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Value of Exercise Stress Electrocardiography for Risk Stratification in Patients With Suspected or Known Coronary Artery Disease in the Era of Advanced Imaging Technologies

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Abstract

Exercise stress electrocardiography (ExECG) is underutilized as the initial test modality in patients with interpretable electrocardiograms able to exercise. Although, stress myocardial imaging techniques provide valuable diagnostic and prognostic information, variables derived from ExECG can yield substantial data for risk stratification, either supplementary to imaging variables, or without concurrent imaging. In addition to exercise-induced ischemic ST depression, such markers as ST segment elevation in lead AVR, abnormal heart rate recovery post-exercise, failure to achieve target heart rate, and poor exercise capacity improve risk stratification of ExECG. For example, patients achieving 10 METS on ExECG have a very low prevalence of inducible ischemia and an excellent prognosis. In contrast, cardiac imaging techniques add diagnostic and prognostic value in higher risk populations (e.g. poor functional capacity, diabetes, chronic kidney disease). Optimal test selection for symptomatic patients with suspected coronary artery disease requires a patient-centered approach factoring in the risk/benefit ratio and cost-effectiveness.

Introduction

Despite considerable improvements in the identification and treatment of coronary artery disease (CAD), this condition remains highly morbid and the most common cause of death in the Western world.(1) Concomitantly, the number of noninvasive radionuclide and echocardiographic imaging studies performed to identify ischemic heart disease has grown considerably. More than 9 million myocardial perfusion imaging (MPI) studies were performed in 2008, at a cost of greater than \$1 billion, with the added risk of radiation exposure.(2,3)

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The latest ACC-AHA guidelines on exercise testing, diagnosis and management of stable ischemic heart disease and ACC-AHA appropriate use criteria for cardiac radionuclide imaging recommend exercise stress electrocardiography (ExECG) as the initial diagnostic test in patients at intermediate pretest risk who are able to exercise and have an interpretable resting electrocardiogram.(4-6) Despite these recommendations, the majority of patients still undergo stress imaging as the initial testing strategy. In the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial, examining the comparative effectiveness of an anatomical versus functional testing approach to evaluate symptoms concerning for ischemia at leading academic medical centers, 89.8% of those undergoing stress testing had imaging performed.(7) A broader administrative database found a similarly high 75% rate of imaging performed with stress testing.(8) This finding is stable over time and likely occurs due to a widespread perception that ExECG alone has insufficient diagnostic accuracy for CAD detection.(9)

As many as 60-70% of MPI studies ordered for CAD detection are normal.(10,11) Advanced imaging modalities, such as positron emission tomography (PET) and cardiovascular magnetic resonance (CMR) MPI, and improved SPECT hardware and protocols can increase the diagnostic accuracy of stress imaging with a reduction in radiation exposure. This shifts the pendulum toward the performance of stress MPI. On the other hand, the rationale for using ExECG alone as the initial test for CAD detection, particularly in patients with good exercise tolerance, has become more compelling with new data published in the literature.(12,13)

This review will summarize the latest advances in ExECG and explore its application in the era of advanced imaging technologies. We will show that this diagnostic testing modality should still play a major role in the noninvasive evaluation of patients with symptoms of suspected ischemic CAD.

Diagnostic and Prognostic Value of Exercise ST Changes

A meta-analysis of 24,047 patients in 147 studies found ExECG to have a pooled sensitivity of 68% and specificity of 77% for detection of CAD.(14) Restricting the analysis to the 3 studies free of workup bias lowered sensitivity considerably to 50% and increased the specificity to 90%.(6) ExECG has a positive likelihood ratio (LR) of 2.18 and a negative LR of 0.32 for CAD.(15) Confounders such as resting ST-depression, digoxin usage, and left ventricular hypertrophy with repolarization changes decrease specificity, while mild single vessel disease decreases sensitivity. Despite these confounders, ExECG is still considered diagnostic in most patients able to reach 85% of their maximum age-predicted heart rate.

