Patient first versus computed tomography first strategy in testing for stable coronary artery disease: dispelling the prevailing myths and biases

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We advocate an evidence-based discussion for a patient first philosophy when considering “the right test for the right patient.” Numerous test options exist for the evaluation of symptoms of possible stable ischemic heart disease. Major guidelines have traditionally focused on functional testing with or without imaging to clarify symptoms, diagnose ischemia, stratify prognosis, and guide management. Recently, industry advocates have emphasized modality-specific approaches such as computed tomography (CT First) as an initial test strategy for possible stable CAD. We review the key evidence to demonstrate that current best practice would focus on a patient first approach rather than a modality-specific approach.

Key Words: CAD < Diseases/processes • CT < Modalities • SPECT < Modalities • Echo < Modalities • PET < Modalities • MPI < Tests

INTRODUCTION

Testing for coronary artery disease (CAD) among patients with symptoms of possible stable angina has undergone significant advancements in the last decade. This has been facilitated by an improved understanding of the disease pathophysiology and the availability of a gamut of highly efficacious tests for the diagnosis of CAD and its prognostication. ACC/AHA multimodality

imaging guidelines identify several imaging-based tests as being appropriate for determination of CAD and its significance; however, they do not identify a preferred test.¹ This is likely due to the lack of comparative studies when these guidelines were written, though new data from large randomized clinical trials have emerged since. However, it is important to critically evaluate data from these trials to enhance our selection of tests to improve clinical outcomes and to dispel the myths surrounding preferred testing for CAD.² The field of cardiovascular imaging has matured to recognize the advantages and disadvantages of various modalities, with a new cadre of multimodality trained imagers who are not bound to traditional silos of cardiovascular testing. Test selection via a philosophy of the “right test for the right patient” has become an integral part of imaging training and clinical practice. Contrary to a

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patient first approach, there have been recently published opinions² about anatomy-first imaging approach using coronary computed tomography angiography (CTA) providing superior risk stratification among patients with suspected CAD. The basis of these reports appears to be a misinterpretation of data from several recent clinical trials, which we clarify in this editorial.

The SCOT HEART³ trial is often cited as representative of a “CT first” approach. However, inspection of the trial design clarifies the approach as “CT second.” All patients in this trial underwent a routine clinical assessment including exercise stress testing in 85% and nuclear stress testing in 9% prior to randomization to standard care alone vs standard care plus CTA. The trial design compared the value of complimentary testing or imaging rather than a CT first approach. Additionally, the primary outcome was a non-clinical endpoint of certainty of angina secondary to CAD. While the standard of care plus CTA arm showed superior identification of angina secondary to CAD, there was no difference in severity of symptoms or hospitalization for chest pain on 6-week follow-up. Additionally, at 1.7 years follow-up, there was no statistically significant difference in secondary outcome of fatal or non-fatal myocardial infarction ($P = 0.0527$). On the contrary, there was a trend toward increased cardiac catheterization and coronary intervention in the standard of care plus CTA arm, although these differences were not statistically significant. It is unlikely that higher upfront coronary revascularization could have improved outcomes in the CTA group, given that other randomized trials of optimal medical therapy vs PCI in patients with stable angina have not shown a difference.⁴⁻⁶

The strength of evidence to recommend a universal “CT first” approach is weak. The 5-year results of the SCOT-HEART trial⁷ show an absolute risk reduction of 1.6% in the primary endpoint (death from CHD and non-fatal MI) which was mainly driven by non-fatal MI, 33 fewer patients experienced an event in the CTA arm compared to the standard care arm. This translates into a number needed to treat of 63 patients with stable chest pain would need to be referred for CTA to prevent 1 fatal or non-fatal event over 5 years. The magnitude of benefit raises concerns for plausibility. Although more patients received preventive therapies in the CTA arm (19.4%, 402 patients) vs standard care arm (14.7%, 305 patients), this difference was small. To conclude that treating 97 additional patients with preventive therapies in the CTA arm would result in 33 fewer MIs defies biological plausibility. Given the open nature of the trial, the risk of biased MI adjudication is high. There was no formal event adjudication and end points were classified primarily on the basis of diagnostic codes. Although

