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Comparative Effectiveness Trials of Imaging-Guided Strategies in Stable Ischemic Heart Disease

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ABSTRACT

The evaluation of patients with suspected stable ischemic heart disease is among the most common diagnostic evaluations with nearly 20 million imaging and exercise stress tests performed annually in the United States. Over the past decade, there has been an evolution in imaging research with an ever-increasing focus on larger registries and randomized trials comparing the effectiveness of varying diagnostic algorithms. The current review highlights recent randomized trial evidence with a particular focus comparing the effectiveness of cardiac imaging procedures within the stable ischemic heart disease evaluation for coronary artery disease detection, angina, and other quality of life measures, and major clinical outcomes. Also highlighted are secondary analyses from these trials on the economic findings related to comparative cost differences across diagnostic testing strategies. (J Am Coll Cardiol Img 2017;10:321–34)

The evaluation of patients with suspected stable ischemic heart disease (SIHD) is among the most common diagnostic evaluations with nearly 20 million imaging and exercise stress tests performed annually in the United States (1-3). Cardiac imaging is an essential component of the SIHD diagnostic evaluation, yet there has been an historic paucity of randomized clinical trials (RCTs) supporting high-quality recommendations for testing. Over the past decade, there has been an evolution in imaging research with an ever-increasing focus on larger registries and RCTs comparing the effectiveness of varying diagnostic algorithms. The current review highlights recent RCT evidence with a particular focus comparing the effectiveness of cardiac imaging procedures within the SIHD diagnostic and prognostic evaluation.

The evidentiary standards for cardiac imaging, summarized in the 2012 SIHD clinical practice guidelines, include 2 diagnostic approaches: functional or stress testing and noninvasive angiography (1). In this guideline, minimal detail is provided on imaging RCTs, because in 2012, there were few. From the SIHD guideline, there was robust evidence on the accuracy of stress testing to predict the presence of obstructive coronary artery disease (CAD) and estimate major adverse cardiovascular events. Diagnostic and prognostic accuracy evidence is helpful in understanding the long-term sequelae of stress test abnormalities and to identify varying practice patterns that form the standard of care for noninvasive testing (1,4,5). The consistency of this evidence supports the utility of many functional stress test procedures including electrocardiography (ECG), echocardiography,

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ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcium

CAD = coronary artery disease

CI = confidence interval

CMR = cardiac magnetic resonance

CTA = computed tomographic angiography

ECG = electrocardiogram

FFR = fractional flow reserve

HR = hazard ratio

MI = myocardial infarction

NICE = National Institute of Health and Care Excellence

QOL = quality of life

RCT = randomized clinical trials

SAQ = Seattle Angina Questionnaire

SIHD = stable ischemic heart disease

SPECT = single-photon emission computed tomography

nuclear, and cardiac magnetic resonance (CMR) as valuable tools for application in the SIHD diagnostic evaluation. Although the diagnostic and prognostic evidence is similarly robust across the diagnostic modalities, competition facilitated many discussions regarding the advantages of perfusion versus wall motion assessment, safety (e.g., radiation exposure), and the ability of a procedure to produce a multiparametric examination (e.g., angiographic, wall motion, perfusion, and ventricular function measurements) (6). In many situations, the comparisons across the modalities do not yield equivalent information, in particular with regards to exercise capacity as compared with modalities using pharmacologic stress (e.g., positron emission tomography or CMR) or anatomic imaging with coronary computed tomographic angiography (CTA). The evolution in thought about the complexities of the diagnostic evaluation and the focus on a long-term assessment of risk was an integral component of RCT design for recent comparative effectiveness trials.

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Noninvasive angiographic evidence, such as for coronary CTA, is also robust and offers advantages in the detection of obstructive CAD, including documentation of plaque morphology, reduced radiation exposure for most patients (compared with other tests requiring radiation), and risk stratification evidence (7,8). Moreover, the high concordance between coronary CTA and invasive angiography yields a higher diagnostic accuracy (9–11) when compared with functional testing. However, coronary CTA has reduced accuracy in the identification of a stenosis that is flow-limiting (e.g., a stenosis with reduced fractional flow reserve [FFR]) (12). The discourse as to whether ischemia- versus anatomy-guided testing is optimal for the SIHD evaluation further fueled the undertaking of the comparative RCTs highlighted herein.

IMAGING-DIRECTED STRATEGIES TO IMPROVE PATIENT OUTCOMES

For any diagnostic procedure, it is the link between the identified abnormalities and a change in patient management that provides the necessary means to improve patient outcome, and not the imaging procedure per se. The necessary intervening link following a test is whether a change in diagnostic thinking triggers alterations in care (4). This link between testing and initiation, intensification, or withdrawal of care is an important part of imaging RCT design (4). This is a theoretical discussion but identifies the importance of adherence to guideline-directed care to interpret results from an imaging RCT. An additional challenge for imaging RCTs is a reliance on observational findings, in particular as it relates to therapeutic risk reduction, as a means to inform estimated event rates for sample size calculations. There are examples from observational registries whereby coronary revascularization was associated with reduced CAD mortality when compared with medical therapy for patients with severe ischemia that have not yet been reproduced in an RCT setting (13–17). The lack of translation of observational findings into RCT results is not uncommon but, to fully understand clinical outcomes, imaging RCTs may require tracking of post-imaging care management and adherence to standard treatment strategies. These examples illustrate the challenges of RCT design in interpreting the significance of patient outcome findings following the index testing procedures.

IMAGING TRIAL DESIGNS

Our current imaging RCTs may be broadly defined as comparative modality effectiveness trials (i.e., 1 test compared with another). There have been several trials comparing the effectiveness of a coronary CTA versus a with stress testing strategy (18,19). There are also several trials comparing stress nuclear versus CMR (6,20–25). Often these trials are pragmatic or "real world" in their approach by allowing each of the testing arms to facilitate downstream care by local teams rather than mandating specific therapies based on imaging findings. Pragmatic trials are beneficial in that they allow follow-up testing and care patterns to occur based on the patient's overseeing physician and not constrained by trial-directed follow-up care, thereby reflecting current real world practices. Although this is often desirable, some practices may be inconsistent with appropriate use criteria for procedural use and clinical practice guideline recommendations (1,26,27).

There are also several additional RCT approaches that include multimodality as compared with single modality randomization schemes. Although we have yet to see a randomized trial including a deferred testing arm, this is increasingly considered as a reasonable RCT option (28), especially in patient populations where the yield of testing is low.

TRIAL ELIGIBILITY: PATIENT SELECTION CHALLENGES

A major challenge for any RCT is defining patient eligibility to fit a trial's primary aims while not hindering enrollment. An important component of comparative effectiveness research is to use broad eligibility criteria, such that RCT findings are applicable to a large sector of the population. The ability to define eligibility criteria and enrolling applicable patients remains critical to answering the trial's primary hypothesis. The appropriate selection of candidates for enrollment must be based on current guideline indications and appropriate use criteria (1,26,27). Thus, for all imaging RCT, the use of pre-test probability or risk should be an important component of eligibility criteria. Enrollment of lower risk patients can result in a reduced event rate, which impacts discrimination between randomized arm outcomes. Tracking of adherence to proposed eligibility criteria is an invaluable coordinating center activity during enrollment.

TRIAL ENDPOINTS

Traditional RCT endpoints in cardiovascular medicine often include all-cause or CAD mortality or myocardial infarction (MI). RCTs based on traditional endpoints, such as death, often require substantially larger sample sizes and are costlier. Recent imaging RCTs use novel endpoints defining strategy failures or late clinical worsening (e.g., worsening angina or heart failure). In treatment trials, these endpoints have been used to define criteria for patient crossover to the alternative treatment arm of a trial. For example, refractory symptoms in a patient assigned to optimal medical therapy is considered an acceptable indication for crossing over to coronary revascularization (29).

