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## Death and myocardial infarction following initial revascularization versus optimal medical therapy in chronic coronary syndromes with myocardial ischemia: A systematic review and meta-analysis of contemporary randomized controlled trials

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SYSTEMATIC REVIEW AND META-ANALYSIS

# Death and Myocardial Infarction Following Initial Revascularization Versus Optimal Medical Therapy in Chronic Coronary Syndromes With Myocardial Ischemia: A Systematic Review and Meta-Analysis of Contemporary Randomized Controlled Trials

Andrea Soares, MD; William E. Boden, MD; Whady Hueb, MD, PhD; Maria M. Brooks, PhD; Helen E. A. Vlachos, MS; Kevin O'Fee, MD; Angela Hardi , MLIS; David L. Brown , MD

**BACKGROUND:** In chronic coronary syndromes, myocardial ischemia is associated with a greater risk of death and nonfatal myocardial infarction (MI). We sought to compare the effect of initial revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) plus optimal medical therapy (OMT) with OMT alone in patients with chronic coronary syndrome and myocardial ischemia on long-term death and nonfatal MI.

**METHODS AND RESULTS:** Ovid Medline, Embase, Scopus, and Cochrane Library databases were searched for randomized controlled trials of PCI or CABG plus OMT versus OMT alone for patients with chronic coronary syndromes. Studies were screened and data were extracted independently by 2 authors. Random-effects models were used to generate pooled treatment effects. The search yielded 7 randomized controlled trials that randomized 10 797 patients. Median follow-up was 5 years. Death occurred in 640 of the 5413 patients (11.8%) randomized to revascularization and in 647 of the 5384 patients (12%) randomized to OMT (odds ratio [OR], 0.97; 95% CI, 0.86–1.09;  $P=0.60$ ). Nonfatal MI was reported in 554 of 5413 patients (10.2%) in the revascularization arms compared with 627 of 5384 patients (11.6%) in the OMT arms (OR, 0.75; 95% CI, 0.57–0.99;  $P=0.04$ ). In subgroup analysis, nonfatal MI was significantly reduced by CABG (OR, 0.35; 95% CI, 0.21–0.59;  $P<0.001$ ) but was not reduced by PCI (OR, 0.92; 95% CI, 0.75–1.13;  $P=0.43$ ) ( $P$ -interaction  $<0.001$ ).

**CONCLUSIONS:** In patients with chronic coronary syndromes and myocardial ischemia, initial revascularization with PCI or CABG plus OMT did not reduce long-term mortality compared with OMT alone. CABG plus OMT reduced nonfatal MI compared with OMT alone, whereas PCI did not.

**Key Words:** coronary artery bypass grafting ■ coronary artery disease ■ myocardial ischemia ■ percutaneous coronary intervention

Ischemic heart disease, which includes the acute coronary syndromes and chronic coronary syndromes (CCS), is the leading cause of death and years of lost life in adults worldwide.<sup>1,2</sup> Annually,  $\approx 1$  in 30 patients

with CCS, also referred to as stable coronary artery disease (CAD) or stable ischemic heart disease, will experience cardiovascular death or myocardial infarction (MI),<sup>3</sup> generally caused by the transition to an

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## CLINICAL PERSPECTIVE

### What Is New?

- This updated systematic review and meta-analysis of randomized controlled trials of patients with chronic coronary syndromes and inducible myocardial ischemia included studies comparing percutaneous coronary intervention plus medical therapy versus medical therapy alone and coronary artery bypass grafting plus medical therapy versus medical therapy alone as well as studies that enrolled patients with chronic kidney disease and severely reduced left ventricular function.
- At a median follow-up of 5 years, initial revascularization with percutaneous coronary intervention or coronary artery bypass grafting plus medical therapy did not reduce death compared with medical therapy alone.
- Coronary artery bypass grafting plus medical therapy reduced nonfatal myocardial infarction compared with medical therapy alone, whereas percutaneous coronary intervention did not.

### What Are the Clinical Implications?

- For most patients with chronic coronary syndromes but without left main coronary disease or severely reduced left ventricular function, shared decision-making about revascularization should be based on discussions of symptom relief and quality of life and not about reduction in mortality.
- For patients in whom reduction in myocardial infarction is a predominant concern, coronary artery bypass grafting plus medical therapy is superior to medical therapy alone and to percutaneous coronary intervention plus medical therapy.

## Nonstandard Abbreviations and Acronyms

<b>BARI 2D</b>	Bypass Angioplasty Revascularization 2 Diabetes
<b>CCS</b>	chronic coronary syndrome
<b>COURAGE</b>	Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation
<b>FAME 2</b>	Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2
<b>FFR</b>	fractional flow reserve
<b>ISCHEMIA</b>	International Study of Comparative Health Effectiveness With Medical and Invasive Approaches

<b>ISCHEMIA-CKD</b>	International Study of Comparative Health Effectiveness With Medical and Invasive Approaches—Chronic Kidney Disease
<b>MASS II</b>	Medicine, Angioplasty, or Surgery Study II
<b>OMT</b>	optimal medical therapy
<b>STICH</b>	Surgical Treatment for Ischemic Heart Failure

acute coronary syndrome, in particular ST-segment-elevation MI.<sup>4</sup> A primary goal of treatment of CCS is to prevent death and MI.

Ischemia in CCS may occur in the presence or absence of obstructive CAD involving the epicardial coronary arteries.<sup>5</sup> Because of the strong association of ischemia on stress testing with an increased risk of death or MI, the presence of myocardial ischemia in patients found to have obstructive CAD, even in the absence of angina, often triggers referral for elective revascularization,<sup>6–9</sup> with the theoretical goal of preventing MI and reducing downstream mortality. However, contemporary randomized controlled trials (RCTs) of initial percutaneous coronary intervention (PCI)-based revascularization plus optimal medical therapy (OMT) versus OMT alone have never demonstrated a reduction in death or MI in patients assigned to PCI. One explanation for the lack of benefit from PCI in earlier trials is that not all patients in those trials had documented ischemia or its surrogate, an abnormal fractional flow reserve (FFR). In theory, the absence of a requirement for documented ischemia might have allowed enrollment of patients at too low risk to benefit from PCI. However, in a prior meta-analysis of 5 clinical trials enrolling a total of 5286 patients with CCS and myocardial ischemia, determined by stress testing or FFR, PCI in combination with OMT did not demonstrate a significant reduction in mortality or nonfatal MI compared with OMT alone, suggesting that the association between ischemia and death or nonfatal MI is not causal.<sup>10</sup> However, that meta-analysis did not include RCTs of patients with ischemia who were randomized to coronary artery bypass grafting (CABG) in combination with OMT versus OMT alone. CABG is an important revascularization modality for which improved survival and reductions in new MI have been consistently demonstrated in CCS.<sup>11</sup> It also included studies in which the angiographic anatomical features were defined before enrollment, which may have resulted in patients with high-risk anatomical features not being enrolled. The recently published ISCHEMIA (International Study of Comparative Effectiveness With Medical and Invasive

Approaches) trial<sup>12</sup> randomized 5179 CCS patients with moderate to severe ischemia to an invasive strategy consisting of PCI, CABG, or no revascularization, as indicated, with OMT versus OMT alone after left main CAD was ruled out and obstructive epicardial disease was demonstrated on coronary computed tomography angiography. Its design addressed potential shortcomings of earlier studies in that enrollment required moderate to severe ischemia on stress testing, randomization was performed before coronary angiography, and complete revascularization was the goal with either PCI or CABG. Nevertheless, the study was underpowered to assess the impact of an invasive strategy on death or nonfatal MI. Given this important new study, we performed an updated, study-level meta-analysis that included the ISCHEMIA trial as well as other studies that included revascularization using PCI or CABG to determine the long-term impact of revascularization on death and nonfatal MI in patients with CCS, obstructive CAD, exclusive of left main CAD, and myocardial ischemia.

## METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request. We performed a systematic review and meta-analysis, reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.<sup>13</sup> The protocol was registered with PROSPERO (International Prospective Register of Systematic Reviews) (registration No. CRD42020158821).

### Search Strategy

The published literature was searched using strategies implemented by a medical librarian using search terms *stable coronary artery disease*, *stable angina*, *percutaneous coronary intervention*, *coronary artery bypass graft surgery*, *medical therapy*, and combinations of these terms. These strategies were executed in Ovid-Medline 1946-, Embase 1947-, Scopus 1923-, the Cochrane Library, and Clinicaltrials.gov. Results were limited to RCTs by using filters recommended by the Cochrane Group for Ovid-Medline,<sup>14</sup> Embase,<sup>15</sup> and a librarian-created filter for Scopus.<sup>16</sup> All searches were completed in April 2020. Search strategies can be found in Data S1.

### Inclusion Criteria

For inclusion, studies were required to be prospective, randomized trials of revascularization (PCI or CABG) plus OMT versus OMT alone in patients with CCS and epicardial obstructive CAD, with the individual outcomes of all-cause death and nonfatal MI

reported. Studies with 3-way randomizations to PCI plus OMT versus CABG plus OMT versus OMT alone were included. To reflect more contemporary interventional and medical practice, inclusion required stent implantation in at least 50% of PCI procedures and use of a statin in at least 50% of patients. Finally, myocardial ischemia or abnormal FFR had to be documented in all patients before randomization. Studies of stable patients following a completed MI were excluded.