Exercise-induced ST depression is also a powerful predictor of cardiac events. Two landmark studies of large, predominately male populations, found the presence and extent of ST depression to be a powerful prognostic marker. In the Duke study of 2,842 patients, the maximum ST deviation was the strongest predictor of both cardiac death and a composite of cardiac death and nonfatal MI.(16) A Coronary Artery Surgery Study (CASS) database analysis by Weiner et al. found the extent of ST depression to be one of the two most powerful prognostic markers on exercise testing, along with the duration of exercise.(17)

Patients who could reach stage 3 of the Bruce protocol with <1mm ST depression had a yearly mortality rate of <1%. In contrast, patients with 1mm ST depression who were unable to complete stage 1 of the Bruce protocol had a 5% yearly mortality rate.

Additional Tools to Increase Diagnostic and Prognostic Utility

Exercise Capacity

There are many additional variables that supplement ST depression and add to the diagnostic and prognostic utility of ExECG. The most powerful of these is exercise capacity.

Multiple studies have correlated exercise workload to the likelihood of significant myocardial ischemia on MPI and subsequent events. Bourque et al. found that patients attaining <7 METS had an 18-fold higher prevalence of substantial (10%) left ventricular (LV) ischemia compared with those reaching 10 METS. The latter group with good exercise tolerance had a very low (0.4%) prevalence of 10% LV ischemia (Figure 1).(18) A follow-up analysis of the cohort reaching 10-METS revealed very low rates of cardiac death (0.1%/year) and nonfatal MI (0.7%/year).(19) The favorable diagnostic and prognostic impact of achieving a high exercise workload has been confirmed in multiple subsequent studies, including a Canadian cohort of 9,605 patients, and an analysis using patients who underwent exercise echocardiography.(20,21) In the Canadian population, there was a 1% risk of 10% LV ischemia and a death or MI rate <2% even in those with 5% LV ischemia. Some studies have shown exercise echocardiography and MPI to retain prognostic significance after accounting for workload.(22,23) The degree of benefit and whether improved diagnostic accuracy and prognostic assessment warrant routine imaging are key issues. Patients with prior MI might be one subgroup that benefits.(22)

Prior studies have shown similar prognostic utility using exercise capacity as a continuous variable. The value of exercise capacity is consistent in both those with and without known CAD.(17,24) In a cohort of 3,400 patients who underwent thallium-201 MPI, exercise capacity was even a stronger predictor of mortality than the extent of perfusion defects. High exercise workload is also a marker of a decreased risk of cardiac events, including cardiac death, nonfatal MI, and coronary revascularization.(19,25-27) These associations remain even in the setting of ischemic ST depression.

Other surrogates of exercise capacity have diagnostic and prognostic value, such as the rate-pressure product (RPP), which predicts the probability of three-vessel or left main CAD.(28) Composite clinical scores, such as the Duke Treadmill Score (DTS), provide added prognostic information by combining multiple predictors into one measure. The DTS incorporates exercise duration, exercise-induced ST changes, and stress-induced angina.(16) It is a strong indicator of any and multivessel obstructive disease and mortality (Figure 2). The DTS is most useful when it falls in the high- and low-risk groups. Myocardial perfusion imaging (MPI) is useful in risk stratifying patients with an intermediate DTS.(29)

Stress Electrocardiographic Findings Beyond ST Depression

Markers other than exercise-induced ST depression have diagnostic and prognostic value, such as the rapidity of recovery of ST segment changes.(30,31) Christman et al. found a low

2% rate of positive imaging or findings of CAD on angiography and a 0.7% rate of a composite endpoint of cardiovascular death, nonfatal MI, or coronary revascularization in patients with a positive exercise treadmill test but rapid ST segment recovery (Figure 3).(30) Other potential enhancements to the standard dichotomous presence of 1mm ST depression include heart rate adjustment in the form of the ST/HR slope and ST/HR index.

Lead AVR is often neglected in ExECG interpretation but has unique vector positioning. This allows it to function as a “pseudo-intracavitary” lead that may identify anterior wall transmural ischemia.(32) Uthamalingam et al. found 1mm AVR elevation during ExECG to be the strongest predictor of an obstructive left main or ostial left anterior descending (LAD) artery stenosis with a diagnostic accuracy of 80% and a 2.6-fold increase in post-test probability.(33) A major limitation of the current AVR data is the absence of studies examining imaging findings and events in the general population not undergoing invasive angiography.

