SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods 1

The REACH and SMART models for risk of recurrent cardiovascular events

Details on the SMART and REACH risk models have been published previously.[1-4] The SMART risk score estimates the 10-year risk of a myocardial infarction, stroke or cardiovascular death for individuals with coronary artery disease, cerebrovascular disease, peripheral artery disease and/or an abdominal aortic aneurysm. The SMART risk score is based on the following predictors: age, sex, current smoking, diabetes mellitus, systolic blood pressure (mmHg), total cholesterol (mmol/L), HDL-cholesterol (mmol/L), presence of CAD, CVD, PAD and/or AAA, eGFR (ml/min/1.73 m²), hsCRP (mg/L) and years since first manifestation of cardiovascular disease.[1] The REACH models estimate the 20-month risk of a myocardial infarction, stroke or cardiovascular death (REACH recurrent event model), or cardiovascular death separately based on the following predictors: age, sex, current smoking, diabetes mellitus, body mass index (kg/m^2), number of locations of cardiovascular disease, cardiovascular event in the past year, congestive heart failure, atrial fibrillation, use of a statin, use of aspirin, geographic region (North America/Western Europe, Eastern Europe/Middle East or Japan/Australia).[4] Due to non-available variables we used sex and location of cardiovascular disease specific averages of hsCRP and HDL cholesterol based on those values in SMART in the REACH data and the variable number of years since first event we set zero if the patient had an event in the last year and one when this was longer ago. In SMART, congestive heart failure was considered absent.

External validation of the REACH and SMART risk models

We externally validated two existing risk scores that were developed in the REACH and SMART data. The 20-month REACH recurrent event score and the 10-year SMART risk score estimate the risk of a recurrent cardiovascular event, defined as the first (re)occurrence of a myocardial infarction, stroke or cardiovascular death (Supplemental Table 1C). A separate REACH cardiovascular death score estimates an individual's 20-month risk of cardiovascular mortality. The REACH scores were tested in SMART and the SMART risk score in REACH Western Europe and North America.

As the follow-up in the REACH cohort was limited, we validated the SMART risk score at 2-year follow-up using the 2-year baseline survival of 0.962 that we derived from the original SMART risk score development dataset. Estimated risks were compared with observed risk in quintiles or deciles of estimated risk (calibration) and were shown in calibration plots. As underlying event rates are known to differ between geographic regions, recalibration of the models was considered based on the calibration plot. As a result, recalibration of the SMART risk score was performed in both the Western Europe and North American REACH population by replacing the 2-year baseline survival (0.962) and mean linear predictor (2.099) of the SMART risk score by the estimates of the validation set.[5, 6] Discrimination (the extent to which patients that develop an event also had higher estimated risk than patients that did not get the event of interest) was expressed with Harrell's c-statistic.[7]

Data S2

Supplemental Methods 2 – Fine and Gray competing risk model

The SMART-REACH lifetime model was based on two Fine and Gray competing risk models. We applied adapted Fine and Gray models in order to enable lifetime predictions, using age as the underlying time axis, thus allowed both left truncation and right censoring.[8]

In traditional survival analysis, the occurrence of a competing event is handled by censoring. This approach assumes that the patient remains alive until the event of interest occurs. In reality, a patient may also die from something else in the meantime. As a result, failure to account for competing events may result in overestimation of cardiovascular risk. This is particularly the case when competing events share mutual risk factors. For example, smoking is a risk factor for both cardiovascular events and non-cardiovascular mortality. Therfore, failure to account for competing risks may result in biased conclusions about an individual's prognosis.

Data S1.

Supplemental Methods 3

The following relative treatment effects were used in the SMART-REACH calculator and the patient examples in Figure 2 (main text) to estimate lifelong treatment benefit in terms of gain in life expectancy free of recurrent cardiovascular disease:

Lipid-lowering treatment: the effect of lipid-lowering treatment on cardiovascular events depends on estimated reduction in LDL-c compared to baseline. A reduction of 1 mmol/l LDL-c

is related to a hazard ratio of 0.78.[9, 10] The percentage decrease in LDL-c for different statins and of ezetimibe (24% LDL-c reduction) are described in meta-analyses.[11, 12] For example, for switching from atorvastatin 10 mg (associated with 37% LDL-c reduction) to atorvastatin 80 mg (associated with 55% LDL-c reduction), the assumed additional LDL-c reduction is 29% (1-(1-0.55)/(1-0.37)). For PCSK9-inhibition, a 59% reduction in LDL-c was assumed.[13]

The individual expected relative risk reduction of cardiovascular disease is calculated by $0.78^{\text{LDL-c reduction in mmol/L}}$, where LDL-c reduction in mmol/L is defined as baseline LDL-c multiplied by the expected percentage LDL-c reduction due to intended treatment.

