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FULL RESEARCH PAPER
Risk Prediction/Assessment & Stratification

Is the SMART risk prediction model ready for real-world implementation? A validation study in a routine care setting of approximately 380 000 individuals

Ailsa J. McKay[1], Laura H. Gunn [2,3]*, Brian A. Ference[4], Jannick A.N. Dorresteijn[5], Gijs F.N. Berkelmans[5], Frank L.J. Visseren[5], and Kausik K. Ray[1]

[1]Imperial Centre for Cardiovascular Disease Prevention, Department of Primary Care and Public Health, Imperial College London, St Dunstan's Road, London W6 8RP, UK; [2]Department of Public Health Sciences and School of Data Science, University of North Carolina at Charlotte, 9201 University City Blvd, Charlotte, NC 28223, USA; [3]Department of Primary Care and Public Health, School of Public Health, Imperial College London, St Dunstan's Road, London W6 8RP, UK; [4]Centre for Naturally Randomized Trials, University of Cambridge, 2 Worts' Causeway, Cambridge CB1 8RN, UK; and [5]Department of Vascular Medicine, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands

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Aims Reliably quantifying event rates in secondary prevention could aid clinical decision-making, including quantifying potential risk reductions of novel, and sometimes expensive, add-on therapies. We aimed to assess whether the SMART risk prediction model performs well in a real-world setting.

Methods and results We conducted a historical open cohort study using UK primary care data from the Clinical Practice Research Datalink (2000–2017) diagnosed with coronary, cerebrovascular, peripheral, and/or aortic atherosclerotic cardiovascular disease (ASCVD). Analyses were undertaken separately for cohorts with established (≥6 months) vs. newly diagnosed ASCVD. The outcome was first post-cohort entry occurrence of myocardial infarction, stroke, or cardiovascular death. Among the cohort with established ASCVD [$n = 244\,578$, 62.1% male, median age 67.3 years, interquartile range (IQR) 59.2–74.0], the calibration and discrimination achieved by the SMART model was not dissimilar to performance at internal validation [Harrell's c-statistic = 0.639, 95% confidence interval (CI) 0.636–0.642, compared with 0.675, 0.642–0.708]. Decision curve analysis indicated that the model outperformed treat all and treat none strategies in the clinically relevant 20–60% predicted risk range. Consistent findings were observed in sensitivity analyses, including complete case analysis ($n = 182\,482$; $c = 0.624$, 95% CI 0.620–0.627). Among the cohort with newly diagnosed ASCVD ($n = 136\,445$; 61.0% male; median age 66.0 years, IQR 57.7–73.2), model performance was weaker with more exaggerated risk under-prediction and a c-statistic of 0.559, 95% CI 0.556–0.562.

Conclusions The performance of the SMART model in this validation cohort demonstrates its potential utility in routine healthcare settings in guiding both population and individual-level decision-making for secondary prevention patients.

Keywords Risk prediction • Secondary prevention • Cardiovascular disease • Risk calculator

* Corresponding author. Tel: +1 704 687 8742, Fax: +1 704 687 1644, Email: laura.gunn@uncc.edu

Introduction

The current population health approach to the secondary prevention of atherosclerotic cardiovascular disease (ASCVD) is to offer a range of well-established interventions, under the assumption that everyone is at sufficiently high risk that the benefits of the interventions outweigh their risks and costs.[1–3] In contrast, primary prevention risk management recommendations (where risks and benefits are, on average, more closely balanced, and absolute benefits smaller) are focused around using individual absolute risk estimates to guide intervention decisions.[3–6] Following the emergence of relatively high cost novel secondary preventive adjunctive therapies that will not be cost effective in all secondary prevention cases, and given emerging evidence about the benefits of relatively nuanced selection of patients for cardiovascular risk modification,[7] guidelines increasingly recognize that secondary prevention may benefit from a similar more individualized approach.[8] However, definitions of high-risk ASCVD patients remain largely qualitative, relying on presence or absence of comorbidities.[8] The lack of a more individualized quantitative approach limits access to some novel interventions because of uncertainties about cost-effectiveness.[8] For instance, although trial data and guidelines recommend broad patient groups for proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapy, uncertainties around cost-effectiveness for individuals hinders their uptake.[9,10] Furthermore, when more than one option exists for such patients, the choice between, for instance, novel anticoagulants such as rivaroxaban and additional lipid lowering therapies,[11–14] could be further informed from quantification of risk. The adoption of an individualized approach to secondary prevention among those with ASCVD has to-date been limited by the lack of validated cardiovascular disease risk estimation tools for this population.

The SMART risk prediction model—which estimates 10-year risk of myocardial infarction (MI), stroke, or cardiovascular death—is one of only two existing models for the general secondary prevention population for which external validity has been explored,[8,15,16] and the only secondary prevention model for which a calculation tool has been made available.[17] To date, assessment of external validity of the models for the general secondary prevention population has been limited largely to trial participants.[16] Information about performance in wider routine care populations is not currently available, but is recognized as important to effective population health approaches,[18] and would aid implementation in practice. We therefore aimed here to assess the performance of the SMART risk prediction tool in predicting the 10-year risk of cardiovascular events in a secondary prevention United Kingdom (UK) routine primary care cohort.