Other suggested measurements on standard ExECG that may have diagnostic value include changes in QRS duration, R-wave amplitude, and length of the rate adjusted QT-interval. (34) A novel marker not routinely available but with substantial potential as a useful adjunct to ST depression is high-frequency mid-QRS (HF-QRS) analysis, an interrogation of the signal in the 150-250 Hz frequency (Figure 4). An abnormal HF-QRS signal increases the sensitivity of ischemia detection from 39% to 69% ($p<0.005$) and the specificity from 82% to 86% ($p<0.05$). (35) This promising tool requires additional validation in independent cohorts and with assessment of cardiac events before it can be routinely applied in clinical practice.

Physiologic Markers and Symptoms

Several physiologic markers during stress testing can augment the diagnostic accuracy of ExECG and have prognostic importance. These includes the heart rate and blood pressure responses to exercise, and symptoms during testing.(36)

An impaired chronotropic response has been associated with a >2-fold increase in perfusion defects and a higher risk of CAD and cardiac events.(37,38) Heart rate recovery post-exercise also carries significant diagnostic and prognostic power. Cole et al. found a relative risk of death of 2.0 (1.5-2.7, $p<0.001$) for those with a <12 bpm heart rate drop 1 minute post-exercise after risk-factor adjustment in 2,428 patients.(39) A retrospective analysis of 2,193 men found a heart rate recovery <22bpm at 2 minutes to be predictive of mortality and the presence of CAD.(40) Heart rate recovery retains its prognostic influence in patients with known CAD.(41)

Changes in blood pressure response during ExECG are also potential indicators of CAD, although less validated than changes in heart rate. The systolic blood pressure (SBP) typically decreases at least 15% by 3 minutes post-exercise. An abnormal SBP recovery ratio of >0.9 (SBP at 3 minutes/SBP at peak exercise) has been found to have comparable diagnostic accuracy to ST depression and incremental value for the identification of CAD. (42) This same ratio correlates with the extent and severity of thallium-201 perfusion defects.(43) A >10mmHg SBP drop during exercise and a delayed decline in SBP after

exercise have been associated with high-risk multi-vessel or left main disease in men with less specificity in women.(44-46)

Treadmill-induced typical angina increases the sensitivity for the diagnosis of CAD and indicates more extensive myocardial ischemia and higher event rates, particularly in the setting of ischemic ST depression.(47-49) The risk of events is substantially higher when symptoms are induced at a lower workload.(47)

Special Populations

Women

The pioneering work on ExECG was done in predominately male populations. Although the prevalence of CAD is less than in men, the mortality from CAD in women is higher.(49,50) There are unique challenges in the female population, as women often present with more atypical symptoms at an older age.(51) Moreover, the diagnostic accuracy of ExECG is lower in women. The pooled sensitivity and specificity in 3,721 women from 19 studies were 61% and 70%, respectively, compared with 68% and 77% in men.(14,52) The decreased specificity of ST depression in women is thought to be partially due to a digoxin-like estrogen effect, lower ECG voltage, and an increased prevalence of baseline ST-T changes.(50,51,53,54)

The lower prevalence of CAD in women decreases the positive predictive value of a positive test compared with men.(50) Barolsky et al. found the positive predictive value in women to be 47% compared with 77% in men; the negative predictive value was not significantly different (78% for women versus 81%).(55) Therefore, although an abnormal test result in women has a higher likelihood of being falsely positive, a negative study is equally effective at ruling out disease. Due to this high negative predictive value, existing guidelines recommend ExECG as the initial study of choice in women at intermediate risk for CAD who are able to exercise.(6,50)

As with men, ExECG has significant prognostic value in women, especially when combined with additional variables such as exercise capacity and heart rate recovery. Exercise capacity is more predictive of mortality in men (hazard ratio 2.89 in men, 0.99 in women). Nevertheless, the Duke Treadmill Score (DTS) has preserved diagnostic and prognostic power in women.(51) Chronotropic incompetence has a stronger relationship with MI in women (HR 2.79 versus 1.29).(56) In asymptomatic women, ST segment depression has not been found to be predictive of cardiac or all-cause mortality.(57)

Many clinicians refer women directly to MPI due to concern about ExECG accuracy. This argument was refuted by the WOMEN trial, in which 824 symptomatic women with good exercise tolerance were randomized to ExECG with or without MPI. The group without MPI had a 48% diagnostic cost savings with no difference in major adverse cardiac events over 2 years of follow-up.(58) This study supports a strategy of ExECG as the initial form of ischemia evaluation in women able to exercise with an interpretable ECG, as recommended for men.

