Circulation

ORIGINAL RESEARCH ARTICLE

Myocardial Infarction in the ISCHEMIA Trial

Impact of Different Definitions on Incidence, Prognosis, and Treatment Comparisons

BACKGROUND: In the ISCHEMIA trial (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches), an initial invasive strategy did not significantly reduce rates of cardiovascular events or all-cause mortality in comparison with a conservative strategy in patients with stable ischemic heart disease and moderate/severe myocardial ischemia. The most frequent component of composite cardiovascular end points was myocardial infarction (MI).

METHODS: ISCHEMIA prespecified that the primary and major secondary composite end points of the trial be analyzed using 2 MI definitions. For procedural MI, the primary MI definition used creatine kinase-MB as the preferred biomarker, whereas the secondary definition used cardiac troponin. Procedural thresholds were >5 times the upper reference level for percutaneous coronary intervention and >10 times for coronary artery bypass grafting. Procedural MI definitions included (1) a category of elevated biomarker only events with much higher biomarker thresholds, (2) new ST-segment depression of ≥1 mm for the primary and ≥0.5 mm for the secondary definition, and (3) new coronary dissections >National Heart, Lung, and Blood Institute grade 3. We compared MI type, frequency, and prognosis by treatment assignment using both MI definitions.

RESULTS: Procedural MIs accounted for 20.1% of all MI events with the primary definition and 40.6% of all MI events with the secondary definition. Four-year MI rates in patients undergoing revascularization were more frequent with the invasive versus conservative strategy using the primary (2.7% versus 1.1%; adjusted hazard ratio [HR], 2.98 [95% CI, 1.87–4.73]) and secondary (8.2% versus 2.0%; adjusted HR, 5.04 [95% CI, 3.64–6.97]) MI definitions. Type 1 MIs were less frequent with the invasive versus conservative strategy using the primary (3.40% versus 6.89%; adjusted HR, 0.53 [95% CI, 0.41–0.69]; *P*<0.0001) and secondary (3.48% versus 6.89%; adjusted HR, 0.53 [95% CI, 0.41–0.69]; *P*<0.0001) definitions. The risk of subsequent cardiovascular death was higher after a type 1 MI than after no MI using the primary (adjusted HR, 3.38 [95% CI, 2.03–5.61]; *P*<0.001) or secondary MI definition (adjusted HR, 3.52 [2.11–5.88]; *P*<0.001).

CONCLUSIONS: In ISCHEMIA, type 1 MI events using the primary and secondary definitions during 5-year follow-up were more frequent with an initial conservative strategy and associated with subsequent cardiovascular death. Procedural MI rates were greater in the invasive strategy and with the use of the secondary MI definition.

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Bernard R. Chaitman, MD
⋮
Judith S. Hochman, MD
On behalf of the ISCHEMIA Research Group

The full author list is available on page 801.

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Clinical Perspective

What Is New?

- This analysis of the ISCHEMIA trial (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) demonstrated that procedural myocardial infarction (MI) definition had an important impact on event frequency and subsequent prognosis.
- When the prespecified secondary MI definition was applied, the conservative strategy had significantly lower composite event rates for the primary and major secondary trial end points because of an increased number of procedural MIs in the invasive strategy.
- Spontaneous type 1 MI events, associated with increased risk of cardiovascular death, were reduced with an invasive strategy (percutaneous coronary intervention or coronary artery bypass grafting).

What Are the Clinical Implications?

- An early invasive strategy is associated with a reduced risk for spontaneous type 1 MI. The mechanism for the reduction requires further study.
- The incidence of procedural MI was determined by the MI definition used. Using the biomarker-specific thresholds established for this trial, procedural MIs were less frequent using creatine kinase-MB in comparison with cardiac troponin.

Spontaneous (type 1) myocardial infarction (MI) is an important outcome in clinical trials used to assess the efficacy and safety of different treatment strategies. The ISCHEMIA trial (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) randomly assigned patients with stable ischemic heart disease and moderate or severe myocardial ischemia on noninvasive testing to an initial invasive or conservative strategy.[1–3] After a median 3.2-year follow-up, there was no statistical evidence of a difference in the primary composite end point of cardiovascular death, MI, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest, or in the major secondary composite outcome of cardiovascular death or MI.[1]

MI was the main contributor to the primary and major secondary composite outcomes. When ISCHEMIA was designed, both the 3rd Universal Definition of Myocardial Infarction (UDMI 3) that gives precedence to cardiac troponin (cTn) values, and the Society for Cardiovascular Angiography and Interventions definition that gives precedence to creatine kinase-MB (CK-MB) values for procedural-related MI had been introduced.[4,5] An abundance of published data had established a relationship between the magnitude of postprocedural CK-MB elevation with a range of thresholds and short- and long-term mortality.[4–18] A similar relationship was observed with cTn assays in some but not all studies.[9–18]

Given the uncertainty of whether a threshold exists above which a procedural MI confers an adverse prognosis, we developed 2 definitions of procedural MI with a plan to evaluate their impact on treatment outcomes. A clinical events committee (CEC) adjudicated all occurrences of elevated cardiac biomarkers after coronary revascularization, and any hospitalizations with elevated cardiac biomarkers using a primary and secondary MI definition, as well. The aim of this report is to compare treatment comparisons of the primary and major secondary composite end points in the ISCHEMIA trial using the primary and secondary MI definitions. We also examined the treatment effect of the invasive and conservative strategies on MI event rates by type using both MI definitions and determined their prognostic significance.

METHODS

ISCHEMIA Trial

Deidentified participant data and a data dictionary will be available starting June 30, 2022. Methods of data sharing will be determined based on the National Institutes of Health data sharing policy and in discussion with the National Institutes of Health and the National Heart, Lung, and Blood Institute program officer. The ISCHEMIA trial design, protocol, baseline characteristics, and major clinical outcomes have been published.[1–3] In brief, the ISCHEMIA trial was a large international trial that tested 2 major treatment strategies in 5179 patients with moderate or severe myocardial ischemia on stress testing, most of whom underwent coronary computed tomography angiography before randomization to confirm the presence of obstructive coronary disease and the absence of unprotected left main disease ≥50%. Angiographic findings of the coronary computed tomography angiogram were blinded to the treating physicians. Patients were randomly assigned to an initial invasive strategy with prompt angiography and coronary revascularization if feasible and intensive medical therapy or an initial conservative approach with intensive medical therapy, with angiography permitted for worsening symptoms. Exclusion criteria included acute coronary syndrome in the previous 2 months, angina that could not be controlled with medical therapy, ejection fraction <35%, estimated glomerular filtration rate <30 mL/min, or severe valvular disease. All patients were prescribed guideline-based medical therapy for secondary prevention. Baseline characteristics of the study population were similar in both treatment strategies (Table I in the Data Supplement).[1,2] The average age of the study population was 64 years and 22.6% were women.

Of the 2588 patients randomly assigned to the invasive strategy, 1524 (58.9%) received percutaneous coronary intervention (PCI), 530 (20.5%) received coronary artery bypass grafting (CABG), and 534 (20.6%) did not undergo a revascularization procedure, 59.6% of whom did not have obstructive coronary disease at cardiac catheterization. Of the 2591

patients assigned to the conservative strategy, 369 (14.2%) patients underwent PCI and 175 (6.8%) underwent CABG during the follow-up phase. The randomization period for ISCHEMIA started August 7, 2012, and ended January 31, 2018. The last patient visit was June 30, 2019. There were 112 (2.2%) patients who withdrew from the study or were lost to follow-up. The median duration of follow-up was 3.2 years (Q1, Q3: 2.2, 4.4). The protocol was approved by the Institutional Review Board at each institution. All patients provided written informed consent. The trial was funded by the National Heart, Lung, and Blood Institute with industry support providing some free drugs and devices.

