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ABSTRACT & COMMENTARY

Where Does Vericiguat Fit into the Heart Failure Medication Algorithm?

By Jamie L. W. Kennedy, MD, FACC

Associate Professor, Division of Cardiology, Advanced Heart Failure & Transplant Cardiology, University of California, San Francisco

Dr. Kennedy reports no financial relationships relevant to this field of study.

SYNOPSIS: Vericiguat reduced cardiovascular death and heart failure hospitalization, although no reduction in overall mortality was observed over a short follow-up period.

SOURCE: Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2020;382:1883-1893.

Cyclic guanosine monophosphate (cGMP) is an intracellular second messenger molecule active in many biochemical pathways throughout the body. In smooth muscle cells, it leads to vasodilation in both the pulmonary and systemic vasculature.

In cardiomyocytes, cGMP prevents maladaptive hypertrophy, protects against ischemia/reperfusion injury, and blunts the effects of catecholamines. cGMP is produced by particulate guanylate cyclase when triggered by natriuretic peptides, and by soluble guanylate cyclase in response to nitric oxide (NO). Sacubitril inhibits neprilysin and increases levels of natriuretic peptides, ultimately increasing intracellular cGMP with beneficial effects in chronic heart failure patients.

Vericiguat also targets the cGMP pathway as a stimulator of soluble guanylate cyclase. Preliminary data revealed beneficial effects in animal models of heart failure and reduction in NT-proBNP in patients with heart failure. VICTORIA was a randomized, double-blind, placebo-controlled trial of vericiguat in patients with recent worsening of chronic systolic heart failure. Enrolled patients were New York Heart Association (NYHA) class II-IV with left ventricular ejection fraction (LVEF) less than 45% and elevated brain natriuretic peptide BNP (300 pg/mL if sinus or 500 pg/mL

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if atrial fibrillation) or NT-proBNP (1,000 pg/mL if sinus or 1,600 pg/mL if atrial fibrillation). Additionally, patients had either been hospitalized for heart failure in the last six months or required intravenous diuretics in the past three months. Unstable patients were excluded, such as patients with systolic blood pressure less than 100 mmHg, intravenous treatment within 24 hours, patients listed at high urgency for heart transplant, and patients awaiting or following left ventricular assist device implantation. Vericiguat is teratogenic; there were strict contraception requirements for women of childbearing potential. Combination treatment with long-acting nitrates or PDE5 inhibitors was not allowed.

Armstrong et al enrolled 5,050 patients, drawn primarily from Eastern Europe (33%) and Asia-Pacific (23%); 11% were North American. The population was otherwise fairly typical for heart failure trials (76% male, mean ejection fraction 29%, and only 1.3% NYHA class IV). On average, patients had been diagnosed with heart failure 4.8 years prior to enrollment. Comorbid conditions were common, including coronary artery disease (58%), atrial fibrillation or flutter (53%), diabetes mellitus (47%), chronic kidney disease stage 3 or worse (53%), and chronic obstructive pulmonary disease (17%). Guideline-directed medical therapy was excellent, with 93% receiving beta-blockers, 70% aldosterone antagonists, 73% angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), and 14.5% angiotensin receptor plus neprilysin inhibitor (ARNI). Overall, 60% were treated with all three medication classes (ACE/ARB/ARNI, beta-blocker, and aldosterone antagonist), 28% had an implantable cardioverter-defibrillator, and 15% had a biventricular pacemaker. Median NT-proBNP was 2,816 pg/mL. Patients started with 2.5 mg daily of vericiguat and titrated up to 10 mg over four weeks, if blood pressure permitted. The median dose achieved was 9.2 mg in both vericiguat and placebo arms.

