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Original research

Paired risk scores to predict ischaemic and bleeding risk twenty-eight days to one year after an acute coronary syndrome

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ABSTRACT

Objective The recommended duration of dual anti-platelet therapy (DAPT) following acute coronary syndrome (ACS) varies from 1 month to 1 year depending on the balance of risks of ischaemia and major bleeding. We designed paired ischaemic and major bleeding risk scores to inform this decision.

Methods New Zealand (NZ) patients with ACS investigated with coronary angiography are recorded in the All NZ ACS Quality Improvement registry and linked to national health datasets. Patients were aged 18–84 years (2012–2020), event free at 28 days postdischarge and without atrial fibrillation. Two 28-day to 1-year postdischarge multivariable risk prediction scores were developed: (1) cardiovascular mortality/rehospitalisation with myocardial infarction or ischaemic stroke (ischaemic score) and (2) bleeding mortality/rehospitalisation with bleeding (bleeding score).

Findings In 27 755 patients, there were 1200 (4.3%) ischaemic and 548 (2.0%) major bleeding events. Both scores were well calibrated with moderate discrimination performance (Harrell's c-statistic 0.75 (95% CI, 0.74 to 0.77) and 0.69 (95% CI, 0.67 to 0 .71), respectively). Applying these scores to the 2020 European Society of Cardiology ACS antithrombotic treatment algorithm, the 31% of the cohort at elevated (>2%) bleeding and ischaemic risk would be considered for an abbreviated DAPT duration. For those at low bleeding risk, but elevated ischaemic risk (37% of the cohort), prolonged DAPT may be appropriate, and for those with low bleeding and ischaemic risk (29% of the cohort) short duration DAPT may be justified.

Conclusion We present a pair of ischaemic and bleeding risk scores specifically to assist clinicians and their patients in deciding on DAPT duration beyond the first month post-ACS.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Most patients are recommended to receive dual anti platelet therapy (DAPT) for at least a month, and up to a year, after an acute coronary syndrome (ACS). Guidelines recommend that estimated bleeding and recurrent ischaemic risk be used to guide the decision regarding DAPT duration. However, there are currently no risk scores which estimate these risks over this period.

WHAT THIS STUDY ADDS

⇒ We have used a comprehensive real-world registry cohort, linked to national administrative datasets, to develop a pair of ischaemic and major bleeding risk scores to estimate ischaemic and bleeding risk up to 1 year post-ACS, in patients who are event free at 1 month.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The risk scores are designed specifically to assist clinicians and their patients in deciding on subsequent DAPT duration by providing objective risk estimates of both the major benefits (reduction in ischaemic events) and harm (increase in major bleeding events) of continuing DAPT beyond 1 month post-ACS. All variables used in the current risk scores are routinely collected in the All NZ ACS Quality Improvement electronic registry for every New Zealander who has a coronary angiogram post-ACS. Consequently, each patient can have individualised bleeding and ischaemic risks automatically generated prior to discharge.

INTRODUCTION

Clinical trials have established that the use of more potent and prolonged antithrombotic medications after an acute coronary syndrome (ACS) can reduce subsequent ischaemic events.[1–3] However, the benefit is at least partly offset by the increased risk of major bleeding.[1–4] Because there is a wide range of individual ischaemic and bleeding risk, post-ACS guidelines recommend the use of multivariable risk scores to estimate the risk of adverse ischaemic and major bleeding outcomes to facilitate optimal management.[5–7]

In current practice, patients are recommended to receive dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor for at least a month post-ACS. The recommended duration of DAPT beyond the first month is based on the estimated risks of bleeding and of recurrent ischaemic events.[7]

Table 1 Baseline characteristics of patients with versus without ischaemic or major bleeding events at 28 days to 1 year after ACS discharge

		Ischaemic events		Major bleeding events	
	Total	No event	Event	No event	Event
n (%)	27 755	26 555 (95.7)	1200 (4.3)	27 207 (98.0)	548 (2.0)
Demographics					
Men	19 460 (70.1)	18 665 (70.3)	795 (66.2)	19 097 (70.2)	363 (66.2)
Mean age (SD), year	63.1 (11.1)	63.0 (11.0)	66.9 (11.3)	63.1 (11.1)	66.2 (10.9)
Māori	3021 (10.9)	2827 (10.6)	194 (16.2)	2934 (10.8)	87 (15.9)
Pacific	1760 (6.3)	1655 (6.2)	105 (8.8)	1709 (6.3)	51 (9.3)
Indian	1288 (4.6)	1221 (4.6)	67 (5.6)	1268 (4.7)	20 (3.6)
Chinese/other Asian	1015 (3.7)	988 (3.7)	27 (2.2)	991 (3.6)	24 (4.4)
European	20 671 (74.5)	19 864 (74.8)	807 (67.2)	20 305 (74.6)	366 (66.8)
Highest deprivation (NZ deprivation Q4 or 5)	12 821 (46.2)	12 167 (45.8)	654 (54.5)	12 549 (46.1)	272 (49.6)
Clinical history					
History of CVD	7850 (28.3)	7237 (27.3)	613 (51.1)	7659 (28.2)	191 (34.9)
History of CHF	590 (2.1)	508 (1.9)	82 (6.8)	572 (2.1)	18 (3.3)
Prior hospitalisation for bleeding	1267 (4.6)	1167 (4.4)	100 (8.3)	1193 (4.4)	74 (13.5)
Diabetes mellitus	6269 (22.6)	5781 (21.8)	488 (40.7)	6110 (22.5)	159 (29.0)
Median total:HDL cholesterol (IQR)	4.2 (3.3, 5.2)	4.2 (3.3, 5.2)	4.0 (3.2, 5.2)	4.2 (3.3, 5.2)	3.9 (3.0, 4.9)
Total:HDL cholesterol unavailable	1952 (7.0)	1833 (6.9)	119 (9.9)	1904 (7.0)	48 (8.8)
Mean SBP (SD), mm Hg	143.3 (26.2)	143.2 (26.1)	144.0 (28.5)	143.2 (26.2)	144.9 (26.8)
Clinical presentation					
ACS type					
STEMI	7522 (27.1)	7264 (27.4)	258 (21.5)	7391 (27.2)	131 (23.9)
NSTEMI	15 693 (56.5)	14 910 (56.1)	783 (65.2)	15 354 (56.4)	339 (61.9)
Unstable angina	4540 (16.4)	4381 (16.5)	159 (13.2)	4462 (16.4)	78 (14.2)
eGFR<60, mL/min/1.73 m^2	5566 (20.1)	5041 (19.0)	525 (43.8)	5381 (19.8)	185 (33.8)
Index admission bleeding	732 (2.6)	696 (2.6)	36 (3.0)	704 (2.6)	28 (5.1)
Worst Killip class II, III or IV	2345 (8.4)	2134 (8.0)	211 (17.6)	2273 (8.4)	72 (13.1)
Investigation and management					
Reduced LVEF (<40%)	2803 (10.1)	2567 (9.7)	236 (19.7)	2741 (10.1)	62 (11.3)
LVEF unavailable	6503 (23.4)	6204 (23.4)	299 (24.9)	6373 (23.4)	130 (23.7)
Obstructive CAD	24 277 (87.5)	23 167 (87.2)	1110 (92.5)	23 773 (87.4)	504 (92.0)
Coronary intervention					
PCI only	17 599 (63.4)	16 951 (63.8)	648 (54.0)	17 232 (63.3)	367 (67.0)
CABG	2775 (10.0)	2700 (10.2)	75 (6.2)	2739 (10.1)	36 (6.6)
Medications at discharge					
Statin	26 413 (95.2)	25 301 (95.3)	1112 (92.7)	25 895 (95.2)	518 (94.5)
Beta-blocker	22 351 (80.5)	21 352 (80.4)	999 (83.2)	21 902 (80.5)	449 (81.9)
ACEi/ARB	20 013 (72.1)	19 113 (72.0)	900 (75.0)	19 617 (72.1)	396 (72.3)
Aspirin	27 155 (97.8)	25 975 (97.8)	1180 (98.3)	26 614 (97.8)	541 (98.7)
P2Y12 receptor inhibitor	22 850 (82.3)	21 827 (82.2)	1023 (85.2)	22 368 (82.2)	482 (88.0)
Clopidogrel	6013 (21.7)	5614 (21.1)	399 (33.2)	5890 (21.6)	123 (22.4)
Ticagrelor	16 802 (60.5)	16 182 (60.9)	620 (51.7)	16 443 (60.4)	359 (65.5)
Prasugrel	35 (0.1)	31 (0.1)	4 (0.3)	35 (0.1)	0 (0)
Dual antiplatelet therapy	22 596 (81.4)	21 584 (81.3)	1012 (84.3)	22 118 (81.3)	478 (87.2)

Data are presented as mean (SD) or median (IQR) as appropriate for continuous variables and as n (column percentage) for categorical data.
ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction; total:HDL cholesterol, ratio of total to high-density lipoprotein cholesterol.

For patients who have recurrent ischaemic or bleeding events in the first month, subsequent antithrombotic treatment needs to be individualised, but in the majority, who are event free by 1 month, it would be useful to have a pair of risk scores which estimate the ischaemic and bleeding risks over the remainder of the year, to inform DAPT duration. Although there are separate risk scores that can stratify patients' post-ACS ischaemic and major bleeding risk,[8–14] no scores have been developed within the same population using a common methodology. Unless both ischaemic and bleeding risk scores are validated in the same target population, calibration errors may lead to substantial overestimation or underestimation of both the absolute levels of risk and the ratio of ischaemic to bleeding risk[15] potentially leading to inappropriate clinical decision making. A further complexity is that ischaemic and bleeding risks vary with time after the ACS event, with the highest event rates in the first

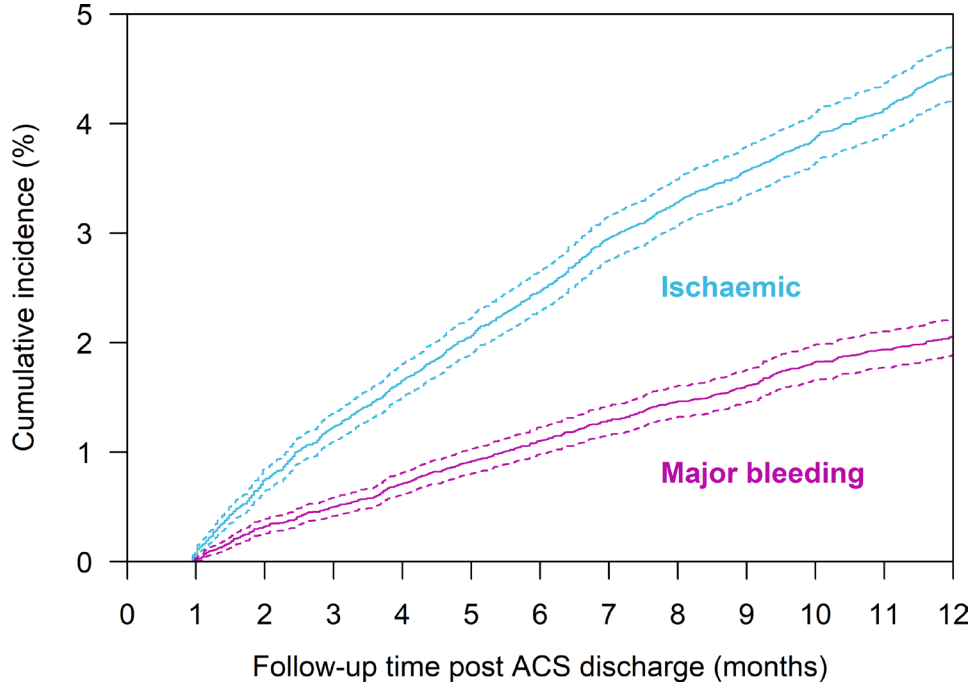

Figure 1 Kaplan–Meier cumulative incidence plots of (A) ischaemic and (B) major bleeding events for patients with ACS who are event free at 28 days postdischarge. ACS, acute coronary syndrome.

month post-ACS.[16 17] Currently, available risk scores include those early events and may therefore overestimate risk beyond the first month. To be most clinically useful, scores need to be customised for the cohort and for the time period over which they are to be applied.