Definitions of MI

A detailed description of the MI definitions and CEC members can be found in the Data Supplement. MI definitions for types 1, 2, 4b, and 4c were based on UDMI 3. The procedural MI definition used in ISCHEMIA included (1) a category of elevated biomarker only events with much higher biomarker thresholds than the level required when ancillary evidence of myocardial ischemia was present (Primary and Secondary MI Definitions in the Data Supplement), (2) new ST-segment depression of ≥1 mm for the primary and ≥0.5 mm for the secondary definition, and (3) new coronary dissections ≥National Heart, Lung, and Blood Institute grade 3. Procedural MI was diagnosed if it occurred within 48 hours and was a consequence of the procedure. Nonprocedural MI events were diagnosed if they occurred later and included MI types 1, 2, 4b, and 4c. For elective revascularization procedures, CK-MB and cTn measurements were protocol requirements preprocedure, and between 8 and 16 hours±2 hours postprocedure or hospital discharge, whichever came first. Additional CK-MB or cTn measurements were acquired as needed for suspected myocardial ischemic events. All biomarker measurements available in the hospital records were available to the CEC for MI adjudication. If preprocedural biomarkers were unavailable, they were assumed to be normal in the absence of a recent change in clinical symptoms or ECG evidence of acute myocardial ischemia indicating a preprocedural acute MI.

The primary MI definition in ISCHEMIA used the site-determined MI decision limit or the upper limit of normal (ULN) for biomarkers, of which cTn was the preferred biomarker for nonprocedural UDMI types 1, 2, 4b, and 4c (unless only CK-MB values were available). For types 4a and 5 procedural-related MI, CK-MB was the preferred biomarker (unless only cTn values were available). A postprocedural CK-MB threshold >5-fold the ULN within 48 hours associated with specific ECG, angiographic, or imaging findings indicating myocardial ischemia defined a type 4a PCI-related MI. For type 5 CABG-related MI, a postprocedural CK-MB threshold >10-fold the ULN within 48 hours associated with new Q waves or persistent left bundle-branch block defined an event. In addition, postprocedure elevated biomarker only criteria were defined by higher thresholds but without supporting evidence of myocardial ischemia. Such extreme biomarker only elevations were also counted as type 4a and 5 MIs for the primary MI definition. The biomarker elevation only thresholds were a postprocedural rise in CK-MB >10-fold the ULN (cTn >70-fold the decision limit if CK-MB was unavailable) for PCI and CK-MB >15-fold the ULN (or cTn >100-fold the decision limit if CK-MB was unavailable) for CABG for the primary definition.

The secondary MI definition used cTn as the preferred biomarker for all MI types, and the manufacturer's recommended 99th percentile of the upper reference limit (URL), with specific clinical, angiographic, ECG, and imaging criteria (Data Supplement).[19] The cTn thresholds for a type 4a MI and type 5 MI were the same as those used for the primary MI definition. As with the primary definition, cTn was the preferred biomarker for nonprocedural UDMI types 1, 2, 4b, and 4c (unless only CK-MB values were available), and similar to the primary MI definition, postprocedure elevated biomarker only criteria were defined by higher thresholds but without supporting evidence of myocardial ischemia and included in the secondary definitions of type 4a and 5 MI. For the secondary definition, a postprocedural rise in cTn >70-fold the manufacturer's recommended 99th percentile URL (or CK-MB >10-fold the ULN if cTn was unavailable) for PCI and >100-fold the 99th percentile URL (or CK-MB >15-fold the ULN if cTn was unavailable) for CABG were used.

In addition to reviewing all procedural biomarker elevations, the CEC reviewed all postrandomization hospital admissions that were associated with elevated cardiac biomarkers. Thus, site-reported, and the remaining triggered cardiac events, as well, were sent to the CEC to maximize sensitivity to capture unreported cardiac events in this open-label trial. Of the 2794 suspected MI or elevated cardiac biomarker events reviewed by the CEC, 1812 (65%) were triggered and 982 (35%) were site reported. Of the 332 site-reported MI events, 258 (77.7%) were confirmed by the CEC. Of the 1812 triggered events, 318 (18%) were classified as an MI by the CEC. St Louis University core ECG laboratory reviewed all pre- and postprocedural ECG tracings, those associated with acute coronary syndrome admissions, and at 1 year, 3 years, and study close-out to determine new ST-segment, T-wave, and Q-wave findings that met protocol criteria.

Complicated and Large MI

An MI was classified by the CEC reviewers as complicated if, after the MI, during the same admission, there was evidence of new or worsening heart failure, hemodynamic instability, cardiogenic shock, a drop in left ventricular ejection fraction >10% from baseline, or electric instability such as life-threatening ventricular tachycardia or ventricular fibrillation complicating the event.

Large MI was classified by peak cTn values. A type 4a or 5 MI was considered large if it met the elevated biomarker only criteria (cTn >70 or >100 times 99th percentile URL for type 4a and 5 MI) and for nonprocedural MIs if the peak cTn was >70 times the 99th percentile URL.

Statistical Analysis

Baseline characteristics, including demographics, cardiovascular risk factors, cardiovascular disease history, and selected laboratory tests are presented for all patients according to randomized treatment strategy. Continuous variables are presented as medians (Q1, Q3) and categorical variables are presented as counts (percentages). The number of MI events

(first MI events, overall, and by type for primary and secondary definitions) are summarized with counts and percentages among all randomly assigned patients. To account for the competing risk of any type of death in the analysis of individual nonfatal MI end points, cumulative incidence rates (95% CI) were estimated for the invasive and conservative groups, and Gray test[20] was applied to compare incidence rates over the duration of follow-up.

Cox regression modeling was used to characterize the association between randomized treatment strategy and time to first occurrence of an MI. Unadjusted and adjusted hazard ratios (95% CI) and *P* values are reported for comparing invasive versus conservative strategies. Each model was adjusted for a set of prespecified prognostically important baseline covariates that included age at randomization, sex, estimated glomerular filtration rate, left ventricular ejection fraction (LVEF), and diabetes. To allow for nonlinear covariate effects, the continuous variables of age, LVEF, and estimated glomerular filtration rate were modeled as restricted cubic splines with knots at the approximate 10th, 50th, and 90th percentiles of each variable's empirical distribution. The association of MI versus no MI on subsequent events of death and hospitalization for heart failure was characterized by reporting the adjusted hazard ratio (95% CI) and *P* value from a Cox regression model in which MI during follow-up was treated as a time-dependent covariate. Models were adjusted for age at randomization, sex, estimated glomerular filtration rate, LVEF, diabetes, randomized treatment strategy, previous heart failure, previous MI, smoking status, low-density lipoprotein cholesterol, and extent of myocardial ischemia. Continuous variables were modeled as restricted cubic splines with knots at the 10th, 50th, and 90th percentiles of each variable's empirical distribution. Additional description of the statistical modeling discussion is found in Statistical Methods in the Data Supplement.

RESULTS

First MI events occurred in 443 (8.6%) of the 5179 patients with the primary definition and 593 (11.5%) with the secondary definition (Table 1). The MIs were fatal within 30 days in 32 (7.2%) and 35 (5.9%) patients with the primary and secondary definitions, respectively (Table II in the Data Supplement). Most fatal MIs that occurred during follow-up were types 1 or 2. The number of fatal procedural MIs was relatively small with the majority being type 5 MIs. Procedural MIs accounted for 20.1% of all MI events with the primary definition and 40.6% of all MI events with the secondary definition (Figure 1). Procedural MIs were classified as complicated MIs significantly less often than nonprocedural MIs for both the primary definition (*P*=0.037) and secondary definition (*P*<0.001; Table III in the Data Supplement). The number of nonprocedural MI (types 1, 2, 4b, and 4c) were similar regardless of whether the site-determined (primary MI definition) or manufacturer's recommended 99th percentile URL (secondary MI definition) decision threshold was used. Three more first type 1 MIs were detected using the manufacturer's 99th percentile URL and 2 fewer first type 4B and 4C MIs.

