

Supplementary Material

Assessing the Suitability of CHA₂DS₂-VASc for Predicting Adverse Limb Events and Cardiovascular Outcomes in Peripheral Artery Disease Patients with Percutaneous Transluminal Angioplasty: A Retrospective Cohort Study

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I. Supplementary Materials

Clinical parameter description

Other diagnostic, clinical, and environmental factors were available for all PAD patients, defined as follows: smoking history classified as ever- and never-smokers, where ever-smokers were smokers who quit or were current smokers; ≥ 10 cigarettes a day for at least 1 year without an attempt to quit; with or without hyperlipidemia (HPL), based on a predefined low-density lipoprotein (LDL) cholesterol threshold set by the National Cholesterol Education program (<70 mg/dl for PAD patients; and <55 mg/dl for coronary artery disease (CAD) patients) [1], whether or not on lipid-lowering medications, and/or newly diagnosed patients at the time of hospitalization; history of CAD; history of coronary artery bypass graft (CABG), history of percutaneous cardiac intervention (PCI), history of old myocardial infarction (MI), history of chronic obstructive pulmonary disease (COPD), history of chronic kidney disease (CKD) with a creatinine clearance test threshold value of CCr.: <60 ml/min, history of hemodialysis (HD) or peritoneal dialysis (PD), history of atrial fibrillation (AF), history of autoimmune disease, information on blood marker levels, such as glycated hemoglobin (HbA1C), cholesterol, LDL, high-density lipoprotein (HDL) cholesterol, triglyceride (TG), and glucose. Information on medications were also included, such as aspirin (ASA), clopidogrel, cilostazol, pentoxifylline, warfarin or direct oral anticoagulant (DOAC), angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), statin, betablocker, calcium channel blockers (CCB), and insulin.

The mean age of patients with MACE was higher than that of patients without MACE, while the mean age of MALE patients was slightly lower than that of those without MALE. Furthermore, patients demonstrating MACE had a significantly higher proportion of CHF, HTN, and DM when compared to patients without MACE, but the trend was reversed in cases with a MALE event. Hyperlipidemia was observed in a significantly higher number of patients with MACE ($P = 0.05$) outcomes when compared against those with no event. Smoking (ever) was observed to be correlated in direct proportion to MACE occurrence (46.93% (MACE); 37.83% (no MACE)), but was inversely and proportionally correlated with MALE. Occurrence of other clinical characteristics, such as CAD, CABG, PCI, Old MI, COPD, CKD, and AF was significantly greater in PAD patients with MACE ($P < 0.0001$) in comparison to those without MACE, but the occurrence was low in patients with MALE as compared with their non-MALE counterparts. Autoimmune diseases were less prevalent or absent in patients with MALE and MACE, respectively. Mean \pm standard deviation (SD) of all diagnostic blood markers are provided in Table 1; no

blood markers were significantly different between MACE and non-MACE, and except for HbA1C (P=0.001) and glucose levels (P=0.02), none showed a significant difference between MALE and non-MALE. Medication usage was also not significantly different among all of the groups with and without events.

Model evaluation

A 10-fold cross-validation process was implemented to confirm the predictive performance of the MCR score and to confirm its reproducibility [15]. Also, the MCR-based regression models' predictions were compared with traditional models that used clinical parameters directly instead of the cumulative score. This was done to determine whether using MCR as the predictor demonstrated any improvement over the traditional methods. **Table 4** lists the average and the standard deviations of the c-indices over all 10CVs for all three regression models for MALE, MACE, and MALE+MACE. The results provide evidence that for a given patient pair, MCR can effectively discriminate the occurrence of MACE events, which indicates it to be a good predictor. However, the discrimination power of MCR for MALE and MALE+MACE were not good enough.

Next, calibration analyses were conducted using 10CV for each of the 5 years for all models. The difference between the proportions for the predicted and observed events were averaged and plotted for MCR models in comparison to the traditional model. For MACE, the differences of the proportions between observed and predicted for both MCR and traditional models were $\leq 5\%$ for the first 2 years, and for the years 3-5 were restricted to $<10\%$, while for both MACE and MALE, the average of differences was quite high (33-49%), except for year 1 ($<5\%$). **Figure 4**, and **Table S4–S9** showcases detailed calibration results.