In Aotearoa New Zealand, virtually all patients with ACS who are managed invasively with coronary angiography are captured in the All New Zealand ACS Quality Improvement (ANZACS-QI) registry and are linked to well-validated national administrative datasets for outcome ascertainment. The aim of this study was to use this real-world ACS cohort to develop a pair of ischaemic and major bleeding risk scores to estimate ischaemic and bleeding risk up to 1 year post-ACS in patients who are event free at 1 month. The risk scores are designed specifically to assist clinicians and their patients in deciding on subsequent DAPT duration.

METHODS

Cohort and data sources

The ANZACS-QI programme is a web-based prospective registry of New Zealand (NZ) residents hospitalised with ACS and undergoing angiography. A mandatory dataset is collected. The registry collects data regarding demographic, clinical history and presentation, investigations and management available by the time of discharge from hospital. A detailed description of data collection has been previously published.[18] The registry undergoes monthly auditing to ensure capture of >99% of all patients admitted with suspected ACS who are investigated with coronary angiography, and annual audit to check the accuracy of data entry.

A cohort which included all those aged 18–84 years who received coronary angiography during the index ACS admission and were discharged alive between 1 January 2012 and 31 August 2020 was created from the ANZACS-QI registry. The index admission was defined as the entire episode of care, from hospital admission to discharge home, and included interhospital transfers. This cohort was linked to national public hospitalisations, mortality and pharmaceutical dispensing databases, using encrypted National Health Index (NHI) numbers.[18] The association between atrial fibrillation (AF) and either ischaemic risk (which includes stroke) or bleeding risk will be confounded by variable anticoagulation use which cannot be adequately addressed in a model where the majority of patients did not have AF. Patients were therefore excluded if they had prior hospitalisation with AF or were dispensed anticoagulant medication in the 6 months before the admission or 3 months after discharge (n=7123). In addition, 83 patients with incomplete data were excluded, as were patients who had an ischaemic or major bleeding event in the first 28 days postdischarge (n=568).

Outcomes

Post-ACS ischaemic model

The primary outcome was cardiovascular disease (CVD) mortality or rehospitalisation for myocardial infarction (MI) or ischaemic stroke between 29 days and 1 year postdischarge. Hospitalisations were identified using primary or secondary International Classification of Diseases, 10th Revision, Australian Modification (ICD-10-AM) diagnosis codes.

Post-ACS bleeding model

The primary outcome was bleeding mortality or rehospitalisation for a primary ICD-10-AM bleeding diagnosis or a secondary bleeding diagnosis with an associated blood transfusion, between 28 days and 1 year postdischarge.[19] Major bleeding events associated with coronary artery bypass grafting (CABG), other surgical procedures or trauma were excluded.

The end of follow-up for both models was 31 December 2020.

ICD-10 AM codes used to define all outcomes are shown in online supplemental appendix table 1. Sixty patients experienced both ischaemic and major bleeding events within 1 year follow-up, which were therefore outcomes in both models.

Table 2 Adjusted multivariable HRs from the final ischaemic and bleeding models

Variable	Levels	Ischaemic events	Major bleeding events
Sex	Women	1	1
	Men	0.91 (0.81, 1.04)	0.96 (0.80, 1.16)
Age per 10 years*		**1.21 (1.13, 1.30)**	**1.29 (1.17, 1.43)**
Ethnicity	European	1	1
	Māori	**1.45 (1.22, 1.73)**	**1.91 (1.48, 2.47)**
	Pacific	1.07 (0.85, 1.34)	**1.72 (1.25, 2.36)**
	Indian	1.08 (0.83, 1.40)	0.87 (0.55, 1.37)
	Chinese/other Asian	0.69 (0.47, 1.02)	1.38 (0.91, 2.09)
NZDep quintile		1.04 (0.99, 1.08)	0.99 (0.93, 1.06)
Heart rate, bpm	60–79	1	1
	<60	0.87 (0.72, 1.06)	0.89 (0.68, 1.16)
	≥80	**1.25 (1.10, 1.41)**	**1.27 (1.06, 1.53)**
Estimated GFR, mL/min/1.73 m^2	≥90	1	1
	60–89	1.17 (0.97, 1.41)	0.80 (0.63, 1.01)
	30–59	**1.75 (1.42, 2.16)**	1.04 (0.78, 1.39)
	<30 without dialysis	**2.94 (2.17, 3.97)**	1.49 (0.93, 2.39)
	<30 with dialysis	**4.06 (2.94, 5.60)**	**1.70 (1.01, 2.86)**
Haemoglobin level at admission	Normal†	1	1
	Low	**1.28 (1.10, 1.49)**	**1.75 (1.41, 2.18)**
CAD severity	No obstructive CAD	1	1
	Single VD	**1.6 (1.24, 2.07)**	**1.71 (1.18, 2.49)**
	Double VD	**2.2 (1.69, 2.86)**	**1.58 (1.07, 2.34)**
	LMS±three VD	**3.0 (2.34, 3.83)**	**1.70 (1.17, 2.48)**
Coronary intervention	Neither PCI nor CABG	1	1
	PCI only	**0.62 (0.54, 0.71)**	1.07 (0.85, 1.34)
	CABG	**0.30 (0.24, 0.39)**	**0.59 (0.40, 0.87)**
History of CVD	No prior CVD	1	–
	Prior MI	**1.75 (1.51, 2.02)**	–
	Other prior CVD	**1.74 (1.49, 2.02)**	–
Diabetes mellitus	No diabetes	1	–
	Diabetes with insulin	**1.62 (1.37, 1.93)**	–
	Diabetes without insulin	**1.24 (1.06, 1.44)**	–
Smoking status	Non-smoker	1	–
	Current smoker	**1.38 (1.20, 1.59)**	–
Type of ACS	NSTEMI	1	–
	STEMI	0.92 (0.79, 1.07)	–
	Unstable angina	**0.72 (0.60, 0.85)**	–
Worst Killip class	I	1	–
	II, III or IV	1.09 (0.92, 1.28)	–
LV ejection fraction	Normal (≥50%)	1	–
	Mid-range (40%–49%)	1.11 (0.94, 1.32)	–
	Reduced (<40%)	**1.50 (1.26, 1.77)**	–
	Unavailable	1.12 (0.96, 1.30)	–
Prior hospitalisation for bleeding		–	**2.45 (1.90, 3.16)**
Index admission bleeding		–	1.37 (0.93, 2.02)
Total:HDL cholesterol	<3	–	1
	3–3.9	–	0.79 (0.62, 1.02)
	4–4.9	–	0.81 (0.63, 1.05)
	≥5	–	**0.70 (0.53, 0.91)**
	Unavailable	–	0.92 (0.66, 1.29)

The value 1 indicates the reference group against which other levels within that group are compared.
HRs are adjusted for all variables included in the model. Values in bold represent statistical significance (p value <0.05).
HRs in the models developed in the full model were very similar to those in a complete case analysis (online supplemental appendix table 5). Internal validation showed similar performance, with good discrimination (online supplemental appendix table 4).
*HR for age is per 10 unit but was modelled per 1 unit for absolute risk calculations.
†The normal range for haemoglobin is ≥115 g/L for women and ≥130 g/L for men.
ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; GFR, glomerular filtration rate; LMS, left main stem; LV, left ventricular; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; NSTEMI, non-ST-elevation myocardial infarction; NZDep, New Zealand Socioeconomic Deprivation of Index; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction; total:HDL cholesterol, ratio of total to high-density lipoprotein cholesterol; VD, vessel disease.

Details of data quality checks performed by the NZ Ministry of Health have been published previously.[20] The ANZACS-QI registry has previously been used to validate the accuracy of ICD-10-AM coded MI hospitalisations.[21]

Predictor variables

Our aim was to develop risk scores for clinical use, requiring a parsimonious set of variables with the greatest predictive ability in each risk score. We identified the predictor variables included in prior published ischaemic and bleeding risk scores, and based on our prior research and clinical experience, we also identified several other possible predictors. From this process, 24 risk predictors were selected a priori for the ischaemic and bleeding models (online supplemental appendix table 2), and exploratory analysis was conducted on the cohort with outcomes available in 2019 (2012–2018 patients). Age and sex were retained as minimum predictors in each model. Additional 'core' variables were defined as those with a strong independent association with each outcome ($p<0.001$), then 'borderline' variables were assessed for inclusion in a backward selection process using Akaike information criterion (AIC)[22] for selection, where the model with the lowest AIC was selected as the final prediction model.

For the ischaemic risk score, the 'core' variables were age, sex, ethnicity, estimated glomerular filtration rate (eGFR), severity of coronary artery disease (CAD), coronary intervention during admission, prior CVD, diabetes, ACS type and worst Killip class, and the additional 'borderline' variables retained were NZ Deprivation index, smoking, haemoglobin, left ventricular ejection fraction (LVEF) and heart rate. Prior hospitalisation for bleeding, ratio of total cholesterol to high-density lipoprotein cholesterol (TC:HDL), systolic blood pressure and prior heart failure were eliminated from the ischaemic model.

Table 3 Clinical example calculations of 28 days to 1 year absolute risk

		Ischaemic events†		Major bleeding events†	
Variable	**Patient variable***	**Coefficient**	**Coefficient×variable**	**Coefficient**	**Coefficient×**
Men	1	−0.089712099	−0.089712099	−0.037556472	−0.037556472
Age per 1 year	72	0.019382063	0.1721243‡	0.025616234	0.2274875‡
Ethnicity					
Māori	–	0.373434015	–	0.648141879	–
Pacific	–	0.066962722	–	0.542698675	–
Indian	–	0.077457822	–	−0.143515782	–
Chinese/other Asian	–	−0.365923487	–	0.320327389	–
NZDep quintile	3	0.034941829	−0.006523639	−0.006048836	0.001129318‡
Heart rate, bpm					
<60	–	−0.133910878	–	−0.113428465	–
≥80	–	0.219259346	–	0.240123107	–
eGFR, mL/min/1.73 m^2					
60–89	–	0.155457744		−0.227167859	
30–59	1	0.560667219	0.560667219	0.039133805	0.039133805
<30 without dialysis	–	1.077164763	–	0.398065019	–
<30 with dialysis	–	1.400375131	–	0.5304006	–
Haemoglobin level					
Low	–	0.246036469	–	0.561164689	–
CAD severity					
Single vessel disease	–	0.471610705	–	0.537180276	–
Double vessel disease	1	0.788332374	0.788332374	0.457974138	0.457974138
LMS±three vessel disease	–	1.097533390	–	0.530820477	–
Coronary intervention					
PCI only	1	−0.479684708	−0.479684708	0.063302503	0.063302503
CABG	–	−1.189545913	–	−0.532577988	–
History of CVD					
Prior MI	–	0.556957649	–	–	–
Other prior CVD	1	0.552807430	0.552807430	–	–
Diabetes mellitus					
Diabetes with insulin	–	0.483253812	–	–	–
Diabetes without insulin	1	0.213634854	0.213634854	–	–
Current smoker	–	0.323093034	–	–	–
Type of ACS					
STEMI	–	−0.087593625	–	–	–
Unstable angina	–	−0.334404656	–	–	–
Worst Killip class II, III or IV	–	0.081714104	–	–	–
LV ejection fraction					
Mid-range (40%–49%)	–	0.105220420	–	–	–
Reduced (<40%)	–	0.402314593	–	–	–
Unavailable	–	0.111326318	–	–	–
Prior hospitalisation for bleeding	1	–	–	0.897189931	0.897189931
Index admission bleeding	–	–	–	0.317676329	–
Total:HDL cholesterol					
3–3.9	1	–	–	−0.229692185	−0.229692185
4–4.9	–	–	–	−0.211781357	–
≥5	–	–	–	−0.362421537	–
Unavailable	–	–	–	−0.083583137	–

$1 - \textit{year risk of major bleeding event} = \left(1 - 0.9883817^{\exp(1.418969)}\right) \times 100 = 4.72\%$.

*A 72-year-old European man admitted to hospital with a confirmed diagnosis of non-STEMI. He is a former smoker with diabetes (without insulin) and normal ejection fraction, has a history of other CVD and bleeding, and his NZDep quintile is 3. His ratio of total-HDL cholesterol is 3.7 units, and eGFR is 54 mL/min/1.73 m^2. His haemoglobin level is 138 g/L and heart rate is 66 bpm. His worst Killip class during admission is class I and he underwent PCI for the treatment of double vessel disease.

