studies have led to the creation of risk scores calibrated to local populations. These scores attempt to quantify the probability of an individual having a cardiovascular event, based on estimations from population studies. In 2010, the NICE guidelines suggested that a >30% risk of cardiovascular disease at 10-years warranted treatment with statins, but then subsequently reduced this to >20% and in the most recent iteration it is >10%.² These cut offs are therefore somewhat arbitrary and are often based on issues of cost-effectiveness, societal acceptability and population prevalence of disease.

Why Are Risk Scores Not Enough?

Risk scores inevitably end up treating nearly all patients who are middle aged, given that age is such a dominant predictor of cardiovascular risk. Indeed, some have suggested all individuals over the age of 50 should receive a statin.^{12,13} Despite widespread and near universal adoption of risk scoring and the substantial associated healthcare resource utilisation and cost, its use is actually empirical. Several studies have questioned the ability of risk scores to predict events highlighting the lack of generalisability in broader populations and that the vast majority of younger patients who present with an event would not have qualified for primary prevention using risk

scores.^{14,15} A recent Cochrane Systematic Review assessed the practice of using risk scores to select individuals for the primary prevention of cardiovascular disease.¹⁶ Although the review identified 41 trials incorporating nearly 200,000 participants, these studies had a high risk of bias and were of low quality. The principal finding of the systematic review was that there was little or no effect on cardiovascular event rates when clinicians did or did not use cardiovascular risk scores (5.4% versus 5.3%; relative risk 1.01, 95% confidence intervals 0.95 to 1.08).

There is a growing body of evidence that suggests not only a disconnect between primary care physicians and their willingness to prescribe statins for primary prevention, but also a reluctance of patients to adhere to therapy. There is major under-prescription in current practice with one large cohort study showing that less than half of over 300,000 individuals deemed “eligible” for prevention were prescribed a statin.¹⁷ When asked, primary care physicians cite difficulty interpreting risk assessment tools and their ever changing thresholds for treatment, as barriers to the use of statin in the primary prevention of cardiovascular disease. Primary care physicians also expressed fears of excessive healthcare resource utilisation and over medicalisation of healthy individuals.¹⁸ On a patient level, there is considerable difficulty in understanding the concept of risk and probabilities which alongside fear of side effects and conflicting reports in the media often results in resistance to taking statin therapy.¹⁹⁻²¹

The current approach to primary prevention needs to improve and would benefit from:

1. An enhanced ability to predict risk more accurately.
2. Better compliance with lifestyle intervention and medications.
3. Improved net clinical and cost effectiveness both for the patient and for society.

Non-invasive Imaging and Primary Prevention

An alternative strategy to applying scores that calculate the probabilistic risk for a disease is to screen for the disease. The use of imaging to guide primary prevention is not novel (**Table 1**). Although various modalities have been tested to a greater or lesser extent, imaging of carotid intima thickness, coronary artery calcium (CAC)

scoring and computed tomography coronary angiography (CTCA) have been studied the most.

Imaging to Enhance Risk Prediction

Carotid Ultrasound

Autopsy studies from the 1960s first suggested a correlation between carotid and coronary atherosclerosis.²² The Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) followed a large cohort of Finnish men through the late 1980s scanning more than 1500 carotid arteries by ultrasound. They were the first to show that those with carotid intimal thickening had more than double the chance of going on to having a coronary event.²³ Carotid intimal thickness measurements can be made using B-mode ultrasonography of the carotid artery (**Figure 1**). This is a relatively inexpensive and readily portable method of detecting early atherosclerosis and does not require the use of ionising radiation.²⁴ Since the 1980s, multiple studies and meta-analyses have shown that intimal thickness is a strong predictor of future vascular events.^{24,25}

In addition to the detection of disease, carotid intimal thickness can be used to track disease progression. Multiple meta-analyses have also reported that statin therapy is associated with a dose-dependent reduction in carotid intimal thickness.^{26,27} A review by the European Society of Cardiovascular Prevention and Rehabilitation (ESCPR) felt that there was sufficient evidence for the use of changes in carotid intimal thickness to be used as a measure of atherosclerotic disease.²⁸ Along with Espeland and colleagues,²⁹ they felt that progression of carotid intimal thickness met criteria of a surrogate for cardiovascular disease endpoints in trials assessing statin therapy.

Cardiac Computed Tomography

Coronary artery calcification is considered pathognomonic of coronary artery disease and can be detected and quantified on computed tomography (CT) of the chest. Such scans require minimal breath holding, do not require administration of intravenous contrast and incur less radiation than mammography or low-dose lung scanning.³⁰ As

a surrogate for coronary artery disease, CT calcium scoring performs better than carotid ultrasound at risk stratification (**Figure 2**).^{31,32}

The progression of coronary artery calcification is, however, a more complex topic. Unlike plaque thickness in B mode ultrasonography, progressive calcification is thought to have a stabilising effect on high-risk plaque. Indeed, studies on the effect of statins on coronary calcium have demonstrated continued progression of calcification which adds to this theory.^{33,34} We suspect that the ability of coronary artery calcium scoring to predict risk is due to the associated presence of high risk (mixed or non-calcific) plaque rather than representing a direct effect of the calcific plaque.³⁵ Indeed when assessed separately, a study of over 3000 participants found that progression of coronary calcium score had little to no effect on future risk prediction.³⁶ There is no doubt however in the power of a zero calcium score in asymptomatic individuals which has repeatedly demonstrated positive prognostic outcomes.³⁷ Ultimately, calcium scoring may therefore be seen as a measure of stable calcific plaques and its absence a marker of the lowest risk. How then do we detect high-risk plaque? Here there is growing interest in the use of computed tomography coronary angiography which has been validated in large randomised trials looking at patients with stable coronary disease (**Figure 3 & 4**).^{38,39}

Computed Tomography Coronary Angiography

Although coronary artery calcification is a very good surrogate of coronary heart disease, it does not provide direct information about the total plaque burden or stenosis severity and can be absent in middle-aged patients with non-calcified plaque. Coronary artery calcium scoring is therefore a surrogate of disease rather than truly identifying the presence or absence of coronary heart disease. In this regard, computed tomography coronary angiography can be considered the gold standard non-invasive imaging technique that can detect the presence of both calcified and non-calcified coronary heart disease with a high degree of accuracy. There are several avenues of novel research that are being investigated in this field. For example, a recent study demonstrated how quantification of the low attenuation (non-calcified) plaque burden, was the most powerful predictor of myocardial infarction, outperforming CT coronary calcium scoring, the severity of luminal stenosis and cardiovascular risk factor assessment (**Figure 5**).⁴⁰

To date, computed tomography coronary angiography has not been used systematically to screen for disease in high risk individuals although there are ongoing prospective longitudinal observational studies, such as the Copenhagen General Population Study and the Swedish CARdioPulmonary bioImage Study (SCAPIS), which will inform upon the power of computed tomography coronary angiography to predict future risk of cardiovascular events.

