SPECT myocardial perfusion imaging-based ischemia-guided early coronary revascularization improves survival: More fuel to the fire

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Stable coronary artery disease (CAD) is a major public health burden worldwide and is prevalent in a significant proportion of the adult population. In the USA between 2011 and 2014, around 6.3% of adults over 20 years of age had coronary heart disease (around 20% of adults over 60 years) with a 3.0% prevalence of myocardial infarction and 3.4% prevalence of angina pectoris.¹ Globally, ischemic heart disease is present in around 110 million people and in 16.5 million adults with in the USA.¹ Patients with obstructive atherosclerotic CAD may be asymptomatic or present with symptoms ranging from stable angina to acute coronary syndromes or sudden cardiac death. The cornerstone treatment of stable CAD is unquestionably the appropriate use of guideline-directed medical therapy to prevent the progression of atherosclerosis, to manage angina symptoms, and to prevent acute coronary syndromes and cardiovascular death.² Whether revascularizing patients with obstructive but stable CAD would improve cardiovascular outcomes has been an ongoing debate for well over 2 decades now.

Furthermore, what is the optimal threshold for differentiating “significant” from “non-significant” CAD and what is the optimal modality for making such a determination remains the most controversial and passionate topic for discussion in current cardiology literature.

In this issue of the journal, Sharir et al have investigated the prognostic effects of early revascularization in around 48,000 consecutive stable CAD patients undergoing single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) and followed for a mean duration of 4 years.³ Of their study population enrolled from 2 medical centers in Israel, 1837 patients had early revascularization (≤ 60 days after stress MPI). Notable findings from this study are (1) Around one in 6 patients (~ 8000 patients) had $\geq 5\%$ ischemia of the left ventricle (based on myocardial uptake in 17 segments). (2) Annual death rate increased with the degree of inducible ischemia on MPI. (3) Patients with moderate-severe ischemia ($\geq 10\%$) had a 33% lower death rate, 31% lower death + myocardial infarction rate, and 20% lower death + myocardial infarction + late revascularization (MACE) rate with early revascularization compared to medical treatment alone. (4) In patients with mild ischemia (5 to 9%), revascularization did not improve survival or myocardial infarction-free survival and was associated with a 30% higher MACE-rate, an effect that was driven primarily by high late revascularization rates. Results of this eloquently done study add to the existing literature that identifies high-risk stable CAD patients who could benefit from early coronary revascularization based on the extent of myocardial ischemia on SPECT-

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MPI. The current study supports the role of non-invasive MPI-based physiological testing with SPECT to identify revascularization candidates among patients with stable CAD.

While data from large randomized controlled trials and meta-analyses failed to demonstrate improved survival or hard cardiac endpoints with routine coronary revascularization in stable CAD patients, several observational studies and post hoc analyses of randomized trials suggested improved survival with revascularization in CAD patients with moderate-to-high-grade ischemia on physiologic testing. Routine revascularization of stable CAD with percutaneous coronary intervention (PCI) in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, and with PCI or coronary artery bypass grafting (CABG) in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, did not reduce the rates of death or myocardial infarction at long-term follow-up when compared to aggressive modern optimal medical therapy. Important to know is that the patients in these trials had angiographically documented anatomic obstructive CAD without knowledge of functional significance of these lesions (ischemia producing or not).

Over half the patients who undergo cardiac catheterization have had a stress test with MPI and it is the most commonly used test to assess the presence and the extent of myocardial ischemia.⁴ SPECT-MPI has a high accuracy for the diagnosis of significant epicardial CAD and confers important prognostic information in patients with known or suspected CAD.^{4,5} Further, it has the benefits on being non-invasive and readily available. Prior studies have shown that in patients with stable chest pain, normal SPECT-MPI is associated with a very low cardiac event rate of < 1.0% per year even in the presence of angiographic CAD.^{6,7} Inducible ischemia during non-invasive physiologic testing with MPI has been shown to be associated with increased risk of cardiac death and myocardial infarction, findings which were also replicated in the current study.^{5,8–11} Smaller studies have demonstrated findings which contradict the prognostic role of stress ischemia, although some used non-imaging-based modalities to ascertain ischemia.^{12,13} The beneficial role of coronary revascularization to reduce the extent of ischemic territory has been shown in the nuclear sub-studies of the COURAGE and the BARI 2D trials, although the clinical benefit of revascularization strategy was not proven in either analyses (utilized different methods to identify degree of ischemia than the 17-segment myocardial uptake model).^{8,10,14}