Methods

Study design and data sources

Our sample was a historical cohort from the Clinical Practice Research Datalink (CPRD) GOLD database—a UK primary care database containing longitudinal patient health record data from 1987 onwards. It is representative of the UK primary care-registered population and includes more than 18 million patients (3 million of whom are currently registered). Linked Hospital Episode Statistics (HES) and Office for National Statistics (ONS) mortality data are available for most patients residing in England. The data are collected during routine general practice activity, which includes most UK cardiovascular disease prevention activity. The database has previously been used in both derivation and external validation of cardiovascular risk prediction tools.[19,20]

We constructed two cohorts of patients with established ASCVD, which differed with regard to time since diagnosis. What we refer to as the 'primary cohort' most closely resembles the derivation study cohort,[15] and includes patients entering the cohort at the first date all of the following criteria were met: 1 January 2000, first anniversaries of both database entry and registration with the relevant general practice passed, age ≥18 and <80 years, the 6th month post-first record of clinically manifest ASCVD (full definition in Supplementary material online, *eMethods*). We required ≥6 months between first record of relevant diagnosis and cohort entry, as entry into the original SMART derivation study was typically several months post-diagnosis.[15] We considered that these cohorts would be receiving secondary preventive ASCVD treatments. To additionally test the performance of SMART among those newly diagnosed with ASCVD, our 'secondary cohort' included patients who entered the cohort 1-week post-diagnosis, if the other above-listed criteria were already met. In both cohorts, the study exit date was the earliest of: a vascular outcome (as defined below), last data upload, transfer out of database, death as per ONS records, first recorded receipt of palliative care treatment, or 31 December 2017. Only patients with linked HES and ONS data were included. The SMART risk model [which includes age, gender, history of smoking, diabetes, coronary artery disease, cerebrovascular disease, aneurysm, peripheral arterial disease, number of years since diagnosis of vascular disease, systolic blood pressure, high-density lipoprotein cholesterol (HDL-C), total cholesterol, estimated glomerular filtration rate (eGFR), and high-sensitivity C-reactive protein (hsCRP)] and code lists applied in deriving both the cohorts and below variables are available in the Supplementary material online, *eMethods*.

Outcome

Our outcome variable described the first occurrence of MI, stroke (ischaemic or haemorrhagic), or cardiovascular death (which includes deaths due to: MI, congestive heart failure, ischaemic stroke, intracerebral haemorrhage, ruptured abdominal aortic aneurysm, and sudden cardiac death) post-cohort entry, as per each patient's CPRD, HES, or ONS record. We did not have information regarding non-cardiovascular deaths associated with cardiovascular procedures, which were included in the definition of cardiovascular death in the SMART study, but otherwise the outcome variable was defined as for model derivation.

Risk factors

The predictor variables were formatted in line with the SMART derivation study,[15] using both published and unpublished information from the model development team. Diabetes mellitus positivity reflected a type 1 or 2 diabetes diagnosis prior to cohort entry, 'current smoking' reflected smoking of any intensity, and history and duration of cerebrovascular, coronary and peripheral arterial disease, and abdominal aortic aneurysm, were all defined in relation to the cohort entry date and the diagnostic criteria and code lists used to define cohort eligibility. Age was also measured at cohort entry. For smoking status and clinical measurements other than hsCRP and eGFR, the first recorded measurement *after* and within 10 years of cohort entry was used in assessment of the primary cohort. The most recent measurement *prior to* and within 10 years of cohort entry was used in assessment of the secondary cohort. Measurements of eGFR were as per those directly recorded, or estimated based on recorded creatinine values using the four-variable Modification of Diet in Renal Disease Study equation,[21,22] and the measurement closest to and within 5 years either side of cohort entry was used. As hsCRP

measurements are not routinely available in the CPRD, values were imputed as described below. The other main differences between our predictor ascertainment methods and those used for the SMART derivation cohort relate to the timing of measurements.

Additional variables of interest included receipt of lipid modifying therapy, antihypertensive, antiplatelet, and/or anticoagulant treatment at baseline (any relevant prescription within the preceding 6 months), baseline body mass index (BMI), and ethnic background. Available BMI measurements were prioritized and used as per the other (non-eGFR) clinical measurements. The latest CPRD- or HES-recorded ethnicity was identified and categorized according to the five Level 1 ONS classifications derived for the 2001 Census.

Statistical analysis

Analyses of the primary and secondary cohorts were undertaken separately. Baseline characteristics were described and data missingness explored. Missing smoking, systolic blood pressure, HDL-C, total cholesterol, and eGFR values, were imputed using multiple imputation, under a missing at random assumption, with the other predictors included in the imputation process. For hsCRP, values were imputed using the median age-group*sex*baseline ASCVD diagnosis-specific values observed in the original derivation cohort (provided by the study authors—see Supplementary material online, *eTable 1*). Where multiple baseline ASCVD diagnoses were present, the largest of the relevant diagnosis-specific hsCRP values was used. The below analyses were then undertaken for each imputed dataset and the results combined using Rubin's rules.

Patient 10-year cardiovascular event risks were calculated using the SMART model (equation available in Supplementary material online, *eMethods*) and their distribution summarized (*Figure 1A*). Calibration was assessed by describing ratios of expected to observed risk, testing the calibrations,[23] examining calibration plots, assessing survival curves for different risk groups, and estimating calibration slope. Discrimination was assessed using Harrell's c-statistic. Performance was broadly compared with that observed for the original validation cohort, and the potential clinical usefulness of the model was estimated across a range of potential treatment thresholds in a decision curve analysis that allowed for censoring.[24] Sensitivity analyses included complete case analyses involving patients with full information for all (non-hsCRP) SMART variables, and analyses with predictor values based on clinical measurements recorded within 3 years of cohort entry only. RStudio v3.5.1 was used for analysis.

