Supplement for World Regional Differences in Outcomes for Patients with Peripheral Artery Disease: EUCLID Trial

Table S1. Stepwise adjusted associations between region and clinical outcomes

	Central/South America		Asia		North America		
Clinical Outcome	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**Global P-value***
CV death/MI/Stroke	0.85 (0.71–1.02)	0.077	1.01 (0.85–1.19)	0.951	1.28 (1.13–1.45)	<.001	<.001
All-cause death	1.43 (1.21–1.68)	<.001	1.14 (0.96–1.37)	0.145	0.99 (0.85–1.15)	0.864	<.001
LER	0.56 (0.45–0.70)	<.001	0.74 (0.62–0.88)	<.001	1.55 (1.40–1.73)	<.001	<.001

*P-value from the overall association test. Reference is Europe. All outcomes adjusted for age, sex, inclusion criteria, and severity of disease. CV death/MI/stroke adjusted for diabetes, smoking, statins, and prior MI, stroke, and carotid stenosis or revascularization. All-cause death adjusted for diabetes, smoking, hyperlipidemia, statins, angiotensin receptor blockers, and prior MI, stroke, and carotid stenosis or revascularization. Lower extremity revascularization adjusted for diabetes, smoking, and prior carotid stenosis or revascularization.
CI indicates confidence interval; CV, cardiovascular; HR, hazard ratio; LER, lower extremity revascularization; MI, myocardial infarction.

Figure S1. Kaplan Meier event curves for cardiovascular death

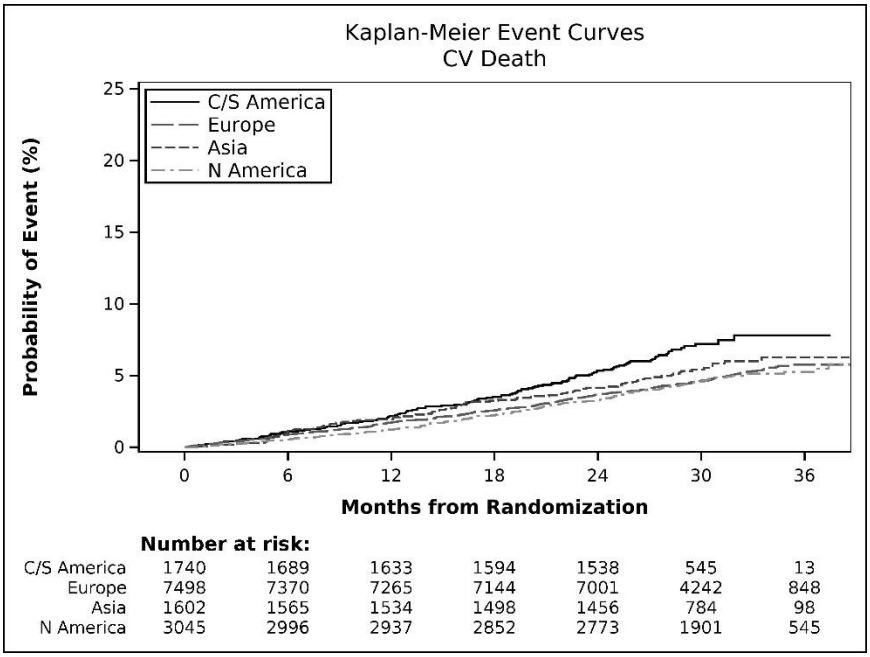


Figure S2. Kaplan Meier event curves for myocardial infarction (MI)