Diabetes Mellitus

Patients with diabetes mellitus are an important subpopulation of those undergoing stress testing. The presence and severity of CAD are greater in patients with diabetes, and the prevalence of this comorbidity is rapidly increasing.(59) Diabetic patients are particularly challenging because they often present with atypical symptoms, and there is a high prevalence of silent ischemia in asymptomatic patients.(60) These factors have led to a high rate of stress testing in patients with diabetes.

ExECG appears to have similar diagnostic accuracy and prognostic significance in patients with and without diabetes.(59,61) However, imaging has typically been performed in this subpopulation, and historical rates of SPECT abnormalities as high as 47-59.5% have supported this practice.(62,63)

However, the prevalence of ischemia and risk of future cardiac events may be decreasing with contemporary aggressive medical therapy in diabetic patients. A recent study of predominately-symptomatic stable outpatient diabetic patients found a 21.8% risk of any ischemia, a lower than expected 5.0% prevalence of 10% LV ischemia, and a low rate of cardiac death/nonfatal MI (0.6%/year), especially given 40.3% had known CAD.(64) Diabetic patients who achieve higher workloads on ExECG (5 METS in Padala et al., 10 METS in Bourque et al.) in contemporary cohorts have a low risk of future cardiac events similar to non-diabetic patients (Figure 5).(18,65)

Advanced imaging modalities can provide additional risk stratification in the diabetic population. The presence of a non-zero computed tomographic (CT) coronary calcium score, unrecognized myocardial scar by CMR, and reduced flow reserve by PET MPI all identify an increased risk of cardiac events.(66-69) Whether these patients should have more aggressive treatment goals remains to be determined.

Given these complex factors, the decision of whether to image patients with diabetes must be individualized. Diabetic patients with good functional capacity who are deemed able to achieve a high exercise workload may receive sufficient risk stratification with ExECG alone. However, for higher-risk patients with diabetes, such as those with poor exercise tolerance, LV dysfunction, nephropathy, vascular disease, or an abnormal resting ECG, and in those in whom microvascular disease is suspected, implementation of cardiac imaging may significantly aid in risk stratification.

Elderly

Age is not a consideration in the recommendation for ExECG in the current guidelines on exercise testing.(6) However, functional limitations and comorbidities in the elderly lead to a higher rate of necessary conversion to pharmacologic stress imaging. Moreover, the elderly are not well represented in studies examining the diagnostic and prognostic value of ExECG. They are an important subgroup given their higher prevalence of CAD and cardiac events.

Studies that have been performed in the elderly confirm the prognostic importance of exercise capacity.(70,71) However, ST depression did not predict cardiac events in a cohort of 514 elderly patients 65 years of age; the DTS did not have prognostic benefit in another elderly cohort.(70,72) However, SPECT perfusion defects were associated with cardiac death in the same elderly cohort.(73) Abnormal SPECT imaging also predicts nonfatal MI and coronary revascularization in the elderly.(71,74,75) These findings suggest that imaging should be considered in the initial workup to detect CAD in the elderly.

Advances in imaging technology have a substantial impact in the elderly population. Given the lower lifetime attributable risk of cancer in older patients, reductions in radiation are less of an issue, though still beneficial.(76) The shortened protocols possible with PET imaging and newer SPECT cameras can be helpful in this cohort with a higher likelihood of musculoskeletal pain and other mechanical limitations that complicate long table times. Sufficient levels of stress are less likely in the elderly due to decreases in exercise capacity and a higher potential for chronotropic incompetence. Combined protocols can ameliorate this issue, facilitating the collection of exercise data followed by vasodilator administration to ensure a diagnostic test.

