Controversies in Diagnostic Imaging of Patients with Suspected Stable Ischemic Heart Disease or Low Risk Chest Pain Syndromes

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Abstract
There has been a tremendous growth in the quality and quantity of high-quality imaging evidence in the area of stable ischemic heart disease. A number of recent comparative effectiveness trials have spurned significant controversies in the field of cardiovascular imaging. The result of this evidence is that many healthcare policies and national guidelines have undergone significant revisions. With all of this evidence, many challenges remain and the optimal evaluation strategy for evaluation of patients presenting with chest pain remains ill-defined. We have enlisted the guidance of numerous experts in the field of cardiovascular imaging to garner their perspective on imaging in stable ischemic heart disease. Each of these vignettes represent editorial perspectives and diverse opinions as to which, if any, should be the primary test in the evaluation of stable chest pain. These perspectives are not meant to be all-inclusive but to highlight many of the commonly-discussed controversies in the evaluation of stable chest pain symptoms. We present these perspectives as a pre-amble to an upcoming ACC / AHA clinical practice guideline which is undergoing revision from the prior report published in 2012 by Fihn *et al.* The evidence has changed considerably since the 2012 stable ischemic heart disease guideline and the current perspectives represent the diversity of available evidence as to the optimal imaging strategy for evaluation of the symptomatic patient.

Challenges in Selecting Appropriate Candidates for Diagnostic Testing: Is There a Value in Assessing Pre-Test Probability in the Diagnostic Work-up for CAD?

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Even though many patients undergo non-invasive testing prior to undergoing invasive coronary angiography (ICA), only 41% of patients referred for elective ICA are found to have obstructive CAD (defined as ≥1 coronary artery with ≥50% stenosis) (1). Using the pre-test probability, we should aim to identify those patients who do not need further testing, those who benefit from noninvasive testing, and those at highest risk who benefit from proceeding to invasive coronary angiography immediately without delay.

The pre-test probability of disease is crucial when deciding whom to test and which test to choose since it determines the predictive value of a diagnostic test (2) and its cost-effectiveness (3). For example, coronary computed tomography angiography (CCTA) with a sensitivity of 98% and specificity of 89% for diagnosing ≥50% stenosis on ICA (4), can reliably rule out the presence of obstructive CAD in patients with a 30% pre-test probability of CAD because the negative predictive value is >99% in such patients. A positive CCTA would increase the likelihood of the presence of obstructive CAD from 30% to 80%, which justifies confirmatory testing with ICA. In patients with only a 10% pre-test probability of CAD however, an abnormal CCTA test is likely to be a false-positive result as the positive predictive value is only 50% in this scenario. This implicates that 50% of those patients will be free of obstructive CAD if referred to ICA (2,5). Likewise, in a patient with a very high probability of CAD based on clinical presentation, an exercise electrocardiogram is not recommended because a negative result will not convince us that CAD is absent. This is the result of its low sensitivity and thus the high risk of false-negative results in patients with a high pre-test probability (6). Thus, when considering a non-invasive diagnostic test for CAD, we are obligated to take into account the pre-test probability, as it affects the interpretation of the test results (7). If we fail to do so, we may expose patients to unnecessary invasive procedures, or conversely delay or forgo work-up and treatment that is needed.

For patients with stable chest pain, the pre-test probability of CAD can be estimated easily based on clinical variables such as age, sex, and type of chest pain. Traditionally, the Diamond and Forrester estimates (8) have been used, as currently recommended by the American College

of Cardiology Foundation / American Heart Association (ACCF/AHA) guideline for the management of stable ischemic heart disease (SIHD) (6) (see Table 1). However, the Diamond and Forrester estimates were published in 1979 and relied exclusively on post-mortem and invasive angiographic data which significantly overestimates the probability of CAD in contemporary patient cohorts being evaluated for noninvasive testing (8). An updated prediction tool developed by the CAD consortium also relies on angiographic prevalence but provides more accurate probability estimates for patients considered for noninvasive imaging in the current era (9) (see Table 1), and has been externally validated in several independent patient populations (10-12). The more extensive CAD consortium clinical model includes risk factors such as diabetes mellitus, hypertension, hyperlipidemia, and smoking, to further refine the probability estimates, which can identify those patients who have a ≤10% probability of CAD (see www.r-calc.com for a free to use web-based calculator). In patients with a very low probability of CAD, one can consider forgoing noninvasive testing (13), although this has not yet been tested prospectively. Thus, we can use readily available clinical data to better risk stratify and select patients both who will benefit and are not likely to benefit from further testing, which is the first step we should take towards improving the yield of ICA and preventing unnecessary invasive procedures.

Table 1. Pre-test probability* (%) of obstructive CAD based on age, sex, and type of chest pain based on Diamond and Forrester (top panel) (8) and the updated CAD consortium algorithm (bottom panel) (9)

Diamond and Forrester						
	Non-specific chest pain		Atypical chest pain		Typical chest pain	
Age	Women	Men	Women	Men	Women	Men
35	1	5	4	22	26	70
45	3	14	13	46	55	87
55	8	22	32	59	79	92
65	19	28	54	67	91	94
75	-	-	-	-	-	-
85	-	-	-	-	-	-

CAD Consortium						
	Non-specific chest pain		Atypical chest pain		Typical chest pain	
Age	Women	Men	Women	Men	Women	Men
35	-	-	-	-	-	-
45	2	6	3	11	11	32
55	3	11	6	19	19	47
65	6	19	10	31	30	63
75	10	30	18	46	45	76
85	17	45	29	61	60	85

* Green shaded cells correspond to ≤10% probability of disease, yellow shaded cells to 10-30% probability of disease, and pink shaded cells to ≥30% probability of disease.

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Are Symptoms Required for the Diagnostic Evaluation? What About High Risk, Asymptomatic Patients?

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Most cardiac clinicians recognize the benefits of non-invasive imaging in risk stratifying patients who presented with chest pain. Cardiac imaging of chest pain patients provides more than a mere detection of CAD but locations and sizes of ischemia and infarction, which across modalities have been robust in prognosticating for cardiac events and aided in decision-making as gatekeepers for costly and invasive testing. In asymptomatic patients, these decisions remain controversial even within practice guidelines and more often than not, clinicians find little support towards justifying imaging of asymptomatic patients. Among the clinical high risk cohort, a 15-60% increased risk of myocardial infarction (MI) and up to a 6-fold increased risk of coronary mortality have been reported.(1)

Designation of symptomatology is ambiguous and subjective: Up to half of all acute MI patients without prior CAD had no history of suggestive symptoms.(2) The designation of symptoms is largely given to patients exhibiting chest pain. Other symptoms that can be related to ischemia, such as dyspnea or syncope, are often inconsistently categorized as noncardiac or asymptomatic or experienced differently between genders.(3) Recent documents of appropriate use criteria for cardiac radionuclide imaging had considered symptoms of anginal equivalents and an abnormal EKG to be distinctly higher in risk and advocated for risk stratification in some subsets of cohorts.(4) It is also clear that in risk stratification clinical assessment of other risk factors such as metabolic syndrome, family history of premature coronary disease, and significant functional disability all come into play to patient's risk.

Randomized Trials and Guidelines: Screening trials in asymptomatic patients with diabetes or metabolic syndromes are challenging due to low event rate or the lack of an effective coupling treatment with justifiable procedural risk profile.(5) Existing randomized control trials are not supportive of routine screening. The landmark Detection of Ischemia in Asymptomatic Diabetics (DIAD) study explored the role of screening with adenosine SPECT myocardial perfusion imaging (SPECT-MPI) in asymptomatic type 2 diabetes.(6) 5-year event rate of non-fatal MI and cardiac death was unanticipatedly low at 2.9% and so was overall revascularization rate at 5.5%. While SPECT-MPI did effectively stratify patients into higher-risk (moderate-large defects and

ischemic ECG) and low-risk (small defects or normal MPI) subsets, there was no impact on clinical outcomes and screening of diabetic patients was not justified. Similarly, in the recent FACTOR-64 randomized clinical trial of 900 asymptomatic diabetic patients with at least 3-5 years duration, CCTA did not reduce the composite rate of cardiac events and screening with CTA was not supported.(7)

It is not surprising for clinical practice guidelines to impose restrictions to curb the routine use of stress imaging for screening of asymptomatic patients. Practice guidelines focus on population trends and practice patterns in the large scale, not decision-making in clinical management for specific patients. With the absence of randomized trials demonstrating benefits in performing stress imaging, the weighing of harms and benefits is based more on experts' opinion which result in inconsistent recommendations. A systemic review of 14 guidelines on imaging of asymptomatic CAD observed conflicting recommendations: 8 recommended against or found insufficient evidence for testing.(21) The other 6 recommended imaging patients at intermediate or high Framingham risk with 5 of the 6 recommended the use of coronary calcium scoring. It remains unclear if any approach could lead to cost-effectiveness from a societal standpoint. Nevertheless, the recent 2018 cholesterol guidelines now provide a class IIa reccomendation for selected intermediate risk patients who do not have known CAD, if there is uncertainty regarding the role of statin therapy.

Concluding Comments: Despite the aforementioned controversies, there is no debate that decisions on patients need to be based primarily on individual CAD risks. We treat patients to reduce risk, often despite the lack of demonstrable benefits from randomized control trials. Current ACCF/AHA AUC considers stress testing as appropriate if pretest CHD risk is high * would double check this; don't think this is appropirate * , coronary calcium score >400, prior incomplete coronary revascularization, or > 5 years after CABG.(4) Patients with long-standing diabetes, extracardiac atherosclerotic vascular disease including PAD, abdominal aortic aneurysm, and carotid disease, and male patients with erectile dysfunction have all been accepted as risk equivalents to patients with established CAD.(4) On the other hand, patients with pre-existing CAD with successful percutaneous coronary intervention and without the above risk factors, routine stress imaging appears to result in very low rate of revascularization and has no value.(8-9) Patients with functional impairment or reduction of exercise tolerance are not truly

asymptomatic and may be at risk. Until more evidence arrives, a detailed history and physical examination are still the most cost-effective.

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Should Coronary Artery Calcium Scoring be Used in the Diagnostic Evaluation of Symptomatic Patients?

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The coronary artery calcium score (CACS) is well established as a simple non-invasive test for identifying patients with coronary atherosclerosis which requires no patient preparation, can be performed within several seconds, is easily interpretable and can be performed with very low (< 1 mSv) radiation exposure using modern scanners. Furthermore, CACS testing influences both patient and physician behavior regarding statin and aspirin usage (1) and is a strong motivating force for reducing cardiac risk factors and decreasing unnecessary downstream testing in a cost effective manner (2).

