

Estimated Life Expectancy Without Recurrent Cardiovascular Events in Patients With Vascular Disease: The SMART-REACH Model

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Background—In patients with vascular disease, risk models may support decision making on novel risk reducing interventions, such as proprotein convertase subtilisin/kexin type 9 inhibitors or anti-inflammatory agents. We developed and validated an innovative model to estimate life expectancy without recurrent cardiovascular events for individuals with coronary, cerebrovascular, and/or peripheral artery disease that enables estimation of preventive treatment effect in lifetime gained.

Methods and Results—Study participants originated from prospective cohort studies: the SMART (Secondary Manifestations of Arterial Disease) cohort and REACH (Reduction of Atherothrombosis for Continued Health) cohorts of 14 259 (REACH Western Europe), 19 170 (REACH North America) and 6959 (SMART, The Netherlands) patients with cardiovascular disease. The SMART-REACH model to estimate life expectancy without recurrent events was developed in REACH Western Europe as a Fine and Gray competing risk model incorporating cardiovascular risk factors. Validation was performed in REACH North America and SMART. Outcomes were (1) cardiovascular events (myocardial infarction, stroke, cardiovascular death) and (2) noncardiovascular death. Predictors were sex, smoking, diabetes mellitus, systolic blood pressure, total cholesterol, creatinine, number of cardiovascular disease locations, atrial fibrillation, and heart failure. Calibration plots showed high agreement between estimated and observed prognosis in SMART and REACH North America. C-statistics were 0.68 (95% confidence interval, 0.67–0.70) in SMART and 0.67 (95% confidence interval, 0.66–0.68) in REACH North America. Performance of the SMART-REACH model was better compared with existing risk scores and adds the possibility of estimating lifetime gained by novel therapies.

Conclusions—The externally validated SMART-REACH model could be used for estimation of anticipated improvements in life expectancy without recurrent cardiovascular events in individual patients with cardiovascular disease in Western Europe and North America. (*J Am Heart Assoc.* 2018;7:e009217. DOI: 10.1161/JAHA.118.009217.)

Key Words: life expectancy • prognosis • risk stratification • secondary prevention • treatment effect

Patients with a clinical manifestation of cardiovascular disease show substantial variation in cardiovascular prognosis.¹ Similar to the primary prevention setting, decisions on initiation or intensification of preventive treatment should be based on anticipated clinical benefit derived from prediction models, rather than based on the level of individual cardiovascular risk factors. In particular with the emergence

of novel therapeutic options such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, novel anticoagulants, or anti-inflammatory agents, tools to predict recurrent cardiovascular events are needed.^{2,3} Recently, 2 risk scores have been developed for the prediction of recurrent cardiovascular events based on the observational REACH (Reduction of Atherothrombosis for Continued Health) and SMART

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Accompanying Data S1 through S3, Tables S1 through S3 and Figures S1 through S3 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.009217>

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Received April 26, 2018; accepted June 18, 2018.

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Clinical Perspective

What Is New?

- In the present study we developed and validated the innovative SMART-REACH (Secondary Manifestations of Arterial Disease-Reduction of Atherothrombosis for Continued Health) model to estimate life expectancy without recurrent cardiovascular events for individuals with coronary, cerebrovascular, and/or peripheral artery disease that enables estimation of preventive treatment effect in terms of lifetime gained.
- The SMART-REACH model was developed and validated in the prospective SMART and REACH cohorts of 14 259 (REACH Western Europe), 19 170 (REACH North America) and 6959 (SMART, The Netherlands) patients with cardiovascular disease.

What Are the Clinical Implications?

- The externally validated SMART-REACH lifetime model can estimate both 10-year cardiovascular event risk and anticipated improvements in life expectancy without recurrent cardiovascular events in individual patients with cardiovascular disease in Western Europe and North America, for example using the calculator on www.U-Prevent.com.
- Clinicians should be aware of the discrepancy in anticipated benefit of treatment using 10-year versus life expectancy without recurrent cardiovascular events, as these may result in different clinical decisions about the appropriate preventive strategy for the individual with cardiovascular disease.

(Secondary Manifestations of Arterial Disease) cohort studies.⁴⁻⁹ These scores estimate the 20-month (REACH) and 10-year (SMART) risk of recurrent major cardiovascular events in patients with established cardiovascular disease. The external validity of these scores needs to be established before widespread use is considered.¹

The ability to estimate risk in patients with cardiovascular disease is a first step toward personalized secondary prevention of cardiovascular events.¹⁰ In addition, recent studies have shown that estimating cardiovascular prognosis from a lifetime perspective may have some advantages over 10-year risk estimation, including a potentially better selection of patients for preventive treatment by accounting for remaining life expectancy and competing events.¹¹⁻¹⁷ For example, the QRISK lifetime model in the primary prevention setting identifies patients with an unfavorable prognosis at a much younger age than the traditional 10-year risk approach.¹¹ In addition, recent data demonstrate that treatment benefit estimated in terms of gain in life expectancy was highest in younger patients with otherwise high risk factor levels and was limited in older patients with relatively low risk factor levels in whom remaining survival may be inadequate for meaningful cardiovascular risk reduction to occur.¹⁷⁻¹⁹

In this article, we aimed to develop, validate, and evaluate the innovative SMART-REACH model for life expectancy without recurrent cardiovascular events for individual patients with clinically manifest coronary, cerebrovascular, and/or peripheral artery disease in Western Europe and North America.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. Both the REACH and SMART data are property of the REACH and SMART study groups, respectively. The Methods, Results, and Supplemental sections provide a detailed description of the applied statistical methods and the formula of the REACH-SMART algorithm.

Study Populations

REACH and SMART are prospective cohort studies of patients with established cardiovascular disease or cardiovascular risk factors. Study details have been described elsewhere.^{6,7,20} In the present study, we included patients with stable clinical coronary artery disease, cerebrovascular disease and/or peripheral artery disease from both cohorts. From REACH, we used patient data from Western Europe (n=14 259) and North America (n=19 170). In the international, prospective REACH cohort, participants were enrolled between 2003 and 2004 from physician outpatient practices in several countries in Western Europe and North America. Participants were followed for a maximum of 4 years for the occurrence of cardiovascular events and mortality. Medical history, physical and laboratory measurements were collected with a standardized international case report form at baseline and then (bi)annually. Outcomes of patients were annually reported by the local investigator and not adjudicated.²⁰ From the ongoing prospective SMART cohort we used data from 6959 patients with a history of cardiovascular disease enrolled between 1996 and 2014 at the University Medical Center Utrecht, The Netherlands. At inclusion, all patients completed a questionnaire, underwent standardized physical examination and fasting blood samples were collected. Follow-up for cardiovascular events and mortality was performed every 6 months by sending letters to every participant and checking medical files. An outcome committee assessed whether outcomes occurred.⁷

Detailed definitions of risk factors at baseline, established cardiovascular disease and clinical outcomes are provided in Table S1. Both studies comply with the Declaration of Helsinki, both studies were approved by an institutional review committee and that the subjects gave informed consent.

The 20-month REACH score and the 10-year SMART risk score were developed in these REACH and SMART

populations respectively. The external validity of the SMART score in the REACH data and of the REACH score in the SMART data was evaluated and is shown in Data S1.

