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Non-invasive quantification of coronary vascular dysfunction for diagnosis and management of coronary artery disease

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INTRODUCTION

The last several decades have seen significant advances in the evaluation and treatment of coronary artery disease. Multiple non-invasive methods for the diagnosis of coronary atherosclerosis have matured and are in wide clinical practice. Improving risk factors and primary^{1,2} and secondary prevention strategies³ have resulted in a decline in cardiac mortality and myocardial infarction.^{4,5} The focus of these diagnostic methods and treatment strategies has been on the identification and treatment of atherosclerotic lesions of the epicardial coronary arteries, particularly obstructive, ischemia causing lesions. While there is no doubt that this approach has been tremendously successful, it must be noted the coronary arterial circulation extends from large epicardial conduit arteries through resistance arterioles (i.e., the microvasculature) to the intra-myocardial capillary bed. Dysfunction of the microvasculature and pre-obstructive disease of the epicardial arteries can not only cause typical anginal symptoms but also may be harbingers of adverse prognosis. In the following paragraphs, we will discuss current approaches to the quantification of coronary vascular function and the evidence supporting its potential diagnostic and prognostic implications with a particular focus on ischemic heart disease.

DIAGNOSIS OF OBSTRUCTIVE CORONARY ARTERY DISEASE

In addition to clinical history and symptoms, stress testing modalities are an integral part of the standard evaluation for epicardial coronary atherosclerotic disease among intermediate risk patients.⁶ Addition of imaging to identify stress-induced perfusion abnormalities substantially improves sensitivity for diagnosing obstructive stenosis. A recent meta-analysis has demonstrated excellent diagnostic performance of both SPECT and PET myocardial perfusion imaging (radionuclide MPI, R-MPI)⁷ with sensitivities of 88% and 84% and specificities of 61% and 81%, respectively. Stress R-MPI can be performed in a wide array

of patients including those in whom other methods may be limited due to obesity or lung disease. Although nuclear methods result in radiation exposure, the effective doses can be substantially limited with modern equipment and protocols.⁸

While the overall per patient sensitivity of these methods is excellent, it is well known that the ability of semi-quantitative myocardial perfusion imaging to delineate the full extent of atherosclerosis remains limited.⁹ This may be, in part, due to the implicit assumption that the best perfused segments are normal when perfusion images are interpreted semi-quantitatively. As a result, the sensitivity for prospective identification of multi-vessel disease remains limited. Incorporation of additional signs such as multi-vessel myocardial perfusion defect pattern,¹⁰ transient ischemic dilation (TID),^{11–13} pulmonary uptake,^{14–17} right ventricular uptake,¹⁸ and decline in stress left ventricular ejection fraction (EF)^{19,20} can improve diagnostic sensitivity for left main and three-vessel coronary artery disease. In one series of patients with left main coronary artery disease, no combination of diagnostic criteria could reliably identify all patients (Figure 1).²¹ Further-more, semi-quantitative perfusion imaging is inherently unable to identify regions where diffuse atherosclerosis is not sufficiently severe to limit tissue perfusion.

Several other imaging modalities also have well-established data supporting their use for the diagnosis of obstructive coronary artery disease. Echocardiography can be performed during exercise or administration of inotropic agents (typically dobutamine) to identify stress-induced regional wall motion abnormalities as markers of ischemia with overall per patient sensitivity 81.2% and specificity of 82.2% for obstructive CAD on angiography.²² Interpretation of results is complicated in patients with prior myocardial infarction due to resting wall motion abnormalities and leads to suboptimal diagnostic performance in this setting.²² This method requires excellent acoustic windows for optimal diagnostic performance, which are often unavailable in patients with obesity or lung disease. Furthermore, image quality is highly operator dependent and may limit test accuracy. As for R-MPI, findings which suggest the presence of extensive CAD such as cavity dilation and decline in global LVEF are frequently absent.^{23–25}

Magnetic resonance imaging (MRI) can also be used to identify stress-induced perfusion defects and/or wall motion abnormalities.⁹ A large prospective single-center evaluation of stress MRI has demonstrated a sensitivity of 86.5% and a specificity of 83.4% for the identification of angiographic CAD,²⁶ although other multi-center studies have suggested considerably lower diagnostic performance.²⁷ Assessment of myocardial perfusion with MRI, at present, requires the use of gadolinium-based contrast media, which are contraindicated in patients with severe renal dysfunction. Obese patients often cannot be accommodated inside the standard-bore or, in some cases, even in wide-bore scanners. Patients who experience claustrophobia or who have difficulty in holding their breath may not be able to tolerate cardiac MRI examinations. Most importantly, at present, many centers lack adequate instrumentation and/or expertise to reliably perform stress cardiac MRI. Finally, MRI is contraindicated in patients using many types of implanted medical devices including most pacemakers and all defibrillators currently approved. However, off-label studies suggest that these studies can, in select cases, be performed safely.²⁸