there was a trend toward higher rate of early revascularization in the CTA group (233—11.2% in CTA vs 201—9.7% in standard group), there was no difference at 5 years—13.5% in CTA (279 patients) vs 12.9% in the standard group (267 patients). Since there were no trial-specific visits and follow-up information was obtained from NHS database, there are no data on lifestyle and behavioral changes and any differential effect it may have had on outcomes is speculation. When appraising these comparator trials, we also must consider a form of expert center bias toward CTA, where ultra-modern CT scanners in expert centers have been compared to basic nuclear lab techniques not necessarily adhering to best practices of attenuation correction, modern scanners, or when possible, quantitative flow by PET. Thus, the full potential of the usual care group is not realized. Furthermore, outside of expert centers, community interpretation of CTA leads to over-estimation of stenosis by 41%, which will significantly increase unnecessary catheterization, PCI, and cost as seen in registries of real-world CTA use.⁸

Specifically, in regard to pragmatic limitations of an emphasis on “CT first,” this approach proves excessively dogmatic, thereby undermining patient-centered imaging and the concept of “the right test for the right patient.” It is imperative to utilize the most appropriate test or tests, based on a patient’s individual characteristics and risks. Cardiology practice must emphasize impartial evidence review and avoid excessive industry bias.² Scholarly works should avoid citing non-peer-reviewed personal communications from industry representatives as scientific evidence, especially when there is contradictory peer reviewed evidence.² We cannot comment on unpublished private insurer catheterization rates, but it is important to recognize that the PROMISE⁹ trial was underpowered to identify the increased catheterization and percutaneous coronary intervention (PCI) after CTA. Medical science has unequivocally demonstrated significantly increased catheterization and coronary revascularization after CTA in four emergency department RCT’s,¹⁰ four outpatient RCT’s,¹¹ and one high-quality non-industry-sponsored registry trial.¹² The lower rate of excess revascularization in the CTA arm of the SCOT-HEART trial compared to the CTA arm in all other trials may be explained by the hybrid nature of the trial where patients with stenosis on CTA but without ischemia on functional testing did not get referred for revascularization procedures.^{11,13} One should not selectively cite individual studies and industry communications versus these nine studies which include almost 300,000 patients (Figure 1).

Furthermore, contrary to recent confusion, ISCHEMIA was not a CTA trial. ISCHEMIA evaluated clinical outcomes among patients with moderate to severe

Increased Catheterization and Revascularization After CCTA

<u>n</u>	<u>Design</u>	<u>Age, yrs</u>	<u>Population</u>	<u>Catheterization</u>	<u>Revascularization</u>
282, 830	Medicare registry	73.6	Stable chest pain, outpatients, Medicare beneficiaries 66 years or older with no claims for CAD in the preceding year	22.9% after CCTA, 12.1% after UC; AOR 2.19 (2.08 to 2.32) p<0.001	PCI: 7.8% PCI after CCTA, 3.4% after UC; AOR, 2.49 (2.28 to 2.72) p<0.001 CABG: 3.7% after CCTA, 1.3% after UC; AOR, 3.00 (2.63 to 3.41) p<.001
3,266	Meta-analysis, 4 CTA vs UC ER RCT	51	Acute chest pain, Emergency dept, non-acute ECG, negative troponin, 3 of 4 exclude known CAD	8.4% after CCTA, 6.3% after UC; OR 1.36 (1.03 to 1.80) p = 0.030	4.6% after CCTA, 2.6% after UC; OR 1.81 (1.20 to 2.72) p = 0.004
14, 817	Meta-analysis, 4 CTA vs UC outpatient RCT	60	Stable chest pain, outpatients, non-acute ECG, negative troponin	12.7% after CCTA, 9.8% after UC ; AOR 1.33 (0.95–1.84) p=0.09; excluding hybrid imaging in SCOT HEART AOR 1.56 (1.38–1.78),p<0.001	7.9% after CCTA , 5.1% after UC OR 1.77 (1.14–2.75) p<0.001

Figure 1. Increased invasive coronary angiography and coronary revascularization after coronary computed tomography angiography (CCTA) versus usual care testing (UC) as demonstrated in eight randomized controlled trials and a high-quality registry study encompassing almost 300,000 patients. AOR, adjusted odds ratio; CCTA, coronary computed tomography angiography; ER, emergency room; RCT, randomized controlled trial; UC, usual care.

ischemia randomized to medical therapy vs medical therapy plus revascularization. Assessment of ischemia by functional testing was a prerequisite for the trial. In ISCHEMIA, CTA was performed to exclude those with significant left main disease out of an abundance of caution, and even then, only 1% of patients in the trial had significant left main disease. The larger PROMISE² trial and SPECT registries do not demonstrate harm from missed left main disease. Any claims on the use of CTA based on data from ISCHEMIA are only hypothesis generating.