Of the 289 type 1 or 2 MI events, 67 (23.2%) were type 2 MIs and were associated with a greater rate of complications than the other MI types (Table III in the Data Supplement). The incident rates for type 2 MIs were similar regardless of treatment strategy or MI definition (Table IV in the Data Supplement). Of the 100 patients with a large nonprocedural MI during follow-up, 71%, 19%, and 10% were types 1, 2, and 4b or 4c MI events.

Treatment Strategy and MI Type

First MI events were more frequent with the conservative than with the invasive strategy using the primary definition, and less frequent with the conservative than with the invasive strategy using the secondary MI definition (Table 1, Figure 2). As expected, significantly more procedural MIs (*P*<0.001) and stent-related type 4b and 4c MIs occurred in the invasive strategy, regardless of MI definition. Table IV and Figure I in the Data Supplement provide a breakdown of procedural MIs by treatment strategy according to whether they were classified by biomarker elevation only, or by MI criteria with supporting evidence of myocardial ischemia (types 4a and 5). The 5-year cumulative incidence rates of the different MI subtypes by treatment strategy using the primary and secondary MI definition are found in Table IV in the Data Supplement. Of the 31 type 4a MI events classified using the primary definition, 24 (77%) had supporting evidence of myocardial ischemia. Of the 64 type 5 MI events classified using the primary definition, 15 (23%) had supporting evidence of myocardial ischemia. The frequency of supportive evidence for myocardial ischemia postprocedure was similar using the secondary MI definition.

The cumulative incidence of type 1 MI by treatment assignment overall was significantly less in the invasive than in the conservative strategy using either MI definition (*P*<0.0001; Table 1, Figure 3). The decreased incidence of type 1 MI events in the invasive strategy was observed for those who underwent PCI or CABG, and in the subset that had no revascularization (59.6% of whom had no obstructive coronary disease at cardiac catheterization; *P*<0.001 for individual comparisons and *P*<0.0001 for the group comparison), as well.

The mean time free from the composite of cardiovascular death, MI, admission for unstable angina, heart failure, or resuscitated cardiac arrest over 5 years was similar between treatment groups using the primary definition of MI.[1] Conversely, the difference in the composite end point was significantly greater in the invasive group using the secondary MI definition (*P*<0.001) because of an increased number of

Table 1. Distribution of First Myocardial Infarction Events by Type and Randomized Treatment Arm

Myocardial infarction type	Primary definition		Secondary definition	
	INV (n=210)	CON (n=233)	INV (n=343)	CON (n=250)
Type 1	75/210 (35.7)	147/233 (63.1)	74/343 (21.6)	151/250 (60.4)
Type 2	32/210 (15.2)	35/233 (15.0)	32/343 (9.3)	35/250 (14.0)
Type 3	1/210 (0.5)	2/233 (0.9)	1/343 (0.3)	2/250 (0.8)
Type 4a	26/210 (12.4)	4/233 (1.7)	98/343 (28.6)	12/250 (4.8)
Type 4b	13/210 (6.2)	6/233 (2.6)	12/343 (3.5)	6/250 (2.4)
Type 4c	6/210 (2.9)	4/233 (1.7)	5/343 (1.5)	4/250 (1.6)
Type 5	43/210 (20.5)	16/233 (6.9)	109/343 (31.8)	22/250 (8.8)
Silent	14/210 (6.7)	19/233 (8.2)	12/343 (3.5)	18/250 (7.2)

Values are shown as counts (%). CON indicates conservative strategy; and INV, invasive strategy.

procedural MIs (Figure 4). Similar findings were seen for the composite of cardiovascular death or MI and for all-cause death or MI (Figure II in the Data Supplement). The difference was the result of the greater number of procedural MI events classified by the secondary definition. The 5-year estimated cumulative event rate for cardiovascular death was 5.2% for the invasive versus 6.5% for the conservative strategy (difference: –1.3% [95% CI, –3.1% to 0.6%]; Cox model HR², 0.87 [95% CI, 0.66–1.15]).

Prognostic Association of MI Type According to the MI Definition

All-cause death subsequently occurred in 25 (11.5%) of 217 patients with a type 1 MI and 5 (5.6%) of 89 patients with a procedural MI using the primary definition (Table 2).The rates for all-cause death were 25 (11.2%) of 223 with a type 1 MI and 16 (6.5%) of 245 with a procedural MI using the secondary definition. All-cause death subsequently occurred in 17 (25.4%) of 67 patients with a type 2 MI; 15 deaths were attributed to cardiovascular causes. All-cause death subsequently occurred in 219 (4.8%) of 4585 patients who had no MI by either the primary or secondary MI definition. Of those 219 deaths, 144 (65.8%) were attributed to cardiovascular causes. The 5-year unadjusted death rate among patients who had no MI (by primary or secondary definition) was 7.7% (95% CI, 6.5%–9.0%).

The hazard ratios for all-cause death, cardiovascular death, and cardiovascular death or admission for heart failure using the primary or secondary definition are shown in Table 2 and Figure 5. There were 11 type 1 and 6 type 4b/4c MIs in which another MI type occurred before the MI of interest. After multivariable adjustment for baseline characteristics and treatment group, a type 1 MI was strongly associated with an increased risk for all-cause death, cardiovascular death, and the composite of cardiovascular death or admission for heart failure in comparison with patients who did

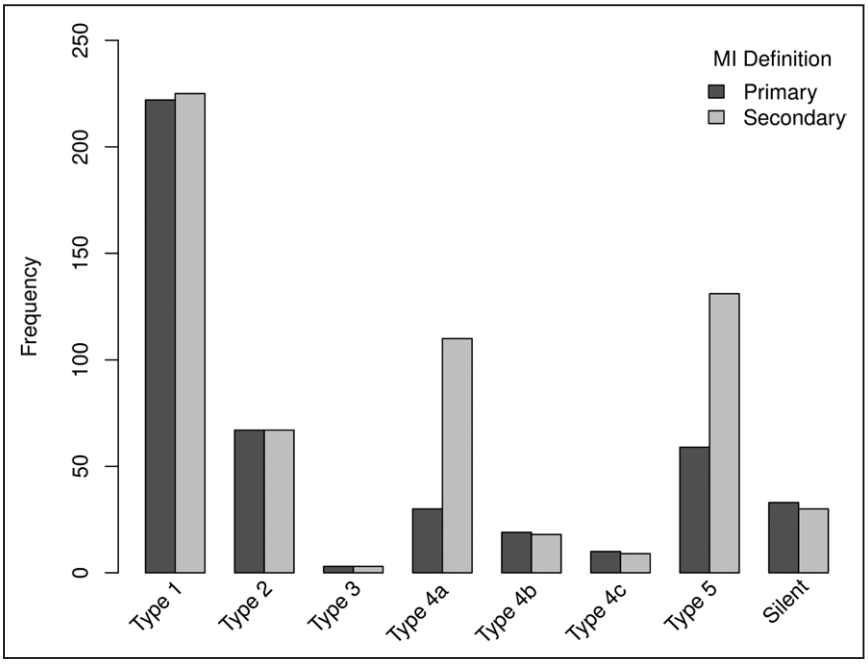

Figure 1. Distribution of first MI events by type.
The difference in total MI rates between the primary and secondary MI definitions was primarily attributable to increased procedural MI events using the secondary MI definition. Type 4a and 5 MIs accounted for 20.1% of all MIs using the primary definition and 40.6% using the secondary definition. MI indicates myocardial infarction.