Imaging and Behavioural Change

Carotid Ultrasound

Compliance is a particularly difficult issue when it comes to primary prevention. Therapies are indicated in asymptomatic people who, in general, live active and fulfilled lives. Why should they take medication based on the potential of developing disease? Moreover, individuals may experience side-effects from treatments that make them feel worse, not better. Imaging has the potential to clarify the concept of risk and provide direct evidence of subclinical disease. Rather than providing a probability of developing disease, patients can visualise coronary or carotid plaque in their own body. This is a significant change in emphasis that can impact on behaviour. For example, in the visualisation of asymptomatic atherosclerotic disease for optimum cardiovascular prevention (VIPVIZA) trial, showing patients pictures of their diseased carotid arteries led to an improvement in their cardiovascular risk scores over 12 months.⁴¹ This lends weight to the argument that patients are more likely to make necessary changes to their behaviour when presented with clear evidence of a disease process occurring in their body, rather than with the probability of a diagnosis. The converse is equally true. The cessation of therapies in patients who do not have the disease has the potential to improve their quality of life.⁴²

Cardiac Computed Tomography

In retrospective cross-sectional studies of asymptomatic patients undergoing calcium scoring, more severe coronary artery calcification is associated with greater lifestyle modifications including medication adherence, dietary modification, weight loss, reduced alcohol intake and increased exercise.⁴³⁻⁴⁶ In a meta-analysis, a non-zero coronary artery calcium score was associated with an increased likelihood of

medication initiation and continuation, dietary change (odds ratio 1.8, 95% confidence interval 1.4 to 2.4) and increased exercise (odds ratio 1.9 95% confidence interval 1.5 to 2.5).⁴⁷ The early identification of subclinical atherosclerosis by non-invasive imaging research (EISNER) trial randomised 2137 participants to risk factor management with and without screening with a calcium score.⁴⁸ The knowledge of the calcium score was associated with better risk factor management with lower blood pressures, cholesterol concentrations, and abdominal girth.⁴⁹ Indeed, the higher the calcium score, the greater the improvements that were seen, underlining the impact of imaging on physician and patient behaviour. Another small randomised trial demonstrated how showing patients their coronary artery calcification was associated with favourable changes in lifestyle such as increased medication compliance, improved lipid profile and reduced smoking.⁵⁰

Computed Tomography Coronary Angiography

There are currently no studies that have assessed the impact of computed tomography coronary angiography on behaviour modification. However, studies are ongoing to address this issue (NCT04156061) with the aim of determining the effects on lifestyle, medication compliance and risk factor modification of computed tomography coronary angiography compared with standard risk score assessments. This study will also investigate whether showing individuals the images of their coronaries has a greater impact on their compliance and behaviour than provision of a verbal report.

Imaging and Clinical Outcomes

Carotid Ultrasound

The true impact of imaging on hard clinical outcomes and cost-effectiveness requires randomised controlled trials. However, in the absence of such data, observational studies can provide some limited information. Van den Oord and colleagues conducted a meta-analysis of more than 32,000 patients demonstrating that the c-statistic on an area under the curve analysis for traditional risk factors was 0.726, and that the addition of carotid intima-media thickness did not provide a meaningful increase in this risk prediction (0.729, $p=0.8$).⁵¹ This was further highlighted in a comparative study conducted by Kavousi and colleagues who calculated the net reclassification index (a measure of how well a new model reclassifies patients) using

a variety of “new markers” for coronary risk prediction including carotid intimal thickness.⁵² They found only a marginal improvement when using carotid ultrasound (reclassifies only 1.6% of the population). The reasons for carotid imaging’s relatively poor performance may lie in the lack of a uniform methodology. In addition, carotid atherosclerosis is remote from the major cause of cardiovascular events, coronary artery disease. Correlation of carotid intimal thickening with the presence of coronary artery disease is modest and unreliable.⁵³ This may be improved by the more comprehensive assessments of carotid plaque burden which can have comparable results to coronary calcium scoring.^{24,54}

Cardiac Computed Tomography

To date, there have been three prospective trials that have attempted to evaluate the clinical and cost outcomes of coronary artery calcium scoring in an asymptomatic population (**Table 2**). The Prospective Army Coronary Calcium (PACC) study (n=1640) aimed to assess the impact of calcium scoring on the management of cardiovascular risk factors.⁵⁵ Although it demonstrated the ability of calcium scanning to shift clinicians’ management of patients, this did not translate into a reduction in risk or cardiovascular events. Within this very low risk and young population (mean age 42 years), 85% of participants had a calcium score of zero in the scanning arm which undoubtedly limited its ability to assess improvements in cardiovascular outcomes.⁴⁹ This again emphasises the importance of targeting risk scores or imaging to populations with a significant prevalence of the disease. From a health economics perspective, the EISNER trial showed that the use of calcium scoring did not add to downstream medical testing or reduce costs.⁴⁸

The St Francis Heart (n=1005) study was a double blinded randomised controlled trial where participants with a mean calcium score of ≥ 500 were given a combination of atorvastatin 20 mg, vitamin C and E, or matched placebo.⁵⁶ The primary outcome was to assess whether aggressive control of lipid risk factors could slow the progression of coronary calcification and thereby reduce cardiovascular events. The investigators found that coronary calcification continued to progress although the rates of cardiovascular event did appear to improve after 5 years (p=0.08).⁴⁹ This study was perhaps underpowered but also again raises the question about the use of coronary

calcium scores to assess disease progression and response to therapy. Given the low number of events in a primary prevention population, large scale long term randomised trials are needed, such as the ongoing Risk Or Benefit IN Screening for Cardiovascular diseases (ROBINSCA) trial.⁵⁷

Computed Tomography Coronary Angiography

The FACTOR-64 trial has been the only computed tomography coronary angiography trial in primary prevention, and it specifically recruited 900 patients with type 1 or 2 diabetes mellitus only.⁵⁸ Participants found to have coronary heart disease on computed tomography coronary angiography were targeted for more intensive risk factor modification, although 75% of trial participants were already on a statin at baseline. Compared to standard of care, those assigned to computed tomography coronary angiography had an LDL-cholesterol concentration that was 0.06 mmol/L lower ($p=0.02$) but there was no difference in blood pressure or haemoglobin A1c concentrations. In the intention-to-treat analysis, the primary end-point occurred in 6.2% of the computed tomography coronary angiography group compared to 7.6% in the control group (hazard ratio, 0.80 [95% confidence interval, 0.49-1.32]; $p=0.38$). In the as-treated analysis, the respective event rates were 5.6% vs 7.9% (hazard ratio, 0.69 [95% confidence interval, 0.41-1.16]; $p=0.16$). The failure to demonstrate a benefit is therefore likely to represent the inability to deliver a major difference in treatment and management consequent on the application of the imaging test, and a lack of power due to the small sample size and lower than anticipated event rate.

