Supplementary Online Content

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

eMethods. Definition of myocardial infarction (MI)

For a spontaneous MI, detection of rise and/or fall of cardiac biomarkers, preferably troponin, with at least one value above the 99th percentile if available or the upper reference limit (URL) from the local lab, together with evidence of myocardial ischemia with at least one of the following:
- o Clinical presentation consistent with ischemia
- o ECG evidence of acute myocardial ischemia
- o New pathological Q-waves
- o Autopsy evidence of acute MI
- Sudden unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-elevation or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- Percutaneous Coronary Intervention-Related Myocardial Infarction: Peri-PCI MI is defined by any of the following criteria. Symptoms of cardiac ischemia are not required.
  1. Biomarker elevations within 48 hours of PCI:
     - Troponin or CK-MB (preferred) >3 x URL <u>and</u>
     - No evidence that cardiac biomarkers were elevated prior to the procedure; ***OR***
     Both of the following must be true:
     - ≥50% increase in the cardiac biomarker result
     - Evidence that cardiac biomarker values were decreasing (e.g., two samples 3 to 6 hours apart) prior to the suspected MI
  2. New pathological Q-waves
  3. Autopsy evidence of acute MI
- Coronary Artery Bypass Grafting-Related Myocardial Infarction: Peri- CABG MI is defined by the following criteria. Symptoms of cardiac ischemia are not required.
  1. Biomarker elevations within 72 hours of CABG:
     - Troponin or CK-MB (preferred) >5 x URL *and*
     - No evidence that cardiac biomarkers were elevated prior to the procedure; **OR**
     Both of the following must be true:
     - ≥ 50% increase in the cardiac biomarker result
     - Evidence that cardiac biomarker values were decreasing (e.g., two samples 3 to 6 hours apart) prior to the suspected MI.
     AND
  2. One of the following:
     - New pathological Q-waves persistent through 30 days
     - New persistent non-rate-related LBBB
     - Angiographically documented new graft or native coronary artery occlusion
     - Other complication in the operating room resulting in loss of myocardium
     - Imaging evidence of new loss of viable myocardium
     OR (regardless of items 1 and 2 above)
  3. Autopsy evidence of acute MI

eTable 1. Adjustment variables for risk of cardiovascular death and acute limb ischemia

following myocardial infarction

MI type	CV death	ALI
Any	region, age, diabetes, prior PCI, prior MI, inclusion criteria, prior carotid revascularization or stenosis, baseline Rutherford score, prior minor amputation, beta blocker use, prior CHF, prior TIA, prior CABG, tobacco use, sex, prior statin use, prior stroke and prior major amputation	region, age, diabetes, prior PCI, prior MI, inclusion criteria, prior carotid revascularization or stenosis, baseline Rutherford score, prior minor amputation, beta blocker use, prior CHF, prior TIA, prior CABG, tobacco use, sex, prior statin use, and baseline ABI
Type 1	diabetes, prior MI, region, prior PCI, prior carotid revascularization/stenosis, baseline Rutherford score, inclusion criteria, prior CHF, prior TIA, prior stroke, prior statin use, and prior major amputation	diabetes, prior MI, region, prior PCI, prior carotid revascularization/stenosis, baseline Rutherford score, inclusion criteria, prior CHF, prior TIA, prior statin use and baseline ABI
Type 2	age, sex, weight, diabetes, region, prior PCI, prior carotid revascularization/stenosis, baseline Rutherford score, inclusion criteria, prior CHF, beta blocker use, prior TIA, prior statin use, prior stroke, and prior major amputation	age, sex, weight, diabetes, region, prior PCI, prior carotid revascularization/stenosis, baseline Rutherford score, inclusion criteria, prior CHF, beta blocker use, prior TIA, prior statin use, and baseline ABI