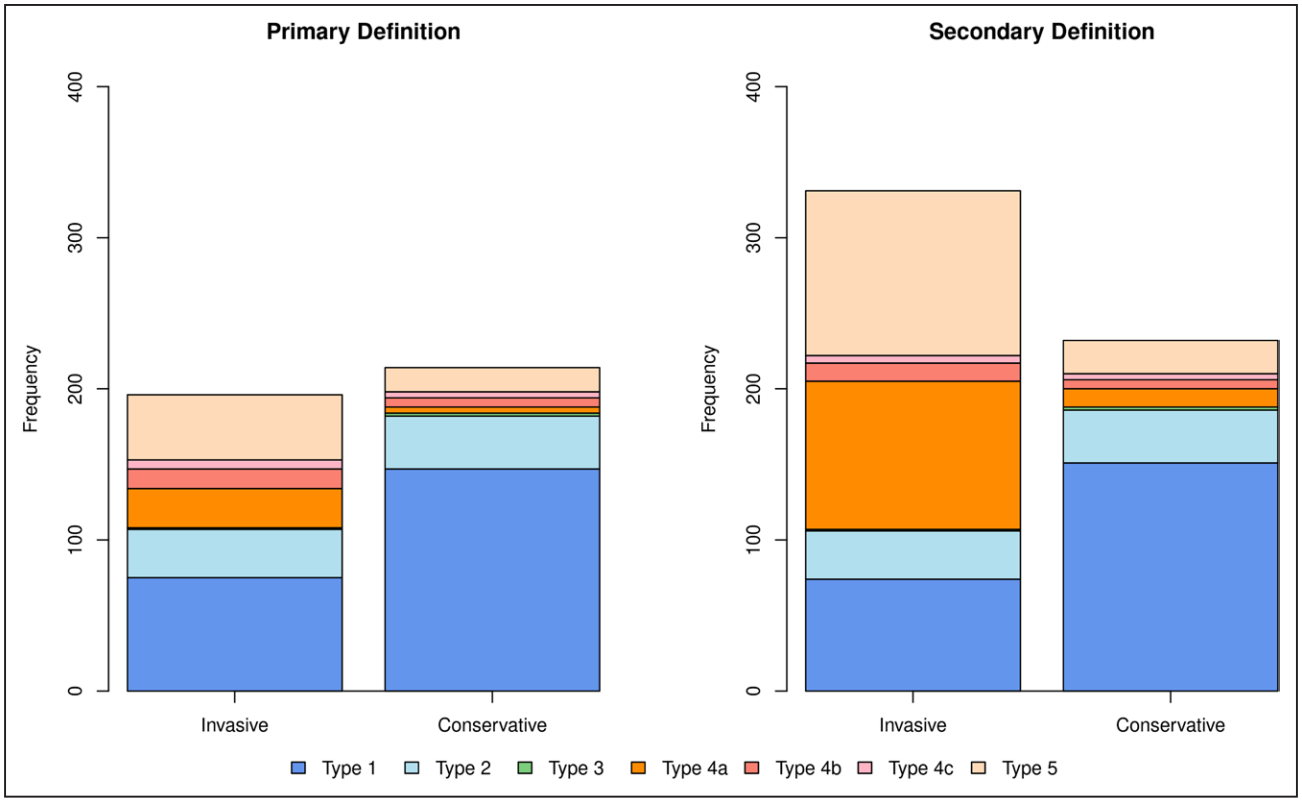

Figure 2. Results for myocardial infarction (MI) type according to treatment strategy.
With the primary definition (**Left**), there were slightly more first MI events in the conservative strategy, whereas the opposite was true using the secondary MI definition. Dark blue shows spontaneous type 1 MIs that were reduced in the invasive strategy regardless of which MI definition was used. The incidence of type 2 MIs shown in light blue were similar. Procedural MIs (orange) were more common in the invasive strategy and, as expected, occurred with greater frequency using the secondary definition (**Right**). Stent related type 4b (stent thrombosis-related) and 4c MIs (in-stent restenosis–related) shown in red were more frequent in the invasive strategy.

not have an MI during follow-up regardless of which MI definition was used (Table 2, Figure 5; $P<0.001$).

Of the 67 procedural MIs (invasive strategy) using the primary MI definition, 4 patients died (Figure 5): 1 had type 4a MI and 3 had type 5 MI. Of the 204 procedural MIs (invasive strategy) using the secondary definition, 15 patients died. Of the 15, 8 had type 4a MIs and 7 had type 5 MIs. During follow-up, 4 patients with a type 4b MI (stent thrombosis) died and 1 patient with a type 4c MI died. MI types 4b and 4c were pooled for analytic purposes because the number of this type of MI was relatively small and both are stent-related events. The hazard ratios for all-cause death, cardiovascular death, and cardiovascular death or admission for heart failure using the primary or secondary definition were greater for types 4b/4c MI than for type 1 or procedural MI using both MI definitions. The impact of elevated preprocedural biomarker values in subjects with a type 4a and 5 MI is shown in Table V in the Data Supplement. Most patients with a procedural MI had normal preprocedure biomarkers. In those with elevated preprocedural biomarkers, subsequent deaths were uncommon and did not occur with the primary MI definition. Postprocedural CK-MB ratio elevations >10 times ULN were uncommon and occurred in <1% and 3.3% of patients post-PCI and post-CABG, respectively. One of the 19 patients with a postprocedural CK-MB elevation >10 times ULN died.

DISCUSSION

MI events were the predominant component of the primary and major secondary outcomes in ISCHEMIA, and interpretation of the overall trial was sensitive to the definition of the procedural MI used. The primary MI definition used CK-MB as the preferred biomarker for assessment of type 4a and 5 procedural MI, whereas the secondary MI definition used similar thresholds of cTn. CK-MB is relatively insensitive in comparison with cTn, resulting in a relatively lower frequency of procedural MI events with the primary in comparison with the secondary procedural MI definition. As expected, procedural MIs were more common with the invasive strategy than with the conservative strategy using both the primary and secondary definition. With the primary ISCHEMIA trial MI definition, there were no major long-term differences in the primary composite event rate and the major secondary composite rate of cardiovascular death or MI. In contrast, as a result of the increased rates of procedural MI with the secondary definition, a significant treatment difference in the primary trial