Although not performed on an asymptomatic population, the Scottish COmputed Tomography of the HEART (SCOT-HEART) trial raised several interesting observations.^{42,59} First, the reduction in coronary events was independent of symptoms. Indeed, the point estimates suggested that patients with non-anginal chest pain showed at least as much benefit from computed tomography coronary angiography (hazard ratio 0.45, 95% confidence intervals 0.19 to 1.03) as those with possible angina (hazard ratio 0.60, 95% confidence intervals 0.37 to 0.96) and those with known coronary heart disease (hazard ratio 0.65, 95% confidence intervals 0.32 to 1.32). Second, a large proportion (40-50%) of patients were on antiplatelet or statin therapy at baseline⁴² and, after 5 years of follow up, the overall rates of prescription of these drugs varied by ~10%.⁵⁹ Indeed, the relative reduction in coronary events was

similar whether participants were taking statin therapy at baseline (hazard ratio 0.57, 95% confidence intervals 0.34 to 0.95) or not (hazard ratio 0.57, 95% confidence intervals 0.28 to 1.15). However, computed tomography coronary angiography guided management markedly increased statin use in those with non-anginal chest who had coronary artery disease on the computed tomography scan irrespective of the risk score (**Figure 6**).⁶⁰ The overall rates of change in statin therapy therefore encompasses both cessation and initiation of therapy, suggesting that computed tomography coronary angiography is a better guide for patient management. Third, the risk score was a poor predictor of coronary artery disease. The average score (10-year cardiovascular risk) was 13 (range 1-59) in patients with normal coronary arteries, and 23 (range 2-62) in those with obstructive coronary artery disease. Indeed, in those undergoing computed tomography coronary angiography, 39% of patients were misclassified using a score of 20, and 33% were misclassified using a score of 10. Finally, the prevention of myocardial infarction requires the targeting of non-obstructive coronary artery disease as 50-65% of patients who suffered a subsequent myocardial infarction had non-obstructive disease on computed tomography coronary angiography at baseline.^{39,59} Thus, the relative and absolute reductions in coronary events were the same irrespective of symptoms, independent of baseline statin use or cardiovascular risk score, and driven by both non-obstructive and obstructive coronary artery disease.

These observations form the basis for the computed tomography coronary angiography for the prevention of myocardial infarction (SCOT-HEART 2) trial which aims to recruit 6000 asymptomatic individuals and will randomise them to a management strategy guided by either computed tomography coronary angiography or a cardiovascular risk score (NCT03920176) (**Table 3**). This will provide the evidence of whether such an imaging strategy has utility in contemporary practice.

CONCLUSION

Prevention of cardiovascular disease is currently guided by probabilistic risk scores that both over and under treat individuals, commit most middle-aged people to pharmacotherapy, and have little evidence base. Fundamentally, imaging in asymptomatic people can prevent over-medicalisation of the truly healthy and promote

treatment and risk factor modification in those with subclinical disease. The evidence for improved acceptance of preventative therapies and lifestyle interventions is growing, but we still require evidence of improved clinical outcomes. Although it is right that we should put these investigations through rigorous trials, we have had the capacity to screen for coronary artery disease for over 20 years. Only now are we beginning to explore what technology and innovation can do to give preventive cardiology its big breakthrough, long-awaited since the death of President Roosevelt.

KEY POINTS

In asymptomatic people:

- Primary prevention of cardiovascular disease is currently guided by probabilistic risk scores that have never been prospectively validated.
- Imaging techniques enhance the ability to predict risk over and above risk scores.
- Imaging techniques improve compliance with medication and promote uptake of positive lifestyle choices.
- Imaging has the potential to improve clinical outcomes by focusing treatments on patients who actually have the disease whilst simultaneously stopping treatments in those who do not require them.

MULTIPLE CHOICE QUESTIONS

1. Which of the following is a true regarding carotid intimal thickness? (**Answer: D**)
 - a. Carotid intimal thickness has strong evidence as a surrogate endpoint in cardiovascular trials assessing the efficacy of aspirin.
 - b. Carotid intimal thickness has strong evidence as a surrogate endpoint in cardiovascular trials assessing the efficacy of any lipid lowering drug.
 - c. Progression of carotid intimal thickness is a poor marker of the atherosclerotic disease process.
 - d. Progression of carotid intimal thickness is better than progression of coronary artery calcium scoring as a surrogate endpoint in cardiovascular trials assessing the efficacy of statin therapy.
 - e. Carotid intimal thickness is the best means of assessing the extent atherosclerosis in the coronary artery.

2. Which of the following is true regarding the use of Cardiac Computed Tomography? (**Answer: D**)
 - a. Coronary calcium is a marker of high-risk coronary artery plaque.
 - b. It requires high dose of radiation.
 - c. Statins reduce the progression of coronary calcification.
 - d. It is better at predicting cardiovascular risk compared to carotid intimal thickness.
 - e. A calcium score of zero means patients will never suffer a cardiovascular event.

3. Which of the following is a randomised trial that assessed the use of computed tomography coronary angiography in a primary prevention population? (**Answer: B**)
 - a. EISNER

- b. FACTOR-64
- c. PACC
- d. St Francis Heart
- e. ROBINSCA

4. Which of the following is true regarding the use of Computed Tomography Coronary Angiography? (**Answer: C**)
- a. Uses the same amount of radiation as mammography or low dose lung scanning
 - b. Is poor at determining luminal stenosis.
 - c. Can be used to identify high risk plaque.
 - d. Has been shown to positively affect physician prescription and patient compliance with preventative medication.
 - e. Has been proven to improve prognosis in a primary prevention setting.
5. Which of the following is currently recommended by European guidelines for primary prevention? (**Answer: A**)
- a. All patients should have a risk score calculated.
 - b. All patients should undergo ultrasound assessment of carotid intimal thickness as part of their risk assessment.
 - c. All patients should undergo cardiac computed tomography to calculate coronary calcium score as routine.
 - d. All patients should undergo computed tomography coronary angiography as part of their risk assessment.
 - e. Imaging is not recommended for primary prevention purposes.
6. Who was responsible for funding the Framingham Heart Study? (**Answer: B**)
- a. The European Society for Cardiovascular Prevention and Rehabilitation.
 - b. The National Heart, Lung and Blood Institute.
 - c. The American College of Cardiology.
 - d. The National Institute for health and Care Excellence.

e. President Roosevelt

ACKNOWLEDGEMENTS

The authors are supported by the British Heart Foundation (FS/19/46/34445, FS/14/78/31020, CH/09/002, RG/16/10/32375, RE/18/5/34216). DEN is the recipient of a Wellcome Trust Senior Investigator Award (WT103782AIA). MRD is supported by a Sir Jules Thorn Award for Biomedical Research 2015.