Blood pressure-lowering treatment: blood pressure-lowering treatment is associated with a hazard ratio of 0.77 per 10 mmHg for a baseline blood pressure of 140mmHg or higher.[14] We assumed no risk reduction from lowering blood pressure below 140 mmHg. The individual expected relative cardiovascular risk reduction is calculated by $0.77^{(\text{Blood pressure reduction in mmHg}/10)}$, where blood pressure reduction in mmHg is defined as the blood pressure of the patient minus the target blood pressure of 140.

Antiplatelet/anticoagulation treatment: the hazard ratio of the effect of dual antiplatelet therapy versus only aspirin (or equivalent) is 0.78.[15] The effect of adding of low dose DOAC to aspirin therapy has a hazard ratio of 0.76.[16]

Canakinumab: the effect of canakinumab has a hazard ratio of 0.85 in patients with a hsCRP>2 mg/L.[17]

Combined individualized treatment effects: the hazard ratios of each separate treatment are multiplied to calculate the relative individualized risk reduction for the combination of treatments. This combined hazard ratio was then applied to the 1-year estimates of the

cardiovascular event model (i.e., the log of the hazard ratio is added to the linear predictor (A) part of the cardiovascular event model, Supplemental Table 3). The effect of treatment was calculated as the difference in life expectancy with and without the additional therapy. The estimation of life-expectancy without recurrent cardiovascular events for an individual person is explained in the main text (Methods).

Supplemental Results

External performance of the REACH and SMART risk models

Calibration of both REACH scores in SMART is shown in Supplemental Figure 1A. Discrimination showed C-statistics of 0.66 (95% CI 0.64-0.68) for the recurrent event score and 0.76 (95% CI 0.74-0.78) for the cardiovascular death score. The SMART score showed clear miscalibration in both REACH populations (Supplemental Figure 1B). After recalibration, the SMART score still showed miscalibration in REACH North America. In Western Europe, overestimation was seen in very high-risk patients (>20% 2-year risk). C-statistics for recurrent cardiovascular events were 0.64 (95% CI 0.63-0.65) in REACH North America and 0.65 (95% CI 0.63-0.66) in REACH Western Europe.

Table S1. **Inclusion and exclusion criteria of the REACH and SMART cohorts and definitions of history of cardiovascular disease and the outcome major cardiovascular events**

A. In- and exclusion criteria of the study populations

	SMART[3]	**REACH**[2]
Inclusion criteria	Patients aged 18-79 years with documented CAD, CVD, or PAD	Subjects aged ≥45 years with documented CAD, CVD or PAD
Exclusion criteria	-Terminal malignancy -Not independent in daily activities (Rankin scale >3) -Not sufficiently fluent in Dutch	-Already participating in a clinical trial -Expected to have difficulties returning for follow-up visits

B. Definitions of risk factors and manifest cardiovascular disease at enrolment

	SMART[3]	**REACH**[2]
Age	Years, as reported by doctor/patient	Years, as reported by doctor/patient
Sex	Male/female, as reported by doctor/patient	Male/female, as reported by doctor/patient
Current smoking	Current vs other (patient's response to question "do you smoke?")	Current vs other; ≥5 cigarettes per day on average within the last month before entry into the Registry
Diabetes mellitus	Either referral diagnosis of DM, self-reported DM, a known history of DM at the time of enrolment or a fasting plasma glucose ≥7 mmol/l	Any history of DM or current DM (diagnosed by at least 2 fasting blood glucose measures >7 mmol/L or >126 mg/dL), treated or not
Systolic blood pressure	mmHg. Measured directly after informed consent mean of two office blood pressure measurements is taken as the blood pressure.	mmHg. Systolic and diastolic blood pressures measured in a seated position after at least 5 minutes of rest and at the date the subject is seen.
Total cholesterol	Mmol/l. Measured in fasting venous sample using commercial enzymatic dry chemistry kits (Johnson and Johnson).	Mg/dL. Transcribed from the clinical record, lipids were not measured in a standard manner in the registry participants.
Creatinine	Creatinine measured using commercial enzymatic dry chemistry kit (Johnson and Johnson)	Serum creatinine measured at baseline.
Atrial fibrillation	Atrial fibrillation confirmed by inclusion ECG	Paroxysmal, persistent, or permanent atrial fibrillation
Congestive heart failure	Not documented	The presence of signs and symptoms of either right or left ventricular failure or both and the diagnosis should be confirmed by noninvasive or hemodynamic measurements.