Recent SIHD trials have also expanded endpoint definitions to include diagnostic confidence or certainty, which may provide insights into rates of repeat testing and alterations in treatment and clinical outcomes (19).

The inclusion of cost or efficiency of resource use and timely diagnosis are important endpoints for imaging RCTs, given the focus of high utilization and costs associated with diagnostic procedures (3,30,31). Cost or resource utilization patterns are generally secondary endpoints following a primary trial aim of clinical effectiveness. Cost analysis often includes tracking inefficiency within near- or long-term test patterns post-randomization (e.g., repeat or layered testing) (32). At times, trials rely on cost modeling without the depth of detail from individual patients and, in this situation, the assumptions informing the decision analysis are highly influential and may not reflect "real world" patterns of resource consumption. There are also additional secondary safety endpoints, such as procedural complications (18). One may also envision that imaging RCTs may consider a secondary aim of adherence to guideline-directed care including use of anti-ischemic and risk factor-modifying therapy use and lifestyle changes (1).

CURRENT RANDOMIZED TRIALS IN SIHD

In the following sections, we highlight the imaging RCTs in 4 sections: 1) major clinical endpoints; 2) angina and other health status endpoints; 3) diagnostic endpoints; and 4) cost comparisons. All trials were identified with queries to PubMed on SIHD RCTs and coronary CTA or stress testing.

COMPARATIVE EFFECTIVENESS FOR MAJOR CLINICAL ENDPOINTS

This section highlights selected RCTs for comparing major endpoints (**Table 1**).

WOMEN TRIAL. The WOMEN (What is the Optimal Method of Ischemia Elucidation in Women?) trial enrolled 824 women with suspected SIHD who were randomized to an exercise ECG-guided or an exercise myocardial perfusion single-photon emission computed tomography (SPECT)-guided strategy (33). This RCT was designed to demonstrate superiority of exercise SPECT based on higher diagnostic and prognostic accuracy when compared with the exercise ECG (33). However, no difference in 2-year endpoints (defined as CAD death, MI, or hospitalization for acute coronary syndrome or heart failure) was observed (1.7% for the exercise ECG arm vs. 2.3% for the exercise SPECT arm; $p = 0.59$). Eligibility was limited to women with Duke Activity Status Index-defined physical capabilities ≥5 metabolic equivalents, contributing to enrollment of a low-risk cohort with few reported events ($n = 17$).

PROMISE TRIAL. Recently, 2 large comparative effectiveness trials were published that randomized large samples of patients with suspected CAD to a functional testing versus anatomic strategy (18,19). PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) was an National Institutes of Health-National Heart, Lung, and Blood Institute-sponsored pragmatic trial that randomized 10,003 symptomatic outpatients without known CAD to coronary CTA or functional testing of the physician's choice including stress nuclear (67%),

TABLE 1 Summary of Primary Endpoint Findings From Randomized Clinical Trials in Stable Ischemic Heart Disease

Trial Name (Ref. #)	Randomization	N, Total and by Arm	Intervention Details	Duration of Follow-Up, yrs*	Major Endpoint†	HR (95% CI) p Value‡
CECaT (20)	Invasive angiography vs. stress echocardiography, SPECT, or CMR	1:1 randomization (N = 898) Angiography n = 222 vs. echocardiography n = 226, SPECT n = 224, or CMR n = 226	Invasive angiography was the comparator vs. SPECT, echocardiography, and CMR	2.0	All-cause mortality	p = 0.054
CRESCENT (36)	Coronary CTA vs. exercise ECG	2:1 randomization (N = 350) Coronary CTA = 242 vs. exercise ECG = 108	Coronary CTA arm included index CAC evaluation with Coronary CTA limited to CAC >0	1.0	All-cause mortality, MI, major stroke, unstable angina, unplanned CAD evaluation, or late revascularization	0.32 (0.13–0.81) p = 0.011
PROMISE (18)	Anatomic (Coronary CTA) vs. functional test strategy	1:1 randomization (N = 10,003) Coronary CTA n = 4,996 vs. stress test n = 5,007	Clinician choice: 67% nuclear, 23% echocardiography, 10% ECG	2.1	Death, MI, unstable angina hospitalization, or major complications	1.04 (0.83–1.29) p = 0.75
SCOT-HEART (19)	SC + Coronary CTA vs. SC	1:1 randomization (N = 4,146) SC + Coronary CTA = 2,073 vs. SC = 2,073	Index evaluation often included exercise ECG (85%)	1.7	Primary: certainty of angina diagnosis caused by CAD Secondary: coronary heart disease death or MI	0.62 (0.38–1.01) p = 0.053
WOMEN (33)	Exercise SPECT vs. exercise ECG	1:1 randomization (N = 824) SPECT n = 412 vs. ECG n = 412	Inclusion of women with DASI estimate ≥5 METs	2.0	CAD death, MI, or hospitalization for acute coronary syndrome or heart failure	1.3 (0.5–3.5) p = 0.59

*Duration of follow-up is reported as median values for PROMISE and SCOT-HEART. †Primary endpoint is reported for all but SCOT-HEART and CECaT trials where outcomes are a secondary endpoint. ‡No HR was reported from the CECaT trial. However, the HR for angiography vs. stress CMR was elevated 2.6-fold (95% CI: 1.1 to 6.2) but not significant for angiography vs. stress echocardiography or SPECT.

CAC = coronary artery calcium; CAD = coronary artery disease; CECaT = Cost-Effectiveness of noninvasive Cardiac Testing; CI = confidence interval; CMR = cardiac magnetic resonance; CRESCENT = Computed Tomography vs. Exercise Testing in Suspected Coronary Artery Disease; CTA = computed tomographic angiography; DASI = Duke Activity Status Index; ECG = electrocardiogram; HR = hazard ratio; MET = metabolic equivalents; MI = myocardial infarction; PROMISE = Prospective Multicenter Imaging Study for Evaluation of Chest Pain; SC = standard care; SCOT-HEART = Scottish Computed Tomography of the HEART; SPECT = single-photon emission computed tomography; WOMEN = What is the Optimal Method of Ischemia Elucidation in Women?

echocardiography (23%), or ECG (10%) (18). Although the functional testing choices within the PROMISE trial have varied indications within our SIHD guidelines (1), randomization was based on intended functional test. This variability in stress test choice may have imparted imprecision in this arm when compared with the alternative arm of a single anatomic test, coronary CTA.

Using a pragmatic design, test interpretation and subsequent care was determined locally with follow-up by patient report. The trial hypothesized that the information obtained from coronary CTA would result in superior outcomes using a composite endpoint of all-cause death, MI, unstable angina hospitalization, or major complications from cardiovascular procedures (including stroke or need for dialysis). Should superiority not be reached, the RCT pre-specified noninferiority testing, with a margin of 10%. The hypothesis of superiority was based on assumptions that the greater diagnostic sensitivity and specificity of coronary CTA versus functional tests would yield fewer false-positive and -negative results, a longer warranty period for negative results (i.e., fewer late unstable angina hospitalizations), and more treatment of prognostically important nonobstructive CAD detected by coronary CTA.

Over (median) 25 months of follow-up, the primary event rate was low (coronary CTA, 3.3% vs. functional testing, 3.0%) and similar by testing strategy (hazard ratio [HR]: 1.04; 95% confidence interval [CI]: 0.83 to 1.29; p = 0.75). At 12 months, however, the prespecified secondary endpoint did reach significance with reduced death or MI among patients randomized to coronary CTA as compared with functional testing (HR: 0.66; 95% CI: 0.44 to 1.00; p = 0.049). Within 90 days of randomization, 1,015 patients underwent invasive coronary angiography: 609 (12.2%) following coronary CTA and 406 (8.1%) following functional testing. Angiography showed no obstructive CAD in 28% of the coronary CTA group and 52% of the functional-testing group, resulting in a significant secondary endpoint (p = 0.02). Revascularization was not an endpoint but was twice as frequent in the coronary CTA arm (6.2%) versus the functional testing arm (3.2%; p < 0.001). Importantly, the greater use of revascularization in the coronary CTA arm was not associated with improved patient outcomes.