The primary endpoint was a composite of cardiovascular death or first heart failure hospitalization, which occurred in 35.5% of patients in the vericiguat group and 38.5% in the control group ($P = 0.02$) at a median follow-up of just 10.8 months. Cardiovascular death occurred in 16.4% in the vericiguat group and 17.5% in the control group. First heart failure hospitalization occurred in 27.4% in the vericiguat group and 29.6% in the control group (confidence intervals for both included 1.00). Total heart failure hospitalizations were lower in the treatment arm (38.3 vs. 42.4 per 100 patient-years; $P = 0.02$). Overall mortality was similar between the two groups (20.3% in the vericiguat group and 21.2% in the control group; $P = 0.38$). The results of a subgroup analysis suggested patients with higher NT-proBNP levels did not benefit from vericiguat treatment. Hypotension and syncope were more common in the treatment arm, although the difference was not statistically significant. Anemia also was more common in the treatment arm. Hemoglobin decreased an average of 0.38 with vericiguat vs. 0.14 with placebo. For patients with high-risk heart failure, the authors concluded patients who took vericiguat experienced less cardiovascular death or hospitalization for heart failure vs. those who took placebo.

■ COMMENTARY

The VICTORIA investigators are to be congratulated for enrolling so many patients with severe heart failure, as demonstrated by the advanced NYHA class (41% III or IV), high NT-proBNP levels, and high event rate. Vericiguat was well tolerated in this high-risk population, with most patients achieving the target dose and similar adverse event rates between the treatment and control arms.

For comparison, the PARADIGM-HF authors found the use of sacubitril/valsartan reduced the combined endpoint of cardiovascular death and heart failure hospitalization from 26.5% to 21.8% ($P < 0.001$). With a median follow-up of 27 months, sacubitril/valsartan also led to a significant reduction in overall mortality (19.8% to 17%). The authors of DAPA-HF used a combined primary endpoint of worsening heart failure and cardiovascular death, resulting in an overall mortality reduction from 21.2%

to 16.2% ($P < 0.001$) over 18.2 months. There also was a significant reduction in overall mortality from 13.9% to 11.6%. Finally, the COAPT authors found percutaneous mitral valve repair reduced heart failure hospitalizations from 67.9% to 35.8% over 24 months (the primary endpoint), and also demonstrated mortality reduction from 46.1% to 29.1% (both $P < 0.001$). The slight differences in primary endpoints among these trials does complicate interpretation, but it is noteworthy that VICTORIA did not demonstrate overall reduction in mortality, while PARADIGM-HF, DAPA-HF, and COAPT did. Perhaps this is a reflection of the short duration of follow-up in VICTORIA, and mortality benefit would have been seen over a longer period.

Where does vericiguat fit into the increasingly complex systolic heart failure treatment algorithm? Patients should be optimally medically managed with ACE/ARB/ARNI (preferably ARNI), beta-blockers, and aldosterone antagonists. The CHAMP-HF registry, an outpatient study of U.S. systolic heart failure patients, revealed 22% were prescribed triple therapy. Just 1% were receiving target doses of all three medication classes. There certainly is room for improvement on this front. After achieving maximally tolerated doses of all three of these foundational therapies, I would favor additional treatments with proven mortality benefit, such as dapagliflozin and percutaneous mitral repair in appropriate candidates. Treatment with vericiguat could be considered after that. In my practice, I imagine I will be deciding between vericiguat and hydralazine/isosorbide. In A-HeFT, hydralazine/isosorbide demonstrated mortality benefit in African Americans; this combination may be the better choice in patients who can take it. However, many patients struggle with medication compliance or cannot tolerate hydralazine/isosorbide because of its side effects. In these situations, vericiguat may be a good choice. ■

ABSTRACT & COMMENTARY

Subclinical Leaflet Thrombosis: Not Just a TAVR Phenomenon

By Jeffrey Zimmet, MD, PhD

Associate Professor of Medicine, University of California, San Francisco Director, Cardiac Catheterization Laboratory, San Francisco VA Medical Center

Dr. Zimmet reports no financial relationships relevant to this field of study.

SYNOPSIS: Imaging-defined leaflet thrombosis was common and similar between transcatheter aortic valve replacement and surgical aortic valve replacement bioprosthetic valves. These findings showed no apparent relationship to valve hemodynamics or to clinical outcomes, including stroke.

SOURCE: Blanke P, Leipsic JA, Popma JJ, et al. Bioprosthetic aortic valve leaflet thickening in the Evolut Low Risk Sub-Study. *J Am Coll Cardiol* 2020;75:2430-2442.

