ORIGINAL RESEARCH

Development and validation of a cardiovascular risk score for patients in the community after acute coronary syndrome

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ABSTRACT

Objective Following acute coronary syndrome (ACS), patients are managed long-term in the community, yet few tools are available to guide patient-clinician communication about risk management in that setting. We developed a score for predicting cardiovascular disease (CVD) risk among patients managed in the community after ACS.

Methods Adults aged 30–79 years with prior ACS were identified from a New Zealand primary care CVD risk management database (PREDICT) with linkage to national mortality, hospitalisation, pharmaceutical dispensing and regional laboratory data. A Cox model incorporating clinically relevant factors was developed to estimate the time to a subsequent fatal or non-fatal CVD event and transformed into a 5-year risk score. External validation was performed in patients (Coronary Disease Cohort Study) assessed 4 months post-ACS.

Results The PREDICT-ACS cohort included 13 703 patients with prior hospitalisation for ACS (median 1.9 years prior), 69% men, 58% European, median age 63 years, who experienced 3142 CVD events in the subsequent 5 years. Median estimated 5 year CVD risk was 24% (IQR 17%–35%). The validation cohort consisted of 2014 patients, 72% men, 92% European, median age 67 years, with 712 CVD events in the subsequent 5 years. Median estimated 5-year risk was 33% (IQR 24%–51%). The risk score was well calibrated in the derivation and validation cohorts, and Harrell's c-statistic was 0.69 and 0.68, respectively.

Conclusions The PREDICT-ACS risk score uses data routinely available in community care to predict the risk of recurrent clinical events. It was derived and validated in real-world contemporary populations and can inform management decisions with patients living in the community after experiencing an ACS.

INTRODUCTION

People fall on a continuum of cardiovascular risk, from the risk of developing risk factors through to the risk of recurrent cardiovascular disease (CVD) events. In practice, the vast majority of the life-course of risk is managed in the community by primary care clinicians. Risk assessment for primary prevention of CVD is well established,[1–4] yet nearly 50% of CVD events occur in people already diagnosed with CVD.[5] The aetiology and severity of CVD, and the effectiveness of its management, vary substantially and consequently there is a wide range of risk of recurrent events among patients with CVD.[6 7] Significant improvements in the management of acute coronary syndrome (ACS) and subsequent chronic ischaemic heart disease (IHD) have led to an increasing prevalence of post-ACS IHD in the community.[8 9] Clinical guidelines provide direction in the short term, yet few tools are available to assess CVD risk and guide patient-clinician communication and long-term risk management of these patients.

As we aspire to realise precision medicine, healthcare decisions, practices and interventions should be tailored to individuals based on their predicted risk of disease. We sought to develop a CVD risk score for use in the community for patients in the convalescent and long-term post-ACS phases of IHD.

METHODS

Derivation cohort

New Zealand's PREDICT web-based decision support programme has been described previously.[10] When used to estimate CVD risk for a patient, PREDICT stores a risk profile in the patient's electronic record plus an anonymised copy in a central database, which are linked to encrypted National Health Index (eNHI) numbers and made available to researchers at the University of Auckland. At the time of these analyses, 527 024 people with and without CVD were in PREDICT, representing over two thirds of people aged >30 years in the Auckland and Northland regions (where PREDICT software is predominantly used). Although existing CVD risk scores are designed for people without CVD, clinical guidelines recommending annual review of people post-ACS augmented by a national health target that at least 90% of the population aged 35–74 years have their CVD risk assessed (irrespective of CVD status), means patients with CVD in the PREDICT cohort will be representative of patients being assessed in primary care.

The derivation cohort for this study included NZ residents aged 30–79 years who had experienced ACS at some time (up to 1988) prior to having their index PREDICT risk assessment between January 2007 and December 2016. Prior ACS was determined from ICD-10-AM coded national routinely collected data on public hospitalisations (see online supplementary appendix B). All appendices are presented as online supplementary data.

