Annals of Internal Medicine ORIGINAL RESEARCH

Predicting Bleeding Risk to Guide Aspirin Use for the Primary Prevention of Cardiovascular Disease

A Cohort Study

Vanessa Selak, MBChB, PhD; Rod Jackson, MBChB, PhD; Katrina Poppe, PhD; Billy Wu, MPH; Matire Harwood, MBChB, PhD; Corina Grey, MBChB, MPH; Romana Pylypchuk, MSc; Suneela Mehta, MBChB, MPH; Andrew Kerr, MBChB, MD; and Sue Wells, MBChB, PhD

Background: Many prognostic models for cardiovascular risk can be used to estimate aspirin's absolute benefits, but few bleeding risk models are available to estimate its likely harms.

Objective: To develop prognostic bleeding risk models among persons in whom aspirin might be considered for the primary prevention of cardiovascular disease (CVD).

Design: Prospective cohort study.

Setting: New Zealand primary care.

Participants: The study cohort comprised 385 191 persons aged 30 to 79 years whose CVD risk was assessed between 2007 and 2016. Those with indications for or contraindications to aspirin and those who were already receiving antiplatelet or anticoagulant therapy were excluded.

Measurements: For each sex, Cox proportional hazards models were developed to predict major bleeding risk; participants were censored at the earliest of the date on which they first met an exclusion criterion, date of death, or study end date (30 June 2017). The main models included the following predictors: demographic characteristics (age, ethnicity, and socioeconomic deprivation), clinical measurements (systolic blood pressure and ratio of total–high-density lipoprotein cholesterol), family history of premature CVD, medical history (smoking, diabetes, bleeding, peptic ulcer disease, cancer, chronic liver disease, chronic pancreatitis, or alcohol-related conditions), and medication use (nonsteroidal anti-inflammatory agents, corticosteroids, and selective serotonin reuptake inhibitors).

Results: During 1 619 846 person-years of follow-up, 4442 persons had major bleeding events (of which 313 [7%] were fatal). The main models predicted a median 5-year bleeding risk of 1.0% (interquartile range, 0.8% to 1.5%) in women and 1.1% (interquartile range, 0.7% to 1.6%) in men. Plots of predicted-against-observed event rates showed good calibration throughout the risk range.

Limitation: Hemoglobin level, platelet count, and body mass index were excluded from the main models because of high numbers of missing values, and the models were not externally validated in non–New Zealand populations.

Conclusion: Prognostic bleeding risk models were developed that can be used to estimate the absolute bleeding harms of aspirin among persons in whom aspirin is being considered for the primary prevention of CVD.

Primary Funding Source: The Health Research Council of New Zealand.

Ann Intern Med. 2019;170:357-368. doi:10.7326/M18-2808 **Annals.org**
For author affiliations, see end of text.
This article was published at Annals.org on 26 February 2019.

The decision to initiate aspirin therapy for the primary prevention of cardiovascular disease (CVD) requires careful consideration of both absolute benefits and harms (1, 2). The most significant harm associated with aspirin is major bleeding (2, 3). The absolute magnitude of aspirin's CVD benefits and bleeding harms depends primarily on baseline (untreated) absolute risks for these outcomes, which vary considerably with a range of risk factors (such as older age, male sex, diabetes, smoking, and high blood pressure [BP]) (4). Risk assessment for CVD is now an internationally accepted strategy for estimating the absolute CVD-related benefits of primary preventive interventions (5, 6). Although many prognostic models for CVD risk can be used to estimate aspirin's absolute benefits for an individual (5, 7–9), few prognostic models for bleeding risk are available to estimate its likely harms (2).

The U.S. Preventive Services Task Force recently published recommendations supporting use of low-dose aspirin for the primary prevention of CVD and cancer among adults aged 50 to 59 years with 10-year CVD risk of at least 10% (10). Estimated rates of CVD, colorectal cancer, and major bleeding based on microsimulation models were used to determine the net balance of benefits and harms across individuals with varying baseline CVD risk (10, 11). Despite a comprehensive review of the relevant literature (2), the Task Force could not find a suitable published study that directly measured bleeding risk in an untreated cohort for use in the simulation models. We recently published such data by sex and age group in 10-year age bands to inform population-level guidelines for primary prevention of CVD (12).

The aim of this study was to take the next step and develop and validate multivariable prognostic models for bleeding risk among persons without CVD who were not treated with antiplatelet therapy.

See also:

Editorial comment 411

Web-Only
Supplement

METHODS

We followed TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) (13) recommendations throughout this article.

Design, Setting, Entry, and Follow-up

We did a prospective, open, cohort study. Participants were automatically recruited into the cohort after their first CVD risk assessment when their primary care physician or nurse entered data into PREDICT, a Web-based decision support program integrated with electronic systems for management of primary care practices in New Zealand (14, 15). The PREDICT study was approved by the Northern Y Regional Ethics Committee in 2003, with subsequent annual approval by the National Multi-region Ethics Committee since 2007. More than one third of primary care practices in New Zealand use the PREDICT software. In these practices, data up to 2015 indicate that approximately 90% of persons eligible for CVD risk assessment (according to national guidelines [16]) had their risk assessed using this software (15). Participants were recruited between 1 January 2007 and 31 December 2016, and the study end date was 30 June 2017 to provide at least 6 months of follow-up across all data sources. Participants were censored at the earliest of the date on which they met an exclusion criterion, date of death, or study end date.

Data Sources and Linkage

When PREDICT is used for a CVD risk assessment, an electronic CVD risk profile is stored both in the practice management system and anonymously in a central database. With the permission of health providers, this database profile was linked to an encrypted National Health Index number, which was used to anonymously link CVD risk profiles to national and regional databases. National databases were used to obtain or confirm data on demographic characteristics (age, sex, ethnicity [prioritized according to New Zealand data protocols] [17], district health board [DHB] region in which the person lived, and socioeconomic deprivation [18]), deaths (19), publicly funded hospitalizations (from 1988 [20]), cancer (defined as primary malignant disease excluding squamous and basal skin, from 1993 [21]), and subsidized pharmaceutical dispensing (from 2006 [22]). Laboratory test results were obtained from TestSafe, a regional laboratory repository for all tests done in hospitals and the community; TestSafe covers nearly all of the PREDICT CVD cohort since 2005 (14).

Participants

All persons who had a PREDICT assessment of CVD risk in primary care from 1 January 2007 to 31 December 2016 were considered for inclusion in this study. Exclusion criteria were any of the following at the time of risk assessment: age younger than 30 years or older than 79 years; history of CVD, congestive heart failure, atrial fibrillation, chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73 m^2 on ≥2 occasions ≥90 days apart), diabetes (with overt nephropathy or other renal disease), or intracerebral bleeding; or dispensing aspirin, an antiplatelet drug, or an anticoagulant in the preceding 6 months. Persons with congestive heart failure, chronic kidney disease, or diabetes with renal disease were excluded because these conditions are considered to be equivalent in risk to established CVD and are managed without CVD risk assessment (23). Those with atrial fibrillation were excluded because this condition is generally managed with an antithrombotic agent (24) (such as aspirin, an antiplatelet drug, or an anticoagulant) and retention of persons with atrial fibrillation who were not receiving an antithrombotic agent could introduce confounding by indication (25). Similarly, persons who were dispensed an antithrombotic agent before baseline were also excluded to minimize risk for confounding by indication, because these medications are not routinely recommended and are not approved by the U.S. Food and Drug Administration for primary prevention. Persons with a prior intracerebral bleeding event were excluded because aspirin would generally be contraindicated for the primary prevention of CVD in this group. Persons who met any of the exclusion criteria (except age) during follow-up were censored on the earliest date on which they met a criterion. **Appendix Tables 1** to **4** (available at Annals.org) further define the exclusion criteria.

Outcomes

The primary outcome was a first major bleeding event after study entry associated with a hospitalization or death. Major bleeding events were classified as gastrointestinal, intracranial, or other. Other bleeding was respiratory (including epistaxis and hemoptysis), ocular (vitreous and retinal), bleeding into a joint, or bleeding into the pericardium or peritoneum. Major bleeding events associated with trauma or procedures were excluded. Hospitalizations associated with a bleeding event were defined as those in which an International Classification of Diseases (ICD) code for bleeding was assigned as a diagnosis for the admission, either on its own if bleeding was the principal diagnosis (that is, the main reason for admission), or when a blood transfusion also occurred during the admission if bleeding was not the principal diagnosis. The transfusion could be of whole blood (ICD, 10th Revision, Australian Modification [ICD-10-AM] code 1370601 or ICD, Ninth Revision, Clinical Modification, Australian Version [ICD-9-CM-A] code 9903] or packed cells [ICD-10-AM code 1370602 or ICD-9-CM-A code 9904]). Potential ICD codes for major bleeding were identified by review of ICD code sets used by other studies to identify bleeding events (26–29) and review (V.S.) of all ICD-9-CM-A and ICD-10-AM codes for any further relevant codes. The final set of ICD-9-CM-A and ICD-10-AM codes for a major bleeding event (**Appendix Table 4**) was compiled after review of all potential ICD codes (V.S. and A.K.).

Predictors

Potential predictors of a major bleeding event among persons without CVD were identified from

meta-analyses of trials of aspirin for the primary prevention of CVD (4) and cohort studies that assessed bleeding rates in community-based populations (27, 30). We obtained data for the following potential predictors (or their proxies, as indicated): demographic characteristics (age, sex, ethnicity, and socioeconomic deprivation [using an area-based measure]), clinical measurements (systolic BP, ratio of total to high-density lipoprotein cholesterol, body mass index [BMI], hemoglobin level, and platelet count), medical history (smoking, diabetes, bleeding, peptic ulcer disease [using admissions or medications for managing the condition; that is, proton-pump inhibitors, H_2 antagonists, or *Helicobacter pylori* eradication medication], heavy alcohol use [using admissions for chronic alcohol-related conditions], chronic liver disease, chronic pancreatitis, and cancer), and medication (nonsteroidal anti-inflammatory agents, corticosteroids, and selective serotonin reuptake inhibitors). Because the prognostic bleeding risk models were intended to be implemented alongside New Zealand's models for predicting CVD risk (15), we also included as predictors family history of premature CVD, BP-lowering medication, and lipid-lowering medication. All of these variables (listed and described in **Appendix Tables 5** and **6**, available at Annals.org) were prespecified and were planned for inclusion in model development.

Missing Data

All variables had complete or nearly complete data (>99% of values available) except BMI (20% missing), hemoglobin level (29% missing), and platelet count (54% missing). These 3 variables were excluded from the main models. We evaluated BMI as an incremental prognostic factor (that is, when added to available predictors) among the subgroup of persons in whom BMI was available; the methods, findings, and discussion of this evaluation are in the **Supplement** (available at Annals.org).

Statistical Analysis

Model Development

Cox proportional hazards modeling was used to develop prediction models for time to a first major bleeding event, and all predictors with complete or nearly complete values were included. Separate models were developed in women and men (15). Time in the study was the time scale and was calculated from index assessment to the earliest date on which participants had their first major bleeding event, died, or met any exclusion criterion or the end of the study (30 June 2017). Reference groups for categorical variables are shown in boldface and italics in **Appendix Table 5**. The proportionality assumption was assessed by using the global Schoenfeld test (31) and plotting log[−log(survival)] versus log(time). The linearity of the association between continuous variables and the outcome was assessed by visual inspection of LOWESS smoothed plots of martingale residuals (32) and fractional polynomials (33). Interaction terms were not assessed because interactions were not clinically suspected. Absolute risk was calculated by using coefficients from Cox models and baseline survival for the reference group at 5 years.

Model Performance

Calibration performance was assessed graphically by categorizing participants into deciles of predicted 5-year rates of bleeding events and plotting mean predicted against observed 5-year event rates. A diagonal line represents perfect calibration. Observed 5-year event rates were obtained by the Kaplan–Meier method (34). We calculated standard statistical metrics of model and discrimination performance (R^2 and c-statistic [35–37]).