History of CAD	Angina pectoris, myocardial infarction or coronary revascularisation (coronary bypass surgery or coronary angioplasty)	Stable angina with documented coronary artery disease, history of unstable angina with documented coronary artery disease, history of percutaneous coronary intervention, history of coronary artery bypass graft surgery, or previous myocardial infarction
History of CVD	TIA, cerebral infarction, amaurosis fugax or retinal infarction, or a history of carotid surgery	Hospital or neurologist report with the diagnosis of TIA or ischemic stroke
History of PAD	Symptomatic and documented obstruction of distal arteries of the leg or surgery of the leg (percutaneous transluminal angioplasty, bypass or amputation)	One or both of the following criteria: current intermittent claudication with ankle-brachial index of <0.9 or a history of intermittent claudication together with a previous and related intervention such as angioplasty, stenting, atherectomy, peripheral arterial bypass graft, or other vascular intervention, including amputation

C. Definitions of outcome major cardiovascular events

	SMART[3]	**REACH**[2]
Outcome evaluation	During follow-up, patients were asked biannually to complete a standardized questionnaire on hospital admissions and outpatient clinic visits. If a vascular event was reported, hospital discharge letters and results of laboratory and radiology examinations were collected. Death was reported by relatives of the participant, the general practitioner or the treating specialist. All possible events were independently evaluated by three members of the endpoint committee, comprising physicians from different clinical departments.	Participants were followed for the development of a subsequent cardiovascular event and were invited to a baseline clinical examination and follow-up evaluation at 12, 24, 36 and 48 months after the baseline. At the follow-up visits, data were collected regarding interim development of clinical outcomes according to self-report and medical records available, and confirmed by local physician; 10% were monitored for source documentation and accuracy. The clinical events were not adjudicated.

Myocardial infarction	Fatal and non-fatal myocardial infarction, characterized by at least two of the following criteria: 1. Chest pain for at least 20 minutes not disappearing after administration of nitrates 2. ST-elevation >1 mm in two following leads or a left bundle branch block on the ECG * 3. CK elevation of at least two times the normal value of CK and an MB-fraction >5% of the total CK	Self-report, hospital documentation and confirmed by local physician
Stroke	Relevant clinical features which have caused an increase in handicap of at least one grade on the modified Rankin scale, accompanied by a fresh infarct on a repeat CT scan.	The diagnosis of stroke was based on a hospital or neurologist report with diagnosis of ischemic stroke.
Cardiovascular death	-Sudden death: unexpected cardiac death occurring within 1 hour after onset of symptoms or within 24 hours given convincing circumstantial evidence -Death from ischemic stroke -Death from congestive heart failure -Death from myocardial infarction -Death from rupture of abdominal aortic aneurysm -Vascular death from other cause, i.e. sepsis following stent placement	-Fatal stroke (within 28 days) -Fatal myocardial infarction (within 28 days) -Other cardiovascular death: other death of cardiac origin; pulmonary embolism; any sudden death including unobserved, and unexpected death (e.g., death while sleeping) unless proven otherwise by autopsy, death following a vascular operation, vascular procedure, or amputation; death attributed to heart failure; death following a visceral or limb infarction; and any other death that could not be definitely attributed to a nonvascular cause.

Table S2. **Age-specific baseline survivals for the SMART-REACH models**

Age	1-year survival free of stroke or MI*	1-year survival for non-cardiovascular mortality**
45	1.0000	1.0000
46	0.8539	0.9855
47	0.8420	1.0000
48	0.9088	0.9950
49	0.9172	1.0000
50	0.8464	1.0000
51	0.7297	0.9949
52	0.8081	0.9958
53	0.8980	1.0000
54	0.8155	0.9896
55	0.7609	0.9966
56	0.8113	0.9935
57	0.8173	0.9842
58	0.7939	0.9869
59	0.8382	0.9935
60	0.8333	0.9938
61	0.8257	0.9934
62	0.8000	0.9734
63	0.7930	0.9683
64	0.7962	0.9768
65	0.7807	0.9725
66	0.7731	0.9724
67	0.8118	0.9586
68	0.7325	0.9683
69	0.7671	0.9720
70	0.7236	0.9539
71	0.6690	0.9439
72	0.7173	0.9469
73	0.6978	0.9299
74	0.6074	0.9369
75	0.6880	0.9537
76	0.6473	0.9172
77	0.7034	0.9018
78	0.6904	0.9280
79	0.6507	0.8622
80	0.5946	0.8688
81	0.5328	0.8381
82	0.4954	0.8647
83	0.5376	0.8478
84	0.4403	0.8125
85	0.5043	0.7855
86	0.5509	0.7284
87	0.5480	0.7685
88	0.3889	0.7197
89	0.3048	0.6469

**Based on the cause-specific cumulative incidence model for cardiovascular disease*

***Based on the cause-specific cumulative incidence model for non- cardiovascular mortality*

Table S3. **SMART-REACH model formulas**

Cardiovascular model

1-year survival = (age-specific 1-yr baseline survival[¥])^exp(A)

A = 0.0720 (if male) + 0.4309 (if current smoker) + 0.4357 (if diabetes mellitus) – 0.0281* systolic blood pressure (in mmHg) + 0.0001* *squared* systolic blood pressure (in mmHg) – 0.3671*total cholesterol (in mmol/L) + 0.0356**squared* total cholesterol (in mmol/L) + 0.0061*creatinine (in umol/L) + 0.3176 (if two locations of cardiovascular disease)[§] + 0.2896 (if three locations of cardiovascular disease)[§] + 0.2143 (if history of atrial fibrillation) + 0.4447 (if history of congestive heart failure)

