Supplemental Material

This Supplemental Material has been provided by the authors to give readers additional information about their work.

Supplement to: Chaitman BR, Cyr D, Alexander KP et al

Cardiovascular and Renal Implications of Myocardial Infarction in the ISCHEMIA-CKD Trial

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II. Supplementary Tables

Table S1. Selected Baseline Characteristics of the Study Population by Treatment Assignment

Characteristic	All Subjects (N=777)	INV (N=388)	CON (N=389)
Demographics			
Age at Randomization (years)			
N	777	388	389
Median (Q1, Q3)	63 (55, 70)	62 (55, 69)	64 (56, 70)
Age ≥70	208/777 (26.8%)	93/388 (24.0%)	115/389 (29.6%)
Male Gender	535/777 (68.9%)	268/388 (69.1%)	267/389 (68.6%)
Race			
American Indian or Alaskan Native	5/747 (0.7%)	2/373 (0.5%)	3/374 (0.8%)
Asian	191/747 (25.6%)	91/373 (24.4%)	100/374 (26.7%)
Native Hawaiian or Other Pacific Islander	6/747 (0.8%)	2/373 (0.5%)	4/374 (1.1%)
Black or African American	63/747 (8.4%)	33/373 (8.8%)	30/374 (8.0%)
White	481/747 (64.4%)	244/373 (65.4%)	237/374 (63.4%)
Multiple Races Reported	1/747 (0.1%)	1/373 (0.3%)	0/374 (0.0%)
Hispanic or Latino	98/735 (13.3%)	54/372 (14.5%)	44/363 (12.1%)
Clinical History			
Hypertension	711/773 (92.0%)	349/386 (90.4%)	362/387 (93.5%)
Diabetes	444/777 (57.1%)	226/388 (58.2%)	218/389 (56.0%)
Cigarette Smoking			
Never Smoked	371/777 (47.7%)	186/388 (47.9%)	185/389 (47.6%)
Former Smoker	322/777 (41.4%)	156/388 (40.2%)	166/389 (42.7%)
Current Smoker	84/777 (10.8%)	46/388 (11.9%)	38/389 (9.8%)
Prior History of CVD or PAD	134/777 (17.2%)	71/388 (18.3%)	63/389 (16.2%)
Prior Myocardial Infarction	133/776 (17.1%)	62/387 (16.0%)	71/389 (18.3%)
Prior PCI	146/777 (18.8%)	74/388 (19.1%)	72/389 (18.5%)
Prior PCI or CABG	162/777 (20.8%)	81/388 (20.9%)	81/389 (20.8%)
Atrial Fibrillation/Atrial Flutter	69/776 (8.9%)	30/388 (7.7%)	39/388 (10.1%)
Dialysis	415/777 (53.4%)	198/388 (51.0%)	217/389 (55.8%)
Angina and Heart Failure History			
Participant Has Ever Had Angina	584/777 (75.2%)	287/388 (74.0%)	297/389 (76.3%)
Asymptomatic Last 4 Weeks	484/776 (62.4%)	234/388 (60.3%)	250/388 (64.4%)
Prior Heart Failure	135/777 (17.4%)	65/388 (16.8%)	70/389 (18.0%)
Ejection Fraction[1]			
N	619	319	300
Median (25th, 75th)	58 (50, 64)	58 (50, 63)	58 (50, 64)
Ejection Fraction <50%	135/619 (21.8%)	74/319 (23.2%)	61/300 (20.3%)
Labs			
LDL Cholesterol (mg/dL)			
N	727	359	368
Median (25th, 75th)	83.0 (60.0, 111.0)	84.0 (58.0, 111.0)	82.0 (60.0, 113.0)
Estimated GFR from Enrollment (mL/min)			
N	777	388	389
Median (25th, 75th)	12 (7, 22)	13 (7, 23)	11 (7, 22)
Estimated GFR <60 (mL/min)	777/777 (100.0%)	388/388 (100.0%)	389/389 (100.0%)
ECG Findings[2]			
Q-waves: Meets UMI Criteria in 2 Leads[3]	78/677 (11.5%)	46/336 (13.7%)	32/341 (9.4%)
ST Segment Depression ≥0.5mm	115/703 (16.4%)	55/349 (15.8%)	60/354 (16.9%)
LVH, IVCD, or Pacemaker	119/689 (17.3%)	64/344 (18.6%)	55/345 (15.9%)
None of the Above	447/699 (63.9%)	223/350 (63.7%)	224/349 (64.2%)

Characteristic	All Subjects (N=777)	INV (N=388)	CON (N=389)