Further evaluation of MCR was conducted using ROC analysis for predicting MALE, MACE and MALE+MACE at time points of 12months, 24 months, 36 months and 48 months, respectively (**Figure 5**). For outcome MACE, the univariate model and the multivariate adjusted model demonstrated a maximum AUC of ~ 0.66 and ~ 0.85 for time points 48 months and 12 months, respectively (**Figure 5B,E**), while for the both outcomes MALE and MALE+MACE the univariate model demonstrated AUCs of <0.6 (**Figure 5A,C**) for all time points whereas the maximum AUC for multivariate models was ~ 0.65 for time points >36 months (**Figure 5D,F**). Based on all of our findings, we can fairly say that CHA₂DS₂-VASc can be claimed as a good predictor of MACE but doesn't qualify as a good predictor of MALE and MALE+MACE for patients with PAD.

1 Supplementary Figures and Tables

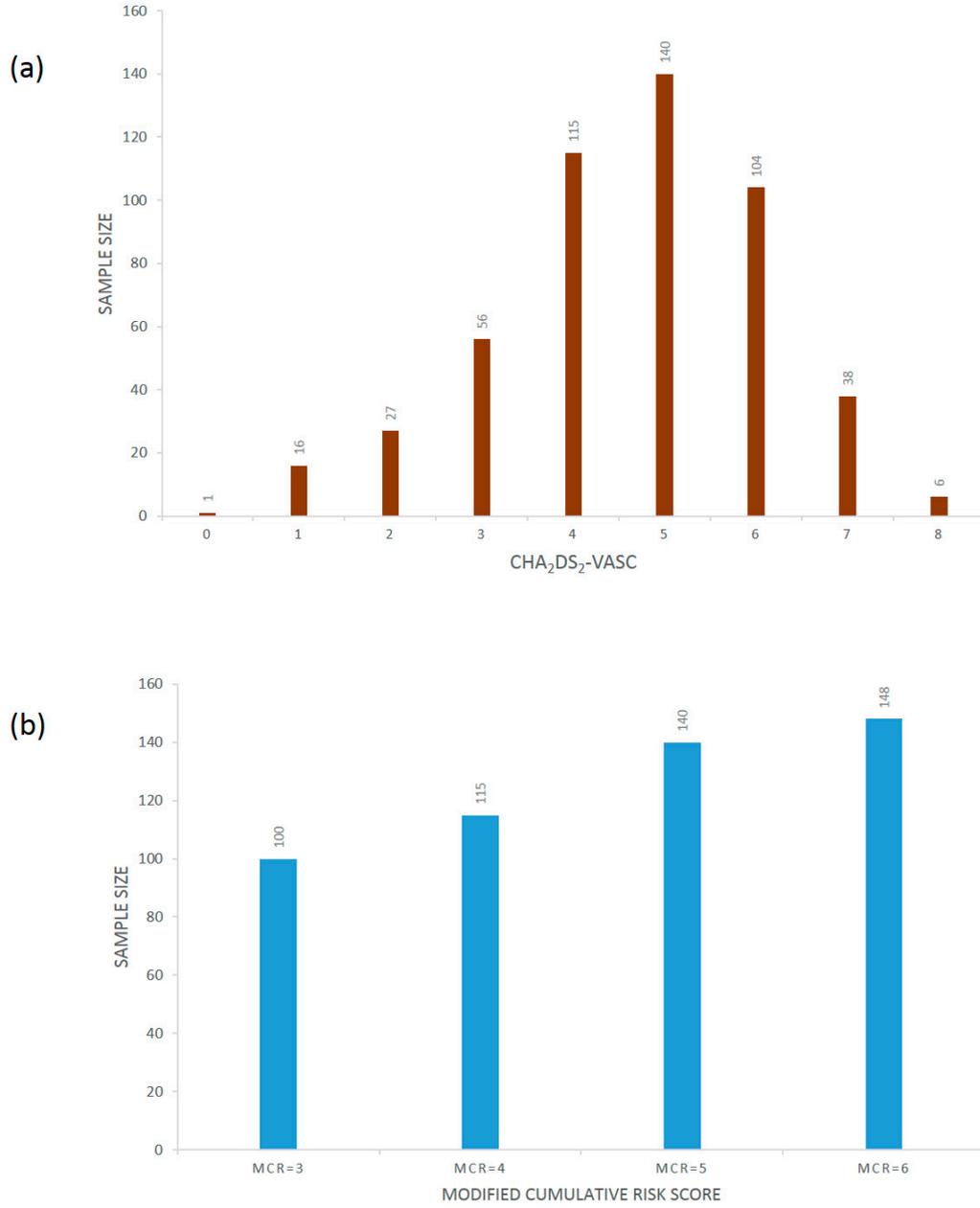


Figure S1. The distribution of PAD samples based on (a) CHA₂DS₂-VASC and (b) MCR scores

Table S1. Description of Rutherford classifications

| Grade | Category | Clinical description | Objective criteria |
|--------------|-----------------|--|---|
| 0 | 0 | Asymptomatic – no hemodynamically significant occlusive disease | Normal treadmill test and ABI \geq 0.9 |
| | 1 | Mild claudication | Treadmill test completed. AP after exercise <50 mmHg |
| I | 2 | Moderate claudication | Between categories 1 and 3 |
| | 3 | Severe claudication | Cannot complete treadmill test and Ankle pressure (AP) after exercise <50 mmHg |
| II | 4 | Ischemic rest pain | Resting Ankle pressure (AP) <40 mmHg, flat or barely pulsatile ankle or metatarsal PVR, TP <30 mmHg |
| III | 5 | Minor tissue loss – non-healing ulcer, focal gangrene with diffuse pedal ischemia | Resting AP <60 mmHg, ankle or metatarsal PVR flat or barely pulsatile, TP <40 mmHg |
| | 6 | Major tissue loss- extending above TM level, functional foot no longer salvageable | Similar to category 5 |

AP: Ankle pressure, PVR: pulse volume recording, TP: toe pressure

Table S2. Demographic and clinico-pathological characteristics for major adverse limb events (MALE) and major adverse cardiovascular events (MACE)