Internal Validation

We used the whole cohort to develop the models and did a split-sample internal validation as a sensitivity analysis (38, 15). The cohort was split into 2 subcohorts, which were defined geographically (based on DHB region of residence) rather than randomly (39). The DHBs of Auckland and Counties Manukau formed the derivation subcohort and those of Waitemata and Northland formed the validation subcohort. The calibration and discrimination performance of the models developed in the derivation subcohort was assessed in the validation subcohort and was compared with that of the models developed in the whole cohort; hazard ratios (HRs) were also compared.

All analyses were done using R, version 3.5.1 (R Foundation; https://cran.r-project.org), which included the package "survival."

Role of the Funding Source

The Health Research Council of New Zealand and Heart Foundation of New Zealand had no role in the design of the study; the collection, analysis, or interpretation of the data; or the decision to approve publication of the finished manuscript.

RESULTS

Between 1 January 2007 and 31 December 2016, cardiovascular risk was assessed for 516 161 persons, of whom 130 970 met 1 or more exclusion criteria; this left 385 191 persons (169 053 women and 216 138 men) in the study cohort (**Table 1**). **Table 2** shows demographic characteristics, medical history, clinical measurements, and medications separately for men and women. The average age was 56 years (SD, 9) for women and 51 years (SD, 10) for men. Participants were ethnically diverse: 55% of the cohort self-identified as European, 13% as Māori (New Zealand's indigenous population), 12% as Pacific, 9% as Indian, and 11% as Chinese or other Asian.

Study participants had 4442 major bleeding events (of which 313 [7%] were fatal) during 1 619 846 person-years of follow-up. Most bleeding events were gastrointestinal (69%), and of the fatal events, most were intracerebral (177 of 313 [57%]) (**Appendix Table 7**, available at Annals.org). The crude incidence of major bleeding events per 1000 person-years was 2.62 (95%

Table 1. Cohort Enrollment, Exclusions, and Incidence of Bleeding Events During Follow-up

Variable	Participants, *n*	Person-Years of Follow-up, *n*	Had Bleeding Event During Follow-up, *n (%)*	Rate of Bleeding Events (per 1000 person-years)
PREDICT cohort with first CVD risk assessment between 1 January 2007 and 31 December 2016*	516 161	1 786 276	5609 (1.09)	3.14
Excluded (can be in >1 exclusion group below)	130 970	166 430	1167 (0.89)	7.01
In ethnic group with <1000 persons†	7674	26 413	87 (1.13)	3.29
Aged <30 y	3679	15 050	21 (0.57)	1.40
Aged ≥80 y	14 788	19 683	280 (1.89)	14.23
CVD	55 369	55 085	497 (0.90)	9.02
Heart failure	19 179	18 802	252 (1.31)	13.40
Atrial fibrillation	19 034	15 386	162 (0.85)	10.53
Chronic kidney disease	5688	6417	103 (1.81)	16.05
Intracerebral bleeding	2277	6200	112 (4.92)	18.07
Received aspirin	86 558	41 347	296 (0.34)	7.16
Received other antiplatelet medication	1360	473	3 (0.22)	6.34
Received anticoagulant	10 608	2613	38 (0.36)	14.54
Included in analysis	385 191	1 619 846	4442 (1.15)	2.74
Women	169 053	716 418	1878 (1.11)	2.62
Men	216 138	903 428	2564 (1.19)	2.84

CVD = cardiovascular disease.
* 1219 individuals had already been removed during data cleaning because they had no meshblock (i.e., a geographic area) record in any recent data from primary health organizations.
† Middle Eastern/Latin American/African, other, and unknown.

CI, 2.51 to 2.74) among women and 2.84 (CI, 2.73 to 2.95) among men.

In the models, all continuous variables were fitted as linear terms after assessment using martingale residual plots, and the fractional polynomials procedure provided no compelling support for fitting nonlinear terms. For women, the *P* value for the global Schoenfeld test was 0.927 and no covariates had *P* values less than 0.05. For men, the *P* value for the global Schoenfeld test was 0.017 but no clear evidence showed violation of the proportional hazards assumption when the log[−log(survival)] curves of the 3 covariates with *P* values less than 0.05 (Indian ethnicity, other Asian ethnicity, and prior bleeding) were plotted over log(time) against their reference group.

Adjusted HRs for major bleeding were similar for women and men, except for those of Chinese or other Asian ethnicity (**Table 3**). Compared with European ethnicity, Chinese or other Asian ethnicity was associated with an increase in risk for major bleeding (HR, 1.46 [CI, 1.28 to 1.67]) among men but no difference in risk among women (HR, 1.05 [CI, 0.88 to 1.24]).

Among women and men, each additional year of age was associated with an estimated relative increase of 4% in 5-year risk for major bleeding. Māori and Pacific people were at increased risk for major bleeding compared with Europeans, whereas Indians were at reduced risk, although this latter effect did not reach statistical significance in women or men. Risk increased per quintile of socioeconomic deprivation. Bleeding risk increased among smokers (former and current) and persons with diabetes. Other established risk factors for CVD—high systolic BP, high ratio of total to high-density lipoprotein cholesterol, and family history of premature CVD—had little association with bleeding risk. Dispensing of BP-lowering medication, but not lipid-lowering medication, was associated with increased risk for major bleeding.

All established bleeding risk factors were associated with increased bleeding risk in both women and men (cancer; prior bleeding; peptic ulcer disease; alcohol-related conditions; chronic liver disease or pancreatitis; and use of medications for peptic ulcer disease, nonaspirin nonsteroidal anti-inflammatory medication, corticosteroids, and selective serotonin reuptake inhibitors). Not all associations were statistically significant: The association with peptic ulcer disease was significant only in women and that with nonaspirin nonsteroidal anti-inflammatory medication only in men.

Table 4 shows variable coefficients, baseline survival, and the mean sum of variables multiplied by coefficients for the 5-year prognostic bleeding risk models, along with an example calculation of absolute risk. Mean estimated 5-year bleeding risk was 1.3% (median, 1.0% [interquartile range, 0.8% to 1.5%]) among women and 1.4% (median, 1.1% [interquartile range, 0.7% to 1.6%]) among men. Plots of predicted versus observed 5-year risk for bleeding showed good model calibration across all risk deciles (**Figure**). The slopes of regression lines comparing predicted versus observed bleeding risk in deciles were 1.00 (CI, 0.92 to 1.08) for women and 0.96 (CI, 0.90 to 1.02) for men. Underprediction or overprediction did not exceed 0.2% in any decile of predicted risk. **Table 5** shows model and discrimination metrics.

In sensitivity analyses, the derivation cohort comprised 103 023 women and 131 802 men and the validation cohort 63 301 women and 80 374 men (**Appendix Table 8**, available at Annals.org). The derivation and full cohorts had similar HRs for major bleeding (**Appendix Ta-**

Table 2. Patient Characteristics*

Variable	Women (*n* = 169 053 [44%])	Men (*n* = 216 138 [56%])
Incident total major bleeding events	1878 (1.11)	2564 (1.19)
Total person-years observed, *n*	716 418	903 428
Crude incidence of total major bleeding events per 1000 person-years (95% CI), *n*†	2.62 (2.51–2.74)	2.84 (2.73–2.95)
Mean follow-up time (SD), *y*	4.24 (2.38)	4.18 (2.39)
Median follow-up time (IQR), *y*	4.10 (2.54–5.72)	4.06 (2.54–5.61)
Mean age (SD), *y*	56.0 (9.1)	51.1 (10.1)
Self-identified ethnicity		
European	92 688 (54.8)	121 013 (56.0)
Māori	23 021 (13.6)	26 941 (12.5)
Pacific	20 297 (12.0)	26 679 (12.3)
Indian	13 436 (7.9)	19 410 (9.0)
Chinese or other Asian	19 611 (11.6)	22 095 (10.2)
NZDep quintile		
1 (least deprived)	38 234 (22.6)	48 347 (22.4)
2	33 789 (20.0)	43 067 (19.9)
3	30 780 (18.2)	39 083 (18.1)
4	31 010 (18.3)	39 376 (18.2)
5 (most deprived)	35 240 (20.8)	46 265 (21.4)
Smoking		
Never-smoker	123 515 (73.1)	141 484 (65.5)
Former smoker	22 610 (13.4)	34 851 (16.1)
Current smoker	22 928 (13.6)	39 802 (18.4)
Family history of premature CVD	19 094 (11.3)	20 045 (9.3)
Diabetes	15 839 (9.4)	15 718 (7.3)
Cancer	11 406 (6.7)	7798 (3.6)
Prior bleeding event	3932 (2.3)	5291 (2.4)
Gastrointestinal	2983 (1.8)	4068 (1.9)
Other	1018 (0.6)	1301 (0.6)
Peptic ulcer disease (nonbleeding)	869 (0.5)	1489 (0.7)
Alcohol-related condition	707 (0.4)	1894 (0.9)
Chronic liver disease or pancreatitis	289 (0.2)	567 (0.3)
Chronic liver disease	214 (0.1)	430 (0.2)
Chronic pancreatitis	78 (0)	151 (0.1)
Mean SBP (SD), *mm Hg*	128 (16.1)	128 (14.7)
Mean ratio of total–HDL cholesterol (SD)	3.7 (1.09)	4.4 (1.25)
Mean BMI (SD), kg/m^2	28.9 (7.2)	28.9 (5.7)
BMI		
Underweight (<18.5 kg/m^2)	1890 (1.1)	809 (0.4)
Normal (18.5–24.9 kg/m^2)	42 615 (25.2)	39 943 (18.5)
Overweight (25–29.9 kg/m^2)	41 151 (24.3)	72 224 (33.4)
Obesity class 1 (30–34.9 kg/m^2)	24 474 (14.5)	38 441 (17.8)
Obesity class 2 (35–39.9 kg/m^2)	13 061 (7.7)	13 973 (6.5)
Obesity class 3 (≥40 kg/m^2)	10 365 (6.1)	7451 (3.4)
Missing	35 497 (21.0)	43 297 (20.0)
Hemoglobin level		
Not reduced	121 144 (71.7)	141 761 (65.6)
Reduced (<115 g/L in women, <130 g/L in men)	6373 (3.8)	5078 (2.3)
Missing	41 536 (24.6)	69 299 (32.1)
Platelet count		
<150 × 10^9 cells/L	1108 (0.7)	2700 (1.2)
150–399 × 10^9 cells/L	82 088 (48.6)	86 918 (40.2)
≥400 × 10^9 cells/L	3780 (2.2)	1571 (0.7)
Missing	82 077 (48.6)	124 949 (57.8)
Medications in 6 mo before index assessment		
Blood pressure–lowering	36 669 (21.7)	30 787 (14.2)
Lipid-lowering	19 023 (11.3)	21 790 (10.1)
Peptic ulcer disease‡	22 405 (13.3)	22 740 (10.5)
Nonsteroidal anti-inflammatory	29 482 (17.4)	39 377 (18.2)
Corticosteroid	10 335 (6.1)	10 339 (4.8)
Selective serotonin reuptake inhibitor	11 653 (6.9)	8088 (3.7)

BMI = body mass index; CVD = cardiovascular disease; HDL = high-density lipoprotein; IQR = interquartile range; NZDep = New Zealand Index of Deprivation; SBP = systolic blood pressure.
* Data are numbers (percentages) of the sex-specific cohort unless otherwise specified. Data are complete or nearly complete (>99% of values available) unless otherwise specified.
† Mid-P exact test, calculated using www.openepi.com/PersonTime1/PersonTime1.htm.
‡ Proton-pump inhibitor, H_2 antagonist, or *Helicobacter pylori* eradication therapy.