Development of the SMART-REACH Model for Estimating Life-Expectancy Without Recurrent Cardiovascular Events

We developed the SMART-REACH model in REACH Western Europe using statistical methods that were previously described in detail.^{17,21} In short, 2 Fine and Gray competing risk models (Data S2) were fitted for cause specific estimates of the cumulative incidence, 1 for recurrent cardiovascular events and 1 for noncardiovascular mortality. Age was used as the underlying time function (ie, left truncation).²⁰ This enables lifetime predictions across the age range from the youngest age at study entry to the highest age at study exit. Predictors were selected based on the original SMART and REACH scores.^{4,5} Because not all of these predictors were available in both the SMART and REACH cohorts, further selection was based on availability of the predictors in both data sets. This resulted in the following nine predictors that were used for both models: sex, current smoking (yes/no), diabetes mellitus (yes/no), systolic blood pressure (mm Hg), total cholesterol (mmol/L), creatinine ($\mu\text{mol/L}$), number of locations of cardiovascular disease (ie, coronary artery disease, cerebrovascular disease, and peripheral artery disease), history of atrial fibrillation (yes/no) and history of congestive heart failure (yes/no). Linearity of the relation between continuous predictors and the outcomes was tested with restricted cubic splines, and transformation was applied when this improved model fit on the basis of Akaike's Information Criterion. Continuous predictors were truncated at the 1st and 99th percentiles to limit the effect of outliers. The proportional hazards assumption was assessed by testing the correlations between scaled Schoenfeld residuals for the various predictors and age.

Missing data (<1% of variables in SMART, and in REACH 20% creatinine, 21% total cholesterol, 3% current smoking, 2% atrial fibrillation and heart failure, and <1% for other variables) were reduced by single imputation using predictive mean matching (aregImpute-algorithm in R, Hmisc-package).²² Analyses were conducted with R statistical software V.3.2.2 (www.r-project.org; packages mstate, survival, cmprsk, pec, rms, Hmisc).

Estimating Life-Expectancy Without Recurrent Cardiovascular Events for Individual Patients

Based on the newly developed SMART-REACH models, life expectancy without recurrent cardiovascular events was estimated for all individual patients in the pooled populations

(REACH Western Europe, SMART and REACH North America, $n=34\ 841$). Beginning at the starting age of each individual, the cumulative survival without recurrent cardiovascular events was estimated for each subsequent year. Therefore, the estimated survival at the beginning of each life-year was multiplied by the survival probability during that year. The survival probability was obtained by subtracting cardiovascular risk and noncardiovascular mortality risk from 1. This was repeated up to the maximum age of 90, as the number of observations beyond the age of 90 was limited in the study populations.¹⁷ Life expectancy without recurrent cardiovascular events of an individual person was defined as the median estimated survival, which is the age where the predicted individual survival curve equals 50%. In addition, the SMART-REACH model can be used to estimate 10-year cardiovascular risk, adjusted for noncardiovascular mortality, which is calculated as the cumulative cause-specific cardiovascular risk truncated at 10 years after the starting age.

To enable use of the SMART-REACH lifetime model in daily clinical practice, we developed a calculator that allows estimation of life expectancy without recurrent cardiovascular events for an individual as well as 10-year cardiovascular risk. Also, the calculator can be used to estimate potential gain in life expectancy by initiating additional therapy, including increasing the statin dose or adding ezetimibe or a PCSK9 inhibitor, anticoagulants, antihypertensives, or the novel inflammation-targeting Canakinumab.²³ The calculations and assumed hazard ratios on which the estimations in the calculator are based are explained in Data S3. Two individual patient examples are shown in the main manuscript.

Model Validation

External validity of the SMART-REACH model was tested in the SMART population at 10-year follow-up and in REACH North America at 2-year follow-up. Calibration (the agreement between predicted and observed events) was assessed for the total survival without recurrent cardiovascular events as well as for the cardiovascular model and the noncardiovascular death models separately. Discrimination was expressed with C-statistics based on the models' 1-year predictions.²⁴ We used 1-year predictions instead of solely the linear predictor to incorporate age in the estimation of discriminative power. To adjust for geographic differences in underlying event rates, the ratio between expected and observed events in the SMART and North American REACH populations was used to update the models to the population of interest. Continuous variables were truncated on the basis of the limits of these values in the Western European REACH development population. In SMART, no information was available on heart failure; therefore, heart failure was assumed to be absent for all SMART participants.

Results

Baseline characteristics of the study populations are shown in Table 1. Different age groups were well represented in the 3 cohorts. Risk factor distribution was similar across the 3 populations, although SMART included more current smokers (32% versus 16% and 13% in REACH Western Europe and North America, respectively), and in REACH more patients had diabetes mellitus: 33% (Western Europe) and 42% (North America) versus 18% in SMART. Loss of follow-up was 8% in REACH Western Europe, 6% in SMART, and 14% in REACH North America. In REACH Western Europe, a total of 1555 cardiovascular events (32% stroke, 20% myocardial infarction, 48% cardiovascular death) and 490 noncardiovascular deaths were observed during a median follow-up of 1.8 years (quartiles, 1.5–2.2). In SMART, 1077 cardiovascular events (25% stroke, 34% myocardial infarction, 41% cardiovascular death) and 554 noncardiovascular deaths occurred during 6.5 (quartiles, 3.4–9.9) years, and in REACH North America 1743 cardiovascular events (22% stroke, 26% myocardial infarction,

52% cardiovascular death) and 679 noncardiovascular deaths occurred during a median follow-up of 1.8 (quartiles, 1.5–1.8) years.

Development and Validation of the REACH-SMART Lifetime Model

Table 2 shows the coefficients and subdistribution hazard ratios of both the cardiovascular and noncardiovascular death models. The age-specific baseline survivals are presented in Table S2. Table S3 provides the calculation formulas of cause-specific survivals on which the SMART-REACH predictions were built. The proportional hazard assumption was met for the cardiovascular event model. In the noncardiovascular death model, nonproportionality was observed for current smoking, with a decreasing effect with increasing age. Therefore, an interaction between age and smoking status was included in this model. We included quadratic terms for systolic blood pressure and total cholesterol in the

Table 1. Baseline Characteristics of the REACH and SMART Populations

	REACH Western Europe (n=14 259)	SMART Cohort (n=6959)	REACH North America (n=19 170)
Age, y	68 (10)	60 (10)	70 (10)
<55 y	1481 (10)	2093 (30)	1658 (9)
55 to 65 y	3525 (25)	2382 (34)	4325 (23)
65 to 75 y	5509 (39)	2005 (29)	6413 (33)
≥75 y	3744 (26)	479 (7)	6774 (35)
Male sex	10 270 (72)	5098 (73)	11 861 (62)
Current smoking	2283 (16)	2195 (32)	2546 (13)
Systolic blood pressure, mm Hg	140 (18)	140 (21)	132 (18)
Diastolic blood pressure, mm Hg	80 (10)	81 (11)	75 (11)
Diabetes mellitus	4771 (33)	1227 (18)	8118 (42)
Cardiovascular history			
Congestive heart failure	2208 (15)	...	3692 (19)
Atrial fibrillation	1629 (11)	79 (1)	2605 (14)
Coronary artery disease	9860 (69)	4367 (63)	15 512 (81)
Cerebrovascular disease	4451 (31)	2124 (31)	5348 (28)
Peripheral artery disease	3343 (23)	1377 (20)	2329 (12)
Laboratory values			
Total cholesterol, mmol/L	5.1 (1.2)	4.8 (1.2)	4.6 (1.1)
Creatinine, μmol/L	93 (28)	88 (77)	100 (35)
Medication use			
Statin	10 176 (71)	4683 (67)	14 787 (77)
Acetylsalicylic acid	9529 (67)	4022 (68)	14 459 (75)
Antihypertensive medication	12 900 (90)	5183 (74)	17 933 (94)

All data are displayed as mean (standard deviation) or n (%). REACH indicates Reduction of Atherothrombosis for Continued Health; SMART, Secondary Manifestations of Arterial Disease.