| | MALE (n=193) | no MALE (n= 310) | P-value | MACE (n=49) | No MACE (n = 454) | P-value |
|------------------|-----------------|---------------------|---------|-----------------|----------------------|---------|
| MCR score | | | | | | |
| =3 | 31 (16.06) | 69 (22.26) | | 3 (6.12) | 97 (21.37) | |
| =4 | 49 (25.39) | 66 (21.29) | | 13 (26.53) | 102 (22.47) | |
| =5 | 63 (32.64) | 77 (24.83) | | 16 (32.65) | 124 (27.31) | |
| =6 | 50 (25.91) | 98 (31.61) | 0.05* | 17 (34.69) | 131 (28.85) | 0.0002* |
| Age | 69.83 ± 12.44 | 71.35 ± 12.34 | 0.182 | 71.75 ± 10.85 | 70.67 ± 12.55 | 0.512 |
| Sex (Male) | 123 (63.73) | 203 (65.48) | 0.701 | 34 (69.39) | 292 (64.31) | 0.537 |
| BMI | 23.687 ± 3.665 | 24.14 ± 4.04 | 0.191 | 24.15 ± 3.502 | 23.94 ± 3.95 | 0.713 |
| CHF (C) | 89 (46.11) | 149 (48.60) | 0.7136 | 34 (69.39) | 204 (44.93) | 0.001* |
| HTN | 165 (85.49) | 271 (87.42) | 0.589 | 47 (95.92) | 389 (85.68) | 0.045* |
| DM | 158 (81.86) | 218 (70.32) | 0.004* | 44 (89.80) | 332 (73.12) | 0.009* |
| Stroke (S)/TIA | 31 (16.06) | 60 (19.35) | 0.405 | 11 (22.24) | 80 (17.62) | 0.434 |
| Vascular Disease | 193 (100) | 310 (100) | 1 | 49 (100) | 454 (100) | 1 |
| HPL | 99 (51.29) | 142 (45.80) | 0.235 | 30 (61.22) | 211 (46.48) | 0.05* |
| SMK | 71 (36.78) | 124 (40) | 0.51 | 23 (46.93) | 172 (37.88) | 0.221 |
| CAD | 101 (52.33) | 162 (52.25) | 1 | 33 (67.49) | 230 (50.66) | 0.034* |
| CABG | 18 (9.33) | 35 (11.29) | 0.551 | 10 (20.41) | 43 (9.47) | 0.026* |
| PCI | 95 (49.22) | 144 (46.5) | 0.582 | 30 (61.22) | 209 (46.03) | 0.05 |
| Old MI | 24 (12.43) | 55 (17.74) | 0.13 | 17 (34.69) | 62 (13.66) | 0.0005* |
| COPD | 7 (3.63) | 14 (4.52) | 0.819 | 5 (10.20) | 16 (3.52) | 0.043* |
| CKD | 120 (62.17) | 199 (64.19) | 0.703 | 41 (83.67) | 278 (61.23) | 0.001* |
| HD/PD | 73 (37.82) | 108 (34.83) | 0.505 | 22 (44.90) | 159 (35.02) | 0.209 |
| Cr | 3.484 ± 3.345 | 3.128 ± 2.846 | 0.236 | 4.237 ± 2.964 | 3.15 ± 3.03 | 0.024* |
| Af | 41 (21.24) | 79 (25.48) | 0.2847 | 19 (38.77) | 101 (22.24) | 0.013* |
| Imd | 6 (3.11) | 15 (4.83) | 0.492 | 0 (0) | 21 (4.62) | 0.248 |
| HbA1C | 7.682 ± 2.017 | 7.104 ± 1.727 | 0.001* | 7.716 ± 1.796 | 7.27 ± 1.876 | 0.114 |
| Cholesterol | 149.63 ± 41.227 | 149.66 ± 38.31 | 0.992 | 143.38 ± 27.496 | 150.33 ± 40.46 | 0.115 |
| LDL | 82.87 ± 34.177 | 83.673 ± 32.87 | 0.796 | 76.22 ± 30.17 | 84.14 ± 33.61 | 0.089 |
| HDL | 42.238 ± 14.915 | 43.37 ± 15.40 | 0.412 | 43.979 ± 14.09 | 42.83 ± 15.34 | 0.591 |
| TG | 131.59 ± 84.48 | 130.41 ± 83.48 | 0.878 | 123.53 ± 71.24 | 131.66 ± 85.06 | 0.46 |
| Glu | 154.88 ± 74.85 | 139.82 ± 65.398 | 0.021* | 149.53 ± 59.80 | 145.18 ± 70.50 | 0.636 |
| ASA | 149 (77.20) | 236 (76.13) | 0.829 | 39 (79.59) | 346 (76.21) | 0.723 |
| clopidgrel | 165 (85.49) | 262 (84.52) | 0.799 | 44 (89.79) | 383 (84.36) | 0.403 |
| cilostazol | 121 (62.69) | 180 (58.06) | 0.349 | 29 (59.18) | 272 (59.91) | 1 |
| pentoxphylline | 1 (0.51) | 0 (0) | 0.383 | 0 (0) | 1 (0.22) | 1 |