The occurrence of subclinical leaflet thrombosis in bioprosthetic aortic valves has been reported for several years, usually characterized by CT scan as hypoattenuated leaflet thickening (HALT) and reduced leaflet motion (RLM). While few of these patients will develop significant valvular dysfunction from leaflet thrombosis, for the remainder the meaning of this phenomenon remains unknown.

The natural history of these abnormalities over time remains unknown, as does the significance of these findings regarding valve durability and risk of outcomes, including stroke. Additionally, although this phenomenon has been described in bioprosthetic valves of all types, most investigations to date have concerned transcatheter aortic valve replacement (TAVR), with no clear answer as to whether the phenomenon is relatively TAVR-specific.

As TAVR has expanded into younger and lower-risk patients, these questions have taken on more importance. As part of the assessment comparing TAVR and surgical aortic valve replacement (SAVR) in low surgical risk patients, the authors of the Evolut Low Risk trial undertook a prespecified substudy to address some of these uncertainties.

Of the 1,403 patients enrolled in the overall trial, 503 were randomized in the substudy, which sought to evaluate HALT and RLM by CT at one-month and one-year post-valve implant. Of these, 375 patients had evaluable CT studies performed within 30 days of the procedure (197 TAVR, 178 SAVR). A few patients (18 TAVR and 39 SAVR) were receiving anticoagulation at the time of the CT, and were excluded from the primary analysis. Among patients who did not receive oral anticoagulation, HALT at

the 30-day CT scan was seen in 31 of 179 TAVR subjects and 23 of 139 SAVR patients (P = 0.856). At the one year, thrombotic findings were seen in a higher proportion of patients, with positive findings in 47 of 152 TAVR patients and 33 of 116 SAVR patients (P = 0.661).

Among TAVR patients, all received the self-expanding supra-annular CoreValve Evolut prosthesis. Smaller annular size (as measured by perimeter) was associated with greater incidence of HALT. However, no procedural characteristics, such as post-dilatation or resheathing/recapture of the valve, were related to HALT frequency. Among SAVR patients, sutureless valve types were associated with greater incidence of HALT.

During the one-year course of the study, valve function was preserved with low transvalvular gradients regardless of the extent of HALT. As in prior studies, surgical valves showed higher mean gradients than TAVR, but did not consistently go up with increasing extent of leaflet thrombosis. Clinical endpoints, including death, stroke, transient ischemic attack (TIA), and myocardial infarction, were extremely low and showed no relationship to the presence or extent of HALT or RLM.

The authors concluded that imaging-defined leaflet thrombosis after bioprosthetic AVR is "frequent but dynamic" in the first year after valve deployment, with no difference between TAVR and SAVR valves. The extent of HALT and RLM did not correlate with hemodynamic status and had no apparent association with clinical outcomes, including stroke and TIA.

■ COMMENTARY

Since its initial description in 2015, the issue of imaging-defined leaflet thrombosis after aortic bioprostheses has represented a problem of uncertain extent and significance. The wide variability in incidence reported in prior studies has, on its own, flummoxed attempts to characterize its effects.

During Evolut Low Risk Substudy, the authors performed CT at two timepoints in the first year and used rigorous imaging criteria to define HALT and RLM in a relatively large cohort. The incidence described here (approximately 16% at 30 days and 30% at one year) likely is accurate for the valve types described in a low-risk population.

The equivalence of thrombotic findings between surgical and transcatheter valves is an interesting finding. Earlier reports, such as the SAVORY study and the RESOLVE registry, had suggested much higher rates of leaflet thrombosis among TAVR valves. This does not appear to be the case, at least among the low-risk patients in this cohort or for the CoreValve platform.

HALT was dynamic over the course of the study. Some patients with HALT at 30 days showed resolution at one year, even without oral anticoagulation, while some without HALT at 30 days showed those findings at one year. This may, in part, explain the large range of leaflet thrombosis reported in earlier studies with less-rigorous imaging timing and image analysis.