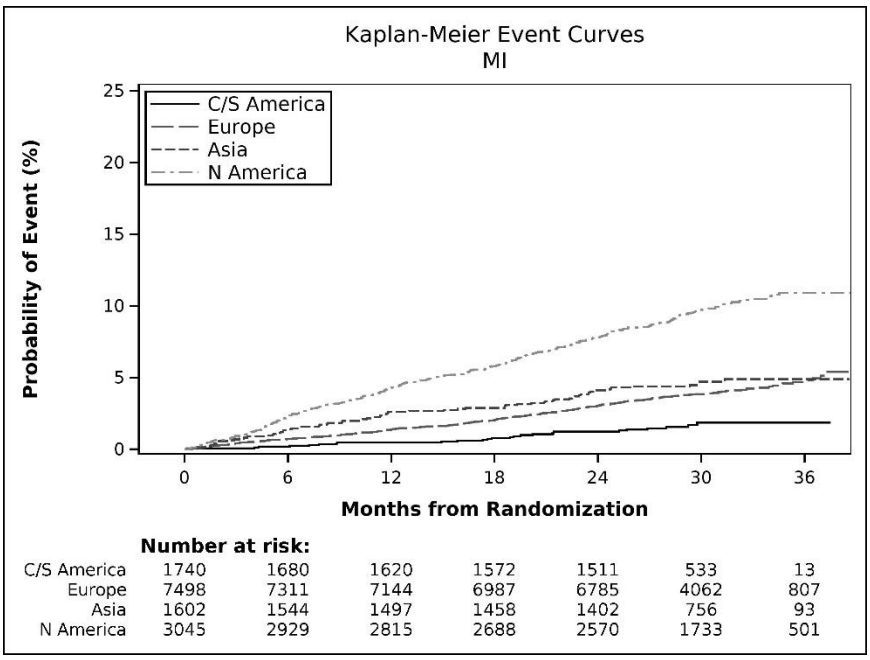
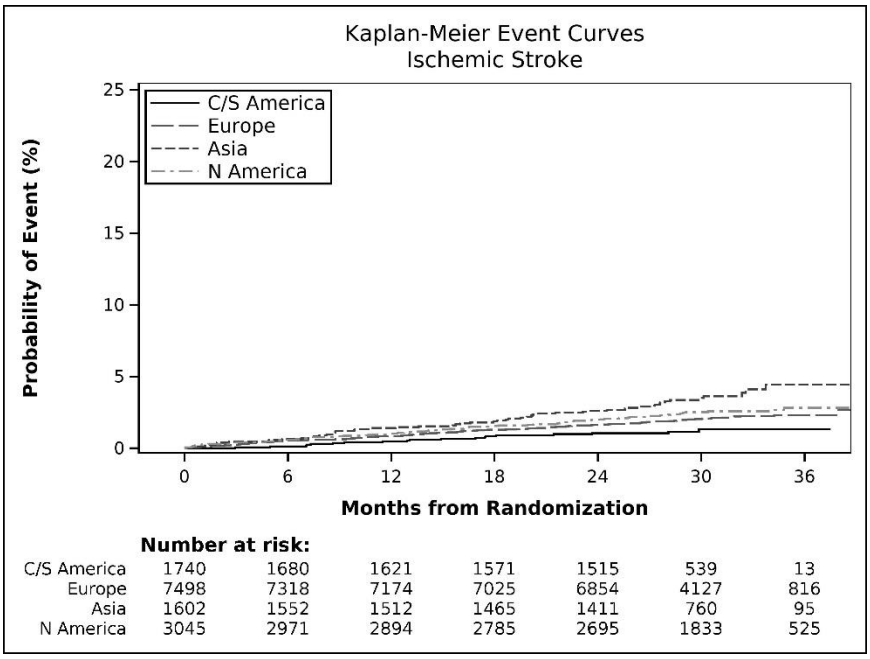


Figure S3. Kaplan Meier event curves for ischemic stroke



As a sensitivity analysis, the European region was divided into Western and Eastern Europe, which coincidentally coincides with the division based on the low- and high-risk classification for cardiovascular disease as specified by the 2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (Piepoli MF et al. European Heart Journal 2016;37:2315-81). Western Europe comprised France, Germany, Italy, Netherlands, Spain, Sweden, United Kingdom. Eastern Europe comprised Bulgaria, Czech Republic, Hungary, Poland, Romania, Russian Federation, Slovakia, Turkey, Ukraine. North America was then taken as the reference region. Results for this analysis are on the following pages.