Data considerations

Clinical data from the cohort were anonymously linked to national hospital discharge and mortality data, pharmaceutical dispensing and regional laboratory tests via their unique eNHI. Routine clinical laboratory data (ratio of total cholesterol to high-density lipoprotein [TC:HDL], creatinine, HbA1c) were limited to the most recent values recorded up to 2 years prior or 2 weeks after the index assessment. Medication use was the dispensing of at least one agent in the designated class within the 6 months prior to the index risk assessment. Medications are defined in online supplementary appendix C.

A clinician-defined diagnosis of heart failure (HF) was not captured by the PREDICT database. Instead, we defined HF as an ICD-coded hospitalisation for HF at any prior date, dispensing of a loop diuretic on at least three occasions in the 5 years prior to the index risk assessment or dispensing of metolazone in the 6 months prior. This definition thus represents the spectrum of HF, including patients who have not been hospitalised.

The outcome of interest was time to first (recurrent) CVD event within 5 years of the index risk assessment, with a CVD event defined as a hospitalisation for ACS, HF, stroke or other cerebrovascular disease, peripheral vascular disease or a CV death. Events were identified from ICD-10-AM coded national hospitalisation and mortality databases (see online supplementary appendix B). Cardiovascular death was defined from the death certificate or if death had occurred within 28 days of a CVD hospitalisation.[11] Patients whose death was not associated with CVD were censored at the date of death. For all others, the end of follow-up was 31 December 2016.

Statistical derivation of the model

Potential predictors were selected a priori based on clinical relevance and availability in routine practice. They were: age, sex, ethnicity, an area-based metric of socioeconomic deprivation, smoking, diabetes, atrial fibrillation (AF), HF, time since most recent ACS, type of most recent ACS (ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), unstable angina (UA)) body mass index (BMI), systolic blood pressure (SBP), TC:HDL, creatinine, dispensing of a BP-lowering medication, a lipid lowering medication or an antiplatelet or anticoagulant. Prespecified interactions between SBP and BP lowering medications, TC:HDL and statins, ethnicity and BMI, ethnicity and diabetes and sex and diabetes, were assessed. Self-identified ethnicity was categorised similar to the national prioritisation protocol for health[12] in the order: Māori, Pacific, Indian, Chinese/Other Asian, European.

The CVD event rate was modelled using multivariable Cox regression. Validity of the proportional hazards assumption was assessed with Schoenfeld residuals and visual inspection of log(log(S_o)) versus log(time) plots; linearity of the relationship between predictors and the log hazard were assessed via plots of Martingale residuals.[13 14] Where non-linear relationships affected more than 5% of patients (age, creatinine, BMI, SBP), variables were categorised at clinically relevant thresholds. Alternative approaches to non-linearity are possible but as the aim was to produce scores for use in clinical practice, categorisation into clinically relevant groups, which also allow for unknown results,[15] was the preferred approach. Online supplementary appendix G shows complete case analyses to assess the impact of missing values for BMI (8%) and creatinine (10%). HbA1c was missing for 34% of people without diabetes and complete case analysis would cause significant bias. Population screening for diabetes began in NZ in 2014 and only 2% of people without diabetes entering the cohort since then are missing HbA1c. Use of a missing category for HbA1c allowed full use of the derivation dataset and validation of the score in cohorts with missing data. Appendix G shows a sensitivity analysis limiting the cohort to patients assessed from 2014 onwards. Time since prior ACS was categorised at predetermined thresholds to allow for uncertainty in the exact date of the prior event (which would be needed to model time as a continuous variable).

Risk scores

Multivariable relative risk was transformed to absolute risk by estimating the baseline hazard at 5 years, at the mean values of continuous and categorical covariates. Although the mean of a categorical variable may have no sensible interpretation, a baseline hazard derived in this way gave the most accurate risk prediction. The prognostic index or sum of each coefficient multiplied by the measured variable, was centred on the mean prognostic index.[16]

Performance

Model calibration is represented by plots of predicted against observed event rate (from Kaplan-Meier estimates) within deciles of predicted risk. Global model fit was assessed with the Cox & Snell R^2 and Nagelkerke's R^2 and 95% CIs derived from 1000 bootstrap samples. Model discrimination was quantified by Harrell's c-statistic and the Gönen & Heller K-statistic.[17] Internal validation was performed using 1000 bootstrap samples.