The antiplatelet techniques differed between SAVR and TAVR groups. While TAVR patients were treated with one month of dual antiplatelet therapy, followed by aspirin alone, SAVR patients were treated with aspirin only (unless there was another indication for oral anticoagulation). This confirms earlier reports suggesting no effect of dual vs. single antiplatelet therapy on HALT.

The apparent lack of any association between imaging-defined leaflet thrombosis and either early valve dysfunction or major clinical outcomes is unsurprising, considering the positive early clinical results with these valves to date. Whether there will turn out to be a link to longer-term structural valve deterioration, and whether oral anticoagulation will be part of a successful therapeutic strategy, is a question that remains unanswered. ■

ABSTRACT & COMMENTARY

Coronary Calcium to Guide Aspirin Primary Prevention

By Michael H. Crawford, MD, Editor

SYNOPSIS: Researchers analyzed the MESA study to determine the comparative value of the pooled risk equation vs. CT coronary artery calcium score for determining which aspirin-naïve patients < age 70 years without overt coronary artery disease would benefit most from primary prevention with aspirin. They found a calcium score of > 100 was superior for this determination.

SOURCE: Cainzos-Achirica M, Miedema MD, McEvoy JW, et al. Coronary artery calcium for personalized allocation of aspirin in primary prevention of cardiovascular disease in 2019: The MESA study (Multi-Ethnic Study of Atherosclerosis). *Circulation* 2020;141:1541-1553.

The results of recent studies have challenged the relative value of aspirin for primary prevention of cardiovascular disease (CVD) and highlighted the increased risk of bleeding. Guidelines now list aspirin as a class IIb recommendation for primary prevention. However, selecting the right patients for aspirin prophylaxis is unclear.

Investigators from the MESA study sought to assess the potential value of coronary artery calcium (CAC) for guiding aspirin allocation for primary prevention. MESA is an ongoing community-based, multi-ethnic study of 6,814 subjects ≥ age 45 years who were free of overt CVD at entry. After excluding those with missing data, aspirin use at baseline, age > age 70 years, or high bleeding risk 3,540 subjects remained. All of the remaining subjects had a CT-determined CAC score at baseline and data for estimating CVD risk by the pooled cohort equation (PCE). The primary outcomes were coronary heart disease events, stroke, CV death, and major bleeding events. The identification of subjects who could be considered for aspirin therapy was defined as a PCE 10-year risk of CVD > 20%. Overall, 4.9% were in this high-risk category at baseline; 79% were men, and 83% were between age 60 and 69 years. CAC scores were > 100 in 42%, 1-99 in 26%, and zero in 32% of subjects. Only 10% of all the subjects were on statins at baseline. In general, the higher the CAC score, the older the age, the higher the proportion of men, and the higher the PCE risk.

Overall rates per 1,000 patient-years were 3.52 for CVD, 2.34 for coronary heart disease, and 1.34 for major bleeding. The higher the CAC, the higher the risk, with the highest risk observed in those with CAC scores > 100 (12.4 per 1,000 patient-years). Based on previous primary prevention trials with aspirin, a five-year number needed to treat (NNT) to prevent one event and a number needed to harm (NNH; bleeding) was determined. The overall NNT with aspirin was 476, and the NNH was 355. These numbers did not vary much based on the PCE risk score. However, in the CAC score > 100 subgroup, the NNT was lower than NNH (NNT = 140; NNH = 518). In the CAC = 0 subgroup, NNT was much higher than the NNH (1,190 vs. 567). The authors concluded that determining CAC scores may be superior to the PCE for deciding whom to treat with aspirin for primary prevention.

■ COMMENTARY

Using the PCE failed to identify those most likely to benefit from aspirin among the aspirin-naïve subjects < age 70 years at baseline in MESA. In fact, at all PCE 10-year risk strata (< 5%, 5-20%, > 20%), the NNT was equal to or greater than the NNH at five years. On the other hand, CAC score was predictive of who might benefit from aspirin. At a CAC score > 100, the NNT dropped well below the NNH. At a CAC score < 100, the NNT was consistently higher than the NNH.

The estimated efficacy of aspirin for preventing CVD events and risk of bleeding were derived from a meta-analysis that included only studies published after 2000 (statin era) and the excluded patients with peripheral artery disease.

