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Opinion paper

SCOT-HEART: Does it live up to the PROMISE?

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1. Introduction

Evaluating patients with stable chest pain syndromes without known coronary artery disease results in nearly 4 million stress tests annually, with cardiac imaging playing an increasing role in these patients' evaluation.[1] From 1993 to 2008, the percentage of stress tests that included cardiac imaging increased from 59% to 87%, of which 34.6% did not meet standards for appropriateness, resulting in annual direct costs of nearly $501 million and a projected 491 future cases of cancer due to radiation exposure.[1] Despite the increase in cardiac imaging rates, there still remains comparatively little information on the health outcomes and comparative-effectiveness of different imaging strategies for identifying coronary artery disease.[2,3] In particular, the relative advantages and disadvantages of traditional "functional" testing vs. "anatomic" imaging with coronary computed tomographic angiography (CTA) are unclear. The development of low-radiation dose CTA has permitted detailed anatomic imaging of the coronary arterial bed with the ability to identify subclinical or nonobstructive coronary artery disease that may not have been otherwise identified on traditional functional testing.[4] Additionally, CTA may provide unique anatomic information that can help risk stratify patients presenting with stable chest pain for conservative versus invasive management.[5]

The comparison of diagnostic testing strategies for patients with new onset stable chest pain was previously evaluated in the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial. The study randomized patients to functional testing with exercise electrocardiography, nuclear stress testing, or stress echocardiography vs. initial anatomic testing with CTA. Over a median follow-up of 2 years, the strategy of initial CTA demonstrated no difference in death, myocardial infarction, hospitalization for unstable angina, or major procedural complications, but had higher overall radiation exposure and rates of cardiac catheterization than functional testing.[6] These data thus cast doubt on the utility of coronary CTA for the routine evaluation of patients with stable coronary artery disease.

2. Initial SCOT-HEART results

Enrolling nearly concurrently with PROMISE was another trial evaluating this issue, the Scottish Computed Tomography of the Heart (SCOT-HEART) trial. The SCOT-HEART trial was a prospective, open-label, parallel group, multicenter trial that randomized 4146 adults (ages 18–75), referred for suspected angina to 12 cardiology clinics across Scotland between November 18, 2010 and September 24, 2014, to an initial strategy of CTA plus standard care or standard care alone in a 1:1 fashion.[7] Patients with suspected or recent (< 3 months) acute coronary syndrome were excluded. Eighty-five percent of enrolled patients in both arms of the trial underwent symptom-limited stress electrocardiography employing the standard Bruce protocol prior to randomization. Ultimately, 2073 patients were randomized to CTA using a 64 or 320 detector row scanner at three imaging sites with an equal number to standard care alone, which included cardiovascular risk stratification with the ASSIGN score, a validated Scottish cardiovascular risk score which incorporates measures of family history of cardiovascular disease and social deprivation.[8] In the initial publication of the SCOT-HEART results in the journal *Lancet* in 2015, the primary endpoint was the proportion of patients diagnosed with angina due to coronary artery disease at 6 weeks as determined by the patient-administered Seattle Angina Questionnaire.[9] The use of CTA changed planned investigations (CTA vs. standard therapy; 15% vs. 1%; $p < 0.001$) and treatments (CTA vs. standard therapy; 23% vs. 5%; $p < 0.001$) but had no effect on angina severity or hospital admission for chest pain at 6 weeks. However, at 1.7 years, CTA was associated with a nonsignificant 38% reduction in fatal and nonfatal MI ($p = 0.0527$). Subsequent post-hoc analysis suggested that despite similar rates of coronary angiography between study arms, the CTA group was more likely to have obstructive coronary artery disease on invasive coronary angiography, receive preventative therapies, and experienced a near 50% relative reduction in rates of fatal and nonfatal myocardial infarction despite higher 6 month costs.[10]

3. Recent SCOT-HEART results

The SCOT-HEART investigators now present their 5-year follow-up results in the September edition of the *New England Journal of Medicine*, and the results are striking.[11] Over a median follow-up of 4.8 years, the rate of death from coronary heart disease or nonfatal myocardial

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infarction was reduced by 41% (CTA vs. standard therapy; 2.3% [48 patients] vs. 3.9% [81 patients]; HR 0.59, 95% CI 0.41–0.84; p = 0.004), driven by lower rates of myocardial infarction in the CTA group (CTA vs. standard therapy; 2.1% [44 patients] vs. 3.5% [73 patients]; HR 0.60, 95% CI 0.41–0.87). While rates of invasive angiography and coronary revascularization were similar at 5 years between study arms, patients in the CTA group were more likely to initiate both preventative therapies such as statins, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, beta-blockers, or calcium channel blockers (OR 1.40; 95% CI 1.19–1.65) and antianginal medications (OR 1.27; 95% CI 1.05–1.54). Thus, we are left to conclude that CTA results in a substantial benefit relative to standard of care. But should we make space in the catheterization laboratory for a new 320 detector row CT scanner, or is more caution warranted when interpreting these results?