Because of the participation of community sites in the trial, the PROMISE population is representative of the greater population undergoing testing for suspected CAD in the United States. Perhaps the most important finding from the PROMISE trial is that such patients have an excellent prognosis (with very low

event rates of only 1% to 2%) and a low prevalence of obstructive CAD requiring revascularization (<5% overall).

SCOT-HEART TRIAL. A second major trial was the SCOT-HEART (Scottish Computed Tomography of the HEART) trial, which randomized 4,146 patients to standard stress testing as compared with standard stress testing with a coronary CTA-guided strategy. All patients had a routine clinical examination including an exercise ECG (in 85% of patients) before randomization. In the standard stress testing arm, a small proportion of patients (9%) had follow-up stress nuclear imaging. The reliance on exercise ECG may have contributed to a reduced diagnostic accuracy and impacted the overall trial findings. Importantly, the minimal use of stress imaging in the usual care arm varies considerably from the PROMISE trial and from U.S. practices.

Within the coronary CTA arm, nearly 1 in 4 had ≥70% stenosis with an additional 38% having mild-intermediate coronary stenosis. For coronary CTA, the primary endpoint of diagnostic certainty was increased over 6 weeks ($p < 0.0001$), likely because of the frequent documentation of stenotic lesions. However, no increase in the downstream use of invasive coronary angiography ($p = 0.45$) or revascularization ($p = 0.061$) procedures was observed.

Secondary endpoint analysis revealed a similar rate of 1.7-year incident rate of coronary heart disease death or MI between randomized arms (HR: 0.62; 95% CI: 0.38 to 1.01; $p = 0.053$); the overall death or MI rate was ~2-fold higher for SCOT-HEART than for the PROMISE trial. Within SCOT-HEART, the event rates were similar through the first several months of follow-up because of delays in patients receiving their coronary CTA procedure and/or their follow-up office visit after index testing. Conjecture remains as to whether longer term follow-up or more prompt coronary CTA-guided care would have elicited significant differences by randomization.

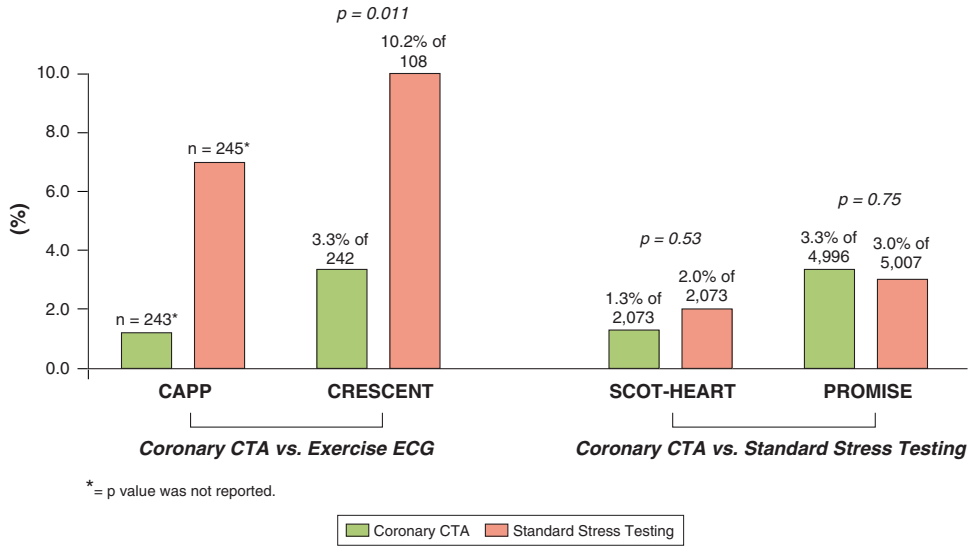
Interestingly, the SCOT-HEART trial documented more frequent initiation of new therapies following the coronary CTA examination. In a post hoc analysis, Williams et al. (34) reported on a statistically significant increased initiation of preventive therapies including a 12.2- and 3.5-fold higher rate of new antiplatelet and statin therapies ($p < 0.001$ for both) among patients randomized to coronary CTA. In this analysis, the median time to treatment initiation was >50 days and thereafter there was an observed halving of incident MI for standard stress testing with coronary CTA versus standard stress testing alone ($p = 0.02$). This intriguing analysis supports the concept that clinical outcome improvement is based on test-driven links to treatment. However, these findings include a total of only 51 observed MIs and requires further validation. The PROMISE trial also documented a higher rate of aspirin, statin, and beta-blocker use for patients with coronary CTA-identified obstructive CAD as compared with those with positive functional tests (35). Details regarding adherence to guideline-directed medical therapy and appropriate use of follow-up CAD procedures are required to fully understand post-randomization strategies of care for both trials.

CRESCENT TRIAL. Imaging RCTs have largely included a comparison of 2 index procedures. Recently, the CRESCENT (Computed Tomography vs. Exercise Testing in Suspected Coronary Artery Disease) trial compared a tiered approach to the diagnostic evaluation whereby index coronary artery calcium (CAC) scoring was followed by selective coronary CTA use for those with detectable CAC (score >0). This trial used a 2:1 randomization scheme with an exercise ECG performed in 108 and selective coronary CTA in 242 symptomatic outpatients (36). Of the 242 patients, only 141 had detectable CAC and underwent coronary CTA. During ~2 years of follow-up, patients with a 0 CAC score had no events (mortality, MI, major stroke, unstable angina with evidence of ischemia or requiring coronary revascularization, nonelective CAD hospitalization, or late revascularization). The CRESCENT trial's novel endpoint represents a composite of traditional events with events related to late clinical worsening. There were few reported adverse events in this trial ($n = 19$) through 1.2 years of follow-up but revealed improved event-free survival of 97% for patients in the coronary CTA arm versus 90% for patients in the exercise ECG arm (HR: 0.32; 95% CI: 0.13 to 0.81; $p = 0.015$). It will remain important to interpret the trial findings in light of the variability in primary endpoints across the varied trials.

CAPP TRIAL. Similarly, the CAPP (Cardiac CT for Assessment of Pain and Plaque) trial, randomized 488 patients to an exercise ECG versus coronary CTA and, in a secondary analysis of all-cause mortality or emergency department visit requiring a CAD hospitalization, there were few events in the coronary CTA arm ($n = 3$ or 1.2% of 243) versus 6.9% ($n = 17$) of 245 in the exercise ECG arm; no p value was reported for the endpoint findings (**Figure 1**) (37).