Validation

External validation was performed by applying the risk score to patients participating in the Coronary Disease Cohort Study (CDCS).[18] The CDCS is a prospective, observational study that recruited 2140 patients with ACS from two major hospitals (Christchurch and Auckland) in NZ from 2002 to 2009. Patients underwent comprehensive clinical assessment including a 12-lead ECG, echocardiography and blood sampling at 1, 4 and 12 months following the index event, with additional annual review for ≥2 years. To assess the accuracy of the risk score for patients who present to their community clinician within 6 months of their ACS event, we elected to use CDCS data from the 4 month visit. In addition, there were 323 (16%) patients older than 79 years, the upper age limit of the derivation cohort. These patients were categorised as 70–79 years when calculating risk and a sensitivity analysis that excluded them was also performed. Outcome events were independently adjudicated from clinical records and aggregated to be consistent with the definitions used in the derivation cohort. Online supplementary appendix A presents an extended comparison of the derivation and validation cohorts.

Analyses were performed using R V.3.4.3.[19] The research process for the derivation cohort study was approved by the NZ Northern Region Ethics Committee Y (AKY/03/12/314) with subsequent annual approval by the National Multi-Region Ethics Committee (MEC/07/19/EXP) and for the validation cohort study was approved by the National Multi-region Ethics Committee (CTY/02/02/018). This research was done without patient involvement in study design, interpretation of results, writing or editing of this document.

RESULTS

The derivation cohort includes 13 703 patients aged 30–79 years who had experienced an ACS and were subsequently risk

Table 1 Characteristics of the derivation (PREDICT) and validation (CDCS) cohorts

	Derivation cohort	Validation cohort
n	13 703	2014
Men	9390 (69%)	1448 (72%)
Age, years	63 (55–70)	67 (58–76)
European ethnicity	7966 (58%)	1852 (92%)
Resident in the most deprived quintile of socioeconomic position	3879 (28%)	0*
Medical history		
Current smoker	2095 (15%)	125 (6%)
Diabetes	4597 (34%)	319 (16%)
Atrial fibrillation	1954 (14%)	107 (5%)
Heart failure	2476 (18%)	686 (34%)
Most recent ACS event		
STEMI	3838 (28%)	463 (23%)
NSTEMI	6501 (47%)	1027 (51%)
Unstable angina	3364 (25%)	524 (26%)
Years since most recent ACS event	1.9 (0.5. 5.3)	0.35 (0.32, 0.38)
Clinical measurements		
Body mass index, kg/m^2	29 (26–33)	27 (24–30)
Systolic BP, mm Hg	130 (120–140)	130 (114–142)
TC:HDL	3.6 (2.9–4.4)	4.2 (3.4–5.2)
HbA1c, mmol/mol—diabetes, no diabetes	55 (47–67), 40 (37–42)	NA*
Creatinine, µmol/L	84 (72–97)	90 (80–110)
Medications		
BP lowering	11 980 (87%)	1852 (92%)
Lipid lowering	11 488 (84%)	1764 (88%)
Anticoagulant or antiplatelet	11 624 (85%)	1952 (97%)
Follow-up		
Total follow-up, years	3.5 (1.6–5.5)	3.8 (2.3–5.6)
Non-fatal or fatal broad CVD at 5 years	3142 (23%)	712 (35%)

Values are n (%) or median (IQR).
*The CDCS did not collect data on socioeconomic status or HbA1c, so all subjects were allocated to a median socioeconomic index quintile of 3 and to the missing HbA1c category.
ACS, acute coronary syndrome; BP, blood pressure; CDCS, Coronary Disease Cohort Study; CVD, cardiovascular disease; NZ, New Zealand; TC:HDL, ratio of total cholesterol to high-density lipoprotein.