Computed tomography (CT)-based methods such as coronary CT angiography can detect both obstructive and non-obstructive epicardial atherosclerosis.²⁹ Although the full anatomic extent of atherosclerotic changes can be readily delineated by CT angiography, this method is unable to reliably assess whether this disease is sufficient to cause myocardial ischemia.³⁰ This distinction is critical to determine whether a patient's symptoms are related to CAD.

QUANTIFICATION OF MYOCARDIAL BLOOD FLOW (MBF) AND FLOW RESERVE

As discussed above, two important limitations of myocardial perfusion imaging arise from semi-quantitative interpretation: the underestimation of the extent of ischemia when all three coronary territories are affected and inability to identify patients with non-obstructive stenosis. Quantitative assessment of MBF offers the opportunity to add important information to semi-quantitative assessments of R-MPI and potentially overcome these limitations. Both absolute stress MBF and flow reserve, expressed as the ratio of stress over rest MBF, have been proposed for this application. A number of invasive and non-invasive methods have been employed to quantify MBF and flow reserve and are briefly discussed below.

Invasive Methods

The gold standard method remains invasive evaluation of coronary flow velocity with a Doppler wire to measure coronary flow reserve (CFR) by comparing rest flow velocity with that during vasodilator stress. More commonly, fractional flow reserve is assessed using a pressure wire to compare the pressure gradient across an area of luminal narrowing before and after administration of adenosine. Semi-quantitative assessments of coronary blood flow and myocardial perfusion such as the TIMI frame count and blush score have largely been confined to research applications and used only for assessing myocardial perfusion at rest.^{31,32} Finally, intra-coronary thermodilution can be used to quantify coronary blood flow using the Fick principle, but is rarely performed in practice. A more detailed comparison of these methods has been undertaken in recent studies³³ and reviews.³⁴

PET Imaging

Similar measurements can be made non-invasively with positron emission tomography (PET) imaging. Advances in software tools have enabled these measurements to be incorporated into routine PET stress testing.³⁵ Initial studies were performed using ¹³N ammonia or ¹⁵O water. ¹³N ammonia is approved for clinical applications in the United States by the Food and Drug Administration. Because of its first-pass myocardial extraction is high even at high blood flow rates, accurate quantification across a wide range of MBF is possible. This tracer also offers excellent image quality for relative myocardial perfusion assessment. However, because the half-life of ¹³N is 9.97 minutes, the tracer must be produced at an onsite or nearby cyclotron facility. ¹⁵O water is freely diffusible, also permitting highly accurate quantification of myocardial perfusion. However, its clinical use is limited due to regulatory constraints (it is not approved by the FDA) and also because it is cumbersome to obtain images for semi-quantitative myocardial perfusion assessment.

Furthermore, the 122-second half-life of ^{15}O requires a cyclotron immediately adjacent to the PET facility.

$^{82}\text{Rubidium}$ is a potassium analog with a half-life of 75 seconds, which is actively transported across myocyte cell membranes. The advent of commercially available generators for onsite production of rubidium-82 has enabled the widespread use of PET imaging without the need for an onsite cyclotron facility. One limitation of this radiotracer is the fact that the maximum kinetic energy of positrons emitted during $^{82}\text{Rubidium}$ decay is significantly higher than that of ^{18}F or ^{13}N . Consequently, the spatial uncertainty in the location of the decaying nucleus—which depends on the distance traveled by the positrons before their annihilation (positron range)—is greater for $^{82}\text{Rubidium}$ (2.6 mm FWHM) than for ^{18}F (0.2 mm FWHM) or ^{13}N (0.7 mm FWHM). Although

$^{82}\text{Rubidium}$ imaging yields excellent image quality with current PET technology, its longer positron range and its short half-life, which requires significant image smoothing to suppress noise, both mitigate somewhat the improved spatial resolution of PET.³⁶ Although the relatively low and nonlinear extraction of ^{82}Rb ³⁷ make quantification more challenging, advances in methodology^{35,38} now permit rapid and reproducible quantification of blood flow with this tracer. However, due to the high cost of rubidium-82 generators, this technology is confined to a relatively small number of high volume centers at present.