Baseline ECG Abnormalities

Several baseline ECG abnormalities affect the test characteristics of ExECG. In a cohort of 1,282 patients referred for chest pain evaluation, resting ST depression <1mm increased the sensitivity of ExECG from 45% to 77% but decreased specificity from 84% to 48% with no change in overall diagnostic accuracy (6,77)

Patients with left bundle-branch block (LBBB) require imaging due to a high false-positive rate.(78,79) The role of ExECG in the setting of right bundle-branch block (RBBB) is less clear. ST changes in the anterior precordial leads have a false-positive rate of 66%, but specificity is preserved in leads V5 and V6.(80) Yen et al. found a decreased sensitivity of 27% but a preserved specificity of 87% using leads V5 and V6 in 133 patients, the largest cohort studied with RBBB.(81) Susmano, on the other hand, showed an excellent sensitivity of 89%, though only 12 patients were analyzed.(82) The ACC-AHA exercise testing guidelines support the use of ExECG in RBBB.(6)

Importance of Reaching 85% Maximum Age-Predicted Heart Rate

Given the late occurrence of ECG changes in the ischemic cascade and known limited sensitivity of ExECG, reaching an adequate level of workload and heart rate is essential. Heller et al. found that reaching only 70% compared with 85% of maximum age-predicted heart rate (MAPHR), leads to a reduction in the incidence of stress defects from 100% to 47% and a reduction in angina from 84% to 26%.(83) Subsequent studies in patients not achieving target heart rates have found reductions in the degree and extent of ischemia on MPI, with decreases seen irrespective of the number of diseased vessels.(84,85) Combination protocols with vasodilator administration in those unable to achieve sufficient exercise workload substantially improve the diagnosis of ischemia and are safe and feasible. (86,87) In one study of symptomatic patients, receiving a combination protocol increased ischemic segments from 7 to 40.(88)

Patient-Centered Approach to Ischemia Evaluation

Advances in imaging technology have created a broad menu of options for the evaluation of ischemic heart disease that facilitate a patient-centered approach to ischemia evaluation.⁽⁸⁹⁾ Patient symptoms, comorbidities, and functional status are used to identify which array of appropriate tests are considered. Patients are referred for the test that provides the most clinically meaningful information with the least risk, cost, and inconvenience.

In many patients, adequate risk stratification is achieved with a simple strategy of ExECG without imaging. A study of the yield of downstream testing and subsequent cardiac events in 3,656 patients undergoing ExECG found low rates of referral to MPI (9.0%) and invasive angiography (2.3%).⁽³⁰⁾ Over a 2.5-year mean follow-up, the rate of cardiac death, nonfatal MI, and coronary revascularization was very low in those with negative (0.2%) and inconclusive (1.3%) stress studies. A large administrative database found a similarly low 6.9% rate of invasive angiography at one year. In the functional testing subgroup of the PROMISE trial, those who underwent stress electrocardiography had a similarly low rate of the combined endpoint of adverse cardiac outcomes as those who underwent imaging.⁽⁷⁾ These data support an initial strategy of ExECG alone in appropriate patients.

Stress myocardial perfusion imaging (MPI) provides minimal incremental value in patients with a low-risk exercise stress test, a low-risk Duke Treadmill Score, or a high rate-pressure product without ST-segment depression.^(18,28,90,91) In addition, the low cardiac event rates in stable patients treated medically in recent landmark studies such as COURAGE and BARI-2D have challenged the paradigm of selecting coronary revascularization as the initial therapeutic strategy, potentially reducing the need for identification of low-levels of ischemia.^(92,93)

However, despite the low risk of events with negative ExECG, there continues to be widespread use of concurrent imaging.⁽⁹⁾ Novel protocols that add additional testing in specific higher risk situations may encourage a strategy of ExECG alone.

Novel Protocols

Two novel protocols that refine ExECG and reduce the likelihood of missing significant ischemia are the use of provisional MPI in patients unable to achieve a high exercise workload and the incorporation of coronary calcium scoring. Given the low prevalence of significant ischemia and cardiac events in patients able to achieve 10-METS, Duvall et al. reviewed a hypothetical protocol where MPI would not be performed in patients <65 years of age with no known CAD and an interpretable rest ECG who achieved a diagnostic heart rate and 10-METS without significant exercise-induced ECG changes or symptoms.⁽⁹⁴⁾ In this low-risk subset, there was a very low rate of significant (10%) LV ischemia (0.6%/year), 5.9% abnormal studies, and a 98.9% 5-year survival, comparable to the favorable survival after negative MPI. Limitations of this provisional MPI testing approach include the low number of patients able to avoid imaging (29% in this study), test supervision issues, patient and physician support, and incompatibility with the current insurance payment models.⁽⁹⁵⁾ Further refinement of this concept is necessary before it will be ready for adoption.