Non-cardiovascular mortality model

1-year survival = (age-specific 1-yr baseline survival[¥])^exp(B)

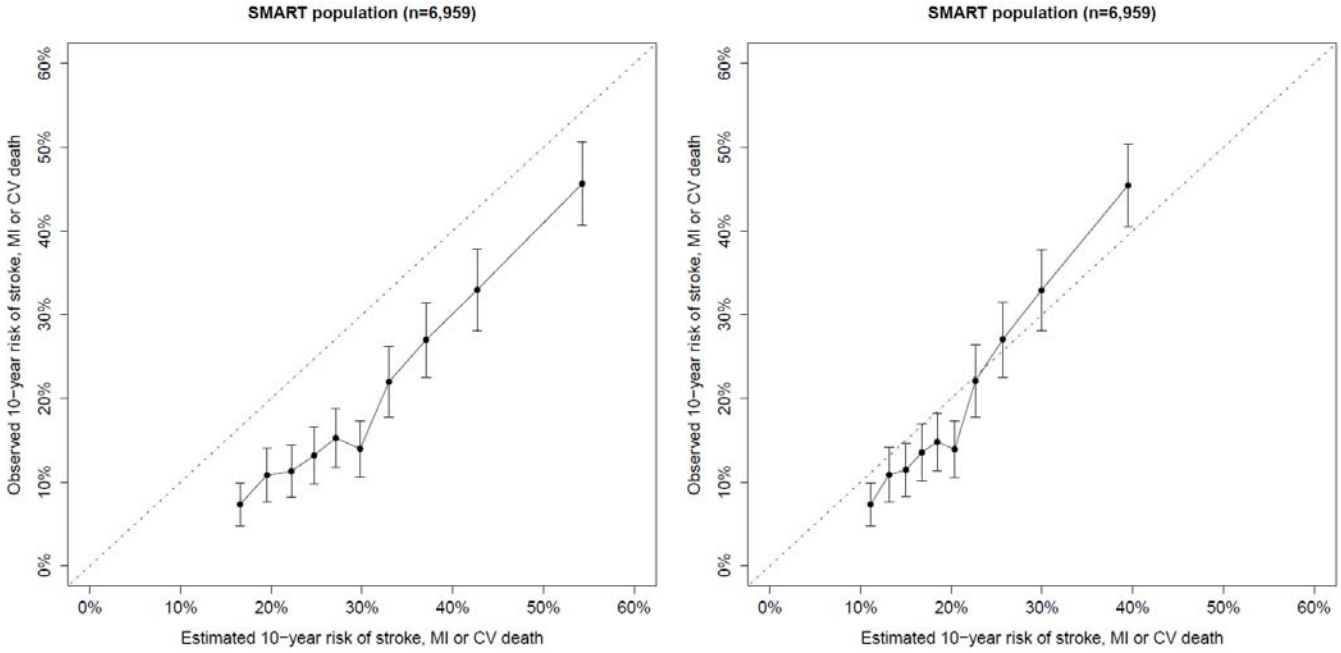
B = 0.5986 (if male) + 4.2538 (if current smoker) – 0.0486*age (if current smoker) + 0.4065 (if diabetes mellitus) – 0.0074*systolic blood pressure (in mmHg) - 0.0030*total cholesterol (in mmol/L) - 0.0189*creatinine (in umol/L) + 0.0001**squared* creatinine (in umol/L) + 0.1442 (if two locations of cardiovascular disease)[§] + 0.5694 (if three locations of cardiovascular disease)[§] + 0.3213 (if history of atrial fibrillation) + 0.2061 (if history of congestive heart failure)

[¥]*Age-specific baseline survivals are shown in Supplemental Table S2 for both models*

