ESC European Society of Cardiology

European Journal of Preventive Cardiology (2021) **28**, 2010–2017
doi:10.1093/eurjpc/zwaa098

FULL RESEARCH PAPER
Risk Prediction/Assessment & Stratification

Predicting cardiovascular disease risk across the atherosclerotic disease continuum

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Received 19 July 2020; revised 11 September 2020; editorial decision 24 September 2020; accepted 28 September 2020; online publish-ahead-of-print 16 October 2020

Aims Cardiovascular disease (CVD) guidelines dichotomize populations into primary and secondary prevention. We sought to develop a risk equation for secondary prevention of CVD that complements existing equations for primary prevention of CVD, and to describe the distributions of CVD risk across the population.

Methods and results Adults aged 30–79 years who had routine CVD risk assessment in 2007–16 were identified from a large primary care cohort (PREDICT) with linkage to national and regional datasets. The 5-year risk of developing CVD among people without atherosclerotic CVD (ASCVD) was calculated using published equations (PREDICT-1°). A new risk equation (PREDICT-2°) was developed from Cox regression models to estimate the 5-year risk of CVD event recurrence among patients with known ASCVD. The outcome for both equations was hospitalization for a CVD event or cardiovascular death. Of the 475 161 patients, 12% (57 061) had ASCVD. For those without ASCVD, median (interquartile range) 5-year risks with the PREDICT-1° score were women 2.2% (1.2–4.2%), men 3.5% (2.0–6.6%), and whole group 2.9% (1.6–5.5%). For those with ASCVD, the 5-year risks with the new PREDICT-2° equation were women 21% (15–33%), men 23% (16–35%), and whole group 22% (16–34%).

Conclusion We developed CVD risk scores for people with ASCVD (PREDICT-2°) to complement the PREDICT-1° scores. Median CVD risk is eight-fold higher among those with ASCVD than those without; however, there was overlap and the widest distribution of CVD risk was among people with ASCVD. This study describes a CVD risk continuum and the limitations of a 'one size fits all' approach to assessing risk in people with ASCVD.

Keywords Cardiovascular risk • Primary prevention • Secondary prevention • Atherosclerotic disease continuum

Introduction

Multivariable models to estimate the risk of a cardiovascular disease (CVD) event and guide management for patients without a history of atherosclerotic CVD (ASCVD) are now embedded in both clinical practice and international guidelines.[1,2] In contrast, patients with known ASCVD have, until recently, been considered in CVD prevention guidelines to be at a uniformly 'clinical high risk' without further risk stratification.[3–5] This division of CVD risk creates an artificial dichotomy between those with or without ASCVD despite the continuum of the underlying atherosclerotic disease process. Multivariable risk stratification models are increasingly available however, in the acute post-event phase,[6–8] and more recently for longer-term post CVD event risk prediction.[9–11]

The New Zealand (NZ) PREDICT CVD Cohort Study was initiated in 2002 to develop CVD risk scores for adult New Zealanders across the continuum of atherosclerotic disease. We have previously used this cohort to develop the PREDICT-1° equations which estimate 5-year CVD risk in people without ASCVD.[12] Our group has also developed an equation for people with ASCVD to estimate the 2-year risk of a 'hard' outcome, comprising CVD death, myocardial infarction (MI), or stroke.[9] However, there is currently no model available which, like the PREDICT-1° equation, estimates the more broadly defined ASCVD risk over a 5-year period for patients with

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known ASCVD. The aim of the current study is to develop, in the same primary care cohort, a complementary 5-year risk equation for secondary prevention of CVD (PREDICT-2°) and describe the distributions of 5-year CVD risk across the population.

Methods

Patient cohorts

The PREDICT web-based clinical decision support programme for CVD risk assessment and management has been described previously.[13] When PREDICT is used by a clinician to estimate CVD risk for a patient, an electronic risk profile is stored both in the patient record and anonymously in a central database. With the permission of health providers, this profile is linked to an encrypted National Health Index number (eNHI) and made available to researchers at the University of Auckland. The PREDICT cohort represents over two-thirds of people aged ≥30 years in the Auckland and Northland regions of NZ (approximately one-third of the national population), where PREDICT software is predominantly used.