[1]Site-reported value, if available. If not available, then core-lab entered value.
[2]Baseline ECG results are only reported on those ECGs with interpretable tracings as determined by the core lab.
[3]Meets universal definition of MI in 2 leads in at least 1 territory (anterior, inferior, or lateral).
Abbreviations: CVD=cerebrovascular Disease; PAD=peripheral artery disease; LVH=left ventricular hypertrophy; IVCD=intraventricular conduction defect (QRS >120 ms); CCTA=Cardiac computed tomography angiography

In the invasive group, multivessel coronary artery disease was present in 51.3% of participants, with left anterior descending (LAD) involvement in 57.2%; 27.1% had no obstructive CAD. In the conservative group, the 3-year cumulative incidence rate of coronary angiography was 31.6% and the rate of revascularization was 19.6%

Table S2. Distribution of First MI Events by Randomized Treatment arm and Subsequent Death Within 30 Days

MI Type	Primary MI Definition			Secondary MI Definition		
	All Participants (N=777)	INV (N=388)	CON (N=389)	All Participants (N=777)	INV (N=388)	CON (N=389)
No. Participants with Event	102/777 (13.1%)	46/388 (11.9%)	56/389 (14.4%)	127/777 (16.3%)	67/388 (17.3%)	60/389 (15.4%)
Fatal†	18/102 (17.6%)	7/46 (15.2%)	11/56 (19.6%)	18/127 (14.2%)	8/67 (11.9%)	10/60 (16.7%)
Type 1	51/102 (50.0%)	20/46 (43.5%)	31/56 (55.4%)	50/127 (39.4%)	20/67 (29.9%)	30/60 (50.0%)
Fatal	12/51 (23.5%)	3/20 (15.0%)	9/31 (29.0%)	11/50 (22.0%)	3/20 (15.0%)	8/30 (26.7%)
Type 2	29/102 (28.4%)	12/46 (26.1%)	17/56 (30.4%)	29/127 (22.8%)	12/67 (17.9%)	17/60 (28.3%)
Fatal	2/29 (6.9%)	1/12 (8.3%)	1/17 (5.9%)	2/29 (6.9%)	1/12 (8.3%)	1/17 (5.9%)
Type 4a	5/102 (4.9%)	5/46 (10.9%)	0/56 (0.0%)	23/127 (18.1%)	21/67 (31.3%)	2/60 (3.3%)
Fatal	2/5 (40.0%)	2/5 (40.0%)	N/A	2/23 (8.7%)	2/21 (9.5%)	0/2 (0.0%)
Type 4b	5/102 (4.9%)	3/46 (6.5%)	2/56 (3.6%)	5/127 (3.9%)	3/67 (4.5%)	2/60 (3.3%)
Fatal	0/5 (0.0%)	0/3 (0.0%)	0/2 (0.0%)	0/5 (0.0%)	0/3 (0.0%)	0/2 (0.0%)
Type 4c	3/102 (2.9%)	2/46 (4.3%)	1/56 (1.8%)	3/127 (2.4%)	2/67 (3.0%)	1/60 (1.7%)
Fatal	0/3 (0.0%)	0/2 (0.0%)	0/1 (0.0%)	0/3 (0.0%)	0/2 (0.0%)	0/1 (0.0%)
Type 4b/c	8/102 (7.8%)	5/46 (10.9%)	3/56 (5.4%)	8/127 (6.3%)	5/67 (7.5%)	3/60 (5.0%)
Fatal	0/8 (0.0%)	0/5 (0.0%)	0/3 (0.0%)	0/8 (0.0%)	0/5 (0.0%)	0/3 (0.0%)
Type 5	5/102 (4.9%)	2/46 (4.3%)	3/56 (5.4%)	13/127 (10.2%)	7/67 (10.4%)	6/60 (10.0%)
Fatal	2/5 (40.0%)	1/2 (50.0%)	1/3 (33.3%)	3/13 (23.1%)	2/7 (28.6%)	1/6 (16.7%)
Procedural (Type 4a/5)	10/102 (9.8%)	7/46 (15.2%)	3/56 (5.4%)	36/127 (28.3%)	28/67 (41.8%)	8/60 (13.3%)
Fatal	4/10 (40.0%)	3/7 (42.9%)	1/3 (33.3%)	5/36 (13.9%)	4/28 (14.3%)	1/8 (12.5%)
Silent/Unrecognized	4/102 (3.9%)	2/46 (4.3%)	2/56 (3.6%)	4/127 (3.1%)	2/67 (3.0%)	2/60 (3.3%)

Note: No first MI events were Type 3.