An additional method of improving the diagnostic accuracy of ExECG is to add coronary calcium scoring under certain higher risk circumstances, such as in patients with particularly high pretest risk, those with a suspected false positive ST segment response, or patients with typical angina and negative ExECG. A coronary calcium score >0 has 98% sensitivity for coronary atherosclerosis, reducing the likelihood of a false negative evaluation.⁽⁹⁶⁾ Identification of non-obstructive CAD can also guide the intensity of medical therapy.⁽⁹⁷⁾ Rozanski et al. showed a low risk of inducible ischemia in patients with low to intermediate pretest probability of disease and a coronary calcium score <400 .⁽⁹⁸⁾ This approach may be especially useful if combined with exercise workload. The demonstration of a 0 coronary calcium score in higher risk patients able to achieve 10-METS with negative ExECG would provide further evidence of low posttest risk of significant CAD, thereby eliminating the need for more costly downstream imaging. (Central Illustration). The optimal protocols to most effectively integrate coronary calcium scoring have not been developed and would need additional study with outcomes assessment prior to widespread adoption.

Conclusions

The studies cited in this review strongly suggest that ExECG remains the recommended method of initial evaluation in intermediate-risk patients with symptoms consistent with CAD. This approach is supported by a large and growing number of supplementary variables, such as exercise workload achieved and ECG changes beyond ST depression, that improve diagnostic accuracy and provide incremental prognostic information. Moreover, there is increasing evidence in the literature suggesting that revascularization may only be beneficial in patients with high levels of ischemia.^(92,99) At the same time, advances in imaging technology have improved diagnostic accuracy while decreasing test duration and radiation exposure, thereby shifting the risk/benefit ratio towards imaging in higher risk patients who cannot achieve a high workload or attain their target heart rate on ExECG.

A stress test selection and performance algorithm is provided in the Central Illustration that incorporates myocardial imaging in select patients with special clinical needs, provisional imaging in patients unable to achieve a high workload, calcium scoring as further evaluation after unexpected negative results, and adjunctive pharmacologic stress in those unable to achieve diagnostic heart rates. Novel imaging protocols and optimal patient selection may assist with appropriate utilization of cardiac imaging technologies, when necessary, to complement ExECG. Application of an algorithm such as this could result in substantial savings to the health care system without reducing the quality of care. Additional research with prospective outcome studies is needed to refine these approaches.

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Abbreviations

CAD	coronary artery disease
CT	computed tomography
DTS	Duke Treadmill score
ECG	electrocardiogram
ExECG	exercise stress electrocardiography
LV	left ventricular
MAPHR	maximum age-predicted heart rate
METS	metabolic equivalents
MPI	myocardial perfusion imaging
PET	positron emission tomography
SPECT	single photon-emission computed tomography

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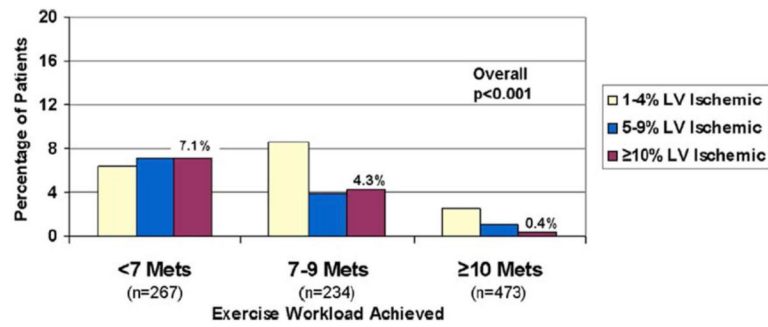


Figure 1. Prevalence of increasing percentages of left ventricular ischemia stratified by exercise workload in patients undergoing exercise stress electrocardiography

There was a significant decrease in prevalence of ischemia as the workload achieved increased. LV= left ventricular; METS=metabolic equivalents. With permission from Bourque et al.(18)

$$\text{Duke Treadmill Score} = \text{Exercise Duration (min)} - 5 \left(\frac{\text{ST Deviation (mm)}}{1} \right) - 4 \left(\frac{\text{Angina Index}}{1} \right)$$