Table 2. Coefficients and Subdistribution Hazard Ratios of the SMART-REACH Lifetime Models

	Coefficient	sHR (95% CI)	P Value
Model 1 (cardiovascular events)			
Male sex	0.0720	1.07 (0.96–1.21)	0.23
Current smoking	0.4309	1.54 (1.34–1.77)	<0.01
Diabetes mellitus	0.4357	1.55 (1.39–1.71)	<0.01
Systolic blood pressure (per 10 mm Hg)	−0.2814		0.07
Systolic blood pressure <i>squared</i> (per 10 mm Hg)	0.0010		0.07
Total cholesterol (mmol/L)	−0.3671		0.02
Total cholesterol <i>squared</i> (mmol/L)	0.0356		0.01
Creatinine (per 10 μmol/L)	0.0612	1.06 (1.05–1.08)	<0.01
Nr. of locations of cardiovascular disease: 1	ref	1 (ref)	
Nr. of locations of cardiovascular disease: 2	0.3176	1.37 (1.22–1.54)	<0.01
Nr. of locations of cardiovascular disease: 3	0.2896	1.34 (1.03–1.73)	0.03
Atrial fibrillation	0.2143	1.24 (1.08–1.42)	<0.01
Congestive heart failure	0.4447	1.56 (1.38–1.76)	<0.01
Model 2 (other causes of mortality)			
Male sex	0.5986	1.82 (1.45–2.29)	<0.01
Current smoking	4.2538		<0.01
Current smoking × age	−0.0486		<0.01
Diabetes mellitus	0.4065	1.50 (1.25–1.80)	<0.01
Systolic blood pressure (per 10 mm Hg)	−0.0741	0.93 (0.88–0.98)	<0.01
Total cholesterol (mmol/L)	−0.0030	1.00 (0.92–1.09)	0.95
Creatinine (per 10 μmol/L)	−0.1886		<0.01
Creatinine <i>squared</i> (per 10 μmol/L)	0.0008		<0.01
Nr. of location of cardiovascular disease: 1	ref	1 (ref)	
Nr. of location of cardiovascular disease: 2	0.1442	1.16 (0.93–1.44)	0.19
Nr. of location of cardiovascular disease: 3	0.5694	1.77 (1.17–2.68)	<0.01
Atrial fibrillation	0.3213	1.38 (1.09–1.75)	<0.01
Congestive heart failure	0.2061	1.23 (0.98–1.55)	0.08

Model 1: competing risk model for recurrent cardiovascular events. The model contains squared terms for systolic blood pressure and total cholesterol. For these terms only, coefficients were provided as the sHRs cannot be interpreted independently. Model 2: competing risk model for noncardiovascular mortality. The model contains squared terms for creatinine and an interaction between smoking and age. For these terms only, coefficients were provided as the sHRs cannot be interpreted independently. CI indicates confidence interval; REACH, Reduction of Atherothrombosis for Continued Health; sHR, subdistribution hazard ratio; SMART, Secondary Manifestations of Arterial Disease.

cardiovascular event model and for creatinine in the noncardiovascular death model.

Discrimination of the estimated survivals showed an overall C-statistic of 0.68 (95% confidence interval, 0.67–0.70) in SMART and 0.67 (95% confidence interval, 0.66–0.68) in REACH North America. The expected/observed ratios in SMART were 1.53 for cardiovascular risk and 0.88 for noncardiovascular death. In REACH North America, the expected/observed ratios were 0.86 for cardiovascular risk and 0.66 for noncardiovascular death.

The agreement between the estimated survival without recurrent cardiovascular events and the observed survival in both SMART and REACH North America is shown in Figure 1,

after correction for differences in geographic event rates (Figure S1, Table S3).

Estimated Life Expectancy Without Recurrent Cardiovascular Events Versus 10-Year Risk

The potential benefit of using life expectancy in addition to estimated 10-year absolute risk is illustrated by individual patient examples in Figure 2 as well as with the Supplemental Calculator, or the online calculator on www.U-Prevent.com, in which estimations can be made for real patient data. Figure 2 illustrates the use of estimated 10-year risk versus estimated life expectancy without recurrent cardiovascular events for

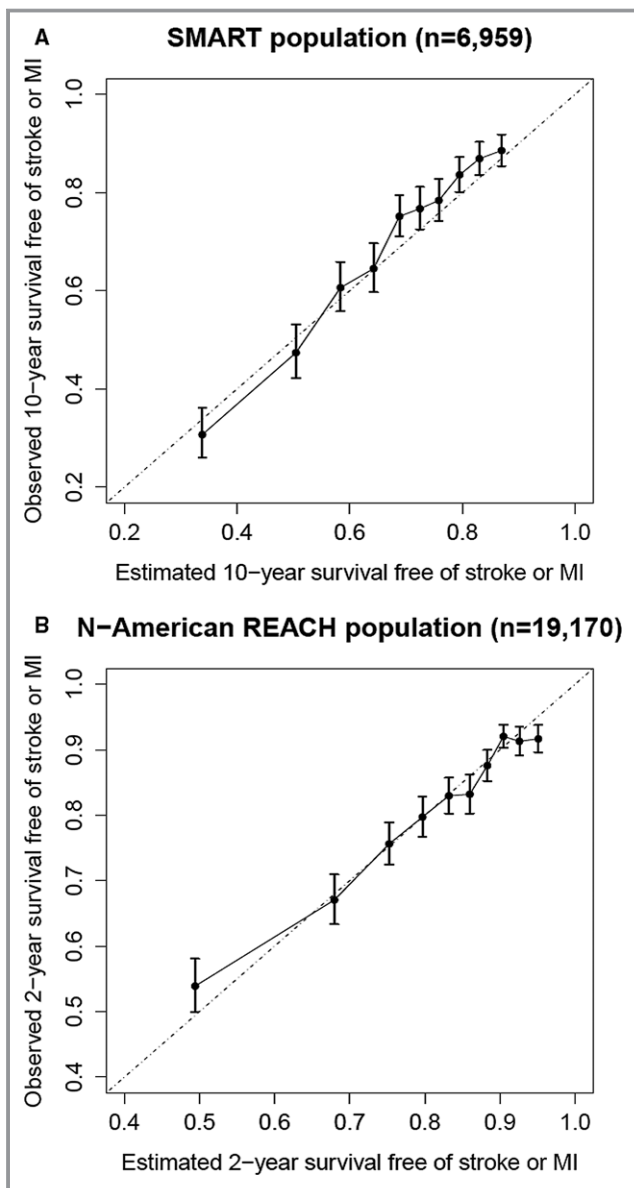


Figure 1. External calibration of estimated survival with the SMART-REACH model. A, Estimated vs observed 10-year survival without recurrent cardiovascular events in the SMART population (after correction for geographic differences in event rates). B, Estimated vs observed 2-year survival without recurrent cardiovascular events in North American REACH (after correction for geographic differences in event rates). MI indicates myocardial infarction; REACH, Reduction of Atherothrombosis for Continued Health; SMART, Secondary Manifestations of Arterial Disease.

making treatment decisions for 2 patient examples. In these examples, the potential benefit of intensifying lipid-lowering treatment by raising atorvastatin 10 to 80 mg is considered. Patient A has a lower estimated 10-year risk than patient B (26.7% versus 32.8%). As patient A is 55 years old, her 10-year risk is driven by her risk factors. Patient B's risk is mainly driven by his age of 75. Note that, due to her higher risk factor levels, patient A has a lower estimated life expectancy without

recurrent cardiovascular events than patient B (70.0 versus 84.3). Importantly, different prognostic estimates may result in different clinical decisions (Figure 2): based on their estimated 10-year risks and 10-year absolute risk reduction, intensification of secondary prevention is deemed more necessary for patient B than for patient A. However, from a lifetime perspective, patient A is likely to benefit more from intensifying preventive secondary prevention than patient B: when atorvastatin 10 mg would be raised to atorvastatin 80 mg, patient A has an estimated gain of 2.0 years versus 0.9 years for patient B. This is because patient A has several risk factors in combination with longer *remaining* life expectancy in which she can benefit from treatment compared with patient B. Similar estimations can be made for several therapeutic options such as novel anticoagulants, PCSK9-inhibitors, or anti-inflammatory agents (Supplemental Calculator; www.U-Prevent.com; Data S3).