Flurpiridaz is a novel ^{18}F -labeled mitochondrial complex I inhibitor with excellent tracer characteristics^{39–41} currently undergoing phase 3 clinical investigation. This tracer has extremely high first-pass extraction⁴² allowing accurate flow quantification across the entire range of clinically relevant flows using traditional⁴⁰ and simplified methods.⁴³ The longer 109.7-minute half-life of the ^{18}F radioligand permits centralized production and unit dose delivery of this agent. Lower barriers to entry, simplified logistics, and most importantly early indications of excellent safety and efficacy⁴⁴ likely portend improved availability of PET myocardial perfusion imaging once this tracer garners regulatory approval.

Other Non-Invasive Methods

MRI can also be utilized to quantify myocardial perfusion in a similar manner,^{45,46} but remains cumbersome and restricted to research applications. Magnetic resonance spectroscopy can also be utilized to identify downstream myocardial metabolic changes, which may result from acute or chronic changes in tissue perfusion, but technically challenging to perform and consequently is largely confined to research applications. Doppler echocardiography of the left anterior descending coronary artery can be used to quantify perfusion in the territory subtended by this vessel at rest and stress in persons with excellent echocardiographic windows.⁴⁷ Quantitative assessment of myocardial perfusion with contrast echocardiography is also possible⁴⁸; however, at present no FDA approved agents are available in the United States for this application, analytical tools remain immature and application is constrained to those individuals with adequate sonographic windows. Dynamic CT can also be used to estimate MBF^{49,50} but is largely limited to research applications due to substantial radiation doses required.

Perhaps the greatest hope for a broadly available non-invasive method for quantification of myocardial perfusion would be to apply SPECT imaging for this purpose. Traditional rotating single- or multi-head SPECT cameras lack the ability to acquire time resolved tomographic volume data required for flow quantification. However, newer dedicated cardiac SPECT cameras utilize high sensitivity CZT detectors permitting acquisition of dynamic (multi-frame) imaging data and quantification of myocardial perfusion.⁵¹ Further investigations will be required to validate these measures.

QUANTITATIVE MBF FOR DIAGNOSIS OF OBSTRUCTIVE CAD

A number of studies have demonstrated that among relatively young patients with modest coronary risk factor burdens and predominantly single-vessel CAD, a relationship exists between MBF or flow reserve and percent diameter stenosis on angiography (Figure 2).^{52–55} These studies demonstrate that myocardial vasodilator capacity is relatively preserved for lesions with <50% stenosis. With increasing severity of stenosis beyond this level, there is progressive worsening of CFR. This observation has been utilized to improve identification of patients with severe CAD involving the left main coronary artery or all three coronary arteries with modest improvements in diagnostic performance^{56–58} compared to semi-quantitative myocardial perfusion assessments.

The modest improvement in diagnostic accuracy is likely multi-factorial. In addition to fixed epicardial obstructive lesions, abnormalities of coronary arterial vasodilation may be due to underlying endothelial and/or vascular smooth muscle dysfunction in large epicardial and/or downstream resistance vessels (the so-called microvascular dysfunction). Furthermore, coronary vascular dysfunction may occur in the absence of any angiographically detectible epicardial atherosclerosis.^{52,59,60} Abnormalities of coronary vascular function have been demonstrated in a variety of disease states known to be associated with accelerated coronary atherosclerosis without overt cardiovascular disease including hypertension,⁶¹ dyslipidemia,^{62,63} tobacco abuse,^{64,65} obesity,^{66,67} metabolic syndrome,⁶⁸ diabetes,^{69–71} and renal dysfunction.⁷² As such, vascular dysfunction represents the earliest form of atherosclerosis, preceding the development of obstructive stenoses that are detectible by traditional imaging modalities,^{64,70,73,74} including coronary calcium scoring.⁷⁵

Coronary risk factors alone, which are highly prevalent in patients referred for diagnostic testing, may result in decreases in peak MBF and flow reserve comparable to that caused by severe coronary artery stenoses.⁵⁹ In some cases, such failure to adequately vasodilate may be sufficient to cause myocardial ischemia even in the absence of epicardial obstructive disease.^{76–78} Because the underlying process in these cases is diffuse atherosclerosis and/or endothelial dys-function, affecting all or most of the coronary tree, regional perfusion abnormalities may be difficult in identifying traditional semi-quantitative approaches. In contrast, non-invasive measures of coronary vascular function provide an integrated measure of the effects of obstructive epicardial stenosis with those of diffuse atherosclerosis and vessel remodeling and microvascular dysfunction.

