Recent clinical trials support continued emphasis on patient-first over modality-first approaches to initial test selection in patients with stable ischemic heart disease

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Received Dec 20, 2021; accepted Dec 20, 2021
doi:10.1007/s12350-022-02908-7

Current guidelines^{1,2} and appropriate use criteria³ used by clinicians in the USA and in Europe acknowledge the central role of cardiovascular imaging in contemporary diagnosis and management of patients with stable ischemic heart disease (SIHD). These documents recommend a tailored, patient-centered approach in selecting exercise electrocardiography (EE), stress echocardiography (SE), stress single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI), stress positron emission tomography (PET) MPI, coronary CT angiography (CCTA), stress cardiac magnetic resonance (CMR) imaging, or invasive coronary angiography (ICA) as the initial diagnostic test in patients with SIHD. Furthermore, as illustrated in Figure 1, these documents emphasize shared decision-making between clinicians and patients that incorporates patient characteristics, test characteristics, and the

clinical presentation to ensure performance of ‘the right test for the right patient at the right time.’

Over the past several years, a number of randomized clinical trials evaluating various testing strategies in patients with SIHD have been published, the most notable of which are SCOT-HEART⁴, PROMISE⁵, and ISCHEMIA⁶. The results of these landmark trials have recently been used by some to advocate for a ‘CCTA-first’ algorithm that emphasizes CCTA as the default initial test in nearly all patients with SIHD.^{7,8,9} In this editorial, we show how these trials support CCTA as a first-line option, but also affirm the clinical value of functional-first testing in patients with SIHD.

SCOT-HEART

The SCOT-HEART trial⁴ is often cited to validate ‘CCTA-first’ testing algorithms in patients with SIHD. However, this is not consistent with the trial design¹⁰ or its results. Among the 4146 patients in this United Kingdom trial, 85% of the patients in the trial underwent EE and nearly a third underwent ‘further investigations’ that included radionuclide stress imaging or ICA before randomization to CCTA. Moreover, it is unclear how pre-randomization testing might have impacted the decision-making of the 2613 eligible patients who

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J Nucl Cardiol

1071-3581/\$34.00

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Figure 1. Selection of initial testing in patients with SIHD should be evidence based, personalized, and safe. A multitude of factors, including patient characteristics, the clinical presentation, and test characteristics, must all be appropriately weighed to achieve the ideal of performing the right test for the right patient at the right time.

declined participation in the trial and the 547 clinicians who declined participation on behalf of their patients. As such, the SCOT-HEART cohort may not be truly representative of all patients with SIHD and it is unclear how applicable the study results are for healthcare systems outside of the United Kingdom. Moreover, it is critically important to understand that SCOT-HEART largely studied a ‘CCTA-second’ testing algorithm. This belies the argument, often used by CCTA-first advocates, that anatomic findings on CCTA alone drove increased utilization of preventive therapies and the significant reduction in non-fatal myocardial infarction (MI) observed at 5 years in the CCTA arm of SCOT-HEART.¹¹ In reality, the anatomic findings on CCTA were interpreted and acted upon in the context of already obtained functional testing. In addition, rates of ICA were higher in the CCTA arm than in the usual care arm in the early follow-up period of SCOT-HEART, a

finding that is consistent with prior studies and meta-analyses.^{12,13} It is possible that early ICA with or without revascularization - not only the previous CCTA - drove earlier utilization of preventive therapies and positive behavioral changes that in turn reduced the risk of non-fatal MI over the duration of the follow-up period. Even if we are willing to ascribe these changes solely to performance of CCTA, the cardiovascular risk threshold for initiation of preventive therapies has been lowered¹⁴ since SCOT-HEART was completed. As such, it is unclear if the benefit ascribed to CCTA could be replicated again today. Taking all of the above together, we do not believe the SCOT-HEART data should be used to advocate for a default CCTA-first testing algorithm in patients with SIHD.