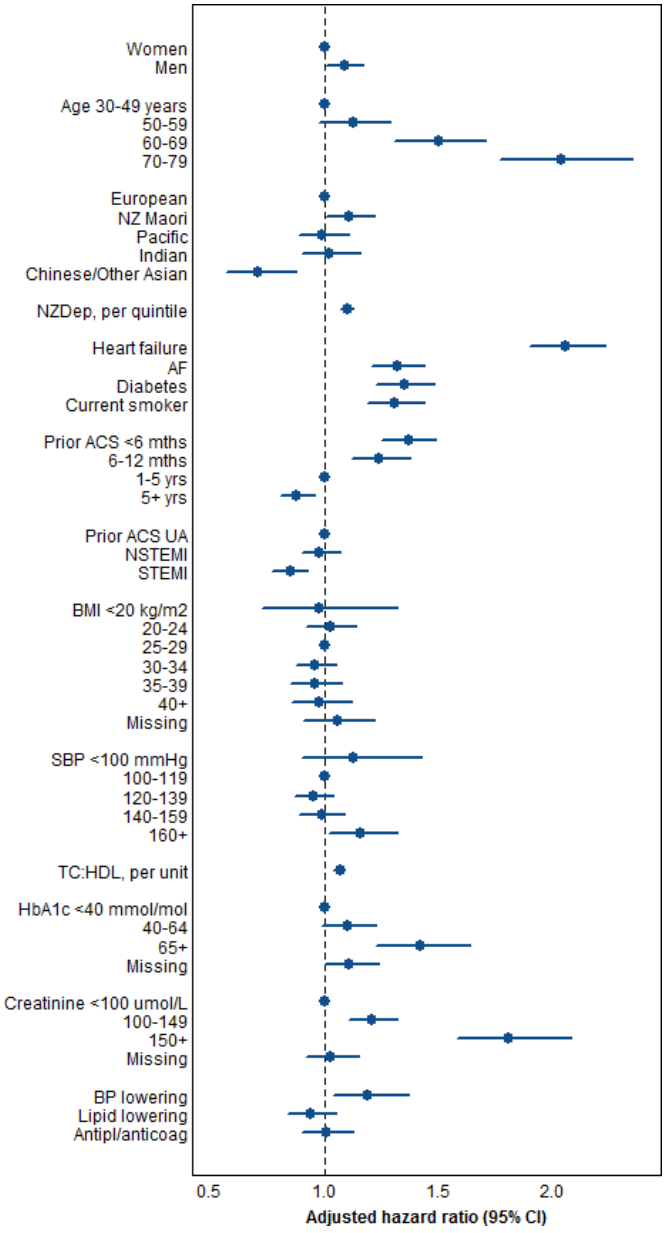

Figure 1 Adjusted HRs and 95% CIs for predictors in the Cox model for fatal or non-fatal CVD. ACS, acute coronary syndrome; AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; NSTEMI, non-STEMI; SBP, systolic blood pressure; STEMI, ST elevation MI; TC:HDL, total cholesterol to high-density lipoprotein.

assessed using the PREDICT software between January 2007 and December 2016 (table 1, online supplementary appendix A).

Two-thirds of the cohort were men and median age was 63 years (IQR 55–70 years). The study population was 16% Māori, 13% Pacific, 9% Indian and 4% Chinese/Other Asian, with the remaining 58% European. One-third had diabetes, 40% had a BMI >30 kg/m^2, 18% had HF and CV medication use was high. Half of the prior ACS events were a NSTEMI, and a wide range of time had passed since the event: median duration 1.9 years (IQR 0.5–5.3 years). A total of 3612 subsequent CVD events occurred, of which 3142 occurred within 5 years (23% mean 5-year event rate).