| | | | | | | |
|----------------------------------|-------------|-------------|--------|------------|-------------|--------|
| direct oral anticoagulant (DOAC) | 25 (12.95) | 48 (15.48) | 0.515 | 7 (14.29) | 66 (14.54) | 1 |
| ACEIARB | 84 (43.52) | 136 (43.87) | 1 | 17 (34.69) | 203 (43.39) | 0.225 |
| statin | 106 (54.92) | 177 (57.09) | 0.645 | 23 (46.93) | 260 (55.51) | 0.175 |
| Betablocker | 76 (39.37) | 113 (36.45) | 0.509 | 15 (30.61) | 174 (37.23) | 0.352 |
| CCB | 74 (38.34) | 127 (40.97) | 0.575 | 15 (30.61) | 180 (37.89) | 0.280 |
| Insulin | 45 (23.32) | 61 (19.68) | 0.368 | 13 (26.53) | 93 (19.38) | 0.356 |
| Rutherford classification | | | | | | |
| 1 | 0 (0) | 0 (0) | 1 | 0 (0) | 0 (0) | 1 |
| 2 | 0 (0) | 0 (0) | 1 | 0 (0) | 0 (0) | 1 |
| 3 | 0 (0) | 0 (0) | 1 | 0 (0) | 0 (0) | 1 |
| 4 | 35 (18.13) | 95 (30.64) | 0.001* | 5 (10.20) | 125 (27.53) | 0.009* |
| 5 | 133 (68.91) | 183 (59.03) | 0.029* | 35 (71.43) | 281 (61.89) | 0.215 |
| 6 | 25 (12.95) | 32 (10.32) | 0.575 | 9 (18.37) | 48 (10.57) | 0.15 |
| Target vessel | | | | | | |
| CIA | 12 (6.22) | 29 (9.35) | 0.243 | 4 (8.16) | 37 (8.15) | 1 |
| EIA | 10 (5.18) | 35 (11.29) | 0.024* | 5 (10.20) | 40 (8.81) | 0.791 |
| CFA | 10 (5.18) | 17 (5.48) | 1 | 3 (6.12) | 24 (5.29) | 0.739 |
| SFA | 113 (58.54) | 172 (55.48) | 0.518 | 27 (55.10) | 258 (56.83) | 0.879 |
| ATA | 100 (51.81) | 148 (47.74) | 0.409 | 26 (53.06) | 222 (48.90) | 0.653 |
| Popliteal | 50 (25.91) | 57 (18.39) | 0.056* | 10 (20.41) | 97 (21.37) | 1 |
| Peroneal artery | 46 (23.83) | 50 (16.13) | 0.036* | 13 (26.53) | 83 (18.28) | 0.181 |
| Tibiofibular TP trunk | 25 (12.95) | 39 (12.58) | 0.891 | 3 (6.12) | 61 (13.44) | 0.178 |
| PTA | 88 (45.59) | 108 (34.84) | 0.018* | 15 (30.61) | 181 (39.87) | 0.221 |
| DPA | 10 (5.18) | 5 (1.61) | 0.029* | 1 (2.04) | 14 (3.08) | 1 |
| Plantar artery | 15 (7.78) | 8 (2.58) | 0.008* | 2 (4.08) | 21 (4.63) | 1 |

BMI: body mass index; CHF (C): HTN: hypertension; DM: diabetes mellitus; Stroke (S)/TIA; HPL: hyperlipidemia; SMK: smoking status; CAD: coronary artery disease; CABG: Coronary Artery Bypass Graft; PCI: Percutaneous coronary intervention; MI: myocardial infarction; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; HD/PD: hemodialysis/peritoneal dialysis; Cr: creatinine; Af: atrial fibrillation; Imd: immune-related disease; HbA1C: hemoglobin A1C, LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: triglyceride; Glu: glucose; ASA: Acetylsalicylic acid; ACEIARB: Angiotensin-Converting Enzyme Inhibitor (ACEI)/Angiotensin Receptor Blocker (ARB); CCB: Calcium channel blockers; CIA: common iliac artery; EIA: external iliac artery; CFA: common femoral artery; SFA: superficial femoral artery; ATA: anterior tibial artery; Tibiofibular TP (tibioperoneal) trunk; PTA: posterior tibial artery; DPA: dorsalis pedis artery.

Table S3. Demographic and clinico-pathological characteristics for outcome major adverse limb events (MALE) + major adverse cardiovascular events (MACE).

| | MALE +MACE (n=224) | no MALE+MACE (n= 279) | P-value |
|------------------|-----------------------|--------------------------|----------|
| MCR score | | | |
| =3 | 34 (15.17) | 66 (23.66) | |
| =4 | 57 (25.45) | 58 (20.79) | |
| =5 | 70 (31.25) | 70 (25.09) | |
| =6 | 63 (28.13) | 85 (30.47) | 0.05* |
| Age | 69.99 ± 12.26 | 71.39 ± 12.47 | 0.208 |
| Sex (Male) | 147 (65.62) | 179 (64.16) | 0.778 |
| BMI | 23.82 ± 3.703 | 24.09 ± 4.06 | 0.443 |
| CHF (C) | 115 (51.34) | 123 (44.09) | 0.107 |
| HTN | 196 (87.50) | 240 (86.02) | 0.692 |
| DM | 185 (82.59) | 191 (68.46) | 0.0002* |
| Stroke (S)/TIA | 37 (16.52) | 54 (19.35) | 0.485 |
| Vascular Disease | 224 (100) | 279 (100) | 1 |
| HPL | 117 (52.23) | 124 (44.44) | <0.0001* |
| SMK | 90 (40.18) | 105 (37.63) | 0.51 |
| CAD | 125 (55.80) | 138 (49.46) | 1 |
| CABG | 25 (11.16) | 28 (10.03) | 0.770 |

