Computed Tomography Coronary Angiography and the SCOT-HEART trial

By Dr. R Ramaesh, Prof. D E Newby and Dr. M C Williams

Coronary heart disease (CHD) is a leading cause of mortality and morbidity, and a frequent cause of primary and secondary care attendance with chest pain. It is therefore paramount that patients who are at high risk are identified early, and appropriate treatment organised. However, clinical assessment alone can be challenging, as patients often present with atypical symptoms and pre-test probability scoring systems both under- and over-estimate risk. Furthermore, whilst non-invasive testing with exercise electrocardiography or functional testing can risk-stratify patients, their application has not demonstrated an improvement in clinical outcomes, such as rates of myocardial infarction. On the other hand, Computed Tomography Coronary Angiography (CTCA) provides a rapid, non-invasive method to evaluate the coronary arteries with a high diagnostic accuracy (sensitivity 96%, specificity 72%, to detect a >70% stenosis [1]) and involves only a relatively low radiation dose.

The results of the SCOT-HEART (Scottish Computed Tomography of the HEART) randomised controlled trial, whose 5-year follow-up data have recently been published, have established the role of CTCA for patients with symptoms of suspected coronary artery disease [2, 3, 4], leading to important changes in guidelines. The SCOT-HEART trial was an open-label, parallel-group, multicentre randomised control trial, recruiting patients who were referred to cardiology outpatient chest pain clinics by their primary care physician or other healthcare providers. Over a four-year period, 4146 eligible patients with suspected angina due to coronary heart disease were randomised to undergo standard care, or standard care plus computed tomography (CT). An important strength of the trial is the fact that SCOT-HEART had broad inclusion criteria, including patients between 18 and 75 years and recruited a half of all eligible patients. The trial therefore investigated a clinical approach that is readily generalisable in the real world.

The aim of the SCOT-HEART trial was to assess the role of CT in the diagnosis, management and outcome of patients with suspected angina compared to standard treatment. For patients in the CT group, the results of the coronary artery calcium score and CTCA were provided to clinicians. For patients in the standard care group, the 10-year cardiovascular risk score was provided. The primary outcome was the diagnosis of angina secondary to coronary heart disease. Long term assessment included outcomes such as death, myocardial infarction, and coronary revascularisation.

At six-weeks, CTCA led to a change in the diagnosis of angina due to coronary heart disease in 23% of patients compared with just 1% of patients in the standard care arm ($p<0.0001$) [3]. According to the clinicians reporting the CTCA scans, this led to an increase in the certainty (relative risk 3.76, 95% confidence interval (CI) 3.61 to 3.89, $p<0{\cdot}0001$) but reduced the frequency (relative risk 0.78, 95% CI 0.70 to 0.86, $p<0{\cdot}0001$) of the diagnosis of angina due to coronary heart disease [3]. This clarification of diagnosis had several important implications for subsequent patient management.

- Firstly, CTCA led to a change in medication use in 23% compared to 5% in the standard care arm ($p<0.0001$) [3]. This included an increase in the use of preventative medication (aspirin, statin, angiotensin converting enzyme inhibitor). CTCA can therefore be used to target appropriate use of medical therapy. It is likely that the early, confident diagnosis of coronary heart disease in the CTCA arm allowed for more frequent and effective preventative treatments.

- Secondly, CTCA led to a change in subsequent investigations. An early criticism of the use of CTCA in the assessment of angina was that it would lead to more frequent, potentially unnecessary, investigations. However, SCOT-HEART has proven the contrary to be true. In the CTCA group, there was a significant change in the number of subsequent planned investigations (15% vs 1%, $p<0{\cdot}0001$) [3]. In the first 12 months, there was a slight increase in the number of invasive coronary angiograms performed in the CTCA group. However, there was also a reduction in the number of