† Death within 30 days of a CEC determined MI event.

Table S3. Mortality According to Elevated Preprocedural Biomarkers

	Type 4a		Type 5	
	No. First MI Events	**No. of Associated Deaths**	**No. First MI Events**	**No. of Associated Deaths**
Primary Definition	5	2	2	2
Total No. with Missing Pre-Procedure Markers	1/5 (20.0%)	0	1/2 (50.0%)	1
Total No. with Non-missing Pre-procedure Markers	4/5 (80.0%)	2	1/2 (50.0%)	1
No. with Pre-procedure CKDB Drawn	3/4 (75.0%)	1	0/1 (0.0%)	0
No. Elevated	0/3 (0.0%)	0	0/0 (NA)	0
No. with Pre-procedure Troponin Drawn	4/4 (100.0%)	1	1/1 (100.0%)	1
No. Elevated	2/4 (50.0%)	1	1/1 (100.0%)	1
No. Unique Patients with Elevated Pre-procedure Markers	2/4 (50.0%)	1	1/1 (100.0%)	1
Secondary Definition	21	10	7	4
Total No. with Missing Pre-procedure Markers	2/21 (9.5%)	1	2/7 (28.6%)	1
Total No. with Non-missing Pre-procedure Markers	19/21 (90.5%)	9	5/7 (71.4%)	3
No. with Pre-procedure CKMB Drawn	18/19 (94.7%)	9	3/5 (60.0%)	1
No. Elevated	2/18 (11.1%)	2	0/3 (0.0%)	0
No. with Pre-procedure Troponin Drawn	18/19 (94.7%)	9	5/5 (100.0%)	3
No. Elevated	4/18 (22.2%)	3	4/5 (80.0%)	2
No. Unique Patients with Elevated Pre-procedure Markers	4/21 (19.0%)	3	4/5 (80.0%)	2

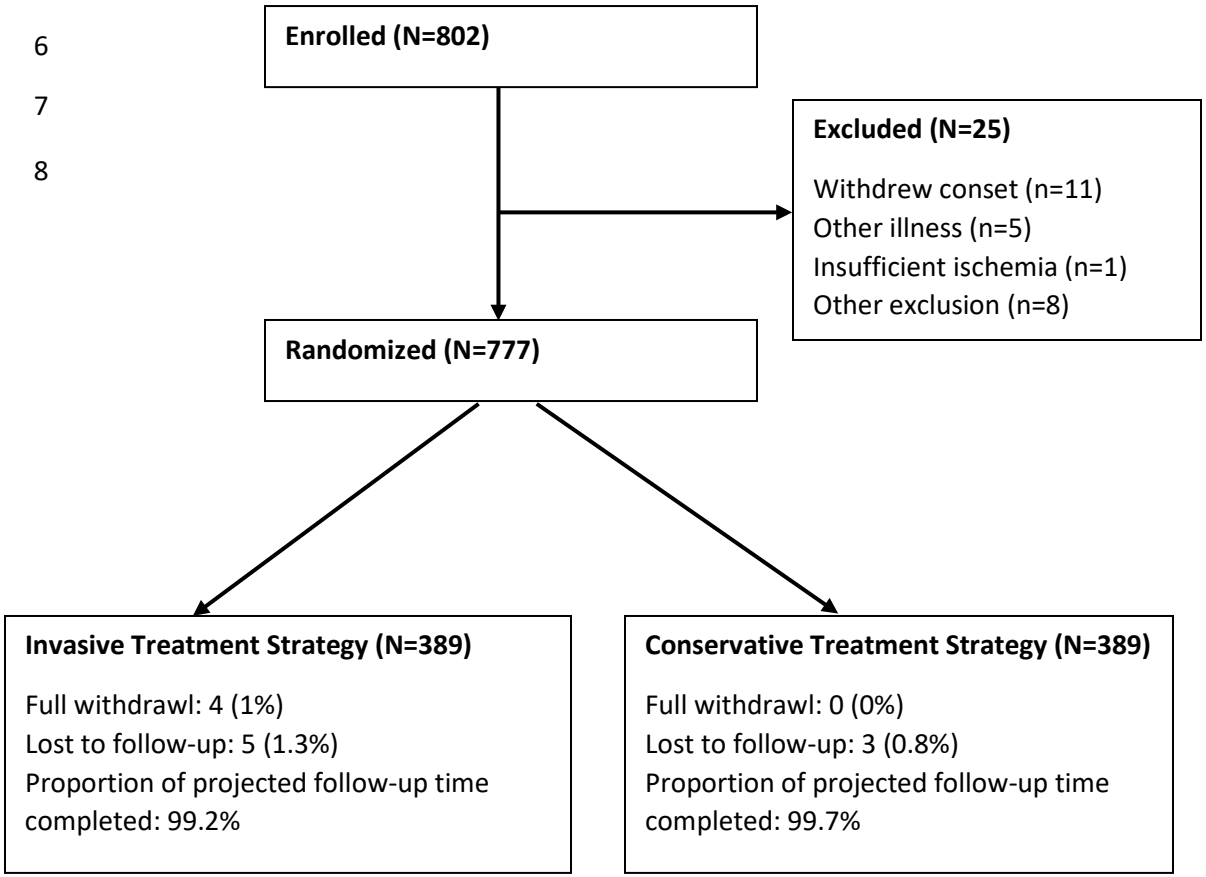
Table S4. Time-Dependent Cox Modeling on Procedural MI Adjusted with Elevated Preprocedure Biomarkers