References

1. The-World-Health-Organisation. Cardiovascular Diseases Factsheet. 2017. [https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-\(cvds\)](https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)) (accessed 04/02/2020).
2. NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification. *National Institute for Health and Care Excellence* 2014.
3. SIGN. Risk estimation and the prevention of cardiovascular disease: A national clinical guideline. *The Scottish Intercollegiate Guidelines Network* 2017.
4. Beswick A, Brindle P, Fahey T, Ebrahim S. A Systematic Review of Risk Scoring Methods and Clinical Decision Aids Used in the Primary Prevention of Coronary Heart Disease (Supplement): Royal College of General Practitioners (UK): London; May 2008.
5. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016; **37**(29): 2315-81.
6. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. *Journal of the American College of Cardiology* 2014; **63**(25): 2889-934.
7. Carpeggiani C, Michelassi C, Landi P, L'Abbate A. Long-term prognosis of unheralded myocardial infarction vs chronic angina; role of sex and coronary atherosclerosis burden. *BMC Cardiovasc Disord* 2018; **18**(1): 156.
8. Mahmood SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. *The Lancet* 2014; **383**(9921): 999-1008.
9. Kannel WB, Dawber T, Kagan A, Revotskie N, J S. Factors of Risk in the Development of Coronary Heart Disease—Six-Year Follow-up Experience: The Framingham Study. *Annals of Internal Medicine* 1961; **55**(1): 33-50.
10. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *The Lancet* 1997; **350**(9080): 757-64.
11. Ford I, Murray H, McCowan C, Packard CJ. Long-Term Safety and Efficacy of Lowering Low-Density Lipoprotein Cholesterol With Statin Therapy: 20-Year Follow-Up of West of Scotland Coronary Prevention Study. *Circulation* 2016; **133**(11): 1073-80.
12. Cholesterol-Treatment-Trialists'-Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *The Lancet* 2012; **380**(9841): 581-90.
13. Ebrahim S, Casas JP. Statins for all by the age of 50 years? *The Lancet* 2012; **380**(9841): 545-7.
14. Lloyd-Jones DM, O'Donnell CJ, D'Agostino RB, Massaro J, Silbershatz H, Wilson PWF. Applicability of Cholesterol-Lowering Primary Prevention Trials to a General Population: The Framingham Heart Study. *Archives of Internal Medicine* 2001; **161**(7): 949-54.
15. Singh A, Collins BL, Gupta A, et al. Cardiovascular Risk and Statin Eligibility of Young Adults After an MI: Partners YOUNG-MI Registry. *J Am Coll Cardiol* 2018; **71**(3): 292-302.

16. Karmali KN, Persell SD, Perel P, Lloyd-Jones DM, Berendsen MA, Huffman MD. Risk scoring for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2017; **3**: CD006887.
17. Wu J, Zhu S, Yao GL, Mohammed MA, Marshall T. Patient factors influencing the prescribing of lipid lowering drugs for primary prevention of cardiovascular disease in UK general practice: a national retrospective cohort study. *PLoS One* 2013; **8**(7): e67611.
18. Kedward J, L D. A qualitative study of barriers to the use of statins and the implementation of coronary heart disease prevention in primary care. *British Journal of General Practice* 2003; **53**: 684-9.
19. Gale N, Greenfield S, Gill P, Guttridge K, Marshall T. Patient and general practitioner attitudes to taking medication to prevent cardiovascular disease after receiving detailed information on risks and benefits of treatment- a qualitative study. *BMC Family Practice* 2011; **12**(59): 1471-81.
20. Fung V, Graetz I, Reed M, Jaffe MG. Patient-reported adherence to statin therapy, barriers to adherence, and perceptions of cardiovascular risk. *PLoS One* 2018; **13**(2).
21. Matthews A, Herrett E, Gasparrini A, et al. Impact of statin related media coverage on use of statins: interrupted time series analysis with UK primary care data. *BMJ* 2016; **353**: i3283.
22. Young W, Gofman J, Tandy R, Malamud N, Waters E. The Quantitation of Atherosclerosis: The Extent of Correlation of Degrees of Atherosclerosis Within and Between the Coronary and Cerebral Vascular Beds. *The American Journal of Cardiology* 1960; **6**: 300-8.
23. Salonen J, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. *Arteriosclerosis and Thrombosis* 1991; **11**: 1245-9.
24. Naqvi TZ, Lee MS. Carotid intima-media thickness and plaque in cardiovascular risk assessment. *JACC Cardiovasc Imaging* 2014; **7**(10): 1025-38.
25. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* 2007; **115**(4): 459-67.
26. Fang N, Han W, Gong D, Zou C, Fan Y. Atorvastatin Treatment for Carotid Intima-Media Thickness in Chinese Patients With Type 2 Diabetes: A Meta-Analysis. *Medicine (Baltimore)* 2015; **94**(44): e1920.
27. Huang Y, Li W, Dong L, Li R, Wu Y. Effect of Statin Therapy on the Progression of Common Carotid Artery Intima-Media Thickness: An Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Journal of Atherosclerosis and Thrombosis* 2013; **20**: 108-21.
28. Peters SA, Grobbee DE, Bots ML. Carotid intima-media thickness: a suitable alternative for cardiovascular risk as outcome? *Eur J Cardiovasc Prev Rehabil* 2011; **18**(2): 167-74.
29. Espeland MA, O'Leary D H, Terry JG, Morgan T, Evans G, Mudra H. Carotid intimal-media thickness as a surrogate for cardiovascular disease events in trials of HMG-CoA reductase inhibitors. *Curr Control Trials Cardiovasc Med* 2005; **6**(1): 3.
30. Hecht HS, de Siqueira ME, Cham M, et al. Low- vs. standard-dose coronary artery calcium scanning. *Eur Heart J Cardiovasc Imaging* 2015; **16**(4): 358-63.
31. Folsom AR, Kronmal RA, Detrano RC, et al. Coronary Artery Calcification Compared With Carotid Intima-Media Thickness in the Prediction of Cardiovascular Disease Incidence. The Multi-Ethnic Study of Atherosclerosis (MESA). *Archives of Internal Medicine* 2008; **168**(12): 1333-9.

