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Opinion paper

SCOT-HEART is the trial that we have been waiting for!

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How do you improve patient outcome is a question that clinicians ask themselves every day and is the core to understanding the plausibility of the positive results observed in the SCOT-HEART trial.[1] For the first time in cardiovascular medicine, the SCOT-HEART trial was able to demonstrate a reduced rate of coronary heart disease death or myocardial infarction for patients randomized to coronary computed tomographic angiography (CTA) as compared to standard care.[1] Critics of this approach decry the falsehood of these results based on simplistic logic that tests only diagnose and do not directly impact outcome. But, do we side with the nihilist or embrace the new paradigm of care created with noninvasive anatomic imaging?

A key to understanding the SCOT-HEART results is to review the varied diagnostic approaches used for evaluation of stable chest pain. There are two diagnostic approaches, one based on anatomy and the other functional assessment; the latter of which is considered the standard evaluation in use for many decades. These two approaches are quite disparate not only in the index testing but also in the manner in which the strategies of care unfold for the patient. Our conventional approach including stress testing has received much criticism for its reduced accuracy, imprecision in selecting candidates for coronary angiography, and a lack of focus on patient-centered care.[2,3] The challenger, CTA, represents a dramatically different approach where the detection of coronary artery disease (CAD) is first and foremost within the evaluation algorithm; an approach so diverse from functional testing where ascertainment of disease status is the final stop in the diagnostic strategy.

Scattered throughout the literature, we saw signs that functional testing was more often operating in a silo and without a demonstrable impact on therapeutic care. Following functional testing, we observed relative inaction where, but a few patients had initiation or intensification of preventive therapy. This is not new as there are abundant examples in the peer-reviewed literature of a disconnect between testing and care.[2,4–6] A synthesis of evidence reveals that only a fraction of patients with abnormal stress tests are prescribed anti-ischemic therapies and the decision making regarding the downstream testing was similarly imprecise with only half of patients with moderate-severe ischemia being referred to invasive coronary angiography.[4–6] A recent statement on quality in imaging from the AHA discussed the importance of the critical link between an identifiable abnormality on a diagnostic procedure and targeted therapeutic intervention, using treatments with known clinical effectiveness, as the approach to ensure improve patient outcomes following diagnostic testing.[2]

Yet, why has functional testing been so divorced from the needs of the patient? Several factors may explain this lack of connection between functional testing and treatment. Certainly, the perceived reduced accuracy may diminish a physician's impetus for changing care based on stress test findings. The testing of lower and lower risk patients, which is commonplace today, further reduces the need for prompt action in treating patients. The reality of today's practice is that many of the symptomatic patients are quite stable and may tolerate (at least in the near term) physician inaction. Also, the complexity of functional testing and the current knowledge required for the many imaging modalities hinders the assimilation of test evidence into patient management. As one example, at what threshold do results become actionable? There is a general disagreement across the modalities as to what are comparable levels of abnormality. For many of the conventional tests which have been available for decades, there is also a lack of contemporary evidence which could inform current post-test strategies of care. A summary of these findings reveals that current standard approaches do not foster coordinated care and often prompt discussions regarding overuse and a lack of quality.

The introduction of anatomic imaging with computed tomography (CT), initially first with coronary artery calcium (CAC) scoring and then more recently with noninvasive angiography (CTA), reveals a post-test care pattern that is quite different from that of functional testing. The CAC literature is replete with evidence reporting that patients undergoing scanning have improved adherence to preventive care and better engagement in lifestyle modifying behaviors.[7,8] For those undergoing CAC, there are notable improvements in blood pressure, cholesterol, and weight which result in a reduced global risk score when compared to patients not undergoing CAC scanning.[8] When patients and physicians discuss their CAC scans, this imparts a strong influence on patient behaviors. But, not only for patients, physicians more often intensify preventive care among those with evidence of atherosclerosis.[9,10] Thus, creating the optimized care setting guided by imaging. The ever-increasing acceptance of the CAC prognostic data and targeted statin initiation among those with high risk CAC findings makes manifest the importance of atherosclerosis detection as a means to guide clinical

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care.[11,12] CAC data provide a key to delineating primary versus secondary care based on the threshold of a zero score.[13] The evolution of evidence has resulted in a greater acceptability of CAC as a means of "de-risking" patients with a zero score who do not require intensified preventive care and is now embraced in the updated ACC/AHA guidelines.

