Predicting 10-year risk of recurrent cardiovascular events and cardiovascular interventions in patients with established cardiovascular disease: results from UCC-SMART and REACH

C.C. van 't Klooster [a], D.L. Bhatt [b], P.G. Steg [c,k], J.M. Massaro [d], J.A.N. Dorresteijn [a], J. Westerink [a], Y.M. Ruigrok [e], G.J. de Borst [f], F.W. Asselbergs [g,h,i], Y. van der Graaf [j], F.L.J. Visseren [a,*], On behalf of the UCC-SMART study group

[a] Department of Vascular Medicine, University Medical Center Utrecht (UMCU), University Utrecht, Utrecht, the Netherlands
[b] Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, Boston, MA, USA
[c] French Alliance for Cardiovascular Trials, Hôpital Bichat, Paris, France
[d] Department of Biostatistics Boston University School of Public Health, Boston, MA, USA
[e] Department of Neurology and Neurosurgery, University Medical Center Utrecht (UMCU), University Utrecht, Utrecht, the Netherlands
[f] Department of Vascular Surgery, University Medical Center Utrecht (UMCU), University Utrecht, Utrecht, the Netherlands
[g] Department of Cardiology, Division Heart & Lungs, UMCU, Utrecht University, Utrecht, the Netherlands
[h] Institute of Cardiovascular Science, Faculty of Population Health Sciences, University College London, London, United Kingdom
[i] Health Data Research UK and Institute of Health Informatics, University College London, London, United Kingdom
[j] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht (UMCU), University Utrecht, Utrecht, the Netherlands
[k] Assistance Publique-Hôpitaux de Paris, Université de Paris, INSERM Unité, 1148 Paris, France

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ABSTRACT

Background: Existing cardiovascular risk scores for patients with established cardiovascular disease (CVD) estimate residual risk of recurrent major cardiovascular events (MACE). The aim of the current study is to develop and externally validate a prediction model to estimate the 10-year combined risk of recurrent MACE and cardiovascular interventions (MACE+) in patients with established CVD.
Methods: Data of patients with established CVD from the UCC-SMART cohort ($N = 8421$) were used for model development, and patient data from REACH Western Europe ($N = 14,528$) and REACH North America ($N = 19,495$) for model validation. Predictors were selected based on the existing SMART risk score. A Fine and Gray competing risk-adjusted 10-year risk model was developed for the combined outcome MACE+. The model was validated in all patients and in strata of coronary heart disease (CHD), cerebrovascular disease (CeVD), peripheral artery disease (PAD).
Results: External calibration for 2-year risk in REACH Western Europe and REACH North America was good, c-statistics were moderate: 0.60 and 0.58, respectively. In strata of CVD at baseline good external calibration was observed in patients with CHD and CeVD, however, poor calibration was seen in patients with PAD. C-statistics for patients with CHD were 0.60 and 0.57, for patients with CeVD 0.62 and 0.61, and for patients with PAD 0.53 and 0.54 in REACH Western Europe and REACH North America, respectively.
Conclusions: The 10-year combined risk of recurrent MACE and cardiovascular interventions can be estimated in patients with established CHD or CeVD. However, cardiovascular interventions in patients with PAD could not be predicted reliably.

1. Introduction

The number of patients in the chronic phase of cardiovascular disease (CVD) is growing as a result of improved survival after acute vascular events, an ageing populations, and deteriorating lifestyle habits such as sedentary behavior and unhealthy diet leading to obesity [1–5]. In order to successfully prevent a second cardiovascular event in a patient with established cardiovascular disease, preventive treatment strategies should be personalized to fit each individual patient. In particular with regard to emerging, and often costly, therapies such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors [6–9] intensified anti-thrombotic treatment schemes [10,11], specific anti-inflammatory [12] or icosapent ethyl treatment [13], it is essential to identify those patients with the highest residual cardiovascular risk, as these patients will benefit the most. Relevant for clinical practice is also that risk estimations can be used to inform patients of their

* Corresponding author at: Department of Vascular Medicine, University Medical Centre Utrecht, PO Box 85,500, 3508 GA Utrecht, the Netherlands.
   E-mail address: f.l.j.visseren@umcutrecht.nl (F.L.J. Visseren).

prognosis and to facilitate shared decision making concerning preventive treatment [14,15].