Table S2. Baseline Characteristics by Region

Characteristic	North America (N=3045)	Central/South America (N=1740)	Asia (N=1602)	Western Europe (N=2373)	Eastern Europe (N=5125)	P-value
Age, median (25th-75th), yrs	67 (61-73)	67 (61-74)	70 (63-75)	67 (60-73)	64 (59-70)	<.001
Female sex, no. (%)	1066 (35.0%)	664 (38.2%)	330 (20.6%)	579 (24.4%)	1249 (24.4%)	<.001
Weight, median (25th-75th), kg	82 (70-94)	74 (65-84)	62 (54-70)	78 (69-88)	80 (70-89)	<.001
Inclusion Criteria for Randomization						<.001
Previous Revascularization, no. (%)	2250 (73.9%)	591 (34.0%)	1162 (72.5%)	1513 (63.8%)	2359 (46.0%)	
ABI value, mean (SD)	0.82 (0.21)	0.70 (0.23)	0.81 (0.25)	0.81 (0.23)	0.72 (0.22)	<.001
ABI or TBI criteria, no. (%)	795 (26.1%)	1149 (66.0%)	440 (27.5%)	860 (36.2%)	2766 (54.0%)	
ABI value, mean (SD)	0.64 (0.12)	0.66 (0.20)	0.62 (0.15)	0.63 (0.12)	0.61 (0.14)	<.001
TBI value, mean (SD)	0.44 (0.16)	0.57 (0.22)	0.46 (0.12)	0.41 (0.16)	0.61 (0.26)	<.001
Limb symptoms, no. (%)						<.001
Asymptomatic	609 (20.0%)	128 (7.4%)	553 (34.5%)	640 (27.0%)	671 (13.1%)	
Mild or moderate claudication	1629 (53.5%)	998 (57.4%)	730 (45.6%)	1239 (52.3%)	2814 (54.9%)	
Severe claudication	690 (22.7%)	508 (29.2%)	212 (13.2%)	427 (18.0%)	1391 (27.1%)	
Pain while at rest	97 (3.2%)	51 (2.9%)	42 (2.6%)	22 (0.9%)	166 (3.2%)	
Minor tissue loss	16 (0.5%)	44 (2.5%)	48 (3.0%)	40 (1.7%)	59 (1.2%)	
Major tissue loss	4 (0.1%)	11 (0.6%)	17 (1.1%)	3 (0.1%)	23 (0.4%)	
Major amputation above the ankle	49 (1.6%)	108 (6.3%)	45 (2.8%)	28 (1.2%)	109 (2.1%)	<.001
Minor amputation	76 (2.5%)	175 (10.1%)	82 (5.1%)	68 (2.9%)	204 (4.0%)	<.001
Medical History, no. (%)						
Stroke	209 (6.9%)	126 (7.2%)	258 (16.1%)	131 (5.5%)	419 (8.2%)	<.001
TIA	191 (6.3%)	42 (2.4%)	62 (3.9%)	86 (3.6%)	126 (2.5%)	<.001
CAD	1437 (47.2%)	449 (25.8%)	308 (19.2%)	588 (24.8%)	1250 (24.4%)	<.001
MI	762 (25.0%)	319 (18.3%)	158 (9.9%)	351 (14.8%)	932 (18.2%)	<.001
Carotid stenosis or carotid revascularization	897 (29.7%)	122 (7.4%)	182 (13.2%)	345 (15.1%)	981 (20.5%)	<.001
Diabetes mellitus type I or II	1220 (40.1%)	989 (56.8%)	689 (43.0%)	779 (32.9%)	1668 (32.5%)	<.001
Hypertension	2627 (86.3%)	1350 (77.6%)	1123 (70.1%)	1792 (75.6%)	3965 (77.4%)	<.001
Hyperlipidemia	2814 (92.4%)	1232 (70.8%)	883 (55.1%)	1942 (81.9%)	3609 (70.4%)	<.001
Tobacco use, no. (%)						<.001
Current	1029 (33.8%)	385 (22.1%)	373 (23.3%)	767 (33.5%)	1735 (33.9%)	
Former	1664 (54.6%)	801 (46.0%)	844 (52.7%)	1254 (54.7%)	1967 (38.4%)	
Never	352 (11.6%)	554 (31.8%)	385 (24.0%)	270 (11.8%)	1423 (27.8%)	
Medication use before randomization, no. (%)						
Aspirin	2327 (76.4%)	1089 (62.6%)	905 (56.5%)	1790 (75.5%)	3160 (61.7%)	<.001
Clopidogrel	1539 (50.5%)	217 (12.5%)	551 (34.4%)	684 (28.8%)	1482 (28.9%)	<.001
Statin	2572 (84.5%)	1134 (65.2%)	1012 (63.2%)	2004 (84.5%)	3459 (67.5%)	<.001
ACE Inhibitor	1381 (45.4%)	706 (40.6%)	205 (12.8%)	998 (42.1%)	2345 (45.8%)	<.001
Angiotensin-receptor blocker	725 (23.8%)	526 (30.2%)	583 (36.4%)	639 (26.9%)	1015 (19.8%)	<.001
Cilostazol	392 (12.9%)	691 (39.7%)	760 (47.4%)	167 (7.0%)	85 (1.7%)	<.001