| | | | |
|-----------------|----------------|----------------|--------|
| PCI | 117 (52.23) | 122 (43.72) | 0.05* |
| Old MI | 37 (16.52) | 42 (15.05) | 0.712 |
| COPD | 11 (4.91) | 10 (3.58) | 0.506 |
| CKD | 144 (64.29) | 175 (62.72) | 0.78 |
| HD/PD | 86 (38.39) | 95 (34.05) | 0.350 |
| Cr | 3.601 ± 3.282 | 3.002 ± 2.826 | 0.036* |
| Af | 52 (23.21) | 68 (24.37) | 0.833 |
| Imd | 6 (2.68) | 15 (5.38) | 0.178 |
| HbA1C | 7.610 ± 1.939 | 7.097 ± 1.769 | 0.002* |
| Cholesterol | 148.69 ± 39.61 | 150.44 ± 39.31 | 0.622 |
| LDL | 82.00 ± 34.18 | 84.46 ± 32.68 | 0.414 |
| HDL | 42.58 ± 14.918 | 43.22 ± 15.46 | 0.639 |
| TG | 128.89 ± 82.27 | 132.45 ± 85.10 | 0.636 |
| Glu | 152.55 ± 72.53 | 140.03 ± 66.56 | 0.046* |
| ASA | 171 (76.34) | 214 (76.70) | 1 |
| clopidgrel | 194 (86.61) | 233 (83.51) | 0.381 |
| cilostazol | 141 (62.95) | 160 (57.35) | 0.234 |
| pentoxophylline | 1 (0.46) | 0 (0) | 0.445 |

Supplementary Material

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| direct oral anticoagulant (DOAC) | 30 (13.39) | 43 (15.41) | 0.610 |
| ACEIARB | 94 (41.96) | 126 (45.16) | 0.526 |
| statin | 121 (54.02) | 162 (58.06) | 0.367 |
| Betablocker | 82 (36.61) | 107 (38.35) | 0.711 |
| CCB | 86 (38.39) | 115 (41.22) | 0.523 |
| Insulin | 56 (25) | 50 (17.92) | 0.061 |
| Rutherford classification | | | |
| 1 | 0 (0) | 0 (0) | 1 |
| 2 | 0 (0) | 0 (0) | 1 |
| 3 | 0 (0) | 0 (0) | 1 |
| 4 | 38 (16.96) | 92 (32.97) | <0.0001* |
| 5 | 156 (69.64) | 160 (57.35) | 0.005* |
| 6 | 25 (13.39) | 27 (9.68) | 0.659 |
| Target vessel | | | |
| CIA | 14 (6.25) | 27 (9.68) | 0,191 |
| EIA | 13 (5.28) | 32 (11.47) | 0.028* |
| CFA | 11 (4.91) | 16 (5.73) | 0.842 |
| SFA | 131 (58.48) | 154 (55.20) | 0.470 |
| ATA | 117 (52.23) | 131 (46.95) | 0.251 |

| | | | |
|-----------------------|------------|------------|-------|
| Popliteal | 55 (24.55) | 52 (18.64) | 0.125 |
| Peroneal artery | 51 (22.77) | 45 (16.13) | 0.067 |
| Tibiofibular TP trunk | 29 (12.95) | 35 (12.54) | 0.893 |
| PTA | 98 (43.75) | 98 (35.12) | 0.053 |
| DPA | 10 (4.46) | 5 (1.79) | 0.112 |
| Plantar artery | 15 (6.69) | 8 (2.87) | 0.053 |

BMI: body mass index; CHF (C): HTN: hypertension; DM: diabetes mellitus; Stroke (S)/TIA; HPL: hyperlipidemia; SMK: smoking status; CAD: coronary artery disease; CABG: Coronary Artery Bypass Graft; PCI: Percutaneous coronary intervention; MI: myocardial infarction; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; HD/PD: hemodialysis/peritoneal dialysis; Cr: creatinine; Af: atrial fibrillation; Imd: immune-related disease; HbA1C: hemoglobin A1C, LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: triglyceride; Glu: glucose; ASA: Acetylsalicylic acid; ACEI/ARB: Angiotensin-Converting Enzyme Inhibitor (ACEI)/Angiotensin Receptor Blocker (ARB); CCB: Calcium channel blockers; CIA: common iliac artery; EIA: external iliac artery; CFA: common femoral artery; SFA: superficial femoral artery; ATA: anterior tibial artery; Tibiofibular TP (tibioperoneal) trunk; PTA: posterior tibial artery; DPA: dorsalis pedis artery.