Initial CACS in Symptomatic Patients. Currently CACS testing is not considered appropriate in symptomatic patients with suspected CAD; however, over the last several years there have been many published studies evaluating cumulatively some 30,000 patients which demonstrate a potential role for CACS in this group (3-8). Patients in these studies had a low to intermediate pre-test likelihood for CAD and most had CACS prior to CCTA. Forty-seven percent (13,999/29,904) had a CACS of 0 and only 3.3% had >50% stenosis on CTA with a low annual MACE of 0.45%. In one study of 10,037 patients, only 3.5% with a CACS of zero had >50% and 1.4% $\geq$70% coronary artery stenosis by CTA (3). Annual MACE was 0.4% with a death/MI rate of 0.3%. Our group recently studied 805 patients who had both CACS and CTA and were followed for 2.3 + 0.9 years (8). In the 354 patients with a CACS of 0 (44%) only 5 (1.4%) had >50% stenosis on CTA and 92% had a normal CTA. CACS severity increased with increasing extent and severity of obstructive CAD, with MACE ranging from 0% in patients with a CACS of zero to 4.2% in patients with a severe CACS>400. All of these results suggest that CACS could be used as an initial test in patients with low-intermediate likelihood of CAD. However, a CACS of zero may not be as reassuring in symptomatic patients at high pre-test likelihood in whom the incidence of significant CAD is considerably higher (6).

Initial use of CACS in Low-intermediate Risk Patients with Acute Chest Pain. Another group where CACS may prove beneficial are in those with no prior history of CAD who have low to intermediate risk acute chest pain. In a prospective study comparing SPECT MPI to CACS in 1031 such patients, only 5 of 625 with a CACS of 0 (0.8%) had an abnormal SPECT

MPI (4/5 with a subsequent normal invasive coronary angiogram) vs. 17% with a CACS >400 (9). The event rate with a CACS of 0 was only 0.3% over 7.4 months of follow-up and the 2 events were in patients who had an elevated troponin on admission, but a normal SPECT MPI and no event following hospital discharge. Conversely, the event rate in patients with a CACS>0 was 7.4%. A recent meta-analysis in 8 studies involving 3,556 patients mirror these results with 60.2 % of patients having a CACS of zero and with a subsequent low death/MI rate of 0.5% over a median 10.5 months of follow-up. (10) Another recent randomized study from our group comparing a strategy of CTA/CACS versus SPECTMPI in 800 patients showed no evidence of obstructive disease by CTA in patients with a CACS of zero and no events over a median follow-up of 6.5 months (11). In this regard CACS might perform well as a first line test in selected patients at low to intermediate risk for CAD who typically undergo CTA – ie. those with no prior history of CAD, normal initial troponin and non-diagnostic ECG for ischemia - with avoidance of additional testing in patients with CACS of 0. In the ED setting this may be particularly advantageous for triaging patients home. Conversely stress SPECT MPI or other forms of functional testing would appear appropriate in the 40% of patients with a CACS>0 and particularly in those with a severe CACS.

Rationale for adding CACS during or following Functional testing. Where does CACS fit in patients with suspected CAD who have already had a functional test such as an ETT or stress MPI? Incremental value of CACS over functional testing would require heterogeneity of CACS results in such patients. In one study of 760 consecutive patients without known CAD had CACS after a normal Rb-82 positron-emission tomography (PET) MPI (12). Sixty-four percent had a CACS>0 with a CACS>100 and >400 in 47% and 22%, respectively. Of note, a CACS>100 increased from 27% in the low/intermediate FRS groups to 51% in the high risk group. Schenker et al likewise reported a high incidence of an abnormal CACS in 59% of patients who had a normal stress Rb-82 PET MPI for suspected CAD and with 19% having a CACS>400 (13). The pretest likelihood of CAD was 59.4%. A recent trial enrolled 4,897 symptomatic patients of whom 91% were of intermediate pretest likelihood for CAD (14). In the 76% of patients with a normal stress SPECT MPI, 69% had a CACS>0 and 15% had a CACS$\geq$400. Conversely, most patients with an abnormal MPI (88%) also had an abnormal CACS with 43% having a severe CACS. In this regard, a large percentage of patients with normal stress MPI will have subclinical coronary atherosclerosis which would otherwise be missed by the perfusion study alone. Relying

on normal SPECT or PET results alone might create a false sense of security and prevent the initiation of appropriate lifestyle changes and medical therapies.

Improving Diagnostic accuracy of MPI with CACS. CACS might aid in the interpretation of an equivocal stress MPI study based on the score result. This concept has been evaluated in several recent studies which provide insight for interpreting a stress MPI based on CACS.(15-16). Uretsky showed that CACS results did not influence the need for rest imaging in patients with a clearly normal or abnormal stress SPECT MPI but avoided rest imaging in patients with a probably normal (72%), equivocal (47%) and probably abnormal (40%) study (15). Thus, adding CACS reduced the need for a rest study in 64% of patients with a borderline SPECT MPI. Attenuation artifacts are common with SPECT MPI and the integration of CACS and MPI results may provide clarity in clinical decision-making based on the results of each individual test. The study by Brokov et al is reflective of this concept where integration of stress PET and CACS results improved per-vessel CAD detection over PET or CACS results alone (16). In this study no vessels with normal PET perfusion and a CACS< 100 had obstructive CAD. However in vessels with a CACS $\geq$400 obstructive CAD increased from 22% of vessels with normal PET perfusion to 92% of those showing a >5% ischemic perfusion defect. Further investigation in this area is warranted.

Conclusion. CACS may be considered as an initial test in patients with suspected CAD at low to intermediate pretest likelihood based on the high percentage who will have a CACS of 0 (50-60%), their very low likelihood of having obstructive CAD or an abnormal stress MPI and their low subsequent MACE rate (<0.5%/year). Additionally, CACS may be considered in patients who have a normal functional test in order to identify the high percentage who will have varying degrees of coronary atherosclerosis (approximately 50%) that has not yet led to ischemia. In such patients, intensive lifestyle modification and treatment of hyperlipidemia may result in reduced subsequent cardiac event rates based on extensive literature showing benefit with statin medications in primary and secondary prevention. The 3-4 year “warranty period” of a normal functional provides an opportunity for intensive treatment before cardiac events begin to occur. Finally, CACS may be considered to improve the diagnostic accuracy of MPI in patients with equivocal or mildly abnormal test results.

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The Conundrum of Index Testing: Anatomic vs. Functional Testing
Part I: A Physiologic Test Should be the First Line Diagnostic Test

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The 2012 ACCF/AHA SIHD guidelines and the 2014 multimodality Appropriate Use Criteria (AUC) strongly favor use of stress testing as the first test of choice in stable, symptomatic patients with suspected CAD.(1,2) Indeed the use of CCTA or ICA is ranked as a IIb indication in the guidelines and either Rarely Appropriate or May Be Appropriate in AUC, based on decades of experience and a large collection of supportive evidence. In addition, stress tests are readily available in almost all settings (including physician offices) and may not require radiation or injection of dye or tracers (stress echocardiography and treadmill testing).

The goals of noninvasive testing in suspected CAD include diagnosing CAD, guiding care, and providing prognostic information in the most cost-efficient manner possible. In addition to documenting the presence or absence of inducible ischemia, exercise stress can reproduce symptoms (or fail to do so), an additional and often important ingredient in risk stratification (angina is a component of the Duke Treadmill Score) and decision making. In the presence of known CAD and especially complex disease, stress imaging may be particularly useful in detecting peri-infarct ischemia, identifying which coronary territory is ischemic, assessing the adequacy of collateral flow, and quantifying the extent of ischemia. Further, unlike CTA, the accuracy of stress imaging is not adversely affected by the presence of coronary stents. For these reasons the UK NICE stable chest pain guidance recommends use of stress imaging tests and not CCTA in patients with known CAD.(3)

The mismatch between coronary stenosis and reduced flow or perfusion is well documented, as are the harms in revascularizing hemodynamically non-significant lesions. Since stress testing,

unlike anatomic testing, detects ischemia, it neither over estimates the importance of a ‘tight’ stenosis nor underestimates that of mild disease, which may also be flow limiting. Indeed functional tests, particularly CMR, more closely approximate invasive FFR than does either CTA or angiographic anatomy due to higher specificity.(4) Finally, stress testing can detect a variety of clinically important coronary abnormalities such as microvascular dysfunction, which cannot be evaluated using a purely anatomic approach.

Exercise stress also provides important prognostic information inherent in its rigorous assessment of exercise tolerance (time to symptoms) and exercise capacity. The latter provides an integrated measure of cardiac, pulmonary and musculoskeletal systems function, which is closely related to mortality independently of the presence or absence of CAD.(5)

Cost efficiency is particularly important in selecting a testing strategy because of the large population undergoing evaluation for suspected CAD. In an innovative network meta-analysis of all randomized trials comparing noninvasive tests in over 22,000 stable chest pain patients, Siontis *et al.* showed that stress imaging was associated with 50-75% fewer downstream tests, with no measurable benefit in reducing events.(6) Studies of direct randomized comparisons of CTA vs stress testing have confirmed the excessive use of coronary angiography in CTA-first strategy;(7) this is of particular concern since one of the drawbacks of functional testing is the high rate of unnecessary angiography (i.e., not finding obstructive or actionable CAD on angiography).

Many of the arguments against a stress test first strategy are better understood and responded to as opportunities to improve clinical decision making and care rather than failings of a stress testing strategy per se. In this respect, improved selection of patients for testing could substantially reduce false positive results as current patterns of testing include large numbers of

low risk patients with infrequent findings of ischemia on testing. In part this is due to reliance on outdated algorithms for pretest probability such as Diamond and Forrester, which was derived decades ago from post mortem and angiographic CAD prevalence, and has been proven to grossly overestimate the likelihood of disease in the current era.(8) Further, validated algorithms now exist to identify patients who are unlikely to have positive testing or events and can be predicted to derive little benefit from testing.(9) SCOT HEART, PROMISE and a meta-analysis all suggest that the risk of MI, but not death or hospitalization, is reduced using a CTA first strategy.(7,10-11) In all cases, this was ascribed to increased use of guideline-directed preventive medical therapy—an intervention which should not require a test to implement. Many if not most patients presenting with suspected CAD have preventive treatment gaps which should be addressed by considering the evaluation for chest pain as a 'teachable moment' during which risk factors should be examined and treated using evidence-based interventions, regardless of the chosen testing strategy.

All foregoing arguments aside, CAD and myocardial ischemia are complex interplay of flow, flow reserve, stenosis and even plaque characteristics. Similar patient profiles can vary dramatically - age, sex, comorbidities, etc. - all affect evaluation and management as well as test performance. As such, there is no 'one best test' but rather a portfolio of options that should be fully utilized in designing care strategies for individual patients.