Angina Index

0 – none, 1 – typical angina, 2 – angina causing test cessation

Score	Risk Group	Stenosis ≥75%	Multivessel Disease	1-Year Mortality
≥5	Low	40.1%	23.7%	0.25%
-10 to 4	Intermediate	67.3%	55.0%	1.25%
≤-11	High	99.6%	93.7%	5.25%

Figure 2. Duke Treadmill Score calculation and utility

Equation for calculation of the Duke Treadmill Score and division into low, intermediate, and high risk groups based on likelihood of having a stenosis ≥75%, multivessel disease, and 1-year all-cause mortality. Adapted from Mark et al.(16,100) and Shaw et al.(101).

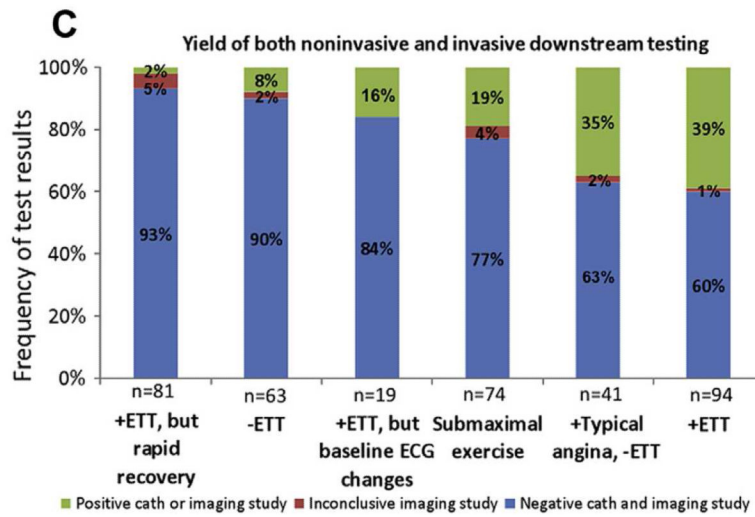


Figure 3. Frequency of positive downstream imaging and invasive angiography by stress electrocardiographic findings

ECG=electrocardiographic; ETT=exercise treadmill testing. With permission from Christman et al.(30)

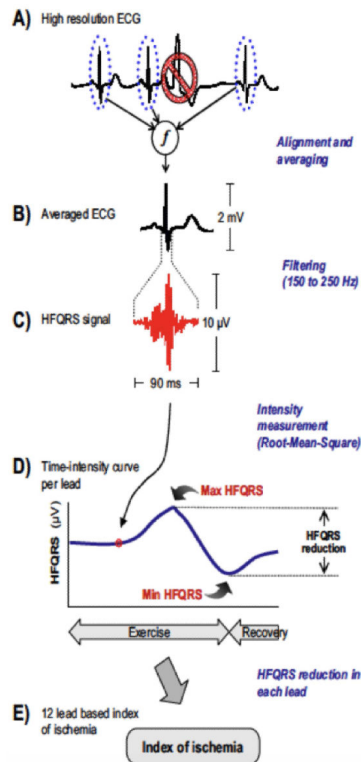


Figure 4. High frequency QRS analysis (HF-QRS)

Multiple representative QRS complexes are aligned and averaged. The signal in the 150-250 Hz frequency band is measured in each of the standard 12 leads, and a time intensity curve is generated. A decrease in the HF-QRS signal that is both 50% and $1\mu\text{V}$ in 3 or more leads is concerning for ischemia. ECG=electrocardiogram. With permission from Sharir et al. (35)