Table 1 and **Figure 1** summarize the endpoint findings of various imaging RCTs, generally reporting no outcome differences by randomized testing strategies. Across most of the RCTs (18,19,36,37) coronary CTA has a higher utilization of downstream invasive

FIGURE 1 Highlighted Endpoint Findings Among Imaging Randomized Clinical Trials for Stable Ischemic Heart Disease That Compared Coronary CTA With Standard Stress Testing



The CAPP and CRESCENT trials randomized patients to coronary CTA versus exercise ECG. The SCOT-HEART randomized patients to coronary CTA versus standard care, and the PROMISE trial randomized patients to coronary CTA versus functional stress testing. Follow-up was 1.0, 1.2, 1.7, and 2.1 years, respectively, for the CAPP, CRESCENT, SCOT-HEART, and PROMISE trials. Varied endpoints were used: CAPP (all-cause mortality, emergency department visit with coronary artery disease hospitalization), CRESCENT (all-cause mortality, MI, major stroke, unstable angina, unplanned coronary artery disease evaluation, late revascularization), SCOT-HEART (coronary heart disease death, MI), and PROMISE (death, MI, unstable angina, procedural complications). The all-cause death or MI rate for PROMISE was 0.6% for coronary CTA versus 0.8% (p = 0.35), lower than that observed in the SCOT-HEART trial. CAPP = Cardiac CT for Assessment of Pain and Plaque; CRESCENT = Computed Tomography vs. Exercise Testing in Suspected Coronary Artery Disease; CTA = computed tomographic angiography; ECG = electrocardiogram; MI = myocardial infarction; PROMISE = Prospective Multicenter Imaging Study for Evaluation of Chest Pain; SCOT-HEART = Scottish Computed Tomography of the HEART.

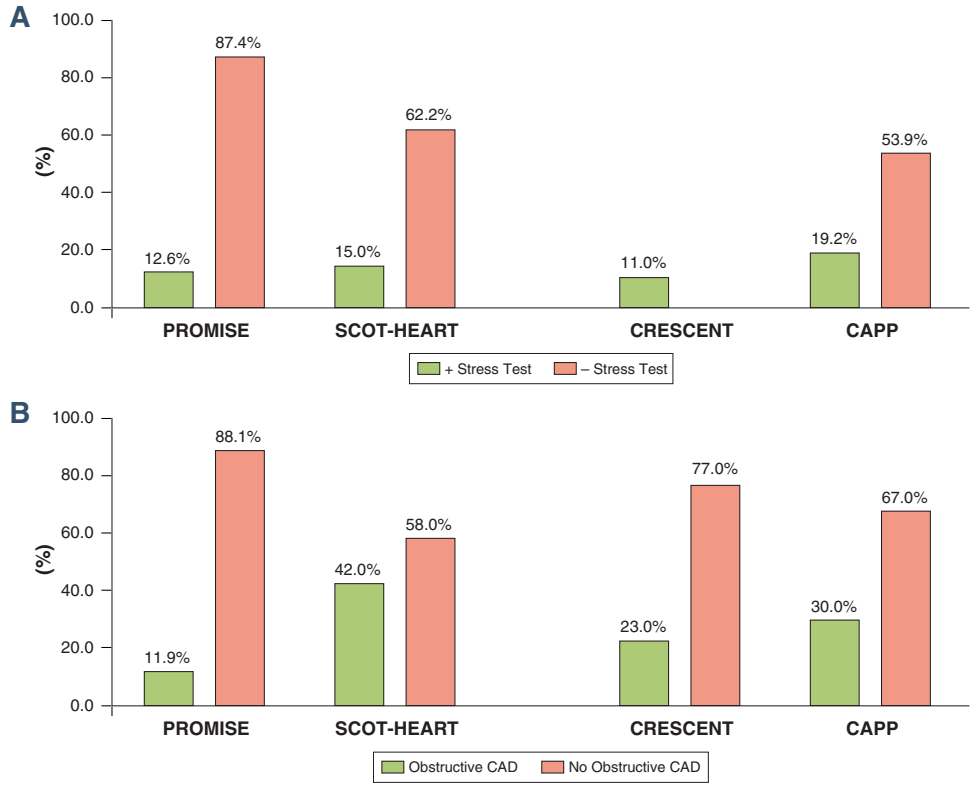
angiography and revascularization, although differences were not statistically significant in the SCOT-HEART (p = 0.45) and CRESCENT (p = 0.84) trials (19,36). **Figures 2A and 2B** report the rates of positive and negative stress test and coronary CTA-defined obstructive and no obstructive CAD from recent RCTs. In most cases, abnormalities on stress tests were less than the coronary CTA-defined burden of obstructive CAD. The diagnostic yield (% of patients undergoing invasive angiography who have obstructive CAD) is compared in **Figure 3** from these RCTs. Coronary CTA generally had a higher diagnostic yield as compared with standard stress testing (pooled statistics: 71% of 1,047 in coronary CTA arms vs. 53% of 819 in standard stress testing arms).

COMPARATIVE EFFECTIVENESS FOR ANGINA AND OTHER HEALTH STATUS ENDPOINTS

PROMISE AND SCOT-HEART TRIALS. Several trials have examined improvement in angina symptoms and functional status as either primary or secondary endpoints (**Table 2**) (37). From the PROMISE trial, quality of life (QOL) measures of angina and functional capabilities (using the Seattle Angina Questionnaire [SAQ] and Duke Activity Status Index) were ascertained in 5,985 patients through 2-years of follow-up (35). Overall improvements in physical functioning, QOL, and angina stability and frequency were reported, with an immediate increase noted at 6 months that was maintained through 2 years of follow-up (35). However, no differences in QOL, including angina, physical capacity, or overall health status were observed by randomized test strategy (35). From the SCOT-HEART trial, early improvements in angina stability and frequency were reported for the coronary CTA (p < 0.001) and standard stress testing (p < 0.001) arms, with no differences reported by randomized groups for any SAQ subscales (19).

CAPT AND CRESCENT TRIALS. One of the first trials using symptoms as a primary endpoint was the CAPP trial of whereby 488 patients were randomized to coronary CTA or an exercise ECG (37). Patients were

FIGURE 2 Rates of Abnormal Stress Testing and Coronary CTA



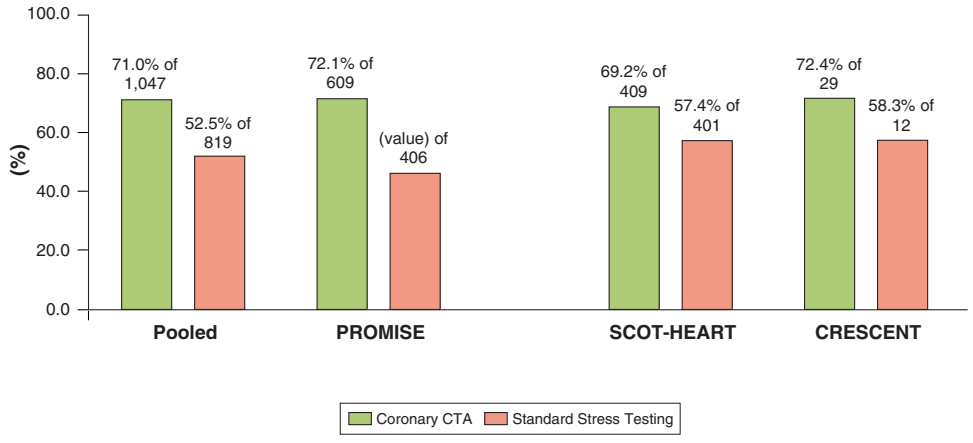
(A) From RCTs that compared standard stress testing with coronary CTA, rates of stress test–defined positive (+) and negative (−) findings as reported in the PROMISE, SCOT-HEART, and CRESCENT trials. In some cases, the total % does not add to 100% because of inconclusive test results. The PROMISE trial did not report inconclusive findings but in the SCOT-HEART and CAPP trials, the rate of inconclusive exercise ECG was 22.8% and 26.9%. The CRESCENT trial only reported the rate of abnormal exercise ECG results. The SCOT-HEART data represent exercise ECG performed during the index evaluation. **(B)** From RCTs that compared standard stress testing with coronary CTA, rates of coronary CTA-detected obstructive (≥50% stenosis) and no obstructive CAD (<50% stenosis) as reported in the PROMISE, SCOT-HEART, and CRESCENT trials. CAD = coronary artery disease; RCT = randomized clinical trial; other abbreviations as in Figure 1.

followed for early (3 months) and 1 year changes in angina symptoms, physical functioning, and overall QOL using the SAQ. This trial revealed early improvements in angina stability and QOL for coronary CTA as compared with the exercise ECG, which persisted through 1 year of follow-up. Similarly, the CRESCENT trial reported 1-year improvements in angina frequency in the selective coronary CTA versus the exercise ECG arm of the trial ($p = 0.012$) (36).