ABI indicates angle-brachial index; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; MI, myocardial infarction; SD, standard deviation; TBI, toe-brachial index; TIA, transient ischemic attack.

Table S3. Unadjusted Associations Between Region and Clinical Outcomes

	Central/South America			Asia			Western Europe			Eastern Europe			North America	
Clinical Outcome	**Incidence Rate (n)**	**HR (95% CI)**	**P-value**	**Incidence Rate (n)**	**HR (95% CI)**	**P-value**	**Incidence Rate (n)**	**HR (95% CI)**	**P-value**	**Incidence Rate (n)**	**HR (95% CI)**	**P-value**	**Incidence Rate (n)**	**Global P-value***
CV death/MI/Stroke	3.87 (151)	0.65 (0.54 - 0.78)	<.001	4.80 (180)	0.80 (0.67 - 0.95)	0.012	3.66 (214)	0.61 (0.52 - 0.72)	<.001	4.09 (510)	0.68 (0.60 - 0.78)	<.001	5.97 (436)	<.001
CV death	2.88 (114)	1.57 (1.23 - 2.01)	<.001	2.23 (87)	1.21 (0.93 - 1.58)	0.163	1.12 (68)	0.61 (0.45 - 0.81)	<.001	2.30 (294)	1.24 (1.02 - 1.52)	0.032	1.85 (143)	<.001
MI	0.66 (26)	0.17 (0.11 - 0.25)	<.001	1.87 (71)	0.68 (0.48 - 0.96) 0.33 (0.22 - 0.48)	0.028 <.001	2.12 (125)	0.53 (0.43 - 0.66)	<.001	1.34 (169)	0.34 (0.28 - 0.41)	<.001	3.96 (292)	<.001
Stroke	0.48 (19)	0.49 (0.30 - 0.81)	0.006	1.44 (55)	1.46 (1.03 - 2.08)	0.032	0.70 (42)	0.72 (0.49 - 1.05)	0.092	0.87 (110)	0.89 (0.66 - 1.20)	0.439	0.97 (74)	<.001
All-cause death	5.05 (203)	1.46 (1.21 - 1.75)	<.001	4.49 (176)	1.28 (1.06 - 1.55)	0.010	2.71 (167)	0.77 (0.64 - 0.93)	0.008	3.43 (440)	0.98 (0.84 - 1.14)	0.774	3.51 (277)	<.001
ALI	0.33 (13)	0.44 (0.24 - 0.80)	0.007	0.60 (23)	0.80 (0.49 - 1.30)	0.372	0.67 (40)	0.91 (0.61 - 1.37)	0.655	0.79 (100)	1.07 (0.77 - 1.49)	0.679	0.74 (56)	0.038
LER	2.49 (95)	0.26 (0.21 - 0.33)	<.001	4.10 (150)	0.44 (0.37 - 0.52)	<.001	8.04 (433)	0.86 (0.76 - 0.98)	0.019	3.53 (429)	0.38 (0.34 - 0.43)	<.001	9.33 (631)	<.001

*Global P-value from the overall association test. Reference is North America. HR (95% CI) and p-values for MI in Asia correspond to time intervals (0,365) and (365,...) days, respectively.
Incidence rate: number of events (n) per 100 patient years.
ALI indicates acute limb ischemia; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; LER, lower extremity revascularization; MI, myocardial infarction.