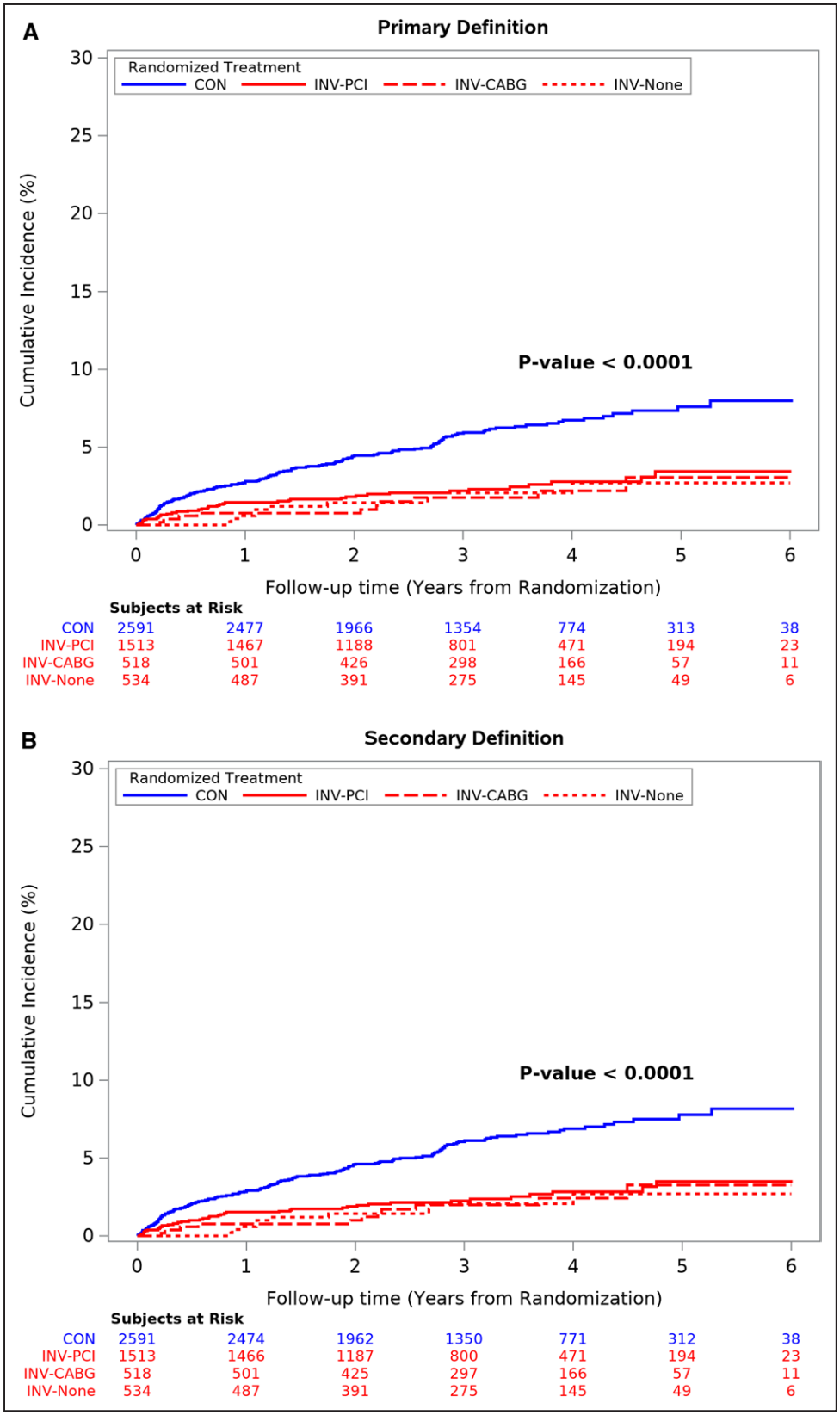

Figure 3. Spontaneous type 1 MI by strategy and by MI definitions management after catheterization by invasive strategy versus conservative strategy. Spontaneous type 1 MI events were significantly more frequent in the conservative strategy regardless of type of revascularization procedure performed or MI definition used. Group differences are significant at $P<0.001$, and individual pairwise comparisons to the CON group are significant at $P<0.001$ after adjustment for multiple comparisons. CON indicates conservative strategy; INV-CABG, patients in the invasive strategy group that received coronary bypass surgery; INV-PCI, invasive strategy patients that received PCI; INV-None, patients in the invasive strategy group that did not receive coronary revascularization (59.6% had nonobstructive coronary disease at catheterization); and MI, myocardial infarction.

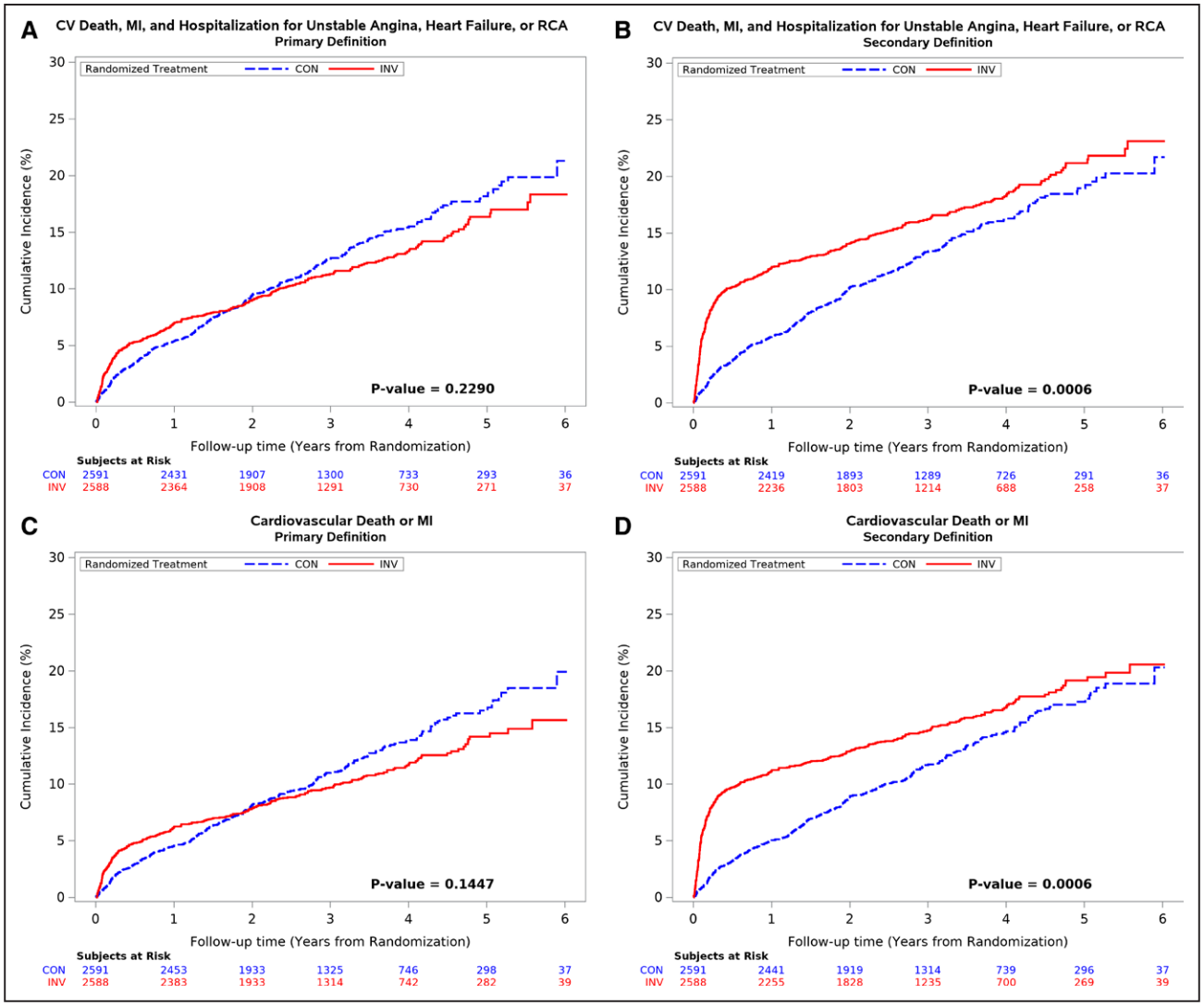

Figure 4. Outcomes according to treatment strategy and MI definition.
Unadjusted cumulative incidence plot of the 5-component primary ISCHEMIA end point using the primary MI (**A**) and secondary MI (**B**) definitions and the composite end point of cardiovascular death or MI using the primary (**C**) and secondary (**D**) MI definitions by randomized treatment strategy. Choice of MI definition had an important impact on the outcome results. The secondary MI definition (**B** and **D**) was associated with an increased number of early procedural MI events in the invasive in comparison with the conservative strategy. The difference between treatment groups attenuated over time using the secondary definition (**B** and **D**) primarily because of the increased number of spontaneous type 1 MI events in the conservative strategy. Cardiovascular death rates were low and not statistically different between treatment groups. CON indicates conservative strategy; CV, cardiovascular; INV, invasive strategy; MI, myocardial infarction; and RCA, right coronary artery.

end point and major secondary composite end point of cardiovascular death or MI was observed favoring the conservative strategy. Removal of biomarker elevation only criteria from types 4a and 5 MIs did not produce a meaningful change in the treatment comparison results or conclusions with either MI definition. Last, the pattern of association of procedural and nonprocedural MIs by the 2 MI definitions with subsequent death were relatively consistent.