MI Type	No. MI Events	Event	No. Events Post-MI	HR (95% CI)[1] MI vs. No MI	P-value
Primary Definition					
Procedural MI	11	All-cause Death	5	2.34 (0.60, 9.09)	0.2181
Procedural MI	11	Cardiovascular Death	4	1.63 (0.28, 9.34)	0.5844
Procedural MI	11	Cardiovascular Death or Hospitalization for Heart Failure	4	1.48 (0.26, 8.38)	0.6600
Secondary Definition					
Procedural MI	39	All-cause Death	17	2.50 (1.08, 5.79)	0.0322
Procedural MI	39	Cardiovascular Death	16	2.55 (1.02, 6.37)	0.0451
Procedural MI	39	Cardiovascular Death or Hospitalization for Heart Failure	17	2.34 (0.96, 5.69)	0.0605

[1] Adjusted for the ISCHEMIA CKD trial covariates: age, sex, kidney function (dialysis status and eGFR in patients not receiving dialysis), left ventricular ejection fraction, diabetes, and elevated pre-procedural biomarkers CK-MB or Troponin (categorical classification as elevated biomarkers, no elevated biomarkers, missing biomarker data). Continuous variables are modeled as restricted cubic splines.

III. Supplementary Figure

Figure S1. Consort Diagram



VI. Primary and Secondary MI Definitions

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. All MI events will be classified based on the Universal MI classification system as follows:

- Type 1: non-procedure MI
- Type 2: Secondary MI
- Type 3: Sudden Death MI
- Type 4a: MI related to PCI
- Type 4b: MI related to stent thrombosis

- Type 4c: MI related to stent restenosis
- Type 5: MI related to CABG
- Silent MI

Non-procedure *MI (Types 1, 2, 4b, 4c)*

Diagnosis of non-procedure 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 (≥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

Non-procedure *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 CK-MB 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.

Non-procedure *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:
≥ 0.2 mV in men >age 40 and ≥ 0.25mV in men <40 years or ≥ 0.15 mV in women in leads V2–V3 and/or ≥ 0.1 mV in other leads, or new LBBB.

Any new Q-wave in leads V2–V3 ≥ 0.02 seconds or QS complex in leads V2 and V3 or Q-wave ≥ 0.03 seconds and ≥ 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 ≥ 0.04 seconds in V1–V2 and R/S ≥ 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
≥ 0.05 mV in two contiguous leads; and/or T-wave inversion ≥ 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 ≥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 ≥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 >0.1mV in 2 contiguous leads), new pathologic Q-waves in ≥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.

NOTE: A type 4a MI will be diagnosed with a rise in CK-MB to >10-fold the ULN (or when CK-MB is unavailable, a rise in troponin to >70 times the MI Decision Limit/ULN) as a biomarker elevation noly criterion. If biomarkers are missing, a type 4a MI will be diagnosed if BOTH ECG criteria (new ST elevation or depression, Q-wave criteria, or new and persistent LBBB) AND angiographic criteria above are present. If pre-PCI cardiac markers are missing, they will be assumed to be normal in those without a preceding event.

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 X ULN will be used.

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

- Symptoms suggestive of myocardial ischemia (≥20 min)
- New ischemic ST changes or new pathological Q waves. (see “ECG Criteria” above) Note the UMI definition uses ≥0.05 mV of STD whereas the ISCHEMIA definition uses ≥ 0.1mV 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.

