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SPECIAL ISSUE: FOCUS ON LV STRAIN FOR PREDICTING HARD OUTCOMES

STATE-OF-THE-ART REVIEW

Optimizing the Assessment of Patient Clinical Risk at the Time of Cardiac Stress Testing

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ABSTRACT

Due to a marked temporal decline in inducible myocardial ischemia over recent decades, most diagnostic patients now referred for cardiac stress testing have nonischemic studies. Among nonischemic patients, however, long-term risk is heterogeneous and highly influenced by a variety of clinical parameters. Herein, we review 8 factors that can govern long-term clinical risk: coronary risk factor burden; patient symptoms; exercise capacity and exercise test responses; the need for pharmacologic stress testing; autonomic function; musculoskeletal status; subclinical atherosclerosis; and psychosocial risk. To capture the clinical benefit provided by both assessing myocardial ischemia and these additional parameters, the authors propose that a cardiac stress tests report have an additional component beyond statements as to the likelihood of obstructive coronary artery disease and/or magnitude of ischemia. This added component could be a comment section designed to make referring physicians aware of aspects of long-term risk that may influence clinical management and potentially lead to changes in the intensity of risk factor management, frequency of follow-up, need for further testing, or other management decisions. In this manner, the increasingly frequent normal stress test result might more commonly influence treatment recommendations and even patient behavior, thus leading to improvement in patient outcomes even in the setting of normal stress test results. (J Am Coll Cardiol Img 2020;13:616–23)

Joanne is a 62-year-old woman who presents with left arm pain while walking. She is sedentary and overweight, with a body mass index of 28.9 kg/m^2. An ex-smoker, Joanne has current risk factors of hypertension and diabetes. Because of her chest pain symptoms, her physician orders a nuclear stress test. Joanne attempts to perform treadmill exercise, but because she exhibits poor exercise tolerance, the test is converted into a regadenoson single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) study. The pharmacologic stress test reveals no myocardial perfusion defects. How should the imaging physician report Joanne's test results?

The answer to this question would seem to be straightforward. Joanne's SPECT-MPI study is normal and will be reported as such. As part of current reporting recommendations, the test should integrate her test information and provide an assessment as to her likelihood of obstructive coronary artery disease (CAD), and if it were present, the magnitude of ischemia. The initial tendency in Joanne's case would be to state that there is a low likelihood of obstructive CAD as the bottom line of a report. Combined, these

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conclusions will convey the impression that Joanne is also at low risk for adverse clinical events. However, is this so?

In this review, the evidence illustrates that Joanne's long-term prognostic risk for clinical events is not low. Based on our review of this evidence, we will propose to expand the reporting of stress testing beyond that of ischemic burden assessment to include the reporting of additional long-term prognostic factors and explain how this assessment may help optimize the recent call to have cardiac imagers play an increasing role in patient care coordination (1).

A HISTORICAL PERSPECTIVE

The advent of cardiac imaging tests in the 1970s coincided with the peak of the 20th-century epidemic in cardiovascular disease. Initially, inducible myocardial ischemia was quite common among stress patients and often severe in magnitude. Moreover, at that time, the principle use of stress tests, such as those listed in **Table 1**, was in their utility for short-term decision making. As a result, the prognostic efficacy of cardiac stress tests was generally based on short-term follow-up. For example, in a meta-analysis of 17 exercise SPECT and 10 stress echo studies evaluating outcomes following testing, the mean follow-up was 36 months for both tests (2).

Since then, the clinical presentation of cardiovascular disease has changed markedly due to advances in the treatment and prevention of CAD. This has resulted in a marked reduction in the annualized mortality rate from heart disease and stroke, with both declining by approximately 70% since the 1970s (3). In addition, myocardial infarction is now less common and tends to be milder in severity (4) and the prevalence of typical angina has also declined (5). Accompanying these favorable trends has been a marked decline in the frequency of inducible myocardial ischemia within stress test populations. For instance, in our analysis of over 39,000 diagnostic patients who underwent stress and/or rest SPECT-MPI over a nearly 20-year period, we observed that the frequency of inducible myocardial ischemia fell from 29.6% in 1991 to only 5% in 2009 (6).