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The Exercise Electrocardiogram (ECG) Remains the Best Stress Test for Many Patients

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The 2012 ACCF/AHA SIHD guidelines(23) gave a class I recommendation to the use of the exercise ECG in patients who are able to exercise, have an interpretable ECG, and have an intermediate probability of ischemic heart disease. Although clinicians can now choose between a wide variety of imaging modalities to evaluate patients with chest pain, the exercise ECG remains a very useful first test. I continue to use it in my practice in patients who meet the criteria outlined in the Class I recommendation. In patients seen at Mayo Rochester, who have chest pain, a normal resting electrocardiogram, and can exercise, a majority undergo an exercise ECG, in compliance with the class I guideline recommendation.

Why do we continue to use this "low tech" older test at Mayo, where we have tremendous cardiovascular imaging expertise? First and foremost, because the test works. The WOMEN Trial(24) was one of the few randomized trials conducted in the area of stress testing. It examined outcomes in middle-aged women with low-to-intermediate probabilities of ischemic heart disease who were able to exercise and had interpretable resting ECGs. These women were randomized to either the exercise ECG or exercise SPECT-MPI. After 2 years of follow up, the cumulative event-free survival was uniformly excellent (and not statistically different) in both groups (Figure 1). The percentage of women who were angina-free in both groups did not differ significantly at 6 months, 1 year, or 2 years. A minority of women in both groups required follow-up testing. Although follow-up testing was almost twice as frequent in the patients randomized to the exercise ECG (17.1% compared to 9.3% in the exercise SPECT-MPI group), more than 4 out of 5 patients randomized to the exercise ECG did not require follow up testing

over 2 years, refuting the commonly held assumption that second tests are very frequent after an exercise ECG. The rates of follow up testing in the WOMEN trial were considerably higher than those seen in the Mayo Rochester practice.

The proper interpretation of the exercise ECG should focus on far more than simply the ST segment. The Duke Treadmill score incorporates exercise capacity, angina, and ST segment interpretation into a single parameter that can categorize patients into low, moderate, and high-risk groups. It was developed retrospectively in the 1980s and tested prospectively in outpatients in the 1990s(25). Increasingly in our practice, physicians also consider the Lauer Score, which places less emphasis on ST segment depression or angina on the treadmill but instead emphasizes patient age and adjusts exercise capacity to the percent of predicted METs achieved, on the basis of age(26). When patients who were categorized as either low-risk or intermediate/high risk by the Duke score and the Lauer Score were compared, the Lauer Score reclassified 21% of all the patients and 64% of the intermediate/high-risk patients.

When interpreted correctly, the exercise ECG is cost effective. In the WOMEN Trial, which calculated cost using Medicare reimbursement rates, the median cost of the exercise ECG was $170, compared to $493 for the median cost of exercise SPECT-MPI. Even when the differences in follow up testing were included, the median total cost in the exercise ECG group remained about 65% lower than the median total cost in the SPECT-MPI group (2).

Although stress imaging studies are often felt to provide more “incremental” prognostic valve, that prognostic value is modest in many situations; the reclassification rates for low risk patients are far lower than commonly assumed. Our laboratory published a careful analysis of the incremental value of myocardial perfusion imaging in patients who had both a low clinical risk by risk factors and a low risk Duke treadmill score(27). We found there was no incremental

value of the summed stress score by nuclear imaging in these patients (Fig, 2). Hachamovitch *et al.* showed that SPECT-MPI had incremental value compared to the Duke treadmill score(28). However, in the low-risk treadmill score group only 51 of 926 patients (5.5%) had a severely abnormal scan and only 4 of these (7.8%) had a cardiac event. The cost of testing (assuming $1,000.00 per SPECT-MPI) in the total group was $926,000.00. The cost of testing per possible event prevented, before even considering the cost of catheterization and revascularization, was therefore $926,000.00 divided by 4 or a prohibitive $231,500.00 per possible event prevented. A similar analysis on an exercise echocardiography study(29) showed that, although there was a significant increase in major cardiac events with an abnormal stress echo in the low pre-test probability patients who had normal exercise ECGs, there were only 25 abnormal echoes in 492 such patients, and only 2 events within those 25. At an estimated cost of $500 per echocardiogram, the low-risk group would require $246,000.00 in diagnostic costs and $123,000.00 in diagnostic costs per possible event prevented. Stress imaging (with either SPECT-MPI or echocardiography) in these low risk patients has not been shown to improve patient outcomes.

The extra societal resources consumed by stress imaging are considerable. In 2013, Medicare RVUs were 2.12 for a stress electrocardiogram, 7.86 for a stress echocardiogram and 13.58 for a stress SPECT-MPI. The non-Medicare differentials were even greater in absolute dollars. Although the very rapid increases in cardiac imaging that were seen between 1995 and 2005 have leveled off and even decreased modestly in some data sets, the continuing societal concern about resource use is reflected in the 2015 Congressional legislation that mandated the use of appropriate use criteria in future ordering systems for high-technology imaging studies (although implementation has been delayed several times). I commend American Society of Nuclear

Cardiology for its position as part of the Choosing Wisely campaign, when it told clinicians "don't perform cardiac imaging for patients who are at low risk". Given the efficacy of risk factor reduction and optimal medical therapy in current medical practice, most patients with chest pain are indeed low risk. This was evident in the WOMEN Trial and in the more recently conducted PROMISE trial(30).

For these reasons, the exercise ECG remains the preferred test in patients with chest pain who have an interpretable electrocardiogram, are able to exercise, and have an intermediate-probability of ischemic heart disease.

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Figure Legends

Figure 1: Cardiovascular outcomes in the WOMEN Trial. Women randomized to the exercise ECG (ETT) had similar outcomes to women randomized to exercise SPECT-MPI. There was no significant difference in 2-year event-free survival between the 2 groups. The number at risk are shown at the bottom. Reproduced from reference 2 with permission.

Figure 2: Seven-year survival in patients at low clinical risk (using age and risk factors) who had low risk treadmill tests (as assessed by the Duke Treadmill score). All the patients underwent exercise SPECT-MPI. The survival by summed stress score is shown in the figure. Patients with a low-risk, intermediate-risk and high-risk summed stress score had no significant difference in survival, which was excellent in all 3 groups. Based on data from Poornima JACC 2004, but not previously published.

Exercise ECG Stress Testing Should be Replaced!

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Whilst the exercise ECG, on a treadmill or bicycle, is a cheap and widely available test, its use in the assessment of SIHD in 2018 is questionable, and with recent advances in stress imaging there is compelling evidence to suggest that it should be replaced with stress imaging as the diagnostic procedure in those with SIHD.

The diagnosis of angina is challenging, especially when based on history alone, and stress (or functional) testing is usually performed as an adjunct to clinical history. Stress testing is based on the principle of demand ischemia, a process whereby, above a patient-specific exercise workload, regional myocardial blood flow is decreased, and ischemia may be induced, in the setting of a functionally-limited stenosis. Ischemic thresholds are pivotal to clinical management of patients with SIHD; as a basis for exercise prescription and to guide prescription of anti-ischemic therapies and/or coronary revascularization [1].

Stress imaging may include SPECT-MPI, with exercise or pharmacological stress, positron emission tomography (PET), stress echocardiography, perfusion CMR and most recently derived FFR using computation flow dynamics on CCTA (FFR-CT). Given the pivotal nature of functional assessment, ischemia imaging should be as accurate and comprehensive as possible; in this regard stress imaging outperforms exercise ECG in four main areas; clinical appropriateness, accuracy, prognostic value, and, in many countries, overall cost-effectiveness. Stress imaging should therefore be considered the most appropriate first line investigation in those with symptomatic SIHD. Taking each area in turn:

Clinical Appropriateness: Although widely available, inexpensive, and easy to perform, evidence over the last decade suggests that symptomatic populations are often unable to exercise sufficiently for an exercise ECG [2,3], with approximately half of referred patients requiring non-exercise approaches to elucidate ischemia (i.e., pharmacologic stress) [1]. This fact alone means that exercise ECG is clinically inappropriate for almost half of those referred for investigation of SIHD symptoms. Moreover, in an era of increasing obesity and reduced exercise capacity in the general population, this figure may yet rise further, with an increasing risk that submaximal exertion on exercise ECG may fail to produce relevant ischemia despite a flow-limiting stenosis. Additionally, abnormalities of the resting EKG may make interpretation of an exercise ECG impossible, such as left bundle branch block, paced rhythms, resting ST segment abnormalities or LVH with strain pattern, whilst additional pathologies such as severe aortic valve disease, uncontrolled hypertension, recent cerebrovascular events, heart failure and uncorrected electrolyte disturbances may be additional contraindications to exercise ECG.

Accuracy: So, if we exclude half of the population who cannot appropriately exercise to induce ischemia, what is the diagnostic accuracy of exercise ECG in those that can, compared with stress imaging modalities? Recent evidence would suggest that heart rate dynamics during exercise and recovery is highly reproducible [5] but the exercise ECG appears less robust. A historic meta-analysis of the accuracy of exercise ECG determined a sensitivity of 68% in a study of over 12,000 patients [4] whilst the most recent ESC guidelines quote the sensitivity of exercise ECG at 45-50%, with SPECT-MPI around 70-90% and most other stress imaging modalities between 72-90% [6]. Perfusion CMR also has a similar sensitivity and specificity than stress echocardiography or nuclear imaging. This suggests that the exercise ECG is a less than ideal test to rule out significant CAD in those presenting with chest pain and most stress imaging

modalities are significantly more accurate. Independent analysis performed by the UK NICE Guideline Group in 2010 highlighted the poor accuracy of exercise ECG in the assessment of SIHD and was the reason that the exercise ECG was removed from the list of recommended investigations for the assessment of stable chest pain [7]. The specificity of exercise ECG is more respectable, at 85-90% in the general population, but this is equivalent to most of the stress imaging modalities. However, the interpretation of the exercise ECG is more challenging in certain subgroups, such as women and diabetics where the specificity may be less robust [8]. It is known that hormonal factors affect the exercise ECG in women, reducing the diagnostic accuracy [9], whilst the use of exercise ECG in diabetics is also felt to be inadequate, due to an excessive likelihood of false negative studies [10].

Prognostic value: Although the exercise ECG provides some prognostic value, based on exercise capacity, it provides no evidence of ischemia localization, unless associated with ST segment elevation, and little in the way of quantification of severity of CAD or ischemic burden. Increasing severity is generally assumed to be associated with early onset of ST segment depression, at a low ischemic threshold; the amount of maximal ST segment depression; horizontal or down-sloping ST segments and prolonged recovery of ST depression after exercise. However, these findings do not correlate strongly with either stress imaging or invasive angiographic findings [11]. Stress imaging on the other hand provides important additional prognostic information (determined by the actual stress imaging used), including total ischemia burden, delineation of the affected myocardial territory, quantification of absolute myocardial blood flow, scar burden, myocardial function (both global and regional), transient ischemic dilation in balanced multivessel disease, and viability and ischemia assessment in those with myocardial hibernation [12].