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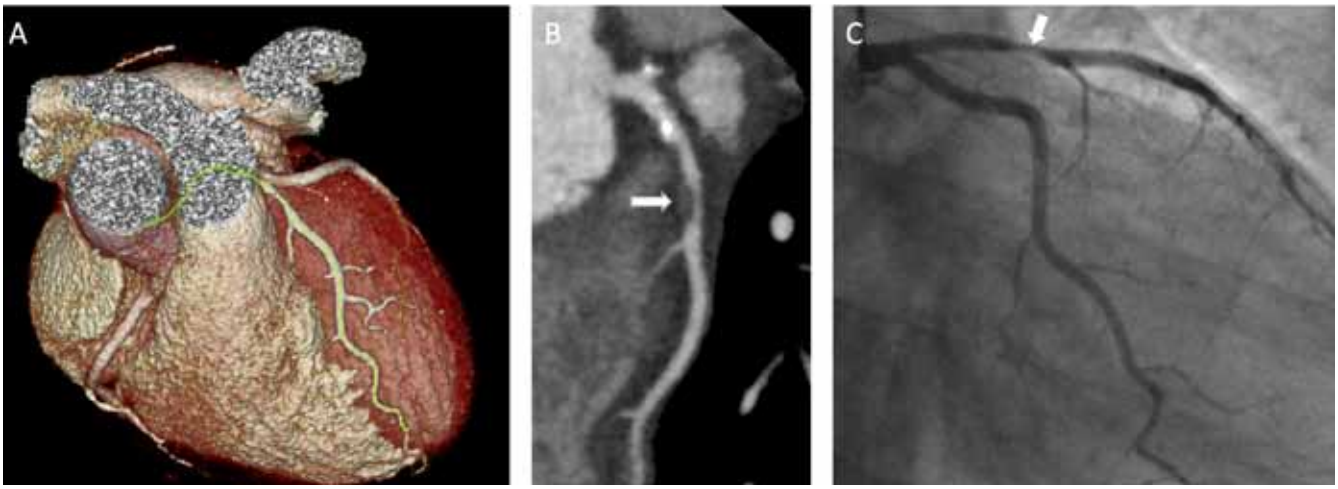

Figure 1. CT (A, B) and invasive coronary angiography (C) images from a 56 year old female who attended the cardiology out patient department with a history of atypical chest pain. She was an ex-smoker with a family history of coronary artery disease. An exercise tolerance test was inconclusive. CTCA curved planar reformation (B) shows a mild calcified plaque and a severe non-calcified plaque (arrow) in the proximal LAD. Invasive coronary angiography (C) showed a severe stenosis in the proximal LAD (arrow) and this was treated with a coronary artery stent.

patients with normal coronary arteries identified at invasive coronary angiography. Beyond the first year, patients in the CTCA group had lower rates of invasive coronary angiography, and at 5 years there was no difference in the frequency of invasive coronary angiography between the two groups (23.6% vs 24.2%, hazard ratio 1.00, 95% CI 0.88 to 1.13) [4]. Similarly, whilst there was a higher rate of coronary revascularisation in the CTCA arm in the first 12 months, at five years there was no difference between the two groups (13.5% vs 12.9%, hazard ratio 1.07, 95% CI 0.91 to 1.27) [4]. This shows that patients in the CTCA group had more appropriate, timely use of invasive coronary angiography and revascularisation compared to those in the standard care group.

"... significantly lower rate of coronary heart disease death or non-fatal myocardial infarction in the CTCA group compared to the standard care group..."

The initial 1.7-year follow-up of the SCOT-HEART trial showed a 38% reduction in the rate of the combined endpoint of fatal and non-fatal myocardial infarction in patients in the CTCA group, which just failed to reach statistical significance (p=0·0527) [3]. A landmark analysis was performed which censored the initial 50 days of the trial period, which was the median time it took to perform imaging, communicate results to clinicians and patients and organise a change in management strategy. This showed a 50% reduction in the rate of myocardial infarction and death in the patients in the CTCA group (hazard ratio 0.50, 95% CI 0.28 to 0.88, p=0.020) [5]. The 5-year results of the SCOT-HEART trial have recently been published. This confirms the significantly lower rate of coronary heart disease death or non-fatal myocardial infarction in the CTCA group compared to the standard care group (2.3% vs. 3.9%, hazard ratio 0.59, 95% CI 0.41 to 0.84, p=0.004) [4]. Thus, for the first time, a management strategy based on an imaging test for patients with suspected coronary heart disease has been shown to significantly improve outcomes. Indeed, the number needed to test (NNT) for CTCA to prevent one fatal or nonfatal myocardial infarction over 5 years is only 63 patients [4].

At the same time as the initial SCOT-HEART trial results were published, the results of the PROMISE trial were also published [6]. PROMISE was a large randomised controlled trial which compared CTCA with functional testing. Over a three-year period, 10,003 patients were recruited and randomised to anatomical testing with CTCA or functional testing (68% nuclear stress testing, 22% stress echocardiography and 10% exercise electrocardiogram). PROMISE demonstrated no differences in mortality between the CTCA and functional testing groups after 2 years of follow-up. Unfortunately, longer term follow-up is not available. A meta-analysis of the 2-year combined results of PROMISE, SCOT-HEART and other smaller studies, with a total of 14,817 patients, demonstrated that there was a 31% relative risk reduction of myocardial infarction for patients undergoing CTCA compared to standard care, but no change in mortality [7].

