Cardiovascular risk stratification in diabetic patients: Is all in METS?

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Diabetes mellitus is a planetary growing problem and the costs to society are high and increasing. There are an estimated 382 million people living with diabetes in 2013 and this number is expected to increase to 592 millions by 2035.¹ Landmark epidemiological studies reported that diabetes is associated with a marked increase in the risk of coronary artery disease (CAD).^{2,3} As cardiovascular diseases account for about 65% of diabetes-related mortality, toward the end of the twentieth century the American Heart Association defined diabetes as coronary heart disease equivalent.⁴ Cardiac autonomic neuropathy and diabetic cardiomyopathy are the other two forms of cardiac involvement in diabetic subjects.⁵

STRESS PERFUSION IMAGING IN DIABETIC PATIENTS

The objective of non-invasive testing diabetic patients is the detection of occult CAD as well as prognostic risk stratification. For these purposes, among the non-invasive imaging modalities, stress myocardial perfusion single-photon emission computed tomography (MPS) is widely used and seems valuable also in asymptomatic diabetic patients.^{6,7} The prospective multinational ischemia assessment with exercise imaging in

asymptomatic diabetes from 12 sites in Asia, Africa, and Latin America found that a higher proportion of the diabetic patients enrolled had MPS abnormalities suggestive of silent ischemia compared with controls (26% vs. 14%; $P < .001$).⁷ Of the participants with MPS ischemia, 17% had ischemic signs on electrocardiography (ECG), whereas 10% of those without ischemia had an ischemic ECG. In a multivariable model, diabetes was independently associated with abnormal MPS ($P < .005$). Women were less likely to have ischemia on MPS than men and concordance between ECG and MPS was much worse in women. In this study of non-selected individuals from developing countries,⁷ the prevalence of ischemia by MPS was higher than was seen in the Detection of Ischemia in Asymptomatic Diabetes (DIAD) trial.⁸ In this latter study, the prevalence of ischemia was only 6%. At follow-up, the DIAD investigators found low event rate with similar outcomes in participants who were randomized to screening MPS vs no screening,⁹ hypothesizing that intensive medical treatment may overcome the possible benefit from screening.¹⁰ However, higher prevalence of silent ischemia by MPS in diabetic subjects has been reported in other studies.^{11,12}

IMPROVEMENT IN RISK ESTIMATION WHEN AN ADDITIONAL TEST IS ADDED TO A STANDARD MODEL

Different methods for quantifying the improvement in risk estimation when an additional test is added to a standard risk prediction model have recently been introduced.¹³ Net reclassification improvement (NRI) has been adopted in diabetic patients with suspected or known CAD to evaluate the extent to which adding MPS imaging findings to a model based on traditional risk factors and ECG stress test data correctly reclassifies the risk of severe CAD and of subsequent cardiac events during a long-term follow-up.^{6,14-17} In the Impact of

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Inducible Ischemia by Stress SPECT (IDIS) trial, risk estimates for a coronary heart disease event were categorized in 822 consecutive diabetic patients as 0% to <3%, 3% to <5%, and $\geq 5\%$ per year using two Cox proportional hazards models.^{16,17} Model 1 used traditional coronary heart disease risk factors and ECG stress test data and model 2 used these variables plus MPS imaging data. Cardiac death, myocardial infarction, and unstable angina requiring coronary revascularization were the outcome measures. Model 2 improved risk prediction compared to model 1 (NRI 0.25; $P < .001$). Overall, 301 patients were reclassified to a higher risk category, with an event rate of 28%, and 26 to a lower risk category, with an event rate of 15%. Among patients at 3% to <5% risk, 53% were reclassified at higher risk and 25% at lower risk (NRI 0.42; $P < .05$). The cost per NRI was \$880.80 for MPS imaging as compared to an outpatient visit with an ECG stress test. Thus, the addition of MPS imaging data to a prediction model based on traditional risk factors and ECG stress test data significantly improved coronary heart disease risk classification in patients with diabetes.¹⁷

PROGNOSTIC VALUE OF EXERCISE LEVEL IN DIABETIC PATIENTS

Exercise stress testing is largely used as non-invasive, cost-effective method to evaluate CAD. Exercise stress test provides other valuable diagnostic and prognostic data, beyond ST-segment depression.¹⁸ These variables include exercise capacity, chronotropic response, heart rate recovery, blood pressure response, and scores such as the Athens QRS score and the Duke Treadmill Score.^{19,20} However, among the various parameters and scores introduced as prognostic markers by the exercise test, one of the most important is the functional capacity assessed as metabolic equivalents (METs).²¹ In the current issue of the Journal, Padala et al²² present data obtained analyzing retrospectively 14,849 consecutive patients (3,654 diabetics and 11,195 non-diabetics) undergoing exercise stress, combined exercise and pharmacologic stress, and pharmacologic stress MPS from 1995 to 2005 at a single tertiary care center. Diabetic and non-diabetic patients were categorized into three groups based on METs achieved: ≥ 5 METs, <5 METs, and pharmacologic stress groups. Annualized event rate for the composite end point of non-fatal myocardial infarction and cardiac death was calculated over a mean follow-up period of 2.4 ± 1.4 years with a maximum of 6 years. In moderate-severe perfusion abnormality category, diabetic patients who were able to achieve ≥ 5 METs had significantly lower annualized event rate compared to diabetic patients who were unable to achieve ≥ 5 METs