Table 3. Adjusted Hazard Ratios for Major Bleeding Events

Characteristic	Adjusted Hazard Ratio (95% CI)*	
	Women	Men
Age, per year	1.04 (1.03–1.04)	1.04 (1.03–1.04)
Self-identified ethnicity		
European	1	1
Māori	1.37 (1.18–1.57)	1.51 (1.33–1.71)
Pacific	1.34 (1.15–1.56)	1.69 (1.49–1.92)
Indian	0.84 (0.67–1.06)	0.98 (0.82–1.18)
Chinese or other Asian	1.05 (0.88–1.24)	1.46 (1.28–1.67)
NZDep quintile, per 1 quintile	1.10 (1.07–1.14)	1.10 (1.06–1.13)
Smoking		
Never-smoker	1	1
Former smoker	1.16 (1.01–1.32)	1.17 (1.05–1.30)
Current smoker	1.64 (1.44–1.87)	1.47 (1.33–1.62)
Family history of premature CVD	1.06 (0.92–1.22)	1.05 (0.92–1.20)
Diabetes	1.20 (1.03–1.40)	1.19 (1.04–1.37)
Cancer	1.35 (1.16–1.57)	1.76 (1.52–2.04)
Prior bleeding event	3.18 (2.70–3.75)	3.13 (2.73–3.59)
Peptic ulcer disease (nonbleeding)	1.53 (1.08–2.17)	1.25 (0.97–1.61)
Alcohol-related condition	2.59 (1.81–3.70)	1.96 (1.54–2.51)
Chronic liver disease or pancreatitis	2.66 (1.66–4.27)	2.17 (1.54–3.06)
SBP, per mm Hg	1.01 (1.00–1.01)	1.00 (1.00–1.01)
Ratio of total–HDL cholesterol, per 1 unit	1.00 (0.96–1.05)	0.95 (0.92–0.98)
Medications in 6 mo before index assessment		
Blood pressure–lowering	1.15 (1.03–1.29)	1.23 (1.10–1.37)
Lipid-lowering	1.01 (0.88–1.16)	0.95 (0.84–1.09)
Peptic ulcer disease	1.45 (1.29–1.63)	1.44 (1.29–1.60)
Nonsteroidal anti-inflammatory	1.11 (0.99–1.25)	1.19 (1.08–1.31)
Corticosteroid	1.39 (1.19–1.62)	1.42 (1.23–1.64)
Selective serotonin reuptake inhibitor	1.18 (1.00–1.39)	1.34 (1.12–1.60)

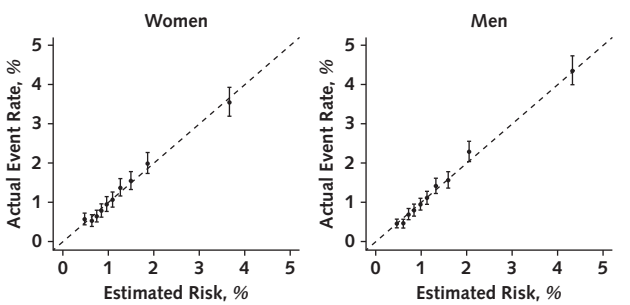
CVD = cardiovascular disease; HDL = high-density lipoprotein; NZDep = New Zealand Index of Deprivation; SBP = systolic blood pressure.
* Adjusted for all other variables in the model; the model included 167 646 women (1407 excluded because of a missing value) and 214 539 men (1599 excluded because of a missing value).

ble 9, available at Annals.org) and similar metrics of model performance and discrimination (**Appendix Table 10**, available at Annals.org). Predicted versus observed 5-year bleeding risk was plotted for the derivation models in the validation populations (**Appendix Figure 1**, available at Annals.org). Calibration was generally good for men, and although bleeding risk tended to be underestimated in women, this was by no more than 0.7% in any decile of predicted risk.

Appendix Figure 2 (available at Annals.org) shows plots of predicted versus observed 5-year risk for bleeding for the full model in each of the 4 DHBs (patient characteristics by DHB are in **Tables 6** and **7**). The plots indicate that the full model overestimated bleeding risk in the population of Auckland DHB (used to develop the model; up to a maximum of 0.8% in women and 0.5% in men in any decile of predicted risk) but performed well overall in the 3 other DHBs.

An ancillary analysis of the prognostic value of BMI in addition to available predictors among persons in whom BMI was available (**Supplement**) indicated some independent associations between BMI and bleeding risk that require further investigation. Metrics of model performance and discrimination were similar regardless of whether BMI was added to available predictors, and integrated discrimination improvement values were extremely low.

Figure. Calibration plot: estimated vs. observed 5-year bleeding risk.



Diagonal lines represent perfect calibration.

DISCUSSION

Sex-specific models to predict risk for a major bleeding event were developed among persons in whom aspirin might be considered for the primary prevention of CVD. The established risk factors were associated with increased bleeding risk in both men and women in this study. Although older age, smoking, and diabetes were associated with increased risk in both sexes, no association was observed with other established risk factors for CVD (high systolic BP, high ratio of total to high-density lipoprotein cholesterol, and

Table 4. Calculating Absolute Risk: Clinical Example*

Characteristic	Coefficients		Example Calculation†	
	Women	Men	Patient Variable*	Coefficient × Variable
Age, per year	0.035028060	0.03538036	65 y	2.2997234
Self-identified ethnicity				
Māori	0.311582316	0.40955001	–	–
Pacific	0.291826502	0.52687151	–	–
Indian	−0.170178670	−0.01815411	–	–
Chinese or other Asian	0.044890076	0.37798865	–	–
NZDep quintile, per 1 quintile	0.098736992	0.09305327	3	0.27915981
Smoking				
Former smoker	0.144844011	0.15536803	1	0.15536803
Current smoker	0.495240401	0.38226181	–	–
Family history of premature CVD	0.055185249	0.05028066	–	–
Diabetes	0.182633821	0.17500777	1	0.17500777
Cancer	0.299418027	0.56636099	–	–
Prior bleeding event	1.157219678	1.14121551	–	–
Peptic ulcer disease (nonbleeding)	0.426358755	0.22227113	–	–
Alcohol-related condition	0.950659950	0.67405759	–	–
Chronic liver disease or pancreatitis	0.979437007	0.77588662	–	–
SBP, per mm Hg	0.004991576	0.00373758	130 mm Hg	0.4858854
Ratio of total–HDL cholesterol, per 1 unit	0.001878851	−0.05009861	5	−0.25049305
Medications in 6 mo before index assessment				
Blood pressure–lowering	0.140874933	0.20741834	1	0.20741834
Lipid-lowering	0.010545182	−0.04636764	1	−0.04636764
Peptic ulcer disease	0.370528961	0.36282612	–	–
Nonsteroidal anti-inflammatory	0.106558040	0.17279428	–	–
Corticosteroid	0.328347624	0.35261644	–	–
Selective serotonin reuptake inhibitor	0.164955070	0.29282150	–	–
Sum	–	–	–	3.30570206
Baseline survival at 5 y	0.98902929	0.98861720	–	–
Mean prognostic index‡	3.262378	2.787439	–	–

CVD = cardiovascular disease; HDL = high-density lipoprotein; NZDep = New Zealand Index of Deprivation; SBP = systolic blood pressure.
* A European man, aged 65 y, with diabetes. He is a former smoker, and his NZDep quintile is 3. His SBP is 130 mm Hg, his low-density lipoprotein cholesterol level is 1.8 mmol/L (70 mg/dL), and his ratio of total–HDL cholesterol is 5 units. He is taking blood pressure–lowering medication and lipid-lowering medication. He has no other medical history of note and is taking no other medications.
† 5-y bleeding risk = $\{1 - \text{baseline survival}^{\exp[(\text{sum of coefficients} \times \text{variables}) - (\text{mean prognostic index})]}\} \times 100 = [1 - 0.98861720^{\exp(3.30570206 - 2.787439)}] \times 100 = [1 - 0.98861720^{\exp(0.51826306)}] \times 100 = (1 - 0.98861720^{1.679108604}) \times 100 = (1 - 0.980961006) \times 100 = 0.019038994 \times 100 = 1.90\%$. 5-y CVD risk = 11.74% (based on the model in reference 15). Over 5 y, we would expect 19 major bleeding events with no aspirin and 29 with aspirin per 1000 persons (difference, 10 events per 1000 persons). Over 5 y, we would expect 117 CVD events with no aspirin and 103 with aspirin per 1000 persons (difference, −14 events per 1000 persons). These expected numbers assume that aspirin is associated with a 54% proportional increase in major bleeding events and a 12% proportional reduction in CVD events, based on the findings of the Antithrombotic Trialists' Collaboration meta-analysis (4).
‡ The average of the sum of (coefficients × variables) for all persons in the derivation cohort. Including it in the linear part of the risk score effectively centers the score and aligns it with the baseline hazard, which was derived at the mean value of all covariates (40).

family history of premature CVD). The models predicted a median 5-year bleeding risk of 1.0% (interquartile range, 0.8% to 1.5%) in women and 1.1% (interquartile range, 0.7% to 1.6%) in men. Plots of predicted against actual event rates showed good calibration throughout the risk range in the models for women and men. Calibration of the full models varied by geographic subpopulation, and bleeding risk was overestimated in 1 subpopulation.

We could not identify other published prognostic models for bleeding risk among persons in whom aspirin might be considered for the primary prevention of CVD (searched MEDLINE on 3 January 2019). The model QBleed predicts bleeding risk among persons in whom anticoagulants can be considered (27). Despite inclusion of key groups that were excluded from this study, the following factors were also associated with increased bleeding risk in QBleed: increased age and socioeconomic deprivation; smoking; alcohol intake; previous bleeding; chronic liver disease or pancreatitis; cancer; and treatment with BP-lowering medications, nonsteroidal anti-inflammatory agents, corticosteroids, and antidepressant medication (27). The Antithrombotic Trialists' Collaboration did a meta-analysis of individual participant data from trials of aspirin for the primary prevention of CVD and found that many risk factors for CVD events were also risk factors for major extracranial bleeding (4). Older age, diabetes, and smoking—but not high cholesterol level—were independent predictors of a major bleeding event in

Table 5. Model Performance

Statistic	Point Estimate	
	Women	Men
R^2, %		
Nagelkerke	2.16	2.65
Discrimination		
c (Harrell) (95% CI)	0.68 (0.66–0.69)	0.70 (0.69–0.71)
K (Gönen and Heller) (95% CI)	0.64 (0.63–0.65)	0.65 (0.63–0.67)