Multivariable model

The risk of experiencing a CVD event increased with increasing age, particularly after age 60 (figure 1; online supplementary appendix D). Compared with Europeans, Māori were at higher risk and Chinese/Other Asians were at lower risk, and risk increased linearly per quintile increase in socioeconomic deprivation index. Risk was significantly higher among people with HF, AF, diabetes or current smokers and when risk had been assessed within 12 months of their last ACS. Patients whose most recent event was a STEMI were at lower risk of experiencing a broadly defined CVD event than patients who had a NSTEMI or UA. There was no significant change in risk associated with BMI, and SBP only increased risk when ≥160 mm Hg. Risk increased with increasing TC:HDL, HbA1c over 65 mmol/mol or not measured and serum creatinine >100 µmol/L. The majority of the cohort were receiving BP-lowering medications and this was also associated with increased risk. Prespecified interactions were assessed (see online supplementary appendix F) and were not included in the final models. When models were developed using complete data on BMI and creatinine, there were no important changes in the HRs or their statistical significance, except the risks associated with sex, with being Māori and with receiving a BP-lowering medication tipped into non-significance (see online supplementary appendix G). Similarly,

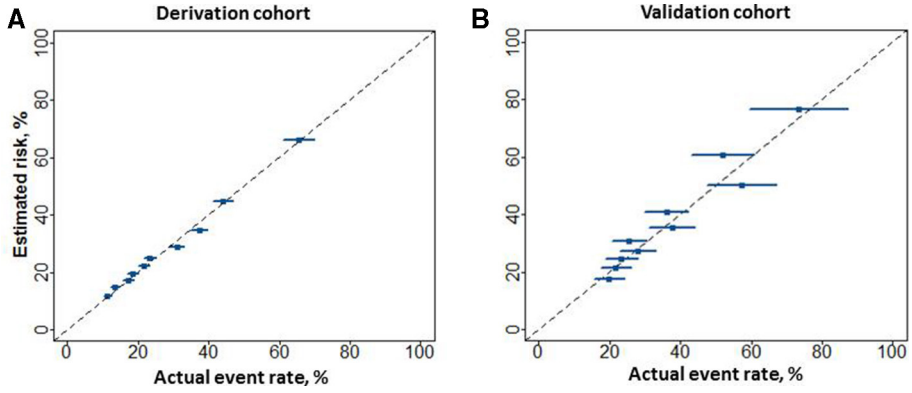

Figure 2 Risk score calibration in the derivation cohort (PREDICT) and the external validation cohort (CDCS). The CVD risk score in (A) the derivation cohort and (B) the validation cohort. Calibration is shown as the estimated risk (in deciles) against survival from Kaplan-Meier analysis. Dashed line=perfect calibration. CDCS, Coronary Disease Cohort Study.

the model using complete data on HbA1c after the introduction of population screening for diabetes had very similar point estimates for the known HbA1c categories (see online supplementary appendix G).

Predicted 5-year risk

Using the baseline survival estimate in online supplementary appendix D, median predicted 5-year risk of a CVD event was 23.9% (IQR 17.2%–35.4%). Average risk in the lowest decile of predicted risk was 11.6% and in the highest decile was 68.8%. The risk equation is in online supplementary appendix H.

Score performance in the derivation cohort

Figure 2A shows excellent calibration of the score throughout the range of risk. Harrell's c-statistic was 0.69 (95% CI 0.68 to 0.70), Gönen & Heller's K-statistic was 0.66 (95% CI 0.65 to 0.67) and Nagelkerke's R^2 was 12% (see online supplementary appendix I). There was very good calibration when stratified by HF status and by type of index ACS (see online supplementary appendix J).

Score performance in the validation cohort

External validation was performed by applying the PREDICT-ACS equation to the CDCS cohort (table 1; online supplementary appendix A). Among the CDCS cohort, 712 (35%) CVD events occurred within 5 years and median estimated risk with the score was 32.8% (IQR 24.3%–50.6%). Figure 2B shows excellent calibration of the score when applied to the CDCS cohort. Calibration remained very good when stratified by HF status, by type of index ACS or by sex (see online supplementary appendix K) and when people aged over 79 (n=323) were excluded from the cohort (data not shown).