Table S4. Calibration analysis for years 1-5 based on multivariate-adjusted MCR models for MALE.

| year | diff_1 | diff_2 | diff_3 | diff_4 | diff_5 | diff_6 | diff_7 | diff_8 | diff_9 | diff_10 | Avg. | Std. dev |
|------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|-------|----------|
| 1 | 0.034 | -0.270 | 0.050 | -0.067 | 0.0913 | 0.038 | 0.212 | 0.083 | 0.117 | 0.141 | 0.043 | 0.132 |
| 2 | 0.173 | 0.237 | 0.400 | 0.232 | 0.1515 | 0.352 | 0.432 | 0.422 | 0.413 | 0.391 | 0.320 | 0.110 |
| 3 | 0.074 | 0.425 | 0.487 | 0.475 | 0.3788 | 0.400 | 0.283 | 0.392 | 0.472 | 0.534 | 0.392 | 0.132 |
| 4 | 0.243 | 0.486 | 0.453 | 0.515 | 0.3101 | 0.431 | 0.429 | 0.498 | 0.539 | 0.479 | 0.438 | 0.093 |
| 5 | 0.445 | 0.420 | 0.548 | 0.508 | 0.5168 | 0.499 | 0.531 | 0.467 | 0.607 | 0.590 | 0.513 | 0.060 |

Table S5. Calibration analysis for year 1 - year 5 based on multivariate-adjusted traditional models for MALE

| year | diff_1 | diff_2 | diff_3 | diff_4 | diff_5 | diff_6 | diff_7 | diff_8 | diff_9 | diff_10 | Avg. | Std. Dev |
|------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|-------|----------|
| 1 | 0.021 | -0.282 | 0.062 | -0.076 | 0.0908 | 0.048 | 0.222 | 0.085 | 0.132 | 0.138 | 0.044 | 0.139 |
| 2 | 0.146 | 0.253 | 0.387 | 0.209 | 0.1498 | 0.369 | 0.448 | 0.425 | 0.428 | 0.388 | 0.320 | 0.119 |
| 3 | 0.064 | 0.438 | 0.492 | 0.449 | 0.3946 | 0.416 | 0.307 | 0.387 | 0.478 | 0.518 | 0.394 | 0.131 |
| 4 | 0.235 | 0.502 | 0.434 | 0.507 | 0.3606 | 0.458 | 0.457 | 0.490 | 0.551 | 0.447 | 0.444 | 0.089 |
| 5 | 0.399 | 0.441 | 0.531 | 0.488 | 0.6104 | 0.527 | 0.556 | 0.434 | 0.582 | 0.587 | 0.516 | 0.072 |

Table S6. Calibration analysis for years 1-5 based on multivariate-adjusted MCR models for MACE.

| year | diff_1 | diff_2 | diff_3 | diff_4 | diff_5 | diff_6 | diff_7 | diff_8 | diff_9 | diff_10 | Avg. | Std. dev. |
|------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|-------|-----------|
| 1 | -0.025 | 0.001 | 0.039 | 0.025 | 0.0002 | -0.016 | 0.064 | -0.092 | 0.072 | 0.072 | 0.014 | 0.052 |
| 2 | 0.114 | 0.020 | 0.024 | 0.094 | 0.0460 | 0.105 | 0.084 | -0.010 | 0.021 | 0.022 | 0.052 | 0.043 |
| 3 | 0.129 | -0.003 | 0.080 | 0.013 | 0.1947 | 0.127 | 0.130 | 0.049 | 0.095 | 0.093 | 0.091 | 0.059 |
| 4 | 0.207 | 0.122 | 0.026 | 0.097 | 0.0386 | 0.180 | 0.159 | 0.036 | 0.092 | 0.118 | 0.108 | 0.062 |
| 5 | 0.362 | -0.249 | 0.093 | 0.119 | 0.2520 | 0.190 | 0.182 | 0.125 | -0.098 | 0.189 | 0.117 | 0.174 |