Overall cost-effectiveness: While exercise ECG may be a less expensive initial investigation, compared with stress imaging modalities, it is not always the least expensive overall investigative strategy in those with SIHD [2]. Cost-effectiveness is clearly dependent on issues such as reimbursement, with the US healthcare system paying five times more for nuclear imaging compared to exercise ECG [13] and 2-3 times more than in other developed nations [14]. However, recent evidence suggests that the initial use of stress imaging results in fewer referrals for invasive angiography, whilst exercise ECG results in the highest overall downstream testing rate [15]. In constrained healthcare systems this is critical, and in the era of quality and value-based imaging, stress imaging would appear to once again be a more prudent first line investigation that exercise ECG.

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Stress Echocardiography is the Best Physiologic Test

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It has long been recognized that stress-induced ischemia results in regional wall motion abnormalities in regions subtended by stenosed coronary arteries, and that these abnormalities can be detected noninvasively using echocardiography (31). Since then, digital technology permitting side by side comparison of rest and stress images as well as storage of multibeat clips, broad familiarity with use and safety of ultrasound enhancing agents (32), and improvements in ultrasound image quality have increased the feasibility of stress echocardiography, which now exceeds 98% in unselected patients (33). Exercise stress may be performed with treadmill, upright bicycle, or supine bicycle exercise. For patients unable to exercise adequately, pharmacologic stress testing with dobutamine or vasodilators may be performed. Exercise stress is preferred in patients who are able to exercise adequately, as the physiologic information about exercise capacity and heart rate and blood pressure responses to exercise are clinically important. **An accuracy superior to that of the exercise electrocardiogram and comparable to that of nuclear perfusion imaging for detection of angiographic coronary artery disease has been demonstrated** (34). Whereas balanced hypoperfusion in severe 3 vessel coronary artery disease can lead to false negative nuclear perfusion studies, ischemia manifested as an increase in end systolic cavity size and decrease in ejection fraction with stress would be readily recognized with stress echocardiography. Moreover, the prognostic role of stress echocardiography in patients with known or suspected ischemic heart disease has now been confirmed in thousands of patients and the test is widely available. A normal exercise echocardiogram in a patient with satisfactory exercise capacity is associated with an annual risk of <1% per year of death, myocardial

infarction, or coronary revascularization (35). Moreover, risk of cardiac events increases not only with the presence of, but extent and severity of regional wall motion abnormalities (36,37) Information provided by the stress echocardiogram is incremental to that provided by clinical variables and the exercise electrocardiogram in predicting risk (38). Even in those situations in which abnormal stress echocardiograms do not correspond with stenoses of major epicardial vessels by invasive coronary angiography, echocardiography results identify patients at increased risk for mortality in whom risk factor modification is indicated (39). Stress echocardiography, particularly when performed with bicycle or dobutamine stress with multistaged imaging, allows accurate recognition of viable myocardium and identifies myocardium with potential for recovery of function(40).

Various methods of quantitating extent and severity of ischemia have been employed. Visual assessment by an experienced observer of endocardial excursion and wall thickening towards the center or midline of the ventricle, representing radial myocardial function, remains the most widely utilized method of analysis of stress echocardiograms. The left ventricle is usually considered in a 16- or 17-segment model (41) .Right ventricular systolic function may also be assessed. Myocardial regions supplied by obstructed coronary arteries are identified by hypokinesis, i.e., reduction in the magnitude of endocardial excursion and wall thickening with stress relative to function at rest in the same region or relative to function with stress in regions with normal coronary supply. In addition to decreasing the amplitude of contraction, ischemia decreases the velocity and delays the onset of contraction, which can be detected using quantitative techniques or by visual assessment using digital technology (42). Myocardial deformation, which can be assessed and quantitated using strain echocardiography, can be a valuable adjunct, especially in situations such as left bundle branch block and severe left

ventricular dysfunction, when visual assessment is particularly challenging. Three-dimensional techniques are not widely utilized as these are associated with a lower frame rate, but this technology continues to improve and provides tomographic imaging of all segments.

Several unique features of stress echocardiography differentiate it from other stress testing technologies: 1. **The versatility of the stress echocardiography is unparalleled**. Not only ischemic wall motion abnormalities, but other causes of cardiac symptoms of chest pain and dyspnea can be readily recognized with the screening imaging performed prior to stress testing. The rest images may reveal unexpected valvular heart disease, hypertrophic cardiomyopathy, pericardial effusion, aortic dissection, pulmonary hypertension, or right heart enlargement which can dictate further assessment at that time, such as a shunt study. Other features which may be prognostically important, such as the presence of left ventricular hypertrophy, can also be readily detected (35). Assessment of mitral inflow E/A pattern and E/e' ratio at rest and with exercise is a useful supplement to wall motion analysis for detection of ischemia; increases in LV filling pressures which may be useful in understanding the etiology of the symptom of exertional dyspnea (43).

2. Stress echocardiography is an extremely safe and convenient test. There are no known contraindications to or adverse biological effects from ultrasound imaging. If an ultrasound enhancing agent is not needed and the patient can exercise, the test can be performed without placement of an intravenous line. Potential cardiac contraindications to stress testing, such as aortic dissection, unexpected regional wall motion abnormalities, or severe valve disease in the symptomatic patient can be immediately recognized on the baseline images, and depending on the situation, may preclude the need for stress testing. Continuous monitoring of wall motion during bicycle exercise or pharmacologic stress enables determination of the ischemic threshold,

the heart rate at which wall motion abnormalities first occur. This information can be used to estimate the severity and extent of disease, and to risk stratify patients with known or suspected coronary disease. It has also been useful in peri-operative management of patients with ischemia (44). Safety of registered nurse-supervised stress echocardiography has been well-documented (45).

3. Stress echocardiography can be performed with widely-available technology, usually at a lower cost than advanced imaging methods. The baseline imaging obtained prior to stress testing provides a great deal of information concerning chamber size and function and valves; this information has not been included in current comparative studies of cost effectiveness.

The 2011 Appropriate Use Criteria (AUC) for Echocardiography describe thirty familiar clinical scenarios in which stress echocardiography is appropriate (46). The more recent AUC document on multimodality assessment of stable ischemic heart disease also found stress echocardiography to be frequently appropriate (47). Stress echocardiography's value and utility in assessing other forms of heart disease, including pulmonary hypertension, cardiomyopathy, diastolic dysfunction, and valvular heart disease, will continue to develop. Its lower price compared to other forms of stress imaging, the absence of radiation, and the absence of any known contraindications to ultrasound make stress echocardiography a particularly attractive alternative to other modalities for assessment of stable ischemic heart disease. In the current era in which cost effectiveness and avoidance of redundant testing are more important than ever, the versatility and comprehensiveness of this effective, widely available, and safe test distinguish it.

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Cardiovascular Magnetic Resonance (CMR) Imaging is the Best Physiologic Test

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Cardiovascular magnetic resonance (CMR) produces high-resolution anatomical and functional images in any plane. In a single multi-parametric study, CMR can be used to assess global and regional ventricular function, detect and localize ischemia, quantify ischemic and infarct burden and determine myocardial viability. The resulting comprehensive clinical information can be used to diagnose, risk stratify and guide subsequent revascularization in patients with stable CAD. CMR is now widely available in most well-developed healthcare systems and has a high level of evidence to support its use in the investigation of stable chest pain [1].

CMR Diagnostic Accuracy: *a) Stress Perfusion CMR:* The diagnostic accuracy of stress perfusion CMR in patients with suspected angina has been the subject of several clinical studies and meta-analyses [2-5]. The CE-MARC study was a large (n=752), single-center, prospective study and showed that stress perfusion CMR had a higher sensitivity (87% vs. 67%, $p<0.0001$), similar specificity (83% vs. 83%, $p=0.916$) and greater overall diagnostic accuracy (AUC: 0.89 vs. 0.74, $p<0.0001$) compared with myocardial perfusion scintigraphy by SPECT-MPI [2]. The subsequent multicenter, multi-vendor MR-IMPACT II trial also confirmed a greater overall diagnostic accuracy for stress perfusion CMR compared to SPECT-MPI (AUC: 0.75 vs. 0.6, $p=0.018$), with a higher sensitivity, but lower specificity using a pre-defined cut-off [3,7]. A meta-analysis of 37 studies demonstrated a pooled sensitivity of 89% and pooled specificity of 76% using CMR for the detection of angiographically significant CAD [5]. Diagnostic accuracy in women was significantly higher with CMR compared to SPECT-MPI in a sub-analyses from the CE-MARC (AUC 0.90 vs 0.67; $p<0.001$) and MR-IMPACT II (AUC 0.76 vs 0.63; $p <0.05$) trials [7].

The above studies used an angiographic end-point to define ischemia and most commonly used SPECT-MPI as the comparator, but more recent meta-analyses have also shown the high diagnostic accuracy of CMR when compared to invasive FFR and have framed its performance against other non-invasive modalities. Li *et al*., showed that with FFR as the reference standard, the pooled sensitivity and specificity of stress perfusion CMR were 90% and 87% respectively [8]. Danad *et al*., additionally made comparisons with other modalities and showed that the sensitivity of CMR (90%, 95%CI: 75-97%), CCTA (90%, 95%CI: 86-93%) and FFR-CT (90%, 95%CI: 85-93%), were all similar but significantly higher than for SPECT-MPI (70%, 95%CI: 59-80%) or stress echocardiography (77%, 95%CI: 61-88%) [9]. The highest specificity was observed for CMR (94%, 95%CI: 79-99%) and the lowest for CCTA (39%, 95%CI: 34–44%); the other modalities lay in between: SPECT-MPI (78%, 95%CI: 68-87%), stress echocardiography (75%, 95%CI: 63–85%), FFR-CT (71%, 95%CI: 65-75%).

b) Dobutamine Stress CMR (DSCMR) is an alternative to perfusion CMR and is performed in a similar manner to dobutamine stress echocardiography (DSE) especially in patients with severe asthma, abnormal course of the proximal coronary arteries or severe allergy to gadolinium-based contrast agents. Ischemia is detected as inducible regional wall motion abnormalities downstream of significant coronary artery stenosis. An advantage over DSE, is that accuracy is not limited by body habitus or poor acoustic windows. DSCMR has been shown to have a superior diagnostic accuracy to DSE and high diagnostic accuracy in several studies, with a pooled sensitivity of 83% and pooled specificity of 86% [10].