Results

Data availability and cohort characteristics

There were 244 578 patients from 393 practices included in the primary cohort, with a median follow-up of 5.25 years [interquartile range (IQR) 2.15–9.63; 23.3% followed-up for ≥10 years], during which 45 327 outcome events were observed. Observed 10-year event risks for males and females were 29.1% [95% confidence interval (CI) 28.8–29.4%] and 26.6% (26.2–27.0%), respectively. There were 136 445 patients from 389 practices included in the secondary cohort, with a median follow-up of 3.74 years (IQR 1.10–7.76; 14.4% followed-up for ≥10 years). During follow-up, 28 115 outcome events occurred and observed 10-year event risks for males and females were 29.6% (95% CI 29.2–30.1%) and 27.9% (27.4–28.4%), respectively. Among the secondary cohort, 14 865 patients (10.9%) had events within 6 months of diagnosis.

Primary cohort baseline characteristics and associated missing data are summarized in *Table 1*. A total of 182 482 primary cohort patients (74.6%) had complete model predictor variable information (with the exception of hsCRP). Corresponding information for the secondary cohort is available in Supplementary material online, *eTable 2*. Compared with the original SMART derivation cohort characteristics, our primary cohort had: (i) higher median age (67.3 vs. 60.0 years); (ii) a lower percentage of males (62.1% vs. 74.0%); and (iii) lower estimated eGFR (66.1 vs. 76.0 mL/min/1.73 m^2). Imputation of hsCRP resulted in a median hsCRP of 2.4 mg/L (IQR 2.1–2.7). Since only medians by sex*age-group*ASCVD cluster were used to impute hsCRP, this resulted in a compressed value range compared with that of the derivation cohort (IQR 1.0–4.7).

Model performance: discrimination and calibration

In the primary cohort, the median 10-year SMART-predicted event risk was 22% (IQR 14–34%), with a wide distribution of risk (*Figure 1A*). Calibration plots displaying the observed vs. predicted risks for groups based on sex*predicted risk decile and sex*age-group are displayed in *Figure 1B and C*, respectively. These show that higher predicted risks are associated with higher observed risks, though with slight under-prediction of risks for men across the lower predicted risk and age deciles. The fitted calibration slopes for men and women were both 0.78 (95% CI 0.75–0.81). The ratios, by sex, of 10-year predicted to observed risks across deciles of both predicted risk and age are shown in *Table 2* ($\chi^2 \geq 148.31$; $P < 0.0001$).

Table 3 shows risk reclassification based on individual risk scores ($\chi^2 = 1198.03$; $P < 0.0001$). Observed risks fell within the predicted ranges in all cases except where predicted risk was <10% (observed risk 12%). This aligns with the mentioned slight under-predictive power, which could be associated with the different age structures of our primary cohort vs. the original derivation and validation cohorts. Population differences may also underlie the larger ratio of those expected at most risk (≥40% predicted risk) to those expected at lowest risk (<10%) in our cohort vs. the original SMART cohort (17.4%/10.3% = 1.69 vs. 13%/18%=0.72). With regard to discrimination, Harrell's c-statistic was 0.639 (95% CI 0.636–0.642), which is not significantly different from the original validation cohort figure ($c = 0.675$, 0.642–0.708).[15]

Clinical utility: decision curve analysis

Figure 1D (top panel) demonstrates the proportion of the population who would receive treatment for each possible predicted risk threshold, and the proportion of total cardiovascular events covered within that treated population. Treatment thresholds range from a threshold of 0% (i.e. everyone treated) to 100% (i.e. no one treated). In describing the ratio of true positives to false positives identified at each threshold, the difference between the curves for these two populations provides information about the clinical utility of the SMART model across all potential thresholds. Our decision curve analysis [*Figure 1D* (bottom panel)] compared the SMART model with treat all and treat none benchmarks. Superior performance to both alternatives was found in the 20–60% predicted risk range, and equivalent performance to treat all, but superior to treat none, in the 0–20% predicted risk range.