The SMART risk score [16] is commonly used for patients with established cardiovascular disease, for patient education and as a clinical decision-support tool. Physicians and patients can access interactive calculators of the SMART risk score in the 'ESC CVD risk calculation'-app, on the ESC-website (https://www.escardio.org/Education/ESC-Prevention-of-CVD-Programme/Risk-assessment/SMART-Risk-Score), and on U-Prevent (http://u-prevent.com). The SMART risk score predicts the 10-year residual risk of recurrent major cardiovascular events (MACE), defined as non-fatal myocardial infarction, non-fatal stroke, or vascular death [16–18]. Incidence rates of these events have however steadily declined by in total 53% between 1996 and 2014 in a cohort of patients with stable cardiovascular disease [19]. As this decline is only partially explained by improved treatment of risk factors [19], it may also be due to earlier detection of atherosclerotic disease [20,21] and subsequent (preventive) cardiovascular interventions, forestalling part of the acute ischemic events. This attention to cardiovascular interventions is also evident from the results of recent cardiovascular prevention trials, which usually report the effects for a combined outcome of major cardiovascular events as well as coronary revascularizations, as secondary [8] or even primary outcome [6], and also include peripheral interventions [10]. Most importantly, cardiovascular interventions such as amputations, peripheral revascularization procedures, cardiac interventions, and carotid endarterectomy cause significant morbidity [22,23], and from a patient's perspective might have a similar clinical impact as classical MACE. For these reasons, calculating the risk of both cardiovascular events and cardiovascular interventions might provide a more accurate estimation of an individual's future health and risk, and provide a more appropriate translation from trial results to clinical practice, thereby aiding in determining preventive treatment strategies, informing patients, and facilitating shared decision making.

Therefore, the aim of the current study is to develop and externally validate a risk prediction model for estimating the 10-year combined residual risk of recurrent MACE and cardiovascular interventions in patients with established cardiovascular disease.

2. Methods

2.1. Study populations

Participants originated from the Utrecht Cardiovascular Cohort-Second Manifestations of ARTerial disease (UCC-SMART) cohort, and the REduction of Atherothrombosis for Continued Health (REACH) Registry, both prospective cohorts including patients with established cardiovascular disease or risk factors for atherosclerotic disease. Study designs and rationales have been described in detail previously [24–32]. From both cohorts, patients with established cardiovascular disease at baseline were included for the current analyses.

UCC-SMART is an ongoing prospective cohort including 18–79 year-old patients referred to the University Medical Center Utrecht (UMCU) in the Netherlands, that started enrollment in 1996 and is still recruiting. At baseline, information on medical history, and physical examination and laboratory measurements are acquired following a standardized protocol. The international REACH registry included patients between 2003 and 2004 from general practitioners or medical specialist outpatient practices from countries in North America, Latin America, Europe, the Middle East, Asia, and Australia. Medical history, physical and laboratory measurements were collected according to a standardized international case report form [26]. Definitions of baseline characteristics of the cohorts are described in detail in Supplemental Table S1A. Both the UCC-SMART cohort and the REACH-registry were approved by an institutional review board, and written informed consent was obtained from all participants. For the current study, patients with established cardiovascular disease from

UCC-SMART enrolled between September 1996 and March 2018 ($N = 8421$) from REACH Western Europe ($N = 14,528$) and from REACH North America ($N = 19,495$) were included.

2.2. Recurrent cardiovascular events and cardiovascular interventions

For the UCC-SMART cohort, information on the occurrence of recurrent MACE, bleeding events, incident diabetes, end stage renal disease, and hospitalizations for cardiovascular interventions was obtained by biannual questionnaires sent out to participants. Additional information was gathered from hospitals and general practitioners. An endpoint committee of three physicians adjudicates all recurrent cardiovascular disease events and experienced research nurses judged all cardiovascular interventions. Conflicting decisions were discussed and resolved in consensus.

Patients from the REACH registry returned for follow-up visits annually with a maximum follow-up duration of 4 years. Occurrence of recurrent cardiovascular events, hospitalization for unstable angina pectoris, congestive heart failure, major bleeding events, and cardiovascular interventions were reported by a local investigator and not adjudicated.

The endpoint for the current study was the combined outcome of recurrent MACE and cardiovascular interventions (MACE+). MACE was defined as non-fatal myocardial infarction, non-fatal stroke, or vascular death. Cardiovascular interventions included percutaneous interventions or revascularization surgery; carotid endarterectomy (CEA), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), lower limb amputations, and peripheral artery stenting, angioplasty or bypass (overview is presented in Table 2, and detailed definitions are presented in Supplemental Table S1 B and C).

2.3. Temporal validation of existing SMART risk score for recurrent MACE

To evaluate the performance of the original SMART risk score from 2013 for the prediction of recurrent MACE [16], temporal validation was performed in the larger UCC-SMART dataset (Supplemental Table S2 for details on number of patients and events) with all patients and in strata of cardiovascular disease at baseline (coronary heart disease (CHD), cerebrovascular disease (CeVD), and peripheral artery disease (PAD)). External validation of the SMART risk score in the REACH datasets has previously been performed [18].

2.4. Predictor selection and data preparation

For the new prediction model, i.e. the extended SMART risk score, to estimate the risk of MACE+ (recurrent MACE and cardiovascular interventions combined), the predictors were selected from the original SMART risk score. A subsequent literature search did not provide additional predictors of incident cardiovascular interventions, resulting in the following 14 predictors: age, sex, current smoking (yes/no), history of diabetes mellitus (yes/no), systolic blood pressure (mmHg), total cholesterol (mmol/L), high density lipoprotein (HDL) cholesterol (mmol/L), high sensitive C-reactive protein (CRP) (mg/L), estimated glomerular filtration rate (eGFR) (mL/1.73 m2) (estimated by CKD-EPI formula [33]), time since first cardiovascular event (years), history of CHD (yes/no), history of CeVD (yes/no), history of PAD (yes/no), and history of aneurysm of the abdominal aorta (yes/no). Missing data (≤1% per variable in UCC-SMART, and in REACH 18% for kidney function, 17% for total cholesterol, 2% for current smoking, and <1% for other variables) was singly imputed by predictive mean matching based on multivariable regression using both baseline and outcome data (aregImpute function in R, Hmisc package). Continuous predictors were truncated to the 1st and 99th percentile to limit influence of outliers (continuous predictors in the REACH datasets were truncated to the limits of these variables in UCC-SMART).