CMR for Risk Stratification: The prognostic value of a negative stress CMR (perfusion or dobutamine) has been confirmed with annualized event rates (AER) for MI and death of ≤1%/year over a 2-year follow-up period [11-14]. Recently, 5-year follow-up data from CE-

MARC showed that an abnormal CMR (HR 2.77, 95%CI: 1.85-4.16, p<0.001) was an independent predictor of MACE [15]. Furthermore, CMR was superior to SPECT-MPI at predicting time to MACE and remained a significant predictor after adjustment for major cardiovascular risk factors, angiography result, or stratification for initial patient treatment.

CMR to Guide Patient Management: *a) Chest Pain*: The multicenter randomized CE-MARC 2 trial (n=1,202) showed that in a broad risk (10-90%) group of patients with suspected angina, first-line use of functional imaging with CMR or SPECT-MPI significantly reduced the incidence of unnecessary invasive angiography compared to management according to NICE (2010) CG95 guidance, without any penalty increase in MACE at 12-months [15]. The primary endpoint of unnecessary invasive angiography (defined by a normal FFR) occurred in 28.8% patients in the NICE guidelines group, 7.5% patients in the CMR-guided group, and 7.1% patients in the SPECT-MPI-guided group. Therefore, in contrast to the updated 2016 NICE CG95 guidelines, these results support broader adoption of functional imaging (CMR or SPECT-MPI), in low, intermediate and high-risk patient groups to reduce rates of unnecessary invasive angiography.

Conclusions: CMR provides highly accurate diagnostic and prognostic information in stable CAD. Importantly, recent comparative effectiveness trials have shown that using CMR to guide patient management can lead to reduced rates of unnecessary angiography compared to NICE clinical guidelines, and less coronary revascularization with similar anginal control and clinical outcomes, compared to an invasive angiography+/-FFR strategy. The excellent diagnostic accuracy and predictive value in combination with its non-invasiveness, lack of ionizing radiation and versatility, makes CMR the method of first choice for the assessment of patients with stable CAD.

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Part II. CCTA Is the Best Frontline Procedure

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Evidence for the beneficial effects of non-invasive anatomic imaging in the diagnosis of patients with CAD has developed rapidly. Initially, large-scale registry studies established the prognostic value of computed tomography coronary angiography (CCTA) in patients with suspected CAD. More recently large randomised controlled trials have shown that changes in management based on noninvasive anatomic imaging can improve outcomes in patients with stable CAD. An important difference compared to ischaemia imaging is that imaging based on anatomy identifies changes to the coronary artery itself, rather than the downstream effects of CAD. Anatomic imaging may therefore be able to identify at risk patients at an early stage of disease, before ischaemia develops. Conversely, this also means that non-invasive anatomic imaging may "overcall" disease compared to ischaemic imaging gold-standards. Recently additional metrics that can be derived from anatomic imaging have been proposed which can indicate the associated functional implications of anatomical abnormalities. These may provide additive value in risk stratification in patients with stable ischaemic heart disease.

CCTA has a good diagnostic accuracy to detect stenosis when compared to invasive coronary angiography, with the high negative predictive value meaning that it is excellent at identifying patients with normal coronary arteries and excluding CAD.[1] Large registry studies have established that the presence of normal coronary arteries on CCTA is an excellent prognostic marker. [2-3] A recent meta-analysis of 122,721 patients in 165 studies showed that for patients with normal coronary arteries on CCTA the subsequent annual event rate was below 1%.[4] The identification of normal coronary arteries on CCTA identifies a group of patients at low risk of

subsequent events, and can provide an excellent "warranty period" which extends beyond 5 years. [2-3] Thus, CCTA can identify patients without CAD and indicates a good prognosis with a low risk of subsequent cardiac events.

Registry studies have also identified the prognostic utility of CCTA both in terms of identifying the presence of CAD, and also determining the extent of CAD. The CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicentre) registry identified that amongst 23,854 patients, having a greater number of vessels involved on CCTA was associated with increased risk of mortality.[2] The severity of CAD on CCTA is also incremental to traditional cardiovascular risk factors in the prediction of subsequent prognosis.[2, 3]

However, it is in the recent randomised controlled trials that the utility of CCTA has been established. The "test and treat" methodology of these studies means that we are able to assess that the prognostic utility of CCTA and the effect of treatment decisions based on CCTA imaging. The PROMISE (PROspective Multicentre Imaging Study for Evaluation of chest pain) trial is the largest trial of this type [5]. PROMISE recruited 10,003 outpatients with symptoms of stable CAD who were awaiting non-invasive investigation for suspected CAD. They randomised patients to undergo either functional testing or CCTA and assessed the primary outcome of all-cause mortality, MI, hospitalisation for unstable angina and major complications of cardiovascular procedures or diagnostic testing. After 25 months of follow-up there was no difference in the primary outcome between anatomical and functional imaging strategies (events 3.3% vs 3.0%, HR 1.04 [95% CI 0.83–1.29], p=0.75). In this PROMISE failed to meet the pre-specified superiority and non-inferiority outcomes. However, PROMISE recruited a relatively low risk group with 27% having symptoms other than chest pain and 11% having non-anginal

chest pain. Subsequent post-hoc analysis of the PROMISE data has identified that the discriminatory capacity of CCTA to predict the presence of subsequent events was higher than in the functional testing group (c-index 0.72 [95% CI 0.68 to 0.76] versus 0.64 [95% CI 0.59 to 0.69], p=0.04).[6]

The SCOT-HEART (Scottish COmputed Tomography of the HEART) trial recruited 4,146 symptomatic stable outpatients from outpatient cardiology clinics (Rapid Access Chest Pain Clinics). Participants were randomised to either standard care or standard care plus CCTA. At 6 weeks CCTA changed the diagnosis in 23% of patients undergoing CCTA compared to 1% of patients in the standard care group. CCTA improved the certainty of the diagnosis and also changed subsequent management. After 20 months of follow-up there was a 38% lower rate of fatal and non-fatal MI in the CCTA group, which just failed to reach statistical significance (p=0.0527).[7] However, in a post-hoc landmark analysis which was censored to the median time for management changes to be implemented (50 days), the rate of fatal and non-fatal MI was reduced by 50% in patients undergoing CCTA (17% vs 34%, p=0.02).[8] The 5 year follow-up of the SCOT-HEART trial found a significant reduction in fatal and non-fatal MI in the CCTA compared to the standard care group (2.3% vs 3.9%, p=0.004), driven largely by the reduction in non-fatal MI.[9] It is the potential for a change in management after non-invasive imaging which leads to improved outcomes for patients. After CCTA in the SCOT-HEART trial 23% of patients had a change in their prescribed medications, with an increased use of preventative medications such as aspirin, statin and ACE inhibitors.[8] At 5 years the rates of invasive coronary angiography and revascularisation were similar between the two groups, suggesting more appropriate use in the CCTA group.[9] Thus these results are in keeping with the hypothesis that treatment changes based on CCTA are associated with improved subsequent outcomes.

CCTA provides more information for risk stratification than just the presence of obstructive disease. CCTA provides a three-dimensional dataset which includes information on the coronary artery wall, atherosclerotic plaque composition and adjacent epicardial fat. At the simplest level of analysis atherosclerotic plaque can be divided into calcified, non-calcified and mixed plaque, with the presence of non-calcified plaque being associated with a worse prognosis. Further CCTA imaging findings that can identify potentially high risk plaques (also known as "vulnerable" or "adverse" plaques) include positive remodelling, spotty calcification, low attenuation plaque and the 'napkin ring' sign.[10-11] Motoyama *et al.* showed that positive remodelling, low attenuation plaque and spotty calcification were more frequent in patients with acute coronary syndromes and that positive remodelling and low attenuation plaque were independent predictors of subsequent acute coronary syndromes at 3.9 years.[12-13] In the PROMISE trial, the presence of positive remodelling, low attenuation plaque and the napkin ring sign was associated with an increased rate of major cardiovascular events at 2 years, independent of cardiovascular risk scores or the presence of obstructive CAD.[14] In the SCOT-HEART trial patients with adverse plaque characteristics and obstructive disease had the highest event rate at 5 years, but this was not independent of coronary artery calcium score.[15] Further understanding of plaque burden and plaque subtypes may therefore improve the identification of lesions that cause ischaemia and be predictive of long term outcomes.

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It is Not One or the Other: It is Both! Combination Testing is the Best Approach for Evaluation of Symptomatic Patients

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Atherosclerotic coronary obstruction limits myocardial perfusion, yet the relation between angiographic stenosis and myocardial blood flow and symptoms is diffuse. While revascularization decisions have traditionally been based on the angiographic coronary disease severity, an expanding body of evidence supports revascularization decisions driven by the severity and extent of myocardial ischemia. Meaningful revascularization decisions require both anatomical and functional information, and catheter-based coronary angiography complemented by fractional flow reserve is the most validated form of hybrid testing for CAD.[1] Observed associations between non-invasively established myocardial ischemia and clinical outcome support its clinical use[2], yet noninvasive stress imaging only partially succeeds in its intended role as gatekeeper to the ICA laboratory.[3] While close concordance between stress imaging and invasive angiography should not be expected, there is also substantial disagreement among functional tests, as well as with fractional flow reserve.[4] Each stress imaging modality has well-acknowledged technical limitations as potential sources of inaccurate test results. Equivocal or conflicting stress test results can be resolved by invasive angiography, or preferably a noninvasive alternative to visualize the coronary anatomy. Contemporary CT technology allows for accurate noninvasive imaging of the coronary arteries in most patients with suspected coronary disease. Because myocardial ischemia is considered uncommon in the absence of angiographic stenosis, the technique is particularly effective in patients with a low probability of disease.[5] However, coronary CT angiography, as well as invasive angiography, generally overestimates the functional disease severity, particularly by conservative 50%-stenosis

thresholds. Without confirmation of hemodynamic relevance CT angiography can increase rates of cardiac catheterization and revascularization procedures without evident prognostic benefit.[6,7] Anatomical combined with functional imaging provides incremental information, leading to better clinical decisions. While neither CT angiography nor stress imaging is without flaws, the combination of both can settle uncertainties and the need for confirmation by invasive procedures. CT angiography can be combined with exercise electrocardiography[8,9], but perhaps more interesting is the combination with stress perfusion imaging. Merged CT and perfusion images from separate exams or acquired by hybrid CT-PET or CT-SPECT systems allow for direct visual correlation between the affected vessels and their dependent myocardium and perform better than each of its parts.[10-12] Angiographic disease on CT without inducible ischemia defers the need for catheterizations, a normal CT angiogram provides reassurance when a false perfusion defect is suspected, and the combination of angiographic stenosis and inducible ischemia support revascularization decisions without the need for invasive fractional flow reserve. Particularly in patients with a high probability or demonstrated CAD comprehensive imaging provides most certainty and the best conditions for meaningful revascularization decisions in patients with probable or established CAD.