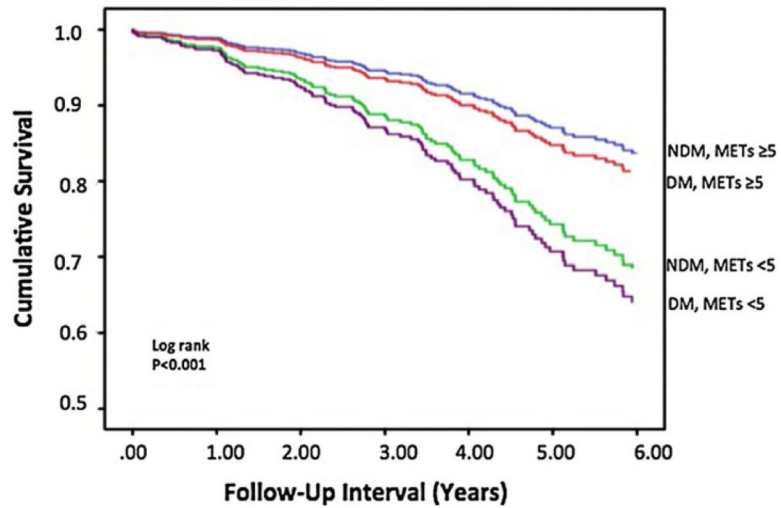
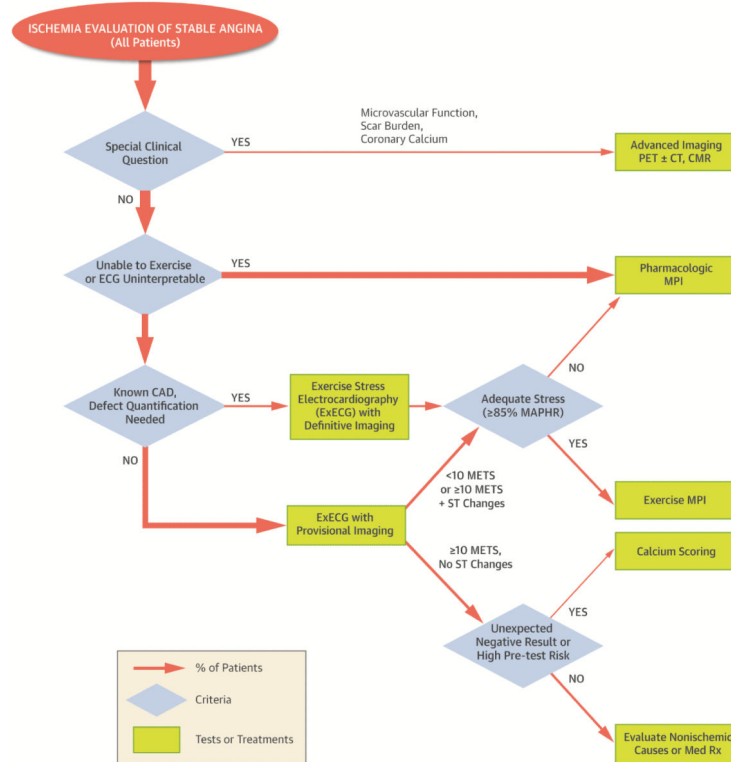


Figure 5. Survival by diabetes status and stress exercise workload achieved

Patients able to achieve ≥ 5 METS of exercise workload have a similar survival irrespective of diabetes status. DM=diabetes mellitus; METS=metabolic equivalents; NDM=no diabetes mellitus. With permission from Padala et al.(65)



Central Illustration. Stress test selection and performance algorithm

Higher risk patients with unique clinical needs, such as assessment of microvascular function, can receive advanced ischemia imaging. In the remainder, those unable to exercise or with an uninterpretable ECG receive pharmacologic MPI. Patients able to exercise with known CAD in whom defect quantification is needed undergo exercise stress MPI. If they do not achieve 85% MAPHR, they receive pharmacologic MPI under a combined protocol. All others undergo ExECG with provisional imaging. If they achieve ≥ 10 METS and have no ST changes, they undergo evaluation for nonischemic chest pain or receive medical therapy. Unexpected negative results in patients with high pre-test risk can trigger calcium scoring for additional risk stratification. All others undergo exercise MPI or a combined protocol with pharmacologic stress if they are unable to achieve an adequate exercise heart rate ($\geq 85\%$ MAPHR). CAD=coronary artery disease; CMR=cardiac magnetic resonance; CT=computed tomography; ECG=electrocardiogram; ExECG=exercise stress electrocardiography; MAPHR=maximum age-predicted heart rate; METS=metabolic equivalents; MPI=myocardial perfusion imaging; PET=positron emission tomography; Rx=treatment.