Sub-cohort with known ASCVD: the cohort used to develop a risk score for secondary prevention of CVD (PREDICT-2°) included people aged 30–79 years who had experienced ASCVD prior to having a PREDICT assessment in primary care between 1 January 2007 and 31 December 2016. Existing ASCVD was defined as at least one of: angina, unstable angina, MI, percutaneous coronary intervention or coronary artery bypass grafts, other coronary heart disease, ischaemic stroke, transient ischaemic attack (TIA), other ASCVD, or peripheral vascular disease (PVD), as determined from ICD-10-AM coded national routinely collected data on public hospitalizations (Supplementary material online, *Appendix SA*) or as recorded by the primary care clinician at the time of risk assessment. The first PREDICT assessment after a hospitalized or non-hospitalized ASCVD event or diagnosis was the index assessment.

Sub-cohort without ASCVD: the absolute risk of developing CVD in the next 5 years was calculated using the published PREDICT-1° risk equations.[12] This was applied to people who had a PREDICT risk assessment in primary care between 1 January 2007 and 31 December 2016 and were aged 30–79 years, but who were not in the sub-cohort with ASCVD defined above. Consistent with the development of the scores, patients with heart failure (HF), diabetic nephropathy, or with eGFR <30 mL/min/1.73 m^2 were also excluded from this sub-cohort.

Data considerations

Clinical data from the PREDICT cohort were anonymously linked to ICD-10-AM coded national hospital discharge and mortality data, pharmaceutical dispensing, and regional laboratory tests via the unique eNHI. Pharmaceutical data were limited to cardiovascular (CV) medications dispensed within 6 months prior to the index assessment. Medication use was defined as at least one dispensing in the 6 months prior to the index risk assessment. Blood pressure (BP)-lowering medication is at least one of: β-blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, or other antihypertensive agent. Lipid-lowering medication is a statin or other lipid-lowering agent. Anticoagulation is defined as warfarin or novel oral anticoagulants, and antiplatelets are aspirin or non-aspirin antiplatelet agents.

For the sub-cohort with ASCVD, the time between the most recent prior ASCVD event and the index PREDICT risk assessment was determined for hospitalized events. Patients whose most recent ASCVD hospitalization was >5 years prior to the index risk assessment, or whose sole prior event or diagnosis was angina, PVD, or non-hospitalized cerebrovascular disease not associated with stroke or TIA, or where the date of hospitalization or diagnosis was unknown, were placed in the same category in the model.

For both sub-cohorts, the outcome of interest was time to first new or recurrent CVD event within 5 years of the index risk assessment. A CVD event was defined as hospitalization for angina, unstable angina, MI, HF, TIA, ischaemic or haemorrhagic stroke or other cerebrovascular disease, PVD, or a CV death. CV death was defined from the death certificate or if death had occurred within 28 days of a CVD hospitalization. Primary and secondary diagnoses were included. The time to event was the time between the index risk assessment and first fatal or non-fatal CVD event (Supplementary material online, *Appendix SA*), or to 31 December 2016 for those who did not experience a subsequent CVD event. Patients having a non-CV death were censored at the date of death.

Statistical approach to developing the PREDICT-2° risk score

Potential predictors were selected a priori based on the published literature[9,14] and whether they were routinely measured in practice. They were age, sex, ethnicity, socioeconomic position (the area-based NZDep Index), diabetes, smoking, atrial fibrillation (AF), HF, time since most recent CVD event, body mass index (BMI), systolic BP (SBP), ratio of total cholesterol to HDL (TC:HDL), glycated haemoglobin (HbA1c), creatinine, dispensing of a BP-lowering medication or a lipid-lowering medication, or an antiplatelet or anticoagulant. Interactions between SBP and BP-lowering medications, and between ethnicity and each of BMI, diabetes, and HbA1c, were assessed. Ethnicity was categorized similarly to the national prioritization protocol for health[15] in the order: Māori (the indigenous population of NZ), Pacific, Indian, Chinese/other non-Indian Asian, and European.

Supplementary material online, *Appendix SE* shows complete case analyses to assess the impact of missing values for BMI (9%) and creatinine (11%). HbA1c was missing for 35% of people without diabetes and complete case analysis would cause significant bias. Population screening for diabetes began in NZ in 2014 and only 3% 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. Supplementary material online, *Appendix SE* shows a sensitivity analysis limiting the cohort to patients assessed from 2014 onwards.

The 5-year event rate was modelled using multivariable Cox regression. Validity of the proportional hazards assumption was confirmed from visual inspection of Schoenfeld residual plots, and linearity of the relationship between each predictor and the log hazard were assessed via plots of Martingale residuals.[16,17] Where non-linear relationships affected >5% of patients, variables were categorized at clinically relevant thresholds (age and creatinine). BMI and SBP were categorized at pre-determined thresholds to assess known U-shaped relationships between these measures and outcome in people with ASCVD.[18] Alternative approaches to non-linearity were possible, but as the aim was to produce risk scores to be used in clinical practice, categorization into clinically relevant groups was the preferred approach.