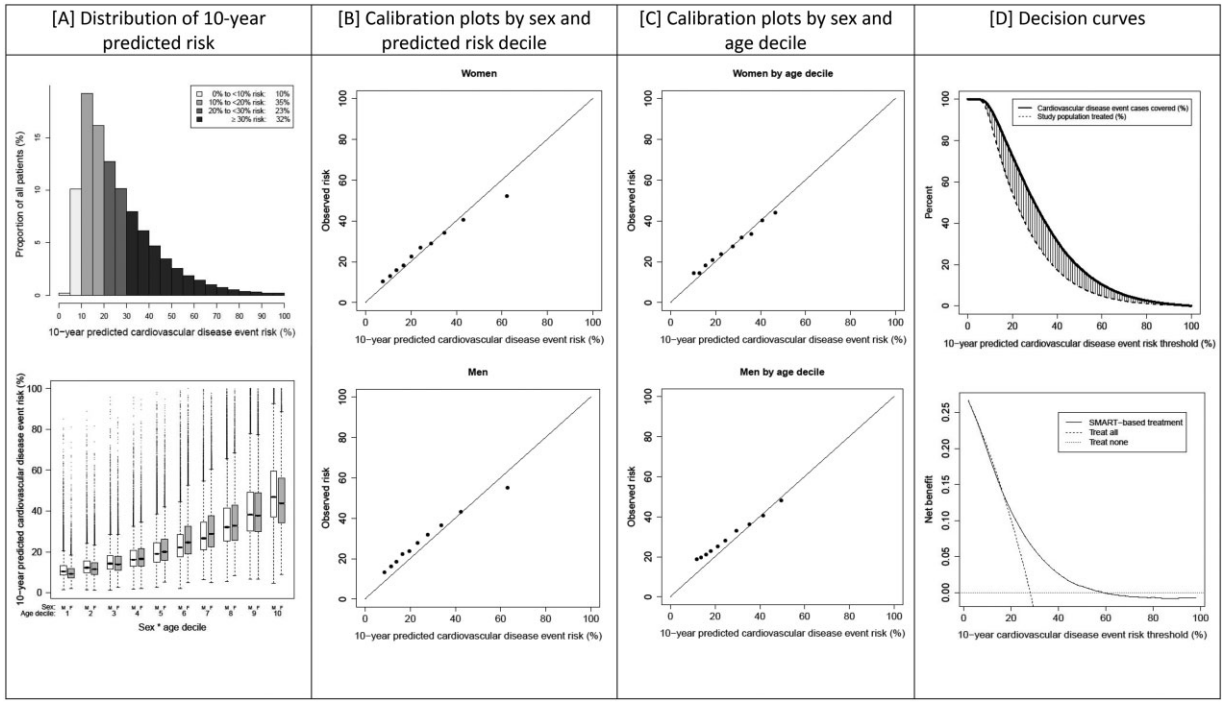

Figure 1 Model performance in primary cohort. The top (*A*) panel displays the distribution of 10-year SMART model-predicted cardiovascular risk overall and by sex*age decile (bottom). Ten-year SMART model-predicted cardiovascular risks and corresponding Kaplan–Meier observed risks are displayed by predicted risk decile (*B*) and age decile (*C*), for both women (top) and men (bottom). The diagonal lines correspond to a perfect fit. The top (*D*) panel displays the percentage of the population who would be treated (dashed line) and percentage of those who would have future cardiovascular events covered (solid line) as functions of utilizing the different displayed 10-year predicted risks as treatment thresholds. The top-left corner corresponds to the 'treat all' scenario (treat all individuals with 10-year predicted risk above a 0% threshold), while the bottom-right corner corresponds to the 'treat none' scenario (treat only those with a predicted risk of 100%). The bottom (*D*) panel displays the net benefit of the SMART model (solid line) against the treat all (dashed) and treat none (dotted) approaches.

Secondary cohort analysis

The results of our secondary cohort analyses are available in Supplementary material online, *eTables 2–4* and *eFigures 1–4*. In keeping with its definition as a newly diagnosed cohort, baseline prevalence of smoking and cardiovascular risk-modifying therapy use were, respectively, higher and lower than in the primary cohort. SMART model performance was relatively weak for this cohort, with slightly more exaggerated under-prediction of risk, and Harrell's c-statistic = 0.559 (95% CI 0.555–0.562).

Sensitivity analysis

The characteristics of those included in the complete case analysis, and model performance for this cohort, were similar to those observed for the primary cohort (see Supplementary material online, *eTables 5–7* and *eFigures 5–8*). Similar results were also obtained when covariate measurements were restricted to within 3 years of cohort entry (Supplementary material online, *eTables 8–10* and *eFigures 9–12*).

Discussion

Among those with established ASCVD, we found that the SMART model slightly under-predicted risk among lower risk groups, but that overall model performance was similar to that observed for the original validation cohort.[15] Decision curve analysis indicated that the model could have utility across a range of clinically relevant treatment thresholds. However, model performance was weaker among those newly diagnosed with ASCVD.

To date, tools enabling individual vascular event risk estimation for secondary prevention populations have been of largely academic interest, and as yet few are routinely used. Several have been developed for specific subgroups (e.g. those with coronary heart disease specifically, rather than any ASCVD),[19,25–28] and focus on specific outcomes (e.g. coronary events rather than any ASCVD event), with many limited to prediction over only 1–2 years.[29,30] In some models, exposures are weighted equally in an ordinal scale (i.e. regardless of their beta coefficients),[31] resulting in variation in risk category thresholds among different trial populations.[32] Furthermore, dichotomization of continuous traits, although useful for identifying characteristics

Table 1 Primary cohort baseline characteristics ($n = 244\,578$)

Risk factor	Median/*n*	IQR/%	Missing: *n* (%)
Age	67.3	59.2–74.0	0
Sex (male)	151 888	62.1%	0
Date of cohort entry	01 January 2004	08 June 2000 to 21 May 2009	0
Vascular disease[a]			0
Cerebrovascular disease	73 520	30.1%	
Coronary heart disease	154 079	63.0%	
Peripheral vascular disease	32 459	13.3%	
Abdominal aortic aneurysm	7048	2.9%	
Years since first vascular event			0
<1 year before enrolment	150 557	61.6%	
1–2 years before enrolment	10 098	4.1%	
>2 years before enrolment	83 923	34.3%	
Current smoking (yes)	48 083	19.7%	24 449 (10.0%)
Diabetes mellitus	38 717	15.8%	0
Systolic blood pressure (mmHg)	140	126–150	12 605 (5.2%)
Total cholesterol (mmol/L)	4.7	4.0–5.6	28 610 (11.7%)
HDL cholesterol (mmol/L)	1.3	1.1–1.6	49 142 (20.1%)
hsCRP (mg/L)	NA	NA	244 578 (100.0%)
eGFR (mL/min/1.73 m^2)	66.1	55.5–77.8	16 334 (6.7%)
BMI (kg/m^2)	27.4	24.5–30.8	43 409 (17.7%)
Medication prescribed in the 6			0
months prior to cohort entry[a]			
Lipid-modifying therapy	148 414	60.7%	
Antihypertensive	187 052	76.5%	
Antiplatelet	168 588	68.9%	
Anticoagulant	18 690	7.6%	
Ethnicity			13 382 (5.5%)
Asian	5589	2.3%	
Black	1985	0.8%	
Mixed	557	0.2%	
White	220 850	90.3%	
Other	2215	0.9%	

BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range.
[a]Individuals can have more than one.

associated with higher-risk and hence those who derive greater benefits from treatments, do not inherently estimate 10-year event rates but rather identify high-risk individuals.[31] That said, they are recognized in some clinical guidelines as an important tool for identifying very high-risk ASCVD patients who may benefit, for instance, from novel more expensive treatment.[33] Both approaches to risk estimating (high risk or 10-year event rates) are valid and perhaps the greatest challenge is optimizing their utility or their implementation in clinical practice.

The appropriateness of any model depends upon the interests of the patient and clinician. However, there are potential advantages of a model applicable to all ASCVD subtypes, such as SMART, given the common pathology of different manifestations of ASCVD and risk of all associated outcomes regardless of the specific ASCVD diagnosis. It is likely that patients with a single ASCVD diagnosis will be interested in their risk of the wider range of relevant outcomes, and whilst these could be considered using multiple models (where available), the interpretation would be relatively complicated.

The SMART model was derived from a prospective Dutch, principally white, cohort. Similar performance was observed among more ethnically diverse patients enrolled in three global trials, and now also in a routine UK established ASCVD cohort.[15,16] Among available models for secondary prevention populations, the present findings in a routine care setting suggest the SMART model is reasonably robust for transfer into electronic health records for general populations. However, whether the SMART model is the most favourable for use depends upon the intended location of use, clinical situation, patient-clinician preferences, and value judgments on the various model performance statistics.[17] Model 'performance' comparisons are not straightforward, as while some aspects of SMART model performance are less favourable than those reported for other models, these do

Table 2 Ratios, by sex, of 10-year predicted to observed risks by 10-year predicted risk score decile and by observed age decile, as well as Chi-square calibration test results

Decile	Risk decile—Men	Risk decile—Women	Age decile—Men	Age decile—Women
1	0.64	0.74	0.63	0.71
2	0.71	0.83	0.70	0.90
3	0.75	0.86	0.75	0.86
4	0.74	0.92	0.79	0.90
5	0.83	0.90	0.85	0.95
6	0.84	0.90	0.87	1.01
7	0.88	0.99	0.89	0.99
8	0.92	1.02	0.98	1.07
9	0.98	1.06	1.03	1.01
10	1.14	1.19	1.03	1.06
χ^{2a}	$\chi^2 = 1048.42$ ($P < 0.0001$)	$\chi^2 = 352.60$ ($P < 0.0001$)	$\chi^2 = 901.33$ ($P < 0.0001$)	$\chi^2 = 148.31$ ($P < 0.0001$)

Decile 1, lowest predicted risk or lowest age decile. Ten-year predicted risks are defined as within-decile SMART-derived risk averages.
[a]Calibration test from Demler *et al.*[23]

Table 3 Ten-year predicted risk range, corresponding Kaplan–Meier observed risks, Chi-square calibration test results, and count and corresponding percentage of the sample within each range

10-year predicted risk (%)	Observed risk (%)	*n* (%)
<10	12	25 132 (10.3)
10 to <20	19	86 483 (35.3)
20 to <30	28	55 912 (22.9)
30 to <40	36	34 501 (14.1)
≥40	49	42 550 (17.4)

$\chi^{2a} = 1198.03$ ($P < 0.0001$).
[a]Calibration test from Demler *et al.*[23]

not necessarily correspond to lower model utility.[34] Comparisons would be best made for particular treatment intentions.

As has become commonplace in primary prevention, a model for secondary prevention like SMART could help promote shared decision-making through enabling more precise discussions based on individual absolute risk rather than a broad 'very high risk' category which, though useful, provides qualitative rather than quantitative information.[35,36] For the population with established ASCVD, estimates of event rates 'on-treatment' could be viewed as estimates of 'residual risk' after initial treatment, and thus would be relevant to guiding optimization of first line interventions for control of traditional risk factors, as well as potential add-on interventions, by helping quantify potential benefits for patients and physicians.[16,37] The SMART tool could also help with wider resource allocation decisions.[18] To date, it has been possible to calculate the cardiovascular risk thresholds at which a given secondary prevention treatment would be cost-effective (as defined by the relevant willingness-to-pay threshold), but *not* possible to determine which individuals fall above or below the thresholds. The result of guidelines considering that all patients with clinical manifestations of ASCVD fall within a general 'very high risk' category,[36] is that quantitative estimation of benefit/risk balance of novel therapies is uncertain between, for instance, two very-high-risk individuals, and access to some interventions may therefore be limited. The SMART tool could help overcome this issue, providing a practical framework for estimating 10-year event rates and thus risk of secondary cardiovascular events. Some practical examples of individual ASCVD clinical cases, and how the SMART tool 10-year risk estimates can be used to translate the relative risk reductions associated with different types of intervention into estimated absolute individual event reductions, are shown in *Table 4*. As well as providing estimates of individual event rates, this tool could be used to estimate the population-based impact of different strategies treating different thresholds of risk (*Figure 2*). Such approaches could help inform strategies for novel therapies which may lend themselves to population-based approaches.[18,38] An open-access calculator that can be used to aid comparisons of the benefits of potential (combinations of) interventions in which an individual may be interested, is available,[39] and is currently being expanded to include risk reduction estimates for a wide range of specific interventions.