PROMISE

In contrast to SCOT-HEART, the PROMISE trial⁵ was a head-to-head trial of CCTA-first versus 'functional-first' testing (i.e., EE, SPECT MPI, PET MPI, or SE) in patients with SIHD. In PROMISE, CCTA-first was equivalent to functional-first testing with respect to the primary study outcome (all-cause death, non-fatal MI, hospitalization for unstable angina, or major procedural complication) over 2-year follow-up. The recently published RESCUE trial¹⁵ also showed no difference in the primary study outcome (cardiac death, myocardial infarction, or revascularization) in patients with SIHD who underwent CCTA compared to those who underwent SPECT MPI as the first imaging test. These two trials suggest that CCTA may have a role as a first-line testing option to evaluate patients with SIHD with characteristics similar to the subjects studied. However, they do not in any way support that CCTA should be the single default test of choice in patients with SIHD as CCTA-first advocates have recommended.

A post hoc analysis of PROMISE showed that a CCTA-first algorithm may result in lower risk of cardiovascular death or MI compared to a functional-first strategy in the subgroup of patients with diabetes and SIHD.¹⁶ In general, post hoc analyses of clinical trials are only hypothesis-generating and should not be used as the basis of changes in health policy. Second, in this particular analysis, patients with diabetes who underwent CCTA had a lower cardiovascular event rate than patients without diabetes who underwent CCTA, strongly suggesting the play of chance and possibly collider stratification (i.e., high-risk diabetes patients were not randomized). Lastly with regard to this analysis, it has the same major limitation as mentioned above for SCOT-HEART – patients in the CCTA-first arm were more likely to undergo early ICA, again raising the possibility that ICA with or without revascularization could have contributed to early utilization of preventive therapies and positive behavioral changes that in turn reduced the subsequent risk of cardiovascular death or MI.

A separate post hoc analysis of PROMISE showed that CCTA, by identifying patients with non-obstructive epicardial CAD, provides better prognostic information than functional testing in patients with SIHD.¹⁷ Indeed, an accumulating body of evidence strongly suggests that total atherosclerotic plaque burden in the epicardial coronary arteries on CCTA may have better prognostic value for adverse cardiovascular events than assessment of stenosis alone. However, data from SCOT-HEART¹⁸ and national clinical registries¹⁹ suggest this risk may be adequately captured with simple non-contrast CAC scoring without the need for a full contrast-enhanced

CCTA to quantify non-calcified plaque. Additionally, in PROMISE classification of stress MPI studies as normal, mildly abnormal, moderately abnormal, and severely abnormal was solely based on EE abnormalities and relative left ventricular (LV) perfusion findings, such as inducible myocardial ischemia, myocardial scar, and transient ischemic dilation. Non-perfusion findings associated with elevated cardiovascular risk (i.e., LV dilatation with reduced LV ejection fraction, increased right ventricular radionuclide uptake) were not included. Nor was PET MPI-derived myocardial blood flow (MBF) quantification, which can identify vasomotor dysfunction and microvascular angina²⁰ and has been shown to improve the prognostic value of PET MPI in numerous patient populations.^{21,22,23,24,25,26} Also not included were CAC scores or visually estimated CAC scores (VECAC) obtained from CT images, now often obtained for attenuation correction in the performance of SPECT and PET MPI and known to improve prognostic value over perfusion interpretation alone.^{27,28,29,30,31} As such, PROMISE was not designed to comprehensively compare the prognostic value nor the cost effectiveness^{32,33} of CCTA versus functional testing, and in some respects may already be outdated given improvements in both MPI and CCTA technologies.

Lastly, CCTA-first advocates often fail to mention key analyses from PROMISE that highlight some of the real-world challenges associated with performance of CCTA. For example, the original clinical CCTA interpretations in PROMISE had fairly poor specificity given that core lab interpretation resulted in 41% fewer patients being reported as having significant CAD.³⁴ Furthermore, incidental findings were much more frequently identified in the CCTA arm (11.6%) than in the functional testing arm (0.7%) in PROMISE.³⁵ Most commonly, these incidental findings were pulmonary nodules that often generated downstream costs associated with additional imaging and clinical visits. More recently, RESCUE showed the same finding; 32.8% patients in the CCTA arm had incidental findings (59 of whom required follow-up imaging), while only 1.7% of patients in the SPECT MPI arm had incidental findings (2 of whom required follow-up imaging).¹⁵ Curiously, this significant cost differential between CCTA and SPECT MPI was not factored into a cost-effectiveness analysis performed by the United Kingdom National Institute for Health and Care Excellence (NICE)³⁶, nor into a more recent cost-effectiveness analysis developed from PROMISE data.³² To be fair, there are data suggesting relatively poor specificity of clinical SPECT MPI interpretations as well. In ISCHEMIA, 14.2% of the patients who were randomized on the basis of site-determined moderate or severe ischemia on stress imaging had only mild or no ischemia on subsequent