32. Jain A, McClelland RL, Polak JF, et al. Cardiovascular imaging for assessing cardiovascular risk in asymptomatic men versus women: the multi-ethnic study of atherosclerosis (MESA). *Circ Cardiovasc Imaging* 2011; **4**(1): 8-15.
33. Houslay ES, Cowell SJ, Prescott RJ, et al. Progressive coronary calcification despite intensive lipid-lowering treatment: a randomised controlled trial. *Heart* 2006; **92**(9): 1207-12.
34. Raggi P, Davidson M, Callister TQ, et al. Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic postmenopausal women: Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES). *Circulation* 2005; **112**(4): 563-71.
35. Shaw LJ, Narula J, Chandrashekar Y. The never-ending story on coronary calcium: is it predictive, punitive, or protective? *J Am Coll Cardiol* 2015; **65**(13): 1283-5.
36. Lehmann N, Erbel R, Mahabadi AA, et al. Value of Progression of Coronary Artery Calcification for Risk Prediction of Coronary and Cardiovascular Events: Result of the HNR Study (Heinz Nixdorf Recall). *Circulation* 2018; **137**(7): 665-79.
37. Shareghi S, Ahmadi N, Young E, Gopal A, Liu ST, Budoff MJ. Prognostic significance of zero coronary calcium scores on cardiac computed tomography. *J Cardiovasc Comput Tomogr* 2007; **1**(3): 155-9.
38. Halon DA, Lavi I, Barnett-Griness O, et al. Plaque Morphology as Predictor of Late Plaque Events in Patients With Asymptomatic Type 2 Diabetes: A Long-Term Observational Study. *JACC Cardiovasc Imaging* 2019; **12**(7 Pt 2): 1353-63.
39. Ferencik M, Mayrhofer T, Bittner DO, et al. Use of High-Risk Coronary Atherosclerotic Plaque Detection for Risk Stratification of Patients With Stable Chest Pain: A Secondary Analysis of the PROMISE Randomized Clinical Trial. *JAMA Cardiology* 2018; **3**(2): 144-52.
40. Williams MC, Kwiecinski J, Mhairi Doris, et al. Low-Attenuation Noncalcified Plaque on Coronary Computed Tomography Angiography Predicts Myocardial Infarction. Results From the Multicenter SCOT-HEART Trial (Scottish Computed Tomography of the HEART). *Circulation* 2020; **141**: In Press.
41. Näslund U, Ng N, Lundgren A, et al. Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention (VIPVIZA): a pragmatic, open-label, randomised controlled trial. *The Lancet* 2019; **393**(10167): 133-42.
42. Scot-Heart-Investigators*, Newby DE, Adamson PD, et al. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *The Lancet* 2015; **385**(9985): 2383-91.
43. Orakzai RH, Nasir K, Orakzai SH, et al. Effect of patient visualization of coronary calcium by electron beam computed tomography on changes in beneficial lifestyle behaviors. *Am J Cardiol* 2008; **101**(7): 999-1002.
44. Kalia NK, Cespedes L, Youssef G, Li D, Budoff MJ. Motivational effects of coronary artery calcium scores on statin adherence and weight loss. *Coron Artery Dis* 2015; **26**(3): 225-30.
45. Schwartz J, Allison M, Wright CM. Health behavior modification after electron beam computed tomography and physician consultation. *J Behav Med* 2011; **34**(2): 148-55.
46. Mamudu HM, Paul TK, Veeranki SP, Budoff M. The effects of coronary artery calcium screening on behavioral modification, risk perception, and medication adherence among asymptomatic adults: a systematic review. *Atherosclerosis* 2014; **236**(2): 338-50.
47. Gupta A, Lau E, Varshney R, et al. The Identification of Calcified Coronary Plaque Is Associated With Initiation and Continuation of Pharmacological and Lifestyle Preventive Therapies: A Systematic Review and Meta-Analysis. *JACC Cardiovasc Imaging* 2017; **10**(8): 833-42.

48. Rozanski A, Gransar H, Shaw LJ, et al. Impact of coronary artery calcium scanning on coronary risk factors and downstream testing the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) prospective randomized trial. *J Am Coll Cardiol* 2011; **57**(15): 1622-32.
49. Rozanski A, Muhlestein JB, Berman DS. Primary Prevention of CVD: The Role of Imaging Trials. *JACC Cardiovasc Imaging* 2017; **10**(3): 304-17.
50. Mols RE, Jensen JM, Sand NP, et al. Visualization of Coronary Artery Calcification: Influence on Risk Modification. *Am J Med* 2015; **128**(9): 1023 e23-31.
51. van den Oord SC, Sijbrands EJ, ten Kate GL, et al. Carotid intima-media thickness for cardiovascular risk assessment: systematic review and meta-analysis. *Atherosclerosis* 2013; **228**(1): 1-11.
52. Kavousi M, Elias-Smale S, Rutten J, et al. Evaluation of Newer Risk Markers for Coronary Heart Disease Risk Classification: A Cohort Study. *Annals of Internal Medicine* 2012; **156**(6): 438-44.
53. Crouse JR, Craven TE, Hagaman AP, Bond G. Association of Coronary Disease With Segment-Specific Intimal-Medial Thickening of the Extracranial Carotid Artery. *Circulation* 1995; **92**(5): 1141-7.
54. Baber U, Mehran R, Sartori S, et al. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BiImage study. *J Am Coll Cardiol* 2015; **65**(11): 1065-74.
55. Taylor AJ, Bindeman J, Feuerstein I, et al. Community-based provision of statin and aspirin after the detection of coronary artery calcium within a community-based screening cohort. *J Am Coll Cardiol* 2008; **51**(14): 1337-41.
56. Arad Y, Spadaro LA, Roth M, Newstein D, Guerci AD. Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: the St. Francis Heart Study randomized clinical trial. *J Am Coll Cardiol* 2005; **46**(1): 166-72.
57. Vonder M, van der Aalst CM, Vliegenthart R, et al. Coronary Artery Calcium Imaging in the ROBINSICA Trial: Rationale, Design, and Technical Background. *Acad Radiol* 2018; **25**(1): 118-28.
58. Muhlestein JB, Lappe DL, Lima JA, et al. Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial. *JAMA* 2014; **312**(21): 2234-43.
59. Newby DE, Adamson PD, Berry C, et al. Coronary CT Angiography and 5-Year Risk of Myocardial Infarction. *N Engl J Med* 2018; **379**(10): 924-33.
60. Adamson PD, Williams MC, Dweck MR, et al. Guiding Therapy by Coronary CT Angiography Improves Outcomes in Patients With Stable Chest Pain. *J Am Coll Cardiol* 2019; **74**(16): 2058-70.