Table S4. Adjusted Associations Between Region and Clinical Outcomes

	Central/South America		Asia		Western Europe		Eastern Europe		
Clinical Outcome	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**Global P-value***
CV death/MI/Stroke	0.66 (0.54 - 0.79)	<.001	0.75 (0.63 - 0.89)	0.001	0.65 (0.55 - 0.76)	<.001	0.75 (0.65 - 0.85)	<.001	<.001
Model 1	0.74 (0.61 - 0.90)	0.003	0.86 (0.72 - 1.03)	0.108	0.74 (0.63 - 0.88)	<.001	0.84 (0.73 - 0.96)	0.012	0.003
Model 2	0.69 (0.57 - 0.84)	<.001	0.80 (0.66 - 0.97)	0.020	0.74 (0.62 - 0.87)	<.001	0.84 (0.73 - 0.97)	0.016	<.001
Model 3	0.69 (0.57 - 0.84)	<.001	0.80 (0.66 - 0.97)	0.026	0.75 (0.63 - 0.89)	0.001	0.84 (0.73 - 0.97)	0.018	0.001
CV death	1.53 (1.18 - 1.97)	0.001	1.11 (0.84 - 1.45)	0.466	0.65 (0.49 - 0.87)	0.004	1.37 (1.11 - 1.68)	0.003	<.001
MI	0.18 (0.12 - 0.27)	<.001	0.65 (0.46 - 0.92) 0.31 (0.21 - 0.46)	0.015 <.001	0.57 (0.46 - 0.70)	<.001	0.38 (0.31 - 0.46)	<.001	<.001
Stroke	0.48 (0.29 - 0.81)	0.005	1.34 (0.94 - 1.91)	0.107	0.73 (0.50 - 1.07)	0.103	0.93 (0.69 - 1.27)	0.653	0.001
All-cause death	1.49 (1.23 - 1.79)	<.001	1.16 (0.96 - 1.41)	0.127	0.82 (0.68 - 0.99)	0.044	1.11 (0.95 - 1.30)	0.189	<.001
Model 1	1.55 (1.28 - 1.87)	<.001	1.22 (1.00 - 1.50)	0.047	0.86 (0.71 - 1.05)	0.138	1.14 (0.97 - 1.34)	0.109	<.001
Model 2	1.45 (1.19 - 1.76)	<.001	1.10 (0.89 - 1.35)	0.366	0.81 (0.66 - 1.00)	0.046	1.11 (0.94 - 1.31)	0.238	<.001
Model 3	1.47 (1.21 - 1.79)	<.001	1.15 (0.93 - 1.42)	0.195	0.84 (0.69 - 1.04)	0.103	1.11 (0.94 - 1.31)	0.222	<.001
ALI	0.69 (0.38 - 1.28)	0.238	0.86 (0.52 - 1.40)	0.541	1.04 (0.69 - 1.57)	0.837	1.43 (1.02 - 2.00)	0.039	0.029
LER	0.35 (0.28 - 0.43)	<.001	0.47 (0.39 - 0.56)	<.001	0.96 (0.85 - 1.09)	0.519	0.45 (0.40 - 0.51)	<.001	<.001
Model 1	0.36 (0.29 - 0.45)	<.001	0.48 (0.40 - 0.57)	<.001	0.99 (0.87 - 1.13)	0.885	0.46 (0.41 - 0.53)	<.001	<.001
Model 2	0.36 (0.29 - 0.46)	<.001	0.49 (0.41 - 0.60)	<.001	1.02 (0.90 - 1.16)	0.741	0.48 (0.42 - 0.55)	<.001	<.001
Model 3	0.36 (0.29 - 0.45)	<.001	0.50 (0.41 - 0.61)	<.001	1.03 (0.90 - 1.17)	0.678	0.48 (0.42 - 0.55)	<.001	<.001

*P-value from the overall association test. Reference is North America.

Hazard ratios, 95% confidence intervals, and p-values for MI in Asia correspond to time intervals [0,365] and [365,..] days, respectively.

All outcomes adjusted for age, sex, inclusion criteria, and severity of disease.

Model 1 adjusts for concomitant cardiovascular diseases (prior stroke, carotid stenosis or revascularization, MI, PCI, CABG).