core lab interpretation.³⁷ Clearly neither CCTA nor SPECT MPI is a ‘perfect’ test in this respect, but that is precisely our point; the available data simply don’t support superiority of any modality-first testing algorithm in patients with SIHD. Overall, we believe PROMISE and its associated post hoc analyses suggest a possible role for CCTA as a first-line option in appropriately selected patients with SIHD, but nothing more than that.

ISCHEMIA

Last but not least, the ISCHEMIA trial⁵ was not a head-to-head trial of initial CCTA versus functional testing, like PROMISE or RESCUE. Instead, ISCHEMIA was designed to study whether an initial invasive strategy, as compared to optimal medical therapy alone, reduced the risk of ischemic events or all-cause death in patients with SIHD and at least moderate ischemia on functional testing (EE, SPECT MPI, or PET MPI). Put more simply, ISCHEMIA was designed to test different therapeutic strategies, not different diagnostic testing strategies. Furthermore, the trial was designed³⁸ similarly to SCOT-HEART in that CCTA was conducted after functional testing (49.6% SPECT or PET MPI, 24.5% EE, 20.9% SE, 5% stress CMR) had already been performed (i.e., ‘CCTA-second’). However, the blinded CCTA had a limited role to exclude enrolled patients with significant unprotected left main coronary artery stenosis and those without obstructive CAD in other epicardial coronary arteries. The first results from ISCHEMIA, after 3 years of follow-up showed that event rates were low in both randomization arms and that an initial invasive strategy did not improve outcomes compared to optimal medical therapy alone.⁵ CCTA-first advocates often contrast this result with that of SCOT-HEART to argue that CCTA is superior to functional testing with respect to its ability to positively impact downstream clinical management and outcomes. However, only 970 of the 5179 randomized patients (18.7%) had $\geq 15\%$ ischemia on SPECT MPI, a previously proposed cutoff for overall mortality benefit from revascularization established by prior long-term observational studies.³⁹ Additionally, there is evidence that the benefits of revascularization were underestimated in ISCHEMIA because of the selective nature of the study population.⁴⁰ Lastly, a more recent prespecified and nuanced analysis of ISCHEMIA including longer follow-up showed that spontaneous type 1 MIs (distinguished from procedure-related MIs) were more frequent in the optimal medical therapy arm and were associated with subsequent cardiovascular death.⁴¹ Together, we believe the data from ISCHEMIA do not support moving to a default CCTA-first algorithm.

SUMMARY

SCOT-HEART, PROMISE, and ISCHEMIA are landmark trials that importantly helped establish CCTA as an appropriate initial test in select patients with SIHD. However, we do not believe the data from these trials provide a strong scientific rationale to move to a default CCTA-first algorithm in the USA. We thus strongly encourage future writing groups updating guidelines and appropriate use criteria for the diagnosis and management of patients with SIHD not to use common misinterpretations of these trials in adopting a default CCTA-first algorithm – or any other default modality-first algorithm. Instead, they should aim to apply scientific, evidence-based, patient-centered approaches that focus on performing the right test for the right patient at the right time.

Declarations

Disclosure

The authors have no relevant disclosures. The views expressed here are those of the authors only and are not to be construed as those of the United States Army, the Department of the Defense, the Defense Health Agency, or the United States Government. The identification of specific products or scientific instrumentation is considered an integral part of the scientific endeavor and does not constitute endorsement or implied endorsement on the part of the author(s), the Department of Defense, or any component agency.

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