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Coronary CTA / FFR-CT Strategy is Superior to a Traditional Stress Testing Approach for Stable CAD

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For decades both exercise and imaging stress tests have served the field of cardiovascular medicine well helping inform both prognosis and guiding decision making regarding revascularization. While exercise stress testing can provide insight into exercise induced physiological changes, stress testing has proven less effective at identifying chest pain patients with suspected obstructive coronary disease[1-3]. In the NCDR, over 80% of patients undergoing invasive coronary angiography (ICA) had prior stress testing and yet the majority of patients had only mild coronary disease not needing revascularization. This is not unique to the US healthcare system with similar results in Europe and Canada, with reported rates of nonobstructive disease in in a recent meta-analysis of 1,219,920 patients across 9 studies showing a 49% negative angiography rate in stable chest pain.[4] Simply put, this algorithm does not work and frankly nor should it be expected to. Stress tests are intended to evaluate myocardial blood flow which is most directly impacted by the microvasculature which contribute the majority of resistance of myocardial blood flow with only a minor related to the epicardial coronary arteries. Given that the first question that is being asked in the evaluation of patients with chest pain is whether a patient has CAD and whether they have a coronary stenosis, a CT/FFR-CT strategy may make more intuitive sense. This approach has been shown to be more effective at identifying patients with obstructive CAD. In the interventional arm of the PLATFORM study, a CTA/FFR-CT resulted in a reduction in non-obstructive disease at the time of ICA from 73 to 12%[5] with 61% of ICA being safely canceled without an event at 1 year in any of the subjects in whom ICA was deferred[6]. These results have been reproduced in a number of centers consistently showing an

enrichment of the population in the catheterization laboratory with a higher burden of obstructive disease[7] and beyond that improved ICA efficiency with higher PCI/ICA ratio in both lower and higher pretest likelihood of CAD[8]. In a post-hoc analysis of the PROMISE Trial, Lu and colleagues noted that a combined CCTA/FFR-CT approach would significantly reduce the rate of positive CTA studies while markedly reducing the incidence of non-obstructive disease at the time of ICA when compared to a stress testing pathway (52vs 12% $p<0.001$)[9].

In settings of national administration of healthcare services, these strong data are having a predictable impact regarding guideline recommendations. In the UK, the NHS and NICE have aligned on a testing pathway for patients with stable chest pain which consists of a CCTA as the initial test, and FFR-CT as the preferred second test if one is required.

Stress testing does not identify severe CAD: Not only has stress testing been shown to not adequately identify those with coronary artery stenosis, stress testing has also proven itself insensitive for the detection of severe triple vessel disease or left main stenosis. In a cohort of subjects with proven LM obstructive stenosis, 44% had normal or mildly abnormal SPECT-MPI studies that would not typically result in ICA[10]. Coronary CTA on the other hand, even without FFR-CT, has been shown to be the most accurate non-invasive test for the identification of obstructive CAD[11]. This combination of overestimation of single vessel disease and poor sensitivity for the identification of prognostic CAD of SPECT-MPI and other functional tests makes traditional ischemia testing a poor upfront strategy for patients presenting with chest pain and suspected but not confirmed CAD. A combined CTA/FFR-CT strategy is not only capable of identifying severe left main and multivessel stenosis with high sensitivity but is able to provide an anatomical physiological roadmap complete with stenosis, plaque information, area at risk and relationship to anatomical branches.

Discrimination of Lesion Specific Ischemia: With the rapid development of CCTA and the growing clinical utility supporting CCTA as a first line test for patients with stable chest pain, many have begun to advocate the use of stress testing to help adjudicate the functional significance of stenosis of uncertain severity or intermediate stenosis on CCTA. Given that revascularization has only been shown to improve outcomes over optimal medical therapy in the setting of lesion specific ischemia by FFR/IFR, for stress testing to be helpful in determining who should be considered for ICA rather than medical therapy alone it would have to be able to adjudicate lesion specific ischemia. This approach was in fact shown to be fallacious in the recent comparative accuracy PACIFIC Trial with the diagnostic performance of a hybrid CTA/SPECT approach for the adjudication of lesion specific ischemia no better than CTA alone[12]. In fact, while the use of stress testing following CTA improved specificity it significantly increased the false negative evaluations resulting in a potentially unsafe approach. FFR-CT, on the other hand, has consistently been shown to be the non-invasive test with the highest diagnostic performance for the discrimination of lesion specific ischemia with a per vessel diagnostic accuracy of 86%[13-14]. There is growing data supporting the clinical utility of a combined CTA/ FFR-CT strategy with evidence that this approach reduces the rate of nonobstructive disease in the ICA laboratory, improves resource utilization with higher PCI/ICA ratio and more appropriate revascularization than following an ischemia testing approach without an increase in overall ICA rates.

Planning Intervention: Beyond the discrimination of those subjects likely to have CAD, the combined anatomic and physiological model allows for lesion specific decision making around revascularization rather than localizing to the territory at best like stress testing. A stress testing pathway provides only modest information to the interventionalist regarding the extent and

severity of CAD and nothing regarding the feasibility of PCI. FFR-CT uniquely allows the evaluation of serial lesions facilitating the extent of pressure loss across each individual lesion enabling a more thoughtful determination of revascularization strategies with the goal of achieving complete ischemic revascularization.[15] Stress testing is unable to provide such granular information leaving the interventionalist needing to adjudicate and interrogate each lesion to confirm its significance.

Beyond baseline anatomical and physiological lesion adjudication, through advance computational processing and fluid dynamics the opportunity to generate an interactive planner to help guide optimal revascularization strategies in advance of the procedure in a unique fashion. With growing evidence of the hazard associated with incomplete ischemic revascularization and the frequency that patients leave the catheterization lab in this fashion the need for a non-invasive tool to help more effectively plan revascularization decision making is profound. While currently data is limited to validation cohorts and singles center case series, the potential is significant and potentially game changing. Stress testing, regardless of future advancements will not be able to provide such rich pre-procedural information to guide decision making.

Concluding comments: In closing, it seems clear that the days of stress testing as the upfront and primary modality for the evaluation of patients with suspected but not confirmed CAD are numbered. CTA / FFR-CT dominates on all accounts: 1) enriches the population referred for ICA 2) Safely identifies high risk CAD 3) is superior for the discrimination of lesion specific ischemia 4) improves angiographic lab resource utilization by providing a patient specific detailed anatomical and physiological map to help inform treatment decision making.

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When to use Comprehensive Computed Tomographic (CT) imaging

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With advancing age, the development of coronary atherosclerosis appears unavoidable, yet its clinical manifestation is variable and unpredictable. Stable angina pectoris as a sign of potential coronary disease generally warrants noninvasive testing, the traditional gatekeeper to the catheterization laboratory. Alternatively, direct coronary visualization by CT angiography rules out angiographic coronary disease more accurately than any noninvasive stress test.[1] In addition, CT angiography (CCTA) visualizes nonobstructive atherosclerotic plaque, which provides opportunity for optimization of prevention. Patients without coronary disease on CCTA have an excellent prognosis[2], perhaps even better than those with normal stress test results. While the negative predictive value of CCTA is high, there is a tendency to overestimate stenosis severity compared to invasive angiography, as well as a tendency to overestimate functional severity compared to functional tests.[3] As a consequence, CCTA is associated with higher subsequent catheterization and revascularization rates without a yet demonstrated benefit in clinical outcome.[4] Instead of ruling out functional significance by invasive fractional flow reserve, or one of several well-established noninvasive functional tests, cardiac CT now offers several options for functional interpretation of CAD. Based on principles similar to other perfusion imaging techniques, cardiac CT can detect myocardial ischemia by the contrast enhancement of the myocardium during pharmacological hyperemia. In conjunction with CT angiography, which adds approximately 20 minutes examination time, CT myocardial perfusion imaging improves the accuracy for the detection of functionally significant lesions.[5-6] Alternatively, computational fluid dynamics applied to CT angiograms allow for the calculation of a virtual fractional flow

reserve without the need for additional imaging or administration of a vasodilator. FFR-CT improves the diagnostic accuracy of CT angiography for the differentiation of hemodynamically significant coronary disease.[7] Incorporation of CT-FFR or perfusion imaging in the diagnostic workup of chest pain improve the yield of invasive angiography and reduce the number of negative angiograms.[8]

Chest pain is a non-specific complaint, and although the spectrum incudes severe CAD, the majority of patients have benign and often self-limiting conditions unrelated to the heart. The very low prevalence of obstructive coronary disease (<10%) in contemporary chest pain cohorts has stirred a debate concerning the incremental value of costly diagnostic tests.[9] Also in symptomatic patients, absent coronary calcium on CT incurs a very low probability of severe coronary disease and a favorable clinical outcome.[10] Calcium imaging is more sensitive than most other noninvasive test, excludes coronary disease in up to 40%,[10] and appears to be a safe and cost-effective initial approach in low-intermediate risk patients with suspected CAD.[8,11]

CAD is not a binary condition and the presence, severity, risk and subsequent treatment of ischemic heart disease cannot be defined by a single diagnostic parameter. Cardiac CT has become a versatile imaging technique offering inexpensive measures of atherosclerotic burden, non-invasive coronary angiography and sophisticated tools for functional interpretation. Comprehensive cardiac CT combines anatomy and function that can be spatially matched to identify coronary lesions that are hemodynamically relevant and potential targets for revascularization. Alternatively, these different cardiac CT applications may be offered in a tiered approach to optimize the (cost-)efficiency of cardiac CT in patients with a low to intermediate probability of CAD.

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Part III. Is Imaging the Gatekeeper for Revascularization?

Goals of Diagnostic Testing for Identification of Candidates for Revascularization

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Decades of observational studies have demonstrated the association of myocardial ischemic burden as determined using electrocardiography, nuclear imaging, echocardiography and cardiac magnetic resonance imaging with adverse outcomes including death and MI. Although there has been no study that has proven that ischemia directly causes death or MI, the strength, consistency and biologic plausibility of the association of ischemia with adverse prognosis has led many to argue that reduction or elimination is ischemia is the primary therapeutic goal in patients with SIHD. Furthermore, a large, single center observational study by Hachamovitch and colleagues using exercise or adenosine SPECT-MPI demonstrated that if a patient had an ischemic burden of more than 10% of the left ventricle, revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) conferred a survival benefit compared to patients who did not undergo revascularization (1). Despite being cited nearly 900 times, this study suffers from important limitations. First, patients underwent stress imaging from 1991 to 1997, a decade before publication of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial and the demonstration of the importance of optimal medical therapy (OMT) for secondary prevention (2). OMT, as defined in COURAGE, consists of lifestyle and risk factor modification as well as disease-modifying (aspirin, statins and angiotensin converting enzyme inhibitors or angiotensin receptor blockers) and anti-anginal (nitrates and beta blockers) pharmacologic therapy. It should not be assumed that patients in the

Hachamovitch study who did not undergo revascularization received OMT. Second, as with all observational studies of treatment efficacy, there is always residual confounding due to selection bias (the selection of healthier patients for revascularization). Third, there was no adjustment for immortal time bias, the time following the MPI study in which any patient that dies before revascularization is considered in the medical treatment arm even if the intended therapy had been PCI or CABG. Each of these limitations would bias the results in favor of revascularization.