Discussion

In this study, we demonstrate the development and external validation of the SMART-REACH model for estimating life expectancy without recurrent cardiovascular events in patients with established cardiovascular disease that is applicable to patients in Western Europe and North America. Using an online calculator as can be downloaded as supplemental material, and found on www.U-Prevent.com, the SMART-REACH model can be used to estimate an individual's potential gain in life expectancy without a recurrent cardiovascular event for several intended therapies.

Compared to risk prediction in the primary prevention setting, estimating prognosis in patients with established cardiovascular disease is challenged by some typical characteristics of the population of interest. Because of shared risk factors, patients with cardiovascular risk are also at increased risk of other causes of death.^{25,26} For example, smoking causes cardiovascular disease but also increases a patient's risk to die from cancer or chronic obstructive pulmonary disease. Risk scores that do not account for these competing risks, such as the original REACH and SMART scores,^{4,5} assume that the patient remains alive until a recurrent cardiovascular event occurs. In reality, a patient may also die from something else in the meantime. Failure to account for these competing events may result in overestimation of cardiovascular risk, particularly in high-risk patients, as was seen in the external performance of the SMART risk score (Figure S3).¹

In the SMART-REACH model for lifetime predictions, we applied methods accounting for competing events and using age as the time axis, which enabled us to make valid 10-year predictions in the external SMART population despite more limited follow-up in the REACH development set (median 1.8 years). As event rates vary between geographic

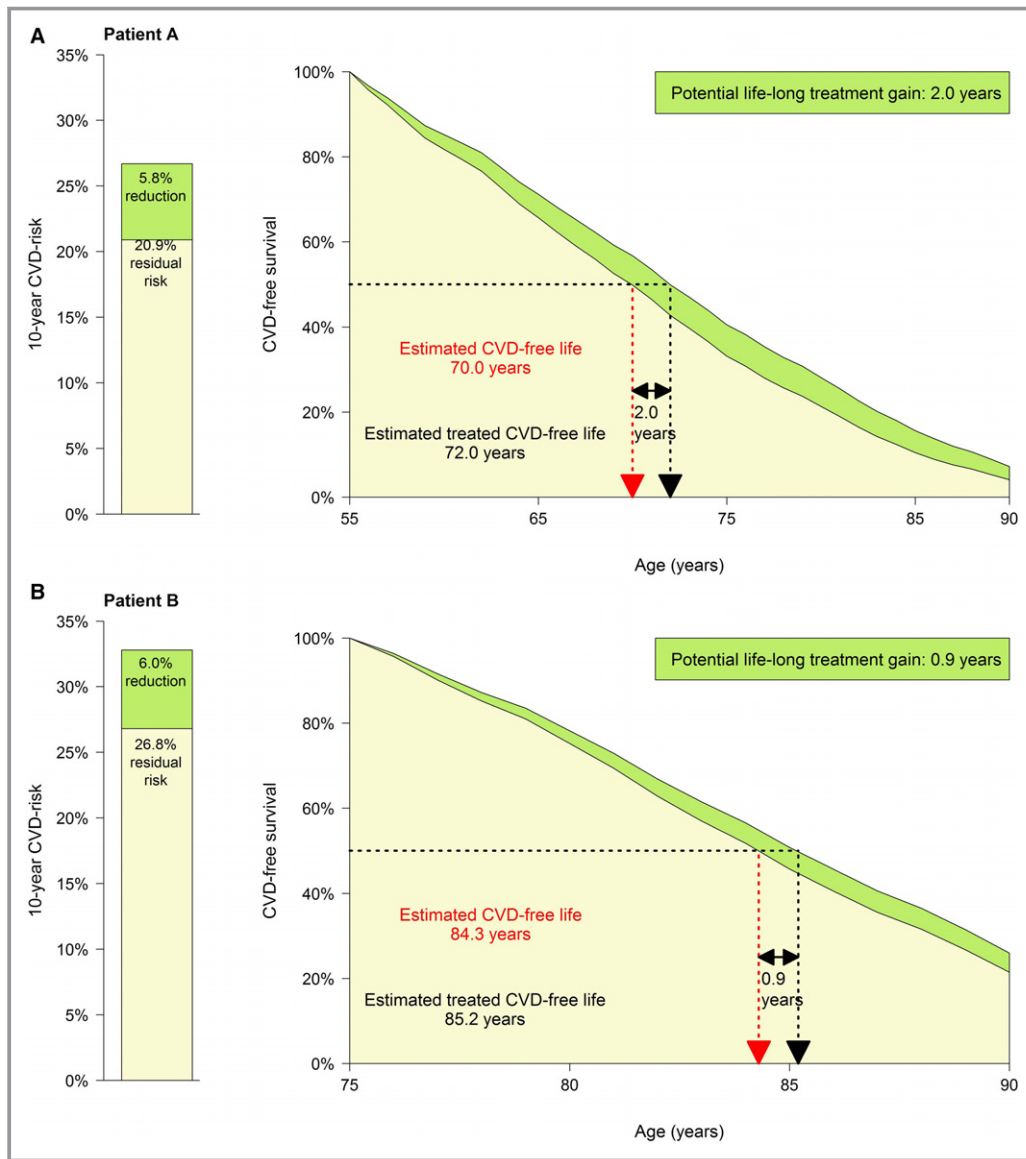


Figure 2. Patient examples. Patient A is a 55-year-old woman. She is a current smoker and has no diabetes mellitus. Her systolic blood pressure is 145 mm Hg. Her laboratory values are total cholesterol, 6.0 mmol/L (LDL-c 4.0 mmol/L); and creatinine, 70 μ mol/L. She has a history of 1 location of cardiovascular disease as well as atrial fibrillation, and she has no congestive heart failure. As lipid-lowering treatment, patient A currently takes atorvastatin 10 mg. The clinician considers raising the atorvastatin dose to 80 mg. Patient A wants to know what her expected benefit is from this change in therapy. The estimated 10-year risk for patient A is 26.7%. Her life expectancy free from recurrent cardiovascular disease is 70.0 years. When she would take atorvastatin 80 mg instead of 10 mg, this would reduce her 10-year risk to 20.9% (–5.8%, or 10-year NNT, 17). The change in therapy would increase her estimated cerebrovascular disease–free life expectancy with 2.0 years to 72.0. Patient B is a 75-year old male who does not smoke and has no diabetes mellitus. His systolic blood pressure is 140 mm Hg. His total cholesterol is 5.0 mmol/L and creatinine 80 μ mol/L. He has a history of 1 location of cardiovascular disease, no atrial fibrillation, and no congestive heart failure. As lipid-lowering treatment, patient B currently takes atorvastatin 10 mg. The clinician considers raising the atorvastatin dose to 80 mg. Patient B wants to know his expected benefit from this change in therapy. The estimated 10-year risk for patient B is 32.8%. His life expectancy free from recurrent cardiovascular disease is 84.3 years. When he would take atorvastatin 80 mg instead of 10 mg, this would reduce his 10-year risk to 26.8% (–6.0%, or 10-year NNT, 17). The change in therapy would increase his estimated cerebrovascular disease–free life expectancy with 0.9 years to 85.2. CVD indicates cardiovascular disease; NNT, number needed to treat.