### Data Extraction

For studies in which all patients had either myocardial ischemia on stress testing or an abnormal FFR,<sup>17</sup> patient characteristics, study design, and outcomes were systematically reviewed and recorded independently by 2 authors (A.S. and D.L.B.). For studies in which not all patients were required to have ischemia on stress testing,<sup>18–20</sup> the primary authors were contacted and provided data on the subset of patients with ischemia at the time of randomization. The data set for the STICH (Surgical Treatment for Ischemic Heart Failure) trial<sup>21</sup> was obtained on request from the Biologic Specimen and Data Repository Information Coordinating Center of the National Heart, Lung, and Blood Institute under a data use agreement. Only patients who had an ischemic response on dobutamine stress echocardiography or a radionuclide stress test within 90 days of randomization and before surgical revascularization were included. The Washington University Human Research Protection Office granted this study an exemption from Institutional Review Board oversight because of the deidentified nature of the data.

The risk of bias was evaluated according to the criteria of Jadad,<sup>22</sup> including verification of randomization, blinding of investigators and patients to treatment allocation, and description of patients who withdrew.

### Outcomes

The following clinical outcomes were analyzed: death from any cause and nonfatal MI. End point definitions were those used in the individual trials. The definition of nonfatal MI varied and became more precise in the more recent studies, with the diagnosis generally requiring appropriate symptoms, biomarker elevation, and/or electrocardiographic changes. Nonfatal post-procedural MI was included as a nonfatal MI outcome. Definitions of MI for each study are included in Data S1.

### Statistical Analysis

As individual patient-level data were only available from one trial,<sup>21</sup> a study-level meta-analysis of summary statistics from individual trials was performed using Comprehensive Meta Analysis software,

version 2 (Biostat, Englewood, NJ). Data were analyzed according to the intention-to-treat principle. The presence of statistically significant between-study heterogeneity that exceeds that expected by chance alone was assessed by the  $Q$  statistic (significant at  $P < 0.10$ ), and the extent of any observed between-study heterogeneity was determined by the  $I^2$  (ranging from 0%–100%). Because the absence of statistical heterogeneity does not guarantee clinical homogeneity, summary odds ratios (ORs) for all end points were calculated with the inverse variance method using a random-effects model from the ORs and 95% CIs for each end point in each study. The random-effects model provides a more conservative summary estimate because it incorporates both within-trial and between-trial variance. Except for the  $Q$  statistic,  $P < 0.05$  was considered statistically significant, and all tests were 2 sided.

Potential associations of treatment effect with study-level variables were examined in subgroup analyses. Studies in which revascularization was performed exclusively or predominantly with PCI were compared with studies in which revascularization was performed exclusively by CABG. In addition, studies in which all randomized patients had ischemia were compared with studies in which only a subset of patients had ischemia before randomization. Subgroups were compared using a mixed effects analysis in which a random effects model is used to combine studies within each subgroup and a fixed effect model is used to combine subgroups and yield the overall effect.

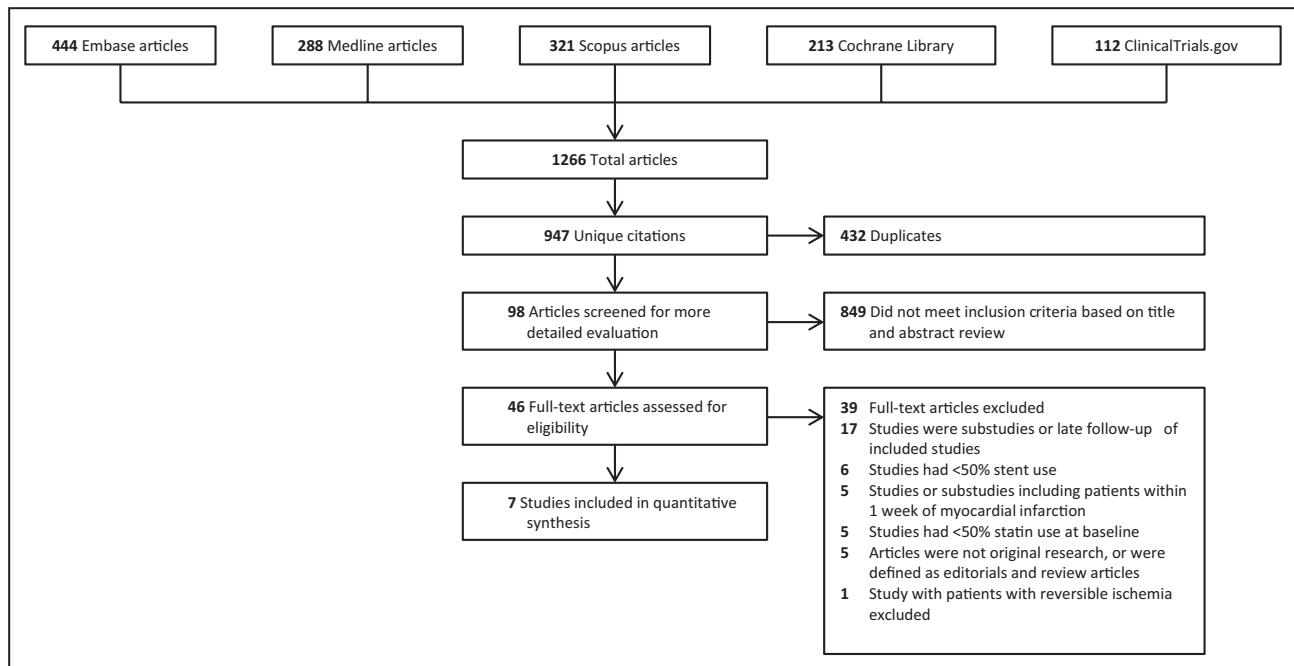
Sensitivity analyses were performed for each outcome to determine whether any single study disproportionately influenced the pooled estimate by excluding individual trials one at a time and recalculating the combined OR for the remaining studies. In addition, the data for nonfatal MI were analyzed using the less restrictive secondary definition of MI (Data S1) in the ISCHEMIA<sup>12</sup> and ISCHEMIA-CKD (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches—Chronic Kidney Disease)<sup>23</sup> trials.

Because the number of studies was  $< 10$  for both mortality and nonfatal MI end points, a funnel plot assessment for publication bias was not performed as the power of the tests is too low to distinguish chance from actual asymmetry.<sup>24</sup>

## RESULTS

### Literature Search

The electronic search yielded 947 unique citations, which were screened by reviewing the title or abstract of each. Of these, 98 publications were reviewed in full and 7 trials were included in the meta-analysis (Figure 1). These were MASS II (Medicine, Angioplasty, or Surgery Study II),<sup>18</sup> COURAGE (Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation),<sup>19</sup> BARI 2D (Bypass Angioplasty Revascularization 2 Diabetes),<sup>20</sup> STICH,<sup>21</sup> FAME 2 (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2),<sup>17</sup> ISCHEMIA,<sup>12</sup> and ISCHEMIA-CKD<sup>23</sup> (Table 1). BARI 2D



**Figure 1. Study selection.**

Flow diagram depicts study selection for inclusion in the meta-analysis, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for reporting systematic reviews and meta-analyses.

consisted of 2 embedded trials, a randomized trial of PCI plus OMT versus OMT alone and a separate randomization to CABG plus OMT versus OMT alone.<sup>20</sup> MASS II included a single 3-way randomization to CABG plus OMT, PCI plus OMT, or OMT alone.<sup>18</sup> The 100 patients in the OMT arm were compared separately with the PCI and CABG arms. The 7 trials enrolled patients between 1997 and 2018. All studies excluded patients with left main stenosis of  $\geq 50\%$ . The stress testing modalities and the criteria used to diagnose ischemia are presented in Table 1. The median follow-up of the 7 trials was 5 years.

Of 10 797 patients with myocardial ischemia at the time of randomization on the basis of stress testing or the presence of at least 1 hemodynamically significant coronary stenosis by FFR, 5413 were randomized to revascularization plus OMT and 5384 were randomized to OMT alone. Baseline characteristics of the study populations are presented in Table 2. Patients enrolled in the studies were predominantly men. Patients with diabetes mellitus comprised 26% to 100% of the study populations, and 16% to 75% had experienced a prior MI. Mean ejection fractions ranged from 26% to 67%. OMT included aspirin,  $\beta$ -blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statins. All studies allowed crossover from OMT to PCI or CABG for refractory symptoms at the discretion of the treating physician. Unplanned revascularization occurred in 19% to 51% of patients in OMT arms related to crossover for treatment of refractory symptoms and in 3.9% to 35% of patients in revascularization arms for progression of disease, graft failure, or restenosis at the site of PCI. Drug-eluting stent use ranged from 0% in early studies to 100% in more contemporary studies (Table 2).

The risk of bias, as assessed by the Jadad criteria,<sup>22</sup> is summarized in Table 3. None of the trials was blinded. All of the studies were randomized and reported on study withdrawals and the completeness of follow-up. All studies used an independent committee to adjudicate end points.