European Society of Cardiology (ESC) guidelines¹⁴ recommend either functional testing for ischemia or CTA as the initial test to diagnose CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone. They further recommend that the initial non-invasive diagnostic test should be selected on the basis of clinical likelihood of CAD, patient characteristics that influence test performance, patient preference, local expertise, and the availability of

tests. Such an approach is patient centered and empowers clinicians to pick the right test for their patient, instead of suggesting policies with no scientific basis and with substantial conflict of interest.² While the ESC guidelines recognize all modalities may be appropriate for testing for CAD, they now provide some guidance on test selection, based on clinical characteristics. The ESC guidelines indicate CTA to be the preferred approach in patients with a lower clinical likelihood of CAD, no known CAD, and characteristics associated with high image quality. CTA is not recommended (class III) when extensive coronary calcification, irregular heart rate, significant obesity, inability to cooperate with breath-hold commands or any other conditions make obtaining good imaging quality unlikely. An important aspect which is often overlooked in trials utilizing CTA for diagnosis of CAD is the contraindication to its performance in patients with chronic kidney disease (CKD). It is critical to note that a glomerular filtration rate < 30 ml/min/1.73 m² or an elevated serum

creatinine was an exclusion criterion in several CTA trials, which underscores the inability for CTA to be an effective technique for diagnosis of CAD in a significant proportion of patients seen routinely in clinical practice. Approximately 25% of the patients were excluded from ROMICAT 2,¹⁵ and 11% from ISCHEMIA⁶ due to renal insufficiency. Excessive emphasis on a dogmatic CT first approach may lead to overlooking safety concerns for patients with CKD and other relative contraindications based upon image quality, including obesity or atrial fibrillation.

ESC guidelines further suggest functional testing to be the preferred approach in patients with higher clinical likelihood of CAD, those in whom revascularization is likely, and in patients with known CAD. While this can be achieved by radionuclide imaging, echocardiography, and cardiac magnetic resonance, radionuclide imaging has no contraindications to the tracer, notwithstanding considerations regarding exercise or pharmacologic stress. Additionally, for patients with very low or low clinical likelihood of symptomatic CAD, no testing or treadmill exercise alone may suffice. Exercise ECG provides diagnostic and prognostic information, such as ST segment changes, exercise tolerance, arrhythmias, blood pressure response, and event risk and also complements imaging-based functional tests. Functional imaging also routinely provides left ventricular systolic function, not available on most CTA acquisitions performed for CAD. Design of four large CTA trials in the emergency department excluded young patients for ethical reasons, not only due to the very low prevalence of disease among young patients with normal troponin and non-acute ECG, but also to avoid unnecessary harm from ionizing radiation to the patient.¹⁰ For these reasons, when evaluating young patients with very low or low clinical likelihood of symptomatic CAD, such as men less than forty or women less than fifty years of age, the American Heart Association expert consensus recommendations have generally recommended to favor zero radiation diagnostic tests such as exercise treadmill test (ETT), stress MRI, or exercise stress echocardiography (ESE).¹⁶ We summarize, in Figure 2, these current considerations to a functional versus CT first approach. While not always absolute, these are general evidence-based approaches for patient first imaging to select “the right test for the right patient.” Functional testing using radionuclide imaging has witnessed major advances with the development of cardiac PET, CZT SPECT, flow quantification with both PET and research involving CZT SPECT, and stress only imaging with ultra-low dose radiation protocols. This has translated to the ability of radionuclide imaging to accurately, efficiently, and safely evaluate the entire coronary circulation down to the level of the

Figure 2. Patient first strategy for stable chest pain evaluation. Functional testing may include exercise treadmill and exercise or pharmacologic echocardiography/radionuclide imaging/MRI. Plaque morphology and extent associate with prognosis which is a relative merit of CTA subject to ongoing research that could lead to evolving considerations. *CCTA*, coronary computed tomography angiography; *GFR*, glomerular filtration rate in ml/min/1.73 m²; *LV*, left ventricle.

microcirculation. The rapidity with which radionuclide imaging has advanced, both diagnostically and prognostically, makes the data from comparative imaging-based trials outdated. Assessment of CAD by radionuclide imaging is not limited to relative perfusion alone, but also extends to the estimation of blood flow and EF reserve.