Model 2 adds cardiovascular disease risk factors to Model 1 (diabetes, smoking, hypertension, hyperlipidemia).

Model 3 adds preventive medications to Model 2 (statins, angiotensin-receptive blockers, ACE inhibitors).

HR, hazard ratio; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; ALI, acute limb ischemia; LER, lower extremity revascularization.

Figure S4. Kaplan Meier event curves for CV death, MI, or ischemic stroke

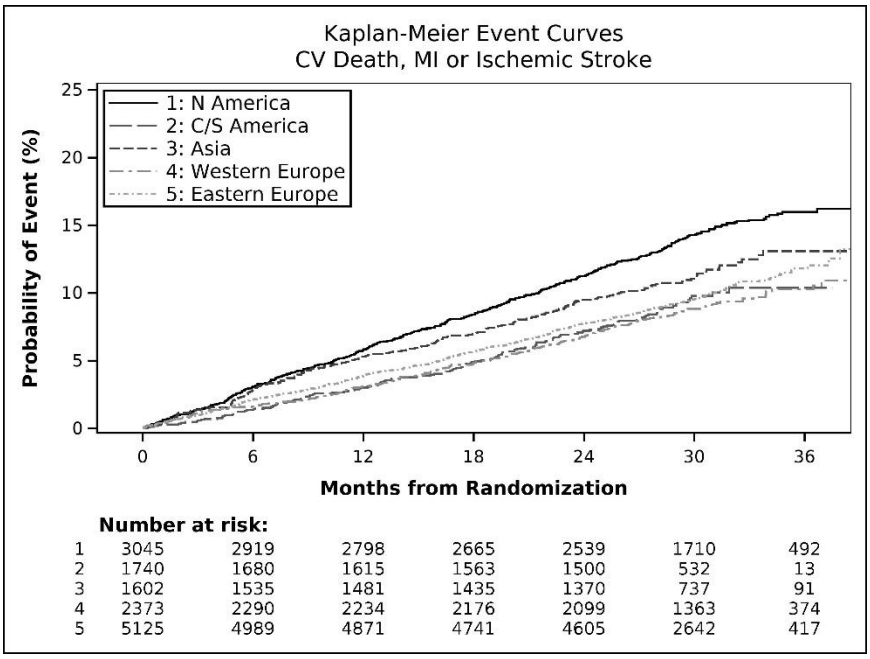


Figure S5. Kaplan Meier event curves for CV death

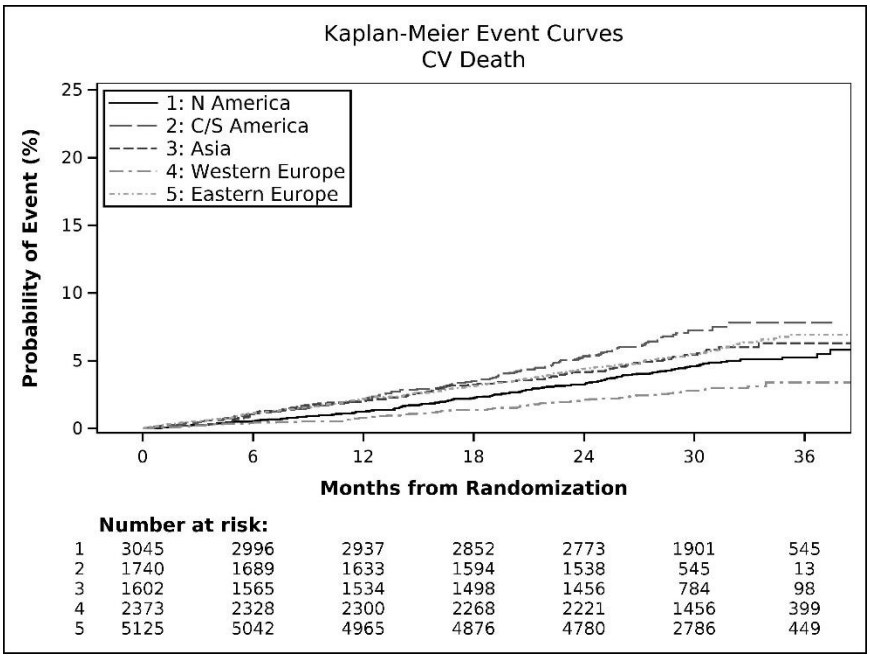


Figure S6. Kaplan Meier event curves for MI

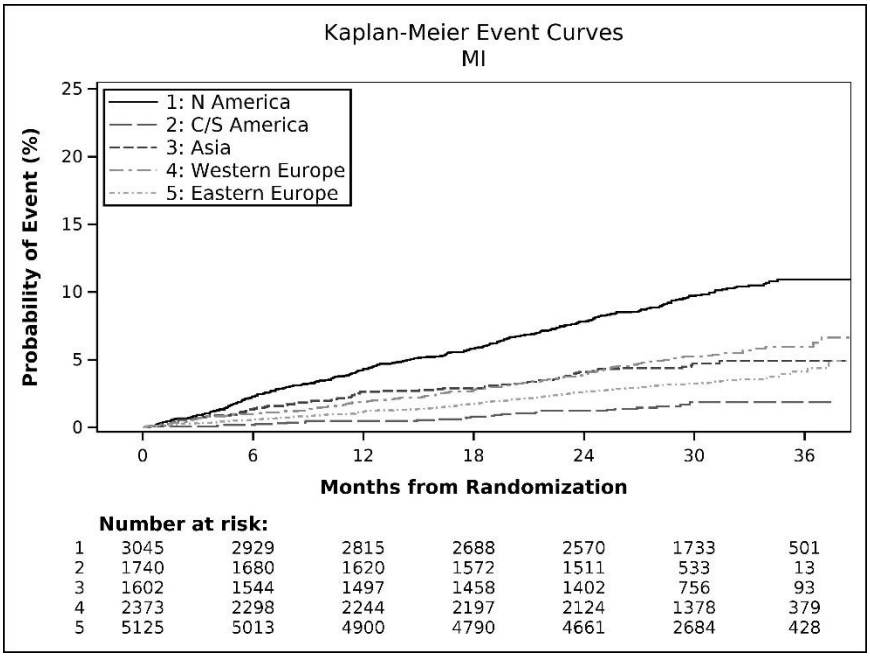


Figure S7. Kaplan Meier event curves for ischemic stroke

