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State of the Art in Cardiovascular CT'

Debates in cardiac CT: Coronary CT angiography is the best test in asymptomatic patients

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ABSTRACT

Cardiovascular disease remains a major cause of mortality, accounting for a third of all global deaths annually. Although there have been major improvements in our ability to detect and to treat patients with coronary heart disease, most myocardial infarctions occur in previously asymptomatic individuals. Identification of individuals at risk of myocardial infarction remains challenging and primary prevention guidelines rely on the use of cardiovascular risk scores that can be supplemented by coronary artery calcium scores. Coronary artery calcium scores provide a simple surrogate late marker of atherosclerosis but is unable to identify the early high risk non-calcified plaque which can be particularly problematic in younger individuals. Coronary computed tomography angiography is increasingly being used as the imaging strategy of choice in patients with symptoms of coronary heart disease. As an anatomical test, it can non-invasively detect the presence of coronary atherosclerosis, providing clinicians with a strong mandate to commence symptom relieving and preventative therapies. For asymptomatic individuals, it allows precise targeting of therapies to those with coronary heart disease rather than those "at risk" of disease. Moreover, our ability to calculate risk using coronary computed tomography angiography is rapidly improving with the use of techniques, such as plaque quantification and characterisation. These techniques have the potential to provide clinicians with tools to target cardiovascular disease prevention in a precision medicine approach. We here debate the ways in which coronary computed tomography angiography could improve the selection of asymptomatic individuals for preventative therapies over and above risk calculators and calcium scoring.

1. Introduction

Global trends in cardiovascular death have fallen and survival rates have improved over the last 30 years, driven by advances in medical and interventional therapies.[1,2] Despite this, it remains the primary cause of mortality, accounting for over 2000 daily deaths in the United States, and a third of all deaths globally.[3–5] Our understanding of the causes of cardiovascular disease is underpinned by a number of landmark observational studies such as the Framingham heart study which identified key cardiovascular risk factors.[6] These observational studies were instrumental in emphasising the importance of managing conditions, such as hypertension and hyperlipidemia, in preventing cardiovascular events. More than 70 years after the inception of the Framingham heart study, most current guidelines continue to use risk calculators based upon such observational data.[7–10] However, is there a way to improve the selecting of individuals for cardiovascular prevention in this era of precision medicine? In this review, we discuss why coronary computed tomography angiography may be best placed to achieve this.

2. The problems of risk scores

At present, guidelines suggest use of locally calibrated risk scores which estimate an individual's risk of future cardiovascular events.[7–10] Local calibration ensures the model coefficients of the risk score are

Abbreviations: AU, Agatston units; CAC, Coronary Artery Calcium; CARDIA, Coronary Artery Risk Development in Young Adults trial; CT, Computed Tomography; SCOT-HEART, Scottish COmputed Tomography of the HEART.

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appropriate: essentially ensuring that the model is appropriately fitted to the local population to which it is applied. Over the last few decades, there have been few changes in how we determine cardiovascular risk, and whilst some scores have been updated to include social deprivation and inflammatory conditions, they continue to both over and under-estimate disease prevalence. The application of risk scoring can therefore lead to unnecessary downstream investigation and treatments.[11] The problem is further magnified when scores are applied to populations that have consistently been underrepresented in the literature, such as in women and black and minority ethnic groups.[12] Moreover, the optimal threshold at which to institute prevention therapies can be influenced by cost and societal preferences, such that treatment thresholds vary not only by region but also evolve with time. This can cause confusion and result in under-prescription amongst those eligible for treatment.[13,14] There is also the problem that individuals have difficulty in understanding the concept of risk and probabilities.[15,16] When combined with conflicting reports in the media about medication side effects, this can negatively impact on adherence to therapies.[17]

Cardiovascular risk is heavily influenced by age and risk scores are therefore more likely to advocate prevention treatment for older patients. Indeed, one review including nearly 3 million patients with no previous history of cardiovascular disease or statin use, found that model performance was weaker in those aged over 65 years and resulted in an over-prediction of risk.[18] Conversely, registry data of 1700 patients suffering myocardial infarction under the age of 50 years found that, if screened before their myocardial infarction, between 50 and 70% of patients would not have been eligible for preventative therapies by current guidelines.[19] As well as being the hardest to identify, these younger individuals arguably have the most to gain from preventative therapies: the greatest reductions in disability and the most life-years gained will be in the younger populations.

In an age of evidence-based medicine, it is important to ask whether risk scores have been proven to improve outcomes. Despite their near universal application across the world, risk scores have not been shown to improve outcomes. In a Cochrane systematic review and meta-analysis, there was little or no effect of applying a cardiovascular risk score on subsequent cardiovascular event rates (5.4% versus 5.3%; relative risk 1.01, 95% confidence interval 0.95 to 1.08; n = 99,070).[20] This begs the question of why risk scores are used at all.