PREDICT-2° risk score and assessment of score performance

Multivariable risk from the Cox model was transformed to absolute risk by estimating the baseline hazard at 5 years, at the mean values of continuous and categorical covariates. The prognostic index, or sum of each coefficient multiplied by the measured variable, was centred on the mean prognostic index.[19]

Model calibration is represented by plots of the observed event rate (from Kaplan–Meier estimates) against predicted event rate within deciles

of predicted risk. Global model fit was assessed with the Cox and Snell R^2 and Nagelkerke's R^2,[20,21] and model discrimination was quantified by Harrell's *c*-statistic[22] and the Gönen & Heller *K*-statistic.[23] Fit and discrimination were assessed using 1000 bootstrap samples.

Analyses were performed using R v3.4.3 statistical software and 'survival' package. Model development and assessment followed guidance provided in the TRIPOD statement[24] however external validation of the new score has not been performed at this stage. The cohort study and research process were 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). The study complies with the Declaration of Helsinki.

Results

There were 475 161 patients in the cohort, of whom 12% (57 061) had ASCVD at the time of their index PREDICT risk assessment (*Table 1*). Compared with patients without ASCVD, those with ASCVD were older, more likely to be male, and to live in an area with greater socioeconomic deprivation. They were also more likely to smoke, have AF, diabetes mellitus, elevated creatinine, and at least one non-cardiac comorbid condition (28% vs. 8%). Median SBP was higher however TC:HDL was lower. Use of BP-lowering, lipid-lowering, antiplatelet, and anticoagulant agents was higher among those with ASCVD than those without.

The most recent admission for ASCVD prior to risk assessment had occurred up to 12 months earlier for 19% of the ASCVD cohort, 1–5 years earlier for 24%, and >5 years earlier for 18%. Forty-four percent of the admissions were for ACS, stroke, or TIA. The remaining 39% of the cohort with ASCVD had either not required hospitalization or their prior hospitalization was solely for angina or PVD.

Cardiovascular disease events in those with and without atherosclerotic cardiovascular disease

The median time to event or end of follow-up (date of index assessment to date of first subsequent event or data extract) was 3.9 and 3.6 years for those with and without ASCVD, respectively (*Table 1*). During this period there were a total of 25 469 first CVD events after index assessment, of which 57% were in those with ASCVD. The type of first CVD event is shown in *Table 2*.

PREDICT-2° 5-year risk model and equation

A detailed description of this model including coefficients, baseline hazard, performance statistics, and a patient example are provided in Supplementary material online, *Appendices SB and SC*. In brief, the model included 17 variables. The risk of a CVD event within 5 years increased with increasing age and socioeconomic deprivation. Risk was higher among smokers, people with HF, AF, diabetes, and those with a more recent event. Being underweight was associated with significantly greater risk. A U-shaped relationship between SBP and outcome was seen, with increased risk when SBP <100 or ≥160 mmHg. Risk increased with increasing TC:HDL and creatinine. Use of BP-lowering and anti-thrombotic medications, but not lipid-lowering therapy, was associated with higher risk. Pre-specified interactions were assessed and not included in the final model (Supplementary material online, *Appendix SD*).

The PREDICT-2° 5-year equation was well calibrated across the range of risk with slight overestimation of risk for women at low levels of risk (Supplementary material online, *Appendix SC*). Nagelkerke's R^2 was 12.98% [interquartile range (IQR) 12.96–12.99%], Harrell's *c*-statistic 0.708 (IQR 0.703–0.713), and Gönen and Heller's *K*-statistic 0.673 (IQR 0.668–0.677). Forty percent of the events ($n = 5760$) occurred in the 20% of the cohort identified as being at highest risk, showing good discrimination.

Distribution of 5-year risk in those with and without atherosclerotic cardiovascular disease

For those without ASCVD, the median (IQR) risks estimated with the PREDICT-1° 5-year equations were: women 2.2% (1.2–4.2%), men 3.5% (2.0–6.6%), and whole group 2.9% (1.6–5.5%). For those with ASCVD, the corresponding risks estimated with the PREDICT-2° 5-year equation were seven to 10-fold higher with a wider distribution of risk: women 21% (15–33%), men 23% (16–35%), and whole group 22% (16–34%). As shown in *Figure 1*, the distribution for those without ASCVD is right-skewed, with a peak (mode) at 0.7% 5-year risk and a long tail through higher risk values, whereas the distribution for those with ASCVD is flatter with a mode at 18% 5-year risk. Risk could not be calculated in 0.1% of the cohort (496 without ASCVD, 2 with ASCVD) due to missing TC:HDL.