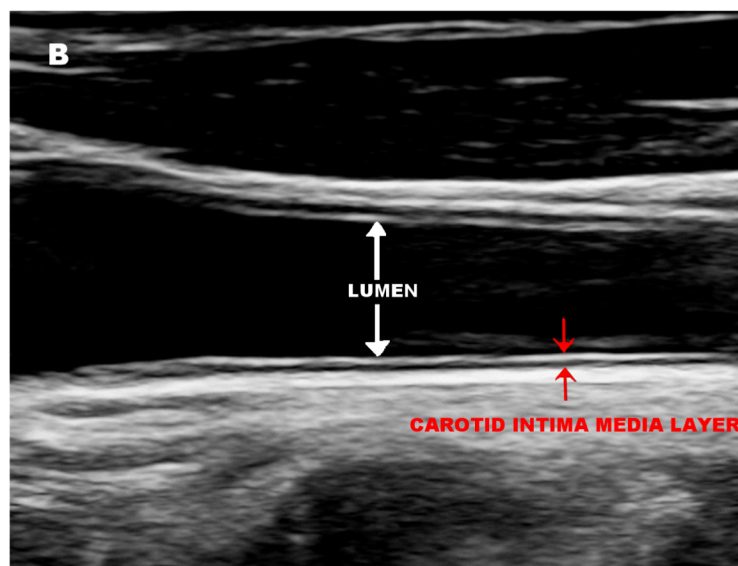
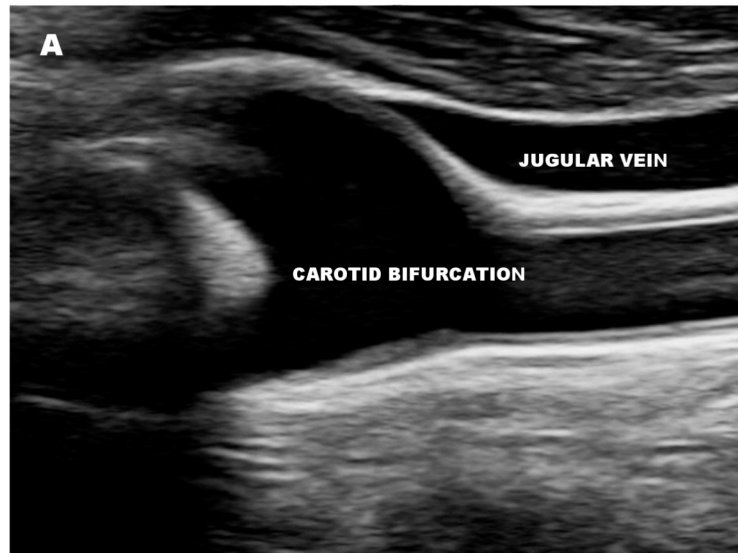


Figure 1: B-mode ultrasonography of the carotid artery.
(A) Shows the carotid bifurcation in relation to the jugular vein.
(B) Demonstrates the carotid intima media layer which measures 0.4-0.7mm depending on age.

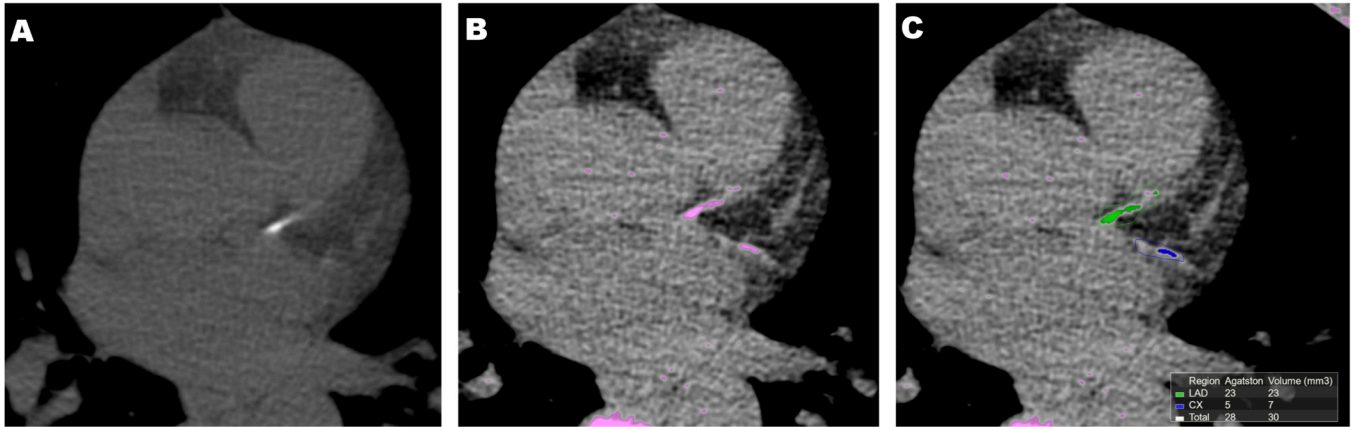


Figure 2: Computed tomography being used to calculate coronary calcium score.

- (A) Raw image showing flecks of calcification in left anterior descending artery.
- (B) Software autodetecting calcified plaque and highlighting them in pink.
- (C) Agatston score calculated by clinician delineating left anterior descending (green), and left circumflex (blue) plaque.

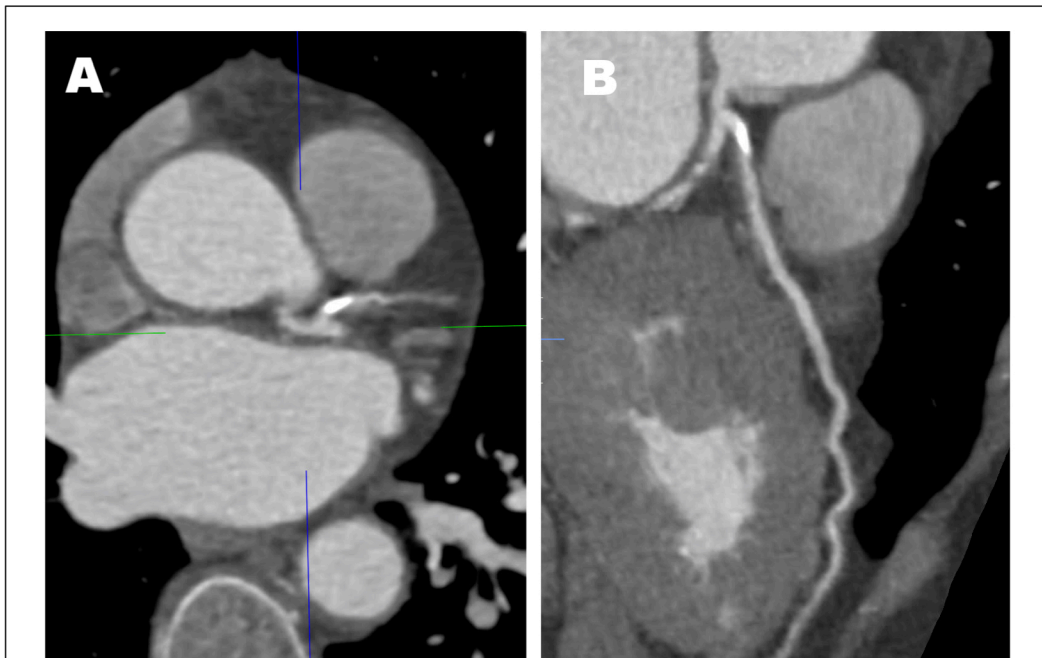


Figure 3: Computed tomography coronary angiography of calcific lesion seen in Figure 2.

- (A) Heavy calcification seen in ostial left anterior descending artery.
- (B) Reconstruction of left anterior descending artery.