Table 6. Patient Characteristics, by DHB: Women*

Variable	Derivation Cohort		Validation Cohort	
	Auckland DHB (*n* = 46 096 [27%])	**Counties Manukau DHB (*n* = 56 927 [34%])**	**Waitemata DHB (*n* = 39 674 [23%])**	**Northland DHB (*n* = 23 627 [14%])**
Incident major bleeding events	323 (0.7)	701 (1.2)	482 (1.2)	354 (1.5)
Total person-years observed, *n*	196 024	242 400	167 992	103 670
Crude incidence of major bleeding events per 1000 person-years (95% CI), *n*†	1.65 (1.48–1.84)	2.89 (2.68–3.11)	2.87 (2.62–3.13)	3.41 (3.07–3.79)
Mean follow-up time (SD), *y*	4.3 (2.3)	4.3 (2.4)	4.2 (2.4)	4.4 (2.4)
Median follow-up time (IQR), y	4.1 (2.7–5.4)	4.1 (2.5–5.8)	4.1 (2.4–5.7)	4.2 (2.8–6.2)
Mean age (SD), y	56.5 (8.9)	54.6 (9.4)	57.1 (8.9)	56.5 (9.1)
Self-identified ethnicity				
European	25 773 (55.9)	24 817 (43.6)	24 479 (61.7)	15 990 (67.7)
Māori	3705 (8)	8278 (14.5)	3794 (9.6)	6783 (28.7)
Pacific	5393 (11.7)	11 038 (19.4)	3356 (8.5)	296 (1.3)
Indian	4509 (9.8)	6435 (11.3)	2178 (5.5)	158 (0.7)
Chinese or other Asian	6716 (14.6)	6359 (11.2)	5867 (14.8)	400 (1.7)
NZDep quintile				
1 (least deprived)	12 006 (26)	12 684 (22.3)	10 742 (27.1)	2339 (9.9)
2	10 158 (22)	9784 (17.2)	9603 (24.2)	3673 (15.5)
3	8417 (18.3)	7909 (13.9)	8611 (21.7)	5279 (22.3)
4	8218 (17.8)	9278 (16.3)	7247 (18.3)	5789 (24.5)
5 (most deprived)	7297 (15.8)	17 272 (30.3)	3471 (8.7)	6547 (27.7)
Smoking				
Never-smoker	36 711 (79.6)	41 265 (72.5)	29 882 (75.3)	13 719 (58.1)
Former smoker	4351 (9.4)	8824 (15.5)	4419 (11.1)	4952 (21)
Current smoker	5034 (10.9)	6838 (12)	5373 (13.5)	4956 (21)
Family history of premature CVD	4928 (10.7)	5332 (9.4)	4712 (11.9)	3907 (16.5)
Diabetes	3995 (8.7)	6679 (11.7)	3255 (8.2)	1721 (7.3)
Cancer	3150 (6.8)	3422 (6)	2784 (7)	1879 (8)
Prior bleeding event	752 (1.6)	1481 (2.6)	985 (2.5)	652 (2.8)
Gastrointestinal	510 (1.1)	1136 (2)	766 (1.9)	522 (2.2)
Other	251 (0.5)	376 (0.7)	235 (0.6)	143 (0.6)
Peptic ulcer disease (nonbleeding)	145 (0.3)	325 (0.6)	218 (0.5)	166 (0.7)
Alcohol-related condition	206 (0.4)	196 (0.3)	131 (0.3)	154 (0.7)
Chronic liver disease or pancreatitis	80 (0.2)	91 (0.2)	73 (0.2)	35 (0.1)
Chronic liver disease	60 (0.1)	67 (0.1)	53 (0.1)	27 (0.1)
Chronic pancreatitis	22 (0)	25 (0)	20 (0.1)	8 (0)
Mean SBP (SD), *mm Hg*	127.1 (15.8)	127.9 (16.2)	128.9 (15.9)	130.1 (16.6)
Mean ratio of total–HDL cholesterol (SD)	3.6 (1.0)	3.8 (1.1)	3.7 (1.1)	3.7 (1.2)
Mean BMI (SD), *kg/m²*	27.8 (6.8)	30.2 (7.6)	28.2 (6.7)	28.8 (6.8)
BMI				
Underweight (<18.5 kg/m²)	655 (1.4)	512 (0.9)	430 (1.1)	272 (1.2)
Normal (18.5–24 kg/m²)	13 450 (29.2)	12 216 (21.5)	10 140 (25.6)	6151 (26)
Overweight (25–29.9 kg/m²)	10 787 (23.4)	14 021 (24.6)	9071 (22.9)	6658 (28.2)
Obesity class 1 (30–34.9 kg/m²)	5550 (12)	9704 (17)	4960 (12.5)	3909 (16.5)
Obesity class 2 (35–39.9 kg/m²)	2708 (5.9)	5873 (10.3)	2417 (6.1)	1852 (7.8)
Obesity class 3 (≥40 kg/m²)	2044 (4.4)	5077 (8.9)	1732 (4.4)	1328 (5.6)
Missing	10 902 (23.7)	9524 (16.7)	10 924 (27.5)	3457 (14.6)
Hemoglobin level				
Not reduced	36 567 (79.3)	43 547 (76.5)	31 322 (78.9)	7842 (33.2)
Reduced	1661 (3.6)	2913 (5.1)	1241 (3.1)	468 (2)
Missing	7868 (17.1)	10 467 (18.4)	7111 (17.9)	15 317 (64.8)
Platelet count				
<150 × 10⁹ cells/L	478 (1)	298 (0.5)	254 (0.6)	66 (0.3)
150–399 × 10⁹ cells/L	28 093 (60.9)	28 196 (49.5)	20 148 (50.8)	4842 (20.5)
≥400 × 10⁹ cells/L	1097 (2.4)	1414 (2.5)	805 (2)	420 (1.8)
Missing	16 428 (35.6)	27 019 (47.5)	18 467 (46.5)	18 299 (77.4)
Medications in 6 mo before index assessment				
Blood pressure–lowering	8992 (19.5)	13 157 (23.1)	8910 (22.5)	5170 (21.9)
Lipid-lowering	5158 (11.2)	7132 (12.5)	4513 (11.4)	2005 (8.5)
Peptic ulcer disease	5595 (12.1)	8191 (14.4)	5495 (13.9)	2827 (12)
Nonsteroidal anti-inflammatory	7196 (15.6)	11 329 (19.9)	6420 (16.2)	4120 (17.4)
Corticosteroid	2432 (5.3)	3935 (6.9)	2325 (5.9)	1500 (6.3)
Selective serotonin reuptake inhibitor	3091 (6.7)	3522 (6.2)	2942 (7.4)	1910 (8.1)

BMI = body mass index; CVD = cardiovascular disease; DHB = district health board (geographically distinct region based on where the person lived); HDL = high-density lipoprotein; IQR = interquartile range; NZDep = New Zealand Index of Deprivation; SBP = systolic blood pressure.
* Data are numbers (percentages) of the sex-specific DHB cohort unless otherwise specified. Data are complete or nearly complete (>99% of values available) unless otherwise specified. 2729 women (2%) did not live in the districts of the Auckland, Counties Manukau, Northland, or Waitemata DHBs.
† Mid-P exact test, calculated using www.openepi.com/PersonTime1/PersonTime1.htm.

Table 7. Patient Characteristics, by DHB: Men*

Variable	Derivation Cohort		Validation Cohort	
	Auckland DHB (*n* = 59 616 [28%])	**Counties Manukau DHB (*n* = 72 186 [33%])**	**Waitemata DHB (*n* = 52 680 [24%])**	**Northland DHB (*n* = 27 694 [13%])**
Incident major bleeding events	507 (0.9)	991 (1.4)	666 (1.3)	372 (1.3)
Total person-years observed, *n*	249 972	306 093	219 271	117 977
Crude incidence of major bleeding events per 1000 person-years (95% CI), *n*†	2.03 (1.86–2.21)	3.24 (3.04–3.44)	3.04 (2.81–3.28)	3.15 (2.85–3.49)
Mean follow-up time (SD), *y*	4.2 (2.3)	4.2 (2.4)	4.2 (2.4)	4.3 (2.4)
Median follow-up time (IQR), *y*	4.1 (2.7–5.3)	4.1 (2.6–5.8)	4.0 (2.5–5.6)	4.0 (2.6–6.0)
Mean age (SD), *y*	51.1 (9.9)	49.8 (10.3)	51.9 (10.1)	53.2 (9.7)
Self-identified ethnicity				
European	33 927 (56.9)	31 458 (43.6)	33 781 (64.1)	19 432 (70.2)
Māori	4666 (7.8)	9691 (13.4)	4626 (8.8)	7337 (26.5)
Pacific	6713 (11.3)	15 098 (20.9)	4173 (7.9)	399 (1.4)
Indian	6659 (11.2)	8984 (12.4)	3225 (6.1)	236 (0.9)
Chinese or other Asian	7651 (12.8)	6955 (9.6)	6875 (13.1)	290 (1)
NZDep quintile				
1 (least deprived)	14 394 (24.1)	15 712 (21.8)	14 675 (27.9)	2864 (10.3)
2	12 815 (21.5)	12 020 (16.7)	12 963 (24.6)	4440 (16)
3	11 143 (18.7)	9793 (13.6)	11 363 (21.6)	5968 (21.5)
4	11 015 (18.5)	11 663 (16.2)	9366 (17.8)	6626 (23.9)
5 (most deprived)	10 249 (17.2)	22 998 (31.9)	4313 (8.2)	7796 (28.2)
Smoking				
Never-smoker	42 598 (71.5)	46 008 (63.7)	34 967 (66.4)	15 358 (55.5)
Former smoker	8896 (14.9)	15 416 (21.4)	8247 (15.7)	6477 (23.4)
Current smoker	8122 (13.6)	10 762 (14.9)	9465 (18)	5859 (21.2)
Family history of premature CVD	5455 (9.2)	5546 (7.7)	5234 (9.9)	3533 (12.8)
Diabetes	4067 (6.8)	6203 (8.6)	3471 (6.6)	1773 (6.4)
Cancer	2213 (3.7)	2251 (3.1)	1952 (3.7)	1262 (4.6)
Prior bleeding event	1160 (1.9)	1939 (2.7)	1294 (2.5)	805 (2.9)
Gastrointestinal	808 (1.4)	1508 (2.1)	1043 (2)	638 (2.3)
Other	363 (0.6)	462 (0.6)	270 (0.5)	180 (0.6)
Peptic ulcer disease (nonbleeding)	246 (0.4)	585 (0.8)	372 (0.7)	262 (0.9)
Alcohol-related condition	591 (1)	569 (0.8)	363 (0.7)	323 (1.2)
Chronic liver disease or pancreatitis	167 (0.3)	185 (0.3)	127 (0.2)	80 (0.3)
Chronic liver disease	125 (0.2)	142 (0.2)	97 (0.2)	58 (0.2)
Chronic pancreatitis	46 (0.1)	50 (0.1)	33 (0.1)	22 (0.1)
Mean SBP (SD), *mm Hg*	127.8 (14.4)	128.0 (14.9)	128.9 (14.5)	130.8 (15.1)
Mean ratio of total–HDL cholesterol (SD)	4.3 (1.2)	4.5 (1.2)	4.4 (1.2)	4.4 (1.4)
Mean BMI (SD), *kg/m²*	28.1 (5.2)	29.8 (6.2)	28.3 (5.2)	29.1 (5.6)
BMI				
Underweight (<18.5 kg/m²)	256 (0.4)	268 (0.4)	191 (0.4)	83 (0.3)
Normal (18.5–24 kg/m²)	12 819 (21.5)	11 832 (16.4)	9724 (18.5)	4919 (17.8)
Overweight (25–29.9 kg/m²)	20 816 (34.9)	23 175 (32.1)	17 014 (32.3)	9972 (36)
Obesity class 1 (30–34.9 kg/m²)	8929 (15)	15 079 (20.9)	8103 (15.4)	5633 (20.3)
Obesity class 2 (35–39.9 kg/m²)	2803 (4.7)	6417 (8.9)	2592 (4.9)	1929 (7)
Obesity class 3 (≥40 kg/m²)	1444 (2.4)	3696 (5.1)	1203 (2.3)	968 (3.5)
Missing	12 549 (21)	11 719 (16.2)	13 853 (26.3)	4190 (15.1)
Hemoglobin level				
Not reduced	43 157 (72.4)	49 823 (69)	37 698 (71.6)	8685 (31.4)
Reduced	1450 (2.4)	1944 (2.7)	1296 (2.5)	322 (1.2)
Missing	15 009 (25.2)	20 419 (28.3)	13 686 (26)	18 687 (67.5)
Platelet count				
<150 × 10⁹ cells/L	1097 (1.8)	751 (1)	651 (1.2)	171 (0.6)
150–399 × 10⁹ cells/L	30 040 (50.4)	28 753 (39.8)	22 292 (42.3)	4847 (17.5)
≥400 × 10⁹ cells/L	494 (0.8)	550 (0.8)	301 (0.6)	205 (0.7)
Missing	27 985 (46.9)	42 132 (58.4)	29 436 (55.9)	22 471 (81.1)
Medications in 6 mo before index assessment				
Blood pressure–lowering	7879 (13.2)	10 525 (14.6)	7695 (14.6)	4222 (15.2)
Lipid-lowering	6183 (10.4)	7776 (10.8)	5438 (10.3)	2081 (7.5)
Peptic ulcer disease	5938 (10)	7984 (11.1)	5461 (10.4)	3010 (10.9)
Nonsteroidal anti-inflammatory	9341 (15.7)	15 687 (21.7)	8491 (16.1)	5225 (18.9)
Corticosteroid	2420 (4.1)	4095 (5.7)	2261 (4.3)	1389 (5)
Selective serotonin reuptake inhibitor	2323 (3.9)	2249 (3.1)	2162 (4.1)	1207 (4.4)

BMI = body mass index; CVD = cardiovascular disease; DHB = district health board (geographically distinct region based on where the person lived); HDL = high-density lipoprotein; IQR = interquartile range; NZDep = New Zealand Index of Deprivation; SBP = systolic blood pressure.
* Data are numbers (percentages) of the sex-specific DHB cohort unless otherwise specified. Data are complete or nearly complete (>99% of values available) unless otherwise specified. 3962 men (2%) did not live in the districts of the Auckland, Counties Manukau, Northland, or Waitemata DHBs.
† Mid-P exact test, calculated using www.openepi.com/PersonTime1/PersonTime1.htm.

that meta-analysis, as well as in our risk prediction models. Unlike the meta-analysis, we observed no association between measured BP and risk for major bleeding, although dispensing of BP-lowering medication (which is likely to reflect long-term increased BP) was associated with increased risk for this outcome.