Treatment Strategy and MI Risk

In ISCHEMIA, the risk of type 1 MIs was reduced for patients who had either a PCI or CABG procedure. In contrast, the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) and BARI 2D trials (Bypass Angioplasty Revascularization Investigation 2 Diabetes) did not show a reduction in spontaneous MI rates with initial PCI and optimal medical therapy versus initial optimal medical therapy alone.[21–24] In the BARI 2D trial, patients with diabetes were randomly assigned after the coronary angiogram was performed and the treating physician then determined if the patient was more suitable for PCI or CABG. Biomarkers were not routinely collected after coronary revascularization in BARI 2D. However, type 1 MI events were significantly reduced by a strategy of prompt CABG in comparison with a conservative strategy in BARI 2 D, in particular, in higher-risk patients.[23,24] Similar findings were reported in the FREEDOM trial

Table 2. Death, Cardiovascular Death, and the Composite of Cardiovascular Death or Hospitalization for Heart Failure Events After an MI

MI type	No. MI events	Event	No. events post-MI	Hazard Ratio (95% CI)* MI vs No MI	*P* value
Primary definition					
Procedural MI	89	All-cause death	5	1.14 (0.42–3.08)	0.803
Procedural MI (INV only)	67	All-cause death	4	1.40 (0.51–3.86)	0.511
Procedural MI (excluding stand-alone MI)	36	All-cause death	3	2.10 (0.67–6.66)	0.205
Type 4B or 4C MI	34	All-cause death	5	3.99 (1.62–9.83)	0.003
Type 1 MI	217	All-cause death	25	2.44 (1.54–3.88)	<0.001
Procedural MI	89	Cardiovascular death	5	1.99 (0.73–5.43)	0.181
Procedural MI (INV only)	67	Cardiovascular death	4	2.77 (0.99–7.76)	0.052
Procedural MI (excluding stand-alone MI)	36	Cardiovascular death	3	3.75 (1.17–11.97)	0.026
Type 4B or 4C MI	34	Cardiovascular death	5	6.80 (2.73–16.93)	<0.001
Type 1 MI	217	Cardiovascular death	21	3.38 (2.03–5.61)	<0.001
Procedural MI	89	Cardiovascular death or hospitalization for heart failure	5	1.45 (0.53–3.93)	0.469
Procedural MI (INV only)	67	Cardiovascular death or hospitalization for heart failure	4	1.95 (0.71–5.39)	0.196
Procedural MI (excluding stand-alone MI)	36	Cardiovascular death or hospitalization for heart failure	3	2.61 (0.82–8.28)	0.103
Type 4B or 4C MI	34	Cardiovascular death or hospitalization for heart failure	8	7.82 (3.58–17.84)	<0.001
Type 1 MI	215	Cardiovascular death or hospitalization for heart failure	23	2.94 (1.82–4.74)	<0.001
Secondary definition					
Procedural MI	245	All-cause death	16	1.06 (0.56–2.02)	0.858
Procedural MI (INV only)	204	All-cause death	15	1.21 (0.63–2.34)	0.569
Procedural MI (excluding stand-alone MI)	115	All-cause death	9	1.38 (0.61–3.15)	0.440
Type 4B or 4C MI	35	All-cause death	5	3.69 (1.50–9.09)	0.005
Type 1 MI	223	All-cause death	25	2.55 (1.60–4.06)	<0.001
Procedural MI	245	Cardiovascular death	13	1.24 (0.57–2.68)	0.592
Procedural MI (INV only)	204	Cardiovascular death	12	1.54 (0.70–3.43)	0.286
Procedural MI (excluding stand-alone MI)	115	Cardiovascular death	8	1.95 (0.79–4.84)	0.149
Type 4B or 4C MI	35	Cardiovascular death	5	6.17 (2.48–15.35)	<0.001
Type 1 MI	223	Cardiovascular death	21	3.52 (2.11–5.88)	<0.001
Procedural MI	245	Cardiovascular death or hospitalization for heart failure	15	1.16 (0.59–2.30)	0.661
Procedural MI (INV only)	204	Cardiovascular death or hospitalization for heart failure	14	1.42 (0.70–2.85)	0.330
Procedural MI (excluding stand-alone MI)	115	Cardiovascular death or hospitalization for heart failure	10	2.00 (0.93–4.31)	0.077
Type 4B or 4C MI	35	Cardiovascular death or hospitalization for heart failure	8	7.07 (3.25–15.38)	<0.001
Type 1 MI	221	Cardiovascular death or hospitalization for heart failure	23	3.07 (1.90–4.97)	<0.001

INV indicates invasive strategy; and MI, myocardial infarction.

*Adjusted for the main ISCHEMIA trial (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) covariates (age at randomization, sex, estimated glomerular filtration rate, ejection fraction, and diabetes) in addition to randomized treatment strategy, prior heart failure, prior MI, smoking status, low-density lipoprotein cholesterol, and degree of ischemia. Continuous covariates are modeled as restricted cubic splines. The prognostic models flag an MI that occurs up to and on the day of the event of interest.

(Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) when the comparator was a PCI strategy.[25] FAME 2 (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) did not show a significant reduction in spontaneous MI events with fractional flow reserve–guided PCI