Fortunately, the next decade would see the conduct and publication of two landmark prospective, randomized trials: COURAGE (2) and Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) (3). Both studies randomized patients with SIHD to an initial strategy of routine revascularization in addition to OMT or to OMT alone. COURAGE randomized 2,287 patients and utilized PCI as the revascularization technique. There was no significant reduction in the primary endpoint of death or MI for patients assigned to the routine PCI strategy over 4.6 years of follow-up. BARI 2D included 2,368 SIHD patients with diabetes, and randomization was stratified according to the method of revascularization—either PCI or CABG—as determined by the responsible physician to be the more appropriate method for each patient after angiography but prior to randomization. The primary endpoint was all-cause mortality, and there was no mortality benefit from early revascularization using either PCI or CABG over 5.3 years of follow-up. MI was reduced by CABG but not by PCI. Both studies included ancillary nuclear studies. The COURAGE nuclear substudy analyzed 314 patients who had SPECT-MPI before randomization and 6-18 months after the baseline SPECT-MPI (4). PCI and OMT was more effective at reducing ischemia than OMT alone. However, patients with a greater than 5% reduction in ischemia using either strategy had lower unadjusted rates of death and MI. This unadjusted analysis has been repeatedly used to justify ischemia-guided PCI in

patients with SIHD (5). However, this effect was no longer significant when risk-adjusted indicating no benefit to ischemia reduction which was consistent with the results of the main trial.

A second COURAGE substudy examined the relationship between baseline stress myocardial ischemia and clinical outcomes based on randomized treatment assignment (6). A total of 1,381 randomized patients (OMT = 699; PCI + OMT = 682) underwent stress MPI prior to entering the trial. Site investigators interpreted the extent of ischemia by the number of ischemic segments using a 6-segment myocardial model. Patients were divided into those with no to mild (<3 ischemic segments) and moderate-to-severe ischemia (≥3 ischemic segments). The composite of death or MI was similar in the OMT and PCI plus OMT treatment groups for no to mild (18% and 19%, p=0.92) and moderate to severe ischemia (19% and 22%, p=0.53, interaction p=0.65). There was no gradient increase in events for the overall cohort with the extent of ischemia. The authors concluded that the extent of ischemia did not predict adverse events and did not alter treatment effectiveness. Similarly, the extent of core laboratory assessed baseline ischemia did not predict cardiovascular events in a follow-up COURAGE analysis of 621 patients after a mean follow-up of 4.7 years, whereas the angiographic extent of atherosclerosis correlated with events (7).

In the BARI 2D nuclear ancillary study, 1,505 patients underwent SPECT-MPI one year following randomization. Patients randomized to medical therapy were more likely to have moderate to severe ischemia, but the severity of residual ischemia was not an independent predictor of outcome (8).

The following decade would see the publication of two additional randomized trials that reported the outcomes of patients with ischemia as a function of randomized treatment

assignment to revascularization with medical therapy versus medical therapy alone. In Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2), patients with an abnormal fractional flow reserve (FFR), a surrogate for ischemia on stress testing, were randomized to PCI and OMT or OMT alone (9). In this unblinded trial, the FFR-guided PCI plus OMT arm had a reduction in the composite endpoint of death, MI and urgent revascularization that was driven entirely by an excess of revascularization procedures in the OMT arm that may have been a function of the unblinded nature of the trial (10). There was no difference in the rate of death or MI between arms. The 5-year follow-up of that trial found no significant differences between the PCI group and the OMT group in the rates of death (5.1% and 5.2%; hazard ratio, 0.98; 95% CI, 0.55 to 1.75) or MI (8.1% and 12.0%; hazard ratio, 0.66; 95% CI, 0.43 to 1.00) (11). A 2014 meta-analysis of five randomized trials of PCI and medical therapy versus medical therapy alone that was limited to 4064 patients with ischemia prior to treatment assignment found no benefit of PCI with medical therapy in reducing mortality or MI compared to medical therapy alone (12). The STICH (Surgical Treatment for IsChemic Heart Failure) trial randomized 399 patients with CAD and EF ≤35% to CABG or medical therapy. Myocardial ischemia was present on stress testing in 256 patients (64% of the study population) (13). There was no difference between patients with and without ischemia in all-cause mortality (hazard ratio: 1.08; 95% confidence interval: 0.77 to 1.50; p=0.66), cardiovascular mortality, or all-cause mortality plus cardiovascular hospitalization. There was no interaction between ischemia and treatment for any clinical endpoint (13). The 10-year follow-up, however, found significantly lower rates of all-cause death, cardiovascular death. and death from any cause or hospitalization for cardiovascular causes among patients who underwent CABG plus medical therapy as

compared with those who received medical therapy alone (14). However, it is unknown whether baseline ischemia or relief of ischemia interacted with 10-year survival.

The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial (15) which randomized 5,179 SIHD patients, is in progress. ISCHEMIA is designed to determine whether an initial invasive strategy of cardiac catheterization and revascularization (with PCI or CABG, if feasible) plus OMT will reduce the primary composite endpoint of cardiovascular death, nonfatal MI, hospitalization for unstable angina, hospitalization for heart failure, or resuscitated cardiac arrest in SIHD patients with moderate or severe ischemia, as compared with an initial conservative strategy of OMT alone, with cardiac catheterization and revascularization reserved for failure of medical therapy.

In summary, while myocardial ischemia is strongly associated with an adverse prognosis and revascularization reduces ischemia to a greater degree than medical therapy, it remains an open question whether revascularization in SIHD patients with ischemia improves prognosis. It is hoped that ISCHEMIA will answer this question because of its larger size and selection of patients with at least moderate ischemia. The link between ischemia and outcomes may be atherosclerotic plaque burden with greater ischemia being a surrogate for more extensive plaque burden with quantitatively more substrate for plaque rupture and MI. In support of this notion, a multivariable analysis of COURAGE that included both ischemic burden and angiographic atherosclerotic burden in a model to predict death, MI, and non-ST-segment elevation acute coronary syndromes found that atherosclerotic burden, not ischemia, was a significant predictor of outcome (18). While there is no dispute that OMT is indicated for all patients with SIHD, the role for revascularization remains uncertain.

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Part IV. Do We Need Imaging at All?

Avoiding Unnecessary Stress Imaging for Low-Risk Patients with Chest Pain

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The primary question that must be asked before ordering any test for a patient is: will the test lead to improved clinical outcomes?[1] For patients presenting with chest pain, we need evidence that testing, which may lead to the diagnosis of coronary artery disease, will ultimately inform treatments or interventions that reduce the downstream risk of myocardial infarction (MI) and cardiovascular death. There is, however, no evidence that noninvasive stress testing improves clinical outcomes for low-risk patients presenting with chest pain.[2] Furthermore, there are no data to support the current practice of routine ordering stress testing on all patients who present with chest pain.

Patients with chest pain can be quickly and easily risk stratified based on clinical history. The key factors include age, sex, and characteristics of presenting symptoms (non-anginal chest pain, atypical angina, or typical angina), described by Diamond and Forrester in their landmark 1979 publication, which still ring true.[3-4] Ultimately, if a patient is deemed low-risk based on history and has undergone an initial testing strategy with electrocardiogram (ECG) and, with clinically unstable symptoms, troponins, he/she is at low risk of major adverse coronary events.

For these lower risk patients, clinical practice guidelines recommend a treadmill ECG, stress myocardial perfusion imaging, or stress echocardiography.[5] However, the value of any additional testing in these low-risk patients has never been shown in a randomized clinical trial. With more

information from additional time and in an outpatient setting, ideally with a physician who knows the patient, it will likely be determined that many patients would not benefit from additional testing and for many of these patients, the pain may have resolved, never to return. Although treadmill testing is generally safe, there can be harms, including risk of MI or arrhythmia as well as the burden of additional time and expense for patients. Additionally, testing often leads to backups in the urgent care areas and stress labs of people waiting for tests they do not need. Patients and their family members may also suffer from anxiety awaiting a test, suffering from a prolonged hospitalization, and from false positive test results. Indeed, accumulating evidence examining variation in use of stress imaging and the results of these tests suggests that we are performing them in many low-risk patients who may not be deriving benefit.[6-7]

Variation is often a marker for overuse of procedures. A study of 549,078 patients with suspected ischemia seen in emergency departments, observation units, or inpatient wards who had received at least 1 cardiac biomarker test and had either a principal discharge diagnosis code for chest discomfort, a sign or symptom of cardiac ischemia, and/or a comorbidity associated with coronary artery disease found hospital-level variation in the use of noninvasive stress imaging, from 6.0% in the lowest quartile to 34.8% in the highest quartile.[6] Patients at hospitals in the highest quartile of stress imaging had higher rates of admissions and coronary angiography, but readmission rates for acute MI were not statistically different. This finding suggests that stress imaging is being used by some hospitals in patients who may not benefit in preventing MI,[8] and being admitted or observed for chest pain in the hospital increasing the chance of getting stress imaging without any benefit on outcomes.[9]

The use of stress imaging in low-risk patients has been increasing, despite the lack of evidence to show benefit. A registry of 39,515 single positron emission computed tomography – myocardial perfusion imaging (SPECT-MPI) studies at Cedars-Sinai Medical Center showed that in 1991, 40.9% of SPECT studies were abnormal but by 2009, only 8.7% were abnormal.[7] Similarly, SPECT-MPI studies showing ischemia declined from 29.6% in 1991 to 5.0% in 2009. As expected, patients with typical anginal symptoms were most likely to have abnormal SPECT-MPI studies. One likely explanation is that low-risk patients – who are unlikely to have ischemia – are more often referred for stress imaging studies.

These risks mean that we must consider if there is any benefit to testing low-risk patients with chest pain. Unfortunately, no definitive randomized clinical trials are available, as studies that have tested diagnostic strategies for patients with chest pain have lacked an arm where patients do not receive testing. Fortunately, three recent studies have examined clinical outcomes from stress imaging tests for low-risk patients presenting with chest pain to the emergency department who receive any test (generally stress imaging) as opposed to no test; their findings are important to inform the balance of risks with possible benefits.

First, a study examined the comparative effectiveness of testing strategies in 693,212 privately insured emergency department patients with chest pain who did not have an MI within the first 24 hours.[8] There was an overall very low rate of MI at 7 days (0.11%) and 190 days (0.33%) in entire cohort. Patients receiving any stress testing or coronary computed tomography angiography (CCTA) compared to those receiving no resting had no difference in MI rates at both time periods. Compared with no testing, though, all testing modalities except stress echocardiography increased the odds of coronary angiography and revascularization.