## Quantitative Outcomes

Of the 1287 deaths in the 10 797 randomized patients with ischemia, 640 occurred in the 5413 patients (11.8%) randomized to revascularization plus OMT, whereas 647 occurred in the 5384 patients (12%) randomized to OMT alone. The OR for revascularization plus OMT versus OMT alone for mortality was 0.97 (95% CI, 0.86–1.09;  $P=0.60$ ;  $Q=6.5$ ;  $P=0.60$ ;  $I^2=0\%$ ) (Figure 2).

Nonfatal MI was reported in 554 of 5413 patients (10.2%) in the revascularization arms compared with 627 of 5384 patients (11.6%) in the OMT arms of

randomized trials. The OR for nonfatal MI for revascularization compared with initial OMT was 0.75 (95% CI, 0.58–0.99;  $P=0.04$ ;  $Q=25.8$ ;  $P=0.001$ ;  $I^2=69\%$ ) (Figure 3A).

## Subgroup Analyses

For mortality, subgroup analysis comparing studies in which revascularization was exclusively or predominantly with PCI (OR, 1.00; 95% CI, 0.87–1.14;  $P=0.95$ ;  $Q=3.13$ ;  $P=0.68$ ;  $I^2=0\%$ ) compared with studies in which revascularization was by CABG only (OR, 0.81; 95% CI, 0.59–1.13;  $P=0.22$ ;  $Q=2.08$ ;  $P=0.35$ ;  $I^2=3.9\%$ ) demonstrated no significant reduction by either modality and no difference in the effect of each modality on mortality ( $P$ -interaction=0.26). For nonfatal MI, subgroup analysis indicated that there was no significant reduction from PCI plus OMT compared with OMT alone (OR, 0.92; 95% CI, 0.75–1.13;  $P=0.43$ ;  $Q=10.8$ ;  $P=0.06$ ;  $I^2=54\%$ ). However, nonfatal MI was significantly reduced in studies in which the revascularization arm was limited to studies of patients who exclusively underwent CABG (OR, 0.35; 95% CI, 0.21–0.59;  $P<0.001$ ;  $Q=0.74$ ;  $P=0.69$ ;  $I^2=0\%$ ) (Figure 3B). The overall effect of CABG on nonfatal MI differed significantly from that of PCI ( $P$ -interaction  $<0.001$ ). There was no significant difference in death or nonfatal MI in the subgroup of studies requiring ischemia or abnormal FFR for enrollment, FAME 2,<sup>17</sup> ISCHEMIA,<sup>12</sup> and ISCHEMIA-CKD<sup>23</sup> trials, compared with the remainder of studies in which stress testing was not universal and ischemia was not required for enrollment (data not shown).

## Sensitivity Analyses

Sensitivity analysis to assess the potential impact of qualitative differences in study design and patient selection showed that exclusion of any single trial (including the largest trial, ISCHEMIA trial<sup>12</sup>; the only trial that enrolled patients with severely reduced left ventricular ejection fraction, STICH trial<sup>21</sup>; and the only trial that enrolled patients with chronic kidney disease, ISCHEMIA-CKD trial<sup>23</sup>) from the analysis for mortality or nonfatal MI did not alter the overall findings of the analysis (data not shown). When the secondary definition of MI was used for the ISCHEMIA<sup>12</sup> and ISCHEMIA-CKD<sup>23</sup> trials, revascularization did not significantly reduce nonfatal MI (OR, 0.83; 95% CI, 0.61–1.11;  $P=0.21$ ;  $Q=33$ ;  $P<0.001$ ;  $I^2=76\%$ ) (Figure 3C). However, consistent with the findings using the primary definition of MI, CABG significantly reduced nonfatal MI (OR, 0.35; 95% CI, 0.21–0.59;  $P<0.001$ ;  $Q=0.74$ ;  $P=0.69$ ,  $I^2=0\%$ ), whereas PCI did not (OR, 1.09; 95% CI, 0.90–1.33;  $P=0.37$ ;  $Q=10.7$ ;  $P=0.06$ ;  $I^2=53\%$ ) ( $P$ -interaction  $<0.001$ ) (Figure 3D).

**Table 1. Characteristics of Included Trials**

Study, Country or Region	Years of Enrollment	Inclusion Criteria	Exclusion Criteria	Techniques for Detection of Myocardial Ischemia	Criteria for Diagnosis of Ischemia	No. of Participants Total/With Ischemia	Follow-Up, y
MASS II, <sup>18</sup> Brazil	1997–2001	Angiographically documented proximal multivessel coronary stenosis of >70% by visual assessment and documented ischemia (stress testing or CCS class)	Refractory angina or acute MI, ventricular aneurysm, LVEF <40%, a history of PCI or CABG, single-vessel disease, and normal or minimal CAD; left main disease ≥50%	Treadmill electrocardiographic testing	Clinical (angina) and/or electrocardiographic (magnitude of horizontal or down-sloping ST-segment depression) and/or scintigraphic (severity and extent of the perfusion defects)	611/344	10
COURAGE, <sup>19</sup> North America	1999–2004	Stable CAD and CCS class IV angina (medically stabilized) At least 70% stenosis in at least 1 epicardial coronary artery and objective evidence of ischemia or at least 1 coronary stenosis of at least 80% and classic angina on provocative testing	Persistent CCS class IV angina; markedly positive stress test (substantial ST-segment depression or hypotensive response during stage 1 of Bruce protocol); refractory heart failure or cardiogenic shock; LVEF <30%; revascularization in the prior 6 mo, coronary anatomical features not suitable for revascularization; left main disease ≥50%	Treadmill testing, exercise or pharmacologic stress imaging (nuclear or echocardiographic imaging)	Any of: >1-mm ST deviation on standard treadmill exercise electrocardiography; ≥1 scintigraphic perfusion defects during exercise <sup>99m</sup> Tc sestamibi or thallium imaging; ≥1 perfusion defects (reversible or partial reversible) with pharmacologic (dipyridamole, adenosine) stress during <sup>99m</sup> Tc sestamibi or thallium imaging; >1 wall motion abnormalities during exercise radionuclide ventriculography or 2-dimensional echocardiography (exercise or dobutamine)	2287/1938	5
BARI 2D, <sup>20</sup> North and South America, Europe	2001–2005	Type 2 diabetes mellitus and CAD documented on angiography (≥50% stenosis of a major epicardial vessel associated with a positive stress test or classic angina)	Required immediate revascularization, creatinine >2.0 mg/dL, hemoglobin A1C >13.0%, class III or IV heart failure, prior PCI or CABG; left main stenosis >50%	Treadmill testing, exercise or pharmacologic stress imaging (nuclear or echocardiographic imaging)	>1-mm horizontal ST-segment depression or down-sloping ST-segment depression or elevation for >60–80 ms after the end of the QRS complex; myocardial perfusion defect; myocardial wall motion abnormality; decline in ejection fraction with stress; Doppler or pressure wire showing coronary flow reserve <2.0 or fractional flow reserve <0.75	2368/1326	5
STICH, <sup>21</sup> North and South America, Europe, Asia	2002–2007	Stable CAD, NYHA class II to IV symptoms, LVEF <35%, coronary anatomy amenable to CABG	CCS class III or IV angina, left main stenosis >50%, valvular disease requiring repair or replacement, cardiogenic shock (<72 h of randomization), planned PCI, MI within 30 d, history of >1 prior cardiac operation, noncardiac illness with life expectancy <3 y, refractory potentially lethal ventricular arrhythmia, prior heart, lung, kidney, or liver transplant	Exercise or pharmacologic stress with radionuclide imaging, or dobutamine stress echocardiogram	Summed difference score of >4 between stress and rest (or viability if available) images using a 17-segment model of the LV on radionuclide stress or worsening systolic wall thickening in >2/16 LV segments during infusion of dobutamine compared with baseline or prior dose	1212/255	10

(Continued)