2.5. Model development for estimating risk of MACE+

A Fine and Gray competing risk-adjusted subdistribution hazard function [34,35] was developed in the UCC-SMART cohort for 10-year predictions. Non-cardiovascular death was considered the competing endpoint. Because of the longer follow-up period, the UCC-SMART dataset was preferred as derivation cohort. To improve the model fit, log and quadratic associations between continuous predictors and the outcome variable were assessed by comparing Akaike's Information Criterion (AIC) [36], and transformations were applied when appropriate. The proportional hazards assumption was assessed visually by plotting scaled Schoenfeld residuals and no violations were observed. The linear predictor was adjusted by a shrinkage factor, acquired by bootstrapping with a 1000 bootstrap samples, to account for optimism.

2.6. External validation in REACH Western Europe and REACH North America

External validation of the extended SMART risk score was performed in REACH Western Europe and REACH North America. As the predictors CRP, HDL cholesterol, and time since first cardiovascular event were not available in the REACH dataset, population averages of UCC-SMART were imputed for these variables. This method is preferred over excluding the predictor and performs similar compared to subgroup mean imputation and multiple imputation if the predictor is less important [37]. Model performance was assessed by the c-statistic (and ROC curves) for discrimination and calibration plots of predicted versus observed risks. The validation was performed for outcome data from 2 years of follow-up (approximation of median follow-up time), by implementing the 2-year baseline hazard from the derivation dataset (UCC-SMART) and using the same coefficients that were determined in the derivation set during model development. To adjust for variation in the underlying event rates, the expected observed ratio in the REACH Western Europe and the REACH North America study populations was used to recalibrate the model. Additionally, the risk score was validated in patients from REACH Western Europe and REACH North America in strata of cardiovascular disease at baseline (CHD, CeVD, and PAD) with the previously determined expected observed ratios. For the current study, abdominal aortic aneurysm (AAA) was not included in the definition of PAD.

All analyses were performed with R statistical software (version 3.5.1). To enable the use of this newly developed risk model in daily clinical practice, an online calculator will be developed that allows estimation of 10-year risk of MACE+ for an individual patient.

3. Results

3.1. Baseline characteristics and number of recurrent MACE and cardiovascular interventions

Baseline characteristics of patients in UCC-SMART, REACH Western Europe, and REACH North America are presented in Table 1. In the REACH cohorts, patients were generally older, with a mean age of 68 (±10) years in REACH Western Europe and 70 (±10) years in REACH North America versus 60 (±10) years in UCC-SMART, and more patients with diabetes were enrolled; 34% in REACH Western Europe and 42% in REACH North America versus 17% in UCC-SMART. In UCC-SMART, more patients were current smokers; 31% versus 15% in REACH Western Europe and 13% in REACH North America. During a median follow-up time of 8.6 years (IQR 4.7–12.8) 2386 cardiovascular interventions occurred in the UCC-SMART cohort, and recurrent MACE was observed in 1671 patients. The competing event non-cardiovascular death was observed in 650 patients. In participants from REACH Western Europe, during a median follow-up time of 1.75 years (IQR 1.50–2.25), 2272 interventions

Table 1
Baseline characteristics for UCC-SMART, REACH W-Europe, and REACH N-America.

	UCC-SMART (N = 8421)	REACH W-Europe (N = 14,528)	REACH N-America (N = 19,495)
Male, n (%)	6214 (74%)	10,455 (72%)	12,080 (62%)
Age (years)[a]	60 ± 10	68 ± 10	70 ± 10
Current smoking, n (%)	2573 (31%)	2227 (15%)	2548 (13%)
Medical history			
Cerebrovascular disease, n (%)	2515 (30%)	4536 (31%)	5433 (28%)
Coronary artery disease, n (%)	5155 (61%)	10,026 (69%)	15,719 (81%)
Peripheral artery disease, n (%)	1486 (18%)	3415 (24%)	2370 (12%)
Abdominal aortic aneurysm, n (%)	711 (8%)	507 (4%)	795 (4%)
Years since first vascular event (years)[a]	0 (0–4)	NA	NA
Diabetes Mellitus, n (%)	1451 (17%)	4888 (34%)	8280 (42%)
Physical examination and laboratory measurements			
Body Mass Index (kg/m²)[a]	27 ± 4	28 ± 4	29 ± 6
Systolic blood pressure (mmHg)[a]	139 ± 20	140 ± 19	132 ± 18
Diastolic blood pressure (mmHg)[a]	81 ± 11	80 ± 10	75 ± 11
Total cholesterol (mmol/L)[a]	4.7 (4.0–5.5)	5.1 ± 1.1	4.6 ± 1.0
HDL cholesterol (mmol/L)[a]	1.2 (1.0–1.4)	NA	NA
Hs-CRP (mg/L)[a]	2.0 (0.9–4.3)	NA	NA
Creatinine (μmol/L)[a]	92 ± 36	105 ± 84	114 ± 95
Medication			
Lipid lowering medication, n (%)	5796 (69%)	10,331 (71%)	15,031 (77%)
Blood pressure lowering therapy, n (%)	6316 (75%)	13,144 (90%)	18,237 (94%)
Anti-platelet therapy, n(%)	6482 (77%)	9669 (67%)	14,675 (75%)