ABI, ankle-brachial index; CABG, coronary artery bypass grafting; CHF, congestive heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

eTable 2. Baseline characteristics of patients included by region

Characteristic	South/Central America (N=1740)	Asia (N=1602)	Europe (N=7498)	North America (N=3045)
Age, years, median (25th, 75th)	67, 61-74	70, 63-75	65, 59-71	67, 61-73
Female sex	664 (38.2%)	330 (20.6%)	1828 (24.4%)	1066 (35.0%)
Weight, kg, median (25th, 75th)	74, 65-84	62, 54-70	79, 70-89	82, 70-94
Inclusion Criteria for Randomization				
Previous revascularization	591 (34.0%)	1162 (72.5%)	3872 (51.6%)	2250 (73.9%)
ABI value, mean (SD)	0.70, (0.23)	0.81, (0.25)	0.76, (0.23)	0.82, (0.21)
ABI or TBI criteria	1149 (66.0%)	440 (27.5%)	3626 (48.4%)	795 (26.1%)
ABI value, mean (SD)	0.66, (0.20)	0.62, (0.15)	0.62, (0.14)	0.64, (0.12)
TBI value, mean (SD)	0.57, (0.22)	0.46, (0.12)	0.49, (0.22)	0.44, (0.16)
Limb symptoms by Rutherford classification				
Asymptomatic	128 (7.4%)	553 (34.5%)	1311 (17.5%)	609 (20.0%)
Mild or moderate claudication	998 (57.4%)	730 (45.6%)	4053 (54.1%)	1629 (53.5%)
Severe claudication	508 (29.2%)	212 (13.2%)	1818 (24.3%)	690 (22.7%)
Pain while at rest	51 (2.9%)	42 (2.6%)	188 (2.5%)	97 (3.2%)
Minor tissue loss	44 (2.5%)	48 (3.0%)	99 (1.3%)	16 (0.5%)
Major tissue loss	11 (0.6%)	17 (1.1%)	26 (0.3%)	4 (0.1%)
Major amputation above the ankle	108 (6.3%)	45 (2.8%)	137 (1.8%)	49 (1.6%)
Minor amputation	175 (10.1%)	82 (5.1%)	272 (3.6%)	76 (2.5%)
Medical History				
Number of vascular beds affected				
1	1131 (65.0%)	1002 (62.5%)	4525 (60.3%)	1146 (37.6%)
2	518 (29.8%)	493 (30.8%)	2386 (31.8%)	1291 (42.4%)
3	91 (5.2%)	107 (6.7%)	587 (7.8%)	608 (20.0%)
Prior stroke	126 (7.2%)	258 (16.1%)	550 (7.3%)	209 (6.9%)
Prior TIA	42 (2.4%)	62 (3.9%)	212 (2.8%)	191 (6.3%)
Prior CAD	449 (25.8%)	308 (19.2%)	1838 (24.5%)	1437 (47.2%)
Prior MI	319 (18.3%)	158 (9.9%)	1283 (17.1%)	762 (25.0%)
Prior PCI	221 (12.7%)	212 (13.2%)	839 (11.2%)	901 (29.6%)
Prior CABG	141 (8.1%)	76 (4.7%)	614 (8.2%)	705 (23.2%)
Prior carotid stenosis/ revascularization	122 (7.0%)	182 (11.4%)	1326 (17.7%)	897 (29.5%)
Prior atrial fibrillation/flutter	26 (1.5%)	44 (2.7%)	267 (3.6%)	159 (5.2%)
Prior CHF	130 (7.5%)	73 (4.6%)	1385 (18.5%)	340 (11.2%)
CCS angina class				
0	1606 (92.3%)	1461 (91.2%)	6194 (82.6%)	2758 (90.6%)
I	72 (4.1%)	89 (5.6%)	587 (7.8%)	177 (5.8%)
II	49 (2.8%)	39 (2.4%)	567 (7.6%)	86 (2.8%)
III	11 (0.6%)	13 (0.8%)	140 (1.9%)	21 (0.7%)
IV	2 (0.1%)	0 (0.0%)	8 (0.1%)	3 (0.1%)
Chronic Kidney Disease	560 (32.9%)	468 (29.6%)	1381 (19.2%)	896 (30.2%)
Family history of CHD	170 (12.9%)	56 (4.6%)	822 (16.4%)	962 (36.9%)
Diabetes mellitus type 1 or 2	989 (56.8%)	689 (43.0%)	2447 (32.6%)	1220 (40.1%)
Hypertension	1350 (77.6%)	1123 (70.1%)	5757 (76.8%)	2627 (86.3%)
Hyperlipidemia	1232 (70.8%)	883 (55.1%)	5551 (74.1%)	2814 (92.4%)
Tobacco Use				
Never smoker	554 (31.8%)	385 (24.0%)	1693 (22.8%)	352 (11.6%)