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areas,^{27,28} recalibration to the population of interest is often necessary. This resulted in accurate estimates of the REACH-SMART model in the external validation sets. The discriminatory ability of the 3 models was moderate, which we considered acceptable, as this is in line with previous studies on models in patients with cardiovascular disease.^{4,5,29,30}

Both the REACH and SMART risk scores as well as the SMART-REACH lifetime model may be of value in daily clinical practice. The 20-month REACH scores and 10-year SMART risk score can be used to identify high-risk patients for intensification of short-term follow-up or for motivating patients for medication adherence and adopting a healthier lifestyle.³¹ Another important application of risk estimates is to select patients for clinical trials that typically need limited follow-up for occurrence of events of interest to improve study power and efficiency.²

For clinical decision making on treatment strategies for individuals, several studies have demonstrated the advantage of lifetime estimates over traditional risk estimation. In the primary prevention setting, lifetime estimates have been shown to identify patients most likely to benefit from treatment at a much earlier age.^{11,13,14,17,32–34} The present study demonstrates that this likely also applies to patients with established cardiovascular disease. Clinicians and guideline makers should be aware of the discrepancy between 10-year risk and estimated life expectancy without recurrent cardiovascular events, as these may result in different therapeutic decisions for the individual with cardiovascular disease (Figure 2). The SMART-REACH model, incorporated in an online calculator (eg, Supplemental Calculator and www.U-Prevent.com), may support clinical decision making on (novel) therapeutic options by estimating an individual's anticipated treatment benefit in terms of life expectancy without recurrent cardiovascular events. This may particularly be of value for novel effective but costly agents such as PCSK9 inhibitors, potent antithrombotics, and anti-inflammatory agents.^{23,35–37} Ideally, such treatment effect estimations are validated on the basis of the original trial data of such novel therapies.

As the SMART and REACH participants originate from daily clinical practice with limited selection criteria, the models presented in this study are broadly applicable to patients with a clinical manifestation of cardiovascular disease. When applying the SMART-REACH model in practice, the physician should consider whether the available literature applies to the individual patient in question. For example, for patients with moderate to severe heart failure, evidence on several preventive therapies is limited, as these patients are often excluded from trials such as was the case for the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial.³⁵ The presented SMART-REACH model can be applied to patients from Western Europe in general. For patients similar to the Dutch

SMART population or the North American REACH population, the geographic correction factors can be applied (Table S3).

Strengths of this study are the observational cohort design representing clinical practice, geographic variation, and the use of a lifetime model that accounts for competing events, which can directly be applied in clinical practice (www.U-Prevent.com). A limitation is that risk factors were measured at baseline and were thus considered to remain constant the rest of a patient's life. A second limitation is that lifetime estimates often go beyond the 10 years of follow-up in which we validated the SMART-REACH model. In a previous study, it was shown that lifetime predictions based on the applied methods are valid for survival up to 17 years.¹⁷ Nevertheless, this type of modeling does not account for survival up to the year of observation, which theoretically may result in biased estimates toward healthier survivors in very long-term predictions. Third, the limited discriminatory ability of the SMART-REACH model is comparable to previous risk scores for patients with clinically manifest vascular disease.^{4,5,29,30} Previous studies have shown that additional risk factors are unlikely to result in relevant improvement.^{4,38} This discriminatory ability may be due to the fact that selecting patients on the basis of a certain disease (vascular disease) results in a relatively homogenous population, in which discrimination becomes more difficult. Notably, the predictive ability of the SMART-REACH model is still a major improvement compared with the current criteria for identification of very high-risk patients with vascular disease, as recommended by the American College of Cardiology/American Heart Association guidelines (C-statistics, 0.53 and 0.54).³⁹ Finally, the present study focuses on the development and validation of the SMART-REACH score. Further studies may be undertaken to evaluate the actual potential clinical impact of the SMART-REACH model.

In conclusion, for patients with established cardiovascular disease, the risk of recurrent cardiovascular events can be estimated with the 20-month REACH scores, or the recalibrated 10-year SMART risk score. In addition, (anticipated improvements in) life-expectancy without recurrent cardiovascular events can be estimated with the externally validated REACH-SMART model for individuals with cardiovascular disease in North America and Western Europe. Clinicians should be aware of the discrepancy in anticipated benefit of treatment using 10-year cardiovascular event risk versus life expectancy without recurrent cardiovascular events, as these may result in different clinical decisions about the appropriate preventive strategy for the individual with cardiovascular disease.

Acknowledgments

The authors gratefully acknowledge the contribution of the SMART research nurses, R. van Petersen (data manager) and B. Dinther (vascular manager), and the members of the SMART Study Group:

P.A. Doevendans, Department of Cardiology; A. Algra; Graaf; D.E. Grobbee; G.E.H.M. Rutten, Julius Center for Health Sciences and Primary Care; Kappelle, Department of Neurology; T. Leiner, Department of Radiology; Borst, Department of Vascular Surgery; Visseren, Department of Vascular Medicine.

Sources of Funding

The SMART study was financially supported by a grant from the University Medical Center Utrecht, The Netherlands. The REACH Registry was supported by Sanofi-Aventis and Bristol-Myers Squibb and is endorsed by the World Heart Federation. For the present study, the above supporting sources had no involvement in study design, analysis, interpretation, or writing of the results or the decision to submit the report for publication.

Disclosures

Bhatt declares the following relationships—Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, and Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran Versus Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor-in-Chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor-in-Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (Secretary/Treasurer), and WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix,

Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, and The Medicines Company; Royalties: Elsevier (Editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); Site Coinvestigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), and Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, PLx Pharma, and Takeda. Kappelle received fees for consultation and presentations from Boehringer Ingelheim, Bayer Health Care, and Bristol Meyers Squibb. Ph Gabriel Steg discloses the following relationships: research grant from Merck, Sanofi, and Servier; speaking or consulting fees from Amarin, AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers-Squibb, CSL-Behring, Daiichi-Sankyo, GlaxoSmithKline, Janssen, Lilly, Merck Novartis, Pfizer, Regeneron, Sanofi, Servier, and The Medicines Company. The remaining authors have no disclosures to report.

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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/m²), 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. Therefore, 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

	SMART³	REACH²
<i>Inclusion criteria</i>	Patients aged 18-79 years with documented CAD, CVD, or PAD	Subjects aged ≥ 45 years with documented CAD, CVD or PAD
<i>Exclusion criteria</i>	-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

	SMART³	REACH²
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.

<i>History of CAD</i>	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
<i>History of CVD</i>	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
<i>History of PAD</i>	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

	SMART³	REACH²
<i>Outcome evaluation</i>	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.

<i>Myocardial infarction</i>	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
<i>Stroke</i>	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.
<i>Cardiovascular death</i>	-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

$$1\text{-year survival} = (\text{age-specific 1-yr baseline survival}^{\ddagger})^{\exp(A)}$$

$A = 0.0720$ (if male) + 0.4309 (if current smoker) + 0.4357 (if diabetes mellitus) – $0.0281 * \text{systolic blood pressure (in mmHg)}$ + $0.0001 * \text{squared systolic blood pressure (in mmHg)}$ – $0.3671 * \text{total cholesterol (in mmol/L)}$ + $0.0356 * \text{squared total cholesterol (in mmol/L)}$ + $0.0061 * \text{creatinine (in umol/L)}$ + 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

$$1\text{-year survival} = (\text{age-specific 1-yr baseline survival}^{\ddagger})^{\exp(B)}$$