3.1. The case for caution

While the possibility of a substantial benefit to CTA in reducing adverse outcomes exists, the magnitude of benefit raises questions of plausibility. The results demonstrate a 1.6% absolute risk reduction in the primary endpoint (i.e. 33 fewer patients in the CTA arm experiencing an adverse outcome compared to the standard therapy arm). This equates with a number needed to treat (NNT) of 63 patients receiving CTA to prevent one event. This compares favorably to or exceeds that of many common cardiovascular therapies such as aspirin for secondary prevention of non-fatal MI (NNT = 77 over a mean of 27 months)[12] and anti-hypertensives to reduce cardiovascular events (NNT = 100 over a mean of 5 years).[13]

But is it reasonable to conclude that a diagnostic test such as CTA can result in similar reduction in risk to these therapies that are cornerstones of the cardiovascular armamentarium? How is this risk reduction achieved? One could surmise that the reduction in myocardial infarction could be mediated by increased revascularization rates in the CTA group. However, in the 5-year SCOT-HEART results, revascularization was performed nearly equally in both arms (279 of the CTA group and 267 of the standard care group). Perhaps instead the effect of CTA was mediated by greater intensification of medical therapy in the CTA group. However, although more patients in the CTA group received cardioprotective medications, this difference was relatively modest (19.4% [402 patients] in the CTA group vs. 14.7% [305 patients] in the usual care group). Could the treatment of 97 more patients with medicines prevent 29 additional MIs? If not mediated through medical therapy or revascularization, how else does treatment change outcomes in those receiving CTA?

Could the timing of treatment have impacted outcomes? While revascularization rates were higher upfront in the CTA arm at 6 weeks in the initial SCOT-HEART publication, they were equivalent at 5-years. Could more upfront PCI lead to the difference? Given the null results from trials randomizing stable angina patients to PCI vs optimal medical therapy,[14] it is unlikely that upfront receipt of revascularization could have mediated the observed effect. Could it be that patients were followed for longer in the SCOT-HEART trial than other trials that did not show such a pronounced effect? In comparison to the PROMISE trial, the longer follow-up time (5-years vs. 2-years) in SCOT-HEART would have allowed for more accrual of events, but even at 1.7 years there was a signal for early benefit in the CTA group in SCOT-HEART which was not the case in PROMISE.

One possible unobserved variable that could mediate the effect of CTA is behavioral modification. It is plausible that demonstration by CTA of nonobstructive CAD influenced behavioral and lifestyle change more than a risk score did for the standard care arm, both for the prescriber and patient, especially given the unblinded nature of the trial. While rates of smoking and exercise were not reported in the SCOT-HEART 5-year results, it is possible that differential change in these and other CHD lifestyle risk factors impacted the observed results. Even still, it remains implausible that these lifestyle changes and medication changes could have resulted in such a profound difference in events at 5 years, and another explanation is needed.

3.2. The bridge halfway

In the weeks since the publication of the 5-year SCOT-HEART results, debate has raged in the medical and scientific community over how to interpret the substantial reduction in events in the CTA arm. While advocates have pointed to the improved risk stratification of CTA and identification of subclinical coronary artery disease, skeptics have pointed to the implausibility of the effect estimates, but is there a middle ground?

First, by anchoring on the point estimates of the effect of CTA, we are committing the fallacy of Type M error.[15] While conventional approaches focus on Type I (false positive) and Type II (false negative) errors, Type M error is an error of *magnitude*.[15] In this situation, we claim that the effect size is large when the effect size is small or vice versa. While it is possible that CTA reduces the primary endpoint by 41%, the 95% confidence interval extends from a 16% relative reduction in the primary endpoint to a 59% relative reduction. While the likelihood of observing an effect size as big or bigger than this despite there no true difference between arms is 0.4%, we cannot be as confident about the magnitude of this reduction. Instead, the observed data are consistent with as little as a 16% relative reduction in the primary endpoint (which translates to an absolute risk reduction of 0.5% or an NNT of 200), a number which is more plausible and consistent with the postulated mechanisms of disease improvement. In the SCOT-HEART sample size calculations, the authors postulated a 2.8% absolute reduction in event rates in the CTA arm from a 13.1% event rate in the standard care arm. This translates to a relative reduction of 21.4%, much more consistent with the likely true effect size.

What are reasons why the point estimate for the effect size may have been overestimated? The first is sample variation. Due to random variation and differences in the included patients, the effect size in a small study may not approximate that of the population. In these cases, it is often necessary to repeat the study in a larger sample in order to validate the findings. Second, there may be publication bias. As studies with large effect sizes are more likely to be published than those with small ones, it is possible that studies showing a null or smaller effect never reach print. Thus, Type M error is often unidirectional. When the sample size is small relative to the true effect size, a result may be statistically significant but non-reproducible.[15] One solution to this problem is to overestimate the sample size needed for a study in order to ensure that the study's results are reproducible regardless of the effect size anticipated, though this strategy has practical and ethical issues associated with it. Another solution is to pool the results of studies using a meta-analysis. Thus, while the possibility of Type M error does not invalidate the SCOT-HEART findings, it suggests that the results should be repeated in a larger sample or pooled with other studies to identify whether the true magnitude of effect differs from that observed.

Moreover, rather than focus solely on the effect size, one can examine the other potential advantages and disadvantages of each diagnostic strategy, evaluating upfront and downstream resource utilization to identify other health services outcomes where CTA may be particularly helpful or harmful. While rates of death may be similar between groups, important findings such as lung cancer identification or admission rates for stable chest pain may be impacted by the particular diagnostic strategy assigned and were not reported in the SCOT-HEART results. These may require long-term follow-up to show differences between groups, but are nevertheless an important downstream consequence of diagnostic testing, and may help clarify the optimal diagnostic strategy for patients presenting with stable chest pain, which despite multiple randomized trials, continues to be in question.

4. Conclusions

While CTA holds promise for the evaluation of patients with suspected angina pectoris, the nature, magnitude, and mechanism of benefit it provides is still in question. Although the 5-year results of the SCOT-HEART trial demonstrated large reductions in adverse outcomes and mortality, the results should be interpreted with an element of caution and skepticism, fueled by desire to discover the true effect size through repetition and verification.

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