UCC-SMART = Utrecht Cardiovascular Cohort-Second Manifestations of ARTerial disease
REACH = REduction of Atherothrombosis for Continued Health; W-Europe = Western Europe; N-America = North America
[a] Data are displayed as mean (standard deviation) or median (quartiles)

were performed, 1776 recurrent MACE were observed, and 436 deaths from non-cardiovascular causes. In REACH North America, during a median follow-up time of 1.75 years (IQR 1.50–1.83) 2194 interventions were registered, 1988 participants were diagnosed with recurrent MACE, and 636 non-cardiovascular deaths. Outcome definitions and numbers are displayed in Table 2. Table 3 provides an overview of outcome numbers and incidence rates in strata of cardiovascular disease at baseline and shows that outcome types vary for patients with CHD, CeVD, or PAD; for example, patients with PAD at baseline had more peripheral interventions and patients with CHD more cardiac interventions, and patients with CeVD had the fewest interventions overall.

3.2. Temporal validation of original SMART risk score in larger UCC-SMART dataset

Temporal validation of the existing SMART risk score in the larger UCC-SMART dataset provided a c-statistic of 0.69 (95%CI 0.68–0.71) (Supplemental Table S2A). Calibration was good, with a slight overestimation in patients with a 10-year risk of >40% (Supplemental Table S2B). Calibration in the larger UCC-SMART dataset in strata of cardiovascular disease at baseline was good (Supplemental Fig. S1).

3.3. Development of the extended SMART risk score for MACE+

Transformations of continuous predictors, subdistribution hazard ratios and 95% confidence intervals of the model predictors are presented in Supplemental Table S3. A shrinkage factor of 0.98 was observed and applied to shrink the model coefficients. The model formula that was used for the risk predictions is shown in Supplemental Table S4.

Table 2

Definitions and numbers of recurrent MACE and cardiovascular interventions in UCC-SMART, REACH W-Europe and REACH N-America.

	UCC-SMART [18,24]	$N = 8421$	REACH [18,26]	W-Europe $N = 14,528$	N-America $N = 19,495$
Follow-up	Time to death or end of follow-up in years, median (IQR)	8.6 (4.7–12.8)	Time to death or end of follow-up in years, median (IQR)	1.75 (1.50–2.25)	1.75 (1.50–1.83)
Combined endpoint	Recurrent major cardiovascular events (myocardial infarction, stroke, vascular death) and cardiovascular interventions	$N = 3020$ IR = 5 / 100 PY	Recurrent major cardiovascular events (myocardial infarction, stroke, vascular death) and cardiovascular interventions	$N = 3512$ IR = 13 / 100 PY	$N = 3653$ IR = 12 / 100 PY
Non-fatal myocardial infarction	At least two of the following: 1. Chest pain; 2. ECG abnormalities; 3. CK elevation	$N = 595$	Self-reported, hospital documentation and confirmed by local physician	$N = 419$	$N = 582$
Non-fatal stroke	Clinical features causing an increase of at least one grade on the modified Rankin scale and fresh infarct or hemorrhage on CT	$N = 424$	Based on information from neurologist or hospital report with diagnosis of stroke, ischemic or hemorrhagic	$N = 623$	$N = 518$
Vascular death	Sudden death or death from stroke, myocardial infarction, congestive heart failure, rupture of abdominal aortic aneurysm, or from other cause, i.e. sepsis following stent placement.	$N = 962$	Sudden death or death from stroke, myocardial infarction, or other cardiovascular death: death following cardiovascular intervention, heart failure, visceral or limb infarction	$N = 878$	$N = 1069$
Cardiac interventions	Percutaneous coronary intervention or coronary artery bypass surgery	$N = 1634$	Percutaneous coronary intervention (angioplasty ± stent), bypass surgery	$N = 1265$	$N = 1469$
Carotid artery interventions	Stent, angioplasty, (thrombo)endarterectomy, bypass surgery	$N = 246$	Stent, angioplasty, (thrombo)endarterectomy, bypass surgery	$N = 278$	$N = 328$
Peripheral interventions (lower limbs)	Stent or graft (endovascular or open surgery), angioplasty, bypass surgery or urokinase treatment. Amputation lower limb due to arterial ischemia.	$N = 837$	Stent or graft (endovascular or open surgery), angioplasty, or bypass surgery. Amputation affecting lower limb due to arterial ischemia.	$N = 988$	$N = 610$

IR = Incidence rate (per 100 person-years). PY = person-years. W-Europe = Western Europe. N-America = North America. Number of events are given for specific outcomes, therefore the separate numbers of cardiovascular interventions and recurrent major cardiovascular events do not exactly count up to the combined endpoint.