3. Risk scores versus screening

Most asymptomatic individuals being commenced on risk score-directed preventative therapies have little or no chance of benefiting from them, because many will not have coronary artery disease and will never go on to experience a clinical event. This is particularly true as risk thresholds have been further reduced.[7,8] This renders most of the population ‘over medicated.’ Why not screen for the condition, rather than guess a probability where interventional thresholds often mean the vast majority of the population are commenced on unnecessary therapy?

The potential benefits of screening for coronary artery disease can be seen in prior trials. In the Scottish COmputed Tomography of the HEART (SCOT-HEART) trial, patients with stable chest pain were evaluated for the presence of coronary heart disease. In patients who had non-anginal chest pain, coronary CT angiography demonstrated that roughly a half of patients had normal coronary arteries and half had non-obstructive or obstructive coronary artery disease. This led to a marked change in use of preventative therapies as well as producing the greatest relative risk reduction in the future risk of myocardial infarction.[21] Crucially, this included both cessation and initiation of therapy, indicating that many patients are taking statins but do not need them, and others require them despite their low risk score. Thus, coronary CT angiography has potential to benefit patients at both ends of the disease spectrum. For those with disease, it appropriately targets therapy, and for those without, it gives reassurance impacting on their quality of life and peace of mind.

4. Coronary artery calcification

The argument to use coronary artery calcium score as a gatekeeper for use of preventative therapies is a strong one. It can be performed quickly, with minimal radiation exposure and without the need for intravenous contrast. Coronary artery calcium score is an independent and incrementally better predictor of future cardiovascular events compared to traditional risk factors alone.[22] Whilst undoubtedly of value when used to rule-in people who may benefit from preventative therapies, its use as a rule-out test is less clear. For example, in the Multi-Ethnic Study of Atherosclerosis cohort, up to a third of total events occurred in patients with a calcium score of zero.[23] In the CAC Consortium cohort, 43% of cardiovascular deaths occurred in participants with a calcium score of zero.[24] The Coronary Artery Risk Development in Young Adults (CARDIA) study, highlighted that a calcium score of 0 is more likely in younger patients (83% of those <45 years old had a calcium score of 0). This is consistent with the strong link between coronary artery calcification and age.[25] Coronary artery calcification therefore faces the same limitation as risk scores, where the youngest with the most to gain can be overlooked.

5. Coronary computed tomography angiography

We know from quantitative plaque analysis that calcified plaque burden represents a small proportion of total plaque burden,[26,27] even in patients with advanced coronary artery disease.[28] Where calcification is present, it is associated with an underlying larger proportion of non-calcified plaque. A zero or low calcium score could therefore give physicians and patients a false sense of security (Fig. 1). A clear distinction is needed between a zero-calcium score and no atherosclerosis for the selection of patients who would benefit from preventative therapies. In a recent post-hoc analysis of SCOT-HEART, coronary artery disease was identified in 16% of patients with a calcium score of 0 and 50% of patients with minimal coronary calcium (1–9 Agatston units, AU). In addition, a third of events occurred in patients with a calcium score

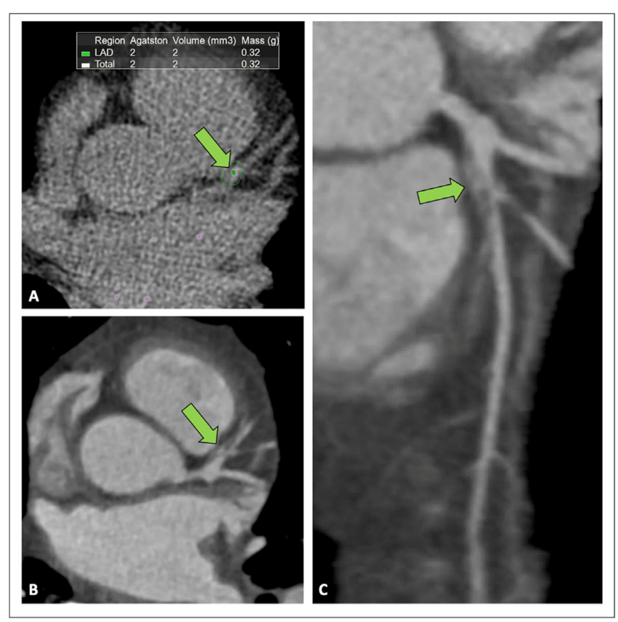

Fig. 1. 50-year-old asymptomatic male recruited to a primary prevention study randomised to CT coronary angiogram. Family history of coronary disease and mildly elevated cholesterol, ASSIGN risk score 17% (threshold for treatment locally is 20%). Coronary calcium score of 2 in the left anterior descending artery **(A)**. CT coronary angiography demonstrates severe stenosis (90%) in the proximal LAD **(B, C)** with spotty calcification and evidence of positive remodelling. Prior to CT scan patient unwilling to start medication as he felt “well”, however on showing him images, patient agreed to start prevention medication.