Strengths and limitations

The strengths of this study include the large sample sizes and use of samples likely to be reasonably representative of the relevant UK populations. Although a retrospective study, outcome reliability is likely to be relatively strong. The outcomes were hard endpoints, the ONS mortality data are generally considered high quality, and UK general practitioners are incentivized to record MI and stroke occurrences using standard coding practices.[40]

The main limitations of the study are the missing data and data quality issues associated with use of routine data. Predictor measurement methods and standards will vary across the cohort, and some predictors were not routinely measured at baseline. As we could only crudely impute hsCRP data, and were required to accept variability in 'baseline' measurement timings, there was potential for model performance to be lower in our cohort than at derivation.

Table 4 **Illustrative cases using individual data to estimate potential risk reduction associated with two different therapeutic interventions for patients with SMART 10-year predicted risks of 20%, 40%, or varied**

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13
Non-HDL cholesterol (mmol/L)	2.79	3.26	2.95	3.07	2.89	2.61	2.79	3.20	3.49	3.49	3.49	3.49	3.49
HDL cholesterol (mmol/L)	0.517	0.517	0.491	0.698	0.646	0.698	0.698	0.517	0.749	0.646	0.465	0.517	0.646
Total cholesterol (mmol/L)	3.31	3.77	3.44	3.77	3.54	3.31	3.49	3.72	4.24	4.13	3.95	4.01	4.13
Age (years)	63.6	57.0	62.6	46.1	74.7	71.0	72.1	72.0	73.4	62.3	69.0	57.1	77.0
Sex	Male	Male	Female	Male	Female	Female	Female	Male	Female	Male	Male	Female	Male
Current smoking status	No	Yes	No	Yes	No	Yes	Yes	No	No	No	No	No	No
Systolic BP (mmHg)	114	150	140	130	165	148	150	160	170	156	160	145	110
Diabetes mellitus	Yes	No	No	No	No	No	No	No	No	No	No	No	No
Coronary heart disease	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	No	Yes	Yes
Cerebrovascular disease	No	No	No	Yes	No	No	No	No	No	Yes	No	No	Yes
Abdominal aortic aneurysm	No	No	No	Yes	No	No	No	No	No	No	No	No	No
Peripheral vascular disease	No	No	No	No	Yes	Yes	No	No	No	No	Yes	No	No
Years since ASCVD	—	—	2.2	—	11.8	—	12.6	14.5	23.9	4.5	7.5	—	21.5
eGFR (mL/min/1.73 m^2)	67.7	71.0	54.1	71.5	78.6	48.4	59.9	75.3	30.9	85.7	54.2	53.1	91.1
hsCRP (mg/L) imputed	2.0	2.3	2.1	4.5	3.4	3.4	2.7	2.5	2.7	2.0	2.4	2.5	2.5
SMART 10-year predicted baseline risk (%)	20.0	20.0	20.0	20.0	40.0	40.0	40.0	40.0	75.7	23.8	45.4	18.1	61.7
Addition of rivaroxaban													
Predicted 10-year risk and 95 % CI	15.2 (13.2–17.2)	15.2 (13.2–17.2)	15.2 (13.2–17.2)	15.2 (13.2–17.2)	30.4 (26.4–34.4)	30.4 (26.4–34.4)	30.4 (26.4–34.4)	30.4 (26.4–34.4)	57.5 (50.0–65.1)	18.1 (15.7–20.5)	34.5 (30.0–39.0)	13.8 (11.9–15.6)	46.9 (40.7–53.1)
Absolute risk reduction (%)	4.8	4.8	4.8	4.8	9.6	9.6	9.6	9.6	18.2	5.7	10.9	4.3	14.8
Addition of a PCSK9 MAb													
Estimated reduction in non-HDL cholesterol (mmol/L)	1.40	1.63	1.47	1.54	1.45	1.30	1.40	1.60	1.74	1.74	1.74	1.74	1.74
Predicted 10-year risk and 95% CI	15.5 (15.0–15.9)	14.8 (14.3–15.3)	15.2 (14.8–15.7)	15.1 (14.6–15.5)	30.6 (29.7–31.5)	31.4 (30.6–32.2)	30.9 (30.0–31.7)	29.7 (28.8–30.7)	54.8 (52.9–56.7)	17.2 (16.6–17.8)	32.9 (32.7–34.0)	13.1 (12.7–13.6)	44.7 (43.1–46.2)
Absolute risk reduction (%)	4.6	5.2	4.8	5.0	9.4	8.6	9.1	10.3	20.9	6.6	12.5	5.0	17.0