†$1\text{-}\textit{year risk of ischaemic event} = (1 - \textit{baselinesurvival}^{\exp(\textit{sumofcoefficientsvariables})}) \times 100 = (1 - 0.9861337^{\exp(1.711646)}) \times 100 = 7.44\%$

‡Mean age of 63.1194 and mean NZDep of 3.1867 in the full cohort. For example, mean centred age used in calculations of coefficient × variable for ischaemic event = 0.019382063 × (72 63.1194) = 0.1721243.

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LMS, left main stem; LV, left ventricular; MI, myocardial infarction; NZDep, New Zealand Socioeconomic Deprivation of Index; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; total:HDL cholesterol, ratio of total to high-density lipoprotein cholesterol.

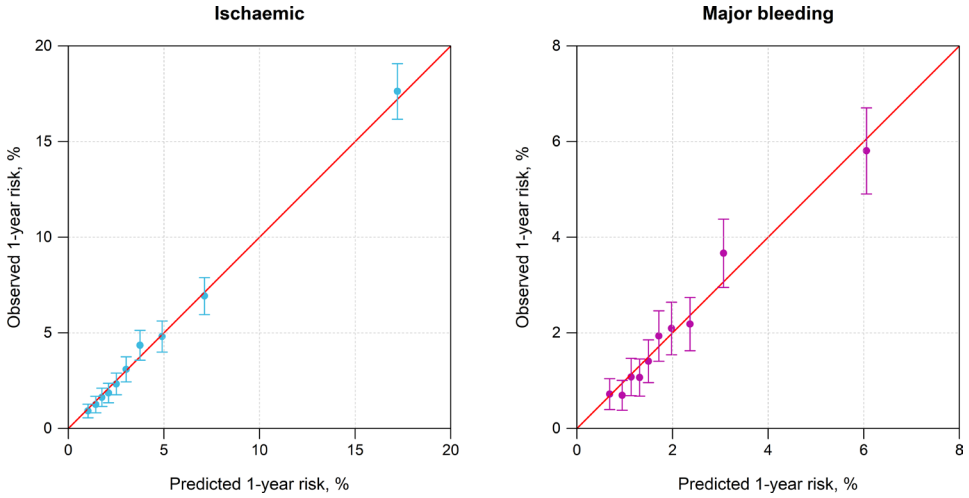

Figure 2 Calibration plots for observed versus predicted 28 day to 1 year risk. Calibration performance of ANZACS-QI risk prediction scores developed in the full cohort. The diagonal line represents perfect calibration. Both the ischaemic and bleeding scores were well calibrated in all subgroups (online supplemental appendix figure 1).

For the bleeding risk score, the 'core' variables were age, sex, ethnicity, eGFR, prior hospitalisation for bleeding, severity of CAD, haemoglobin and index admission bleeding, and the additional 'borderline' variables retained were NZ Deprivation index, coronary intervention during admission, heart rate and TC:HDL. Systolic blood pressure, non-steroidal anti-inflammatory medication/corticosteroids or gastric protection medication were eliminated from the bleeding model. Values of TC:HDL and LVEF were missing for 7% and 23% of the cohort, respectively, and assumed missing at random based on prior registry analyses. Missing TC:HDL and LVEF were included as categories to allow application of the risk scores to patients where it is similarly unavailable due to variability in practice or resource availability.

Statistical analysis

See online supplemental appendix for full description. Comparisons between patients with and without 1-year events were made with χ^2 test, two-sample t-test or the Mann-Whitney U test (when the normality assumption was not met) as appropriate. Multivariable Cox proportional hazards regression was used to develop models from 28 days postdischarge for the index ACS event to the first subsequent MI, ischaemic stroke or major bleeding event, date of death or end date (data extraction). The correlation between estimated ischaemic and bleeding risk was assessed using the Pearson correlation coefficient.

To facilitate a discussion of clinical implications, the risk scores are presented in categories of risk ≤2% (low), >2 to <4% (intermediate), ≥4 (high). The 2% and 4% cut-points were based on previously proposed cut-points for high-risk bleeding. A PRECISE-DAPT score ≥25, equating to a 1-year Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding risk of just under 2%, has been proposed as a high-risk criterion for patients undergoing percutaneous coronary intervention (PCI).[23] In contrast, a recent consensus statement from the Academic Research Consortium for High Risk Bleeding (ARC-HBR) proposed that a 1-year bleeding risk of ≥4% be considered high risk for patients undergoing PCI.[24] For comparison, the same categories were applied for ischaemic risk.

Predictive performance was assessed using calibration, global model fit and discrimination. Calibration was also assessed for subgroups: age (<70 years vs ≥70 years), sex, ACS type (ST

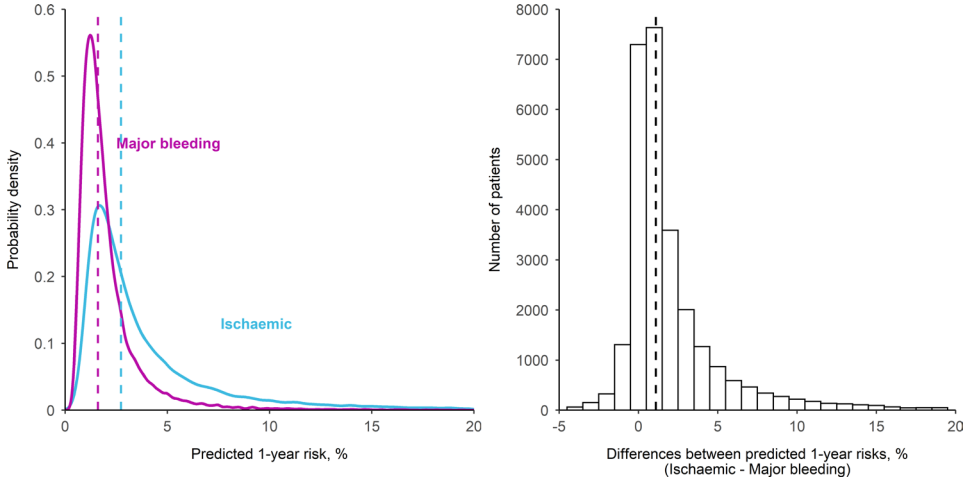

Figure 3 Distribution of absolute 28-day to 1-year predicted risks (left panel) and differences between individual patient ischaemic and major bleeding risk scores (right panel). The dashed lines represent the medians of the distributions. The x-axis has been truncated at 20% (left panel) and at −5% and 20% (right panel) for clarity.

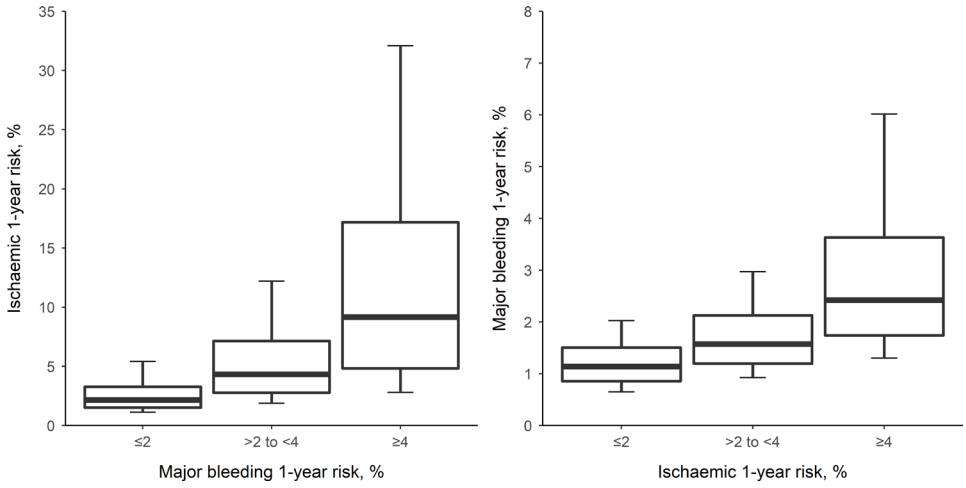

Figure 4 Distribution of ischaemic risk by bleeding and ischaemic risk categories. This box and whisker plot shows the median inside a box defined by the 25th and 75th percentiles, with whiskers running from the ninth percentile to the 91st percentile.

elevation MI vs non-ST elevation ACS), coronary intervention (PCI/CABG vs none), on DAPT beyond 3 months postdischarge versus not, and geographical region. Model fit was measured with Nagelkerke's R^2 and 95% CIs derived from 1000 bootstrap samples. Model discrimination was quantified by Harrell's c-statistic and Gönen and Heller's K-statistic. Internal validity was assessed via 1000 bootstrap samples.

Models from complete case analysis of patients with no missing data (n=21 255 and 25 803 for ischaemic and bleeding risk scores, respectively) were compared with those for the full cohort.

Model development and assessment was completed in accordance with the recommendations of the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement[25]; external validation has not been performed due to the absence of a relevant external cohort at this stage. All analyses were performed using R software, V.4.0.0, and packages.

Table 4 Risk classification table stratified by ischaemic and major bleeding risk scores

	Major bleeding risk			
Ischaemic risk	≤2%	>2% to <4%	≥4%	Total
≤2%				
Number, n (%)	8129 (29.3)	772 (2.8)	75 (0.3)	8976 (32.3)
Ischaemic event, n	99	8	1	108
Major bleeding event, n	94	16	4	114
>2% to <4%				
Number, n (%)	6985 (25.2)	2520 (9.1)	342 (1.2)	9847 (35.5)
Ischaemic event, n	179	84	15	278
Major bleeding event, n	74	58	17	149
≥4%				
Number, n (%)	3139 (11.3)	3934 (14.2)	1859 (6.7)	8932 (32.2)
Ischaemic event, n	187	343	284	814
Major bleeding event, n	44	124	117	285
Total				
Number, n (%)	18 253 (65.8)	7226 (26.0)	2276 (8.2)	27 755 (100.0)
Ischaemic event, n	465	435	300	1200
Major bleeding event, n	212	198	138	548

The table compares the categories of predicted 28-day to 1year risk from ischaemic and bleeding prediction models. Values are n (% of total cohort). The observed number of events are also shown in each cell.

RESULTS

The cohort comprised 27 755 patients admitted to hospital with ACS who had coronary angiography and were event free by 28 days postdischarge. Baseline characteristics of the cohort are shown in table 1. By 1 year postdischarge, there were 1200 (4.3%) ischaemic events and 548 (2.0%) bleeding events (figure 1). The ischaemic events comprised 919 (76.6%) MI, 124 (10.3%) stroke and 157 (13.1%) deaths. Of the major bleeding events, 376 (68.6%) were gastrointestinal, 45 (8.2%) intracerebral/intraocular and 127 (23.2%) other aetiologies.

Risk scores and performance

The adjusted multivariable HRs from the final ischaemic and bleeding models are shown in table 2. The coefficients and baseline survival for each risk score and example calculations are in table 3. There was excellent calibration of the scores throughout the range of predicted risk (figure 2). The ischaemic model had a slope of 0.999 (0.947, 1.053) and an intercept of −0.0002 (−0.057, 0.056), and the bleeding model had a slope of 1.000 (0.889, 1.111) and an intercept of −0.0001 (−0.084, 0.084).

The scores stratified risk of ischaemia and major bleeding well, with an approximately 10-fold range of risk between the lowest and the highest deciles of predicted risk. The mean 1-year predicted and observed ischaemic risks in the lowest decile were 1.0% and 0.9%, and in the highest decile 17.2% and 17.6%. In contrast, the mean 1-year predicted and observed major bleeding risks in the lowest decile were 0.7% and 0.7%, and in the highest decile 6.1% and 5.8%. Measures of model performance are shown in online supplemental appendix table 3. Both models had moderate discrimination, with Harrell's c-statistic 0.75 (95% CI, 0.74 to 0.77) and 0.69 (95% CI, 0.67 to 0.71), respectively.