<100 AU. These patients were more likely to be young and female.[29] There are, therefore, many exceptions to the low calcium score rule and one must consider age, sex and comorbidities before choosing to undertake coronary calcium scanning.

Thin-capped fibroatheroma have been established in post-mortem studies to be the precursor to plaque rupture and erosion.[30] As CT technology has improved, we have gained a greater ability to detect these pathological changes. For example, an area of low-attenuation surrounded by higher attenuation, the so-called the 'napkin-ring' sign, correlates well with the thin-capped fibroatheroma and histologically defined advanced coronary lesions.[31,32] These lesions are rarely associated with calcification.[32,33]

Developing analytic approaches have enabled the rapid and reproducible detection, characterisation and quantification of plaque on coronary CT angiography.[34] The highest future risk appears to be associated with low-attenuation plaque (defined as Hounsfield unit <30) reflecting the presence of a lipid-rich necrotic core. We have previously demonstrated that the burden of low-attenuation plaque was the strongest independent predictor of future fatal and non-fatal myocardial infarction, being superior to both coronary artery calcium score and stenosis severity.[27] This process requires dedicated software tools and these are increasingly being automated.

There are several other techniques that place coronary CT angiography ahead of coronary artery calcium scoring in its ability to predict risk. Novel techniques utilising machine learning algorithms can provide further measures of risk by analysing pericoronary adipose tissue attenuation. This has potential to add predictive value beyond coronary artery calcium score, degree of stenosis and high-risk plaque features.[35] In addition, machine learning tools and radiomic characteristics of the plaque itself can provide incremental prognostic information.[36]

For symptomatic patients, coronary CT angiography is the only non-invasive diagnostic modality to demonstrate a prognostic benefit in randomised controlled trials.[37] In asymptomatic patients, there has only been one randomised trial assessing the use of coronary CT angiography in a primary prevention setting. The FACTOR-64 study recruited 900 asymptomatic patients with diabetes mellitus, and whilst it failed to demonstrate a clinical outcome benefit, it suffered from a small sample size and a lower than anticipated event rate (16% anticipated, 7% observed).[38] Recruited patients' medical therapy were for the most part already optimised with 75% of patients on statin therapy at baseline. The failure to demonstrate a benefit therefore likely reflects the inability to deliver a meaningful difference in treatment as a consequence of the imaging test.

Larger studies, such as the SCOT-HEART 2 trial (NCT03920176), are currently underway to provide evidence on whether a coronary CT angiography-based strategy for asymptomatic patients with at least one risk factor is of benefit in clinical practice. It hopes not only to answer the question of whether coronary CT angiography is better than risk scoring, but how to apply an imaging based screening tool.

6. Limitations of coronary CT angiography

There are several barriers to progressing from a risk score-based approach to one that incorporates coronary CT angiography. Exposure to radiation requires some consideration. Whilst substantial radiation dose reduction is now commonplace, the residual exposure is not without some risk. Current estimates suggest calcium scoring has an effective radiation dose of 1–3 mSv, whereas with coronary CT angiography it can range between 1 and 5 mSv, with background radiation estimated to be 2–3 mSv per year.[39] The estimated risk of developing radiation induced fatal cancer as a result of coronary CT angiography is around 0.03% which needs to be viewed in the context of the general population lifetime risk of cancer of 50%.[40] The use of contrast and medications, such as beta-blockers and nitrates, to optimise image quality brings a small risk of adverse reactions. While these events are uncommon, they necessitate the presence of an on-site physician during scan conduct. Finally, the use of coronary CT angiography has the potential for further 'down-stream' testing in patients felt to have a 'severe' burden of disease or have clinically important incidental findings. This would require careful consideration and may be the subject of future research.

7. Conclusion

The field of preventative medicine has relied on risk scores for decades with only modest progress on improving the accuracy of risk prediction. Coronary CT angiography can change the prevention paradigm using a precision medicine approach to identify the presence, rather than the risk, of coronary artery disease. Coronary CT angiography can provide additional information over and above the presence of coronary artery calcification, including the burden of all plaque types, the visual and quantitative assessment of high-risk plaque phenotypes, and in the future addition of machine learning and radiomic plaque characteristics. In our opinion, coronary CT angiography is the best placed and definitive method to guide patients and physicians in the prevention of coronary artery disease.

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The authors have no disclosures to report.

Declaration of competing interest

None.

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