NOTE: A type 4a MI will be diagnosed with a rise in troponin to >70 times the 99th percentile URL (or, when troponin is unavailable, a rise in CK-MB to >10 times the ULN) as a biomarker elevation only criterion. If biomarkers are missing, a type 4a MI will be diagnosed if BOTH ECG criteria (new ST elevation or depression, Q-wave criteria, or new and persistent LBBB) AND angiographic criteria above are present. If pre- PCI cardiac markers are missing, they will be assumed to be normal in those without a preceding event.

CABG-Related MI (Type 5)

Primary Definition

CK-MB is the preferred serum biomarker and takes precedence over cTn. 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 ≥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.

NOTE: A type 5 MI will be diagnosed with a rise in CK-MB to >15-fold the ULN (or when CK-MB is unavailable a rise in troponin to >100 times the MI Decision Limit/ULN) as a biomarker elevation only criterion. If biomarkers are missing, an MI will be diagnosed if the ECG criteria (New pathologic Q waves or new persistent LBBB) AND new substantial wall motion abnormality are BOTH present. If pre-CABG cardiac markers are missing, they will be assumed to be normal in those without a preceding event.

Secondary Definition

Elevation of troponin values >10 X 99th percentile URL within 48 hrs post-CABG in patients with normal baseline troponin values (≤ 99th percentile URL). If the troponin 99th percentile is not available, the ULN may be used. If troponins are not available, CKMB elevation >10 X 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.

NOTE: A type 5 MI will be diagnosed with a rise in troponin to >100 times the 99th percentile URL (or when troponin is unavailable a rise in CK-MB to >15 times the ULN) as a biomarker elevation only criterion. If biomarkers are missing, an MI will be diagnosed if the ECG criteria (New pathologic Q waves or new persistent LBBB) AND new substantial wall motion abnormality are BOTH present. If pre-CABG cardiac markers are missing, they will be assumed to be normal in those without a preceding event.

Complicated MI and Large MI

Complicated MI: Prognostically important MIs may also be identified as those with complications such as hemodynamic instability, cardiogenic shock, drop in EF >10% from baseline, electrical instability with life-threatening VT or VF, or heart failure complicating MI. Complicated myocardial infarctions may typically require ICU care, invasive support (eg. intubation, IABP, PA catheters) and intravenous medications (eg. inotropes or antiarrhythmics.) CEC adjudicators will identify complicated MIs based upon the information available to them in the eCRF and source documents.

- Hemodynamic instability: requiring fluids, inotropic or vasopressor support to maintain end-organ perfusion. May progress to shock if also accompanied by end-organ underperfusion.
- Shock: Compromise of end-organ perfusion due to hemodynamic instability and sustained hypotension. Often manifested by hypotension, increased creatinine, shock liver, and decreased mentation.
- Life-threatening VT or VF: Requiring antiarrhythmics or defibrillation to return sinus rhythm. Transient runs of VT (eg. during reperfusion) are not associated with hemodynamic instability are not usually considered life-threatening.

- Decreased EF ≥ 10%: EF assessment during the event which indicates a drop from prior assessments (eg. EF 30% from previous EF 55%)
- HF in the setting of an MI is defined on the basis of the physician's decision to treat HF with an intravenous (IV) diuretic, IV inotropic agent or IV vasodilator and at least 1 of the following:
  - Presence of pulmonary edema or pulmonary vascular congestion on chest radiograph believed to be of cardiac cause.
  - Rales greater than 1/3 up the lung fields believed to be due to HF.
  - Pulmonary Capillary Wedge Pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) greater than 18 mmHg.
  - Dyspnea, with documented paO2 less than 80 mmHg on room air or O2 saturation less than 90% on room air, without significant lung disease

Large MI: A T4A or T5 MI was considered large if it met the biomarker elevation only biomarker criteria and for non-procedure MI's if the peak cTn > 70 times the upper reference limit. The size of MI will be assessed by examining peak levels of cardiac biomarkers as a continuous function.

V. Additional Statistical Methodology

Imputation: To maximize the amount of information each covariate provides to a covariate-adjusted analysis, multiple imputation was used to impute missing covariate data. The statistical techniques used for multiple imputation include chained equations and predictive mean matching (PMM). PMM using chained equations does not require too many assumptions and the imputations do not change much when those assumptions are violated (Buuren S. Flexible imputation of missing data. Boca Raton, FL: Chapman & Hall/CRC; 2012.). PMM first involves fitting an ordinary linear model on an outcome variable using all covariates of interest. Predictions of the outcome variable can be determined based on the model where continuous covariates are expanded into restricted cubic splines that usually have 3 knots. For a given covariate, PMM then replaces a missing value with an observed value whose predicted value is very close to the predicted value for the missing value. PMM does not assume a conditional distribution form for the covariate being imputed.