Sensitivity analyses

Both the ischaemic and bleeding risk scores were well calibrated in all subgroups (online supplemental appendix figure 1). HRs in the models developed in the full cohort with categories for

Table 5 Using the ischaemic versus bleeding risk matrix to inform DAPT duration: a potential clinical algorithm and future research directions

		Major bleeding risk	
		≤2%	>2%
Ischaemic risk	≤2%	29% of cohort Currently 3 months DAPT Trials to test 1 to 3 months DAPT then P2Y12 receptor inhibitor monotherapy	3% of cohort Currently 1 to 3 months DAPT then anti-platelet monotherapy
	>2%	37% of cohort Currently 12 months DAPT Trials of shortening to 6 months then P2Y12 receptor inhibitor monotherapy	31% of cohort Currently 1 to 3 months DAPT then anti-platelet monotherapy

The percentages of ANZACS-QI cohort in each cell are shown.
The ANZACS-QI risk categories have been applied to the current European Society of Cardiology 2020 recommendations for antithrombotic therapy for non-ST-segment elevation acute coronary syndrome patients without atrial fibrillation.[7]
ANZACS-QI, All New Zealand ACS Quality Improvement; DAPT, dual anti-platelet therapy.

missing data were very similar to those for the complete case analysis (online supplemental appendix table 4), as was model performance during internal validation. The mean (95% CI) of the bootstrap validated Harrell's c-statistic for the ischaemic and bleeding models, respectively, was 0.75 (0.74 to 0.77) and 0.69 (0.67 to 0.71) (online supplemental appendix table 3).

Ischaemic versus bleeding risk

The distributions of 28-day to 1-year risk and the individual differences between ischaemia and major bleeding risks are shown in figure 3. The median absolute 1-year risk of cardiovascular death/MI/stroke event was 2.7% (IQR 1.8%–4.9%) and of major bleeding was 1.6% (IQR 1.1%–2.4%). For 85% of patients, the risk of dying or having an ischaemic event outweighed the major bleeding risk (median absolute difference 1.2%, IQR 0.5%–2.8%), and 42% had an ischaemic risk at least double that of the major bleeding risk. There was a moderate correlation between individual ischaemic and major bleeding risk estimates (r=0.643, 95% CI 0.636 to 0.650). The median ischaemic risk increased from 2.2% to 4.3% to 9.2% for low (≤2%), intermediate (>2% to <4%) and high bleeding risk (≥4%) categories (figure 4). When each patient's individual ischaemic and bleeding risks were classified in these categories (table 4), 34% had an intermediate or high bleeding risk, of whom most (91%) had an intermediate or high ischaemic risk. Of the 66% with a low bleeding risk, 55% had a medium or high ischaemic risk.

DISCUSSION

In this real-world national ACS cohort, paired risk scores have been developed to estimate the 28-day to 1-year postdischarge risk of ischaemic and major bleeding events. The risk scores are well calibrated, both overall, and in demographic and relevant clinical subgroups. Median 1-year ischaemic risk is nearly twofold higher than major bleeding risk, but for 15% of patients the risk of a major bleeding event outweighed that of an ischaemic event. Of the two-thirds of patients with a low bleeding risk, half had an intermediate or high ischaemic risk. Of the remaining third with an elevated bleeding risk, most also an elevated ischaemic risk.

To our knowledge, there are no other paired multivariable risk scores available to predict postdischarge ACS ischaemic and bleeding risk. There are two prior post-PCI studies where ischaemic and major bleeding risks were modelled, either in the 2-year post-PCI in the PARIS registry[26] or beyond 1 year in the DAPT study.[27] However, in addition to estimating risk over different time periods, these PCI cohorts were at lower overall ischaemic risk than our post-ACS cohort. Only 12% of patients had troponin-positive ACS in PARIS, and although half of patients in the DAPT study were post-ACS, they were enrolled 12 months post-PCI. Other investigators have developed either post-ACS ischaemic or bleeding risk scores. The GRACE investigators presented a model to estimate the risk of death or MI within 6 months postdischarge.[28] More recently, the Epicor risk score estimates 1-year mortality risk postdischarge after ACS.[8] The BleeMACS postdischarge ACS bleeding model, like ours, utilised rehospitalisation for bleeding to define bleeding endpoints.[14] The Trilogy bleeding score was developed from a clinical trial cohort enrolled 10 days after ACS without revascularisation.[11] Other bleeding scores have either included in-hospital bleeding[10 12] or were in post-PCI cohorts.[26 27] Similarly, other post-ACS scores included in-hospital events.[9 29]

The finding that most patients have an ischaemic risk which exceeds their major bleeding risk has implications regarding DAPT use after ACS. Because the benefits of medical therapies for cardiovascular prevention including anti-platelet agents are known to be proportional to the absolute ischaemic risk,[30–32] high ischaemic risk patients might be expected to benefit most from more prolonged DAPT. However, several recent studies suggest that the ischaemic risk in patients at high bleeding risk may be less modifiable by prolonged DAPT. A meta-analysis of coronary stenting trials assessing short versus longer duration DAPT found that ischaemic events were reduced by longer DAPT for patients at low bleeding risk, but in those at high bleeding risk, defined using the Precise-DAPT score, longer DAPT duration was associated with similar ischaemic event rates but higher bleeding rates.[23] In the subgroup with acute coronary syndromes, they reported a similar result although with relatively small numbers of events. Two subsequent clinical trials in patients at high bleeding risk treated with modern generation stents have reported similar findings.[33 34]

Weighting of ischaemic and bleeding events

In benefit–harm models, ischaemic and major bleeding outcomes have been weighted equivalently.[26] In this analysis, we have endeavoured to identify only the most serious ischaemic and bleeding events. In this study, 15% of patients had a bleeding risk higher than the ischaemic risk. If ischaemic events were subjectively weighted more than bleeding events, the proportion with net harm would be less than 15%. Treating the ischaemic and bleeding events as equivalent is lent support by a recent study which reported that after ACS both postdischarge bleeding and postdischarge MI were associated with a similar increase in subsequent all-cause mortality.[35] The equivalence of ischaemic and bleeding risk does not imply that changing the intensity or duration of DAPT will modify bleeding and ischaemic risk by the same amount. For example, clinical trials of short compared with

long-term DAPT report a greater relative increase in bleeding events than decrease in ischaemic events with long-term DAPT.[36]

In the current 2020 European Society of Cardiology (ESC) guidelines 'algorithm for antithrombotic treatment in NSTEACS patients without AF undergoing PCI', it is not possible to quantitatively compare ischaemic and bleeding risks for an individual patient. The guideline defines high bleeding risk using either of two different scores (PRECISE-DAPT and the ARC-HBR criteria) while ischaemic risk prediction is more qualitative.[7]

Clinical implications and implementation

In an era of shared decision making, it is important to provide patients and clinicians with objective risk estimates as a basis for deciding on management.[37] The ANZACS-QI risk scores presented here are calculated at hospital discharge using data consistently available at that time point. They provide an estimate of risks from 28 days to 1 year as long as the patient remains event free at 1 month. Consequently, they can be used at discharge to plan DAPT duration beyond a month. In clinical practice, if an event does occur within the first 28 days the estimated risks are no longer relevant and the decision to stop or continue DAPT must be individualised.

The evidence around DAPT duration post-ACS continues to evolve,[38] and the role of ischaemic and bleeding risk scores requires justification in prospective clinical trials. In table 5, we have proposed a potential clinical and research algorithm based on the recent ESC recommendations applied to the ANZACS-QI risk categories.[7] The one-third of the cohort at elevated bleeding risk were also mostly at elevated ischaemic risk. As discussed above, recent clinical trials suggest that in these patients the efficacy of DAPT for reducing ischaemic events may be less than for patients at lower bleeding risk and an abbreviated DAPT duration is recommended. The ESC currently recommend a default 12 months of DAPT in all those at low bleeding risk. However, the ESC also recommends that for those at low risk of major bleeding and an elevated ischaemic risk (37% of our cohort), more prolonged DAPT may be justified, and for those with low bleeding and ischaemic risk (29% of our cohort) a shorter period of DAPT may be justified. In clinical practice, there are other factors which might also influence the decision regarding DAPT duration. These include procedural variables such as stent type, lesion location and length, and vessel size, and specific clinical situations such as the need for non-cardiac surgery. In addition to informing DAPT duration decisions, the bleeding risk estimates are useful to decide on whether to use a potent P2Y12 receptor inhibitor (ticagrelor or prasugrel) or the less potent clopidogrel.[7]

All variables used in the current scores are routinely collected in the ANZACS-QI electronic registry for every New Zealander who has a coronary angiogram post-ACS. Consequently, each patient can have bleeding and ischaemic risks automatically generated prior to discharge. We plan to develop separate risk scores for patients with AF post-ACS and for those who do not have a coronary angiogram.

Limitations

These risk scores have not been externally validated but are well validated in the population in which they are intended for use. While the current lack of external validation limits implementation of our scores in other jurisdictions, this study demonstrates the feasibility and potential accuracy of developing paired quantitative ischaemic and bleeding risk scores within a national registry linked to administrative health data. The scores' coefficients are provided to enable other groups to validate and potentially recalibrate the scores for their use. A comprehensive set of predictors were considered a priori to optimise discrimination and calibration. However, several recognised risk factors for bleeding were not included in development of the ANZACS-QI bleeding score: platelet and white cell count were not available for this study, and others occurred with very low frequency in the cohort—liver disease (1.1%), cancer (0.6%) and prior intracerebral bleeding (0.5%). The ANZACS-QI risk scores are both very well calibrated, but measures of global discrimination are slightly better for the ischaemic score. This is consistent with other studies in the literature predicting similar outcomes.[9 14] Outcome data in this study were obtained by de-identified linkage to national health datasets. It is therefore not possible to independently validate these events, and events not associated with re-hospitalisation or death are not captured.

Conclusion

In this real-world national ACS registry cohort, paired risk scores have been developed which simultaneously estimate the 28-day to 1-year postdischarge risk of ischaemic and major bleeding events. In the era of personalised medicine, application of these scores may help inform the appropriate intensification of management after ACS.

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Contributors AK, RS, HDW, MJAW, GD, VS, RTJ and KP conceptualised and designed the study. AK, RS, HDW, MJAW, GD, MAWL and KP were involved in the data collection process. YC analysed the data with input from AK, KP and MAWL. All authors were involved in data interpretation. AK, YC and KP drafted the manuscript and all authors revised the manuscript. All authors approved the final version and agreed to be accountable for the manuscript.

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Competing interests None declared.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by NZ National Multi Region Ethics Committee (MEC07/19/EXP). All data were de-identified in the analyses so individual patient consent was not required.

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Data availability statement Data are available upon reasonable request and appropriate permissions.

Author note The first author (AJK) accepts full responsibility for the work and conduct of the study, had access to the data, and controlled the decision to publish.