The table shows baseline clinical information and associated SMART predicted risks for 13 patients. Patients 1–4 have a predicted risk of 20%, Patients 5–8 a predicted risk of 40%, and Patients 9–13 variable predicted risks, but common levels of non-HDL cholesterol (non-HDL-C; 3.49 mmol/L). The anticipated absolute risk reductions (ARR) that would be associated with use of rivaroxaban [where the relative risk reduction (RRR) is a fixed proportion of global risk][a] or a PCSK9 inhibitor at maximal dose, where relative risk reduction depends upon the baseline cholesterol levels and therefore varies considerably between individuals, are also shown. The estimated ARRs associated with use of PCSK9 inhibitors require knowledge of the pre-treatment lipid profile as treatment effects are estimated based on RRR per unit absolute cholesterol reduction.[b] The associated rows in the table display the estimated impact of PCSK9 treatment on non-HDL-C levels (50% RRR)[c] and how this translates into absolute reduction of non-HDL-C (constant for a given baseline cholesterol level), and absolute cardiovascular risk reduction (variable even where baseline cholesterol levels are the same, if the baseline cardiovascular risk differs). For Patients 9–13 with identical non-HDL-C levels (3.49 mmol/L), 10-year predicted risks vary between 18.1% and 75.7%, depending upon additional factors. Thus if a monoclonal antibody to PCSK9 were added, although the non-HDL-C relative risk reduction, and absolute HDL-C reduction, would be constant for each patient, the absolute overall cardiovascular risk benefit would depend upon the SMART baseline predicted risk and could range from 5.0% to 20.9%. In contrast, a treatment such as rivaroxaban would be associated with a constant overall cardiovascular risk RRR of about 24% (i.e. this would not depend upon a specific baseline clinical measurement), and absolute cardiovascular risk reductions would be estimated to range from 4.3% to 18.2%. We have chosen the examples of rivaroxaban and PCSK9 inhibitors to demonstrate how the cardiovascular risk effects of interventions that do and do not depend on baseline variable measurements can be estimated from an individual global cardiovascular risk estimate. The principles can be generalized to any (pharmacological, lifestyle, social, or other) risk factor for which the relative risk reduction associated with intervention has been described, so long as the relevant baseline measurements are available, where relevant.

[a]The relative risk reduction was estimated to be 24% [hazard ratio = 0.76; 95% confidence interval (CI), 0.66–0.86] based on the COMPASS trial.[11]

[b]Absolute CVD risk reduction (%) estimated from a 16.9% relative risk reduction per mmol/L non-HDL-C derived from the Cholesterol Treatment Trialists' Collaboration data (see Supplementary material online, *eTable 11*).

[c]A 50% reduction in baseline non-HDL-C was assumed based on a conservative estimate of the OSLER, FOURIER, and ODYSSEY LONG TERM trials,[12–14] which used the maximal doses of two different PCSK9 inhibitors.