CECaT TRIAL. The primary endpoint of the CECaT (Cost-Effectiveness of noninvasive Cardiac Testing) trial was exercise capacity (i.e., exercise time on the modified Bruce protocol) at 18 months of follow-up (24). In this trial, a total of 898 patients were randomized to angiography (n = 222), stress myocardial perfusion SPECT (n = 224), stress CMR perfusion (n = 226), or stress echocardiography (n = 226). At 18 months of follow-up, differences in exercise duration were minimal (i.e., ~1 min or less; $p = 0.074$). By 18 months, approximately one-half of patients were symptom-free but changes in the Canadian cardiovascular class were similar across randomized groups ($p = 0.17$). No differences were observed across the SAQ subscales by test strategy ($p > 0.29$).

In summary, the use of diagnostic testing generally improved angina and QOL; however, differences by randomized testing strategy were largely nonsignificant (Table 2). With exception, the CAPP and CRESCENT trials reported 1-year improvement in angina for coronary CTA as compared with the exercise ECG (36,37). The extent to which indeterminate findings from the exercise ECG (Figure 2A) drive clinical indecision and persistent symptoms is unknown but may contribute to these findings (33,38,39).

FIGURE 3 Diagnostic Yield by Randomized Test Strategy: Coronary CTA Versus Standard of Care or Stress Testing From the CRESCENT, PROMISE, and SCOT-HEART Trials



The diagnostic yield is defined as the % of patients undergoing invasive coronary angiography with obstructive CAD (≥50% stenosis). The number of follow-up invasive coronary angiograms was higher in the coronary CTA arm of most RCTs (but not statistically different in the SCOT-HEART [p = 0.45] and CRESCENT [p = 0.84] trials; the p value was not reported in PROMISE). Data from the PROMISE trial are ≤90 days. Abbreviations as in Figures 1 and 2.

COMPARATIVE EFFECTIVENESS FOR DIAGNOSTIC ENDPOINTS

In this section, we highlight specific trials with diagnostic endpoints for detection of obstructive CAD.

DeFACTO TRIAL. Recent controlled clinical trials have assessed the added diagnostic accuracy of FFR_{CT}, a newly introduced technique for measuring the physiologic significance of a stenosis based on computational fluid dynamic modeling estimates of rest and hyperemic pressure estimation of FFR, as compared with coronary CTA alone (12). From the DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography) trial, there was a higher diagnostic accuracy with FFR_{CT} (73%) versus coronary CTA alone (64%);

TABLE 2 Summary of Findings on Angina From Imaging Randomized Clinical Trials in Stable Ischemic Heart Disease

Trial Name (Ref. #)	Target Population	SAQ Findings		Other Symptom Findings
		Improvement at Follow-up	Difference by Randomization	
CRESCENT (36)	N = 350	Both testing arms reported improvement in angina stability/frequency and disease perception at 1 yr	1-yr improvement in angina frequency for coronary CTA vs. exercise ECG (p = 0.012) but not for other SAQ subscales	1-yr angina-free rates: 39% for and 25% for coronary CTA vs. exercise ECG (p = 0.012)
CAPP (37)	N = 488	Both testing arms reported improvement in angina stability and frequency and QOL at 1 yr but no p values reported	1-yr improvement in angina stability and QOL for coronary CTA vs. exercise ECG (p = 0.028, p = 0.041) but not for other SAQ subscales	1-yr emergency department visit leading to hospitalization (p = 0.009) and CAD outpatient visit (p = 0.036) rates higher for exercise ECG vs. coronary CTA
PROMISE (35)	N = 5,985	Both testing arms reported significant improvements in SAQ subscales at 6 months and through 2 yrs	No difference by randomization across SAQ subscales through 2 yrs	
SCOT-HEART (19)	N = 4,146	Both testing arms reported significant improvement in angina stability and frequency at 6 weeks	No difference by randomization in angina stability (p = 0.22) and frequency (p = 0.21) at 6 months	No difference by randomization in hospitalization for chest pain (p = 0.51)
WOMEN (33)	N = 503	Not reported	Not reported	2-yr angina-free rates: 60% and 65% for exercise ECG vs. SPECT (p = 0.25)

CAPP = Cardiac CT for Assessment of Pain and Plaque; QOL = quality of life; SAQ = Seattle Angina Questionnaire; other abbreviations as in Table 1.

however, this trial failed to meet its pre-specified primary endpoint of per-patient diagnostic accuracy (12).

PLATFORM STUDY. Recently, the PLATFORM (Prospective Longitudinal Trial of FFR Outcome and Resource Impacts) study was completed and enrolled 584 patients with de novo chest pain to a strategy of usual testing (n = 287), including a planned noninvasive or invasive diagnostic evaluation, as compared with FFR_{CT} (n = 297) (40). The 90-day primary endpoint (no CAD) was defined as no stenosis ≥50% or invasive FFR measure ≤0.80. Among those with a planned invasive evaluation, 73% of the usual testing versus only 12% of the FFR_{CT} arm had no CAD ($p < 0.001$). Among this invasive subset, FFR_{CT} resulted in a cancellation of follow-up invasive angiography in ~60% of patients, and an average savings of $4,018 (41). However, no differences were observed between usual testing and FFR_{CT} for those with a planned noninvasive evaluation ($p = 0.95$). Current, RCT data are not available comparing the effectiveness of coronary CTA plus FFR_{CT} with coronary CTA alone.

CE-MARC TRIALS. Because imaging technology offers the ability to assess multiple imaging markers (e.g., rest and stress global or segmental left ventricular function and myocardial perfusion), several RCTs have compared a multiparametric approach with that of conventional stress imaging (6,20). Most notable among these is the CE-MARC (Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease) trial, which randomized 752 patients to multiparametric CMR (including balanced steady-state free precession cine imaging, stress/rest perfusion, 3D CMR angiography, and late gadolinium enhancement) versus stress myocardial perfusion SPECT (6). The primary endpoint was obstructive CAD on invasive coronary angiography. CE-MARC reported significant improvement in diagnostic accuracy for CMR versus SPECT; a secondary analysis validated a higher accuracy for women (6,42). Diagnostic sensitivity and specificity was 87% and 83% for the multiparametric CMR and 67% and 83% for stress myocardial perfusion SPECT, with significant differences noted for diagnostic sensitivity ($p < 0.001$). More recently, 5-year rates of cardiovascular death, acute coronary syndrome, and unplanned revascularization or CAD hospitalization were reported from the CE-MARC trial (43). The 5-year relative hazard for events was 2.8 ($p < 0.001$) for CMR versus 1.6 ($p = 0.014$) for SPECT imaging. Importantly, only CMR findings remained predictive in multivariable models including risk factors, angiographic findings, and index patient treatment.