It was not appropriate to retain BMI, hemoglobin level, or platelet count in the main models because many values were missing. The findings of an ancillary complete-case analysis suggest that BMI has limited value for bleeding risk overall in addition to available predictors, but it may improve risk prediction for individuals who are underweight. Major bleeding events in this study were identified from coded diagnoses associated with hospitalizations and deaths throughout New Zealand. Although diagnoses were not adjudicated, CVD risk models are similarly based on coded diagnoses (15, 41). We have excluded traumatic and postprocedural bleeding because this report focuses on primary prevention, but we acknowledge that this may lead to underestimation of the overall burden of bleeding risk.

Generalizability of these models to non–New Zealand populations is unknown, although external validation in a U.K. population is planned and validation in other populations in whom relevant data are available will be considered. Although the socioeconomic deprivation score used in the models is specific to New Zealand, an equivalent score can be derived for any person using a set of 8 questions (42). This approach has already been used in applying the New Zealand prognostic models for CVD risk to non–New Zealanders (43).

Recently published randomized controlled trials that sought to determine the balance of aspirin's benefits and harms in populations with intermediate CVD risk recruited participants at lower risk than expected (44–46). Although an updated meta-analysis incorporating these latest trials would provide a more accurate estimate of the proportional effect of aspirin on CVD and bleeding, the direction of that effect on either event is unlikely to change. The question of in whom the benefits of using aspirin for primary prevention are likely to outweigh its harms could be addressed by an individualized estimate of the numbers of CVD events likely to be avoided with, and bleeding events caused by, aspirin. Such a tool, using the prognostic bleeding risk models described in this article, is under development.

From University of Auckland, Auckland, New Zealand (V.S., R.J., K.P., B.W., M.H., C.G., R.P., S.M., S.W.); and University of Auckland and Middlemore Hospital, Auckland, New Zealand (A.K.).

Acknowledgment: The authors thank the primary health care organizations, affiliated primary care physicians, nurses, and patients for their contributions to this study. The development of the PREDICT cohort is the result of a collaboration among epidemiologists and other clinical researchers at the University of Auckland, information technology specialists at Enigma Solutions (a private information technology company that developed and maintains the PREDICT software and Web server), primary health care organizations (and their member primary care physicians), nongovernmental organizations (New Zealand Guidelines Group, Heart Foundation of New Zealand, Diabetes New Zealand, and Diabetes Auckland), several DHBs, and the Ministry of Health. The PREDICT software platform is owned by Enigma Publishing (PREDICT is a trademark of Enigma Solutions).

Financial Support: By project grant 15/165 from the Health Research Council of New Zealand. Profs. Jackson, Harwood, Kerr, and Wells; Drs. Grey, Mehta, and Poppe; and Mr. Wu are receiving funding from the Health Research Council of New Zealand for program, project, and clinical research training grants for CVD research. Dr. Poppe is the recipient of a Heart Foundation of New Zealand Hynds Senior Fellowship, and Dr. Grey is the recipient of a Heart Foundation of New Zealand Research Fellowship. Prof. Wells was the recipient of a Fellowship in Health Innovation and Quality Improvement, funded by the Stevenson Foundation. Outside this research, Prof. Wells and Dr. Poppe have received funding from the Heart Foundation of New Zealand (project grants for quality improvement and structural heart disease, respectively) and Prof. Wells from Roche Diagnostics (project grant for point-of-care testing trial).

Disclosures: Dr. Selak reports grants from the Health Research Council of New Zealand during the conduct of the study. Prof. Jackson reports grants from the University of Auckland during the conduct of the study. Dr. Poppe reports grants from the Health Research Council of New Zealand and Heart Foundation of New Zealand during the conduct of the study. Mr. Wu reports grants from the Health Research Council of New Zealand during the conduct of the study. Prof. Harwood reports grants from the Health Research Council of New Zealand during the conduct of the study. Dr. Grey reports grants from the Heart Foundation of New Zealand and Health Research Council of New Zealand during the conduct of the study. Dr. Mehta reports grants from the Health Research Council of New Zealand during the conduct of the study. Dr. Kerr reports grants from the Health Research Council of New Zealand during the conduct of the study. Prof. Wells reports grants from the Health Research Council of New Zealand and the Stevenson Foundation during the conduct of the study and grants from the Heart Foundation of New Zealand and Roche Diagnostics outside the submitted work. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M18-2808.

Reproducible Research Statement: *Study protocol and data set:* Not available. *Statistical code:* Available from Dr. Selak (e-mail, v.selak@auckland.ac.nz).

Corresponding Author: Vanessa Selak, PhD, Section of Epidemiology and Biostatistics, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand; e-mail, v.selak@auckland.ac.nz.

Current author addresses and author contributions are available at Annals.org.

References

1. **Robinson JG, Ray K.** Moving toward the next paradigm for cardiovascular prevention [Editorial]. Circulation. 2016;133:1533-6. [PMID: 27142603] doi:10.1161/CIRCULATIONAHA.116.022134
2. **Whitlock EP, Burda BU, Williams SB, Guirguis-Blake JM, Evans CV.** Bleeding risks with aspirin use for primary prevention in adults: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2016;164:826-35. [PMID: 27064261] doi:10.7326/M15-2112
3. **McQuaid KR, Laine L.** Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. Am J Med. 2006;119:624-38. [PMID: 16887404]
4. **Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al; Antithrombotic Trialists' (ATT) Collaboration.** 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. [PMID: 19482214] doi:10.1016/S0140-6736(09)60503-1
5. **Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines.** 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S49-73. [PMID: 24222018] doi:10.1161/01.cir.0000437741.48606.98
6. **Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al; European Association for Cardiovascular Prevention & Rehabilitation (EACPR).** European guidelines on cardiovascular disease prevention in clinical practice (version 2012): the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur J Prev Cardiol. 2012;19:585-667. [PMID: 22763626] doi:10.1177/2047487312450228
7. **Anderson KM, Odell PM, Wilson PW, Kannel WB.** Cardiovascular disease risk profiles. Am Heart J. 1991;121:293-8. [PMID: 1985385]
8. **Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al; SCORE project group.** Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24:987-1003. [PMID: 12788299]
9. **Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, et al.** Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ. 2008;336:1475-82. [PMID: 18573856] doi:10.1136/bmj.39609.449676.25
10. **Bibbins-Domingo K; U.S. Preventive Services Task Force.** Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2016;164:836-45. [PMID: 27064677] doi:10.7326/M16-0577
11. **Dehmer SP, Maciosek MV, Flottemesch TJ, LaFrance AB, Whitlock EP.** Aspirin for the primary prevention of cardiovascular disease and colorectal cancer: a decision analysis for the U.S. Preventive Services Task Force. Ann Intern Med. 2016;164:777-86. [PMID: 27064573] doi:10.7326/M15-2129
12. **Selak V, Kerr A, Poppe K, Wu B, Harwood M, Grey C, et al.** Annual risk of major bleeding among persons without cardiovascular disease not receiving antiplatelet therapy. JAMA. 2018;319:2507-20. [PMID: 29946729] doi:10.1001/jama.2018.8194
13. **Collins GS, Reitsma JB, Altman DG, Moons KG.** Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): the TRIPOD statement. Ann Intern Med. 2015;162:55-63. [PMID: 25560714] doi:10.7326/M14-0697
14. **Wells S, Riddell T, Kerr A, Pylypchuk R, Chelimo C, Marshall R, et al.** Cohort profile: the PREDICT cardiovascular disease cohort in New Zealand primary care (PREDICT-CVD 19). Int J Epidemiol. 2017;46:22. [PMID: 26686841] doi:10.1093/ije/dyv312
15. **Pylypchuk R, Wells S, Kerr A, Poppe K, Riddell T, Harwood M, et al.** Cardiovascular disease risk prediction equations in 400 000 primary care patients in New Zealand: a derivation and validation study. Lancet. 2018;391:1897-907. [PMID: 29735391] doi:10.1016/S0140-6736(18)30664-0
16. **Ministry of Health.** Cardiovascular disease risk assessment. Updated 2013. In: New Zealand Primary Care Handbook 2012. Wellington: Ministry of Health; 2013.
17. **Ministry of Health.** HISO 10001:2017 Ethnicity Data Protocols. Wellington: Ministry of Health; 2017.
18. **Ministry of Health.** National Health Index data dictionary (version 5.3). Wellington: Ministry of Health; 2009.
19. **Ministry of Health.** Mortality Collection data dictionary (version 1.3). Wellington: Ministry of Health; 2009.
20. **Ministry of Health.** National Minimum Dataset (Hospital Inpatient Events) Data Mart data dictionary (version 7.8). Wellington: Ministry of Health; 2016.
21. **Ministry of Health.** New Zealand Cancer Registry data dictionary (version 1.2). Wellington: Ministry of Health; 2010.
22. **Ministry of Health.** Pharmaceutical Claims Data Mart (PHARMS) data dictionary (version 4.1). Wellington: Ministry of Health; 2012.
23. **Ministry of Health.** Cardiovascular disease risk assessment and management for primary care. Wellington: Ministry of Health; 2018.
24. **January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines.** 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64:e1-76. [PMID: 24685669] doi:10.1016/j.jacc.2014.03.022
25. **Grobbee DE, Hoes AW.** Confounding and indication for treatment in evaluation of drug treatment for hypertension. BMJ. 1997;315:1151-4. [PMID: 9374894]
26. **Voss WB, Lee M, Devlin GP, Kerr AJ.** 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. [PMID: 27362596]
27. **Hippisley-Cox J, Coupland C.** Predicting risk of upper gastrointestinal bleed and intracranial bleed with anticoagulants: cohort study to derive and validate the QBleed scores. BMJ. 2014;349:g4606. [PMID: 25069704] doi:10.1136/bmj.g4606
28. **Nishtala PS, Gnjidic D, Jamieson HA, Hanger HC, Kaluarachchi C, Hilmer SN.** 'Real-world' haemorrhagic rates for warfarin and dabigatran using population-level data in New Zealand. Int J Cardiol. 2016;203:746-52. [PMID: 26590888] doi:10.1016/j.ijcard.2015.11.067
29. **Rikala M, Kastarinen H, Tiittanen P, Huupponen R, Korhonen MJ.** Natural history of bleeding and characteristics of early bleeders among warfarin initiators - a cohort study in Finland. Clin Epidemiol. 2016;8:23-35. [PMID: 26917975] doi:10.2147/CLEP.S91379
30. **De Berardis G, Lucisano G, D'Ettorre A, Pellegrini F, Lepore V, Tognoni G, et al.** Association of aspirin use with major bleeding in patients with and without diabetes. JAMA. 2012;307:2286-94. [PMID: 22706834] doi:10.1001/jama.2012.5034
31. **Schoenfeld D.** Partial residuals for the proportional hazards regression model. Biometrika. 1982;69:239-41.
32. **Therneau TM, Grambsch PM, Fleming TR.** Martingale-based residuals for survival models. Biometrika. 1990;77:147-60.
33. **Royston P, Sauerbrei W.** Mutivariable Model-Building: A Pragmatic Approach to Regression Analysis Based on Fractional Polynomials for Modelling Continuous Variables. Chichester, United Kingdom: Wiley; 2008.
34. **Kaplan EL, Meier P.** Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53:457-81.
35. **Royston P.** Explained variation for survival models. Stata J. 2006;6:83-96.
36. **Harrell FE Jr, Califf RM, Pryor DB, Lee KL, Rosati RA.** Evaluating the yield of medical tests. JAMA. 1982;247:2543-6. [PMID: 7069920]
37. **Royston P, Sauerbrei W.** A new measure of prognostic separation in survival data. Stat Med. 2004;23:723-48. [PMID: 14981672]