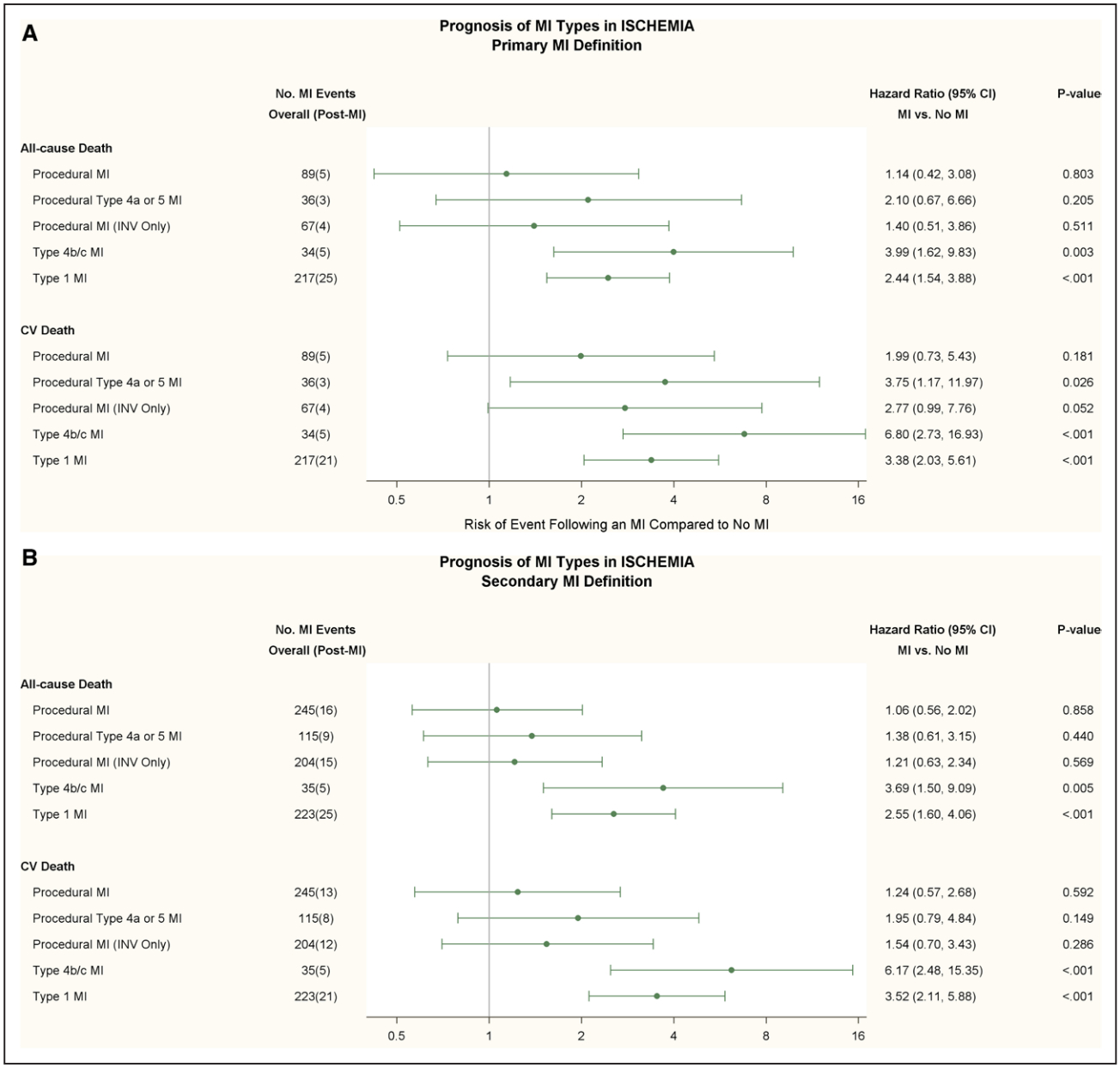

Figure 5. Adjusted risks of MI on subsequent all-cause and cardiovascular death according to MI definition.
The multivariate adjusted relative risk of all-cause death and cardiovascular death for the primary (**Upper**) and secondary (**Lower**) MI definitions are shown in this forest plot for procedural MI, procedural type 4a, or 5 MI with ancillary evidence of myocardial ischemia, procedural MI in the invasive strategy only (Procedural MI [INV Only]), types 4b/c stent related MIs, and type 1 MIs. Total number of MI events and subsequent deaths are shown in the second column. In patients assigned to the invasive strategy, the adjusted hazard ratio for cardiovascular death was 2.77 times greater in patients who had a procedural MI and no nonprocedural MI with the primary MI definition in comparison with patients who had no MI during follow-up (P=0.052). The adjusted risk of subsequent all-cause death and cardiovascular death was increased for patients that had a type 1 MI and no procedural MI in comparison with patients that had no MI during follow-up with the primary and secondary MI definitions (P<0.001), respectively. The adjusted risk for cardiovascular death was greater for patients that sustained a type 4b/c (stent-related) MI (P<0.001). CON indicates conservative strategy; CV, cardiovascular; and MI, myocardial infarction.

after 3 years of follow-up, although a trend toward decreased MI events was observed after 5 years.[26,27] The reason(s) why PCI conferred protection against type 1 MI is not clear, because spontaneous MI events often occur in nonstented vessels or non–flow-limiting lesions.[28] Possible explanations include more effective revascularization than was previously possible, increased use of dual antiplatelet therapy, ascertainment bias, or other aspects of the invasive strategy.[29–32] More potent dual antiplatelet therapy has been shown to reduce de novo atherothrombotic events in addition to preventing complications associated with stenting of the culprit lesion after acute coronary syndrome.[30] However, dual antiplatelet therapy usage for patients assigned to the invasive strategy in ISCHEMIA was greatest in the initial 18 months after the procedure, yet type 1

MIs continued to occur with greater frequency in the conservative strategy throughout follow-up.[1] It is also possible that clinicians would be more likely to admit a patient with chest pain if they were assigned to the conservative strategy and therefore more likely to have an MI diagnosed (ascertainment bias).[1]

Prognostic Impact of MI Type

The type 1 MI events that occurred in ISCHEMIA were associated with an increased risk for all-cause death, cardiovascular death, and the composite of cardiovascular death or heart failure admission in comparison with patients without an MI after adjustment for treatment strategy and regardless of MI definition. In contrast, the risk of subsequent all-cause death or cardiovascular death after procedural MI events in comparison with patients without an MI was less than type 1 MIs, and the MIs were less likely to be complicated. Our findings support previous reports comparing nonprocedural with procedural MI events that show a higher mortality with spontaneous MI events.[28,33–37] Procedural MIs are often related to baseline risk, atherosclerosis burden, and procedural complexity.[33] Patients with a type 1 MI are at higher risk of thrombotic complications because of acute evolving intracoronary thrombosis, later (out-of-hospital) presentation after symptom onset, and different mechanisms in that elective PCI-related infarcts tend to result from microembolism, dissection, or temporary occlusions that occur when the procedure is performed and can often be treated. Thus, type 1 MI events in comparison with procedural MIs are generally associated with a worse prognosis. We did not observe substantial differences in the rates of type 2 MI between treatment strategies. The frequency of complications after a type 2 MIs was greater than the other MI types and associated with a worse prognosis than type 1 or procedural MIs. A higher incidence of adverse outcomes with type 2 MIs in comparison with type 1 MIs has been previously reported.[38–40]

Types 4b/c MIs accounted for 9.1% of all first MIs in patients assigned to the invasive strategy and were associated with a greater risk for all-cause death and cardiovascular death, than type 1 or procedural MIs. The mortality rate for type 4b (stent thrombosis) was greater than for type 4c (restenosis) and accounted for 65% of the type 4b/4c MIs. This finding is consistent with other reports, such as the CORONOR registry (Suivi d'une cohorte de patients Coronariens stables en région Nord-pas-de-Calais) in patients with stable coronary disease and PCI, in which late stent thrombosis accounted for 20% of all MI types and was associated with a 4-fold increased mortality rate in comparison with spontaneous MIs after 5 years of follow-up. Although stent-related MI events are a consequence of randomization to the invasive strategy, and are associated with a greater risk of death, they accounted for <10% of all postrandomization MIs in the selected sites in the ISCHEMIA trial. Type 1 (spontaneous) MIs that were unrelated to the stented lesion were also associated with increased mortality in comparison with procedural MIs and accounted for 51% of all MIs with the primary MI definition.