**Table 1. Continued**

Study, Country or Region	Years of Enrollment	Inclusion Criteria	Exclusion Criteria	Techniques for Detection of Myocardial Ischemia	Criteria for Diagnosis of Ischemia	No. of Participants Total/With Ischemia	Follow-Up, y
FAME 2, <sup>17</sup> Europe and North America	2010–2012	Stable CAD considered for PCI with at least 1 functionally significant stenosis (fractional flow reserve <0.80)	Patients in whom the preferred treatment is CABG; recent (<1 wk) MI; prior CABG; LVEF <30%; left main stenosis >50%	Fractional flow reserve	Fractional flow reserve <0.80 during adenosine-induced hyperemia in at least 1 major coronary artery	888/888	5
ISCHEMIA, <sup>12</sup> North and South America, Europe, Asia	2012–2018	Stable CAD with moderate to severe ischemia (>50% stenosis in a major epicardial vessel in patients with a positive stress echocardiogram or >70% stenosis in proximal or mid vessel in patients with a positive EIT	Patients with NYHA class III–IV heart failure, unacceptable angina despite OMT, LVEF <35%, ACS (<2 mo), PCI or CABG (<1 y), eGFR 30 mL/min or on dialysis, left main stenosis >50%	Exercise or pharmacologic nuclear (PET or SPECT), echocardiography, or CMR stress testing. Exercise electrocardiographic testing without imaging.	>10% LV ischemia on nuclear testing, >3 segments of stress-induced moderate or severe hypokinesis or akinesis, >12% ischemic myocardium and/or wall motion with >3/16 segments with stress-induced severe hypokinesis or akinesis, >1.5-mm ST-segment depression in >2 leads or >2-mm ST-segment depression in single lead at <7 METs with angina	5179/5179	5
ISCHEMIA-CKD, <sup>23</sup> North and South America, Europe, Asia	2014–2018	CAD with moderate to severe ischemia on an exercise or pharmacologic stress test, ESRD on dialysis or eGFR <30 mL/min per 1.73 m <sup>2</sup>	NYHA class III–IV heart failure, unacceptable angina despite OMT, LVEF <35%, left main stenosis >50%, acute coronary syndrome (<2 mo), PCI (<1 y), stroke (<6 mo)	Exercise or pharmacologic nuclear (SPECT or PET), echocardiography, or CMR stress testing. Exercise electrocardiographic testing without imaging.	>10% ischemic myocardium on nuclear perfusion via SPECT or PET; >3/16 segments with stress-induced severe hypokinesis or akinesis on echocardiography; >12% ischemic myocardium and/or >3/16 segments with stress-induced severe hypokinesis or akinesis on CMR; absence of resting or akinesis on CMR; absence of resting ST-segment depression >1 mm or noninterpretable ECG and additional exercise-induced horizontal or down-sloping ST-segment depression >1.5 mm in 2 leads or >2 mm in any lead and either workload at which ST-segment criteria were met not exceeding completion of stage 2 of standard Bruce protocol or 7 METs or ST-segment criteria met at <75% of maximum predicted HR on exercise test without imaging	777/777	3

ACS indicates acute coronary syndrome; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CMR, cardiac magnetic resonance; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; EIT, exercise treadmill test; FAME 2, Fractional Flow Reserve vs Angiography for Multivessel Evaluation 2; HR, heart rate; ISCHEMIA, International Study of Comparative Health Effectiveness With Medical and Invasive Approaches; ISCHEMIA-CKD, International Study of Comparative Health Effectiveness With Medical and Invasive Approaches—Chronic Kidney Disease; LV, left ventricle; LVEF, left ventricular ejection fraction; MASS II, Medicine, Angioplasty, or Surgery Study II; MET, metabolic equivalent task; MI, myocardial infarction; NYHA, New York Heart Association; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; PET, positron emission tomography; SPECT, single-photon emission computed tomography; and STICH, Surgical Treatment for Ischemic Heart Failure.

**Table 2. Characteristics of Patients With Documented Ischemia**

Characteristic	MASS II PCI <sup>18</sup>		MASS II CABG <sup>18</sup>		COURAGE <sup>19</sup>		BARI 2D PCI <sup>20</sup>		BARI 2D CABG <sup>20</sup>		STICH <sup>21</sup>		FAME 2 <sup>17</sup>		ISCHEMIA <sup>12</sup>		ISCHEMIA-CKD <sup>23</sup>	
	PCI + OMT	OMT	CABG = OMT	OMT	PCI + OMT	OMT	PCI + OMT	OMT	CABG + OMT	OMT	CABG + OMT	OMT	PCI + OMT	OMT	Invasive + OMT*	OMT	Invasive + OMT†	OMT
Nc.	115	100	119	100	968	970	483	489	176	178	129	126	447	441	2588	2591	388	389
Age, mean (SD or IQR), y	61 (7)	59 (8)	60 (9)	59 (8)	62 (10)	62 (10)	63 (9)	62 (9)	65 (8)	64 (8)	62 (9)	61 (10)	64 (9)	64 (10)	64 (58–70)	64 (58–70)	62 (55–69)	64 (56–70)
Men, N (%)	73 (63)	77 (77)	85 (71)	77 (77)	830 (86)	826 (85)	353 (73)	357 (73)	147 (84)	144 (81)	118 (92)	108 (86)	356 (80)	338 (77)	1982 (77)	2029 (78)	268 (69)	267 (69)
Diabetes mellitus, N (%)	30 (26)	35 (35)	34 (29)	35 (35)	314 (32)	336 (35)	483 (100)	489 (100)	176 (100)	178 (100)	51 (40)	52 (41)	123 (28)	117 (27)	1071 (41)	1083 (42)	226 (58)	218 (56)
Prior MI, N (%)	30 (26)	28 (28)	32 (27)	28 (28)	342 (35)	348 (36)	125 (26)	122 (26)	45 (26)	50 (29)	91 (71)	95 (75)	164 (37)	165 (37)	495 (19)	496 (19)	62 (16)	71 (18)
Ejection fraction, mean (SD or IQR), %	62 (4)	67 (6)	65 (5)	67 (6)	61 (11)	61 (10)	57 (11)	57 (11)	54 (12)	56 (11)	26 (8)	27 (9)	NR	NR	60 (55–65)	60 (55–65)	58 (50–63)	58 (50–64)
Unplanned revascularization, N (%)	49 (43)	45 (45)	12 (10)	45 (45)	194 (20)	287 (30)	137 (28)	187 (38)	20 (11)	77 (43)	5 (4)	26 (21)	60 (13)	225 (51)	396 (15)	544 (21)	NR	73 (19)
Drug-eluting stent during index procedure, N (%)	0 (0)	NA	NA	NA	29 (3)	NA	172 (37)	NA	NA	NA	NA	NA	435 (97)	NA	1388/1418 stents (98)	NA	146/146 stents (100)	NA
Medical therapy, N (%)																		
Aspirin	92 (80)	88 (88)	93 (78)	88 (88)	905 (93)	898 (93)	467 (97)	466 (95)	161 (92)	175 (98)	108 (84)	111 (88)	390 (87)	396 (90)	2443 (97)	2429 (96)	314 (84)	302 (82)
β-Blocker	92 (80)	90 (90)	88 (74)	90 (90)	802 (83)	806 (83)	445 (92)	447 (91)	160 (91)	169 (95)	114 (88)	112 (89)	338 (76)	344 (78)	NR	NR	NR	NR
ACEI or ARB	90 (78)	94 (94)	91 (76)	94 (94)	714 (74)	705 (73)	456 (94)	461 (94)	165 (94)	174 (98)	119 (92)	116 (92)	308 (69)	309 (70)	1685 (65)	1731 (67)	184 (48)	186 (48)
Statins	80 (70)	85 (85)	81 (68)	85 (85)	862 (89)	876 (90)	465 (96)	468 (96)	163 (93)	177 (99)	103 (80)	106 (84)	370 (83)	361 (82)	2441 (94)	2463 (95)	316 (82)	313 (81)

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; CABG, coronary artery bypass grafting; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; FAME 2, Fractional Flow Reserve vs Angiography for Multivessel Evaluation 2; IQR, interquartile range; ISCHEMIA, International Study of Comparative Health Effectiveness With Medical and Invasive Approaches; ISCHEMIA-CKD, International Study of Comparative Health Effectiveness With Medical and Invasive Approaches—Chronic Kidney Disease; MASS II, Medicine, Angioplasty, or Surgery Study II; MI, myocardial infarction; NA, not applicable; NR, not reported; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; and STICH, Surgical Treatment for Ischemic Heart Failure.

\*The invasive strategy resulted in revascularization in 79% of patients (PCI in 74% and CABG in 26%).

†The invasive strategy resulted in revascularization in 51% of patients (PCI in 85% and CABG in 15%).

**Table 3. Quality Metrics of Included Studies**

Study	Study Blinding	Blinding Technique	Random Assignment	Withdrawal Descriptions
MASS II <sup>18</sup>	No	No	Yes	Yes
COURAGE <sup>19</sup>	No	No	Yes	Yes
BARI 2D <sup>20</sup>	No	No	Yes	Yes
STICH <sup>21</sup>	No	No	Yes	Yes
FAME 2 <sup>17</sup>	No	No	Yes	Yes
ISCHEMIA <sup>12</sup>	No	No	Yes	Yes
ISCHEMIA-CKD <sup>23</sup>	No	No	Yes	Yes

BARI 2D indicates Bypass Angioplasty Revascularization Investigation 2 Diabetes; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; FAME 2, Fractional Flow Reserve vs Angiography for Multivessel Evaluation 2; ISCHEMIA, International Study of Comparative Health Effectiveness With Medical and Invasive Approaches; ISCHEMIA-CKD, International Study of Comparative Health Effectiveness With Medical and Invasive Approaches—Chronic Kidney Disease; MASS II, Medicine, Angioplasty, or Surgery Study II; and STICH, Surgical Treatment for Ischemic Heart Failure.