Over 70% of those without ASCVD had a 5-year risk of <5% but almost none of those with existing ASCVD was in this category. In contrast, risk was ≥20% for only 1.2% of those without ASCVD but for 58% of those with ASCVD (*Table 3*). However, there was overlap between the risk distributions: 27% of those without clinically evident ASCVD and 42% of those with ASCVD had a 5-year risk between 5% and 20%, translating to 29% ($n = 136\,862$) of the whole cohort. Breaking this down, 18% of the whole cohort were at 5–10% risk (mainly those without ASCVD), 7% were at 10–15% risk, and 4% were at 15–20% risk (*Table 3*).

Discussion

PREDICT is a large, prospective cohort study representative of patients in primary care who are recommended for CVD risk assessment in NZ.[5] We have derived the PREDICT-2° equation, a risk score for secondary prevention of CVD, to complement our previously published PREDICT-1° scores developed in the same primary care cohort. By applying the pair of equations to the nearly half a million patients enrolled in the PREDICT cohort, we have been able to describe the distributions of 5-year CVD risk across the population with and without ASCVD. Over half of the CVD events occurred in the 12% of the cohort with known ASCVD, who had a median 5-year risk eight times higher than those without ASCVD. The distribution of risk was wider for those with ASCVD than for those without, however there was overlap between the distributions, with 29% of people with and without ASCVD at 5–20% 5-year CVD risk (11% at 10–20% risk).

Table 1 Characteristics of the PREDICT cohorts with and without atherosclerotic cardiovascular disease

	Without ASCVD	With ASCVD
n	418 100	57 061
Men	233 505 (56%)	35 410 (62%)
Age (years)	54 (46–61)	64 (57–71)
≥70	32 706 (8%)	17 013 (30%)
Ethnicity		
European	234 769 (56%)	33 729 (59%)
NZ Māori	52 727 (13%)	9300 (16%)
Pacific	50 286 (12%)	6781 (12%)
Indian	35 199 (8%)	4149 (7%)
Chinese/other Asian	45 119 (11%)	3102 (5%)
NZDep index, quintile		
1 (least deprived)	94 481 (23%)	9808 (17%)
2	83 661 (20%)	9721 (17%)
3	75 950 (18%)	10 137 (18%)
4	76 662 (18%)	11 717 (21%)
5 (most deprived)	87 346 (21%)	15 678 (28%)
Medical history		
Ex-smoker	70 556 (17%)	17 134 (30%)
Current smoker	58 995 (14%)	8363 (15%)
Family history of premature CVD	43 412 (10%)	9776 (17%)
Atrial fibrillation	6189 (2%)	9040 (16%)
Diabetes	40 846 (10%)	19 504 (34%)
Heart failure	—	10 007 (18%)
Modified Charlson comorbidity index[a]		
0	384 311 (92%)	41 026 (72%)
1–2	28 212 (7%)	11 349 (20%)
≥3	5577 (1%)	4686 (8%)
Most recent ASCVD diagnosis		
ACS	—	16 580 (29%)
Other CHD including angina		14 257 (25%)
Stroke or TIA	—	8433 (15%)
Other cerebrovascular disease		396 (0.7%)
PVD		4856 (9%)
Non-hospitalized diagnosis	—	12 539 (22%)
Time since prior hospitalized ASCVD[b]		
Prior event within last 6 months	—	7101 (12%)
Prior event in last 6–12 months	—	4342 (7%)
Prior event in last 1–5 years	—	13 547 (24%)
Prior event 5+ years ago	—	10 076 (18%)
Clinical measurements		
Body mass index (kg/m^2)	28 (25–32)	29 (26–33)
<20	9160 (2%)	1084 (2%)
20–25	81 703 (20%)	9666 (17%)
25–30	123 730 (30%)	18 919 (33%)
30–35	69 845 (17%)	12 873 (23%)
35–40	29 901 (7%)	5752 (10%)
≥40	19 629 (5%)	3846 (7%)
Missing	84 132 (20%)	4921 (9%)
Systolic BP (mmHg)	128 (120–138)	130 (120–140)
<100	4880 (1%)	920 (2%)
100–120	99 319 (24%)	10 142 (18%)