Consequently, the differentiation of multi-vessel epicardial CAD from diffuse non-obstructive athero-sclerosis and/or microvascular dysfunction causing a global reduction in

MBF and flow reserve in a patient without regional perfusion defects can be quite challenging, especially because in many patients these conditions may co-exist to varying degrees. As discussed below, this has important implications for decisions regarding referral for cardiac catheterization. It is unclear that this distinction can be made using a single severity threshold, as many patients often show profound reduction in myocardial flow reserve even in the absence of obvious epicardial stenosis (Figure 3).

The addition of coronary CTA can be quite helpful to identify obstructive stenosis, which may contribute to reduced flow reserve. Indeed, Kajander et al⁷⁹ demonstrated that the addition of information concerning the presence of epicardial coronary stenosis with CTA was able to increase the specificity of the quantitative PET findings (Figure 4). With state-of-the-art scanners and modern protocols, hybrid PET MPI and coronary CTA examinations to simultaneously identify obstructive and non-obstructive epicardial atherosclerosis and define its physiologic significance can be accomplished at a relatively low radiation exposure (6–10 mSv), or perhaps less using combined PET/MRI scanners. Conversely, by defining flow-limiting disease quantitative myocardial flow reserve measures improve the specificity of coronary CTA findings. On the other hand, the presence of a regional perfusion defect by semi-quantitative visual analysis combined with diffusely reduced myocardial flow reserve can be quite helpful for identification of multi-vessel CAD (Figures 4, 5).

PROGNOSTIC IMPLICATIONS OF CORONARY VASCULAR DYSFUNCTION

Because quantitative measures of coronary vascular function integrate the fluid dynamic effects of atherosclerosis throughout the coronary arterial tree including epicardial stenoses with early changes to endothelial and/or smooth muscle function, quantitative myocardial flow reserve may be a superior measure of overall vascular health that provides unique information about clinical risk. Five studies have demonstrated that PET measures of myocardial flow reserve improve cardiac risk assessment (Table 1).^{80–84} The largest of these studies⁸⁰ demonstrated that among 2,783 patients with known or suspected CAD evaluated with ⁸²Rb PET, patients with CFR < 1.5 were at nearly 16-fold increased risk of death from cardiac causes compared to patients with CFR > 2.0. After adjustment for a wide array of risk factors and rest and stress imaging findings, these patients remained at nearly 6-fold increased risk of cardiac mortality (Figure 6). Furthermore, approximately half of patients who would be classified as intermediate risk based on clinical risk factors, systolic function and combined scar and ischemia extent are reclassified as either low or high risk (Figure 7).

Importantly, an abnormal CFR identified increased risk of cardiac death even among those normal scans by semi-quantitative visual analysis. This likely reflects the observation that vasomotor dysfunction abnormalities are manifested in patients with the earliest stages of atherosclerosis without overt CAD and angiographically normal coronary arteries,⁸⁵ and have been linked to both disease progression⁸⁶ and adverse cardiovascular events including sudden death, myocardial infarction, heart failure, and coronary revascularization.^{87–90}

MEDICAL TREATMENT OF CORONARY VASCULAR DYSFUNCTION

Despite growing understanding of the pathophysiologic basis and prognostic significance of coronary vasomotor dysfunction, the treatment implications of this condition remain uncertain. Several standard treatments which have been proven to reduce risk in persons with atherosclerosis including statins^{91–98} and multiple classes of antihypertensive medications^{99–117} have been shown to improve CFR with short- to medium-term use. Similarly, exercise¹¹⁸ and weight loss¹¹⁹ have also been shown to improve CFR. All these interventions are already indicated in persons with overt atherosclerosis. However, the impact of these treatments on prognosis in patients with vasodilator abnormalities without overt epicardial coronary atherosclerosis remains uncertain and merits further investigation.