This meta-analysis revealed a relative risk reduction for primary prevention of CVD events of 9% and a relative risk of bleeding of 39%, which clearly did not support aspirin for general primary prevention. These results influenced the new guidelines (i.e., that only in subjects at high risk of CVD and low-bleeding risk should aspirin be considered).

The MESA study participants were a relatively low-risk population (mean age, 50 years; 10% diabetics) and the NNT was relatively high. Even at a CAC score > 400, the NNT was 97. In contrast to the meta-analysis, using a CAC score > 100 to prescribe aspirin improved the relative risk reduction from 9% to 12%, which still is modest.

Although MESA is a multiethnic population, it does not include all ethnicities nor does it mimic the populations of other large studies used to estimate the potential benefits of aspirin. MESA did not assess bleeding risk on the initial visit; this was added later, and it was not designed to capture all bleeding events (only hospital records were used). Subgrouping by statin use was not possible because of low use at baseline in the population. Finally, this was an observational study; as such, it should be considered hypothesis-generating.

For the likely modest net benefit of using aspirin in primary prevention, should a relatively expensive test that involves some radiation exposure be used to decide? It does not seem reasonable right now for general application, but could be valuable in selected subjects, such as those with a bad family history, which is not included in the PCE. Also, bleeding risk rises with the CAC score, so finding equipoise here could be problematic. However, if a CT scan performed for another reason shows calcium in the coronary arteries, we should take that into consideration. ■

ABSTRACT & COMMENTARY

Clinical vs. Genetic Risk for Coronary Disease

By Michael H. Crawford, MD, Editor

SYNOPSIS: A study of the utility of a polygenetic score for coronary artery disease risk was compared to the pooled cohort equation (PCE) for determining which primary prevention patients would benefit from statin use. Only at the top 5% risk stratum did the genetic score exceed an odds ratio for coronary disease of 2. Using these data would increase statin recommendations by 4% vs. the PCE.

SOURCE: Aragam KG, Dobbyn A, Judy R, et al. Limitations of contemporary guidelines for managing patients at high genetic risk of coronary artery disease. *J Am Coll Cardiol* 2020;75:276-280.

Genetic risk prediction is a goal of precision medicine. Polygenomic risk scores (PRS) are available, but their performance in the clinical setting is unclear.

Aragam et al assessed more than 47,000 individuals from three northeastern U.S. medical center biobanks and their linked clinical information. The PRS were normalized for genetic ancestry. Strata, such as 5% or 20% risk for coronary artery disease (CAD), were defined. The pooled cohort equation (PCE) was used to calculate the 10-year risk of CAD based on clinical data. The entire cohort was 54% women, 62% of European ancestry, mean age 60 years, and 23% had CAD.

The PRS for CAD was associated with incident CAD (odds ratio [OR], 1.4), as was high PRS (top 20%; OR, 1.9) and the top 5% (OR, 2.3). Among those without CAD (primary prevention), high PRS did not correlate with guideline recommendations for statin use based on the PCE. Also, if a high PRS was employed as a guideline-enhancing factor, an additional 4% of primary prevention patients would be recommended for statin therapy. The authors concluded the prevention of CAD may be enhanced by considering polygenetic susceptibility to CAD in addition to clinical risk.

■ COMMENTARY

American Heart Association/American College of Cardiology guidelines for blood cholesterol management recommend the consideration of certain risk-enhancing factors not included in the PCE for determining statin therapy eligibility. These include a family history of premature CAD, a high sensitivity C-reactive protein > 2.0 and a lipoprotein(a) > 50. These and other such factors should meet the criteria of an OR > 2.0.

Aragam et al explored whether genetic testing should be added to the list. A propensity to CAD can be the result of a single gene or, more often, polygenetic. The PRS used in this study is based on 6 million common single nucleotide polymorphisms (SNPs) and has been shown to be predictive of CAD in population studies. In previous attempts to define the potential clinical utility of a PRS in primary prevention populations, such as ARIC, MESA, and the UK biobank, a PRS was not found to be superior to the PCE. One reason for the difference may be these studies were more heterogeneous in the subject's ancestry. Most subjects in the Aragam et al study were of European ancestry; the same goes in the studies used to develop the PRS. Thus, it works better in a European population. Aragam et al had to adjust the PRS for patients of non-European origin. Based on these earlier studies, those authors concluded that although the risk OR for a PRS were statistically robust, they were not strong enough to be clinically useful.