DISCUSSION

Contemporary healthcare continues to evolve, with the goal being to individualise patient assessment and management. For patients with CVD, it is expected that care will be appropriate for their type and stage of disease, yet there are few tools to assist medium to long-term management of people who survive an acute coronary event.[20] People who have experienced ACS are not all at the same risk of a recurrent event[6 7] and risk does not cease to be relevant after the 6 month horizon predicted by most acute scores. We have developed a score for use by primary and specialist healthcare professionals to enhance risk assessment and management of patients in the convalescent and late post-ACS phases of IHD.

CVD can be viewed on a life-course continuum, progressing from risk factors, to subclinical atherosclerosis, through to symptomatic CVD, including ACS and late sequelae such as HF and death. Risk assessment in the context of primary prevention of CVD is well established, with numerous risk scores available to inform patient management.[1–4] Yet few equivalent scores are available for use in primary care for patients with established CVD. For these patients, long-term management in most jurisdictions takes place in the community (primary care) and risk scores that integrate markers that can be readily assessed in the community are required to inform ongoing risk management. Cardiac imaging and advanced biomarkers are not routinely available in primary care, so it is not yet practical to include them in a score for this setting.

Whether a risk score for secondary prevention is appropriate for a given population depends on the type of CVD and time of risk assessment postevent. We have previously developed a secondary prevention score for patients with any type of established CVD.[6] This has a broad application; however, the baseline risk of the cohort will clearly be different to that of a group of patients who have had an ACS event. While other scores have not focused on ACS or have projected risk across a longer timeframe,[21] a recent 5-year score developed from the multinational CLARIFY registry[9] defined stable coronary artery disease (CAD) as >3 months post-myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention, or >50% coronary stenosis or chest pain with confirmed myocardial ischaemia. The CALIBER group has also developed a 5-year score for people with stable CAD,[22] defined as 6 months post-ACS or a history of CAD prior to the 10-year study period starting in the year 2000. When externally validated, the CLARIFY score underestimated risk[23] and the CALIBER score both underestimated and overestimated risk depending on the event rate. This is not to say the scores are 'invalid'. One of the validation cohorts used by CLARIFY included patients with MI or coronary revascularisation; however, unlike the CLARIFY registry, it did not exclude patients with other CV (or non-CV) comorbidities.[24] The other two cohorts were placebo groups from trials[25 26] where very specific entry criteria inevitably define a different patient group from routine care. The CALIBER score was applied to a cohort who had undergone coronary angiography in 1996/1997, in a different era with respect to CAD management. The definition

of stable CAD and time since the prior event in these cohorts will be different to those used to derive the risk scores, and the findings of validation inform the boundaries of their use.

The risk score developed in this study is for application to patients post-ACS and, importantly, acknowledges the dependence of risk on the time elapsed between the prior ACS and risk assessment. To test robustness of this adjustment, we assessed performance of the risk score in a validation cohort where risk was calculated 4 months post-ACS for all patients, and the score remained very accurate. Compared with the derivation cohort, the validation cohort had nearly three times as many CV deaths in the 5 years following risk assessment at 4 months and half the rate of HF readmissions. The range of clinical events in the outcome are more likely to occur in different phases post-ACS, so although risk in the validation cohort was assessed when patients were at a higher risk of death,[27] they were at a lower risk of readmission for HF compared with a cohort assessed at a later time post-ACS. It may be appropriate to include elective revascularisation for progressively limiting symptoms in the CVD outcome for this cohort; however, the meaning of this would be affected by local clinical practice and has not been included at this stage.