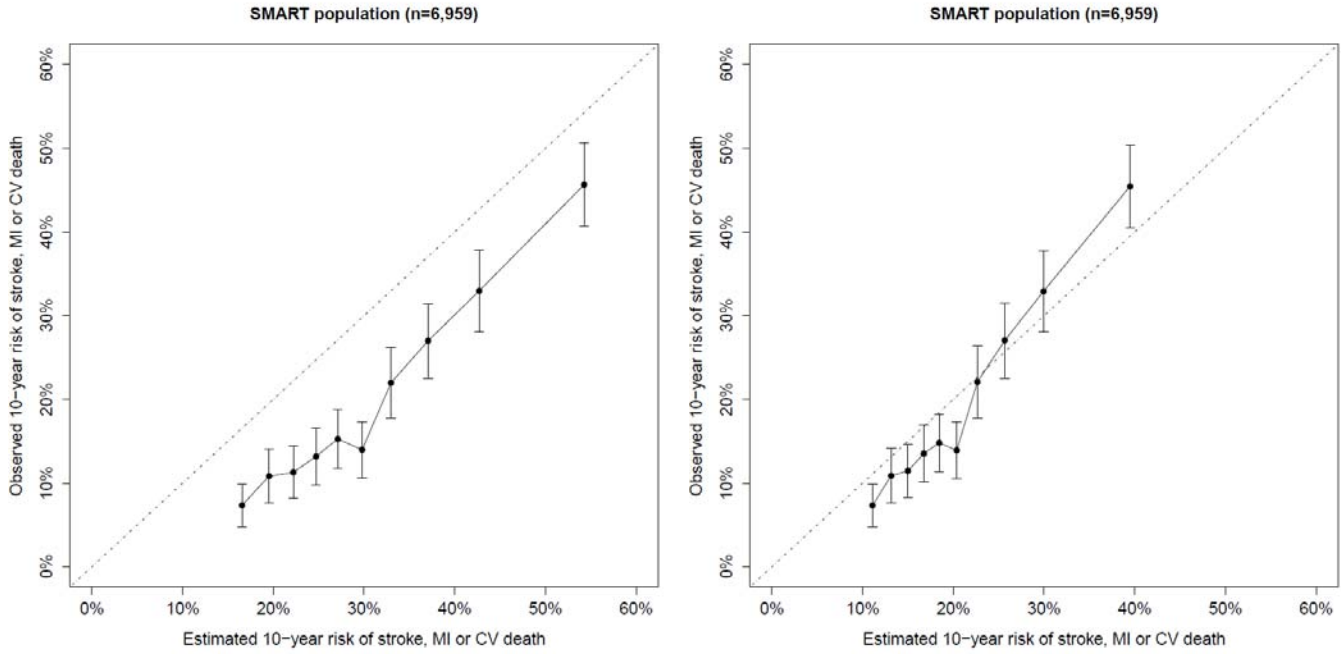
$B = 0.5986$ (if male) + 4.2538 (if current smoker) – $0.0486 * \text{age (if current smoker)}$ + 0.4065 (if diabetes mellitus) – $0.0074 * \text{systolic blood pressure (in mmHg)}$ – $0.0030 * \text{total cholesterol (in mmol/L)}$ – $0.0189 * \text{creatinine (in umol/L)}$ + $0.0001 * \text{squared creatinine (in umol/L)}$ + 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

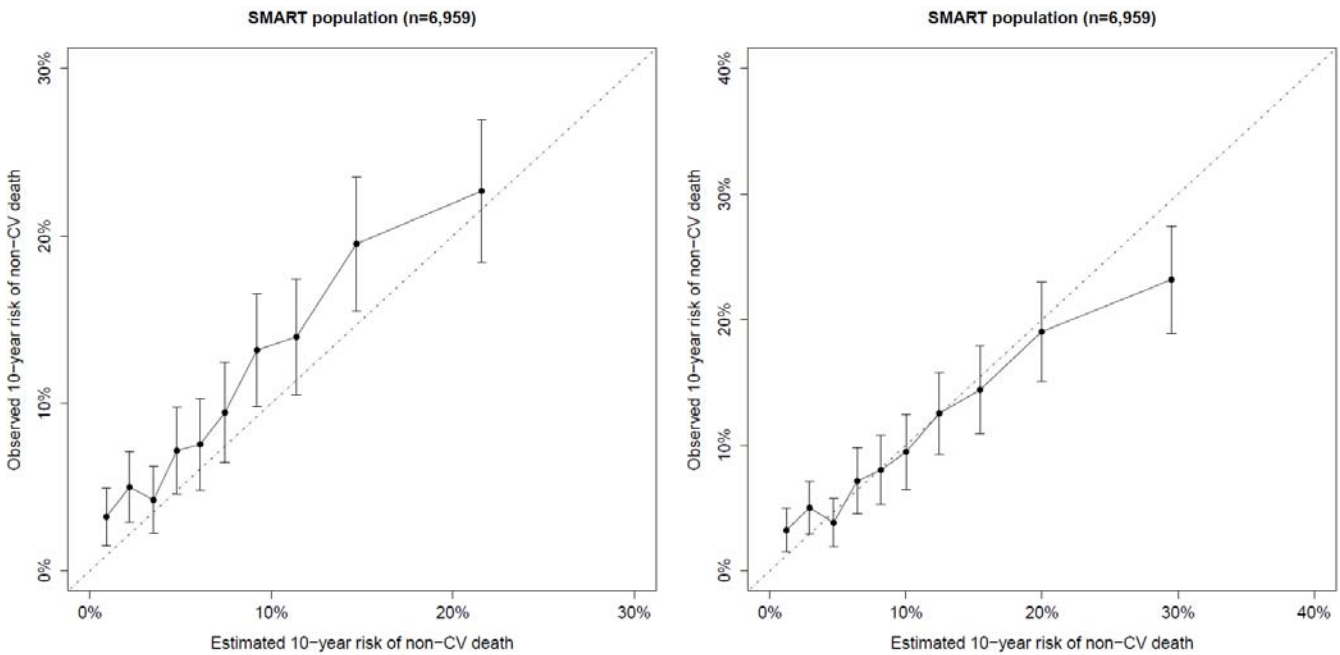
[§] The coefficients for number of locations of cardiovascular disease (CAD, CVD, PAD) should not be added up. So, if the patient has two locations of cardiovascular disease, add 0.3176 to A and 0.1442 to B; if the patient has three locations of cardiovascular disease, add 0.2896 to A and 0.5694 to B.

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.

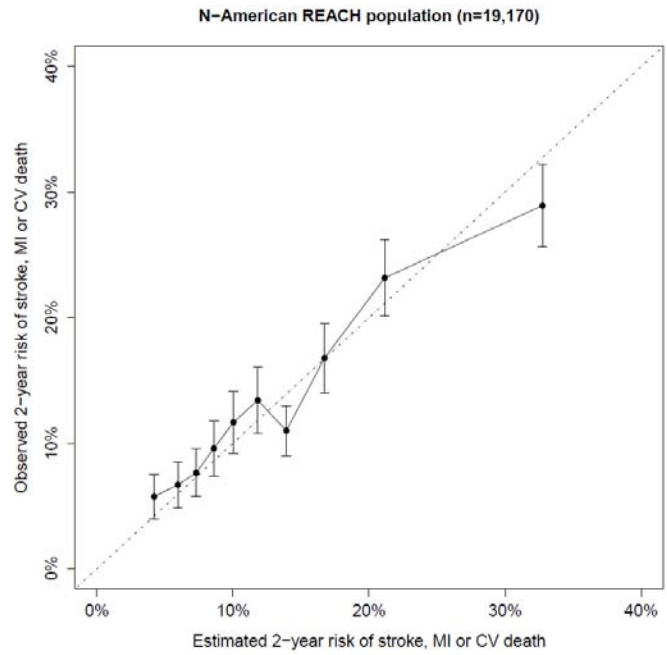
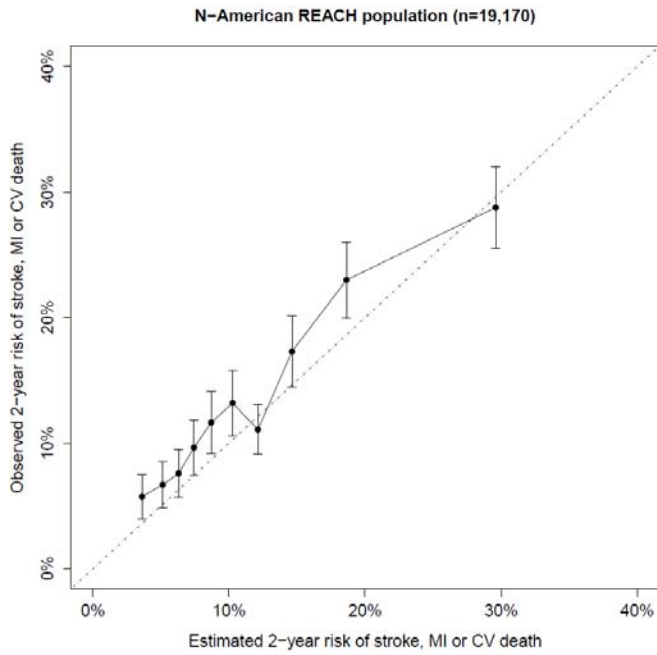
Figure S1. External calibration of the SMART-REACH cardiovascular risk and non-cardiovascular death models