Does the Aragam et al study challenge this conclusion? Of 47,000 subjects, 16,000 showed no evidence of vascular disease. Of these, about 6,000 recorded an intermediate PRS, and about 1,000 recorded a PRS risk > 20%. An additional 650 were not on statins. Using the PRS would capture 4% more candidates for statins (650 ÷ 16,000 = 0.041). Also, only the top 5% of PRS scores achieves an OR > 2.0 (2.3, to be precise). The top scorers in the Aragam et al study would be 800 individuals (0.05 × 16,000 = 800). However, the cost of a genetic profile is now < $100, and it only has to be performed once. Perhaps a PRS would be a cost-effective addition to the PCE. But what if we add other measures of risk, such as coronary calcium scores? Then, we drive up the cost.

There were limitations to the study. The data for the PCE were pulled from charts and could be inaccurate. The data were limited to three health centers with fairly homogeneous European ancestry populations. However, results from the three centers, when considered individually, were not significantly different, and one center in New York did feature a greater ethnic mix. There were limited data on other risk enhancers, so comparison studies could not be conducted. Aragam et al focused on those with a PRS strata

of > 20%; other cutpoints may have changed the results. The biobank volunteers from the three centers may represent a biased sample. Finally, this was an associative study; a randomized, controlled study with cardiovascular disease outcomes would have to be conducted to establish PRS as a solid enhancer that changes outcomes. With the wide availability of genetic testing, we may be increasingly confronted by patients who have completed such assessments, along with a cardiac CT scan they underwent at the mall and perhaps other commercially available tests to assess their risk. I use these data if presented to me, but the only test I order in difficult decision cases is a coronary calcium score. I do consider family history as an enhancer. PRS may be just a more sophisticated family history, which is perhaps more accurate. ■

ABSTRACT & COMMENTARY

Is Exercise ECG Testing Dead?

By Michael Crawford, MD, Editor

SYNOPSIS: A post-hoc analysis of the SCOT-HEART trial demonstrated exercise ECG is predictive of future coronary heart disease events and mortality. However, coronary CT angiography is more accurate for the detection of coronary artery disease and is more strongly associated with future coronary events.

SOURCE: Singh T, Bing R, Dweck MR, et al. Exercise electrocardiography and computed tomography coronary angiography for patients with suspected stable angina pectoris: A post hoc analysis of the randomized SCOT-HEART trial. *JAMA Cardiol* 2020; Jun 3. doi: 10.1001/jamacardio.2020.1567. [Online ahead of print].

Some guidelines recommend exercise ECG as the initial test for intermediate-risk patients despite its low sensitivity. Coronary CT angiography (CCTA) is becoming a popular recommendation for this purpose because of its excellent sensitivity.

In the Scottish Computed Tomography of the heart (SCOT-HEART) trial, Singh et al performed a post-hoc analysis in the 79% of participants who had an exercise ECG test to assess the diagnostic, therapeutic, and prognostic benefits of exercise ECG in a contemporary clinical practice and compared it to CCTA. The study population consisted of 3,283 patients who underwent exercise ECG in both the standard care and standard care plus CCTA arms. The attending clinician categorized the exercise ECGs as abnormal, inconclusive, or normal, and were not adjudicated further. Obstructive coronary artery disease (CAD) was defined as a stenosis > 70% of the cross-sectional area or > 50% in the left main coronary artery. Non-obstructive was 10-70%, and normal was < 10% obstruction. The primary endpoint was death from coronary heart disease or a non-fatal myocardial infarction (MI) at five years.