38. **Steyerberg EW.** Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating. New York: Springer; 2009.
39. **Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, et al.** Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med. 2015;162:W1-73. [PMID: 25560730] doi:10.7326/M14-0698
40. **Royston P, Altman DG.** External validation of a Cox prognostic model: principles and methods. BMC Med Res Methodol. 2013;13: 33. [PMID: 23496923] doi:10.1186/1471-2288-13-33
41. **Hippisley-Cox J, Coupland C, Brindle P.** Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ. 2017;357: j2099. [PMID: 28536104] doi:10.1136/bmj.j2099
42. **Salmond C, Crampton P, King P, Waldegrave C.** NZiDep: a New Zealand index of socioeconomic deprivation for individuals. Soc Sci Med. 2006;62:1474-85. [PMID: 16154674]
43. **McCormack J, Pfiffner P.** The absolute CVD risk/benefit calculator. 2017. Accessed at http://chd.bestsciencemedicine.com/calc2.html on 14 September 2018.
44. **Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, et al; ASCEND Study Collaborative Group.** Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med. 2018;379:1529-39. [PMID: 30146931] doi:10.1056/NEJMoa1804988
45. **Gaziano JM, Brotons C, Coppolecchia R, Cricelli C, Darius H, Gorelick PB, et al; ARRIVE Executive Committee.** Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet. 2018;392:1036-46. [PMID: 30158069] doi:10.1016/S0140-6736(18)31924-X
46. **McNeil JJ, Wolfe R, Woods RL, Tonkin AM, Donnan GA, Nelson MR, et al; ASPREE Investigator Group.** Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med. 2018; 379:1509-18. [PMID: 30221597] doi:10.1056/NEJMoa1805819

Current Author Addresses: Profs. Jackson, Harwood, Kerr, and Wells; Drs. Selak, Poppe, Grey, and Mehta; Mr. Wu; and Ms. Pylypchuk: University of Auckland, Private Bag 92019, Auckland 1142, New Zealand.

Author Contributions: Conception and design: V. Selak, R. Jackson, S. Mehta, S. Wells.
Analysis and interpretation of the data: V. Selak, R. Jackson, K. Poppe, C. Grey, R. Pylypchuk, S. Mehta, S. Wells.
Drafting of the article: V. Selak, S. Wells.
Critical revision of the article for important intellectual content: V. Selak, R. Jackson, K. Poppe, C. Grey, R. Pylypchuk, S. Mehta, S. Wells.
Final approval of the article: V. Selak, R. Jackson, K. Poppe, B. Wu, M. Harwood, C. Grey, R. Pylypchuk, S. Mehta, A. Kerr, S. Wells.
Provision of study materials or patients: R. Jackson.
Statistical expertise: V. Selak, K. Poppe, R. Pylypchuk.
Obtaining of funding: V. Selak, R. Jackson, K. Poppe, M. Harwood, S. Wells.
Administrative, technical, or logistic support: R. Jackson, B. Wu, M. Harwood.
Collection and assembly of data: V. Selak, R. Jackson, B. Wu, S. Wells.

Appendix Table 1. Definitions of Exclusion Criteria

Criterion	Source	Definition
Demographic characteristic		
Age	NHI	<30 y or ≥80 y
Indications for antiplatelet/anticoagulant therapy and/or not a primary prevention population		
CVD	Multiple	History of angina, MI, IHD, PTCA, CABG, stroke, TIA, or PVD (PREDICT) AND/OR Prior hospitalization in which atherosclerotic CVD diagnosis (including angina, ischemic stroke, hemorrhagic stroke, and TIA) was noted AND/OR Prior hospitalization in which hemorrhagic stroke diagnosis was noted AND/OR Dispensing of ≥1 antianginal medication on ≥3 occasions in the past 5 y. ICD codes used to identify relevant hospitalizations (principal and secondary diagnoses considered) are listed in **Appendix Table 2.** Medications included within each drug class are listed in **Appendix Table 3**.
CHF	Multiple	Prior hospitalization in which CHF diagnosis was noted (any of ICD-10-AM codes I50, I110, I130, or I132) AND/OR Dispensing of ≥1 loop diuretic (frusemide or bumetanide) on ≥3 occasions in the past 5 y AND/OR Any dispensing of metolazone in the past 6 mo.
AF	Multiple	History of AF from PREDICT AND/OR Prior hospitalization in which AF diagnosis was noted (ICD-10-AM code I48).
Diabetes and renal disease	Multiple	Either of the following selected during the index assessment: Diabetes with overt nephropathy (albumin–creatinine ratio 30 mg/mmol OR urinary albumin 200 mg/L) OR Diabetes with other renal disease causing renal impairment (eGFR ≤45 mL/min/1.73 m^2).
Chronic kidney disease	Multiple	eGFR was calculated from serum creatinine values obtained from TestSafe ≤5 y before the index assessment. Persons were categorized as having chronic kidney disease if they met both of the following criteria: eGFR <30 mL/min/1.73 m^2 using creatinine measurement nearest to index assessment AND 1 other eGFR measurement <30 mL/min/1.73 m^2 using creatinine measurement >3 mo (90 d) before the creatinine measurement nearest to the index assessment. The time difference between measures (>3 mo) was selected for consistency with the KDIGO definition of chronic kidney disease (47). Notes: 1. Relevant international consensus (KDIGO) eGFR categories (endorsed in reference 48) are G5 (kidney failure [eGFR <15 mL/min/1.73 m^2]) and G4 (severely decreased eGFR [15–29 mL/min/1.73 m^2]). 2. eGFR was calculated using the CKD-EPI equation (as recommended by the Australasian Creatinine Consensus Working Group in reference 49).
Contraindication to antiplatelet therapy		
Prior intracranial bleeding	NMDS	Hospitalization before the index assessment in which a relevant (intracranial) bleeding ICD code was listed. Relevant ICD codes are listed in **Appendix Table 4.**
Already receiving antiplatelet/anticoagulant therapy		
Aspirin	Pharmaceutical Claims Data Mart	≥1 dispensing of aspirin (regardless of dosage, excluding combinations for cold and flu and excluding any nonoral formulations) in 6 mo before index assessment.
Other antiplatelet	Pharmaceutical Claims Data Mart	≥1 dispensing of other antiplatelet medication (clopidogrel, dipyridamole, ticagrelor, or ticlopidine) in 6 mo before index assessment.
Anticoagulant	Pharmaceutical Claims Data Mart	≥1 dispensing of anticoagulant (warfarin, dabigatran, phenindione, or rivaroxaban) in 6 mo before index assessment.

AF = atrial fibrillation; CABG = coronary artery bypass graft; CHF = congestive heart failure; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; ICD = International Classification of Diseases; ICD-10-AM = ICD, 10th Revision, Australian Modification; IHD = ischemic heart disease; KDIGO = Kidney Disease: Improving Global Outcomes; MI = myocardial infarction; NHI = National Health Index; NMDS = National Minimum Dataset; PTCA = percutaneous transluminal coronary angioplasty; PVD = peripheral vascular disease; TIA = transient ischemic attack.

Appendix Table 2. ICD-10-AM Codes Used to Identify History or Development of CVD From Hospital Records

Category	ICD-10-AM Codes*
Cardiac arrest	I46†
IHD	Angina pectoris: I20† Acute MI: I21† Subsequent MI: I22† Complications of acute MI: I23† Other IHD: I24† (except I241, Dressler syndrome) Chronic IHD: I25†
Coronary procedures	Angioplasty/stent(s): 3530400-3530401, 3530500-3530501, 3530906-3530909, 3531000-3531005 Bypass: 3849700-3849707, 3850000-3850004, 3850300-3850304, 9020100-9020103 Other: 3845619, 3850500, 3850700, 3850800, 3850900, 3863700 Presence of coronary procedure: Z951, Z955, Z958, Z959
Ischemic stroke	Cerebral infarction: I63† Stroke, not specified as hemorrhage or infarction (because these are usually ischemic): I64 (no subcategories) Sequelae of cerebral infarction: I693 Sequelae of stroke, not specified as hemorrhage or infarction: I694
Hemorrhagic stroke	Subarachnoid hemorrhage: I60† Intracerebral hemorrhage: I61† Sequelae of subarachnoid hemorrhage: I690 Sequelae of intracerebral hemorrhage: I691
Other CeVD	TIA: G45† (except G454, transient global amnesia), G46† Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction: I65† Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction: I66† Dissection of cerebral arteries, nonruptured: I670 Cerebral atherosclerosis: I672 Sequelae of other and unspecified CeVD: I698
PVD	Atherosclerosis with symptoms: I702† Atherosclerosis (other): I700, I701, I7020, I708, I709 Aortic aneurysm and dissection: I71† PVD, unspecified: I739 Arterial embolism and thrombosis: I74† DM with circulatory complications: E105†, E115†, E145†
PVD procedures	Aneurysm excisions, repairs and replacements, bypasses, endarterectomies and patch grafts, resections, and reanastomoses involving the following arteries: Carotid: 327000-3271011, 3270300, 3310000, 3350000 Aorta: 3270800-3270803, 3311200, 3311500, 3311800, 3312100, 3315100, 3315400, 3315700, 3316000, 3350900, 3351200, 3351500 Femoral: 3271200-3271201, 3271500-3271503, 3271800-3271801, 3273900, 3274200, 3274500, 3274800, 3275100-3275103, 3275400-3275402, 3275700-3275701, 3351501, 3352100, 3354200 Mesenteric : 3273000-3273001, 3273300-3273301, 3273600, 3353001, 3353300, 3353600 Other: 3276300-3276303, 3276305-3276314, 3276316-3276319, 3305000, 3305500, 3307500, 3308000, 3312400, 3312700, 3313000, 3316300, 3317800, 3318100, 3350600-3350601, 3351800, 3352400, 3352700, 3353000, 3353900, 3354800-3354803, 3355100, 3355400, 3530306-3530307, 3531200-3531201,3531500-3531501, 9022900, 902300

CeVD = cerebrovascular disease; CVD = cardiovascular disease; DM = diabetes mellitus; ICD-9-CM-A = International Classification of Diseases, Ninth Revision, Clinical Modification, Australian Version; ICD-10-AM = ICD, 10th Revision, Australian Modification; IHD = ischemic heart disease; MI = myocardial infarction; PVD = peripheral vascular disease; TIA = transient (cerebral) ischemic attack.

* These are the codes used by the Vascular Informatics Using Epidemiology and the Web (VIEW) team, Department of Epidemiology and Biostatistics, University of Auckland (at March 2016) to identify persons with CVD from hospital records from 1 January 1988 to 30 June 2017. Only ICD-10-AM codes were used because diagnoses and procedures were mapped by the Ministry of Health to ICD-10-AM 2nd edition (where mappings existed), as well as the original submitted ICD-9-CM-A/ICD-10-AM version.

† Includes any subcategories that come after the last number, unless specified as excluded.