As the clinical symptoms and manifestations of CAD have declined in severity, there has been an increasing interest in identifying longer-term predictors of CAD outcomes. This has led to studies with progressively longer follow-up studies. An important lesson from these studies is that clinical factors that do not necessarily predict short-term clinical risk can be important predictors of long-term risk. For example, the magnitude of coronary artery calcium (CAC) on noncontrast computed tomography (CT) scanning is a well-established risk predictor, but it may underestimate risk if the follow-up period is too short, as shown by Chang et al. (7). Herein we review 8 clinical parameters other than myocardial ischemia that can influence long-term outcomes following stress testing (**Table 2**).

ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcium

CAD = coronary artery disease

CT = computed tomography

MPI = myocardial perfusion imaging

SPECT = single-photon emission computed tomography

CARDIAC RISK FACTORS

Although CAD risk factors alone are weak predictors of clinical risk with respect to short-term outcomes, they can exert a significant effect on longer-term risk among patients with normal stress tests. For example, Supariwala et al. (8) followed 2,567 patients with normal exercise SPECT-MPI studies for a mean of 6.8 years. Three CAD risk factors were significant predictors of all-cause mortality: hypertension; diabetes; and smoking. When all 3 were absent, the long-term all-cause mortality rate averaged 0.2%/year, but all-cause mortality increased to 1.8%/year among patients with all 3 risk factors. Similar findings were observed in another study of 12,232 patients with normal exercise SPECT-MPI studies who were followed for a mean of 11.2 years (9).

CHEST PAIN SYMPTOMS

Chest pain symptoms have traditionally been important predictors of cardiac events, but within recent stress test populations, chest pain symptoms have manifested less prognostic accuracy (9). Various factors may be contributing to this trend. First, the widespread adoption of the Diamond-Forrester algorithm for assessing CAD likelihood in the 1970s (10) led to a current tendency to merely evaluate chest pain according to 3 variables at the time of stress testing: its location; its precipitants; and whether the pain is relieved with rest or nitroglycerin. However, this limited inquiry may not be

TABLE 1 Use of Stress Testing for Common Acute Management Decision

Determine if ischemia is the cause of chest pain (diagnostic use)
Decide between medical therapy versus revascularization
Assess the functional significance of borderline coronary stenoses
Assess is new symptoms post-myocardial revascularization are due to ischemia
Determine if ischemia is contributing to heart failure symptoms
Assess pre-operative risk for non-coronary surgery

JACC: CARDIOVASCULAR IMAGING, VOL. 13, NO. 2, 2020
FEBRUARY 2020:616-23

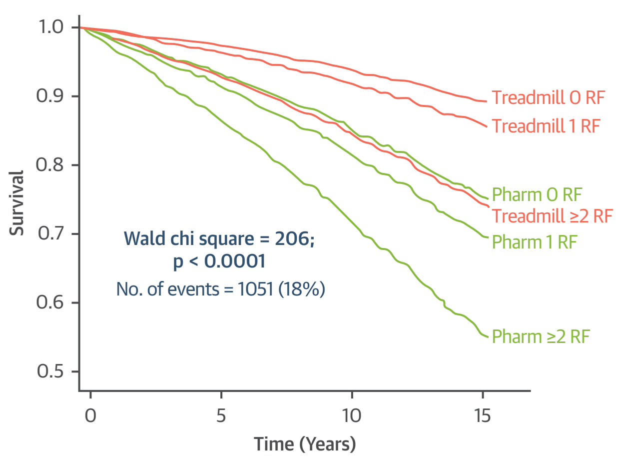
TABLE 2 Clinical Factors That Modify Long-Term Cardiovascular Risk Among Patients Undergoing Cardiac Stress Testing

CAD risk factors
Chest pain
Exercise capacity
Unable to perform treadmill exercise
Musculoskeletal function
Autonomic dysfunction
Subclinical atherosclerosis
Psychosocial risk factors

CAD = coronary artery disease.

sufficient to distinguish chest pain patterns of high clinical risk. Second, the predictive accuracy of chest pain might be influenced by several referral biases, including the potential to directly refer patients with more severe or increasing anginal symptoms directly to cardiac catheterization rather than to stress testing. Third, the factors leading to the general taming of CAD may also be serving to diminish the intensity and predictive accuracy of chest pain symptoms.