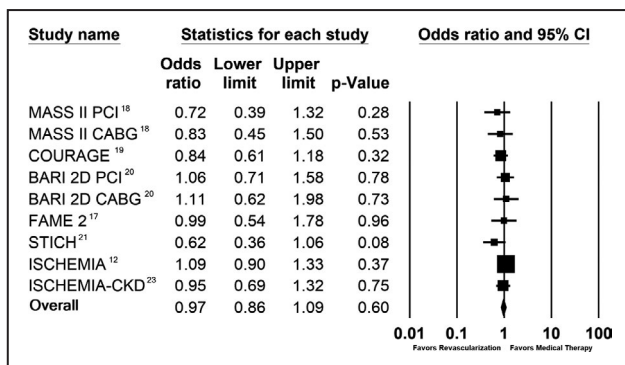
## DISCUSSION

The principal findings of this meta-analysis of RCTs of patients with CCS who have both obstructive, but not left main, CAD and myocardial ischemia are 2-fold. First, a strategy of initial PCI or CABG, in combination with OMT, resulted in no significant reduction in mortality compared with initial OMT with crossover to revascularization, as clinically indicated, at a median follow-up of 5 years. Second, although a strategy of initial revascularization with PCI or CABG,

in combination with OMT, was associated with an overall reduction in nonfatal MI, subgroup analysis revealed that CABG plus OMT resulted in a significant reduction in nonfatal MI compared with OMT alone, whereas PCI plus OMT did not significantly reduce nonfatal MI compared with OMT alone. To our knowledge, this is the only meta-analysis of RCTs of patients with CCS and objectively documented myocardial ischemia in which revascularization included both PCI and CABG. Furthermore, it is the first meta-analysis to include patients with CCS and severely reduced left ventricular ejection fraction as well as those with CKD. As such, it should be of significant interest to healthcare providers, healthcare systems, third-party payers, and patients.

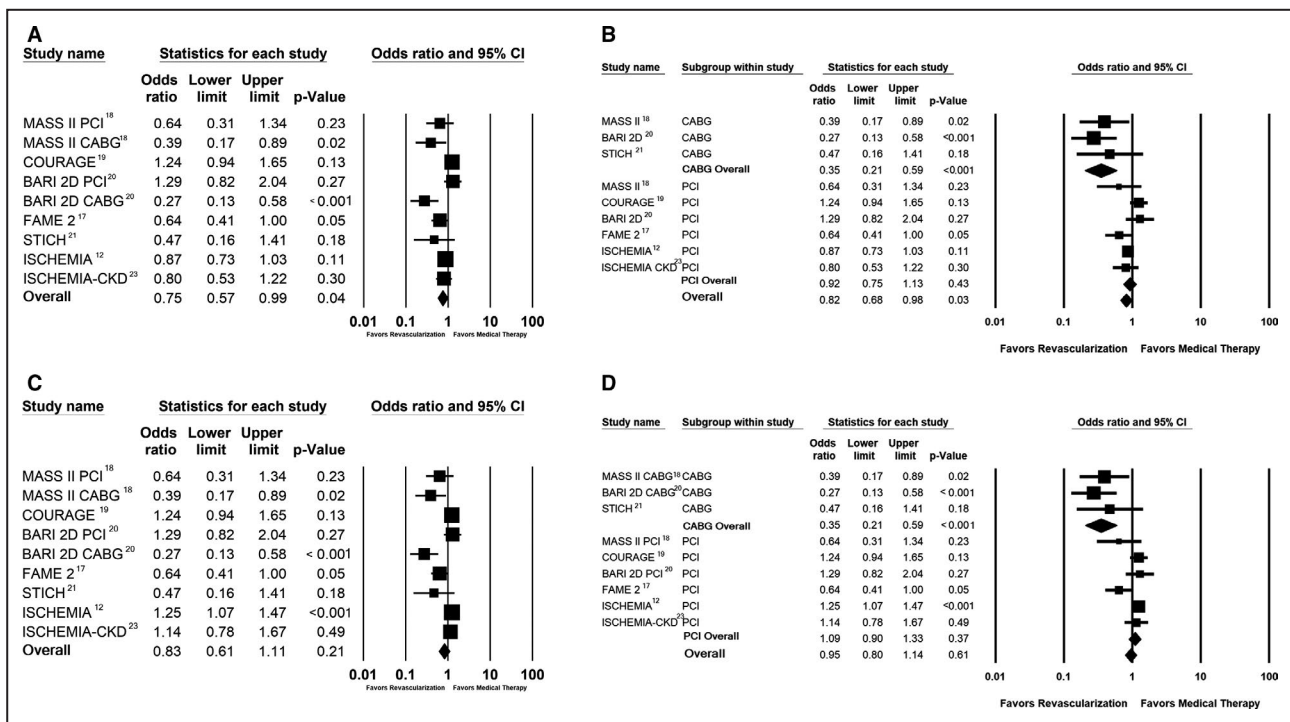
Given the profound impact of ischemic heart disease on mortality worldwide,<sup>1</sup> the primary goal of treatment is to prevent death. In the setting of an acute coronary syndrome, in particular ST-segment-elevation MI, short-term mortality is reduced by timely revascularization by PCI<sup>25</sup> to salvage myocardium and minimize myocyte loss; however, in the long-term setting, there has been no conclusive evidence for an incremental benefit of revascularization on mortality beyond that achieved by disease-modifying OMT and lifestyle modification. As acute MI has long been assumed to be on the causal pathway to mortality in patients with CCS, reducing mortality is logically dependent on preventing the progression of stable disease to acute MI. Thus, for revascularization to favorably impact survival, it should prevent the development of or mitigate the consequences of MI.

In patients who undergo revascularization for CCS, 2 types of MI are recognized,<sup>26</sup> periprocedural (type 4a or type 5) or spontaneous (type 1 or type 2). Type 4a MI occurs following PCI, whereas type 5 MI occurs after CABG. Spontaneous MIs are categorized by their pathophysiological characteristics as being caused by plaque disruption and superimposed thrombosis (type 1) or by a mismatch between oxygen supply and demand (type 2). Unlike



**Figure 2. Comparison of revascularization and optimal medical therapy vs optimal medical therapy alone in patients with chronic coronary syndromes, obstructive coronary artery disease, and myocardial ischemia for all-cause mortality during follow-up.**

All included studies are shown by name along with point estimates of the odds ratios and respective 95% CIs. The size of the squares denoting the point estimate in each study is proportional to the weight of the study. BARI 2D indicates Bypass Angioplasty Revascularization Investigation 2 Diabetes; CABG, coronary artery bypass grafting; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; FAME 2, Fractional Flow Reserve vs Angiography for Multivessel Evaluation 2; ISCHEMIA, International Study of Comparative Health Effectiveness With Medical and Invasive Approaches; ISCHEMIA-CKD, International Study of Comparative Health Effectiveness With Medical and Invasive Approaches—Chronic Kidney Disease; MASS II, Medicine, Angioplasty, or Surgery Study II; PCI, percutaneous coronary intervention; and STICH, Surgical Treatment for Ischemic Heart Failure.



**Figure 3. Comparison of revascularization and optimal medical therapy vs optimal medical therapy alone in patients with chronic coronary syndromes, obstructive coronary artery disease, and myocardial ischemia for nonfatal myocardial infarction (MI) during follow-up.**

All included studies are shown by name along with point estimates of the odds ratios and respective 95% CIs. The size of the squares denoting the point estimate in each study is proportional to the weight of the study. **A**, Comparison of revascularization and optimal medical therapy vs optimal medical therapy alone in patients with chronic coronary syndromes, obstructive coronary artery disease, and myocardial ischemia for nonfatal MI using the primary definition of MI from the ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches)<sup>12</sup> and ISCHEMIA-CKD (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches—Chronic Kidney Disease)<sup>23</sup> trials. **B**, Subgroup comparison of nonfatal MI where revascularization was performed exclusively or predominantly with percutaneous coronary intervention vs studies in which revascularization was exclusively by coronary artery bypass grafting. Nonfatal MI was defined using the primary definition in the ISCHEMIA<sup>12</sup> and ISCHEMIA-CKD<sup>23</sup> trials. **C**, Comparison of revascularization and optimal medical therapy vs optimal medical therapy alone in patients with chronic coronary syndromes, obstructive coronary artery disease, and myocardial ischemia for nonfatal MI using the secondary definition of MI in the ISCHEMIA<sup>12</sup> and ISCHEMIA-CKD<sup>23</sup> trials. **D**, Subgroup comparison of nonfatal MI where revascularization was performed exclusively or predominantly with percutaneous coronary intervention vs studies in which revascularization was exclusively by coronary artery bypass grafting. Nonfatal MI was defined using the secondary definition in the ISCHEMIA<sup>12</sup> and ISCHEMIA-CKD<sup>23</sup> trials. BARI 2D indicates Bypass Angioplasty Revascularization Investigation 2 Diabetes; CABG, coronary artery bypass grafting; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; FAME 2, Fractional Flow Reserve vs Angiography for Multivessel Evaluation 2; MASS II, Medicine, Angioplasty, or Surgery Study II; PCI, percutaneous coronary intervention; and STICH, Surgical Treatment for Ischemic Heart Failure.