Continued

Table 1 *Continued*

	Without ASCVD	With ASCVD
120–140	217 888 (52%)	27 053 (47%)
140–160	80 376 (19%)	14 433 (25%)
≥160	15 637 (4%)	4513 (8%)
TC:HDL	3.9 (3.2–4.8)	3.6 (2.9–4.4)
HbA1c (mmol/mol)—diabetes	54 (47–68)	54 (47–66)
Missing	2.1%	1.3%
HbA1c (mmol/mol)—no diabetes	39 (36–41)	40 (37–42)
Missing	41%	35%
Creatinine (μmol/L)	76 (65–87)	83 (71–97)
<100	284 954 (68%)	39 374 (69%)
100–149	24 029 (6%)	8882 (16%)
≥150	488 (0.1%)	2443 (4%)
Missing	108 629 (26%)	6360 (11%)
Medications (prior 6 months)		
BP lowering	93 407 (22%)	44 581 (78%)
Lipid lowering	62 938 (15%)	41 449 (73%)
Anticoagulant	2911 (1%)	5691 (10%)
Antiplatelet	35 912 (9%)	38 807 (68%)
Follow-up		
Time to first event or end of follow-up (years)	3.9 (2.8–6.1)	3.6 (1.7–5.6)
Non-fatal or fatal broad CVD	10 876 (2.6%)	14 593 (26%)
At 5 years	7975 (1.9%)	12 668 (22%)
CV death	2330 (0.6%)	3622 (6.3%)
Any death	9752 (2.3%)	7199 (13%)

Values are *n* (%) or median (interquartile range).
ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CV, cardiovascular; NZ, New Zealand; TC:HDL, ratio of total cholesterol to HDL.
[a]Cardiac conditions removed from updated Charlson score.[25]
[b]Hospitalized events excluding those solely due to angina or peripheral vascular disease.

Table 2 Type of first CVD event that occurred after the index assessment in cohorts with and without atherosclerotic cardiovascular disease

	Without ASCVD	With ASCVD
First events	10 876	14 593
Cardiovascular death	990 (9.1%)	792 (5.4%)
Non-fatal		
Ischaemic heart disease	3967 (36%)	6272 (43%)
Heart failure	2376 (22%)	3101 (21%)
Stroke, TIA, and other cerebrovascular disease	2966 (27%)	2406 (16%)
Peripheral vascular disease	577 (5.3%)	2022 (14%)

Times to event are median (interquartile range).

To our knowledge, this is the first time that CVD risk scores for primary and secondary prevention have been derived from and applied to a large, contemporary, and representative primary care cohort. Prior studies have presented equations for primary[4,25,26] and more recently secondary prevention[9–11] of CVD, but due to methodological differences including endpoint definitions and time periods for risk prediction, application in a cohort spanning those with and without ASCVD has not been possible.

Overlap in cardiovascular disease risk prediction variables

Consistent with a common underlying atherosclerotic disease process for those with and without ASCVD, many of the associations between risk factors and outcome were the same in both the primary and secondary models. These included increased risk with increasing age, BP, TC:HDL, Māori ethnicity, socioeconomic deprivation,

smoking, diabetes, and AF. Other variables included only in the PREDICT-2° equation were measures of cardiac and other end-organ disease burden (HF and renal dysfunction) and time from the most recent ASCVD event, which can be considered a surrogate for disease activity. The use of BP medication had similar weighting in both equations, which may represent the impact of high BP which is poorly captured by 1–2 BP measurements recorded for calculation of CVD risk.

Clinical implications and implementation

Over half of the CVD events over 5 years occurred in those with known ASCVD (12% of the cohort) and very few of these patients had a 5-year risk <10%. There were high levels of secondary prevention medication (average of two medications per person), comparable with other ASCVD cohorts,[27,28] thus risk assessment can now quantify the degree of residual risk. While the risk assessment process developed here cannot define the mechanism of residual risk it can provide a starting point for engagement between patients and clinicians for decisions as part of individualized care planning. Relatively lower risk in this context of secondary prevention should not be used as justification for reducing standard secondary prevention treatment. While the risk assessment is on-treatment risk, this does not imply that dosages of medications were optimal for individuals nor that other risk factors have been optimally addressed. The clinical value of risk stratification in resource limited health systems is to help identify patients with excess residual risk who will benefit the most from more intensive follow-up. This may include obtaining additional biomarkers such as troponin, hs-CRP, Lp(a), or genetic markers, in addition to lifestyle and further medication interventions. For example, several expensive new agents are becoming available which reduce risk in patients post-ACS, including newer anti-platelet agents, proprotein convertase subtilisin/kexin type 9 inhibitors and gliptins, but in many cost-constrained healthcare systems these will need to be targeted to those who are most likely to receive the greatest benefit.[29] Further research will be required to determine optimal strategies to improve outcomes using individualized approaches based on level of risk in patients with ASCVD.