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REFERENCES

1 Wallentin L, Becker RC, Budaj A, *et al*. Ticagrelor versus Clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045–57.
2 Bonaca MP, Braunwald E, Sabatine MS. Long-term use of Ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015;373:1274–5.
3 Yusuf S, Zhao F, Mehta SR, *et al*. Effects of Clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494–502.
4 Udell JA, Bonaca MP, Collet J-P, *et al*. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. *Eur Heart J* 2016;37:390–9.
5 Ibanez B, James S, Agewall S, *et al*. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European society of cardiology (ESC). *Eur Heart J* 2018;39:119–77.
6 Chew DP, Scott IA, Cullen L, *et al*. National heart foundation of Australia & cardiac society of Australia and New Zealand: Australian clinical guidelines for the management of acute coronary syndromes 2016. *Heart, Lung and Circulation* 2016;25:895–951.
7 Collet JP, Thiele H, Barbato E. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2020;41:3495–7.
8 Pocock S, Bueno H, Licour M, *et al*. Predictors of one-year mortality at hospital discharge after acute coronary syndromes: A new risk score from the EPICOR (long-tErm follow uP of Antithrombotic management patterns in acute coronary syndrome patients) study. *Eur Heart J Acute Cardiovasc Care* 2015;4:509–17.
9 Fox KAA, Dabbous OH, Goldberg RJ, *et al*. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE).[See comment]. *BMJ* 2006;333:1091.
10 Subherwal S, Bach RG, Chen AY, *et al*. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines) bleeding score. *Circulation* 2009;119:1873–82.
11 Alfredsson J, Neely B, Neely ML, *et al*. Predicting the risk of bleeding during dual antiplatelet therapy after acute coronary syndromes. *Heart* 2017;103:1168–76.
12 Mathews R, Peterson ED, Chen AY, *et al*. In-hospital major bleeding during ST-elevation and non-ST-elevation myocardial infarction care: derivation and validation of a model from the ACTION Registry®-GWTG™TM. *Am J Cardiol* 2011;107:1136–43.
13 Mehran R, Pocock SJ, Nikolsky E, *et al*. A risk score to predict bleeding in patients with acute coronary syndromes. *J Am Coll Cardiol* 2010;55:2556–66.
14 Raposeiras-Roubín S, Faxén J, Íñiguez-Romo A, *et al*. Development and external validation of a post-discharge bleeding risk score in patients with acute coronary syndrome: the Bleemacs score. *Int J Cardiol* 2018;254:10–5.
15 Lin A, Devlin G, Lee M, *et al*. Performance of the GRACE scores in a new Zealand acute coronary syndrome cohort. *Heart* 2014;100:1960–6.
16 Voss WB, Lee M, Devlin GP, *et al*. Incidence and type of bleeding complications early and late after acute coronary syndrome admission in a new Zealand cohort (ANZACS-QI-7). *N Z Med J* 2016;129:27–38.
17 Grey C, Jackson R, Wells S, *et al*. Twenty-eight day and one-year case fatality after Hospitalisation with an acute coronary syndrome: a nationwide data linkage study. *Aust N Z J Public Health* 2014;38:216–20.
18 Kerr A, Williams MJ, White H, *et al*. The all New Zealand acute coronary syndrome quality improvement programme: implementation, methodology and cohorts (ANZACS-QI 9). *N Z Med J* 2016;129:23–36.
19 Selak V, Kerr A, Poppe K, *et al*. Annual risk of major bleeding among persons without cardiovascular disease not receiving antiplatelet therapy. *JAMA* 2018;319:2507–20.
20 Mehta S, Jackson R, Exeter DJ, *et al*. Data resource: vascular risk in adult new Zealanders (VARIANZ) Datasets. *Int J Popul Data Sci* 2019;4:1107:1107.:.
21 Kerr AJ, Lee M, Jiang Y, *et al*. High level of capture of coronary intervention and associated acute coronary syndromes in the all New Zealand acute coronary syndrome quality improvement cardiac Registry and excellent agreement with national administrative Datasets (ANZACS-QI 25). *N Z Med J* 2019;132:19–29.
22 Akaike H. Information theory and an extension of the maximum likelihood principle. In: Parzen E, Tanabe K, Kitagawa G, eds. *Selected Papers of Hirotugu Akaike* New York, NY: Springer, n.d.: 1998. 199–213.
23 Costa F, van Klaveren D, James S, *et al*. Derivation and validation of the predicting bleeding complications in patients undergoing Stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient Datasets from clinical trials. *Lancet* 2017;389:1025–34.
24 Urban P, Mehran R, Colleran R, *et al*. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the academic research consortium for high bleeding risk. *Eur Heart J* 2019;40:2632–53.
25 Collins GS, Reitsma JB, Altman DG, *et al*. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *Ann Intern Med* 2015;162:735–6.
26 Baber U, Mehran R, Giustino G, *et al*. Coronary thrombosis and major bleeding after PCI with drug-Eluting Stents: risk scores from PARIS. *J Am Coll Cardiol* 2016;67:2224–34.
27 Yeh RW, Secemsky EA, Kereiakes DJ, *et al*. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA* 2016;315:1735–49.
28 Eagle KA, Lim MJ, Dabbous OH, *et al*. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month Postdischarge death in an international Registry.[See comment]. *JAMA* 2004;291:2727–33.
29 Antman EM, Cohen M, Bernink PJ, *et al*. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision Making.[See comment]. *JAMA* 2000;284:835–42.
30 Blood pressure lowering treatment trialists C. blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. *Lancet* 2014;384:591–8.
31 Cholesterol Treatment Trialists C, Mihaylova B, Emberson J. The effects of lowering LDL cholesterol with Statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *The Lancet* 2012;380:581–90.
32 Antithrombotic Trialists C, Baigent C, Blackwell L. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;373:1849–60.
33 Costa F, Van Klaveren D, Feres F, *et al*. Dual antiplatelet therapy duration based on ischemic and bleeding risks after coronary Stenting. *J Am Coll Cardiol* 2019;73:741–54.
34 Valgimigli M, Frigoli E, Heg D, *et al*. Dual antiplatelet therapy after PCI in patients at high bleeding risk. *N Engl J Med* 2021;385:1643–55.
35 Marquis-Gravel G, Dalgaard F, Jones AD, *et al*. Post-discharge bleeding and mortality following acute coronary syndromes with or without PCI. *J Am Coll Cardiol* 2020;76:162–71.
36 Bularga A, Meah MN, Doudesis D, *et al*. Duration of dual antiplatelet therapy and stability of coronary heart disease: a 60 000-patient meta-analysis of randomised controlled trials. *Open Heart* 2021;8:e001707.
37 Broadbent E, Leggat A, McLachlan A, *et al*. Providing cardiovascular risk management information to acute coronary syndrome patients: a randomized trial. *Br J Health Psychol* 2013;18:83–96.
38 Bhatt DL. Optimal antiplatelet therapy Revisited: when is a single better than a double? *J Am Coll Cardiol* 2023;81:553–6.

Appendix : Statistical analysis

Comparisons between patients with and without events within 1 year were made with the Chi-squared test, two-sample t-test or the Mann-Whitney U test (when the normality assumption was not met) as appropriate. The cumulative incidence rates of ischaemic and major bleeding events were plotted with Kaplan-Meier curves. Multivariable Cox proportional hazards regression was used to develop models from 28 days post-discharge for the index ACS event to the first subsequent MI, ischaemic stroke or major bleeding event, date of death, or end date (data extraction). Continuous predictors were centred about their means. Model assumptions of proportional hazards and linearity were assessed, respectively, by visual inspection of plots of scaled Schoenfeld residuals and of LOWESS smoothed Martingale residuals against continuous predictors. Heart rate was subsequently categorised at clinically relevant thresholds due to a non-linear relationship with outcome.

Multivariable relative risk was transformed to absolute risk by estimating the baseline survival for each outcome at 1 year (assessed at mean values of continuous variables and the reference group of categorical variables). The correlation between ischaemic and major bleeding risks was assessed using Pearson's correlation coefficient of log-transformed data..

Predictive performance was assessed using calibration, global model fit, and discrimination. Model calibration is represented by plots of predicted against observed 1-year event rate (from Kaplan-Meier estimates) within deciles of predicted risk. A diagonal line with intercept zero indicates perfect calibration. Calibration was also assessed for subgroups: age (<70 years vs ≥70 years), sex, ACS type (ST elevation MI [STEMI] vs non-ST elevation ACS [NSTEACS]), coronary intervention [PCI or CABG vs none], on DAPT beyond 3 months post-discharge vs not, and geographical region. Model fit was measured with Nagelkerke's R^2 and 95% confidence intervals derived from 1000 bootstrap samples. Model discrimination was quantified by Harrell's c-statistic and Gönen and Heller's K-statistic. Internal validity was assessed via 1000 bootstrap samples.
Models from complete case analysis of patients with no missing data (n = 21255 and 25803 for ischaemic and bleeding scores, respectively) were compared to those for the full cohort.
Model development and assessment was completed in accordance with the recommendations of the TRIPOD statement[25]; external validation has not been performed due to the absence of a relevant external cohort at this stage. All statistical analyses were performed using R software, version 4·0·0, and packages.

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Appendix Table 1 ICD codes used to identify events during follow-up from hospital records.

Category	**ICD-10-AM codes***
Myocardial infarction	I210, I211, I212, I213, I214, I219, I220, I221, I228, I229
Ischaemic stroke	I630, I631, I632, I633, I634, I635, I636, I638, I639, I64
Major bleeding	1. Intracerebral and intraocular bleeding codes listed below as either primary or secondary diagnosis. I600, I601, I602, I603, I604, I605, I606, I607, I608, I609, I610, I611 , I612, I613, I614, I615, I616, I618, I619, I620, I621, I629, H356, H431 OR 2. Bleeding codes listed below as either primary or secondary diagnosis AND transfusion code. Bleeding codes are I850, I983, K226, K250, K251, K252, K254, K255, K256, K260, K261, K262, K264, K265, K266, K270, K271, K272, K274, K275, K276, K280, K281, K282, K284, K285, K286, K290, K2921, K2931, K2941, K2951, K2961, K2971, K2981, K2991, K3182, K5522, K5703, K5711, K5713, K5721, K5723, K5731, K5733, K5741, K5743, K5751, K5781, K5783, K5791, K5793, K625, K661, K920, K921, K922, M2500, M2501, M2502, M2503, M2504, M2505, M2506, M2507, M2508, M2509, R040, R041, R042, R048, R049 Transfusion codes are ICD-10-AM, 1370601, ICD-9-CM-A, 9903, ICD-AM-10 1370602, ICD-9-CM-A 9904.

* ICD = International Classification of Diseases; ICD-9-CM-A = ICD, Ninth Revision, Clinical Modification, Australian Version; ICD-10-AM = ICD, 10th Revision, Australian Modification.

Bleeding events associated with CABG (coronary artery bypass grafting) and/or PCI (percutaneous coronary intervention), trauma or procedures were excluded.

Kerr AJ, *et al. Heart* 2023;0:1–10. doi: 10.1136/heartjnl-2023-322830

Appendix Table 2 Risk predictors included in ANZACS-QI risk prediction models. Exploratory analysis using patients in 2012 to 2018.

Definition*	**Ischaemic events ****	**Major bleeding events ****
Sex		
Patient's gender: ***Women***, Men	Men: 0.88 (0.80, 0.97)	Men: 1.04 (0.87, 1.23)
Age		
Age (years) was derived from the patient's index admission date and their date of birth. Modelled per 1 year but hazard ratios presented per 10 years.	Age per 10 years: 1.12 (1.06, 1.18)	Age per 10 years: 1.24 (1.13, 1.36)
Prioritised ethnicity		
Patients with more than one ethnicity were assigned to a single category based on the national ethnic prioritisation protocol (https://www.health.govt.nz/publication/hiso-100012017-ethnicity-data-protocols) in the following order: New Zealand Māori, Pacific, Indian, Chinese, Other Asian, Middle-Eastern/Latin American/African (MELAA), Other ethnicity, ***European***, and unknown/ not answered/ not stated. The 'Other' ethnic groups (including MELAA and Other) were included in the European ethnic group due to insufficient patient numbers (≈ 1% of the cohort).	Māori: 1.17 (1.01, 1.35) Pacific: 1.03 (0.85, 1.25) Indian: 0.97 (0.80, 1.19) Chinese/ Other Asian: 0.73 (0.54, 0.99)	Māori: 1.19 (0.91, 1.56) Pacific: 1.47 (1.06, 2.03) Indian: 0.97 (0.67, 1.40) Chinese/ Other Asian: 1.46 (0.99, 2.15)
Deprivation quintile		
New Zealand socioeconomic deprivation index (NZDep 2013) is a census-based small area 10-point index of deprivation based on the patient's domicile, with higher values equating to greater deprivation. Included as a continuous variable in the final scores. Deprivation quintile 1 (least deprived) = NZDep 1 or 2 Deprivation quintile 2 = NZDep 3 or 4 Deprivation quintile 3 = NZDep 5 or 6 Deprivation quintile 4 = NZDep 7 or 8 Deprivation quintile 5 (most deprived) = NZDep 9 or 10	NZDep per quintile: 1.03 (0.99, 1.07)	NZDep per quintile: 1.07 (1.01, 1.13)
History of CVD		

This variable was categorised as: ***No prior CVD***, Prior MI, Other prior CVD MI/ other CVD if: History of MI or other CVD entered in the ANZACS-QI registry	Prior MI: 1.16 (1.02, 1.31) Other prior CVD: 1.24 (1.10, 1.40)	Prior MI: 0.88 (0.70, 1.10) Other prior CVD: 0.97 (0.78, 1.21)
History of CHF		
No/yes Yes if: History of CHF entered in the ANZACS-QI registry AND/OR Prior hospitalisation in which CHF was ICD coded	1.25 (1.06, 1.47)	1.07 (0.78, 1.48)
COPD		
No/yes Yes if: Long term use of bronchodilators or steroids for lung disease entered in the ANZACS-QI registry	1.10 (0.95, 1.27)	0.96 (0.74, 1.25)
Prior hospitalisation for bleeding		
No/yes Yes if: Any prior hospitalisation for non-procedural, non-trauma related bleeding using primary and secondary diagnostic ICD codes in the last 5 years	1.31 (1.11, 1.54)	2.68 (2.14, 3.36)
NSAID and/or corticosteroid treatment		
No/ yes Yes if: ≥1 dispensing of NSAID and/or corticosteroid within 6 months prior to index admission (National pharmaceutical claims data) Non-aspirin NSAID: diclofenac, diflunisal, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, naproxen, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid Corticosteroid: dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone	1.05 (0.95, 1.16)	1.10 (0.93, 1.31)
Gastric protection medication		
No/yes Yes if:	1.14 (1.03, 1.25)	1.15 (0.97, 1.35)