Recently, the CE-MARC 2 trial was reported (25). This trial randomized 1,202 symptomatic patients to 1 of 3 test strategies: stress 3T CMR-guided (n = 480), SPECT-guided (n = 480), or the UK guideline-directed testing (n = 240). This latter arm is based on the 2010 National Institute of Health and Care Excellence (NICE) guidance document for SIHD diagnostic testing, which is based on the patient's pretest probability; low-risk patients have an index CAC followed by selective coronary CTA, intermediate-risk patients undergo SPECT imaging, and high-risk patients are referred for coronary angiography. CE-MARC 2 was a superiority trial for CMR-guided management as compared with the other testing approaches with the primary endpoint of avoiding unnecessary coronary angiography, defined as a FFR >0.80 or no or mild obstructive CAD stenosis. Nearly 29% of patients in the NICE group were deemed to have unnecessary angiography and only 7.5% and 7.1% in the CMR and SPECT imaging arms ($p < 0.001$ of CMR vs. NICE guideline arm and no difference between CMR vs. SPECT imaging arms, $p = 0.32$). The NICE guideline group included recommended testing based on pre-test risk from low (recommend CAC with or without coronary CTA), intermediate (recommend stress imaging), to high (recommend immediate angiography) risk. Within the NICE guideline group, the frequency of stress imaging (37%) and immediate angiography (35%), and CT (23%) requires additional details as to which pre-test risk strata more often led to unnecessary angiography. For the secondary endpoint of major CAD events, no statistical differences were reported. The variable findings between CE-MARC trials may be in that the initial trial was a single center (with uniform imager expertise) and the latter trial was a multicenter RCT (with more diverse imager expertise).

EVINCI TRIAL. Nonrandomized, controlled clinical trials have also used a primary endpoint of obstructive CAD. Recently, the EVINCI (Evaluation of Integrated CAD Imaging in Ischemic Heart Disease) trial examined the diagnostic accuracy of varied noninvasive tests. In EVINCI, all 475 patients underwent coronary CTA and invasive coronary angiography but selectively underwent stress imaging including stress myocardial perfusion positron emission tomography (n = 96) and SPECT (n = 293), dobutamine wall motion CMR (n = 85), and echocardiography (n = 263) (44). The results revealed that coronary CTA had the highest accuracy with sensitivity and specificity of 90% and 93%; of the stress imaging procedures,

TABLE 3 Summary of Economic Evidence From Imaging Randomized Clinical Trials in Stable Ischemic Heart Disease

Trial Acronym	Target Population	Near-Term Δ Cost	Long-Term Δ Cost	Overall Cost Findings
PROMISE (32)	N = 9,504	Δ $254 at 90-days (p = NS)	Δ $627 at 3 yrs (p = NS)	3-yr cumulative costs were $7,213 for coronary CTA vs. $6,586 for functional testing (p = NS)
SCOT-HEART (34)	N = 4,146	Index cost $342 higher for coronary CTA (p < 0.001)	$462 at 6 months higher for coronary CTA (p < 0.0001)	6-month cumulative costs were $1,900 for coronary CTA vs. $1,438 for SC (p < 0.0001); when excluding index coronary CTA cost, no differences in downstream costs: Δ $89 (p = 0.27)
CRESCENT (36)	N = 350	Index cost $164 higher for Selective coronary CTA	€71 at 1 yr higher for exercise ECG (p < 0.0001)	1-yr cumulative costs were €369 for coronary CTA vs. €440 for exercise ECG (p < 0.0001)
WOMEN (33)	N = 824	Index cost $341 higher for exercise SPECT (p < 0.001)	$35 higher for exercise ECG (p = 0.0008)	2-yr diagnostic procedural costs: $338 for exercise ECG vs. $643 for exercise SPECT (p < 0.001)

NS = not statistically significant; other abbreviations as in Table 1.

positron emission tomography had the highest accuracy (sensitivity of 80%; specificity of 89%).

A synthesis of this evidence supports that coronary CTA has a higher diagnostic accuracy as compared with stress testing. Importantly, not all obstructive stenosis are ischemic (**Figures 2A and 2B**) and this forms the basis for discordance with functional testing approaches. This would impact diagnostic accuracy, if functional significance is the gold standard, because coronary CTA would be less accurate in detecting a CAD stenosis that is flow-limiting (e.g., a stenosis with reduced FFR). This concept is fundamental to interpreting diagnostic accuracy trials.

COMPARATIVE COSTS FOR DIAGNOSTIC TEST STRATEGIES

Many recent RCTs also include economic substudies that are highlighted in this section (**Table 3**) (20,32-34,36,45).

WOMEN TRIAL. In the WOMEN trial, the index procedural costs for the exercise ECG ($145) were lower than exercise myocardial perfusion SPECT ($495; p < 0.001). However, 2-year follow-up costs were higher for those in the exercise ECG arm (p = 0.008) with ~1 in 5 women in the exercise ECG arm having a follow-up myocardial perfusion SPECT study. The higher follow-up costs among those in the exercise ECG arm did not exceed the index procedural costs for myocardial perfusion SPECT, resulting in reduced diagnostic costs (average costs, $338 for exercise ECG vs. $643 for exercise myocardial perfusion SPECT; p < 0.001).

SCOT-HEART TRIAL. This example, from the WOMENs trial, supports the notion that a cheaper, index procedure may prove economically advantageous when follow-up testing includes selective use of higher cost procedures. From the SCOT-HEART trial, 6-month costs were slightly higher in the coronary CTA arm (Δ = $462) but this difference represented only the upfront procedural cost because there were no cost differences associated with outpatient (p = 0.16) and inpatient (p = 0.98) services or medication use (p = 0.50) (34).

PROMISE TRIAL. Similarly, in the PROMISE trial, near-term (≤90 day) cost differences were not significant by randomized test strategy of coronary CTA versus functional testing (Δ = $254) (32). In the near-term (i.e., ≤90 days post-randomization), coronary CTA was associated with slightly (but nonsignificant) higher costs associated with invasive coronary angiography and revascularization. Conversely, the functional testing arm of the PROMISE trial had a slightly higher (but nonsignificant) near-term costs associated with downstream repeat or serial stress testing. Through 3 years of follow-up, the difference in costs by randomized test strategy in PROMISE was nonsignificant (Δ = $627), with similar findings for stress nuclear, echocardiography, and ECG testing. These longer-term cost findings identify the importance of follow-up testing patterns as reflecting the cost-consequences of a given index procedure (28).

CRESCENT TRIAL. By comparison, the CRESCENT trial reported that randomization to the exercise ECG strategy had more frequent follow-up noninvasive diagnostic testing (53% in the exercise ECG arm versus 25% in the selective coronary CTA arm; p < 0.0001). In this trial, they reported a 16% cost savings associated with the selective coronary CTA diagnostic approach when compared with the exercise ECG strategy (€440 versus €369; p < 0.0001). Similar findings from the CAPP trial of higher rate of downstream testing at 1-year in the exercise ECG vs. coronary CTA arms were also reported (p < 0.001) (37).

A synthesis of evidence supports that cost differences by randomized test strategy to coronary CTA versus standard stress testing strategies are generally minimal over the near- and longer-term of follow-up (**Table 3**).

ONGOING RCTs

There are several ongoing trials that will further add to the current understanding of comparative effectiveness research in SIHD imaging. The RESCUE (Randomized Evaluation of Patients with Stable Angina Comparing Utilization of Diagnostic Examinations) trial randomized 1,050 of 4,300 pre-defined patients with suspected CAD to a coronary CTA- as compared with SPECT-guided strategy of care. The primary endpoint for this trial is 2-year death, MI, or revascularization. This Agency for Healthcare Research and Quality-funded comparative effectiveness trial has been completed and is currently under review.

Another trial is the MR-INFORM (Magnetic Resonance Perfusion Imaging to Guide Management of Patients with Stable CAD) trial (23). The main hypothesis of MR-INFORM is that CMR stress perfusion is noninferior to invasive coronary angiography with FFR measurements in guiding treatment of SIHD patients. The primary endpoint is 1-year rate of death, MI, or repeat coronary revascularization. Recruitment of 918 patients has been completed with the 1-year follow-up ending in August 2016.