3.4. External validation of the extended SMART risk score for MACE+

External validation of the risk model in the REACH cohorts, showed a c-statistic of 0.60 (95%CI 0.59–0.61) in REACH Western Europe, and 0.58 (95%CI 0.57–0.59) in REACH North America. ROC curves are shown in Supplemental fig. S2. Expected observed ratios were 0.96 and 0.82 in REACH Western Europe and REACH North America respectively. External calibration was good, as is shown in Fig. 1. External validation in strata of cardiovascular disease at baseline in REACH Western Europe showed c-statistics of 0.60 (95%CI 0.59–0.61) for patients with CHD, 0.62 (95%CI 0.61–0.64) for CeVD, and 0.53 (95%CI 0.52–0.55) for PAD. Calibration was good for patients with CHD and CeVD, but poor calibration was observed for patients with PAD (Fig. 2). In REACH North America, c-statistics were 0.57 (95%CI 0.56–0.59) in patients with CHD, 0.61 (95%CI 0.59–0.63) for CeVD, and 0.54 (95%CI 0.52–0.57) for PAD. Similarly, calibration was good in patients with CHD and CeVD, and poor calibration was observed in patients with PAD.

4. Discussion

In patients with established cardiovascular disease, cardiovascular interventions are more common than major cardiovascular events. The 10-year risk of a combined outcome of recurrent cardiovascular events and cardiovascular interventions (MACE+) can be estimated in patients with established cerebrovascular and coronary heart disease by the currently developed prediction rule: the extended SMART risk score. Performance of the current residual cardiovascular risk model is inadequate in patients with established PAD. The combined outcome might provide a more accurate representation of a patient's true risk and a more appropriate translation from trial results to clinical practice and is clinically relevant from a patient's perspective.

Validation of the current model showed good calibration and moderate discrimination with c-statistics of 0.60 and 0.58 in REACH Western Europe and North America respectively. In comparison, the original SMART risk score for estimating 10-year risk of major recurrent cardiovascular events in patients with established cardiovascular disease, showed c-statistics ranging from 0.62 to 0.66 upon external validation in seven datasets including the REACH registry [18,38]. Calibration of the SMART risk score in those 7 external datasets was good in patients with PAD and in general, even though miscalibration in REACH North America and slight overestimation of risk in patients with very high predicted risks (10-year risks of more than 40% and 2-year risk of more than 20%) was observed [18,38]. Discriminative power was slightly lower for the current model (extended SMART risk score) than the original SMART risk score, possibly due to the great diversity of the current outcome ranging from elective percutaneous interventions to vascular death. However, for assessment of prediction model performance, calibration is a more clinically relevant performance measure than discrimination with the c-statistic [39]. In short, it is more important to correctly estimate the risk in a given patient (calibration) then whether it discriminates between a high and low risk patient (discrimination and c-statistic).

In patients with PAD, the model performed inadequately. Possible explanations for this inadequate performance concern both the outcome and the patient population. With regard to the outcome, in patients with PAD, peripheral vascular interventions occurred more often, and these interventions are potentially challenging to predict. Predictors for a limb salvage operation due to critical limb ischemia might be very different from predictors for endovascular treatment of a restenosis. For example, salvage amputation is only performed when no other options are available or have already been tried and when the patient is not a candidate for extensive bypass surgery. Restenosis occurs quite frequently (18–40% within one year after stenting in the femoropopliteal segment [40,41]). The precise form, site and length of the endovascular intervention for PAD markedly influences restenosis risk, and thus earlier treatment influences the risk for new treatment, and these factors are not included in the model. As restenosis usually manifests between 3 and 6 months after initial intervention [42], these patients will be regarded as high risk due to an early event, but might not necessarily have a very high risk factor profile. Although this could also be true for coronary restenosis, restenosis is reported more often after peripheral interventions [40,41,43]. Additionally, in patients with a new diagnosis of claudication, indication for early peripheral vascular interventions depended on the treating physician [44]. It could be hypothesized that in patients with established PAD, indication for peripheral (re-)intervention might also rely partly on clinician

Table 3

Recurrent MACE and cardiovascular interventions in UCC-SMART, REACH W-Europe and REACH N-America, in strata of cardiovascular disease at baseline.