Characteristic	South/Central America (N=1740)	Asia (N=1602)	Europe (N=7498)	North America (N=3045)
Former smoker	801 (46.0%)	844 (52.7%)	3221 (43.4%)	1664 (54.6%)
Current smoker	385 (22.1%)	373 (23.3%)	2502 (33.7%)	1029 (33.8%)
Medications Before Randomization				
Aspirin	1089 (62.6%)	905 (56.5%)	4950 (66.0%)	2327 (76.4%)
Clopidogrel	217 (12.5%)	551 (34.4%)	2166 (28.9%)	1539 (50.5%)
Statin	1134 (65.2%)	1012 (63.2%)	5463 (72.9%)	2572 (84.5%)
ACE inhibitor	706 (40.6%)	205 (12.8%)	3343 (44.6%)	1381 (45.4%)
Angiotensin receptor blocker	526 (30.2%)	583 (36.4%)	1654 (22.1%)	725 (23.8%)
Beta-blocker	691 (39.7%)	760 (47.4%)	252 (3.4%)	392 (12.9%)
Cilostazol	614 (35.3%)	369 (23.0%)	2953 (39.4%)	1704 (56.0%)

Values are no. (%), unless otherwise indicated. Chronic kidney disease was defined as an estimated glomerular filtration rate of <60 ml/min/1.73m^2.
ABI, ankle-brachial index; ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; MI, myocardial Infarction; PCI, percutaneous coronary intervention; SD, standard deviation; TBI, toe-brachial index; TIA, transient ischemic attack.

eTable 3. Incidence rates of myocardial infarction by region

Outcome	Asia Rate (# Events)	Central/South America Rate (# Events)	Europe Rate (# Events)	North America Rate (# Events)
MI	1.87 (71)	0.66 (26)	1.59 (294)	3.96 (292)
Type 1 MI	1.23 (47)	0.46 (18)	1.01 (188)	2.17 (162)
Type 2 MI	0.70 (27)	0.15 (6)	0.53 (99)	1.79 (135)
The median follow-up time was 30 months. Rate calculated as the number of events per 100 patient years of follow-up.				

eTable 4. Electrocardiography characteristics of the first myocardial infarction during follow-up

Characteristic		Any type	Type 1 MI	Type 2 MI
STEMI vs. NSTEMI		**N=683**	**N=405**	**N=236**
STEMI		63 (9%)	54 (13%)	1 (<1%)
NSTEMI		522 (76%)	312 (77%)	194 (82%)
Unknown		98 (14%)	39 (10%)	41 (17%)
New Q-Wave*		**N=413**	**N=294**	**N=91**
Yes		22 (5%)	17 (6%)	3 (3%)
No		325 (79%)	238 (81%)	71 (78%)
No ECG available		66 (16%)	39 (13%)	17 (19%)
Peak Troponin I/T Elevation		**N=683**	**N=405**	**N=236**
≤1		2 (<1%)	0 (0%)	2 (<1%)
>1-3		144 (21%)	66 (16%)	76 (32%)
>3-5	x ULN	51 (7%)	21 (5%)	28 (12%)
>5-10		79 (12%)	36 (9%)	41 (17%)
>10		312 (46%)	221 (55%)	70 (30%)
Missing†		95 (14%)	61 (15%)	19 (8%)

*Q-wave status was assessed by the site investigator only.
†Ratio not calculated due to missing values for the ULN or peak level elevation of troponin I/T.
Values are n (%).
ECG, electrocardiogram; NSTEMI, non-ST-elevation MI; STEMI, ST-elevation MI; ULN, upper limit of normal; others as in Table 1.