Importantly, in assessing response to treatment, either in the clinic or as part of investigational protocols, regression of plaques is usually modest.¹²⁰ Improvement of myocardial ischemia by stress perfusion imaging typically demonstrates very small improvements with treatment.^{121–123} Coronary calcifications are unlikely to regress even in the face of treatments with proven benefit from adverse outcome reduction. Conversely, because vasodilator function is a more dynamic marker of vascular health it may be useful to assess early response to therapies in persons with atherosclerosis, guide further intensification of therapy and encourage sustained patient adherence. The correlation between improvement in vasodilator capacity and decreased risk of adverse cardiac outcomes should be studied further.

IMPLICATIONS FOR ANGIOGRAPHY AND REVASCULARIZATION

While the use of CFR to identify candidates for medical therapy remains untested, even less certainty exists about how to incorporate CFR into decision making for angiography and revascularization. As discussed above, addition of CFR to other high-risk findings on stress testing may improve identification of patients with high-risk coronary anatomy (i.e., left main or three-vessel coronary disease).^{56,57} However, because diffuse atherosclerotic changes and microvascular dysfunction can also lower CFR, improvements in sensitivity are likely to be accompanied by loss of specificity and subsequent increase in false positives (Figure 8).^{57,58} Thus, to avoid unnecessary referrals to angiography, careful consideration must be made of clinical history and imaging findings prior to each referral. Furthermore, the optimal diagnostic thresholds remain undefined and commonly cited values of <2.0 and <1.8 are largely unvalidated. As discussed above, addition of CT coronary angiography may be quite useful as a screen to identify patients in whom the cause of low CFR is obstructive epicardial stenosis as opposed to diffuse atherosclerosis and/or microvascular dysfunction.⁷⁹

Conversely, increasing evidence¹²⁴ shows that revascularization guided by ischemia as determined by fractional flow reserve evaluated with a pressure wire in the cardiac catheterization lab leads to better outcomes when compared to angiography-driven revascularization. As such, current guidelines recommend objective documentation of ischemia prior to percutaneous revascularization.¹²⁵ Potentially, addition of CFR may improve selection of patients who would benefit from angiography and revascularization compared to overt ischemia alone, thereby simultaneously reducing complications and cost

of unnecessary angiography while also improving the benefit accrued to those who do undergo revascularization. Data from one large study,⁸⁰ suggest that even among patients with moderate-to-severe ischemia, global CFR can identify patients with relatively favorable prognosis. Conceivably, these patients may have less benefit (but equal risk) from revascularization. This too deserves further investigation.

CONCLUSIONS

Despite major progress in the evaluation and treatment of coronary artery disease, focus has largely been on epicardial atherosclerosis. Methods to evaluate coronary vasodilator function are rapidly maturing and are complementary to current standard of care. These tools offer the potential to identify earlier stages of atherosclerotic coronary disease as well as to improve risk stratification and selection and titration of medical and revascularization therapies.

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Figure 1.

Underestimation of extent of CAD by R-MPI. Despite excellent overall per patient sensitivity for the presence of disease, traditional relative myocardial perfusion imaging (R-MPI) often underestimates disease extent and is unable to reliably distinguish patients with severe CAD from those with milder disease. Even addition of ancillary signs of advanced CAD such as decreased EF, defects involving multiple vessel territories, lung uptake, wall motion abnormalities and TID were not able to capture all cases of left main disease. Adapted with permission from Berman et al.²¹ * $P < .05$ compared to >10% defect.

Figure 2. Relationship between MPR and epicardial stenosis severity plot demonstrating that MPR determined by ^{13}N ammonia PET declines rapidly for stenoses with $>50\%$ diameter stenosis on quantitative coronary angiography. Adapted with permission from Di Carli et al.⁵³

Figure 3.

Severely reduced MPR in the absence of severe epicardial stenosis relative perfusion images (*top*) from a 37-year-old man with diabetes, chronic kidney disease requiring hemodialysis, dyslipidemia hypertension, and past smoking referred for evaluation of chest pain and ST-segment depression on exercise testing show a small region of moderate stress-induced perfusion abnormality in the apex. The CFR measured with ^{82}Rb PET was severely diminished at 1.22. Coronary angiography (*bottom*) showed no hemodynamically significant epicardial coronary lesions.

Figure 4.

Addition of CTA to quantitative PET improves diagnostic accuracy sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall diagnostic accuracy for coronary CT angiography (CTA), quantitative ^{15}O water PET stress perfusion or both among 107 prospective patients compared to quantitative invasive coronary angiography and fractional flow reserve assessments. Addition of CTA to PET significantly improved overall diagnostic accuracy compared to CTA alone ($P = .004$) or PET alone ($P = .01$). Adapted with permission from Kajander et al⁷⁹.