≥1 dispensing of gastric protection medications within 6 months prior to index admission (National pharmaceutical claims data) Proton Pump inhibitors (PPIs) or H2 antagonist: Lansoprazole Omeprazole Pantoprazole Ranitidine		
Diabetes mellitus		
This variable was categorised as: ***No diabetes***, Diabetes without insulin, Diabetes with insulin Diabetes (combined type I, type II or type unknown) if: History of diabetes in the ANZACS-QI registry Diabetes with insulin if: Diabetes and ≥1 dispensing of diabetic medication within 6 months prior to index admission (National pharmaceutical dispensing data) Diabetic medication: insulin lispro, insulin neutral, insulin isophane, insulin zinc suspension, insulin aspart, insulin glargine, glucagon hydrochloride	Diabetes with insulin: 1.44 (1.25, 1.67) Diabetes without insulin: 1.07 (0.94, 1.21)	Diabetes with insulin: 0.90 (0.68, 1.19) Diabetes without insulin: 0.80 (0.64, 1.00)
Smoking status		
This variable was categorised as: ***Current smoker*** = current cigarette smoker including former smoker who quit smoking <12 months before index admission Non-smoker = never-smoker at admission or quit ≥12 months before index admission	1.17 (1.05, 1.30)	1.13 (0.93, 1.37)
Total:HDL cholesterol		
Ratio of total to high-density lipoprotein cholesterol. This variable was categorised as: ***<3***, 3-3.9, 4-4.9, ≥5, Missing	3-3.9: 1.05 (0.91, 1.21) 4-4.9: 1.08 (0.94, 1.25) ≥5: 1.18 (1.02, 1.35) Unavailable: 1.16 (0.96, 1.41)	3-3.9: 0.89 (0.71, 1.11) 4-4.9: 0.80 (0.63, 1.01) ≥5: 0.72 (0.57, 0.92) Unavailable: 0.87 (0.62, 1.22)
SBP		

Systolic blood pressure assessed at index admission. Modelled per 1 mmHg but hazard ratios presented per 10 mmHg.	SBP per 10mmHg: 1.01 (0.99, 1.02)	SBP per 10mmHg: 1.02 (0.99, 1.05)
Type of ACS		
This variable was categorised as: STEMI, Non-STEMI, Unstable angina	STEMI: 1.05 (0.94, 1.18) Unstable angina: 0.54 (0.46, 0.62)	STEMI: 0.95 (0.78, 1.16) Unstable angina: 0.92 (0.73, 1.15)
Heart rate		
First heart rate recorded on arrival to hospital. Where the suspected ACS occurs late after hospital admission e.g. post operatively, the GRACE variables were those recorded at the time the ACS was first suspected. This variable was categorised as: ***<60***, 60-79, ≥80 bpm	<60: 1.04 (0.91, 1.19) ≥80: 1.16 (1.05, 1.28)	<60: 0.97 (0.76, 1.23) ≥80: 1.27 (1.07, 1.51)
Cardiac arrest at admission		
No/ yes Yes if: Resuscitated cardiac arrest at admission recorded in the ANZACS-QI registry	0.85 (0.65, 1.11)	0.96 (0.60, 1.53)
Estimated GFR		
The estimated glomerular filtration rate (eGFR) is a measure of kidney function with normal levels being above 90 mL/min/1.73m^2. If the eGFR is consistently less than 30 mL/min/1.73m^2, then the individual has chronic renal failure. This was derived using the CKD-EPI equation.[1] This variable was categorised as: ***≥90***, 60-89, 30-59, <30 mL/min/1.73m^2	60-89: 1.09 (0.96, 1.25) 30-59: 1.24 (1.06, 1.45) <30: 1.95 (1.56, 2.43)	60-89: 0.90 (0.72, 1.14) 30-59: 1.36 (1.04, 1.79) <30: 2.05 (1.40, 3.00)
Haemoglobin level at admission		
Blood haemoglobin was categorised in accordance with the Test Guide of Auckland District Health Board's laboratory Lab Plus (http://testguide.adhb.govt.nz/EGuide/): ***Normal*** (≥130 g/L for men, ≥115 g/L for women), Low (<130 g/L for men, <115 g/L for women), Missing (no laboratory results available)	Low: 1.14 (0.99, 1.31) Unavailable: 1.04 (0.93, 1.16)	Low: 1.89 (1.52, 2.35) Unavailable: 1.21 (0.99, 1.47)
Index admission bleeding		
No/ yes Yes if: Any bleeding event at index admission except for CABG-related bleeding	1.07 (0.84, 1.35)	1.67 (1.21, 2.30)

Worst Killip class in hospital		
This variable was categorised as: ***Class I***, Class II-IV Class I = no CHF Class II = pulmonary rales and/or jugular venous distention Class III = pulmonary oedema Class IV = cardiogenic shock	II, III, or IV: 1.19 (1.05, 1.36)	II, III, or IV: 1.05 (0.82, 1.35)
Left ventricular ejection fraction		
Left ventricular ejection fraction (EF) assessed by echo or left ventricular angiogram or other modality on index admission and was categorised as follows: ***Normal (≥50%)***, Mid-range (40-49%), Reduced (<40%), Unavailable	Mid-range: 1.01 (0.88, 1.15) Reduced: 1.26 (1.09, 1.44) Unavailable: 1.10 (0.99, 1.23)	Mid-range: 0.81 (0.63, 1.03) Reduced: 0.60 (0.45, 0.82) Unavailable: 0.85 (0.71, 1.03)
CAD severity		
This variable was categorised as: ***No obstructive CAD***, Single or double vessel disease (VD), LMS ± three vessel disease	Single VD: 1.90 (1.56, 2.31) Double VD: 2.48 (2.03, 3.02) LMS ± three VD: 3.30 (2.73, 3.99)	Single VD: 1.50 (1.08, 2.09) Double VD: 1.64 (1.17, 2.31) LMS ± three VD: 1.77 (1.28, 2.47)
Coronary intervention		
This variable was categorised as: ***Neither PCI at index admission nor referred for CABG***, PCI only, CABG (in-patient only) with or without PCI (CABG)	PCI only: 0.68 (0.61, 0.75) CABG: 0.31 (0.26, 0.39)	PCI only: 1.08 (0.88, 1.33) CABG: 0.66 (0.47, 0.93)

ANZACS-QI = All New Zealand Acute Coronary Syndrome Quality Improvement programme; NMDS = national minimum dataset (hospital events); CVD = cardiovascular disease; MI = myocardial infarction; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; NSAID = non-steroidal anti-inflammatory drug; Total:HDL cholesterol = ratio of total to high-density lipoprotein cholesterol; SBP = systolic blood pressure; ACS = acute coronary syndrome; STEMI = ST-elevation myocardial infarction; NSTEMI = Non-ST-elevation myocardial infarction; CKD = chronic kidney disease; CAD = coronary artery disease; LMS = left main stem; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting.

* Reference groups for categorical variables are italicized and in bold.

** Hazard ratios (HRs) are adjusted for all variables included in the model.

Appendix Table 3 Performance metrics in ANZACS-QI risk prediction models.

	Statistic	Point estimate (95% CI)	
		Ischaemic events	Major bleeding events
Final model			
Model fit	Nagelkerke's R^2 *	0.074 (0.063, 0.080)	0.029 (0.026, 0.038)
Discrimination	Harrell c-statistic	0.752 (0.738, 0.766)	0.690 (0.667, 0.713)
	Gönen & Heller k-statistic	0.688 (0.678, 0.698)	0.649 (0.632, 0.666)
Internal validation of final model			
Model fit	Nagelkerke's R^2 *	0.072 (0.064, 0.084)	0.029 (0.024, 0.040)
Discrimination	Harrell c-statistic	0.752 (0.735, 0.769)	0.689 (0.665, 0.713)
	Gönen & Heller k-statistic	0.686 (0.675, 0.697)	0.647 (0.629, 0.665)

* Confidence intervals (CIs) derived from 1000 bootstrap samples.

Appendix Table 4 Adjusted multivariable hazard ratios from ANZACS-QI risk prediction models for the sub-group with complete data.

Variable	Levels	Excluding patients	
		Missing LV ejection fraction	Missing total:HDL cholesterol
n		21255	25803
Sex	Women	1	1
	Men	0.91 (0.78, 1.05)	0.97 (0.80, 1.18)
Age per 10 years		**1.16 (1.07, 1.26)**	**1.26 (1.14, 1.40)**
Ethnicity	European	1	1
	Māori	**1.42 (1.16, 1.74)**	**2.07 (1.60, 2.69)**
	Pacific	1.06 (0.82, 1.36)	**1.72 (1.23, 2.39)**
	Indian	0.97 (0.72, 1.31)	0.88 (0.55, 1.40)
	Chinese/ Other Asian	0.67 (0.43, 1.05)	1.45 (0.95, 2.20)
NZDep quintile		1.03 (0.98, 1.09)	0.97 (0.91, 1.04)
Heart rate, bpm	60-79	1	1
	<60	0.96 (0.78, 1.19)	0.96 (0.74, 1.26)
	≥80	**1.20 (1.03, 1.38)**	**1.25 (1.04, 1.52)**
Estimated GFR, mL/min/1.73m^2	≥90	1	1
	60-89	1.23 (0.99, 1.53)	0.80 (0.62, 1.02)
	30-59	**1.82 (1.42, 2.32)**	1.03 (0.76, 1.38)
	<30 without dialysis	**2.88 (2.03, 4.10)**	1.61 (0.98, 2.64)
	<30 with dialysis	**4.47 (3.10, 6.45)**	1.72 (0.99, 2.97)
Haemoglobin level at admission	Normal*	1	1
	Low	**1.34 (1.13, 1.60)**	**1.77 (1.40, 2.24)**
CAD severity	No obstructive CAD	1	1
	Single VD	**1.58 (1.16, 2.14)**	**1.59 (1.07, 2.36)**
	Double VD	**2.35 (1.72, 3.19)**	1.48 (0.98, 2.24)
	LMS ± three VD	**3.02 (2.26, 4.05)**	**1.59 (1.07, 2.36)**
Coronary intervention	Neither PCI nor CABG	1	1
	PCI only	**0.62 (0.53, 0.73)**	1.15 (0.90, 1.47)
	CABG	**0.29 (0.22, 0.38)**	**0.61 (0.41, 0.93)**
History of CVD	No prior CVD	1	-
	Prior MI	**1.74 (1.47, 2.06)**	-
	Other prior CVD	**1.79 (1.50, 2.14)**	-
Diabetes mellitus	No diabetes	1	-
	Diabetes with insulin	**1.58 (1.30, 1.94)**	-

	Diabetes without insulin	**1.23 (1.02, 1.46)**	-
Smoking status	Non-smoker	1	-
	Current smoker	**1.38 (1.17, 1.62)**	-
Type of ACS	NSTEMI	1	-
	STEMI	0.98 (0.83, 1.15)	-
	Unstable angina	**0.80 (0.64, 0.99)**	-
Worst Killip class	I	1	-
	II, III or IV	1.11 (0.93, 1.33)	-
LV ejection fraction	Normal (≥50%)	1	-
	Mid-range (40-49%)	1.11 (0.94, 1.33)	-
	Reduced (<40%)	**1.51 (1.27, 1.79)**	-
	Unavailable	-	-
Prior hospitalisation for bleeding		-	**2.53 (1.95, 3.30)**
Index admission bleeding		-	**1.51 (1.01, 2.26)**
Total:HDL cholesterol	<3	**-**	1
	3-3.9	-	0.79 (0.62, 1.01)
	4-4.9	-	0.80 (0.62, 1.03)
	≥5	-	**0.68 (0.52, 0.89)**
	Unavailable	-	-

NZDep = New Zealand Socioeconomic Deprivation of Index; CVD = cardiovascular disease; MI = myocardial infarction; Total:HDL cholesterol = ratio of total to high-density lipoprotein cholesterol; ACS = acute coronary syndrome; NSTEMI = Non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction; GFR = glomerular filtration rate; LV = left ventricular; CAD = coronary artery disease; LMS = left main stem; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting.

The value 1 indicates the reference group against which other levels within that group are compared.

Hazard ratios (HRs) are adjusted for all variables included in the model. Values in bold represent statistical significance (p-value < 0.05).