OMT, revascularization procedures uniquely expose patients to periprocedural MIs that result in myonecrosis, as demonstrated by cardiac magnetic resonance imaging.<sup>27</sup> Large periprocedural MIs adversely affect prognosis, whereas the clinical significance of smaller type 4a or type 5 MIs is controversial. The prevalence of periprocedural MI depends on the biomarker selected and the threshold for abnormality used as well as the rigor of the surveillance strategy. In response to trials, such as the FAME 2<sup>17</sup> and ISCHEMIA<sup>12</sup> trials, in which the overall rate of MI was similar in both invasive and OMT arms, it has been argued that revascularization increased periprocedural MIs, which have little prognostic consequence,

but, in turn, decreased spontaneous MIs, which are thought to be prognostically important despite any reduction in mortality in the revascularization arms of these trials.<sup>27</sup>

All patients with CCS are at risk for the development of both spontaneous type 1 and type 2 MIs, which are both associated with impaired survival, albeit by different mechanisms. Type 1 MI adversely affects survival by causing significant myonecrosis and subsequent scarring that may reduce left ventricular function<sup>28</sup> and/or contribute to a proarrhythmic substrate.<sup>29</sup> Patients with type 2 MIs generally experience less myonecrosis but are at higher risk of death from noncardiovascular than cardiovascular causes.<sup>30</sup> Unfortunately, because

accurate differentiation between spontaneous MI types 1 and 2 would require invasive intracoronary imaging to directly visualize the presence of disruption and thrombosis at the site of the culprit plaque, the currently applied clinical and angiographic criteria are imprecise, at best.<sup>31</sup>

Given that patients with CCS and obstructive CAD can meet the diagnostic requirements for spontaneous type 2 MI, including chest pain, ischemic electrocardiographic changes, and troponin elevation,<sup>32</sup> following the supply:demand mismatch intentionally induced by a treadmill stress test, it is reasonable to assume that PCI can reduce type 2 MI by reducing the hemodynamic effects of an obstructive lesion on oxygen supply during episodes of increased oxygen demand. Because it is known that most spontaneous type 1 MIs following PCI occur because of progression of atherosclerotic disease in non-flow-limiting lesions anatomically distant from the originally instrumented lesion,<sup>33</sup> it is not biologically plausible that PCI prevents those spontaneous type 1 MIs that originate from new plaque disruption events occurring at minimally stenotic remote coronary locations. Furthermore, if PCI prevented more type 1 spontaneous MIs than the periprocedural MIs it causes, mortality should be reduced. But this analysis and all prior analyses have failed to detect any impact of PCI on mortality.

The fact that patients with type 2 MI are at higher risk of death from noncardiovascular causes<sup>30</sup> may fundamentally explain why mortality from CCS has never been reduced by PCI in contemporary RCTs of PCI versus OMT and meta-analyses of these studies, despite the likely reduction in spontaneous but predominantly type 2 MI. In contrast to the mechanism of PCI reducing the hemodynamic effect of discrete obstructive lesions, CABG supplies an alternative conduit for oxygen delivery to the myocardium in the event of thrombotic occlusion of the bypassed native coronary artery. It is therefore much more likely that CABG would reduce both type 1 and type 2 MI in patients with CCS, resulting in a significantly greater number of MIs prevented, as shown in this study. It is also notable that the reduction of MI in the CABG arm of the STICH trial of patients with severely reduced left ventricular function translated into reduced mortality at 10 years of follow-up.<sup>21</sup> Thus, it is reasonable to postulate that, because patients with severely reduced left ventricular systolic function can least well tolerate a new MI with a further decline in ventricular function, they are the CCS subgroup most likely to derive a mortality benefit from CABG.

Placed in context of prior data, our results suggest that all patients with CCS have a basal risk of type 1 and type 2 spontaneous MI that is reduced by OMT and lifestyle modification. Revascularization with PCI increases periprocedural MI, plausibly reduces type

2 MI, and has minimal effect on type 1 MI, resulting in a neutral effect on mortality. Revascularization with CABG increases periprocedural MI, reduces type 2 MI, and prevents or mitigates the effect of type 1 MI, with a neutral effect on mortality in patients with preserved left ventricular function.

The results of this study-level meta-analysis should be interpreted in the context of certain limitations. First, complete information on the extent and severity of myocardial ischemia was not available for all studies, which limited analysis to patients with any degree of objectively documented ischemia. However, the ISCHEMIA trial did not demonstrate any relationship between the severity and extent of ischemia and improved outcomes with revascularization.<sup>12</sup> Second, not all participants in MASS II,<sup>18</sup> COURAGE,<sup>19</sup> BARI 2D,<sup>20</sup> and STICH<sup>21</sup> underwent stress testing. Although those who did undergo stress testing may not have been representative of the entire study population, their outcomes mirrored those of the entire study populations. Third, we limited our analysis to relatively bias-resistant outcomes and did not include angina as an end point in this meta-analysis as recent data suggest the impact of PCI on angina relief may be partially attributed to a placebo effect,<sup>34</sup> and none of the studies included was blinded to treatment assignment. Fourth, although there have been improvements in stent technology over the past 2 decades that may induce heterogeneity in results over time, no mortality difference has been demonstrated between bare metal and drug-eluting stents.<sup>35</sup> Fifth, we could not determine the revascularization modality-specific outcomes of patients in the ISCHEMIA<sup>12</sup> and ISCHEMIA-CKD<sup>23</sup> trials who underwent PCI or CABG. However, inclusion of the small percentage of patients who underwent CABG in both studies in the PCI subgroup would bias the nonfatal MI results in favor of PCI. Sixth, we did not have access to individual patient data from the RCTs included, except for the STICH trial. Thus, our ability to examine the impact of randomized treatment assignment on many subgroups was limited. Finally, data were extracted only from RCTs that may not be representative of the unselected patients seen in daily clinical practice.

In summary, in patients with CCS, obstructive CAD, exclusive of significant left main CAD, and objective evidence of myocardial ischemia, an initial strategy of revascularization with PCI or CABG and OMT does not reduce mortality compared with a strategy of initial OMT alone with crossover to revascularization as necessary for refractory symptoms. Although there was a significant reduction in nonfatal MI among patients who underwent CABG plus OMT, PCI combined with OMT did not confer a benefit in reducing MI compared with OMT alone, which supports a mechanistic difference in the type of revascularization performed and its impact on MI.

Thus, for most patients with CCS but without left main CAD, shared decision-making about revascularization should be based on discussions of symptom relief and quality of life. For patients in whom reduction in MI is an overarching goal, such as those with severely reduced left ventricular ejection fraction, CABG plus medical therapy is superior to OMT alone and to PCI plus OMT.

## ARTICLE INFORMATION

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None.

### Supplementary Material

Data S1

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# **SUPPLEMENTAL MATERIAL**



## Data S1.

### Search Strategy

#### Embase.com

('stable coronary artery disease'/exp OR ('coronary artery disease'/exp AND stable:ti,ab,kw) OR ('coronary artery disease'/de AND stable:ti,ab,kw) OR (stable NEAR/3 ('coronary disease\*' OR 'coronary artery disease\*' OR 'coronary atherosclerosis' OR 'coronary heart disease\*'))))

AND

((('percutaneous coronary intervention'/exp OR 'coronary artery bypass graft'/exp) OR ('percutaneous coronary intervention\*' OR 'percutaneous coronary angioplast\*' OR 'balloon angioplasty' OR 'coronary angioplasty' OR 'PCI' OR 'percutaneous coronary revascularization\*' OR 'coronary artery bypass\*' OR 'coronary artery bypass graft\*' OR 'coronary bypass graft\*' OR 'coronary vein bypass\*' OR 'coronary venous bypass graft\*' OR 'aortocoronary bypass\*' OR 'aortocoronary anastomosis' OR 'CABG'):ti,ab,kw)

AND

(drug therapy'/de OR ('medical therap\*' OR 'medical-therap\*' OR 'drug therapy' OR 'non surgical' OR 'diet' OR 'exercise' OR 'lifestyle intervention'):ti,ab,kw)

AND

('clinical trial'/de OR 'randomized controlled trial'/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'prospective study'/de OR 'randomized controlled' NEXT/1 trial\* OR rct OR 'randomly allocated' OR 'allocated randomly' OR 'randomized trial' OR 'random allocation' OR allocated NEAR/2 random OR single NEXT/1 blind\* OR double NEXT/1 blind\* OR (treble OR triple) NEAR/1 blind\* OR placebo\*)

#### Ovid-Medline

((Coronary Artery Disease/ AND stable.ti,ab.) OR (Coronary Disease/ AND stable.ti,ab.) OR (stable.mp. ADJ3 ("coronary disease\*".mp. OR "coronary artery disease\*".mp. OR "coronary atherosclerosis".mp. OR "coronary heart disease\*".mp.)))

AND

((exp Percutaneous Coronary Intervention/ OR exp Coronary Artery Bypass/) OR ("percutaneous coronary intervention\*" OR "percutaneous coronary angioplast\*" OR "balloon angioplasty" OR "coronary angioplasty" OR "PCI" OR "percutaneous coronary revascularization\*" OR "coronary artery bypass\*" OR "coronary artery bypass graft\*" OR

"coronary bypass graft\*" OR "coronary vein bypass\*" OR "coronary venous bypass graft\*" OR "aortocoronary bypass\*" OR "aortocoronary anastomosis" OR "CABG").ti,ab.)

AND

Combined Modality Therapy/ OR Drug Therapy/ OR ("medical therap\*" OR "medical-therap\*" OR "drug therapy" OR "non surgical" OR diet OR exercise OR "lifestyle intervention").ti,ab.)

AND

(randomized controlled trial.pt. OR controlled clinical trial.pt. OR randomized.ab. OR placebo.ab. OR drug therapy.fs. OR randomly.ab. OR trial.ab. OR groups.ab.)