Table S7. Calibration analysis for years 1-5 based on multivariate-adjusted traditional models for MACE.

| year | diff_1 | diff_2 | diff_3 | diff_4 | diff_5 | diff_6 | diff_7 | diff_8 | diff_9 | diff_10 | Avg. | Std. dev. |
|------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|-------|-----------|
| 1 | -0.025 | -0.001 | 0.037 | 0.023 | 0.0007 | -0.013 | 0.065 | -0.094 | 0.071 | 0.070 | 0.013 | 0.052 |
| 2 | 0.116 | 0.021 | 0.022 | 0.091 | 0.0461 | 0.104 | 0.086 | -0.014 | 0.023 | 0.020 | 0.051 | 0.044 |
| 3 | 0.137 | 0.003 | 0.079 | 0.015 | 0.1930 | 0.122 | 0.133 | 0.062 | 0.101 | 0.090 | 0.093 | 0.058 |
| 4 | 0.211 | 0.121 | 0.024 | 0.108 | 0.0181 | 0.171 | 0.158 | 0.045 | 0.097 | 0.114 | 0.107 | 0.064 |
| 5 | 0.378 | -0.249 | 0.075 | 0.111 | 0.2774 | 0.181 | 0.181 | 0.186 | -0.079 | 0.175 | 0.124 | 0.178 |

Table S8. Calibration analysis for years 1-5 based on multivariate-adjusted MCR models for MALE + MACE

| year | diff_1 | diff_2 | diff_3 | diff_4 | diff_5 | diff_6 | diff_7 | diff_8 | diff_9 | diff_10 | Avg. | Std.dev. |
|------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|-------|----------|
| 1 | 0.003 | -0.253 | 0.060 | -0.069 | 0.0614 | 0.043 | 0.269 | 0.004 | 0.135 | 0.172 | 0.043 | 0.141 |
| 2 | 0.272 | 0.319 | 0.381 | 0.276 | 0.1557 | 0.371 | 0.420 | 0.394 | 0.348 | 0.425 | 0.336 | 0.083 |
| 3 | 0.146 | 0.540 | 0.533 | 0.436 | 0.4538 | 0.524 | 0.416 | 0.351 | 0.453 | 0.477 | 0.433 | 0.116 |
| 4 | 0.340 | 0.605 | 0.390 | 0.536 | 0.3836 | 0.511 | 0.509 | 0.395 | 0.561 | 0.626 | 0.486 | 0.101 |
| 5 | 0.737 | -0.313 | 0.660 | 0.581 | 0.5705 | 0.551 | 0.526 | 0.514 | 0.430 | 0.708 | 0.496 | 0.299 |

Table S9. Calibration analysis for years 1-5 based on multivariate-adjusted traditional model for MALE + MACE

| year | diff_1 | diff_2 | diff_3 | diff_4 | diff_5 | diff_6 | diff_7 | diff_8 | diff_9 | diff_10 | Avg. | Std. dev. |
|------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|-------|-----------|
| 1 | -0.006 | -0.265 | 0.066 | -0.079 | 0.0603 | 0.054 | 0.274 | 0.006 | 0.149 | 0.170 | 0.043 | 0.147 |
| 2 | 0.253 | 0.324 | 0.367 | 0.257 | 0.1549 | 0.393 | 0.427 | 0.396 | 0.362 | 0.424 | 0.336 | 0.088 |
| 3 | 0.143 | 0.539 | 0.533 | 0.423 | 0.4707 | 0.537 | 0.433 | 0.345 | 0.463 | 0.462 | 0.435 | 0.119 |
| 4 | 0.341 | 0.605 | 0.373 | 0.536 | 0.4296 | 0.529 | 0.525 | 0.379 | 0.580 | 0.600 | 0.490 | 0.100 |
| 5 | 0.715 | -0.296 | 0.592 | 0.568 | 0.6617 | 0.572 | 0.542 | 0.543 | 0.417 | 0.698 | 0.501 | 0.293 |

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