An additional ongoing trial is the CONSERVE (Coronary Computed Tomographic Angiography for Selective Cardiac Catheterization) trial. This trial's primary endpoint is 1-year death, acute coronary syndrome, stroke, nonelective coronary revascularization, or cardiovascular hospitalization. The CONSERVE trial will randomize 1,500 patients to a coronary CTA plus selective invasive coronary angiography versus invasive angiography alone. Enrollment is limited to patients with elective indications for invasive coronary angiography including those with previously documented ischemia on stress testing. This trial design is that of noninferiority for coronary CTA as compared with invasive coronary angiography.

KNOWLEDGE GAPS AND RCT LIMITATIONS

Several themes emerge from reviewing recent RCTs in SIHD imaging. First, most of the clinical outcome findings are within the near-term (i.e., 1 to 3 years). Variable patterns may emerge with longer-term follow-up time periods. The variability in clinical endpoints may contribute to the null findings of these RCTs. Moreover, the improvements in angina (frequency or stability) may reflect the influence of baseline symptom burden or may be specific to the comparative procedure (e.g., the exercise ECG).

The recent RCTs often enrolled lower-risk patients resulting in reduced occurrence of clinical endpoints, a common issue for RCTs. This is particularly problematic when follow-up duration is short. Although this is representative of the current population undergoing testing for suspected SIHD, it may not reflect appropriate test candidates and the reported lower-risk findings prompt consideration of alternative statistical approaches (e.g., reduced effect size, smaller alpha, higher beta levels, or larger standard deviation estimates) to incorporate greater uncertainty into sample size calculations (46).

The often neutral RCT findings support equivalence among functional and anatomic test strategies. The preponderance of negative trials reveals weaknesses in trial design, eligibility criteria, or other factors that uniquely impact cardiovascular imaging. Alternative approaches in all aspects of trial methodology and longer funding cycles (i.e., >5 years) should be considered. The lower-risk findings coupled with lower costs of care also support consideration of deferred testing arms for future RCTs (28). Many of the RCTs rely on pre-test risk estimates derived from older patient series that significantly overestimate CAD prevalence in contemporary patient cohorts. This contributes to a perceived higher risk status and an observed lower event rate. Importantly, there remains an opportunity to impact RCT clinical endpoints only when there is a sufficient pool of patients whose chance of an event is elevated.

Important considerations emerge from the SCOT-HEART trial that may be key to future RCTs. First, the overall coronary heart disease death or MI rates in SCOT-HEART were >2-fold higher than for the PROMISE trial, thus enrolling a higher-risk cohort. Second, given the borderline p value for SCOT-HEART (19), one may posit whether coronary CTA may prove beneficial in a cohort with more prevalent CAD. The coronary CTA obstructive CAD prevalence was 42.0% for SCOT-HEART but only 11.9% (47) for PROMISE. With a higher CAD prevalence, more patients would require the use of preventive and anti-ischemic therapies with established effectiveness, as illustrated in the analysis by Williams et al. (34). A final consideration is the extent to which diagnostic certainty favors coronary CTA and results in a more proactive pattern of patient care remains ill-defined.

Current RCTs largely compare 1 test with another, but often not serial or selective testing approaches. Detail is lacking on adherence to guideline-directed management or the appropriate use of downstream procedures. RCT data are generally lacking on differences among key patient subsets (e.g., women) (47). Future RCTs should incorporate more innovative trial designs to focus on reducing novel clinical outcomes while achieving cost minimization. Possible RCTs may also consider randomization by varied diagnostic/therapeutic or care planning management approaches and their impact on clinical outcomes.

HEALTH POLICY IMPLICATIONS OF IMAGING RCTs AND IMPLEMENTATION SCIENCE

Post hoc reviews have criticized recent RCTs as having limited generalizability of the main findings. Issues of implementation science and the degree to which the trial findings are assimilated into new imaging policies guiding clinical practice (including performance metrics) has not been a focus of many health technology assessment programs, with few exceptions. The UK NICE and European Health Technology Assessment have performed systematic reviews following the reporting of major RCTs. Standards for the development and use of performance metrics based on imaging RCTs will be essential for future quality improvement initiatives. The extent to which RCTs influence current medical practice remains an important consideration for understanding the value of information derived from the monetary investment in any given trial.

In 2012, the NICE recommended coronary CTA as an index diagnostic procedure for patients with a low-intermediate pre-test risk, because of the reduced accuracy of the exercise ECG (48). Several RCTs reveal that coronary CTA was associated with improved event-free survival, less angina, and reduced healthcare costs (36,37). The high rate of indeterminate findings (~20%; **Figure 2A**), reduced exercise capacity, and lower diagnostic accuracy are disadvantages for the exercise ECG (1,38,39). By comparison, coronary CTA is associated with high diagnostic certainty, timely documentation of mild and obstructive CAD, and fewer normal (downstream) invasive coronary angiograms (**Figure 3**), yet exposes patients to ionizing radiation. Guidelines committees and coverage policy discussions should be ongoing as to the value of coronary CTA as a first-line procedure in lieu of the exercise ECG in SIHD patients. The role of index CAC scoring as a means to selectively use coronary CTA or the exercise ECG should be included in this discussion.

RCT FUNDING

RCTs are costly and exceed the investment for clinical registries. There are several funding agencies that have supported recent RCTs but the list is limited and not all agencies prioritize funding of imaging RCTs to the extent that they have treatment trials. There is general consensus that there should be a greater investment in imaging RCT from a broad array of funding sources.

The imaging community must embark on novel approaches to reduce the costs of future RCTs. As proposed in a recent National Heart, Lung, and Blood Institute workshop (49), an imaging trialist network could provide economies of scale in the conduct of RCTs. Trialist networks reduce costs by creating interoperability among electronic health records and have centralized data coordination and analysis, among other factors. Moreover, RCTs embedded in imaging registries may also reduce costs and prove fruitful for enrollment and randomization within well-defined cohorts.

CONCLUSIONS

When compared with years past, there are now several RCTs that are published and have vastly changed the landscape of comparative effectiveness research in CAD imaging. We have synthesized major findings and, at times, the trial results are conflicting or neutral but highlight a sea change in focus for the imaging community. Evolution in trial design, unique endpoints, follow-up clinical management tracking, and optimal patient selection are anticipated for future imaging RCTs as the imaging community learns from the recent RCTs. Contemporary thought now defines CAD as incorporating stenosis severity with physiologic measures of ischemia (e.g., FFR) or reduced coronary flow reserve; this definition will likely be more common in future RCTs.

From the recent RCTs, 1 modality has not emerged as superior to all others and across all patient subgroups. Clinical implications from these varied RCTs supports that common diagnostic modalities are similarly effective with generally low per-patient costs. Test ordering practices, in the setting of similar clinical and economic outcomes, should be driven by local expertise, timeliness of scheduling,

and the ability of a given test to provide other information (e.g., exercise capacity, reproducing symptoms). The current RCT evidence should provide assurance to the clinical community that data are sufficiently robust to guide appropriate and high-quality imaging utilization.

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REFERENCES

1. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease. J Am Coll Cardiol 2012;60:e44–164.

2. Duszak R Jr., Optican RJ, Brin KP, Woodard PK. Cardiac CT and coronary CTA: early Medicare claims analysis of national and regional utilization and coverage. J Am Coll Radiol 2011;8:549–55.

3. Shaw LJ, Marwick TH, Zoghbi WA, et al. Why all the focus on cardiac imaging? J Am Coll Cardiol Img 2010;3:789–94.

4. Shaw LJ, Berman DS, Picard MH, et al. Comparative definitions for moderate-severe ischemia in stress nuclear, echocardiography, and magnetic resonance imaging. J Am Coll Cardiol Img 2014;7:593–604.

5. Metz LD, Beattie M, Hom R, Redberg RF, Grady D, Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. J Am Coll Cardiol 2007;49:227–37.