FIGURE 1 Mortality Risk According to RF Burden and Mode of Stress



Kaplan-Meier survival curves among 5,762 patients with a normal single-photon emission computed tomography-myocardial perfusion imaging followed for a mean of 8.4 years. Patients were stratified according to mode of stress testing (treadmill vs. pharmacologic stress) and coronary disease risk factor (RF) burden. Survival curves for exercise are shown in **pink**. Those for pharmacologic testing are shown in **green**. The data are adjusted for age, sex, coronary artery disease risk factors, and chest pain. Annualized mortality rates ranged from 0.8%/year among exercise patients who had no major coronary artery disease risk factors to 4.2%/year among pharmacologic stress who had ≥2 coronary artery disease risk factors. Reproduced with permission from Supariwala et al. (12).

EXERCISE CAPACITY, PHARMACOLOGIC TESTING, AND MUSCULOSKELETAL HEALTH STATUS

Exercise capacity is a potent predictor of clinical risk that strongly shapes the clinical risk associated with a normal stress MPI study and strongly modifies the risk associated with CAD risk factors. For example, in a large study of 12,232 patients with nonischemic exercise MPI studies who were followed for a mean of 11.2 years, patients exercising <6 min and having 2 or more CAD risk factors had an approximately 7-fold increase in mortality risk compared with the risk in a referent group that exercised >9 min and did not have any of 3 CAD risk factors (hypertension, smoking, or diabetes) (9). Similarly, patients who require pharmacologic testing at the time of MPI have higher clinical risk than exercising patients, even when propensity-matched into groups of similar age and clinical profiles (11). High coronary risk factor burden and the need for pharmacologic stress can markedly increase patient risk despite the presence of a normal stress MPI study, as shown by Supariwala et al. (12) (**Figure 1**).

In addition, there is growing interest in musculoskeletal dysfunction as a complement to cardiac risk assessment. This is due to increasing recognition of skeletal muscle as a metabolically active organ system whose function is highly influenced by physical activity. Exercise serves to preserve muscle mass and strength and enhance insulin sensitivity and mitochondrial biogenesis and function, whereas inactivity has deleterious effects on muscle function (13,14). Newer data indicate that physical activity also stimulates the production of numerous myokines that not only exert beneficial autocrine and/or paracrine effects on skeletal muscle but also positive endocrine effects within other organ systems, including adipose tissue, liver, gut, brain, and bone (**Figure 2**) (15). Over time, progressive physical inactivity and musculoskeletal dysfunction places patients at future risk for pre-frailty and eventual frailty. To this end, both questionnaire items and simple tests that assess slowing gait and decreasing muscle strength (e.g., handgrip strength) have been employed to identify patients at risk for pre-frailty (16). Given its ease of use, evaluation of gait speed may also be of interest for expanding the risk assessment of patients who are relatively immobile at the time of stress testing. The test can be readily performed by asking individuals to walk at their normal walking speed over very short intervals such as 4 m (~13 feet). Gait speed measured in this way bears a proportional inverse relationship to mortality risk among older individuals (**Figure 3**) (17).