MI Reference Limits

Bagai et al[19] reported substantial variability in the decision limit performed for various cTn assays in a cohort study of 276 hospital laboratories in 31 countries participating in the ISCHEMIA trial. Twenty-one unique troponin assays from 9 manufacturers were in use at these sites. Approximately one-third of sites applied the suggested 99th percentile URL with the ratio of troponin value to the manufacturer's recommended decision limit sometimes varying more than 10-fold, regardless of whether the sites were in the United States or whether the assay used was conventional or high-sensitivity cTn. In a large multinational trial, such as ISCHEMIA, laboratory sheets from individual institutions usually do not indicate which assay was used or if the MI decision limit used is the manufacturer's 99th percentile. In fact, it was not rare that sites using the same assay had different URL values. To minimize this type of variability, we used the manufacturer's recommended 99th percentile URL for individual assays using the secondary MI definition in ISCHEMIA with sex-specific thresholds when available. We used site-determined local decision limits for the primary definition. The choice of site determined versus the suggested manufacturer's 99th percentile URL did not have a substantial impact on incidence rates of nonprocedural MI events. In many cases, the magnitude of biomarker release after MI usually exceeded both reference limits, and, during the course of the trial, many hospital laboratories in this international study had adopted the manufacturer's recommended 99th percentile URL, in particular, for high-sensitivity cTn.

Elevated Preprocedural Biomarkers

In the setting of elective PCI, an association of elevated preprocedural high-sensitivity cTnT values and subsequent increased mortality has been reported.[12] Elevated preprocedural biomarkers usually indicate acute or chronic myocardial injury, both of which are known to adversely impact prognosis.[14] In 1 retrospective series of 5626 patients undergoing elective PCI, an increase in postprocedural high-sensitivity TnT level did not offer prognostic information beyond that provided by the baseline level of the biomarker. In this series, isolated biomarker increases only were reported and MI events were not classified.[12] In ISCHEMIA, the CEC determined if the elevated preprocedural biomarker value based on

clinical, electrocardiographic, and imaging findings was the result of a type 1, 2, 4b, or 4c MI. If the preprocedural value was missing and the patient had no recent change in symptoms or clinical evidence of myocardial ischemia, the preprocedure biomarkers were presumed to be normal. When preprocedural values were elevated and postprocedural values increased >20% associated with clinical evidence of myocardial ischemia, the procedural MI was classified as a type 4a or type 5 MI. Preprocedural biomarkers were normal in 75% to 86% of subjects in ISCHEMIA (Table V in the Data Supplement). A normal baseline biomarker value was usually based on the single protocol required sample for elective procedures. Determination of a stable baseline preprocedure based on a single sample would impact the definition of normal more for the primary than the secondary MI definition given the relative insensitivity of CK-MB in comparison with cTn.

Study Limitations

ISCHEMIA had a median follow-up of 3.2 years, which is relatively short for a chronic disease process, and it may take longer to observe the association of spontaneous and procedural MI events on all-cause mortality, cardiovascular mortality, and heart failure and for differences between treatment strategies to emerge. In CASS (Coronary Artery Surgery Study), which randomly assigned mild to moderately symptomatic or asymptomatic patients with coronary artery disease to CABG or medical therapy, CABG neither prolonged life nor prevented MI after 5 years in comparison with medical therapy.[41] However, a significant improvement in 7-year survival was reported in a relatively small subset of patients with 3-vessel disease and LVEF >34% and <50% with elective bypass surgery. Although that subset was <100 patients, and the trial was conducted in an era of minimal medical therapy, this result changed clinical practice.[41–43] Similarly, the benefits of CABG in patients with LVEF ≤35% in the STICH trial (Surgical Treatment for Ischemic Heart Failure) only emerged with a 10-year follow-up.[44]

Both ISCHEMIA definitions of procedural MI included biomarker elevation only criteria and not MI as defined in the UDMI 3 or 4.[14] Thus, the rates of procedural MIs in ISCHEMIA are greater than the rates that would have been observed had the UDMI definition been used (Table IV in the Data Supplement). In some studies, elevated biomarker only criteria have been associated with increased mortality.[12] The implications of using different procedural MI definitions after coronary revascularization in terms of outcomes and prognosis has been well described.[45–48] We did not observe a relationship between magnitude of CK-MB ratio and all-cause mortality. The patients enrolled in ISCHEMIA were stable at the time of randomization; only a small number of patients had postprocedural CK-MB values that exceeded 10 × ULN and the number of deaths was insufficient to test the relationship of larger postprocedural CK-MB elevations to mortality.

The number of patients with procedural MIs that had elevated preprocedural biomarkers was relatively small, precluding a robust analysis of the prognostic value of elevated preprocedural biomarkers and their relationship to postprocedural values and subsequent prognosis. Last, deaths after procedural MIs were relatively infrequent in ISCHEMIA, and prognostic correlation of subsequent death after a procedural MI should be interpreted with caution regardless of MI definition.

Conclusions

Our data show that choice of MI definition influences MI event rates, which were the most frequent component of the primary end point in the ISCHEMIA trial. With the use of the primary MI definition, the invasive and conservative strategies resulted in similar rates of the primary and secondary composite end points, whereas using the secondary MI definition, we observed a greater frequency of the primary and secondary composite end points in patients assigned to the invasive strategy. In contrast to procedural MIs, spontaneous type 1 MIs were more strongly associated with an increased risk of death and were significantly reduced in patients randomly assigned to the invasive strategy. However, it is unclear whether this reduction was attributable to revascularization, dual antiplatelet therapy, ascertainment bias, or some other mechanism. Type 4b/c MIs were relatively infrequent but associated with a greater risk of subsequent death. Longer-term follow-up may determine if the differences in MI rate and type translate into differential treatment effects on cardiovascular mortality.

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Authors

Bernard R. Chaitman, MD; Karen P. Alexander, MD; Derek D. Cyr, PhD; Jeffrey S. Berger, MD, MS; Harmony R. Reynolds, MD; Sripal Bangalore, MD, MHA; William E. Boden, MD; Renato D. Lopes, MD, PhD, MHS; Marcin Demkow, MD, PhD; Gian Piero Perna, MD; Robert K. Riezebos, MD, PhD; Edward O. McFalls, MD, PhD; Subhash Banerjee, MD; Akshay Bagai, MD, MHS; Gilbert Gosselin, MD; Sean M. O'Brien, PhD; Frank W. Rockhold, PhD; David D. Waters, MD; Kristian A. Thygesen, MD; Gregg W. Stone, MD; Harvey D. White, DSc; David J. Maron, MD; Judith S. Hochman, MD; On behalf of the ISCHEMIA Research Group

Correspondence

Bernard R. Chaitman, MD, Saint Louis University School of Medicine, 3635 Vista Ave, St. Louis, MO 63110. Email bernard.chaitman@health.slu.edu

Affiliations

Saint Louis University School of Medicine, MO (B.R.C.). Duke Clinical Research Institute, Durham, NC (K.P.A., D.D.C., R.D.L., S.M.O., F.W.R.). New York University Grossman School of Medicine, New York (J.S.B., H.R.R., S.B., J.S.H.). VA New England Healthcare System, Boston, MA (W.E.B.). Institute of Cardiology, Warsaw, Poland (M.D.). Ospedali Riuniti of Ancona, Italy (G.P.P.). Heartcentre OLVG, Amsterdam, The Netherlands (R.K.R.). Minneapolis V.A. Medical Center, MN (E.O.M.). Veterans Affairs North Texas Health Care System, Dallas (S.B.). Terrence Donnelly Heart Centre, St Michael's Hospital, University of Toronto, ON, Canada (A.B.). Montreal Heart Institute, QC, Canada (G.G.). University of California, San Francisco (D.D.W.). Aarhus University Hospital, Denmark (K.A.T.). The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, and the Cardiovascular Research Foundation, New York, NY (G.W.S.). Green Lane Cardiovascular Services, Auckland City Hospital, and University of Auckland, New Zealand (H.D.W.). Department of Medicine, Stanford University School of Medicine, CA (D.J.M.).

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Supplemental Materials

Clinical Event Committee Membership
Data Supplement Tables I–V
Data Supplement Figures I and II
Data Supplement Statistical Methods
Primary and Secondary MI Definitions

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