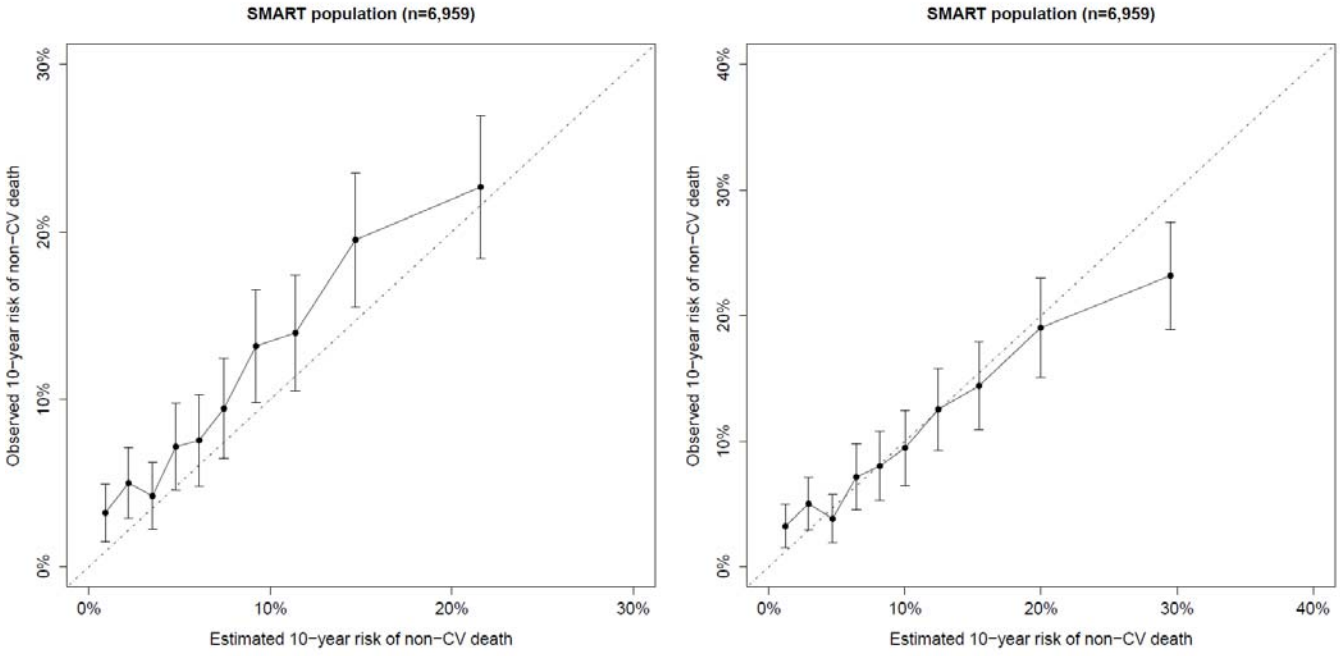
[§] *The coefficients for number of locations of cardiovascular disease (CAD, CVD, PAD) should not be added up. So, if the patient has two locations of cardiovascular disease, add 0.3176 to A and 0.1442 to B; if the patient has three locations of cardiovascular disease, add 0.2896 to A and 0.5694 to B.*

For patients similar to the Dutch (SMART) population: add –0.4246 to A and 0.1232 to B. For North American patients or patients similar to the North American REACH population: add 0.1552 to A and 0.4134 to B.

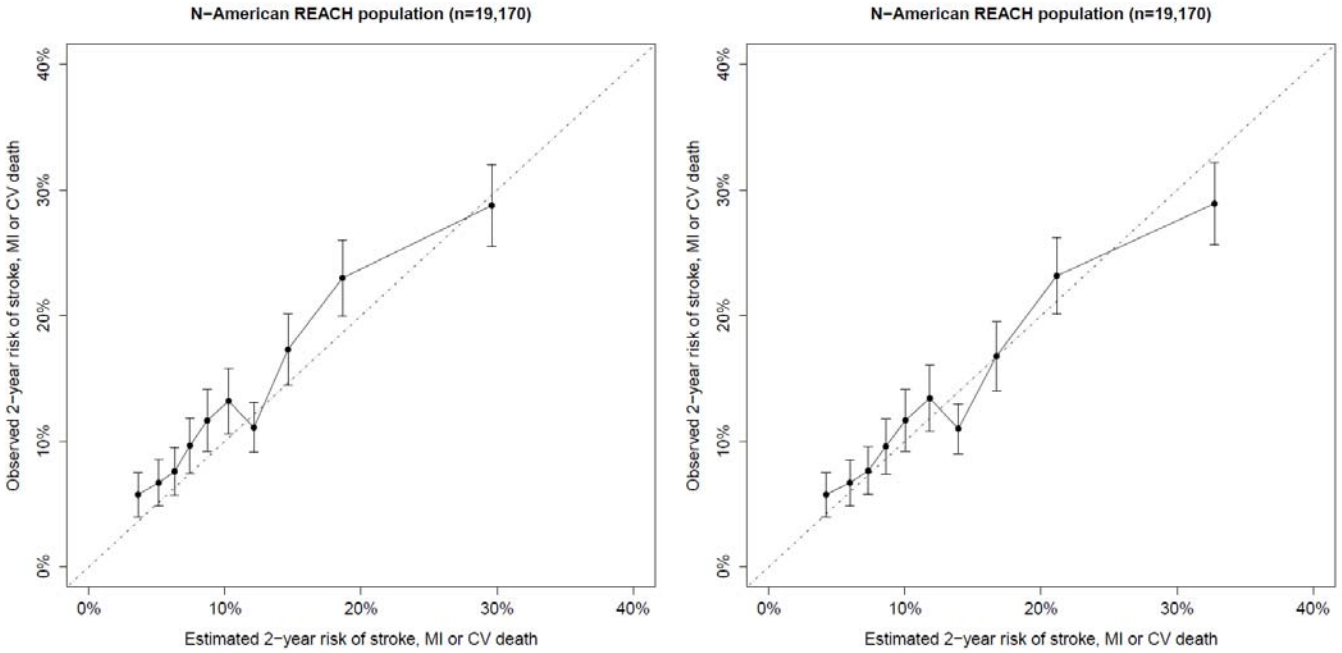
Figure S1. **External calibration of the SMART-REACH cardiovascular risk and non-cardiovascular death models**