(3% vs. 5.5%; $P < .05$), and non-diabetic patients unable to achieve ≥ 5 METs (3% vs. 4.8%; $P < .001$). Diabetic patients who achieved a high workload (≥ 10 METs) had a low annualized event rate of 0.9%. After adjustment for cardiovascular risk factors, the percentage decrease in cardiac event rate for every 1-MET increment in exercise capacity was 10% in the overall cohort, 12% in diabetic group, and 8% in non-diabetic group. Thus, despite significant perfusion defects, diabetic patients who achieve ≥ 5 METs during stress MPS have significantly reduced risk for future cardiac events. The findings of Padala et al²² support the view that exercise capacity obtained during MPS is a surrogate for outcomes also among diabetic patients undergoing nuclear stress testing. When a concept gains general acceptance, its underlying basis may no longer be questioned. Thus, the limitations intrinsic in its assumption are ignored, and the possibility of misusing the concept may increase. There are some limitations in using METs. The definition of a MET is problematic when applied for specific persons because it is not clear how or when the 1 MET value of $3.5 \text{ mL O}_2 \text{ kg}^{-1} \text{ min}^{-1}$ (or $1 \text{ kcal kg}^{-1} \text{ h}^{-1}$) was derived.²³ Yet, it is a common practice for researchers and practitioners to use the MET values to judge the energy cost of different activities.²⁴ The conventional MET is not specifically a constant that equates resting values. Byrne et al²⁵ measured MET level for moderate-intensity walking in an overweight cohort and found an average value of 4.6 ± 0.5 , 22% higher than the compendium value of 3.8. Previous studies by Bourque et al²⁶ suggested that in patients who exercise >10 METs, MPS adds little to the diagnosis of CAD and to risk stratification.²⁷ Noteworthy, the difference in threshold used by Padala et al²² (5 METs) and Bourque et al^{26,27} (10 METs) seems not negligible as these thresholds relate to stage 1 and stage 3 of the Bruce protocol, respectively. Remarkably, the prevalence of ischemia and its prediction of events are unclear in outpatients with diabetes mellitus in the modern era of intensive medical management. Bourque et al²⁸ recently sought to identify the prevalence of ischemia, subsequent cardiac events, and impact of sex, stress type, and symptom status on these findings in a cohort of stable outpatients with diabetes mellitus referred for MPS. Known CAD was present in 40.3% of subjects and 29% were asymptomatic at the time of stress testing. In this cohort of stable outpatients with diabetes mellitus, independent predictors of cardiac death/non-fatal myocardial infarction were known CAD, pharmacological stress, and MPS ischemia. In the subgroup of 200 patients who underwent exercise stress, there were 1.6-fold and 3.8-fold increases in any and $\geq 10\%$ of the left ventricle ischemia in those unable to reach 10 METs of exercise workload; however, these

differences were not statistically significant. There were no significant differences in summed stress or rest scores by symptom status in subjects undergoing pharmacological stress. However, asymptomatic patients undergoing exercise stress were more likely to achieve a high exercise workload of ≥ 10 METS (58.3% vs. 23.1%; $P = .007$), and to have a summed stress score > 3 (29.7% vs. 12.9%; $P = .011$) despite being able to attain a higher workload. Noteworthy, in this study nearly one third of patients with events had a normal MPS, indicating a need for improved risk stratification.²⁸ Thus, the relationship among METS, stress-induced ischemia, and prognosis in diabetic subjects remains unclear. In another recent study, Duvall et al²⁹ showed that a provisional injection protocol defined as age < 65 , normal rest ECG, no history of CAD, and high level exercise (≥ 10 METS) with a negative ECG response and no symptoms has a very low 5-year all-cause mortality and low yield of MPS. If adopted, this protocol would decrease radiation exposure and save time and health care costs without jeopardizing prognosis. Based on the available retrospective data regarding the very low prevalence of significant ischemia and excellent prognosis for patients achieving ≥ 10 METS without ischemic ST depression, including those reported in this issue by Padala et al,²² this provisional injection protocol deserves further consideration and prospective evaluation in randomized controlled study.³⁰ This approach might best identify which patients do not require MPS at the outset for evaluation of symptoms suggestive of CAD. Indeed, a non-imaging exercise ECG stress test could be performed alone as the first test in patients prospectively identified as having good functional capacity and deemed at low or low-intermediate pre-test probability for CAD.

Conflict of interest

The authors have indicated that they have no financial conflict of interest.

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