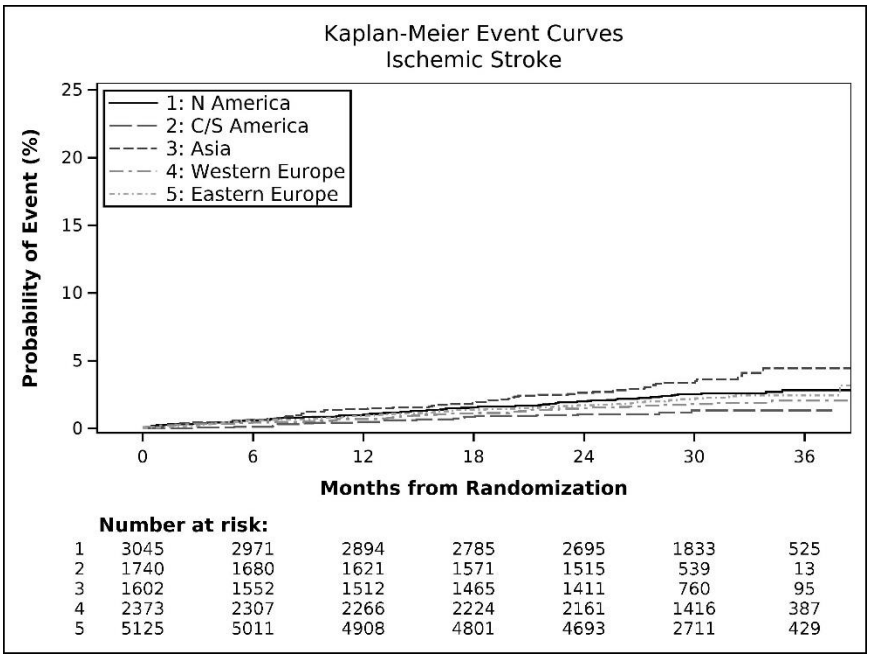


Figure S8. Kaplan Meier event curves for all-cause death

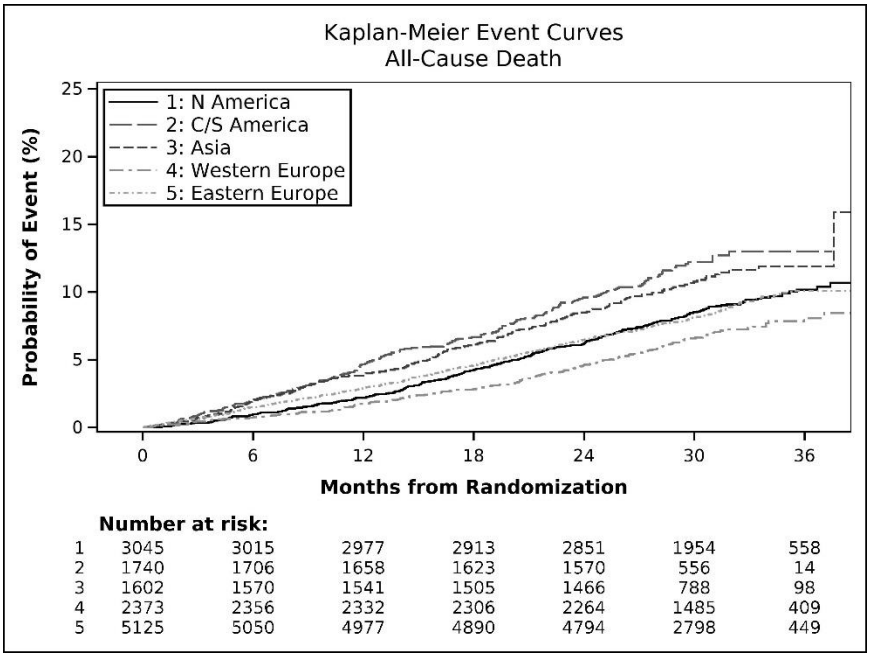


Figure S9. Kaplan Meier event curves for ALI hospitalization

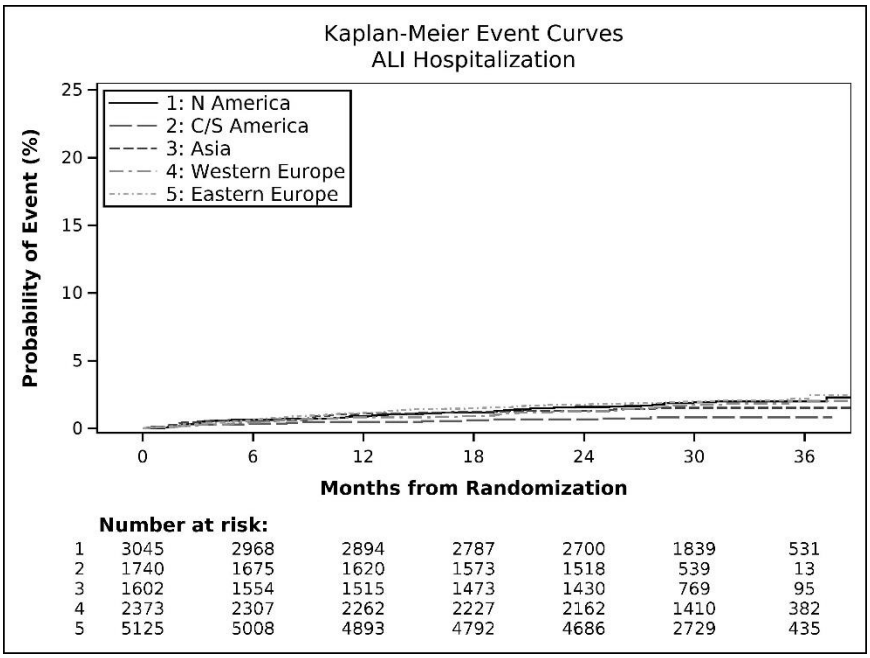


Figure S10. Kaplan Meier event curves for lower extremity revascularization