Accuracy of risk prediction was the same regardless of the type of prior ACS (STEMI, NSTEMI, UA) or whether patients had HF or not. Similarly, although the scores were derived in patients up to 80 years of age, calibration did not change when older patients in the validation cohort were categorised into the 70–79 year age group or were excluded. To capture the cardiovascular risk associated with impaired glucose metabolism, diabetes was defined from a composite of the PREDICT database, prior hospitalisation data and dispensing records. As such, type of diabetes could not be identified and accuracy of risk prediction may vary among diabetes subtypes.

Not all patients in the derivation cohort had data on BMI, HbA1c or creatinine. To minimise limitations on using the score in clinical practice, we chose to model these variables with a category for missing values, aware that this can lead to bias in parameter estimates and poor performance when applied to new patients. Redeveloping the models using only those patients with a value for BMI and creatinine (complete case analysis, n=11 344) did not result in a difference in the relative risk estimates or performance in the validation cohort, which had a different pattern of missing data. HbA1c is now available in all adults undergoing CVD risk assessment in NZ, so the category for missing HbA1c will rarely be required in practice.

Risk prediction, communication and subsequent management titrated against risk are all required to improve clinical outcomes for patients post-ACS. The risk score presented here can be used in clinical practice to guide clinicians and patients towards individualising healthcare. Clearly, there are standard clinical recommendations for risk factor modification and medications which apply to all patients post-ACS. A lower risk estimate in the post-ACS setting would not be a reason to withdraw medications. Rather, the risk profile can be a tool to inform clinician-patient interactions where clear communication can facilitate reinforcement of, and higher intensity of, risk factor modification. A recent study randomised patients post-ACS to receive clopidogrel (control) or to receive clopidogrel or ticagrelor on the basis of their ischaemic and bleeding risks predicted by the GRACE and CRUSADE scores.[28] Patients whose bleeding risk outweighed their need for more potent ischaemic risk reduction received clopidogrel, whereas patients with higher ischaemic risk received ticagrelor. The 2-year CV event rate was significantly lower in the risk stratified group than the control group (adjusted HR 0.65), supporting the use of risk scores to guide antiplatelet therapy after ACS. How such risk tools are used will depend on the local healthcare environment. The current risk score, using routinely available clinical data, has the advantage of potential application across different healthcare settings, including primary care and outpatient-based secondary care. Implementation programmes will be required to ensure appropriate clinical use, including strategies to reach those at highest need who often have least access to healthcare. Such programmes have been successfully established in the context of primary prevention, and given the understanding of the lifecourse of CVD, it is a logical evolution to use this experience in the post-ACS setting. Once established, the scores may also be used to inform decisions about novel therapies, which may also be trialled in the context of changes in quantifiable risk.

In conclusion, we have developed a risk score for use in both primary and specialist care of patients following ACS, which uses routinely available clinical data. The score can clearly predict the risk of recurrent clinical events and thus has the potential to inform clinical decision-making to individualise patient care. The score adds to existing risk scores which are available for individuals across the life-course of CVD.

Key questions

What is already known on this subject?

- Improvements in the management of acute coronary syndrome (ACS) have contributed to an increasing number of people with established cardiovascular disease in the community. Clinical guidelines provide direction in the short term, yet few tools are available to guide patient-clinician communication and long-term cardiovascular disease risk management for these patients.

What might this study add?

- The PREDICT-ACS secondary prevention score shows that cardiovascular risk in the convalescent and long-term post-ACS phases is heterogeneous. This risk score incorporates routine clinical data commonly available in primary care and, by incorporating time since event, allows re-evaluation of risk of recurrent clinical events a year or more after an ACS event.

How might this impact on clinical practice?

- Appropriate risk stratification can enhance patient-clinician communication and inform clinical decision-making to individualise patient care for patients following ACS.

Contributors KP, AK, RND, SW and RTJ conceived and designed the primary aim and method of this study. RTJ, SW, AK, RND, RWT and AMR designed and implemented data collection. KP, BW and NJE analysed the data. KP drafted the manuscript. All authors critically reviewed and developed the final manuscript.

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Competing interests Outside the submitted work, RWT reports grants from Roche Diagnostics and personal fees from Merck.

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