PET is considered the gold standard for quantifying myocardial blood flow and coronary flow reserve. Coronary flow reserve (CFR) calculated as the ratio of hyperemic to rest absolute myocardial blood flow provides an integrated assessment of the hemodynamic effects of epicardial CAD, diffuse atherosclerosis, and microvascular dysfunction on myocardial tissue perfusion. CFR has been shown to refine the diagnosis and provide incremental prognostic value across the entire spectrum of ischemic heart disease from obstructive multivessel epicardial CAD to diffuse non-obstructive CAD and CMD. In the intermediate risk symptomatic patient without high risk features on PET MPI, a preserved CFR portends a benign prognosis. Patients

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Investors

Investor	Investor Type	Location	Participating Rounds
BlueCross BlueShield Venture Partners	Corporate Venture	Chicago, Illinois, United States	Series D - II, Series D, Series C
Capricorn Investment Group	Asset/Investment Management	Palo Alto, California, United States	Series E
HealthCor Management	Private Equity	New York, New York, United States	Series E, Series D - II, Series D, Series C
GE Ventures	Corporate Venture	Menlo Park, California, United States	Series D, Series C
Baillie Gifford & Co.	Asset/Investment Management	Edinburgh, Scotland, United Kingdom	Series E - II

Figure 3. Publicly available information on investors in HeartFlow with potential conflict of interest highlighted. Accessed from <https://www.cbinsights.com/company/heartflow-funding>.

with an impaired CFR have a worse prognosis independent of the presence of high risk angiographic CAD.¹⁷ Trials studying radionuclide imaging as a part of the functional testing arm have only relied on relative perfusion imaging, and thus not utilized its full diagnostic and prognostic ability. Future prospective studies evaluating the role of ischemia, revascularization, optimal medical therapy, and cardiovascular outcomes in stable coronary artery disease should utilize the full potential of functional testing by assessment of CFR.

Current best practices recommend diagnosing and managing patients using methods with radiation exposure as low as reasonably achievable.¹⁶ Third generation, or beyond 64 detector, CT scanners have published very low radiation use, but only a small minority of expert centers actually implement these scanners. Many community hospitals use second generation scanners, and in clinical practice CT radiation exposure to the patient is widely variable and often far higher than expert experience. For example, the recent PROTECTION VI study noted a 37-fold variability in median dose observed between the hospitals with lowest and highest reported dose-length-product.¹⁸ SPECT or PET MPI also involve radiation exposure, which must be taken into consideration. When appropriate, radiation dose may be reduced in the nuclear lab via favoring technetium versus thallium use for MPI, stress first imaging, weight-based technetium dosing, camera technology such as CZT, and perhaps in the future via machine learning. Although the cancer risk to the patient is not quantifiable, current consensus states that the

theoretical increase in cancer risk may require ten to forty years to manifest clinically. Therefore, by the linear no threshold theory, clinicians ought to take reasonable steps to reduce radiation exposure, including to favor zero radiation testing particularly in young patients whenever reasonably possible.

In conclusion, we recognize that CTA trials have demonstrated a role to consider anatomic evaluation in select patients where clinically appropriate. Rather than a non-evidence-based dogmatic “CT first” approach, we agree with contemporary AHA/ACC and ESC guidance to thoughtfully select the most appropriate test for a patient, based on clinical and laboratory characteristics and test availability. While we do not imply the clichéd conclusion of the need for further clinical trials, we do emphasize the importance of careful clinical evaluation of patients and a pragmatic, patient-centered approach to testing for CAD. Clinicians with industry conflicts of interest should exercise discretion advocating for CTA in clinical settings that promote increased medical and device interventions beyond evidence-based guideline directed practice. We also call for careful appraisal of scientific evidence and statements connected to for-profit organizations² in order to avoid industry bias in guidelines and health policy (Figure 3).

Disclosure

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