6. Greenwood JP, Maredia N, Younger JF, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC). Lancet 2012;379:453–60.

7. Min JK, Dunning A, Lin FY, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. J Am Coll Cardiol 2011;58:849–60.

8. Min JK, Shaw LJ, Berman DS. The present state of coronary computed tomography angiography a process in evolution. J Am Coll Cardiol 2010;55:957–65.

9. Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. J Am Coll Cardiol 2008;52:1724–32.

10. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med 2008;359:2324–36.

11. Meijboom WB, Meijs MF, Schuijf JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. J Am Coll Cardiol 2008;52:2135–44.

12. Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. JAMA 2012;308:1237–45.

13. Hachamovitch R, Rozanski A, Hayes SW, et al. Predicting therapeutic benefit from myocardial revascularization procedures: are measurements of both resting left ventricular ejection fraction and stress-induced myocardial ischemia necessary? J Nucl Cardiol 2006;13:768–78.

14. Hachamovitch R, Rozanski A, Shaw LJ, et al. Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. Eur Heart J 2011;32:1012–24.

15. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. Circulation 2003;107:2900–7.

16. Fassa AA, Wijns W, Kolh P, Steg PG. Benefit of revascularization for stable ischaemic heart disease: the jury is still out. Eur Heart J 2013;34:1534–8.

17. Gibbons RJ, Miller TD. Should extensive myocardial ischaemia prompt revascularization to improve outcomes in chronic coronary artery disease? Eur Heart J 2015;36:2281–7.

18. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med 2015;372:1291–300.

19. SCOT-HEART investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. Lancet 2015;385:2383–91.

20. Thom H, West NE, Hughes V, et al. Cost-effectiveness of initial stress cardiovascular MR, stress SPECT or stress echocardiography as a gatekeeper test, compared with upfront invasive coronary angiography in the investigation and management of patients with stable chest pain: mid-term outcomes from the CECaT randomised controlled trial. BMJ Open 2014;4:e003419.

21. Schwitter J, Wacker CM, van Rossum AC, et al. MR-IMPACT: comparison of perfusion-cardiac magnetic resonance with single-photon emission computed tomography for the detection of coronary artery disease in a multicentre, multivendor, randomized trial. Eur Heart J 2008;29:480–9.

22. Ripley DP, Brown JM, Everett CC, et al. Rationale and design of the Clinical Evaluation of Magnetic Resonance Imaging in Coronary heart disease 2 trial (CE-MARC 2): a prospective, multicenter, randomized trial of diagnostic strategies in suspected coronary heart disease. Am Heart J 2015;169:17–24.

23. Hussain ST, Paul M, Plein S, et al. Design and rationale of the MR-INFORM study: stress perfusion cardiovascular magnetic resonance imaging to guide the management of patients with stable coronary artery disease. J Cardiovasc Magn Reson 2012;14:65.

24. Sharples L, Hughes V, Crean A, et al. Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial. Health Technol Assess 2007;11:iii–iv, ix–115.

25. Greenwood JP, Ripley DP, Berry C, et al. Effect of care guided by cardiovascular magnetic resonance, myocardial perfusion scintigraphy, or NICE guidelines on subsequent unnecessary angiography rates: the CE-MARC 2 Randomized Clinical Trial. JAMA 2016;316:1051–60.

26. Wolk MJ, Bailey SR, Doherty JU, et al. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease. J Am Coll Cardiol 2014;63:380–406.

27. Patel MR, Bailey SR, Bonow RO, et al. ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 appropriate use criteria for diagnostic catheterization. J Am Coll Cardiol 2012;59:1995–2027.

28. Xie JX, Shaw LJ. Measuring diagnostic health care costs in stable coronary artery disease: should we follow the money? Ann Intern Med 2016;165:147–8.

29. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503–16.

30. Mark DB, Anderson JL, Brinker JA, et al. ACC/AHA/ASE/ASNC/HRS/IAC/Mended Hearts/NASCI/RSNA/SAIP/SCAI/SCCT/SCMR/SNMMI 2014 health policy statement on use of noninvasive cardiovascular imaging. J Am Coll Cardiol 2014;63:698–721.

31. Iglehart JK. The new era of medical imaging: progress and pitfalls. N Engl J Med 2006;354:2822–8.

32. Mark DB, Federspiel JJ, Cowper PA, et al. Economic outcomes with anatomical versus

functional diagnostic testing for coronary artery disease. Ann Intern Med 2016;165:94–102.

33. Shaw LJ, Mieres JH, Hendel RH, et al. Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: results from the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial. Circulation 2011;124:1239–49.

34. Williams MC, Hunter A, Shah AS, et al. Use of coronary computed tomographic angiography to guide management of patients with coronary disease. J Am Coll Cardiol 2016;67:1759–68.

35. Mark DB, Anstrom KJ, Sheng S, et al. Quality-of-life outcomes with anatomic versus functional diagnostic testing strategies in symptomatic patients with suspected coronary artery disease: results from the PROMISE randomized trial. Circulation 2016;133:1995–2007.

36. Lubbers M, Dedic A, Coenen A, et al. Calcium imaging and selective computed tomography angiography in comparison to functional testing for suspected coronary artery disease: the multicentre, randomized CRESCENT trial. Eur Heart J 2016;37:1232–43.

37. McKavanagh P, Lusk L, Ball PA, et al. A comparison of cardiac computerized tomography and exercise stress electrocardiogram test for the investigation of stable chest pain: the clinical results of the CAPP randomized prospective trial. Eur Heart J Cardiovasc Imaging 2015;16:441–8.

38. Baldassarre LA, Raman SV, Min JK, et al. Noninvasive imaging to evaluate women with stable ischemic heart disease. J Am Coll Cardiol Img 2016;9:421–35.

39. Mieres JH, Gulati M, Bairey Merz N, et al. Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease. Circulation 2014;130:350–79.

40. Douglas PS, Pontone G, Hlatky MA, et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFR(CT): outcome and resource impacts study. Eur Heart J 2015;36:3359–67.

41. Hlatky MA, De Bruyne B, Pontone G, et al. Quality-of-life and economic outcomes of assessing fractional flow reserve with computed tomography angiography: PLATFORM. J Am Coll Cardiol 2015;66:2315–23.

42. Greenwood JP, Motwani M, Maredia N, et al. Comparison of cardiovascular magnetic resonance and single-photon emission computed tomography in women with suspected coronary artery disease from the Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease (CE-MARC) Trial. Circulation 2014;129:1129–38.

43. Greenwood JP, Herzog BA, Brown JM, et al. Prognostic value of cardiovascular magnetic resonance and single-photon emission computed tomography in suspected coronary heart disease: long-term follow-up of a prospective, diagnostic accuracy cohort study. Ann Intern Med 2016 May 10 [E-pub ahead of print].

44. Neglia D, Rovai D, Caselli C, et al. Detection of significant coronary artery disease by noninvasive anatomical and functional imaging. Circ Cardiovasc Imaging 2015;8:e002179.

45. Walker S, Girardin F, McKenna C, et al. Cost-effectiveness of cardiovascular magnetic resonance in the diagnosis of coronary heart disease: an economic evaluation using data from the CE-MARC study. Heart 2013;99:873–81.

46. Gogtay NJ. Principles of sample size calculation. Indian J Ophthalmol 2010;58:517–8.

47. Pagidipati NJ, Hemal K, Coles A, et al. Sex differences in functional and CT angiography testing in patients with suspected coronary artery disease. J Am Coll Cardiol 2016;67:2607–16.

48. CT coronary angiography. Shared learning database. Available at: https://www.nice.org.uk/sharedlearning/ct-coronary-angiography. Accessed September 1, 2016.

49. Hlatky MA, Douglas PS, Cook NL, et al. Future directions for cardiovascular disease comparative effectiveness research. J Am Coll Cardiol 2012;60:569–80.

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