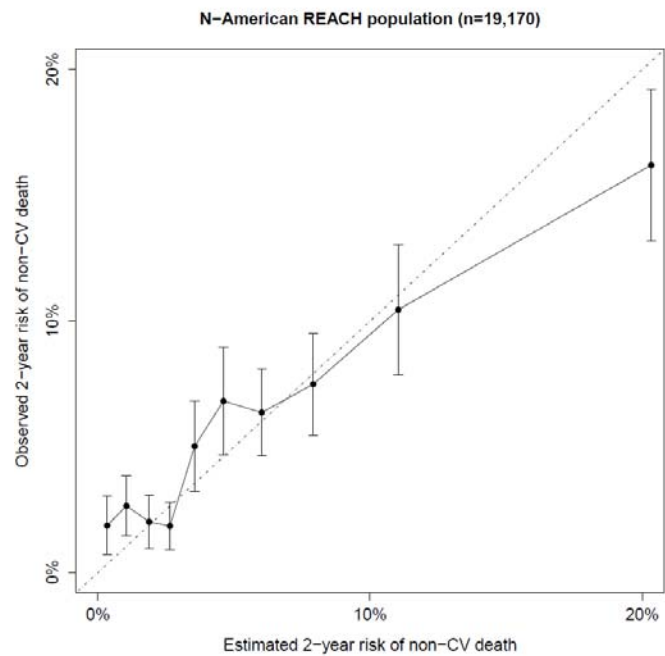
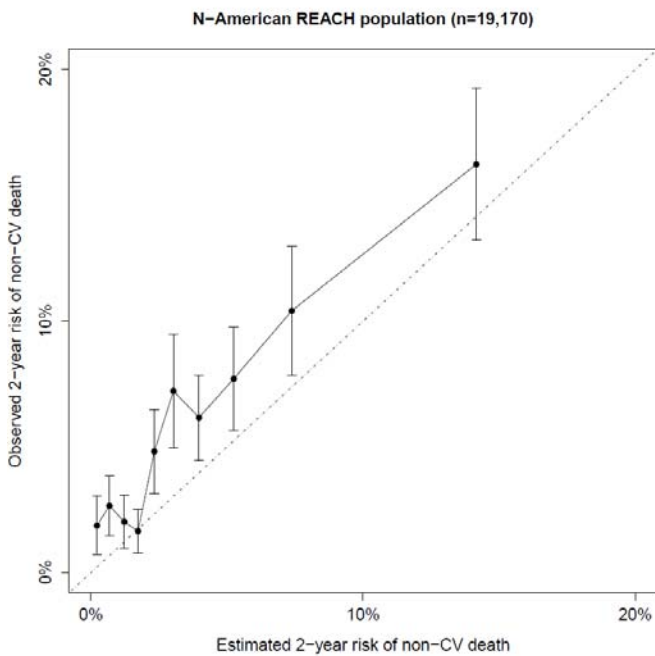
A. Estimated versus observed 10-year cardiovascular risk in the SMART population (left, E/O ratio 1.53) and after recalibration adjusting for the E/O ratio (right)



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)

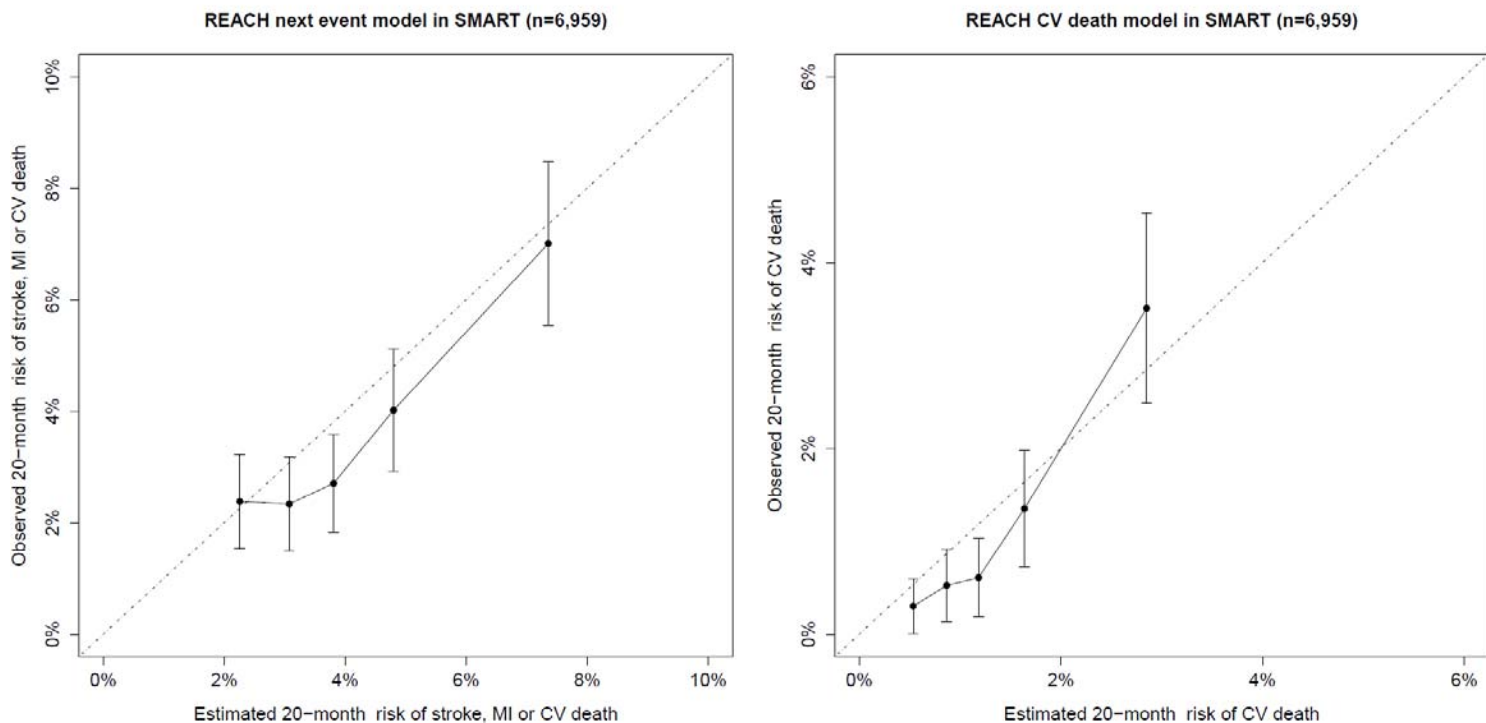


C. Estimated versus observed 2-year cardiovascular risk in the North American REACH population (left, E/O ratio 0.86) and after recalibration adjusting for the E/O ratio (right)