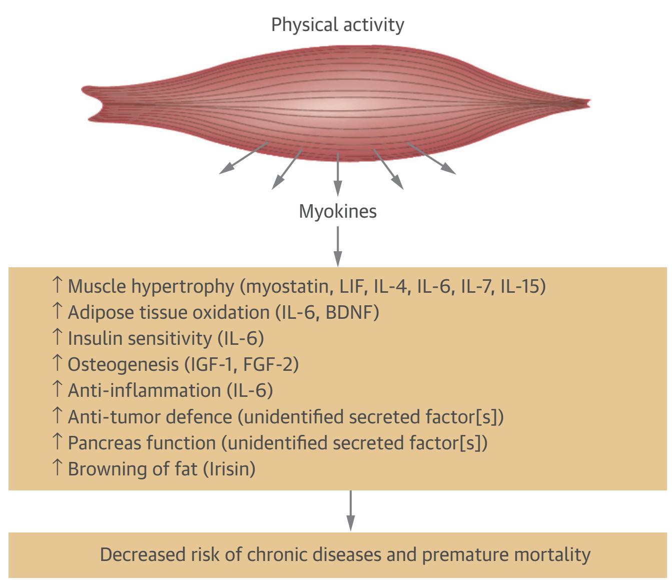
SUBCLINICAL ATHEROSCLEROSIS

The assessment of CAC indirectly reflects the overall burden of coronary atherosclerosis and provides in an individual patient the integration of all factors causing disease—those known and unknown. As such, it takes into account the magnitude and duration of risk factor exposure as well as patients' individual response to these factors. Large registries and population-based trials have consistently demonstrated a proportional relationship between the magnitude of CAC abnormality and the likelihood of future adverse cardiac events. Importantly, the frequency of CAC abnormality is common among patients referred for stress testing without inducible myocardial ischemia. For instance, in a meta-analysis of 20 studies involving patients who underwent both stress and/or rest MPI and CAC scanning, CAC was present among 72% of the patients without inducible ischemia (18). Moreover, the range of CAC abnormality among patients with normal stress tests is quite heterogeneous. For instance, in a study of diagnostic patients undergoing both exercise SPECT-MPI and CAC scanning, there was a comparable frequency of patients who had CAC scores of 0, 1 to 99, 100 to 399, and >400 among nonischemic patients (**Table 3**) (19). Assessment of CAC has also been shown to enhance physicians' management of CAD risk factors as well as patient adherence to medications and recommended lifestyle changes (20).

OTHER CLINICAL VARIABLES

Other dimensions of clinical risk include the assessment of autonomic dysfunction and psychosocial status. Three hemodynamic factors that reflect disturbed autonomic nervous system function have been strongly linked to adverse clinical events among patients undergoing stress-rest MPI: the presence of a delayed heart rate recovery to baseline following peak exercise (21,22); a blunted heart rate response during exercise (22); and a blunted heart rate response during pharmacologic testing (23,24). A variety of psychosocial factors have also been linked to cardiovascular risk (25), but depression and anxiety are particularly relevant among patients referred for cardiac stress testing due to their common occurrence and potential etiological role in provoking chest pain symptoms. In addition, depression augments the risk associated other cardiovascular risk factors (26).

FIGURE 2 **Influence of Myokines**



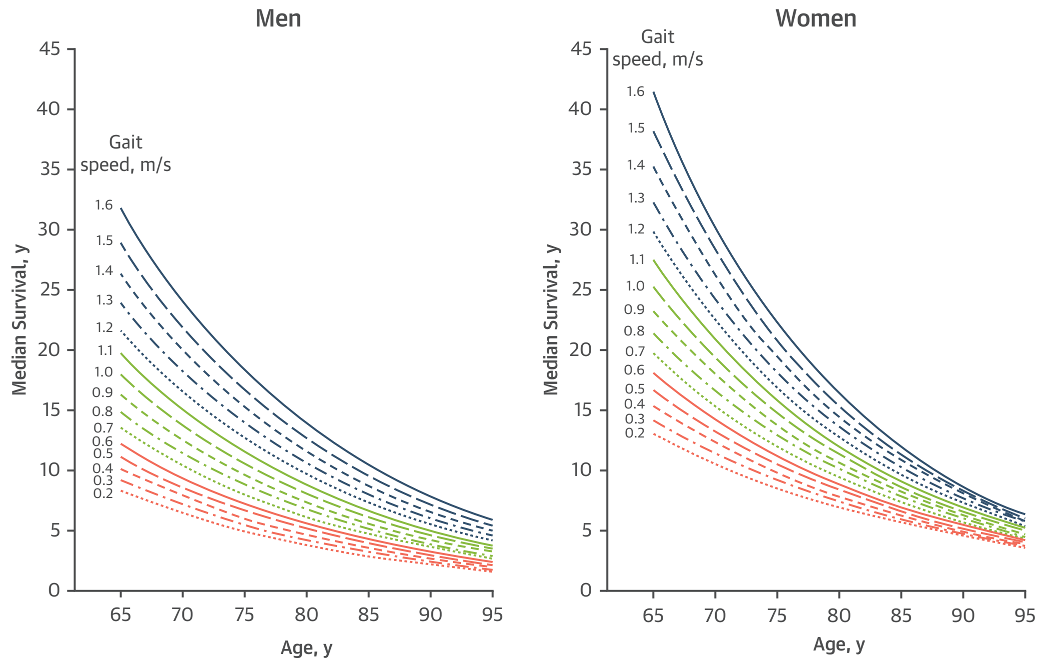
Physical activity leads to the production and secretion of myokines, which may aid in the protection from chronic diseases through their beneficial effect on skeletal muscle and various target organ systems. Reprinted with permission from Pedersen and Febbraio (15). BDNF = brain-derived neurotrophic factor; FGF = fibroblast growth factor; IGF = insulin-like growth factor; IL = interleukin; LIF = leukemia inhibitory factor.