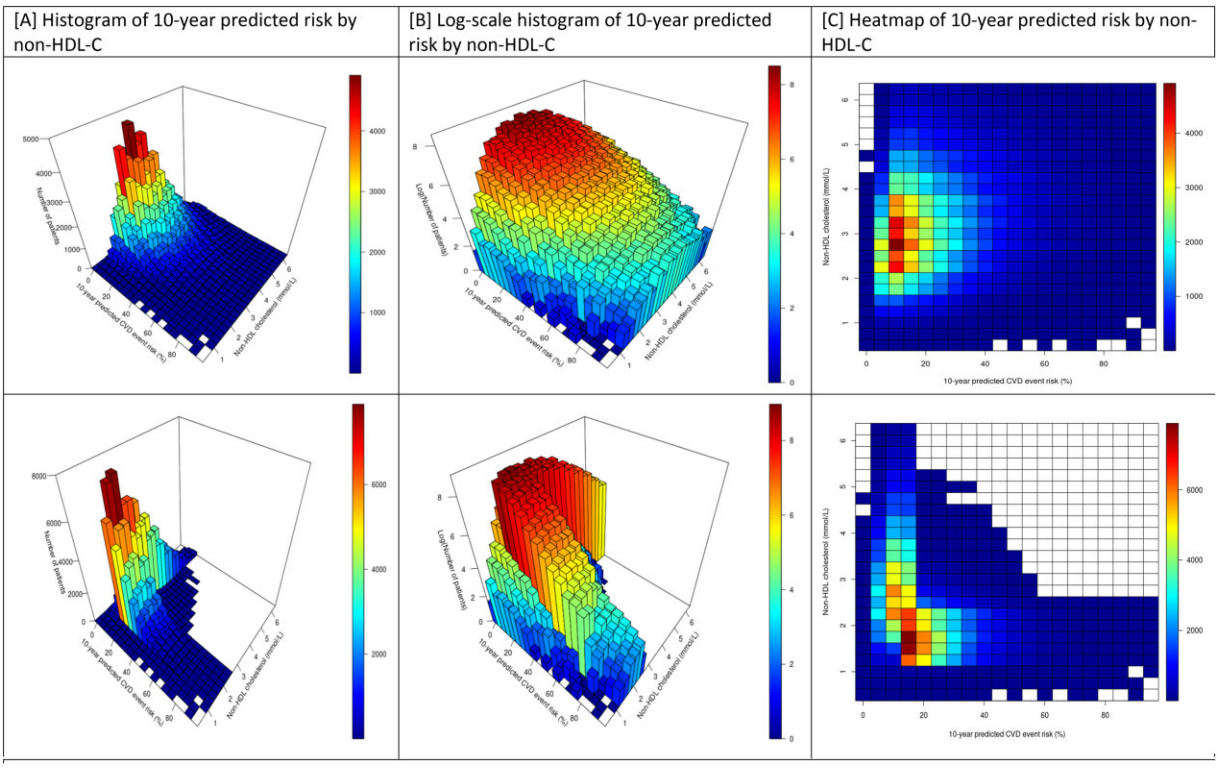

Figure 2 Estimated impact of potential interventions for patients with SMART 10-year predicted risks above 20% and non-HDL-cholesterol above 2.6 mmol/L. The top row of plots displays the distribution of 10-year SMART model-predicted cardiovascular risk by baseline non-HDL-C for n = 244 490 patients, which excludes those with baseline non-HDL-C levels above 11 mmol/L, presented as: (*A*) a 3D histogram including the number of patients; (*B*) a 3D histogram including the natural log of the number of patients; and (*C*) a heatmap showing what would be seen when looking at (*A*) directly from above, which helps to see the numbers behind the tall bins of the histogram. In order to identify differences between low numbers and zeros, white bins in the plots represent exact zero values. The bottom row of plots contains the distribution of estimated 10-year cardiovascular event risks in the study population upon treating those with non-HDL-C above 2.6 mmol/L and 10-year SMART model-predicted cardiovascular risk above 20% (n = 107 371; 43.92%) with a PCSK9 inhibitor at maximal dose. This row also presents: (*A*) a 3D histogram including the number of patients; (*B*) a 3D histogram including the natural log of the number of patients; and (*C*) a heatmap, again emphasizing the number of patients represented in (*A*). Treatment effects are estimated based on relative risk reduction (RRR) per unit absolute cholesterol reduction,[a] with the second row of plots demonstrating the estimated impact of PCSK9 treatment on non-HDL-C levels (50% RRR)[b] and how this translates into absolute reduction of non-HDL-C (constant for a given baseline cholesterol level), and absolute cardiovascular risk reduction (variable even where baseline cholesterol levels are the same, if the baseline cardiovascular risk differs). The plots show a shift away from high-cholesterol and high 10-year cardiovascular risk to lower cholesterol and lower 10-year cardiovascular risk, representing steeper 3D histograms.

[a]Absolute CVD risk reduction (%) estimated from a 16.9% relative risk reduction per mmol/L derived from the Cholesterol Treatment Trialists' Collaboration data (see Supplementary material online, *eTable 11*). [b]A 50% reduction in baseline non-HDL-C was assumed based on a conservative estimate of the OSLER, FOURIER, and ODYSSEY LONG TERM trials,[12–14] which used the maximal doses of two different PCSK9 inhibitors.

Although we did not observe this, it is still the case that model performance could be altered by more 'complete' data, but relatively unlikely that data more in keeping with derivation dataset measurement standards would lead to lower performance. The imputation of hsCRP and its reliability is especially limited for some clusters, e.g. those <40 years old, for which counts were small in the original derivation and validation cohorts, as well as our primary cohort. Despite the limitation of absent hsCRP data, model performance was similar to that reported for the original validation cohort, which included full information on all covariates, thus supporting robustness to imputation. Moreover, in two further cohorts the model has performed well without hsCRP data.[16,41] Therefore, while hsCRP is useful, the model appears to be clinically useful with imputation of this data as needed. Additionally, the imputation step provides some imputed information regarding hsCRP, although obviously limited. Complete case analyses provided support regarding the impact of imputation more generally. Similarly, analyses using covariate measurements made within 3 years of cohort entry showed outcomes comparable to those obtained in the less restrictive primary analysis. Future work could build on the present approach, by embedding the SMART risk score into clinical trials, to ascertain quantitative risk thresholds and, by comparison, treatment benefits. This could help improve future guidelines from being largely qualitative (binary) decision-making systems to more precision and personalized based medicine. This could better aid implementation of novel therapies, where health economic

evaluations based on average risk have led to a reluctance to implement many therapies.

Conclusions

For patients with established ASCVD, the SMART model offers a reliable tool for assessment of 10-year residual risk in routine clinical care settings. This tool can aid personalized informed decision-making by offering clinicians, patients, and policy-makers an additional tool to help decide to whom to offer novel therapies.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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Conflict of interest: K.K.R. reports acting as a consultant for Amgen, Sanofi, Regeneron, Medicines Company, Cerenis, Lilly, Ionis/AKCEA, Esperion, Novartis, Silence Therapeutics, Resverlogix, and Abbvie; and as a speaker for Amgen, Sanofi, Kowa, AstraZeneca, Pfizer, Takeda, Boehringer Ingelheim, Algorithm, Cipla. He has received research grants from Sanofi, Regeneron, Amgen, Merck Sharpe & Dohme, Daiichi Sankyo, and Pfizer through his institution. B.A.F. reports receiving personal fees from Merck & Co., Amgen, Regeneron, Sanofi, Pfizer, CiVi BioPhama, and KrKA Phamaceuticals, and grants from Merck & Co., Amgen, Novartis, and Esperion Therapeutics. No conflicts of interest are reported by the other team members.

Data availability

The data used in this manuscript were obtained from the UK Clinical Practice Research Datalink. Due to CPRD license restrictions, we are unable to make the data publicly available; however, the data can be requested from CPRD.

Ethical approval

Permission for data usage was obtained from the CPRD Independent Scientific Advisory Committee (protocol number 18_272). Linked pseudonymized data were provided by CPRD. Data are linked by NHS Digital, the statutory trusted third party for linking data, using identifiable data held only by NHS Digital. Select general practices consent to this process at a practice level with individual patients having the right to opt-out.

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