Second, a study examined outcomes in 926,000 adults aged 18 to 64 years who presented to the ED with chest pain but without acute ischemia.[9] The authors performed an instrumental variable analysis, comparing patients presenting between Monday to Thursday with those presenting Friday to Sunday. As expected based on resource availability during the work week, patients who presented in the former group were more likely to receive cardiovascular testing within 2 or 30 days (18.2% and 26.1%, respectively) compared to patients in the latter group (12.3% and 21.4%, respectively) even though there was minimal difference in risk factors between the two groups. Stress testing within 2 days was associated with a significant increase in coronary revascularization, but no difference in acute MI admissions. Similarly, stress testing was associated with an increase in coronary angiography and revascularization at 1 year, but again, no significant change in acute MI admissions. No subgroups had a reduction in acute MI admissions.

Third, the prospective experience of 619 consecutive low-risk patients who presented to a single academic medical center over a 2-year period is informative about what outcomes may be expected for low-risk patients in chest pain units.[10] An internal medicine physician determined if patients were referred for testing and, if so, the type of test. In total, 46% of patients were discharged without any test. There were no major adverse cardiac events at 30 days in any patients; at 6 months, there was no significant difference in the incidence of major adverse cardiac events (1.1% overall) between patients who received a test and those who did not receive a test. These findings suggest that clinician discretion can reduce unnecessary testing, without adverse outcomes for patients.

These studies provide important, helpful data showing a lack of benefit to routine testing of low-risk patients who present with chest pain. The assumption that a test must be performed is

unproven and probably unwarranted. Ultimately, to provide definitive evidence, we need an RCT of testing versus no testing that is powered to clinical cardiovascular outcomes and mortality. [11-12]

Until such data are generated, how can we achieve higher value care for low-risk patients who present with chest pain? A potential path forward was demonstrated by a pragmatic clinical trial conducted at six United States emergency departments that included 898 patients with chest pain who were being considered for admission for cardiac testing.[13] All patients were low-risk, as defined by no known history of CAD and initial negative ECG and troponin results. Patients were randomized to the use of a decision aid (which described their risk of acute coronary syndrome within 45 days) to facilitate shared decision making or to usual care. Patients randomized to the decision aid were less likely to opt for admission for cardiac testing (37% vs 52%, $p<0.001$) and undergo cardiac testing within 30 days (38% vs 46%, $p=0.01$). Ultimately, there were 25.8 fewer advanced imaging tests per 100 patients.[14] There were no major adverse cardiac events due to the intervention.[15] There were benefits as well: patients randomized to the decision aid arm had higher knowledge of their risk of acute coronary syndrome and were more engaged in the decision-making process. More than 62% of clinicians stated that they would recommend the decision aid to others, and the mean length of discussion between clinicians and patients was only 1.3 minutes longer. The findings from this RCT suggest that patients can make an informed decision with their clinicians about whether and when to pursue stress testing – including stress imaging – and that patients will more often avoid cardiac testing without any adverse clinical consequences.

In summary, low-risk patients with chest pain who have non-ischemic ECGs and negative troponins are unlikely to benefit from stress imaging studies but are subject to harms, including

radiation and further downstream testing and treatments. Randomized data comparing testing to no testing in these patients are needed to better inform clinical management strategies.

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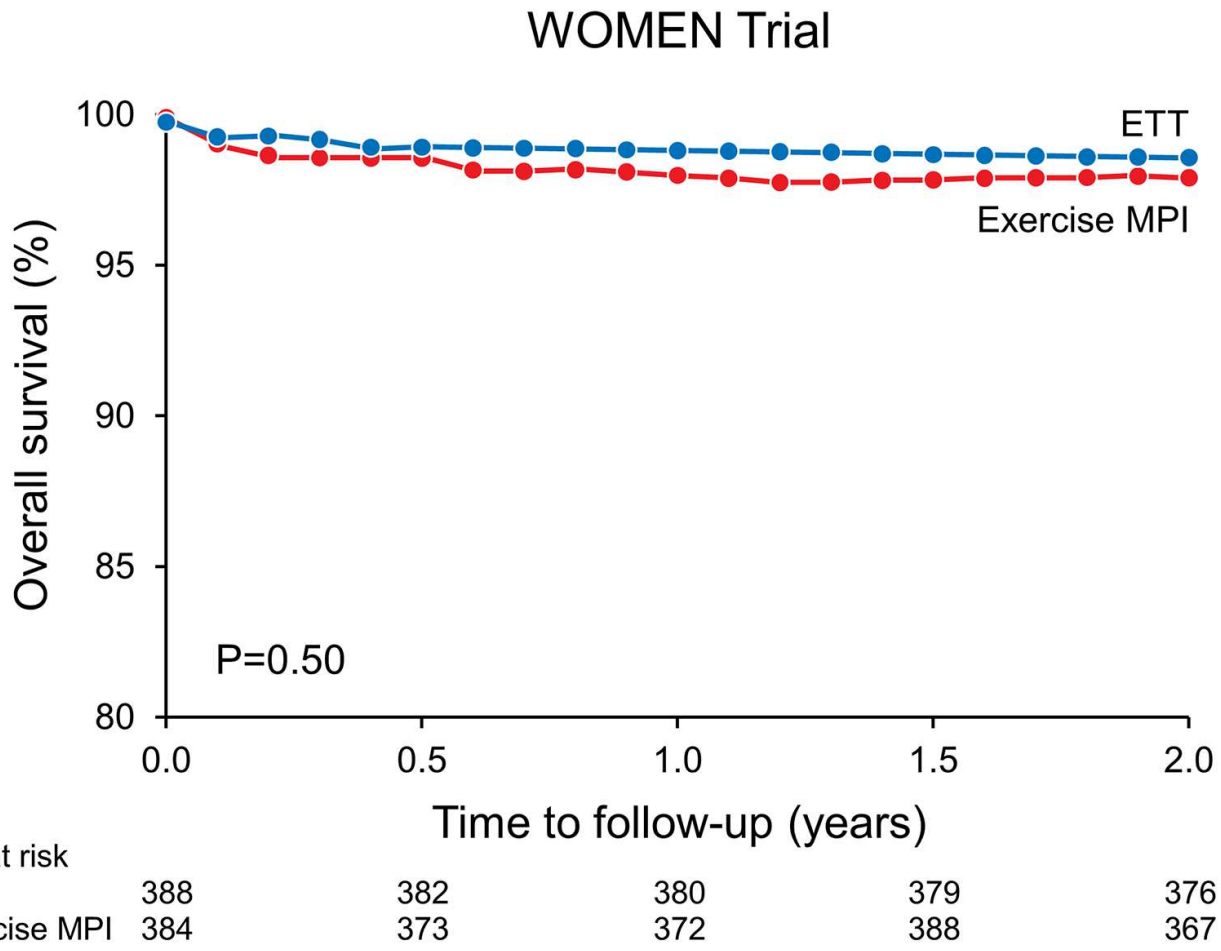
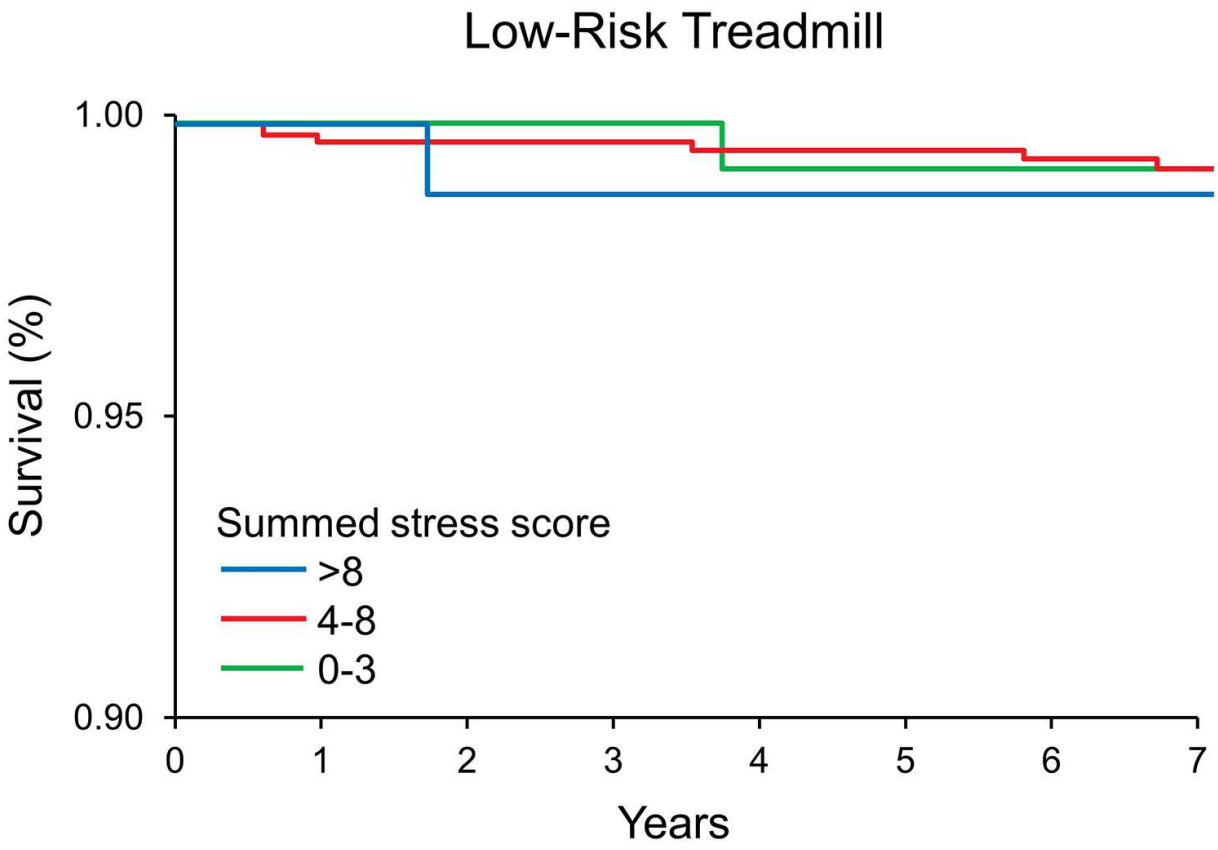


No. at risk					
ETT	388	382	380	379	376
Exercise MPI	384	373	372	388	367


Low-Risk Treadmill
1.00
0.95
0.90
Survival (%)
Summed stress score
>8
4-8
0-3
0
1
2
3
4
5
6
7
Years