TEST REPORTING AS A BRIDGE TO BETTER PATIENT CARE

For many years, the value of cardiac tests was based merely on their ability to predict clinical events. Now the focus has shifted toward evaluating the ability of tests to reduce future clinical events—a standard of therapeutic effectiveness. We posit that incorporating the clinical variables reviewed herein (**Central Illustration**) could form the basis for more accurate risk assessment at the time of cardiac stress testing and lead to enhanced recommendations for treatment and favorable lifestyle changes that could reduce long-term risk following stress testing.

It is notable that the current standard for reporting the results of cardiac stress tests was first developed in the late 1970s and has changed little over the years. For diagnostic patients, a summary statement is usually rendered as to the patient's likelihood of having obstructive coronary disease. If the patient has known CAD, then the likelihood of inducible myocardial ischemia is reported instead. This assessment is based on the stress imaging results, the electrocardiographic response to stress and induction of any associated clinical symptoms. These likelihood assessments are very useful for addressing the acute

FIGURE 3 Gait Speed and Survival



Predicted median life expectancy according to age and gait speed based on an analysis of the data in 34,485 community-dwelling individuals, age ≥65 years, pooled from 9 cohort studies. Reproduced with permission from Studenski (17).

management decisions that may emanate from cardiac stress testing, such as deciding whether chest pain symptoms are of an ischemic etiology or evaluating patients' pre-operative risk for noncardiac surgery. However, an exclusive short-term temporal focus would serve to exclude many of the important long-term prognostic predictors that have been discussed in this review.

However, how to best incorporate the assessment of long-term predictors into standard cardiac test reporting will require prospective consideration. Cardiac risk can be reported in many ways, ranging from a simple listing of risk factors to the development of global risk algorithms. From a practical point of view, the inclusion of information regarding the long-term modifiers of patient risk might be accomplished by adding a simple narrative comment section at the end of a stress test report. Alternatively, standardized text could be adopted that provides a checklist as to the presence or absence of clinical risk predictors that can be assessed at the time of stress testing. We foresee this type of reporting developing in real time through the active collaboration among imaging physicians and patients' referring physicians who can guide the development of this type of reporting through their active feedback.