### Scopus

(TITLE-ABS-KEY(stable W/3 "coronary disease\*") OR TITLE-ABS-KEY(stable W/3 "coronary artery disease\*") OR TITLE-ABS-KEY(stable W/3 "coronary atherosclerosis") OR TITLE-ABS-KEY(stable W/3 "coronary heart disease") OR TITLE-ABS-KEY(stable W/3 "coronary disease\*"))

AND

TITLE-ABS-KEY("percutaneous coronary intervention\*" OR "percutaneous coronary angioplast\*" OR "balloon angioplasty" OR "coronary angioplasty" OR "PCI" OR "percutaneous coronary revascularization\*" OR "coronary artery bypass\*" OR "coronary artery bypass graft\*" OR "coronary bypass graft\*" OR "coronary vein bypass\*" OR "coronary venous bypass graft\*" OR "aortocoronary bypass\*" OR "aortocoronary anastomosis" OR "CABG")

AND

TITLE-ABS-KEY("medical therap\*" OR "medical-therap\*" OR "drug therapy" OR "non surgical" OR diet OR exercise OR "lifestyle intervention")

AND

( INDEXTERMS ( "clinical trials" OR "clinical trials as a topic" OR "randomized controlled trial" OR "Randomized Controlled Trials as Topic" OR "controlled clinical trial" OR "Controlled Clinical Trials" OR "random allocation" OR "Double-Blind Method" OR "Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "multicenter study" OR "double blind procedure" OR "single blind procedure" OR "crossover procedure" OR "clinical trial" OR "controlled study" OR "randomization" OR "placebo" ) ) OR ( TITLE-ABS-KEY ( ( "clinical trials" OR "clinical trials as a topic" OR "randomized controlled trial" OR "Randomized Controlled Trials as Topic" OR "controlled clinical trial" OR "Controlled Clinical Trials as Topic" OR "random allocation" OR "randomly allocated" OR "allocated randomly" OR "Double-Blind Method" OR "Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "cross-over trial" OR "single blind" OR "double blind" OR "factorial design" OR "factorial trial" ) ) ) OR ( TITLE-ABS ( clinical trial\* OR trial\* OR rct\* OR random\* OR blind\* ) )

### Cochrane Library

((stable NEAR/2 “coronary disease\*”) OR (stable NEAR/2 “coronary artery disease\*”) OR (stable NEAR/2 “coronary atherosclerosis”) OR (stable NEAR/2 “coronary heart disease\*”)):ti,ab,kw

AND

((“percutaneous coronary intervention\*” OR “percutaneous coronary angioplast\*” OR “balloon angioplasty” OR “coronary angioplasty” OR “PCI” OR “percutaneous coronary revascularization\*” OR “coronary artery bypass\*” OR “coronary artery bypass graft\*” OR “coronary bypass graft\*” OR “coronary vein bypass\*” OR “coronary venous bypass graft\*” OR “aortocoronary bypass\*” OR “aortocoronary anastomosis” OR “CABG”)):ti,ab,kw

AND

((“medical therap\*” OR “medical-therap\*” OR “drug therapy” OR “non surgical” OR diet OR exercise OR “lifestyle intervention”)):ti,ab,kw

## **Definitions of Nonfatal Myocardial Infarction (MI) in the Included Trials**

### **MASS II**

MI was defined as the presence of significant new Q waves in at least two electrocardiographic (ECG) leads or symptoms compatible with MI associated with creatine kinase (CK), MB fraction concentrations that were more than three times the upper limit of the reference range

### **COURAGE**

The prespecified definition of MI (whether periprocedural or spontaneous) required a clinical presentation consistent with an acute coronary syndrome and either new abnormal Q waves in two or more electrocardiographic leads or positive results in cardiac biomarkers. Silent MI, as detected by abnormal Q waves, was confirmed by a core laboratory and was also included as an outcome of MI.

### **BARI 2D**

The MI criteria used were modified from the universal MI definition in that a two-fold elevation of abnormal biomarker profile above the upper limits of normal was used rather than the 99th

percentile. When cardiac troponin and CK-MB were simultaneously acquired, cardiac troponin took precedence over CK-MB in establishing the diagnosis. MI was confirmed if abnormal cardiac biomarkers occurred and there was evidence of angina or angina equivalent symptoms, or ECG or imaging evidence of new myocardial ischemia. Cardiac biomarkers were not routinely collected after coronary revascularization. When they were collected, a 3-fold elevation in CKMB following a PCI procedure and a 10-fold increase in CK-MB following coronary bypass surgery were used as the cut-points to define abnormality.

### **STICH**

A patient must have an increase in cardiac enzymes (CK–MB greater than twice the ULN or troponin T or I greater than three times the ULN) and at least one of the two following criteria:

Typical clinical presentation

OR

Typical ECG changes (evolving ST-segment or T-wave changes in two or more contiguous leads, the development of Q waves in two or more contiguous leads, or the development of new LBBB).

An MI that occurs after a coronary bypass procedure will be adjudicated as a STICH MI only if there are new Q-waves present and the CK-MB is greater than 5 times the ULN and two times the pre – surgery level for CABG.

### **FAME 2**

Within 24 hours after randomization or any PCI:

I. CK-MB above 10 x 99th percentile upper reference limit (URL) determined on a single measurement,

OR

II. CK-MB above 5 x 99th percentile URL determined on a single measurement PLUS at least one of the following:

- o new pathological Q waves in at least 2 contiguous leads or new persistent non-rate related left bundle branch block (LBBB),
- o angiographically documented native coronary artery occlusion,
- o imaging evidence of new loss of viable myocardium

More than 24 hours after randomization:

I. Detection of rise and/or fall of cardiac biomarkers, CK-MB or troponin with at least one value above the 99th percentile of the URL together with evidence of myocardial ischemia with at least one of the following:

- o Symptoms of ischemia
- o ECG changes indicative of new ischemia (new ST-T changes or new LBBB),

OR

II. Development of pathological Q waves

in  $\geq 2$  contiguous precordial leads or  $\geq 2$  adjacent limb leads) of the ECG,

OR

Imaging evidence of loss of viable myocardium or new regional wall motion abnormality

## **ISCHEMIA**

Two versions of MI will be adjudicated in ISCHEMIA: a primary definition and secondary definition. Each definition includes a hierarchy of markers and threshold values as well as a set of rules for diagnosing MI when one or more key elements of the medical record are missing.

The Primary Definition is based upon the Universal Definition of MI, but relies upon site-reported MI decision limits for troponin (which may or may not be the same as the manufacturer 99% URL), and has selected unique marker criteria for MI after PCI or CABG (Type 4a, 5).

The Secondary Definition is also based upon the Universal Definition of Myocardial Infarction, but specifically uses the 99%URL from the assay manufacturer's package insert (which may or may not be the site's MI decision limit) and uses the same supporting criteria (eg. angiographic and ECG) as the UMI definition.

### **Spontaneous MI**

Marker elevation, as outlined below and at least 1 of the following:

- Symptoms of ischemia, usually lasting > 20 minutes in duration
- New ischemic ST and/or T wave and/or Q-wave ECG changes, or new LBBB
- Imaging evidence of new loss of viable myocardium in comparison to the baseline imaging test
- Angiographic evidence of intracoronary thrombus, stent thrombosis (4b) or high-grade in-stent restenosis ( $\geq 50\%$ ) (4c)

Marker data not available and at least 2 of the following:

- New ischemic ST and/or T wave and/or Q-wave ECG changes, or new LBBB, as described below
- Imaging evidence of new loss of viable myocardium in comparison to the baseline imaging test
- Angiographic evidence of intracoronary thrombus.

Autopsy evidence of a fresh myocardial infarction as stand-alone criterion

### **Silent MI**

This event includes evidence of new silent Q-wave MI detected during routine protocol or clinically obtained ECG follow-up. Silent MI events will be classified as a type 1 MI.

### **Sudden death MI**

MI events in which a presentation consistent with infarction is present but the patient dies before the biomarkers are drawn or within the first few hours of the event before the biomarkers become

positive. Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST-segment elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

### **PCI-Related MI**

CK-MB is the preferred biomarker and takes precedence over troponin. For subjects with normal baseline biomarker level pre-PCI, peri-PCI MI requires a rise in CK-MB to >5-fold the ULN (or a rise in troponin to >35 times the MI Decision Limit/ULN, when CK-MB is unavailable) within 48 hours post-PCI. If pre-PCI cardiac markers (CKMB or cTn) are elevated, they must be stable or falling as indicated by two samples at least 6 h apart. The post-PCI CKMB level should reflect a rise of >20% over pre-PCI levels. In addition to biomarker criteria, peri-PCI MI requires at least one of the following:

- Post- procedure angiographic TIMI 0/1 flow in a major coronary artery or a side branch with reference vessel diameter  $\geq 2.0$  mm which had TIMI 2-3 flow at baseline, or TIMI 2 flow in a major coronary artery or a side branch with reference vessel diameter  $\geq 3.0$  mm which had TIMI 3 flow at baseline or Type C dissection (NHLBI classification) or greater in the target vessel.
- New ECG changes (ST segment elevation or depression  $>0.1$  mV in 2 contiguous leads), new pathologic Q-waves in  $\geq 2$  contiguous leads, or new persistent LBBB present on a post-PCI ECG obtained at least 30 minutes and up to 48 hours post procedure in the absence of any intervening coronary event between the time of the PCI procedure and the ECG showing changes.