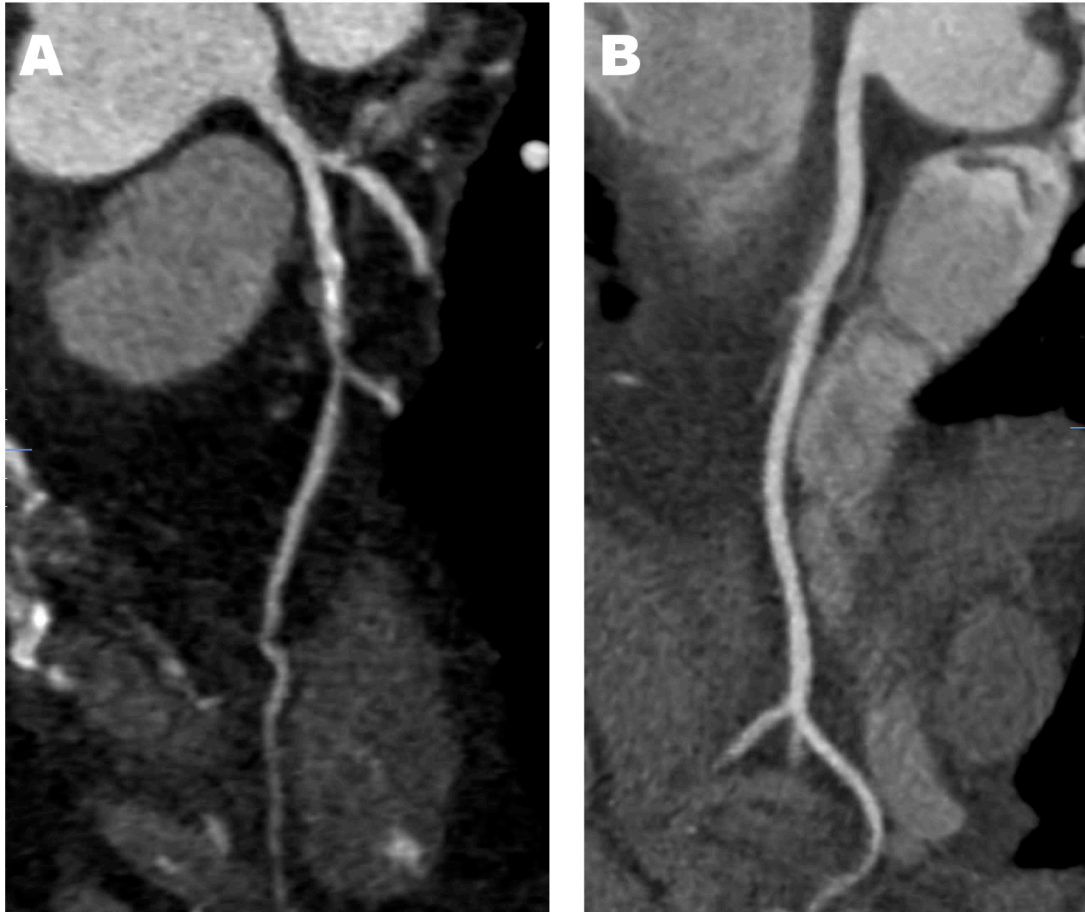


Figure 4: Comparison of normal versus abnormal computed tomography coronary angiography.

- (A) A high-risk, mixed plaque lesion in a diseased left anterior descending artery with severe stenosis at the bifurcation with the first diagonal vessel.
- (B) Normal right coronary artery

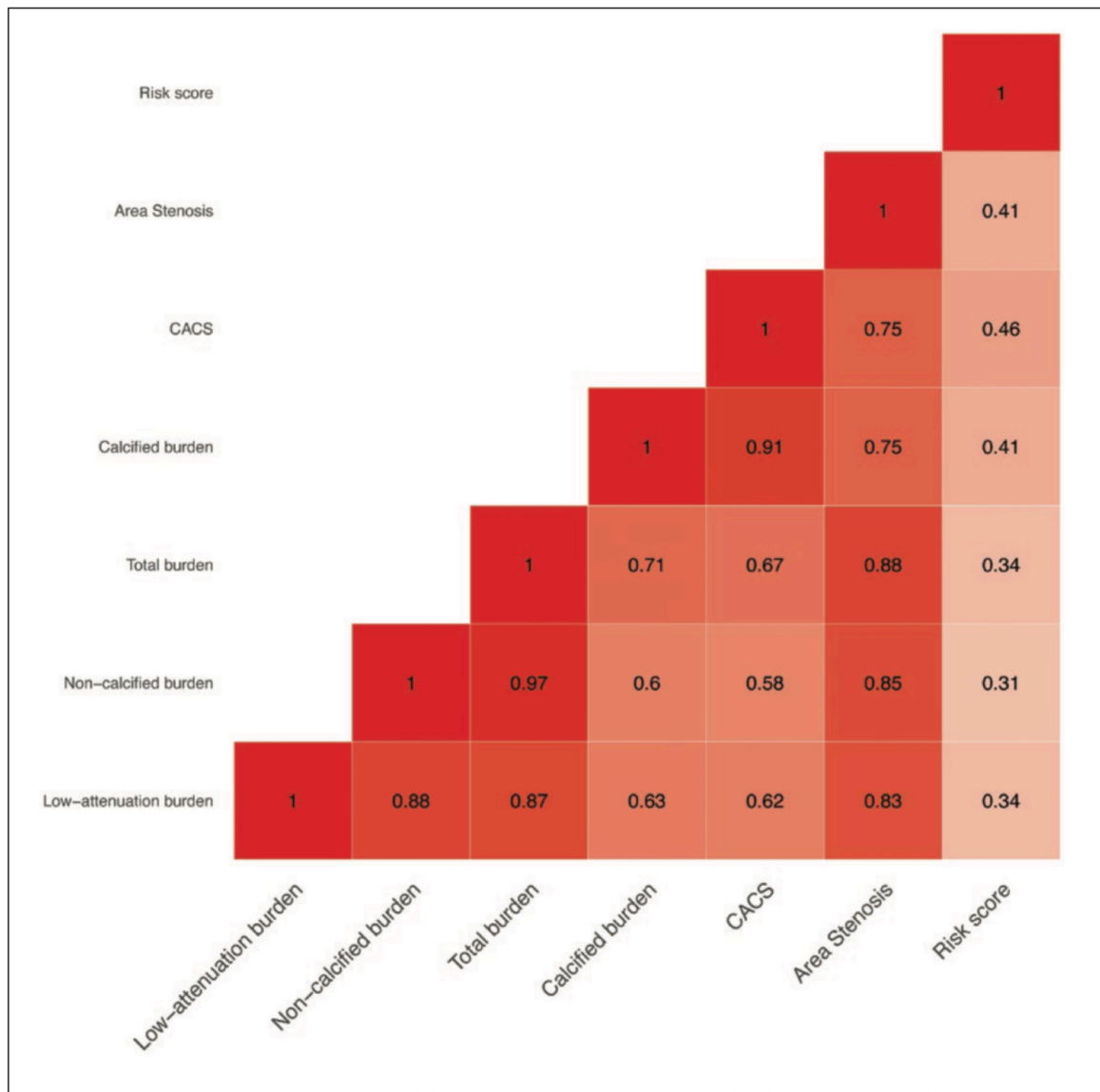


Figure 5: Reproduced from Williams et al ⁴⁰

Correlation between plaque burden subtypes, calcium score, coronary stenosis and cardiovascular risk using ASSIGN score (assessing cardiovascular risk using SIGN guidelines). $P < 0.001$ for all. CACS indicates Agatston coronary artery calcium score.