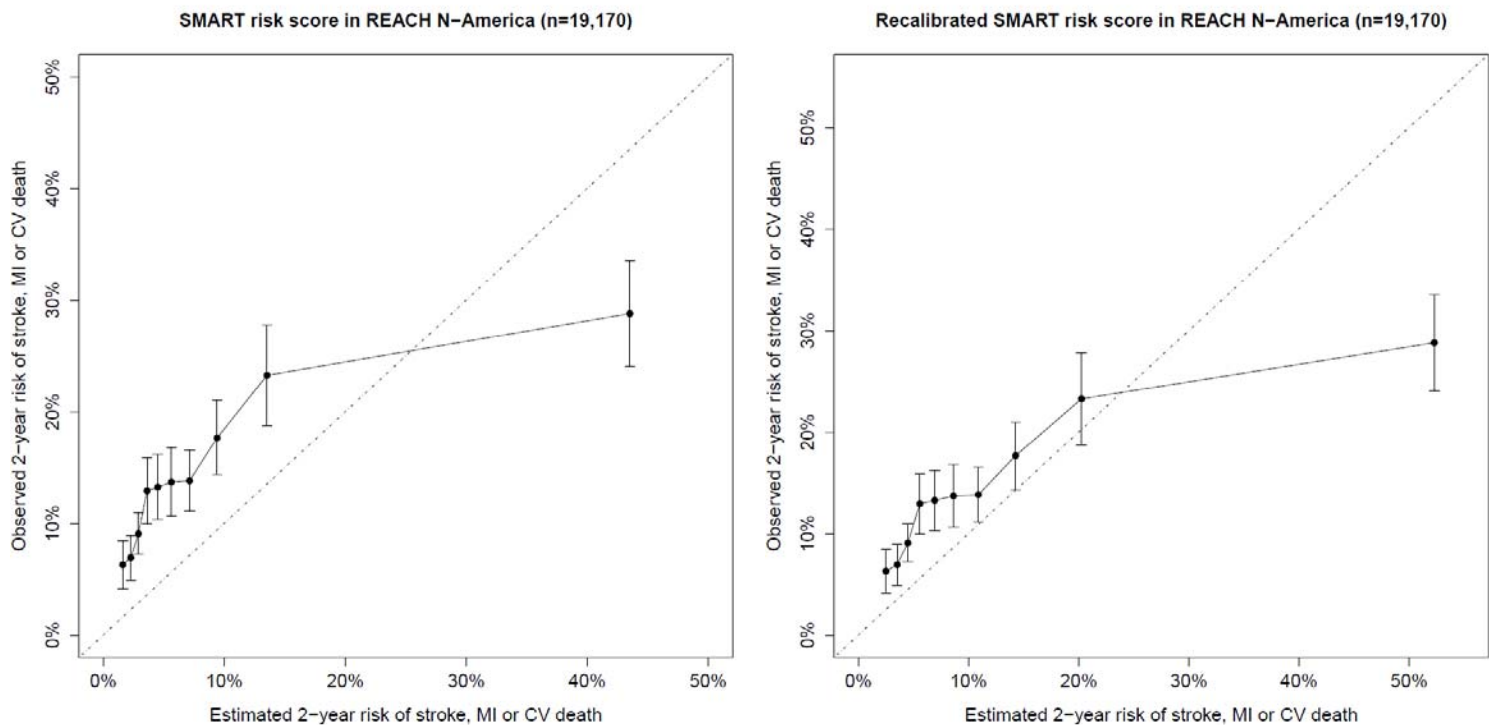
D. Estimated versus observed 2-year risk of non-cardiovascular death in the North American REACH population (left, E/O ratio 0.66) and after recalibration adjusting for the E/O ratio (right)

Figure S2A. Calibration of the REACH risk models in SMART

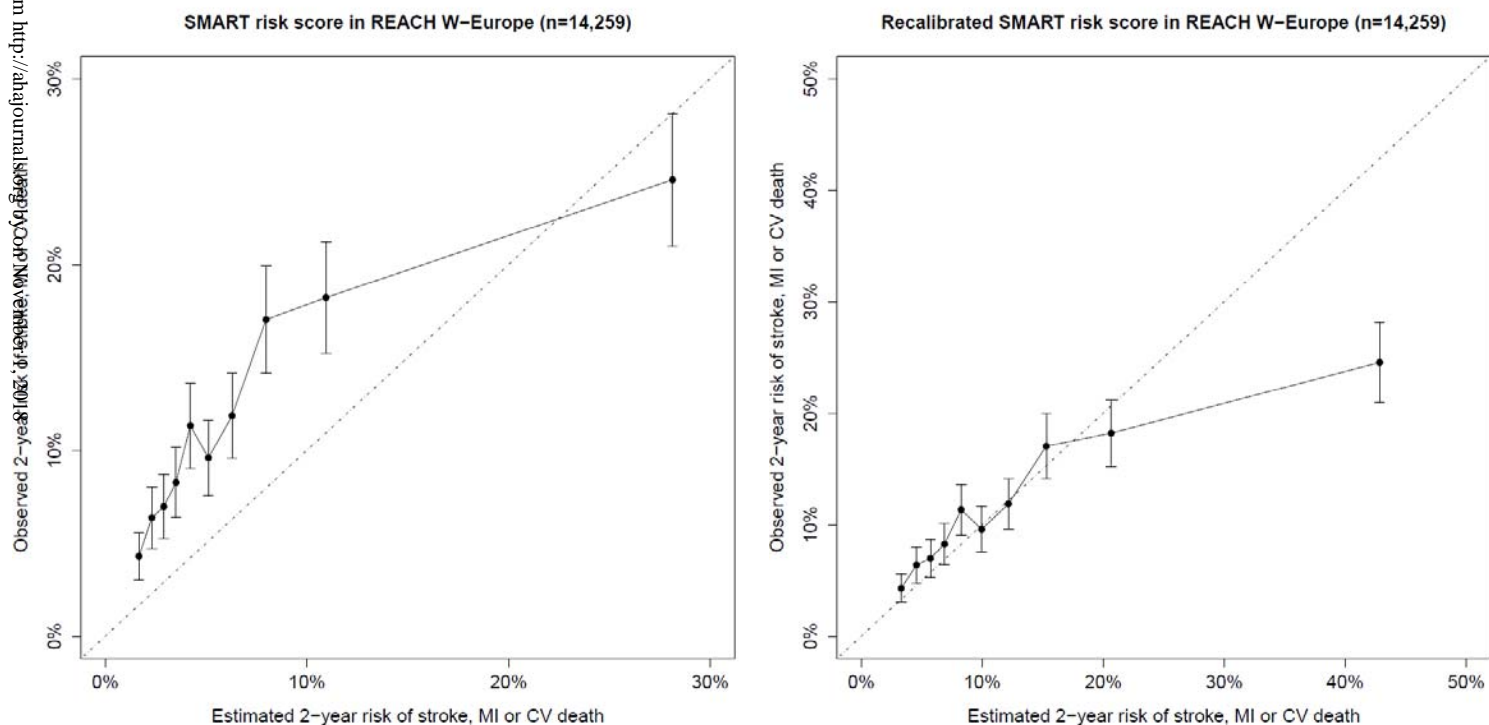


Calibration of the REACH recurrent event model (left) and REACH cardiovascular death model (right) in the SMART population

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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