|	Coronary heart disease	Cerebro-vascular disease	Peripheral artery disease
UCC-SMART	N = 5155	N = 2515	N = 1486
Myocardial infarction			
Number (%)	433 (8%)	122 (5%)	111 (8%)
Incidence rate / 100 PY (95%CI)	1.00 (0.91–1.10)	0.58 (0.49–0.70)	0.83 (0.68–1.00)
Stroke			
Number (%)	212 (4%)	199 (8%)	88 (6%)
Incidence rate / 100 PY (95%CI)	0.48 (0.41–0.54)	0.97 (0.8401.11)	0.65 (0.52–0.80)
Vascular death			
Number (%)	525 (10%)	339 (14%)	302 (20%)
Incidence rate / 100 PY (95%CI)	1.15 (1.06–1.25)	1.57 (1.41–1.75)	2.15 (1.92–2.41)
Carotid interventions			
Number (%)	113 (2%)	118 (5%)	70 (5%)
Incidence rate / 100 PY (95%CI)	0.25 (0.21–0.30)	0.57 (0.48–0.69)	0.52 (0.41–0.66)
Coronary interventions			
Number (%)	1305 (25%)	279 (11%)	238 (16%)
Incidence rate / 100 PY (95%CI)	3.61 (3.41–3.81)	1.38 (1.22–1.56)	1.93 (1.69–2.19)
Peripheral interventions			
Number (%)	357 (7%)	165 (7%)	521 (35%)
Incidence rate / 100 PY (95%CI)	0.82 (0.74–0.91)	0.80 (0.69–0.94)	5.07 (4.64–5.52)
REACH Western Europe	N = 10,026	N = 4536	N = 3415
Myocardial infarction			
Number (%)	320 (3%)	112 (3%)	126 (4%)
Incidence rate / 100 PY (95%CI)	1.57 (1.40–1.75)	1.21 (1.00–1.46)	1.85 (1.54–2.20)
Stroke			
Number (%)	363 (4%)	353 (8%)	151 (4%)
Incidence rate / 100 PY (95%CI)	1.78 (1.69–1.97)	3.90 (3.50–4.33)	2.22 (1.88–2.60)
Vascular death			
Number (%)	618 (6%)	302 (7%)	289 (9%)
Incidence rate / 100 PY (95%CI)	3.00 (2.77–3.25)	3.26 (2.90–3.65)	4.22 (3.75–4.74)
Carotid interventions			
Number (%)	170 (2%)	114 (3%)	114 (3%)
Incidence rate / 100 PY (95%CI)	0.83 (0.71–0.97)	1.24 (1.03–1.49)	1.69 (1.39–2.02)
Coronary interventions			
Number (%)	1080 (11%)	253 (6%)	286 (8%)
Incidence rate / 100 PY (95%CI)	5.49 (5.15–5.82)	2.79 (2.45–3.15)	4.29 (3.81–4.82)
Peripheral interventions			
Number (%)	542 (5%)	202 (5%)	676 (20%)
Incidence rate / 100 PY (95%CI)	2.70 (2.47–2.93)	2.22 (1.93–2.55)	10.76 (9.96–11.60)
REACH North America	N = 15,719	N = 5433	N = 2370
Myocardial infarction			
Number (%)	510 (3%)	170 (3%)	77 (3%)
Incidence rate / 100 PY (95%CI)	2.00 (1.83–2.18)	1.96 (1.67–2.27)	2.05 (1.62–2.56)
Stroke			
Number (%)	335 (2%)	288 (5%)	65 (3%)
Incidence rate / 100 PY (95%CI)	1.31 (1.18–1.46)	3.35 (2.97–3.76)	1.73 (1.33–2.20)
Vascular death			
Number (%)	898 (6%)	351 (7%)	218 (9%)
Incidence rate / 100 PY (95%CI)	3.50 (3.27–3.74)	4.01 (3.60–4.45)	5.77 (5.03–6.59)
Carotid interventions			
Number (%)	268 (2%)	98 (2%)	83 (4%)
Incidence rate / 100 PY (95%CI)	1.05 (0.93–1.19)	1.13 (0.92–1.38)	2.23 (1.78–2.76)
Coronary interventions			
Number (%)	1351 (9%)	272 (5%)	151 (6%)
Incidence rate / 100 PY (95%CI)	5.49 (5.20–5.79)	3.18 (2.82–3.58)	4.11 (3.48–4.82)
Peripheral interventions			
Number (%)	465 (3%)	161 (3%)	309 (13%)
Incidence rate / 100 PY (95%CI)	1.84 (1.67–2.01)	1.87 (1.59–2.18)	8.75 (7.80–9.78)

All first events of a specific outcome are counted. Therefore carotid + coronary + peripheral interventions do not exactly count up to the number of all cardiovascular interventions. Similarly, myocardial infarction + stroke + vascular death do not exactly count up to the number of recurrent cardiovascular disease.

PY = person-years; CI = confidence interval.

characteristics rather than patient factors. With regard to the patient population, patients with PAD might have a less varied risk factor profile compared to patients with CHD or CeVD and consequently have fewer distinguishing factors for predicting higher or lower risk within this particular population.