More recently, evidence is also available that CTA is similarly impactful in prompting preventive care.[14,15] In 2016, an exploratory analyses from the SCOT-HEART trial revealed a significantly higher use of statins and antiplatelet therapy for patients randomized to the CTA versus standard care strategy.[14] These results were similarly validated in the PROMISE trial.[15] The SCOT-HEART investigators boldly hypothesized that their observed 50% relative risk reduction for incident myocardial infarction in the CTA arm was likely the product of a greater intensity of preventive care. This concept put forth in SCOT-HEART is one of imaging-guided care whereby those at-risk are accurately detected and promptly treated which thereby reduces the predicted risk for the patient. When such a pattern of imaging-guided care is undertaken in a sufficient number of enrolled patients, then population risk is positively impacted. Simple as that!

A key design element is also of primary consideration and influencing the clinical outcome findings in the SCOT-HEART trial. It is not only that the investigators observed differences in preventive care but the clinical coordinating center recommended initiation/intensification of treatment for those patients with obstructive and nonobstructive atherosclerosis.[1] This trial was not one of the more commonly used pragmatic trials which allow care to be dictated locally or allowing "real world" patterns of care.[16] The SCOT-HEART data clearly identify a difference in guided vs. "real world' care based on imaging and may provide the important clue as to why the SCOT-HEART trial results are so compellingly positive. If we are so engrained within the imaging community to accept the status quo of suboptimal care patterns, then the SCOT-HEART results would be difficult to comprehend. Importantly, for trial design purposes, the literature is full of evidence that patients are under-treated and often not at preventive care goals. Thus, the concept of pragmatism, as the basis for study design, is flawed and skewed toward a null effect within any trial. In the setting of "real world" care being suboptimal, the key design element of prompting care for those at-risk patients was genius on the part of the SCOT-HEART investigators and illustrated that connecting imaging to therapeutic intervention is the pathway to improve patient outcomes.

Another key to understanding the SCOT-HEART findings has to do with the abundant therapeutic trial data supporting improvement in patient outcomes for both primary and secondary prevention.[17–20] The 5-year clinical outcome results for SCOT-HEART revealed a nearly 40% relative risk reduction in coronary heart disease death or nonfatal myocardial infarction.[1] These dramatic results have not escaped the wrath of many incredulous of the trial results. However, are they really that hard to understand? We know from the statin trials that there is an anticipated 30–35% reduction in major coronary events and a more than 40% relative risk reduction in the setting of secondary prevention with statins as compared to controls[21,22]; findings similar to SCOT-HEART. These combined findings form a consistent pattern of improved clinical outcomes for targeted prevention strategies.

Thus, concordance of findings between the prevention and SCOT-HEART trials further validates the importance of disease detection as a core component within the diagnostic evaluation. For functional testing, there are important limitations including a focus on detecting only functionally-significant (or ischemic), obstructive CAD. It may be estimated that nearly half of obstructive CAD is non-ischemic but remains prognostically important. Missing of non-ischemic obstructive coronary artery disease and nonobstructive atherosclerosis is another important limitation to functional testing and likely contributes to worsening patient outcome. If you review the PROMISE trial findings, patients without any plaque or stenosis on CTA had a reduced rate of major CAD events when compared to those assigned to the functional testing arm with normal or mildly abnormal findings.[23] It may be postulated that undetected atherosclerosis was prevalent within those undergoing functional testing and with lower risk findings.[24] The detection of a functionally-significant coronary stenosis has been the primary aim of functional testing and dismisses the importance of non-ischemic disease states which importantly impact prognosis. Our current standard care approaches which focus on demand ischemia are outdated and the findings from the SCOT-HEART trial clearly demonstrate that we must first and foremost know a patient's anatomy in order to guide care. To transcend current practices, one must see past the status quo in order to envision a new approach that will have a demonstrable impact on patient outcomes. Index anatomic testing, prior to functional testing, can more effectively guide clinical care of symptomatic patients.[1]

To understand the SCOT-HEART trial results, one must also embrace the concept of an imaging strategy and visualize the varied pathways that could result in a patient having an event-free state over a given period of time. This pathway of intensified care, if persistent, has the potential to stabilize plaque and reduce noncalcified plaque volume as well as halting disease progression including reducing acute coronary events.[25] Thus, these translational findings are also of import to further lend credence as to why the SCOT-HEART trial results makes sense. We now more clearly understand the high risk plaque signature associated with coronary events and the impact on preventive care on atherosclerosis is also well established from invasive imaging and CTA.[25–27] For patients receiving statins, there is an observed reduction in noncalcified plaque volume and in incident high risk plaque features (e.g., spotty calcification or positive remodeling). We know from this last statement that we can observe and with guided-intervention alter the natural history of atherosclerotic disease progression. Visualizing this pathway as detailed within the SCOT-HEART trial is a key to impacting population outcomes. It does not take faith to believe but an understanding of the facts from across the decades supporting that SCOT-HEART is real!

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