Appendix Table 3. Medications Included in Drug Classes*

Increase bleeding risk
- Aspirin
  - Aspirin (regardless of dosage, excluding combinations for cold and flu)
- Anticoagulant
  - Dabigatran
  - Phenindione
  - Rivaroxaban
  - Warfarin
- Other antiplatelet
  - Clopidogrel
  - Dipyridamole
  - Prasugrel
  - Ticagrelor
  - Ticlopidine
- Corticosteroid
  - Betamethasone
  - Cortisone
  - Dexamethasone
  - Fludrocortisone
  - Hydrocortisone
  - Methylprednisolone
  - Prednisolone
  - Prednisone
- Other NSAID
  - Diclofenac
  - Diflunisal
  - Fenbufen
  - Fenoprofen
  - Flurbiprofen
  - Ibuprofen
  - Indomethacin
  - Ketoprofen
  - Mefenamic acid
  - Naproxen
  - Phenylbutazone
  - Piroxicam
  - Sulindac
  - Tenoxicam
  - Tiaprofenic acid
- Selective serotonin reuptake inhibitor
  - Citalopram
  - Escitalopram
  - Fluoxetine
  - Nefazodone
  - Paroxetine
  - Sertraline

Peptic ulcer disease medication
- PPI or H_2 antagonist
  - Lansoprazole
  - Omeprazole
  - Pantoprazole
  - Ranitidine
- *Helicobacter pylori* eradication
  - Clarithromycin, 500 mg
  - Combination of bismuth, metronidazole, and tetracycline
  - Combination of omeprazole, amoxicillin, and clarithromycin or metronidazole

Treat other diseases
- Heart failure
  - Bumetanide
  - Frusemide
  - Metolazone
- Antianginal
  - Glyceryl trinitrate
  - Isosorbide dinitrate/mononitrate
  - Nicorandil
  - Pentaerythritol tetranitrate
  - Perhexiline maleate

Appendix Table 3—Continued

- Diabetes
  - Insulin
  - Acarbose
  - Chlorpropamide
  - Glibenclamide
  - Gliclazide
  - Glipizide
  - Metformin
  - Pioglitazone
  - Rosiglitazone
  - Tolazamide
  - Tolbutamide

Blood pressure–lowering†
- ACE inhibitor
  - Benazepril
  - Captopril
  - Cilazapril
  - Enalapril
  - Lisinopril
  - Perindopril
  - Quinapril
  - Trandolapril
- ARB
  - Candesartan
  - Losartan
- β-Blocker
  - Acebutolol
  - Alprenolol
  - Atenolol
  - Bisoprolol
  - Carvedilol
  - Celiprolol
  - Labetalol
  - Metoprolol
  - Nadolol
  - Oxprenolol
  - Pindolol
  - Propranolol
  - Sotalol
  - Timolol
- CCB
  - Amlodipine
  - Diltiazem
  - Felodipine
  - Isradipine
  - Nifedipine
  - Verapamil
- Thiazide
  - Bendroflumethiazide
  - Chlorthalidone
  - Chlorothiazide
  - Cyclopenthiazide
  - Hydrochlorothiazide
  - Indapamide
  - Methyclothiazide
- Other
  - Amiloride
  - Clonidine
  - Clopamide
  - Hydralazine
  - Methyldopa
  - Triamterene

Lipid-lowering
- Statin
  - Atorvastatin
  - Fluvastatin
  - Pravastatin
  - Simvastatin

Appendix Table 3–Continued

Other
Acipimox
Bezafibrate
Cholestyramine
Clofibrate
Colestipol
Ezetimibe
Gemfibrozil
Nicotinic acid

ACE = angiotensin-converting enzyme; ARB = angiotensin II–receptor blocker; CCB = calcium-channel blocker; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton-pump inhibitor.
* Medication dispensing information (pharmaceutical claims collection database) was available from 1 January 2005 to 30 June 2017. Formulations included oral (tablet, capsule, or liquid), patch, suppository, and injection (insulin only). Formulations excluded cream, ointment, powder, inhaler, and injection (except for insulin).
† α-Blockers, loop diuretics (bumetanide and frusemide), metolazone, and spironolactone were excluded because their primary indication is not usually to reduce blood pressure.

Appendix Table 4. ICD Codes Used to Identify History or Development of Bleeding Events From Hospital Records and Bleeding Deaths From Mortality Records*

Category	ICD-10-AM Codes†‡	ICD-9-CM-A Codes†
Gastrointestinal bleeding		
Peptic ulcer with bleeding and/or perforation	Gastric: K250, K251, K252, K254, K255, K256 Duodenal: K260, K261, K262, K264, K265, K266 Gastrojejunal: K280, K281, K282, K284, K285, K286 Peptic: K270, K271, K272, K274, K275, K276	Gastric: 53100, 53101, 53110, 53111, 53120, 53121, 53150, 53151, 53160, 53161, 53140, 53141 Duodenal: 53200, 53201, 53210, 53211, 53220, 53221, 53250, 53251, 53260, 53261, 53240, 53241 Gastrojejunal: 53400, 53401, 53410, 53411, 53420, 53421, 53440, 53441, 53450, 53451, 53460, 53461 Unspecified site: 53300, 53301, 53310, 53311, 53320, 53321, 53340, 53341, 53350, 53351, 53360, 53361
Diverticulitis with bleeding or diverticulosis with bleeding	K5703, K5713, K5711, K5721, K5723, K5731, K5733, K5741, K5743 K5751, K5753, K5781, K5783, K5791, K5793	56202, 56203, 56212, 56213
Angiodysplasia with bleeding	K3182, K5522	53783, 56985
Mallory–Weiss tear	K226	5307
Gastritis with bleeding, gastroduodenitis with bleeding, or duodenitis with bleeding	K290, K2921 (8th), K2931 (8th), K2941 (8th) (atrophic gastritis with hemorrhage), K2951 (8th), K2961 (8th), K2981 (8th), K2971 (8th), K2997 (8th)	53501, 53511 (atrophic gastritis with hemorrhage), 53531, 53541, 53551, 53561
Hemorrhage of anus and rectum	K625	5693
Hematemesis	K920	5780
Melena	K921	5781
Gastrointestinal hemorrhage, unspecified	K922	5789
Esophageal varices with bleeding	I850, I9821 (1st, 2nd, 3rd), I983 (6th, 8th)	4560, 45620
Esophageal hemorrhage	Not included because only applicable code includes nonbleeding events	53082
Intracranial bleeding		
Subarachnoid hemorrhage	I60§	430
Intracerebral hemorrhage	I61§	431
Other nontraumatic intracranial hemorrhage	I62§	4320, 4321, 4329
Sequelae of subarachnoid hemorrhage	I690‖	Not included because only applicable code includes sequelae of intracerebral infarction
Sequelae of intracerebral hemorrhage	I691‖	Not included because only applicable code includes sequelae of intracerebral infarction
Sequelae of other intracranial hemorrhage	I692‖	Not included because only applicable code includes sequelae of intracerebral infarction
Other bleeding		
Ocular (vitreous and retinal)	H356, H431	36281, 37923
Respiratory passage (including epistaxis and hemoptysis)	R04	7847, 7848, 7863
Hemopericardium/hemoperitoneum	I312, K661	4230, 56881
Hemarthrosis	M250§	71910, 71911, 71912, 71913, 71914, 71915, 71916, 71917, 71918, 71919

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

* Hospital and mortality records were available up to 30 June 2017. Traumatic and procedural bleeding events were excluded. All codes were used to identify persons with a history of bleeding (before index assessment) and those who had a bleeding event during follow-up (nonfatal or fatal) unless otherwise specified.

† Relevant codes were identified from each of 6 clinical coding systems in which data were submitted in New Zealand (i.e., ICD-9-CM-A and ICD-10-AM 1st, 2nd, 3rd, 6th, and 8th editions).

‡ Same codes were used for all ICD-10-AM editions used in New Zealand to date (i.e., 1st, 2nd, 3rd, 6th, and 8th) unless otherwise specified in parentheses.

§ Includes any subcategories that come after the last number, unless specified as excluded.

‖ Used only to identify persons with a history of bleeding (i.e., not for bleeding events, nonfatal or fatal, during follow-up).

Appendix Table 5. Definitions of Predictors

Variable	Source	Definition*
Demographic characteristics		
Age	NHI database	Age at index assessment (continuous)
Ethnicity	NHI database	Self-reported ethnicity was categorized using the prioritized output method according to national ethnicity data protocols (www.health.govt.nz/publication/hiso-100012017-ethnicity-data-protocols). The South Asian population has elevated risk for CVD. The ethnicity classification in use during the conduct of the study enabled identification of the Indian group (which comprises approximately 90% of South Asians in New Zealand and includes individuals recorded as having both Pacific and Indian ethnicity who were assumed to be Fijian Indian) but not other South Asians (such as Sri Lankans, Pakistanis, Bangladeshis, or Nepalis) who were therefore included in the Other Asian group. Order of prioritization: New Zealand Māori > Pacific > Indian > Chinese/other Asian > ***European*** > MELAA > other > unknown/not answered/not identifiable (No_not_stated) Persons with ethnicity in the last 3 categories (MELAA, other, and unknown) were excluded from the analysis because of small numbers.
Deprivation quintile	NHI database	We used the NZDep as a measure of socioeconomic position. The NZDep was constructed from 9 census-derived variables representing 8 dimensions of deprivation. In this study, deprivation quintiles (1 = least deprived; 5 = most deprived) rather than the conventional NZDep 2006 deciles were used. That is: ***Deprivation quintile 1 (least deprived)*** = NZDep decile 1 or 2 Deprivation quintile 2 = NZDep decile 3 or 4 Deprivation quintile 3 = NZDep decile 5 or 6 Deprivation quintile 4 = NZDep decile 7 or 8 Deprivation quintile 5 (most deprived) = NZDep decile 9 or 10
History		
Smoking status	PREDICT	Smoker = current smoker or former smoker who quit smoking <12 mo before index assessment Former smoker = quit ≥12 mo before index assessment ***Never-smoker*** = never-smoker at index assessment
Family history of premature CVD	PREDICT	***No***; yes Yes if family history of premature CVD
Diabetes	Multiple	***No***; yes Yes if: History of diabetes (PREDICT) AND/OR Prior hospitalization in which diabetes or associated condition was noted (ICD-10-AM code E10-14 or ICD-9-CM-A code 250) AND/OR ≥1 dispensing of diabetes medication (see **Appendix Table 3** for medications included in class) in the past 6 mo
Cancer	NMDS and NZCR	***No***; yes Yes if included in NZCR before index assessment. NZCR is a population-based register of all primary malignant diseases diagnosed in New Zealand, excluding squamous and basal cell skin cancers. Reporting is a legislative requirement. Sources of data are laboratories, hospitals, and mortality collection. Data from the NZCR were available only up until the end of 2014; therefore, cancer history was supplemented with hospitalization data. Persons were classified as having a history of cancer if they had a hospitalization before the index assessment in which a relevant cancer ICD code was listed. Relevant cancer ICD codes were those listed in the MoH ICD code list with eligible cancer status A (always registerable). This ICD code list is used to assist in identifying persons potentially eligible for the NZCR.
Prior bleeding event	NMDS	***No***; yes Yes if a relevant (gastrointestinal or other) bleeding ICD code was listed in a hospitalization before the index assessment. Relevant ICD codes are in **Appendix Table 4.**
Peptic ulcer disease (nonbleeding)	NMDS	***No***; yes Yes if a relevant ICD code was listed in a hospitalization before the index assessment. Relevant ICD codes are in **Appendix Table 6.**
Alcohol-related condition	NMDS	***No***; yes Yes if a relevant ICD code was listed in a hospitalization before the index assessment. Relevant ICD codes are in **Appendix Table 6.**
Chronic liver disease or pancreatitis	NMDS	***No***; yes Yes if a relevant ICD code was listed in a hospitalization before the index assessment. Relevant ICD codes are in **Appendix Table 6.**

Contiued on following page

Appendix Table 5–Continued

Variable	Source	Definition*
Measurements		
Systolic BP	PREDICT	Mean of 2 systolic BP measurements obtained at index assessment (continuous)
Ratio of total–HDL cholesterol	PREDICT	1 measure, fasting or nonfasting (continuous)
BMI	PREDICT	BMI obtained at index assessment. Categorized according to WHO categories: Underweight (BMI <18.5 kg/m^2) ***Normal*** (BMI, 18.5–24.9 kg/m^2) Overweight (BMI, 25–29.9 kg/m^2) Obesity class 1 (BMI, 30–34.9 kg/m^2) Obesity class 2 (BMI, 35–39.9 kg/m^2) Obesity class 3 (BMI ≥40 kg/m^2)
Hemoglobin level	TestSafe	Calculated using blood hemoglobin level before index assessment. Where multiple values were available, the level nearest in time to the index assessment was used. ***Not reduced*** (≥115 g/L for women, ≥130 g/L for men) Reduced (<115 g/L for women, <130 g/L for men) (115 and 130 g/L are the lower limits of normal for women and men, respectively, according to the Test Guide of Auckland District Health Board's Lab Plus, www.labplus.co.nz/clinical-resources/test-guide.)
Platelet count	TestSafe	Categorized using blood platelet count before index assessment. Where multiple values were available, the level nearest in time to the index assessment was used. Low (<150 × 10^9 cells/L) ***Normal*** (150–399 × 10^9 cells/L) High (≥400 × 10^9 cells/L)
Pharmaceutical dispensing		
Blood pressure– lowering Lipid-lowering Peptic ulcer disease medication Nonaspirin nonsteroidal anti-inflammatory Corticosteroid Selective serotonin reuptake inhibitor	Pharmaceutical Claims Data Mart	***No***; yes Yes if ≥1 dispensing in the 6 mo before index assessment. See **Appendix Table 3** for medications included in class.