Currently, the SMART risk score [16] and the SMART-REACH model [18] are the most used 10-year and lifetime residual risk prediction algorithms for patients with established CVD. The current model, the extended SMART risk score, estimating the risk of MACE+ will provide a valuable addition to those existing risk scores. Although the extended SMART risk score does not perform well in patients with PAD specifically, these patients often also have other types of cardiovascular disease and are therefore seen by various specialists. The advantage of a general risk score applicable to all patients with any type of CVD is that it can be used by all types of specialists, and care for patients with established CVD will not become segregated. However, the current model performs inadequately in patients with PAD and the use is not recommended in clinical practice for these patients specifically. Future studies could investigate increasing model performance in these patients, for example by limiting peripheral interventions to urgent or

A REACH Western Europe

B REACH North America
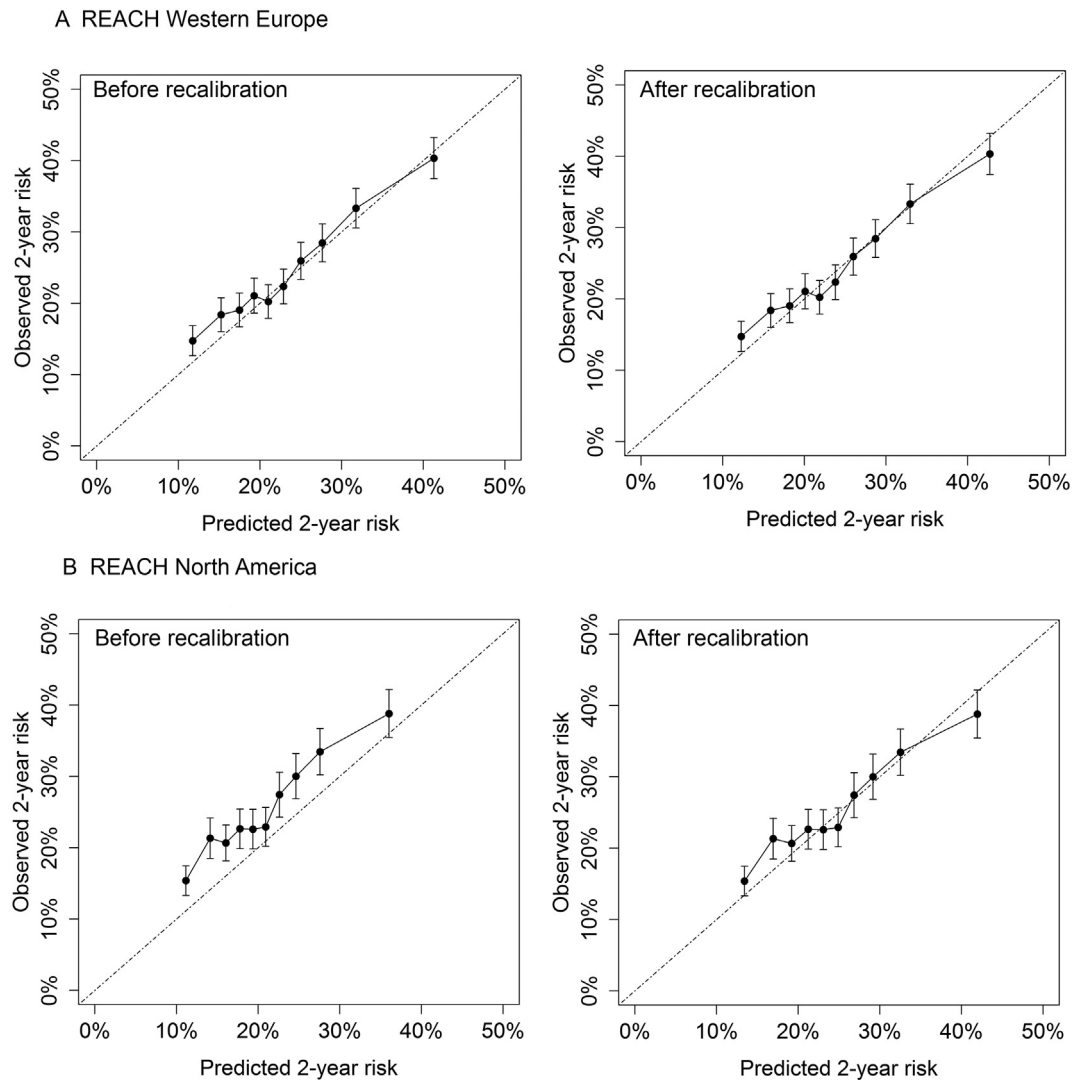
Fig. 1. Plots of external calibration of the extended SMART risk score for MACE+ in REACH W-Europe and REACH N-America before and after recalibration.

salvage procedures, by excluding restenosis, or by including procedural information, such as stent location and length, as additional predictors. The combined outcome is highly diverse, but all outcomes could be regarded as clinically relevant from a patient's as well as from an economic perspective. Incidence rates of recurrent major cardiovascular events have declined [19] and the number of percutaneous cardiac revascularization procedures has risen quickly, with a more than 7 times increase in the United Kingdom from 1993 to 2013 [45] and a more than double number in 2012 compared to a decade earlier in the Netherlands [46], as a replacement for open surgery, and with expanding indications due to further developed technical options. It could be hypothesized that these trends will amplify over the next few years, and the risk of a combined endpoint of recurrent MACE and cardiovascular interventions (MACE+) might become a more fitting representation of an individual's true cardiovascular risk.