However, several observational analyses in the last 2 decades provided evidence to support early

revascularization to improve outcomes in stable CAD and at least moderate inducible ischemia on SPECT stress MPI.¹⁵ First of these was the study by Hachamovitch et al who examined the role of early revascularization in 10,627 patients without prior CAD who had a mean 2-year follow-up after a SPECT stress MPI. Of the study population, 671 patients received early coronary revascularization within 60 days from the MPI.¹⁶ The authors reported that patients undergoing medical therapy demonstrated a survival advantage over patients undergoing revascularization in the setting of no or mild ischemia (< 10%), whereas patients undergoing revascularization had an increasing survival benefit over patients undergoing medical therapy when moderate-to-severe ischemia was present (> = 10%). These findings persisted despite the presence of prior CAD in a larger series of around 14,000 patients in whom patients with significant ischemia and without extensive myocardial scar were likely to realize a survival benefit from early revascularization, whereas patients with minimal ischemia had better survival with medical therapy without early revascularization.¹⁷

Similar findings were replicated in several other observational series.^{18,19} Other studies have also demonstrated that with normal MPI, revascularization in stable CAD conferred a higher risk of all-cause death.²⁰ Results from the current study are in line with these findings from prior studies which favor medical therapy in stable CAD patients with mild or no ischemia on stress testing, and a more aggressive approach with coronary revascularization in patients with at least moderate ischemia. A finding from the current study which contradicts prior reports is the neutral role of the presence of myocardial scar tissue on survival outcomes after revascularization. In a prior study by Hachamovitch et al, the presence of scar involving > 10% myocardium nullified the beneficial role of coronary revascularization despite the presence of significant ischemia on SPECT-MPI testing.¹⁷

This study by Sharir et al adds more fuel to the ongoing debate that imaging-based stress MPI identifies high-risk stable CAD candidates for coronary revascularization to improve mortality and cardiac outcomes. However, the study is not without limitations associated with existing observational data including selection bias from lack of randomization, and center specific practices which might influence choice of therapy and outcomes. To overcome these limitations, the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial randomized 5179 stable CAD patients in 37 countries and 320 sites with moderate-severe ischemia on stress testing and without non-obstructive CAD or unprotected significant left main coronary artery CAD (assessed on subsequent

CCTA imaging) to either optimal medical therapy or medical therapy plus early optimal coronary revascularization.²¹ Around 50% ($N = 2563$) of the study population had nuclear stress MPI testing, 25% patients had other stress imaging modalities (stress echocardiography, magnetic resonance imaging), and 25% underwent exercise stress testing. Of the randomized sample, around 90% patients had moderate-to-severe ischemia. At a median 3.3-year follow-up, an initial invasive strategy with revascularization as compared with an initial conservative strategy with only optimal medical therapy did not reduce the risk for the primary composite endpoint of cardiovascular death, myocardial infarction, hospitalization for unstable angina, heart failure or resuscitated cardiac arrest, or the risk for secondary composite endpoint of cardiovascular death or myocardial infarction. Results were consistent across the various degrees of ischemia and across the various stress testing modalities utilized.

The recently reported ISCHEMIA trial questions the role of early revascularization to improve survival and cardiovascular outcomes in patients with stable CAD, and particularly the role of functional ischemia testing to identify revascularization candidates. However, the median follow-up was only 3.3 years and around 25% of the patients randomized to the conservative strategy crossed over to the revascularization arm (half of which were due to failure of medical therapy or non-adherence and the other half due to an acute coronary syndrome). In fact, there were more primary outcome events in the revascularization group until around 2 years after which the Kaplan–Meier curves diverged in favor of the revascularization strategy although non-statistically significant. Further, peri-procedural MIs were increased in the invasive strategy arm but spontaneous MIs were reduced in this arm. Favorable improvement in quality of life was noted with the invasive strategy in patients with an extensive disease burden at randomization, who had significantly more improvement in anginal symptoms. Findings from these trials raise the question whether there would be significant difference in outcomes favoring the revascularization strategy with longer follow-up and after accounting for crossover. Long-term follow-up of the patients (planned for an additional 5 years) beyond the currently reported median 3.3-year follow-up results will definitively confirm if there is a role for ischemia-guided early revascularization in these patients.

In clinical practice, it is not uncommon to encounter situations in which cardiologists are required to risk stratify or “clear” patients with stable CAD for employment, exercise-related activities, and for elective non-cardiac surgeries. Answers to such questions are highly variable and depend largely on physician

preferences and are usually given with extreme caution. While the goal of therapy for stable CAD should be to allow patients to lead an active and normal life, knowledge of ischemic burden of stable CAD might prevent achieving such goals when only optimal medical therapy is utilized. Despite the clinical implications of the ISCHEMIA trial results, SPECT-MPI does have an important application in risk stratifying stable CAD patients to facilitate informed physician–patient discussions regarding the need for aggressive optimal medical therapy or revascularization. In the current real-world study by Sharir et al, only around 5% patients had moderate-severe ischemia on SPECT-MPI testing, and survival was lower with increasing extent of ischemia. These findings call for research to identify if medical therapy can be optimized to the degree of inducible myocardial ischemia on nuclear MPI testing. Furthermore, the goal of therapy in patients with stable CAD is to have them lead an active and unrestricted life to a normally expected life span. Until we have longer term follow-up data from the ISCHEMIA trial, perhaps it is acceptable to continue to identify high-risk patients from stress-rest perfusion imaging for consideration of revascularization.

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