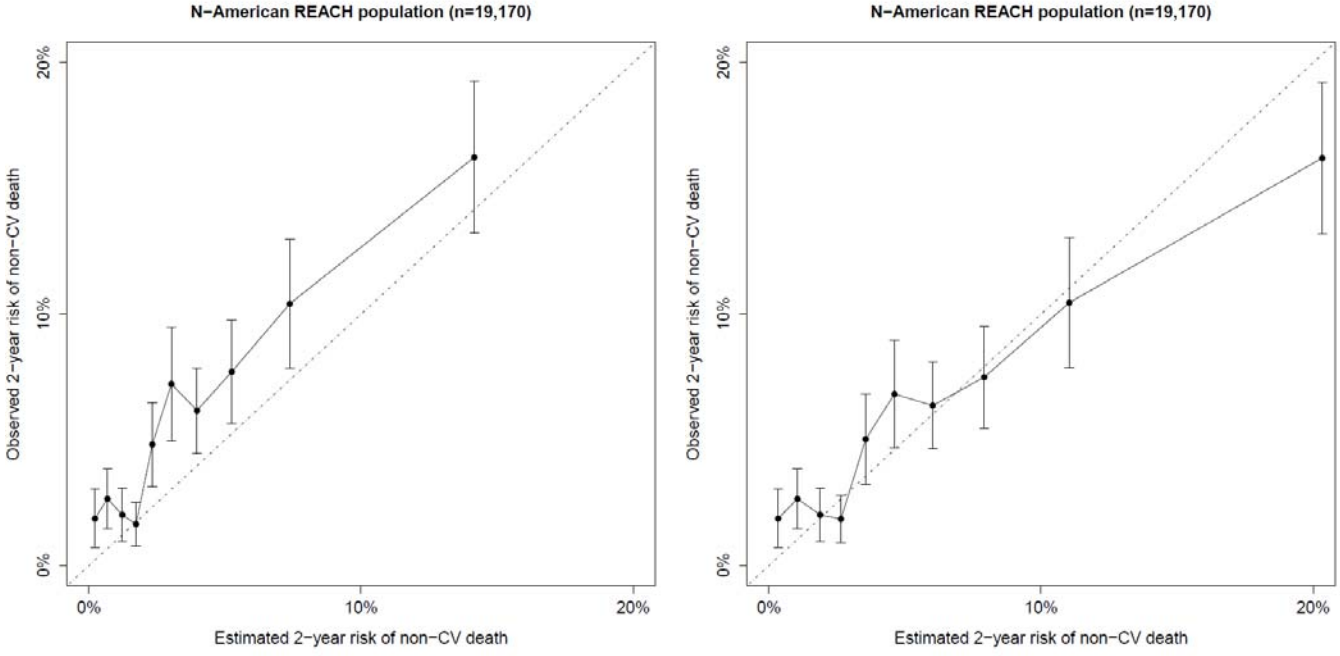
A. Estimated versus observed 10-year cardiovascular risk in the SMART population (left, E/O ratio 1.53) and after recalibration adjusting for the E/O ratio (right)



B. Estimated versus observed 10-year risk of non-cardiovascular death in the SMART population (left, E/O ratio 0.88) and after recalibration adjusting for the E/O ratio (right)