The current study had several strengths, including the large datasets enrolling patients with different types of established cardiovascular disease, and the long follow-up duration in the derivation dataset (UCC-SMART). Furthermore, due to adjustment for competing events accurate risk estimations of the event of interest are provided in a specific population that is also at risk of dying from other diseases, such as cancer [47]. By accounting for competing risks, overestimation of the event of interest is prevented [48]. However, limitations should be

acknowledged and include the limited length of follow-up in the validation sets. Although the coefficients were the same for 10-year and 2-year risk predictions, the baseline hazard for 2-year risk predictions was separately derived from the derivation set and the assumption is made that the expected observed ratio for 2-year predictions is similar for 10-year risk predictions. Due to certain sampling methods for the REACH and UCC-SMART cohorts, it is possible that the absolute risk predictions are not applicable to all patients with established cardiovascular disease globally. There is no reason to assume coefficients would be different, however, there might be variations in underlying baseline hazards. Lastly, indications for cardiovascular interventions or procedural information, such as location or length of the stent, potentially improving model performance in patients with PAD, were not available in the datasets.

In conclusion, the 10-year combined risk of recurrent cardiovascular events and cardiovascular interventions can be estimated in patients with established CHD or CeVD. However, cardiovascular interventions in patients with PAD could not be predicted reliably.
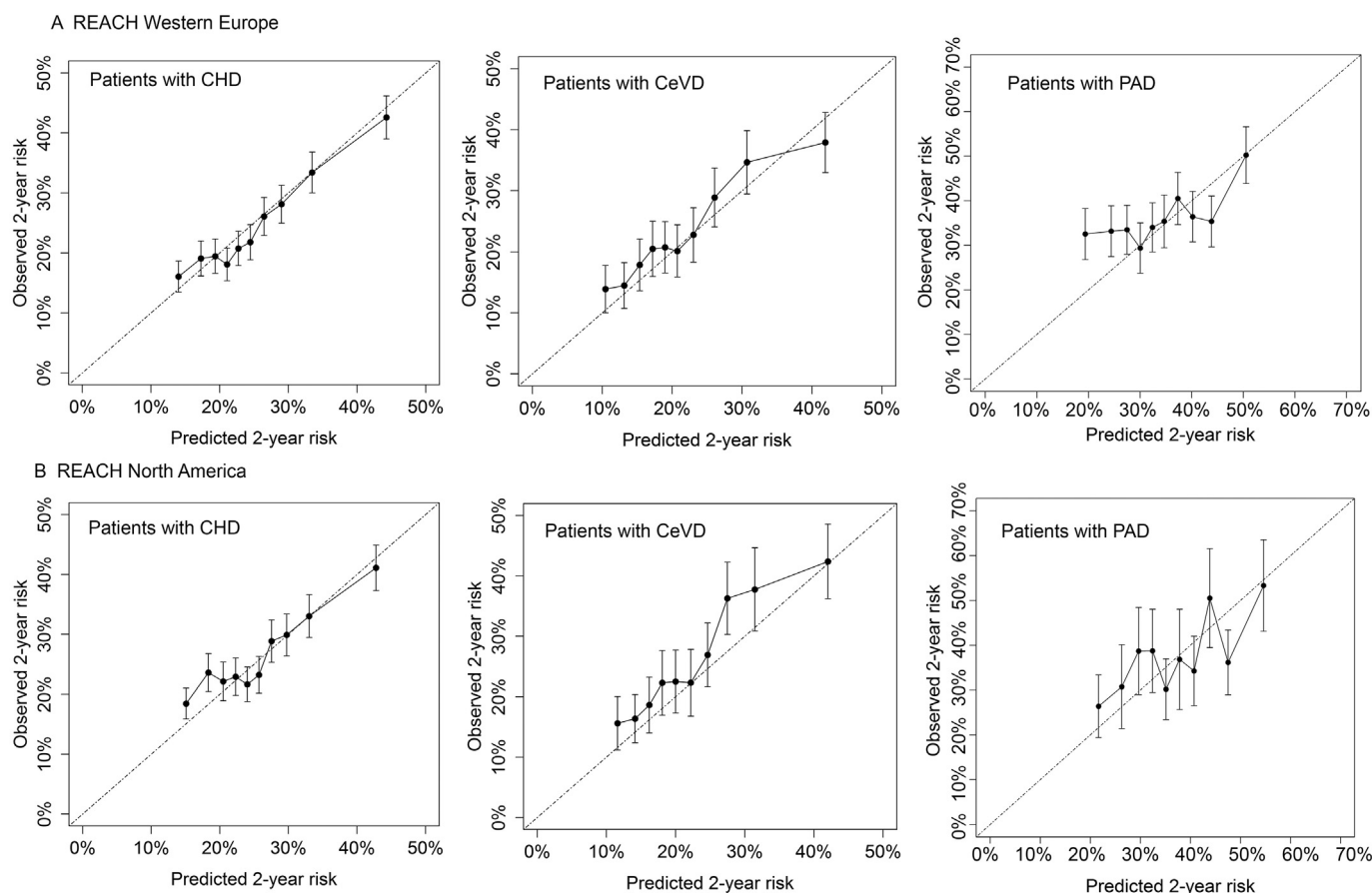
Fig. 2. External calibration plots of the extended SMART risk score for MACE+ in strata of cardiovascular disease at baseline in REACH W-Europe and REACH N-America.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.09.053.

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