TABLE 3 Frequency of CAC Abnormalities Among Diagnostic Patients Referred for Stress and/or Rest SPECT-MPI

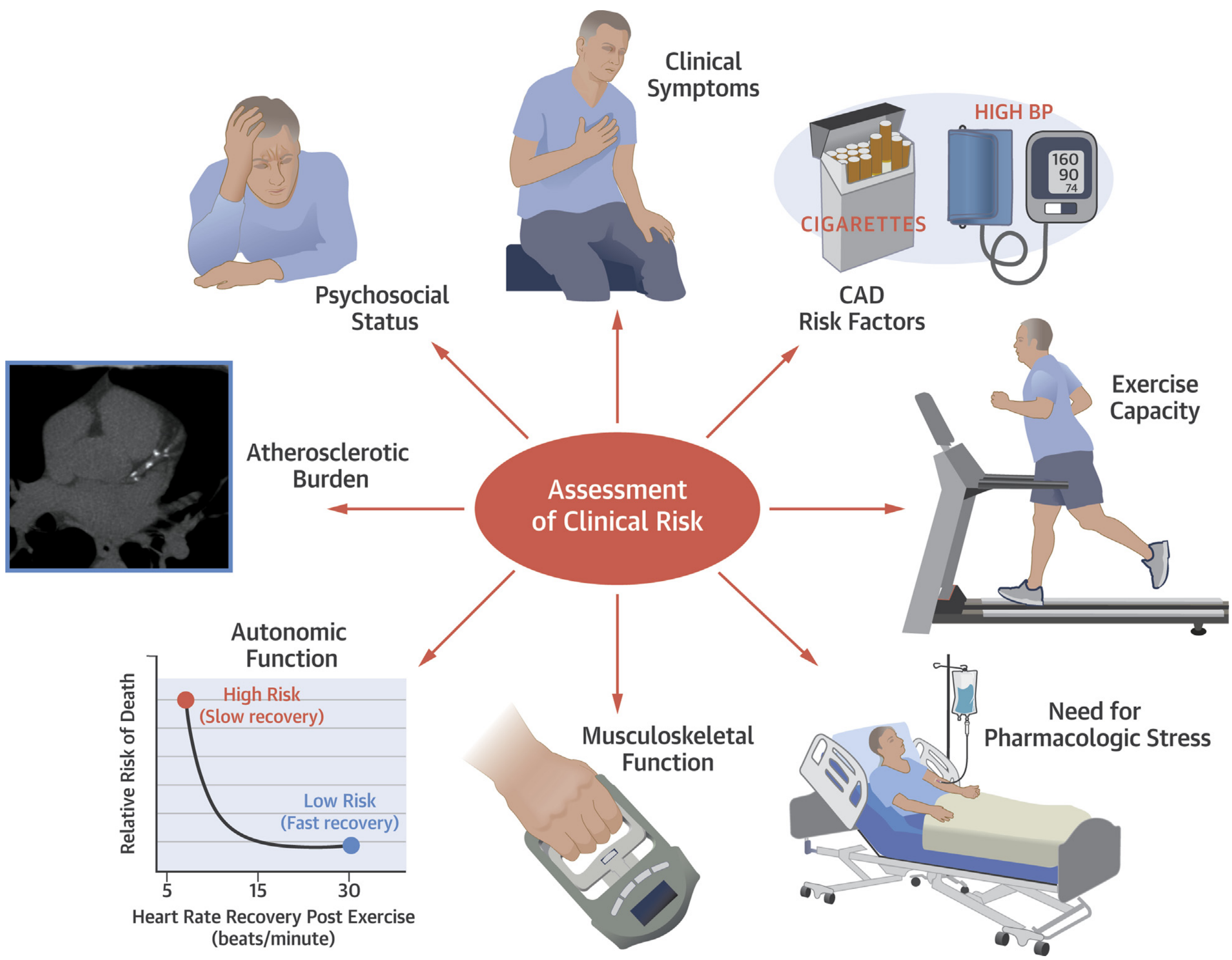
CAC Scores	Frequency
Normal SPECT patients	n = 1,119
0	22
1-99	22
100-399	25
>400	31
Abnormal SPECT patients	n = 1,119
0	5
1-99	7
100-399	20
>400	68

Data adapted from Berman et al. (19).
Abbreviations as in Table 1.

OPTIMIZING VARIABLES COLLECTED FOR RISK ASSESSMENT

Among the risk parameters we have reviewed, a number may benefit from improved methods of evaluation. First, the concurrent convention to assign chest pain categories according to 3 standard questions—its location, precipitants, and relief by rest or

CENTRAL ILLUSTRATION Factors Influencing Long-Term Outcomes at the Time of Cardiac Stress Tests



Rozanski, A. et al. J Am Coll Cardiol Img. 2020;13(2):616–23.