## **CABG-Related MI**

CK-MB is the preferred serum biomarker and takes precedence over cardiac troponin. For subjects with normal baseline biomarker level pre-CABG, peri-CABG MI requires a rise in CK-MB to >10-fold the ULN (or a rise in troponin to >70 times MI Decision Limit/ULN when CK-MB is unavailable) within 48 hours post-CABG. In addition to biomarker criteria, peri-CABG MI requires at least one of the following:

- A new substantial wall motion abnormality by cardiac imaging (CEC assessed), except new septal and apical abnormalities. The CEC will have latitude in determining whether a new wall motion abnormality is “substantial” in the context of the clinical event.
- New pathologic Q-waves in  $\geq 2$  contiguous leads or new persistent LBBB is present on post CABG ECG obtained day 3 post CABG, or hospital discharge, whichever comes earlier in the absence of any intervening coronary event between the time of the CABG procedure and the ECG

## **ISCHEMIA CKD**

Two versions of MI will be adjudicated in ISCHEMIA-CKD: a primary definition and secondary definition. Each definition includes a hierarchy of markers and threshold values as well as a set of rules for diagnosing MI when one or more key elements of the medical record are missing.

The Primary Definition is based upon the Universal Definition of MI, but relies upon site-reported MI decision limits for troponin (which may or may not be the same as the manufacturer 99% URL), and has selected unique marker criteria for MI after PCI or CABG (Type 4a, 5).



The Secondary Definition is also based upon the Universal Definition of Myocardial Infarction, but specifically uses the 99%URL from the assay manufacturer's package insert (which may or may not be the site's MI decision limit) and uses the same supporting criteria (eg. angiographic and ECG) as the UMI definition.

### **Spontaneous MI (Types 1, 2, 4b, 4c)**

Diagnosis of spontaneous MI will be satisfied by a clinical setting consistent with acute myocardial ischemia and any one or more of the following criteria:

Marker elevation, as outlined below and at least 1 of the following:

- Symptoms of ischemia, usually lasting > 20 minutes in duration
- New ischemic ST and/or T wave and/or Q-wave ECG changes, or new LBBB, as described below
- Imaging evidence of new loss of viable myocardium in comparison to the baseline imaging test
- Angiographic evidence of intracoronary thrombus, stent thrombosis (4b) or high- grade in-stent restenosis ( $\geq 50\%$ ) (4c)

Marker data not available and at least 2 of the following:

- New ischemic ST and/or T wave and/or Q-wave ECG changes, or new LBBB, as described below
- Imaging evidence of new loss of viable myocardium in comparison to the baseline imaging test
- Angiographic evidence of intracoronary thrombus.

Autopsy evidence of a fresh myocardial infarction as stand-alone criterion

### **Spontaneous MI Marker Criteria**

Troponin, including high-sensitivity troponin, is the preferred biomarker and takes precedence over CK-MB for both definitions.

Primary Definition: Preferentially uses a troponin threshold value reported as MI Decision Limit or the Upper Limit of Normal (ULN). Marker elevation is defined as troponin > ULN/MI decision limit. If troponin is not done or not available, then CK-MB > ULN will qualify. If both troponin and CKMB are not done or not available, then CK > 2 x ULN will qualify.

Secondary Definition: Preferentially uses a troponin threshold reported by the manufacturer, namely, the manufacturer 99th percentile. Marker elevation is defined as troponin > 99th percentile. If the troponin 99th percentile is not reported, then troponin > ULN will qualify. If troponin is not done or not available, then CK-MB > ULN will qualify. If both troponin and CK-MB are not done or not available, then CK > 2 x ULN will qualify.

### **Spontaneous MI ECG Criteria**

ECG criterion is considered to be met if any of the following:

ST elevation: New ST elevation at the J-point in two contiguous leads with the cutpoints:

$\geq 0.2$  mV in men >age 40 and  $\geq 0.25$ mV in men <40 years or  $\geq 0.15$  mV in women in leads V2–

V3 and/or  $\geq 0.1$  mV in other leads, or new LBBB.

Any new Q-wave in leads V2–V3  $\geq 0.02$  seconds or QS complex in leads V2 and V3 or Q-wave  $\geq 0.03$  seconds and  $\geq 0.1$  mV deep or QS complex in leads I, II, aVL, aVF, or V4–V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4–V6; II, III, and aVF) or R-wave  $\geq 0.04$  seconds in V1–V2 and R/S  $\geq 1$  with a concordant positive T-wave in the absence of a conduction defect.

ST depression and/or T-wave changes, new horizontal or down-sloping ST depression  $\geq 0.05$  mV in two contiguous leads; and/or T-wave inversion  $\geq 0.1$  mV in two contiguous leads. The ST-T wave criteria only apply in the absence of findings that would preclude ECG analysis such as LBBB, LVH with repolarization abnormalities, pre-excitation and pacemakers.

### **Silent MI**

This event includes evidence of new silent Q-wave MI detected during routine protocol or clinically obtained ECG follow-up. Silent MI events will be classified as a type 1 MI.

### **Sudden death MI (Type 3)**

MI events in which a presentation consistent with infarction is present but the patient dies before the biomarkers are drawn or within the first few hours of the event before the biomarkers become positive. Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST-segment elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

## PCI-Related MI (Type 4a)

### Primary Definition

CK-MB is the preferred biomarker and takes precedence over troponin. For subjects with normal baseline biomarker level pre-PCI, peri-PCI MI requires a rise in CK-MB to >5-fold the ULN (or a rise in troponin to >35 times the MI Decision Limit/ULN, when CK-MB is unavailable) within 48 hours post-PCI. If pre-PCI cardiac markers (CKMB or cTn) are elevated, they must be stable or falling as indicated by two samples at least 6 h apart. The post-PCI CKMB level should reflect a rise of >20% over pre-PCI levels. In addition to biomarker criteria, peri-PCI MI requires at least one of the following:

- Post-procedure angiographic TIMI 0/1 flow in a major coronary artery or a side branch with reference vessel diameter  $\geq 2.0$  mm which had TIMI 2-3 flow at baseline, or TIMI 2 flow in a major coronary artery or a side branch with reference vessel diameter  $\geq 3.0$  mm which had TIMI 3 flow at baseline or Type C dissection (NHLBI classification) or greater in the target vessel.
- New ECG changes (ST segment elevation or depression  $>0.1$  mV in 2 contiguous leads), new pathologic Q-waves in  $\geq 2$  contiguous leads, or new persistent LBBB present on a post-PCI ECG obtained at least 30 minutes and up to 48 hours post procedure in the absence of any intervening coronary event between the time of the PCI procedure and the ECG showing changes.

### Secondary Definition

Elevation of troponin values  $>5$  X 99th percentile URL within 48 hours post-PCI in patients with normal baseline troponin values pre-PCI AND a rise of troponin values  $>20\%$  if the

baseline values are elevated pre-PCI and are stable or falling. If the troponin 99th percentile is not available, the MI Decision Limit / ULN may be used. If troponins are not available, CKMB elevation  $>5 \times$  ULN will be used.

In addition to biomarker criteria, peri-PCI MI requires at least one of the following:

- Symptoms suggestive of myocardial ischemia ( $\geq 20$  min)
- New ischemic ST changes or new pathological Q waves. (see “ECG Criteria” above)

Note

- the UMI definition uses  $\geq 0.05$  mV of STD whereas the ISCHEMIA definition uses  $\geq 0.1$  mV
- for PCI related ECG criteria
- Angiographic evidence of a flow limiting complication, such as loss of patency of a side branch, persistent slow-flow or no re-flow, embolization, or Type C dissection (NHLBI classification) or greater in the target vessel.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

### **CABG-Related MI (Type 5)**

#### **Primary Definition**

CK-MB is the preferred serum biomarker and takes precedence over cardiac troponin. For subjects with normal baseline biomarker level pre-CABG, peri-CABG MI requires a rise in CK-MB to  $>10$ -fold the ULN (or a rise in troponin to  $>70$  times MI Decision Limit/ULN when CK-

MB is unavailable) within 48 hrs post-CABG. In addition to biomarker criteria, peri-CABG MI requires at least one of the following:

- A new substantial wall motion abnormality by cardiac imaging (CEC assessed), except new septal and apical abnormalities. The CEC will have latitude in determining whether a new wall motion abnormality is “substantial” in the context of the clinical event.
- New pathologic Q-waves in  $\geq 2$  contiguous leads or new persistent LBBB is present on post CABG ECG obtained day 3 post CABG, or hospital discharge, whichever comes earlier in the absence of any intervening coronary event between the time of the CABG procedure and the ECG showing changes.

### **Secondary Definition**

Elevation of troponin values  $>10 \times$  99th percentile URL within 48 hrs post -CABG in patients with normal baseline troponin values ( $\leq$  99th percentile URL). If the troponin 99th percentile is not available, the ULN may be used. If troponins are not available, CKMB elevation  $>10 \times$  ULN will be used. In addition to biomarker criteria, peri-CABG MI requires at least one of the following:

- New pathologic Q waves or new LBBB
- Angiographic evidence of new graft or new native coronary artery occlusion.
- Imaging evidence of new loss of viable myocardium.