Exercise ECG was normal in 67%, abnormal in 16%, and inconclusive in 17%. In the CCTA arm, among those with a normal exercise ECG, 56% had obstructive (15%) or non-obstructive (41%) CAD by CCTA. Among the 768 patients who underwent invasive coronary angiography, abnormal results on exercise ECG had a 39% sensitivity, a specificity of 91%, a positive predictive value of 58%, and a negative predictive value of 82% for detecting obstructive CAD.
An abnormal exercise ECG was associated with a 14-fold increase in coronary revascularization at one year and a three-fold increase in coronary heart disease death or MI at five years ($P < 0.001$). Compared to exercise ECG alone, CCTA was more strongly associated with five-year coronary death or MI (hazard ratio, 11; 95% confidence interval, 2-49; $P = 0.002$). The authors concluded that although an abnormal exercise ECG is associated with future coronary heart disease death, MI, or revascularization, CCTA is more accurate for the detection of CAD and is more strongly associated with future coronary events.

■ COMMENTARY

This study confirms the poor sensitivity (39%) and high specificity (82%) of exercise ECG for detecting obstructive CAD. CCTA was much better, with a sensitivity of 97% and a specificity of 86%. Thus, if detecting obstructive CAD is the only goal, there is no contest. However, there are other values to exercise ECG testing, such as the reproducibility, severity, and consequence of exercise-induced symptoms. ECG testing also assesses functional capacity and has been shown to carry prognostic value in many prior studies. The Singh et al study confirms the prognostic value of exercise testing in a contemporary setting, although CCTA performed better in this regard. CCTA detects non-obstructive CAD and can inform risk reduction therapies that an inconclusive or normal exercise ECG test does not.

An exercise ECG may be of value in the initial evaluation of patients with chest pain or other symptoms suggestive of CAD. If abnormal, the test would be highly predictive of obstructive CAD. However, if an exercise ECG is inconclusive, further testing may be

required. Additional assessments could include an imaging stress test, which would be expected to be more sensitive in the search for obstructive CAD, but feature a similar specificity as an exercise ECG.

Perhaps CCTA should be the next step for inconclusive exercise ECG patients. The Singh et al study supports that conclusion because many of their patients underwent both tests. What is was not considered here is the decision to include imaging in the initial exercise test. Despite the added cost, exercise imaging might be the best first test in those with stable symptoms. Although CCTA probably is more sensitive when trying to detect obstructive and non-obstructive CAD, it does not provide the other information an exercise ECG does.

There were limitations to this study. It really was an observational study because not all patients underwent both tests, and the application of exercise ECG was not randomized. This was a pragmatic study, with no core lab to adjudicate the test results. But the biggest criticism is CCTA patients received more risk reduction therapy than those who only underwent exercise ECG testing because non-obstructive CAD was detected. The real conclusion of this study is that exercise ECG testing carries therapeutic and prognostic significance, but CCTA offers the added benefit of informing preventive care. Also, exercise ECG is a relatively static technology, whereas CCTA is evolving, with promise for plaque characterization data, microcirculatory assessment, and other measures of potential significance. ■

CME/CE QUESTIONS

1. **According to an analysis of the MESA data, what coronary CT calcium score cutpoint best discriminated which primary prevention patients should be on prophylactic aspirin therapy?**
   a. 0
   b. 50
   c. 100
   d. 400

2. **Use of a polygenomic risk score for coronary artery disease would increase statin recommendations by how much over the pooled cohort equation estimates?**
   a. 4%
   b. 8%
   c. 16%
   d. 33%

3. **After a median follow-up of 11 months in heart failure patients treated with vericiguat compared to placebo, researchers observed significant reductions in:**
   a. total mortality.
   b. cardiovascular death.
   c. first heart failure hospitalization.
   d. total heart failure hospitalizations.

4. **After one-year follow-up of newly implanted surgical or transcatheter bioprosthetic heart valves with imaging-defined valve thrombus at 30 days, researchers observed increases in:**
   a. valve thrombus.
   b. valve gradient.
   c. stroke.
   d. mortality.

5. **An analysis of the SCOT-HEART study, a comparison of exercise ECG to coronary CT angiography for the evaluation of patients with symptoms suggestive of coronary heart disease, showed exercise ECG is superior for:**
   a. detecting coronary artery disease.
   b. predicting coronary heart disease events.
   c. predicting who would undergo revascularization.
   d. predicting subsequent mortality.

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