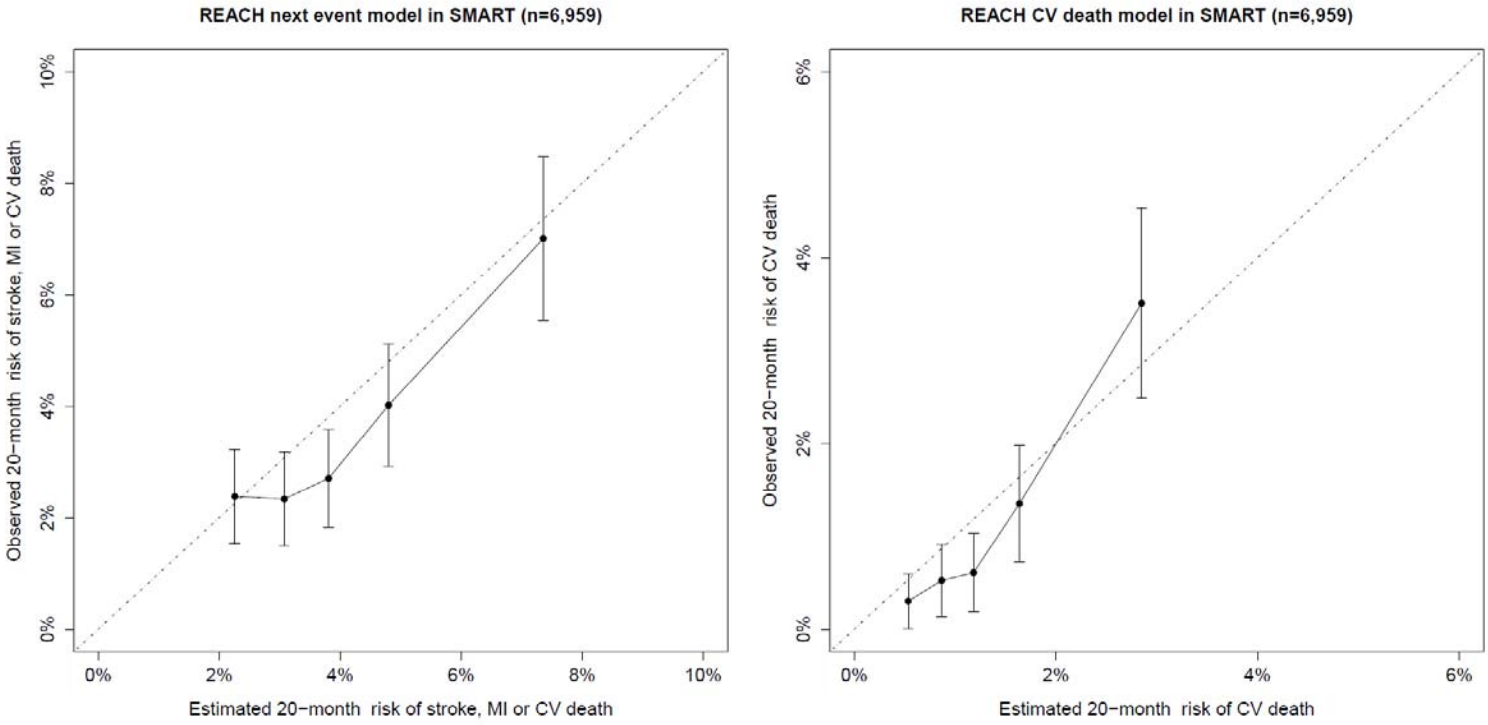


C. Estimated versus observed 2-year cardiovascular risk in the North American REACH population (left, E/O ratio 0.86) and after recalibration adjusting for the E/O ratio (right)



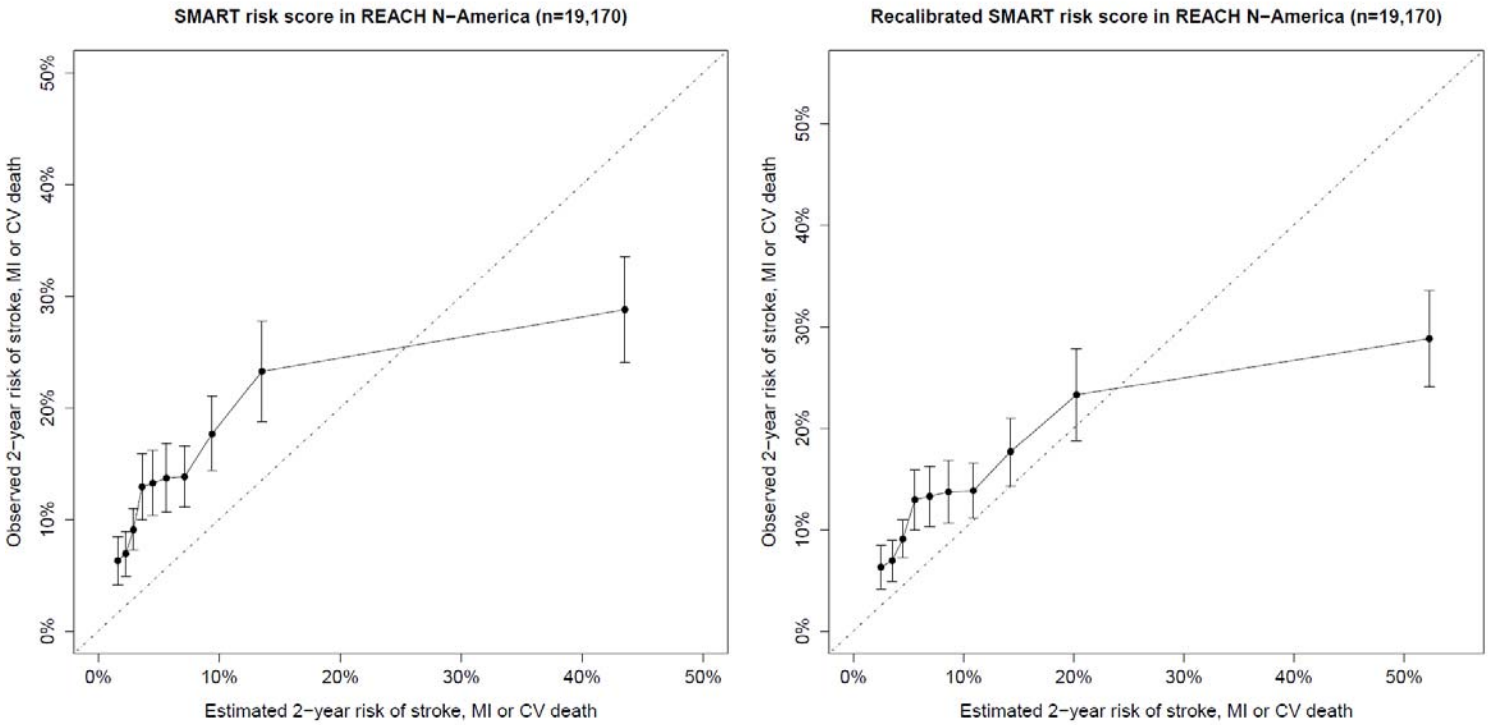
D. Estimated versus observed 2-year risk of non-cardiovascular death in the North American REACH population (left, E/O ratio 0.66) and after recalibration adjusting for the E/O ratio (right)