* The normal range for haemoglobin is ≥115g/L for women and ≥130g/L for men.

Appendix Table 5 Unadjusted hazard ratios from the final ischaemic and bleeding models.

Variable	Levels	Ischaemic events	Major bleeding events
Sex	Women	1	1
	Men	**0.83 (0.74, 0.94)**	**0.83 (0.70, 1.00)**
Age per 10 years*		**1.40 (1.33, 1.48)**	**1.32 (1.22, 1.43)**
Ethnicity	European	1	1
	Māori	**1.67 (1.43, 1.95)**	**1.65 (1.30, 2.08)**
	Pacific	**1.55 (1.27, 1.90)**	**1.66 (1.24, 2.23)**
	Indian	**1.33 (1.04, 1.71)**	0.87 (0.55, 1.36)
	Chinese/ Other Asian	**0.68 (0.46, 0.99)**	1.34 (0.89, 2.02)
NZDep quintile		**1.14 (1.10, 1.19)**	1.06 (1.00, 1.12)
Heart rate, bpm	60-79	1	1
	<60	0.87 (0.72, 1.05)	0.92 (0.71, 1.20)
	≥80	**1.52 (1.35, 1.71)**	**1.36 (1.13, 1.62)**
Estimated GFR, mL/min/1.73m^2	≥90	1	1
	60-89	**1.43 (1.20, 1.70)**	1.01 (0.81, 1.27)
	30-59	**3.32 (2.76, 3.98)**	**1.81 (1.41, 2.31)**
	<30 without dialysis	**8.30 (6.33, 10.87)**	**3.66 (2.35, 5.68)**
	<30 with dialysis	**14.33 (10.93, 18.81)**	**5.28 (3.28, 8.49)**
Haemoglobin level at admission	Normal**	1	1
	Low	**2.97 (2.61, 3.37)**	**2.66 (2.20, 3.23)**
CAD severity	No obstructive CAD	1	1
	Single VD	1.07 (0.84, 1.35)	**1.60 (1.16, 2.21)**
	Double VD	**1.71 (1.34, 2.17)**	**1.59 (1.13, 2.24)**
	LMS ± three VD	**2.94 (2.35, 3.68)**	**1.80 (1.29, 2.50)**
Coronary intervention	Neither PCI nor CABG	1	1
	PCI only	**0.56 (0.50, 0.63)**	1.06 (0.87, 1.28)
	CABG	**0.41 (0.32, 0.52)**	**0.65 (0.45, 0.93)**
History of CVD	No prior CVD	1	-
	Prior MI	**2.84 (2.48, 3.25)**	-
	Other prior CVD	**2.56 (2.22, 2.95)**	-
Diabetes mellitus	No diabetes	1	-
	Diabetes with insulin	**3.74 (3.24, 4.33)**	-
	Diabetes without insulin	**1.79 (1.55, 2.06)**	-
Smoking status	Non-smoker	1	-
	Current smoker	1.02 (0.90, 1.16)	-
Type of ACS	NSTEMI	1	-
	STEMI	**0.68 (0.59, 0.79)**	-
	Unstable angina	**0.69 (0.58, 0.82)**	-

Worst Killip class	I	1	-
	II, III or IV	**2.41 (2.07, 2.79)**	-
LV ejection fraction	Normal (≥50%)	1	-
	Mid-range (40-49%)	**1.33 (1.13, 1.58)**	-
	Reduced (<40%)	**2.60 (2.23, 3.04)**	-
	Unavailable	**1.35 (1.17, 1.56)**	-
Prior hospitalisation for bleeding		-	**3.38 (2.65, 4.32)**
Index admission bleeding		-	**2.00 (1.37, 2.93)**
Total:HDL cholesterol	<3	**-**	1
	3-3.9	-	**0.73 (0.57, 0.93)**
	4-4.9	-	**0.69 (0.54, 0.89)**
	≥5	-	**0.56 (0.43, 0.72)**
	Unavailable	-	0.91 (0.65, 1.28)

NZDep = New Zealand Socioeconomic Deprivation of Index; CVD = cardiovascular disease; MI = myocardial infarction; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; NSAID = non-steroidal anti-inflammatory drug; Total:HDL cholesterol = ratio of total to high-density lipoprotein cholesterol; SBP = systolic blood pressure; ACS = acute coronary syndrome; NSTEMI = Non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction; GFR = glomerular filtration rate; LV = left ventricular; CAD = coronary artery disease; LMS = left main stem; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting.

The value 1 indicates the reference group against which other levels within that group are compared.

Values in bold represent statistical significance (p-value < 0.05).

* HR for age is per 10 unit but was modelled per 1 unit for absolute risk calculations.

** The normal range for haemoglobin is ≥115g/L for women and ≥130g/L for men.

Appendix Table 6 Ratio of ischaemic to bleeding events by month between 28 days and 1 year

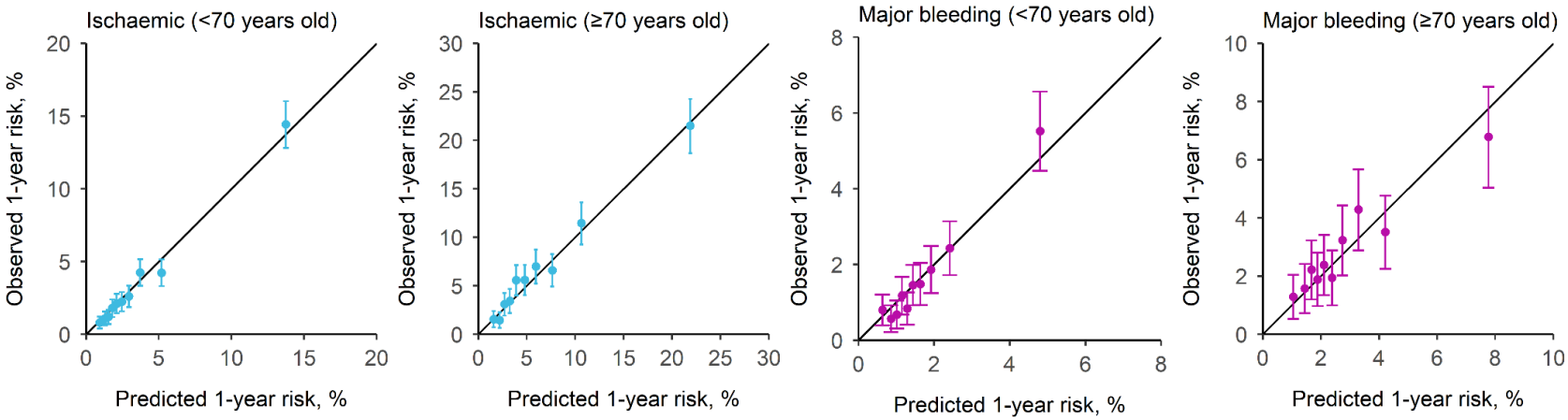
Follow-up time post ACS discharge (months)	Ischaemic (I) event	Bleeding (B) event	Ratio of I to B events
2	188	83	2.3
3	136	51	2.7
4	116	58	2.0
5	113	57	2.0
6	109	50	2.2
7	129	49	2.6
8	88	46	1.9
9	74	35	2.1
10	79	57	1.4
11	65	28	2.3
12	85	29	2.9

Appendix Table 7 Number of people dispensed DAPT (dual antiplatelet therapy) consistently up to 3 months, 6 months, 9 months, and 12 months.

	0-3 months	**3-6 months**	**6-9 months**	**9-12 months**
Number of people who were alive at each defined time period	27648 alive up to 3 months	27497 alive up to 6 months	27355 alive up to 9 months	27227 alive up to 12 months
Number of people dispensed DAPT at each defined time period	23271 dispensed DAPT in the first 3 months (84.2%)	19058 dispensed DAPT in the first 3 months and 3-6 months (69.3%)	16167 dispensed DAPT in the first 3 months, 3-6 months, and 6-9 months (59.1%)	12440 dispensed DAPT in the first 3 months, 3-6 months, 6-9 months, and 9-12 months (45.7%)

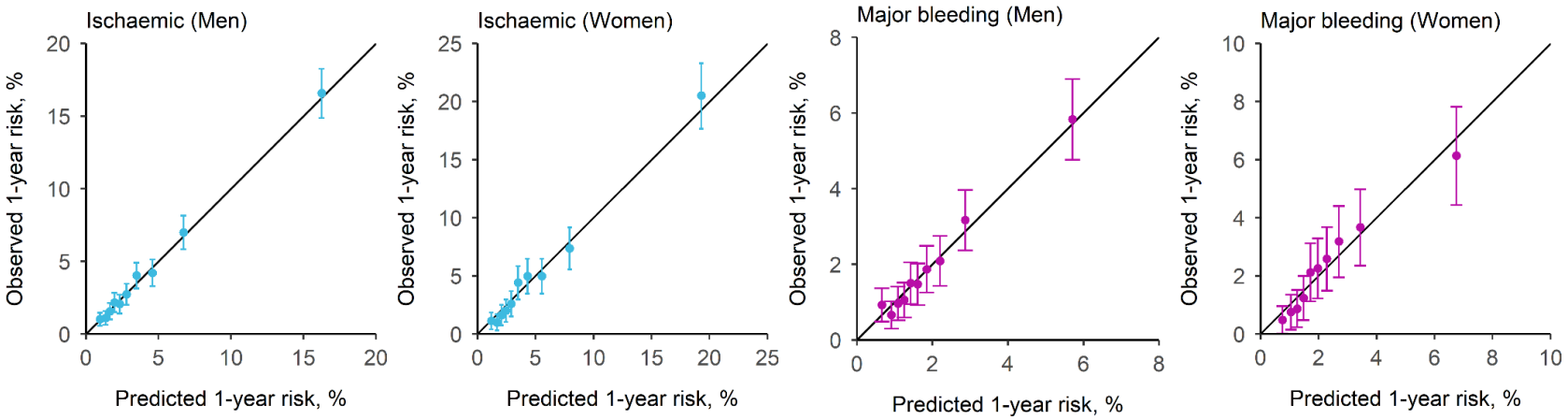
Appendix Figure 1 Calibration plots for observed versus predicted 28 day to 1-year risk by sub-group.

(1) By age group



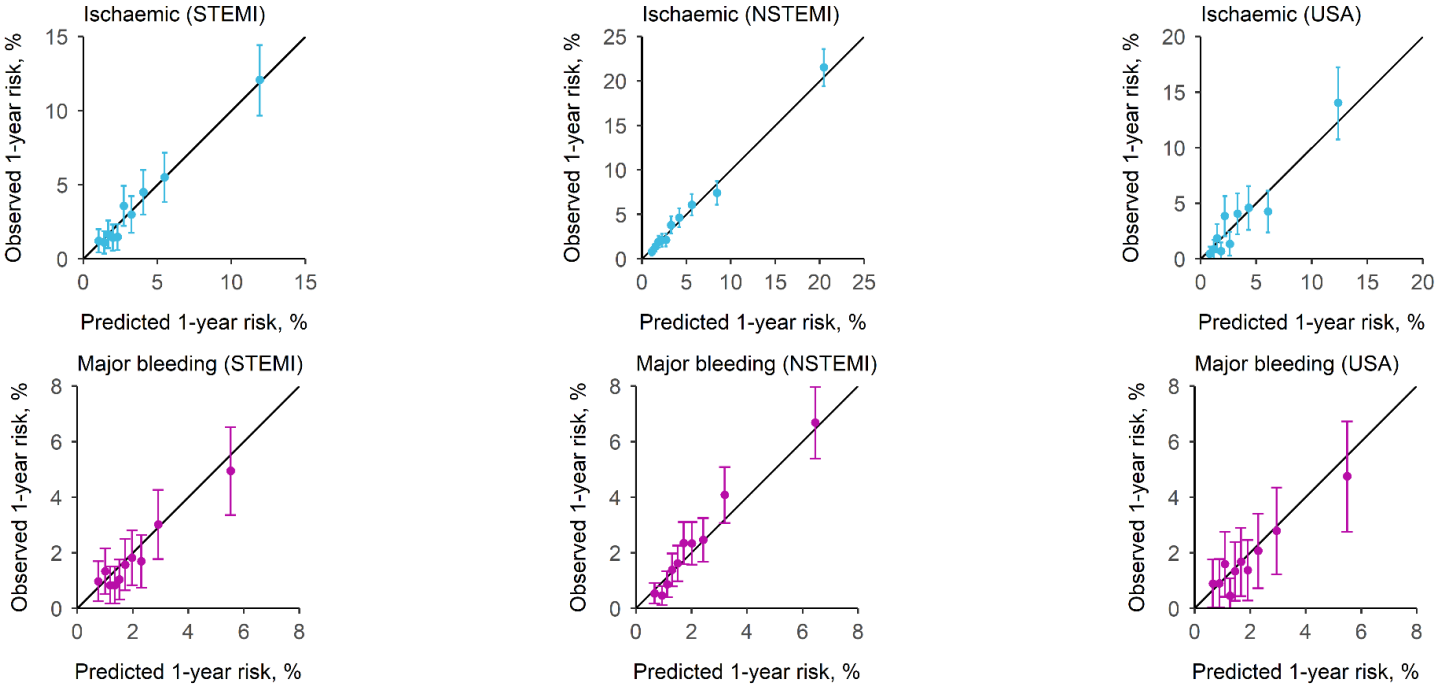
Calibration of ANZACS-QI risk scores for ischaemic and major bleeding events in the full cohort by age group. The diagonal line represents perfect calibration.