Subsequent registry studies have confirmed the ability of CTCA to appropriately target medical management and revascularisation identified in SCOT-HEART. A large Danish registry study of 86,705 patients showed that there was a change in medication use in patients undergoing CTCA compared to functional testing (26% vs 9% statin use, p < 0.001 and 13% vs 9% aspirin use, p < 0.001) [8]. The PROMISE study and other registry studies have also shown that CTCA can more appropriately select patients for invasive coronary angiography and reduce the proportion of patients with normal coronary arteries at invasive coronary

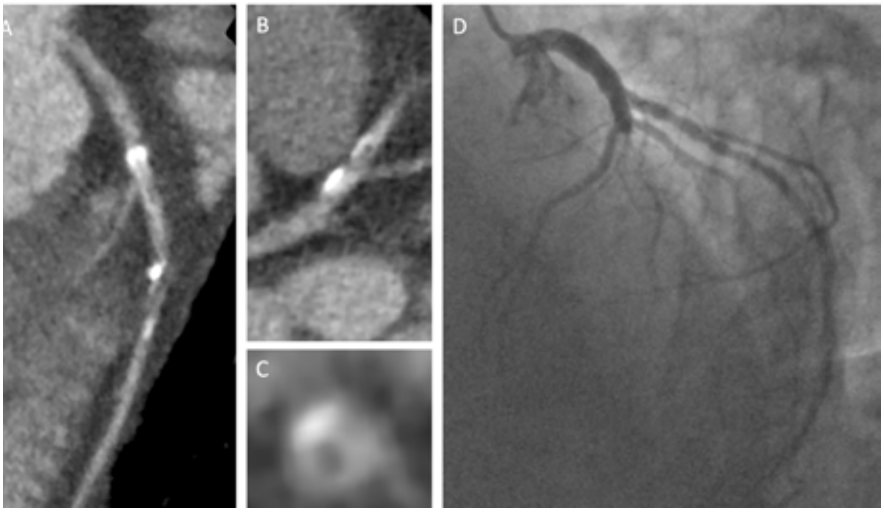

Figure 2. A 49-year old male attended the cardiology outpatient clinic with a history of typical chest pain. He was a non-smoker with no cardiovascular risk factors. He underwent CTCA which showed severe mixed plaque in the mid and distal left anterior descending coronary artery (A, curved planar reformation; B axial images). A cross sectional image through the plaque shows shows adverse plaque characteristics including positive remodelling and low attenuation plaque. While waiting for an appointment for an outpatient invasive coronary angiogram, he was admitted to the emergency department with a non-ST elevation myocardial infarction (NSTEM). Invasive coronary angiography showed a subtotal occlusion in the LAD which was treated with a drug eluting stent.

angiography. Thus, the results of the SCOT-HEART trial have been supported by other subsequent research.

CTCA now has a central role in the UK NICE (National Institute of Health and Care Excellence) guidelines for patients with stable chest pain [1]. The NICE guidelines no longer advocate assessment of the pre-test probability of obstructive coronary artery disease and CTCA is the first line test for patients with possible angina [Figures 1 and 2]. The current European Society of Cardiology and American College of Cardiology reserve CTCA for certain subgroups. However, these guidelines were published in 2013 and 2012, and are therefore likely to be revised.

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An ongoing challenge for patients and clinicians is the fact that myocardial infarction frequently occurs in coronary arteries without prior obstructive coronary artery disease. In the SCOT-HEART trial, patients with obstructive disease had the highest rate of myocardial infarction, but for those with non-obstructive disease, the event rate was also higher than those with normal coronary arteries. In the PROMISE trial over 50% of myocardial infarctions occurred in patients with normal functional stress tests or non-obstructive coronary artery disease on CTCA. On CTCA adverse coronary artery plaque characteristics can be identified which correlate with invasive assessment of plaque vulnerability. In both the SCOT-HEART and the PROMISE trial, the presence of adverse coronary artery plaque characteristics has been associated with worse outcomes [9, 10]. However, at 5 years in the SCOT-HEART trial this was not independent of the overall coronary artery plaque burden assessed with the coronary artery calcium score. This is in keeping with our current understanding of atherosclerosis as a dynamic process, where vulnerable atherosclerotic plaques may stabilise without clinically apparent myocardial infarction. In addition, the future cornerstone to improve coronary artery disease outcomes may be the early identification of atherosclerotic plaque burden, prior to the onset of symptoms. With this in mind, the SCOT-HEART 2 randomised controlled trial will assess the use of CTCA in asymptomatic populations.

CONCLUSION

In conclusion, the SCOT-HEART trial has established the role of CTCA in patients with suspected coronary heart disease. CTCA lead to more appropriate targeted use of medical therapies, subsequent investigations and revascularisation. Importantly, SCOT-HEART has shown, for the first time, that a management strategy based on an imaging test for patients with suspected coronary heart disease can improve clinical outcomes.

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