Figure 5.

MPR is abnormal in occult multi-vessel CAD relative perfusion images (*top*) from a 64 year-old man referred for evaluation of substernal chest pain at rest showed only a small region of stress-induced perfusion abnormality in the inferolateral wall. Angiography (*bottom*) performed the next day demonstrated a complex 80% left main stenosis involving the ostia of the left circumflex and left anterior descending coronary arteries. The CFR measured with ^{82}Rb PET was decreased at 1.63.

	Log-Rank P-Value	Adjusted P-Value	Adjusted HR
Lower vs. Upper	<0.0001	<0.0001	5.6 [2.5-12.4]
Middle vs. Upper	<0.0001	0.003	3.4 [1.5-7.7]

Figure 6.

Cardiac mortality by MPR unadjusted Kaplan-Meier cardiac mortality by tertiles of MPR in 2,783 patients referred for PET stress testing. Patients with the lowest perfusion reserve (*red* <1.5) and intermediate perfusion reserve (*blue* 1.5–2.0) had a 5.6-fold increased rate of cardiac mortality compared to those with preserved flow reserve (*green* >2.0) after adjustment for age, sex, hypertension, dyslipidemia, diabetes, family history of premature CAD, tobacco use, prior history of CAD, BMI, chest pain, dyspnea, and early revascularization. Adapted with permission from Murthy et al.⁸⁰ HR, Hazard ratio.

Figure 7.

Risk reclassification by MPR illustration of risk reclassification by addition of MPR to a model containing clinical risk factors, rest and stress imaging findings. The *upper horizontal bar graph* represents the distribution of risk across categories of <1 (green), 1–3 (blue), and >3% (red) per year risk of cardiac death as estimated by a model containing clinical risk factors, rest LVEF, LVEF reserve and the combination of myocardial scar and ischemia. The pie graphs represent the proportions of patients in each pre-MPR category reassigned to each risk category after the addition of MPR to the risk model. The *vertical bar charts at the bottom* represent the annualized rates of cardiac mortality in each of the post-MPR risk categories. Adapted with permission from Murthy et al.⁸⁰

Figure 8.

Probability of three-vessel CAD by MPR unadjusted probability of three-vessel CAD (*red line*) as a function of MPR with 95% confidence intervals (CI, *blue lines*). Although there is a clear increase in the proportion of patients with three-vessel CAD as MPR declines, even among patients with severely reduced MPR between 1.0 and 1.5, only a minority have three-vessel disease. Thus, the positive predictive value of reduced MPR is modest. Adapted with permission from Ziadi et al.⁵⁷

Table 1.

Studies of prognostic impact of myocardial perfusion reserve (MPR)

Study	Number of subjects	Follow-up duration (years)	Primary endpoint	Radiotracer	Adjusted covariates	Hazard ratio
Herzog ⁸²	256	5.4	MACE (cardiac death, non-fatal mi, late revascularization, cardiac hospitalization)	¹³ N Ammonia	Age, diabetes, smoking, abnormal perfusion (binary)	1.6 (MFR <2.0 vs 2.0)
Tio ⁸³	344	7.1	Cardiac death	¹³ N Ammonia	Age, sex	4.1 (per 0.5 MFR)
Murthy ⁸⁰	2,783	1.4	Cardiac death	⁸² Rb	Age, sex, hypertension, dyslipidemia, diabetes, family history of premature cad, tobacco use, history of cad, BMI, chest pain, dyspnea, early revascularization, rest LVEF, summed stress score, LVEF reserve	5.6 (MFR <1.5 vs >2.0) 3.4 (MFR 1.5–2.0 vs [2.0])
Fukushima ⁸¹	224	1.0	MACE (cardiac death, non-fatal mi, late revascularization or catheterization, hospitalization for heart failure)	⁸² Rb	Age, summed stress score (dichotomized >4)	2.9 (MFR <2.11 vs 2.11)
Ziadi ⁸⁴	677	1.1	MACE (cardiac death, non-fatal mi, late revascularization, cardiac hospitalization)	⁸² Rb	History of MI, stress LVEF, summed stress score (dichotomized 4)	3.3 (MFR <2.0 vs >2.0)

MACE, Major adverse cardiac events; MI, myocardial infarction; CAD, coronary artery disease; BMI, body mass index; LVEF, left ventricular ejection fraction; MFR, myocardial flow reserve.