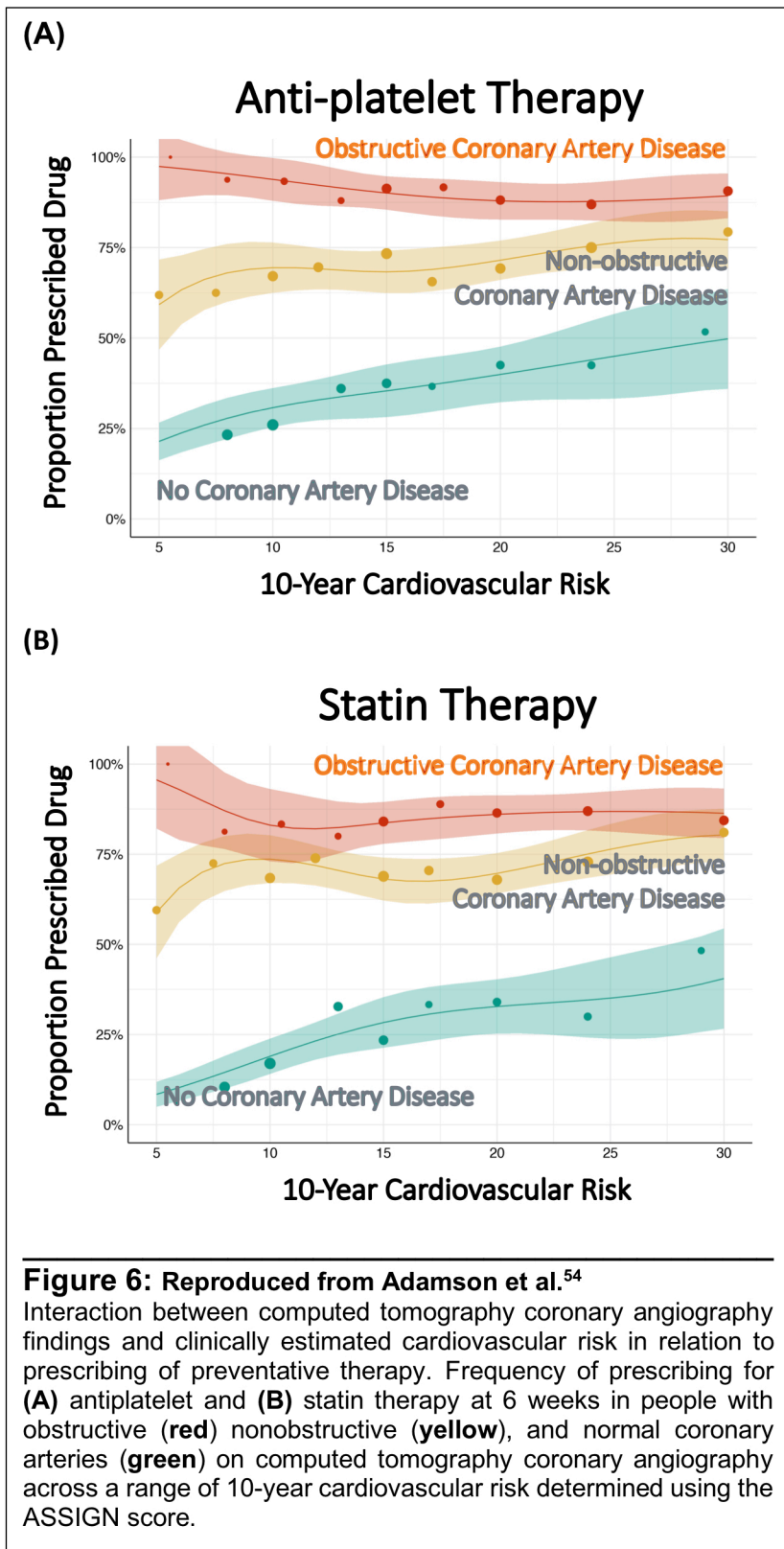


TABLE 1: Current guideline recommendations on imaging in primary prevention

Guideline	Carotid Intima Media Thickness	Coronary Calcium Scoring
ESC/EACPR 2012.⁵	Recommends measurements in asymptomatic individuals at moderate risk (Class IIa)	Recommends measurements in asymptomatic individuals at moderate risk (<u>Class IIa</u>)
ACC/AHA 2013.⁶	Not recommended in clinical practice for risk assessment (Class III)	Recommended if, after quantitative risk assessment, decision is uncertain (<u>Class IIb</u>)

ESC, European Society of Cardiology; EACPR, European Association for Cardiovascular Prevention and Rehabilitation; ACC, American College of Cardiology; AHA, American Heart Association.

TABLE 2: Imaging trials on cardiovascular disease prevention

Trial	Imaging mode	N	Objective/Finding
DIAD⁵⁶	Myocardial perfusion imaging	1123	Small population with lower than anticipated event rates. Myocardial perfusion scanning had no discernible effect on subsequent cardiac events.
St Francis⁵⁰	Coronary artery calcium score	1005	Small population, event curves diverged at 5 years, no effect on slowing progression of coronary calcification.
PACC⁴⁹	Coronary artery calcium score	1640	Small population with a high level of zero score scans limiting event numbers. Additionally, found to have positive effect on physician prescribing preventive medication and compliance.
EISNER⁴²	Coronary artery calcium score	2137	Demonstrated better risk factor control without increasing downstream medical testing in those who underwent calcium scan.
FACTOR-64⁵²	Computed tomography coronary angiography	900	Small study with no difference detected in outcomes, though close comparison shows failure to deliver treatments depending on scan results.

TABLE 3: Ongoing trials on computed tomography in cardiovascular disease prevention

Ongoing Trial	Imaging mode	N	Objectives
ROBINSCA ⁵¹	Coronary artery calcium score	39,000	1:1:1 randomisation to risk score, screen with calcium score, or a control group with no screening.
CorCAL (NCT03439267)	Coronary artery calcium score	18,000	1:1 randomisation to statin therapy based on CAC score or standard risk assessment
DANCAVAS ⁵⁷	Thoracoabdominal non-contrast CT	10,471	Recruiting men only, completed in 2017, baseline findings reported 33.2% of patients had a calcium score >400.
SCOTHEART-2 (NCT03920176)	Computed tomography coronary angiography	6000	1:1 randomisation to preventative therapies based on CTCA result, or standard risk assessment.