Eight determinants of long-term outcomes among patients referred for cardiac stress testing.

nitroglycerin—may be too limited. Rather, other distinguishing aspects of chest pain could help improve its characterization, including query as to its severity and duration, ease of provocation, associated symptoms, and recent change in the frequency or intensity of the pain. The assessment of CAD risk factors could also be improved by considering their chronicity, given the relationship between the time of exposure of a given CAD risk factor and its associated clinical risk (27,28).

Second, although it is important to note whether patients require pharmacologic stress testing in lieu of exercise testing, the reasons for employing pharmacologic stress can vary widely, from protocol-driven factors such as left bundle block, to poor exercise tolerance and musculoskeletal conditions, to the presence of serious comorbidities such as pre-frailty and severe chronic illnesses (29). Reporting these reasons could form the basis for obtaining useful epidemiological data as well as providing enhanced information about patients to physicians. In addition, the higher risk associated with pharmacologic testing raises the question as to whether additional forms of risk assessment should be performed in pharmacologic patients. A potential approach might be to consider using short questionnaire items to assess 3 of the 5 core components of frailty—patients' physical activity levels, sense of exhaustion, and unintentional weight loss—coupled with assessment of gait speed in selected patients

JACC: CARDIOVASCULAR IMAGING, VOL. 13, NO. 2, 2020
FEBRUARY 2020:616–23

(16). Sergi et al. (30) recently assessed these predictors among 1,567 individuals age ≥65 years who were initially free of frailty or disability. During a follow-up of 4.4 years, 3 factors emerged as event predictors: low levels of physical activity during the week; slow gait speed; and exhaustion, as measured by a single-item ("do you feel full of energy?").

Third, in light of the proven ability of CAC scanning to detect subclinical atherosclerosis among patients undergoing MPI (7,19) and its ability to add incremental information to the prediction of clinical risk following stress testing (7), strong consideration should be given for making CAC scanning a routine part of diagnostic stress testing. The assessment of CAC is well-suited for today's hybrid SPECT/CT and PET/CT scanners, which permit the simultaneous assessment of CAC and myocardial perfusion. Alternatively, inexpensive, standalone CAC scanning can be performed in conjunction with stress testing.

SUMMARY

We conclude by returning to the case of Joanne, who we selected as prototypical of many patients who are now referred for cardiac stress testing. Because Joanne has a normal stress test, she has a current low short-term risk for developing adverse cardiac events. However, her long-term clinical risk is not low. Rather, Joanne's CAD risk factor burden coupled with an inability to exercise is indicative of substantially elevated long-term risk (**Figure 1**) (12). If Joanne is merely informed about her low short-term ischemic risk, it may be less likely that she and her physician might work to aggressively modify the risk factors that presently place her at risk for developing future disability, additional comorbidities, and/or premature death. In Joanne's case, reporting her elevated long-term risk could lead toward efforts to ameliorate the factors that prohibited her from exercising at the time of stress testing. In our current era of declining myocardial ischemia during stress testing (6) but rising prevalence of other risk factors that can drive clinical risk, such as obesity (31), diabetes (32), an inability to exercise at the time of stress testing (6,33,34), and musculoskeletal dysfunction (35), characterization of the factors driving patients' long-term risk may augment the future relevance and clinical effectiveness of cardiac stress testing.

HIGHLIGHTS

- Although most cardiac stress tests are now nonischemic tests, long-term risk is quite heterogeneous.
- Risk factor burden, symptoms, exercise capacity, and the need for pharmacologic stress influence long-term risk.
- Other predictors include atherosclerosis (coronary calcium) burden, autonomic dysfunction, musculoskeletal status, and psychosocial risk factors.
- Optimal test reporting should integrate assessment of ischemia with these other determinants of patient risk.

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KEY WORDS cardiac stress testing, coronary artery disease, exercise, ischemia