(2) By sex



Calibration of ANZACS-QI risk scores for ischaemic and major bleeding events in the full cohort by sex. The diagonal line represents perfect calibration.

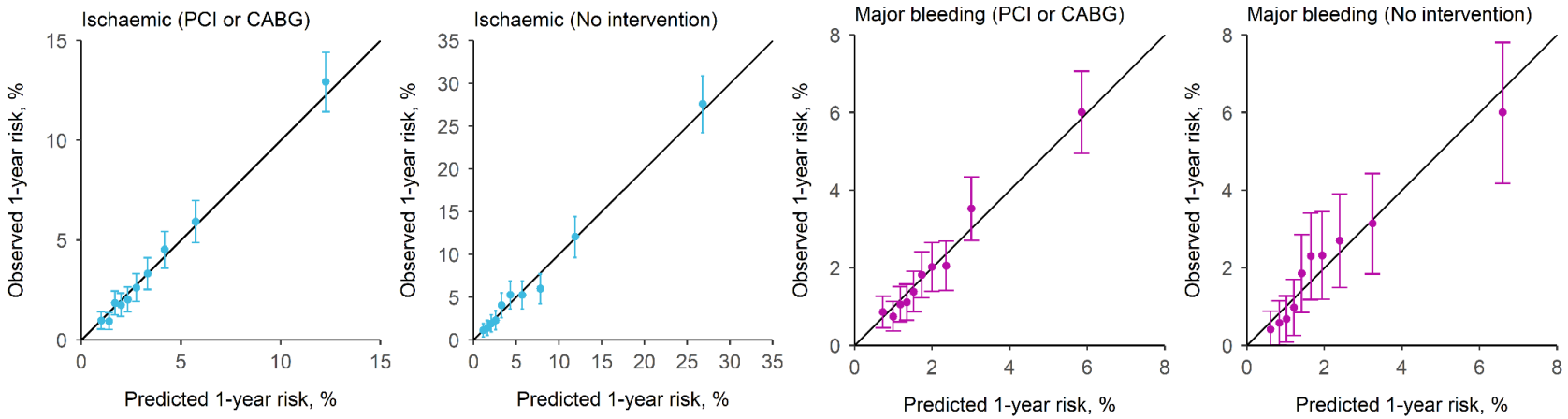
(3) By ACS type



ACS = acute coronary syndrome; STEMI = ST-elevation myocardial infarction; NSTEMI = Non-ST-elevation myocardial infarction; USA = unstable angina.

Calibration of ANZACS-QI risk scores for ischaemic and major bleeding events in the full cohort by type of ACS. The diagonal line represents perfect calibration.

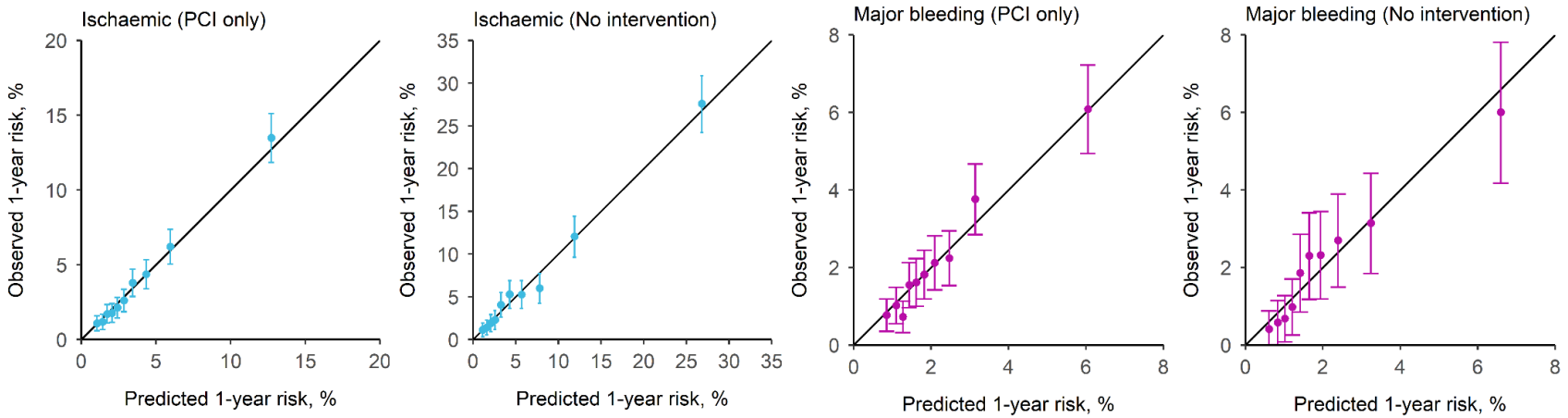
(4a) By coronary intervention



PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting.

Calibration of ANZACS-QI risk scores for ischaemic and major bleeding events in the full cohort by intervention. The diagonal line represents perfect calibration.

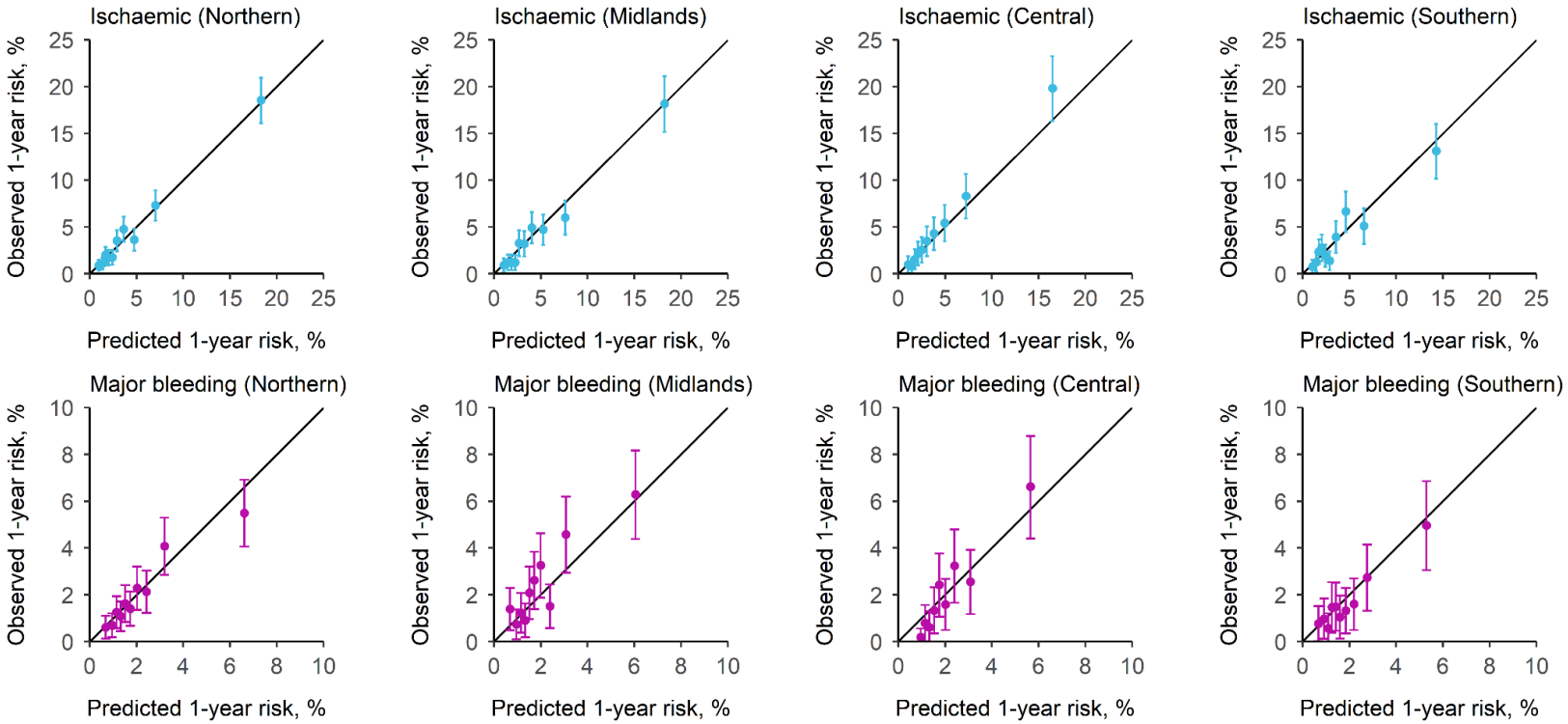
(4b) By coronary intervention



PCI = percutaneous coronary intervention.

Calibration of ANZACS-QI risk scores for ischaemic and major bleeding events in the full cohort by intervention. The diagonal line represents perfect calibration.

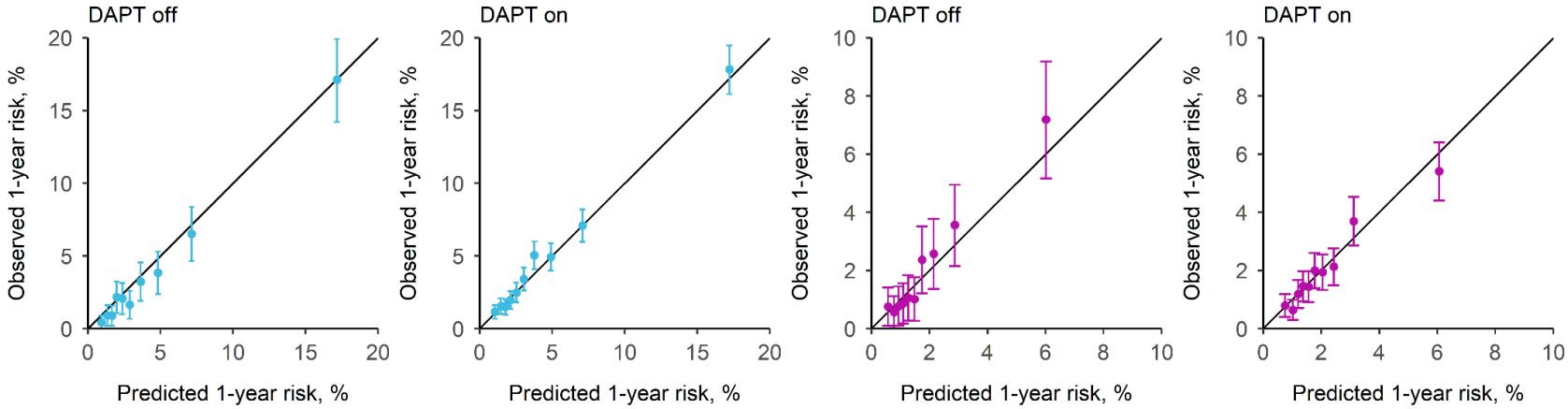
(5) By geographical region



Calibration of ANZACS-QI risk scores for ischaemic and major bleeding events in the full cohort by geographical region. The diagonal line represents perfect calibration.

There are only 9 deciles of predicted major bleeding risk in Central region patients. The observed risk was not calculable due to there being no events observed in the lowest decile of predicted risk.

(6) DAPT (dual antiplatelet therapy)



Calibration of ANZACS-QI risk scores for ischaemic and major bleeding events in the full cohort by whether patients were on DAPT beyond 3 months post-discharge. The diagonal line represents perfect calibration.