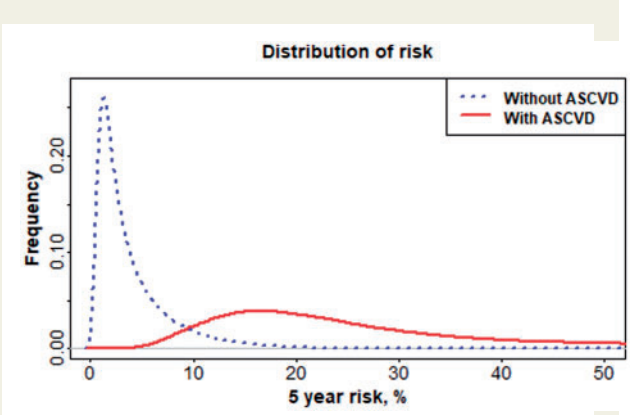

Figure 1 Distribution of risk estimates for those with and without atherosclerotic cardiovascular disease. Median risk (interquartile range) without atherosclerotic cardiovascular disease = 2.9% (1.6–5.5%) and with atherosclerotic cardiovascular disease = 22% (16–34%).

The pathophysiology of atherosclerosis is a continuum from early through to advanced vascular disease. At some point across that continuum the patient has a symptomatic first clinical event, but at that point the patient may have anywhere from very early to advanced atherosclerosis. Rather than the traditional approach of dichotomizing patients into primary and secondary prevention groups based on this first clinical event, we believe that a more useful concept to inform clinical practice is to estimate every patient's risk based on all available risk factors and present this in a common CVD risk format. This approach can help to support the equitable treatment of high-risk primary and secondary prevention patients by ensuring both clinicians and patients are informed by a standardized quantitative risk assessment.

The PREDICT 1° and 2° risk equations can be implemented electronically, with an algorithm to choose the equation that is most appropriate to each patient based on inclusion and exclusion criteria, and then present the appropriate 5-year CVD risk for each individual.

Limitations

Additional variables that may inform CVD risk, including biomarkers (such as NT-proBNP, cardiac troponins, or hsCRP) and measures of frailty and cognitive status, are not routinely measured in all patients and so were not available for inclusion in risk model development. CVD history and non-fatal outcomes were defined from admissions to public hospitals only and did not include data from private

Table 3 Comparison of patients with and without ASCVD in each risk band

	Without ASCVD	With ASCVD	Without:with ASCVD
n with risk calculated	417 604	57 059	
<5%	299 402 (72%)	29 (<0.01%)	10 324
5–9.9%	80 317 (19%)	3339 (6%)	24
10–14.9%	24 618 (6%)	9384 (16%)	2.6
15–19.9%	8199 (2%)	11 005 (19%)	0.7
20–24.9%	2967 (0.7%)	9037 (16%)	0.3
25–29.9%	1203 (0.3%)	6289 (11%)	0.2
≥30%	898 (0.2%)	17 976 (32%)	0.05

hospitals; however, in NZ, patients with acute CVD events are almost all admitted to the public health system.

Conclusions

We have developed the PREDICT-2° risk equation to complement the PREDICT-1° risk scores for primary prevention of CVD. The equations have good discrimination and are well calibrated to the NZ population. They enable quantitative CVD risk assessment across the adult population using the same outcome and risk horizon. Whilst median CVD risk is eight-fold higher among those with ASCVD compared with those without, the distribution of individual patient risk in each cohort is wide and there is overlap between them. These equations can therefore be used to rationally and transparently target more intensive interventions to those at elevated CVD risk across the population, rather than by using the more traditional, but pathophysiologically artificial, primary vs. secondary dichotomy.

Supplementary material

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

Funding

This work was supported by the Health Research Council of NZ via project grants [03/183, 08/121] and a programme grant [11/800]. K.K.P. is the New Zealand Heart Foundation Hynds Senior Fellow and R.N.D. holds the New Zealand Heart Foundation Chair of Heart Health.

Conflict of interest: none declared.

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