Figure S2A. **Calibration of the REACH risk models in SMART**

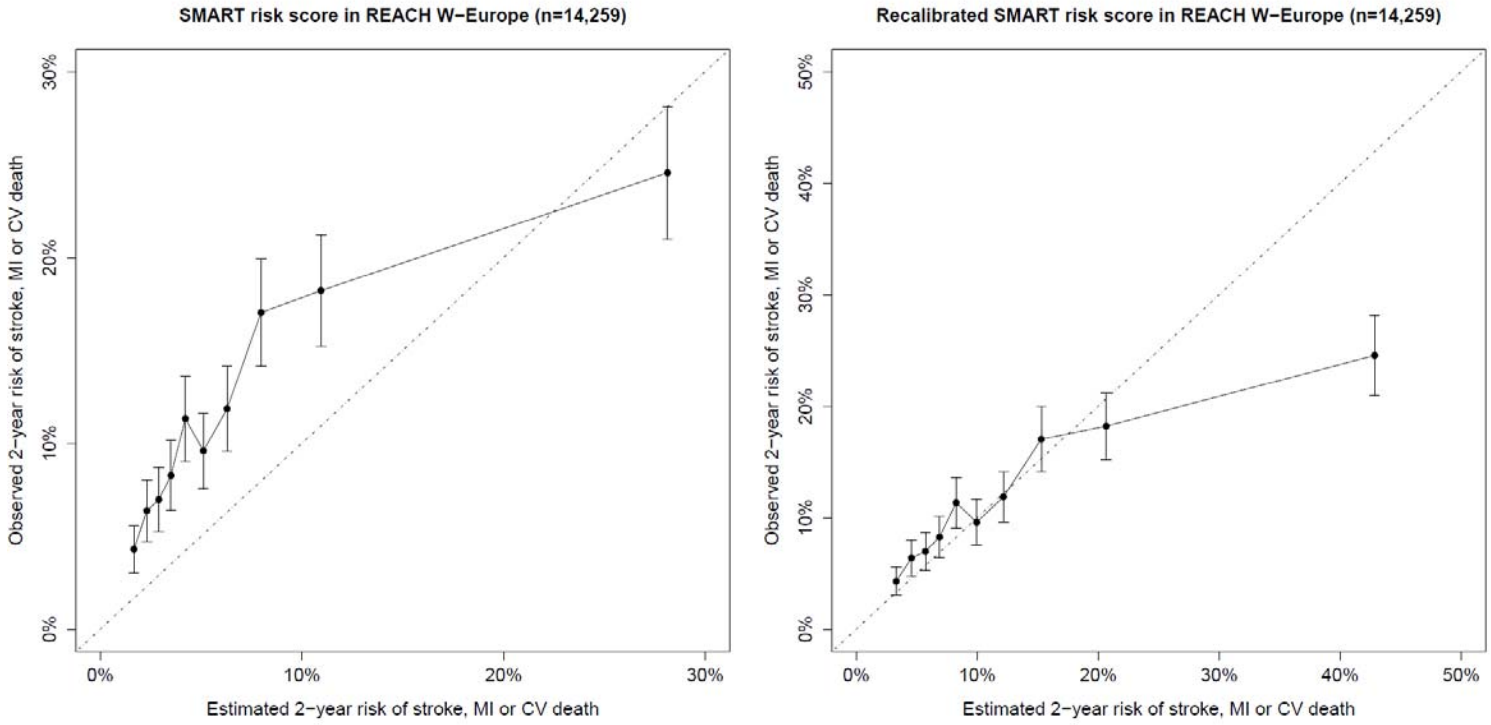


Calibration of the REACH recurrent event model (left) and REACH cardiovascular death model (right) in the SMART population

Figure S 2B. **Calibration of the SMART risk score in the REACH cohort**



A. Calibration of the SMART risk score in REACH North America before (left) and after (right) recalibration for the baseline survival (0.855 instead of 0.962) and mean linear predictor (1.142 instead of 2.099)



B. Calibration of the SMART risk score in REACH Western Europe before (left) and after (right) recalibration for the baseline survival (0.882 instead of 0.962) and mean linear predictor (1.611 instead of 2.099)

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