BMI = body mass index; BP = blood pressure; CVD = cardiovascular disease; HDL = high-density lipoprotein; ICD = International Classification of Diseases; ICD-9-CM-A = ICD, Ninth Revision, Clinical Modification, Australian Version; ICD-10-AM = ICD, 10th Revision, Australian Modification; MELAA = Middle Eastern/Latin American/African; MoH = Ministry of Health; NHI = National Health Index; NMDS = National Minimum Dataset; NZCR = New Zealand Cancer Registry; NZDep = New Zealand Index of Deprivation; WHO = World Health Organization.
* Reference categories included in the models are italicized and in boldface.

Appendix Table 6. ICD Codes Used to Identify History of Nonbleeding Medical Conditions From Hospital Records

Medical Condition	ICD-10-AM Codes*†	ICD-9-CM-A Codes*
Peptic ulcer disease (nonbleeding)		
Esophagus	K221	5302
Gastric	K253, K257, K259	53130, 53131, 53170, 53171, 53190, 53191
Duodenal	K263, K267, K269	53230, 53231, 53270, 53271, 53290, 53291
Peptic/site unspecified	K273, K277, K279	53330, 53331, 53370, 53371, 53390, 53391
Gastrojejunal	K283, K287, K289	53430, 53431, 53470, 53471, 53490, 53491
History of peptic ulcer disease	Z8711	V1271
Alcohol-related condition (chronic high use)		
Alcohol-induced pseudo-Cushing syndrome	E244	Not included because includes non–alcohol-induced condition
Degeneration of nervous system due to alcohol	G312	Not included because includes non–alcohol-induced condition
Alcoholic polyneuropathy	G621	3575
Alcoholic myopathy	G721	Not included because includes non–alcohol-induced condition
Alcoholic cardiomyopathy	I426	4255
Alcoholic gastritis	K292 (1st, 2nd, 3rd, 4th), K2920 (8th), K2921(8th)	53530, 53531
Alcoholic liver disease	K70‡	5710, 5711, 5712, 5713
Alcohol-induced chronic pancreatitis	K860	Not included because includes non–alcohol-induced condition
Mental and behavioral disorders due to use of alcohol	F10 (except acute intoxication [F100] and harmful use [F101])‡	2910, 2911, 2912, 2913, 2915, 2918, 2919, 30390, 30391, 30392, 30393
History of alcohol use disorder	Z8641	V1584
Alcohol counseling, detoxification, or rehabilitation	Z502, Z714, 9201000, 9200200, 9200300, 9200400, 9200800, 9200900,	Not included to avoid including irrelevant diagnoses with same clinical code
Chronic liver disease		
Gastroesophageal varices	I850, I859, I864	4560, 4561
Alcoholic chronic liver disease	K702, K703, K704	5712
Chronic hepatic failure	K721	–
Other cirrhosis of liver (including biliary and toxic)	K717, K743, K744, K745, K746	5715, 5716
Portal hypertension	K766	5723
Hepatorenal syndrome	K767	5724
Chronic pancreatitis	K860, K861	5771

ICD-9-CM-A = International Classification of Diseases, Ninth Revision, Clinical Modification, Australian Version; ICD-10-AM = ICD, 10th Revision, Australian Modification.
* Relevant codes were identified from each of 6 clinical coding systems in which data were submitted in New Zealand (i.e., ICD-9-CM-A and ICD-10-AM 1st, 2nd, 3rd, 6th, and 8th editions). Hospital records were available from 1 January 1988 to 30 June 2017.
† Same codes were used for all ICD-10-AM editions used in New Zealand to date (i.e., 1st, 2nd, 3rd, 6th, and 8th) unless otherwise specified.
‡ Includes any subcategories that come after the last number, unless specified as excluded.

Appendix Table 7. Number and Type of First Major Bleeding Events

Type	Nonfatal Events (*n* = 4129 [93%]), *n*	Fatal Events (*n* = 313 [7%]), *n*	Total Events (*n* = 4442), *n (%)*
Gastrointestinal	2972	110	3082 (69)
Intracerebral (including hemorrhagic stroke)	518	177	695 (16)
Other*	639	26	665 (15)

* Respiratory (including epistaxis and hemoptysis), ocular (vitreous and retinal), bleeding into a joint, and bleeding into the pericardium or peritoneum.

Appendix Table 8. Patient Characteristics: Derivation and Validation Cohorts*

Variable	Women		Men	
	Derivation (Auckland and Counties Manukau) (*n* = 103 023 [27%])	**Validation (Northland and Waitemata) (*n* = 63 301 [34%])**	**Derivation (Auckland and Counties Manukau) (*n* = 131 802 [16%])**	**Validation (Northland and Waitemata) (80 374 [21%])**
Incident major bleeding events	1024 (0.99)	836 (1.32)	1498 (1.14)	1038 (1.29)
Total person-years observed, *n*	438 424	271 662	556 066	337 248
Crude incidence of major bleeding events per 1000 person-years (95% CI), *n*†	2.34 (2.20–2.48)	3.08 (2.87–3.29)	2.69 (2.56–2.83)	3.08 (2.90–3.27)
Mean follow-up time (SD), *y*	4.26 (2.38)	4.29 (2.38)	4.22 (2.39)	4.20 (2.39)
Median follow-up time (IQR), *y*	4.11 (2.63–5.66)	3.50 (2.90–4.30)	4.09 (2.63–5.61)	4.30 (3.50–5.10)
Mean age (SD), *y*	55.4 (9.1)	56.9 (9.1)	50.4 (10.1)	52.3 (10.1)
Self-identified ethnicity				
European	50 590 (49.1)	40 469 (63.9)	65 385 (49.6)	53 213 (66.2)
Māori	11 983 (11.6)	10 577 (16.7)	14 357 (10.9)	11 963 (14.9)
Pacific	16 431 (15.9)	3652 (5.8)	21 811 (16.5)	4572 (5.7)
Indian	10 944 (10.6)	2336 (3.7)	15 643 (11.9)	3461 (4.3)
Chinese or other Asian	13 075 (12.7)	6267 (9.9)	14 606 (11.1)	7165 (8.9)
NZDep quintile				
1 (least deprived)	24 690 (24)	13 081 (20.7)	30 106 (22.8)	17 539 (21.8)
2	19 942 (19.4)	13 276 (21)	24 835 (18.8)	17 403 (21.7)
3	16 326 (15.8)	13 890 (21.9)	20 936 (15.9)	17 331 (21.6)
4	17 496 (17)	13 036 (20.6)	22 678 (17.2)	15 992 (19.9)
5 (most deprived)	24 569 (23.8)	10 018 (15.8)	33 247 (25.2)	12 109 (15.1)
Smoking				
Never-smoker	77 976 (75.7)	43 601 (68.9)	88 606 (67.2)	50 325 (62.6)
Former smoker	11 872 (11.5)	10 329 (16.3)	18 884 (14.3)	15 324 (19.1)
Current smoker	13 175 (12.8)	9371 (14.8)	24 312 (18.4)	14 724 (18.3)
Family history of premature CVD	10 260 (10)	8619 (13.6)	11 001 (8.3)	8767 (10.9)
Diabetes	10 674 (10.4)	4976 (7.9)	10 270 (7.8)	5244 (6.5)
Cancer	6572 (6.4)	4663 (7.4)	4464 (3.4)	3214 (4)
Prior bleeding event	2233 (2.2)	1637 (2.6)	3099 (2.4)	2099 (2.6)
Gastrointestinal	1646 (1.6)	1288 (2)	2316 (1.8)	1681 (2.1)
Other	627 (0.6)	378 (0.6)	825 (0.6)	450 (0.6)
Peptic ulcer disease (nonbleeding)	470 (0.5)	384 (0.6)	831 (0.6)	634 (0.8)
Alcohol-related condition	402 (0.4)	285 (0.5)	1160 (0.9)	686 (0.9)
Chronic liver disease or pancreatitis	171 (0.2)	108 (0.2)	352 (0.3)	207 (0.3)
Chronic liver disease	127 (0.1)	80 (0.1)	267 (0.2)	155 (0.2)
Chronic pancreatitis	47 (0)	28 (0)	96 (0.1)	55 (0.1)
Mean SBP (SD), *mm Hg*	127.5 (16.1)	129.3 (16.1)	127.8 (14.7)	129.5 (14.7)
Mean ratio of total–HDL cholesterol (SD)	3.7 (1.1)	3.7 (1.1)	4.4 (1.2)	4.4 (1.2)
Mean BMI (SD), *kg/m^2*	29.2 (7.2)	28.4 (7.2)	29.1 (5.7)	28.6 (5.7)
BMI				
Underweight (<18.5 kg/m^2)	1167 (1.1)	702 (1.1)	524 (0.4)	274 (0.3)
Normal (18.5–24 kg/m^2)	25 666 (24.9)	16 291 (25.7)	24 651 (18.7)	14 643 (18.2)
Overweight (25–29.9 kg/m^2)	24 808 (24.1)	15 729 (24.8)	43 991 (33.4)	26 986 (33.6)
Obesity class 1 (30–34.9 kg/m^2)	15 254 (14.8)	8869 (14)	24 008 (18.2)	13 736 (17.1)
Obesity class 2 (35–39.9 kg/m^2)	8581 (8.3)	4269 (6.7)	9220 (7)	4521 (5.6)
Obesity class 3 (≥40 kg/m^2)	7121 (6.9)	3060 (4.8)	5140 (3.9)	2171 (2.7)
Missing	20 426 (19.8)	14 381 (22.7)	24 268 (18.4)	18 043 (22.4)
Hemoglobin level				
Not reduced	80 114 (77.8)	39 164 (61.9)	92 980 (70.5)	46 383 (57.7)
Reduced	4574 (4.4)	1709 (2.7)	3394 (2.6)	1618 (2)
Missing	18 335 (17.8)	22 428 (35.4)	35 428 (26.9)	32 373 (40.3)
Platelet count				
<150 × 10^9 cells/L	776 (0.8)	320 (0.5)	1848 (1.4)	822 (1)
150–399 × 10^9 cells/L	56 289 (54.6)	24 990 (39.5)	58 793 (44.6)	27 139 (33.8)
≥400 × 10^9 cells/L	2511 (2.4)	1225 (1.9)	1044 (0.8)	506 (0.6)
Missing	43 447 (42.2)	36 766 (58.1)	70 117 (53.2)	51 907 (64.6)
Medications in 6 mo before index assessment				
Blood pressure–lowering	22 149 (21.5)	14 080 (22.2)	18 404 (14)	11 917 (14.8)

Contiued on following page

Appendix Table 8–Continued

Variable	Women		Men	
	Derivation (Auckland and Counties Manukau) (*n* = 103 023 [27%])	Validation (Northland and Waitemata) (*n* = 63 301 [34%])	Derivation (Auckland and Counties Manukau) (*n* = 131 802 [16%])	Validation (Northland and Waitemata) (*n* = 80 374 [21%])
Lipid-lowering	12 290 (11.9)	6518 (10.3)	13 959 (10.6)	7519 (9.4)
Peptic ulcer disease	13 786 (13.4)	8322 (13.1)	13 922 (10.6)	8471 (10.5)
Nonsteroidal anti-inflammatory	18 525 (18)	10 540 (16.7)	25 028 (19)	13 716 (17.1)
Corticosteroid	6367 (6.2)	3825 (6)	6515 (4.9)	3650 (4.5)
Selective serotonin reuptake inhibitor	6613 (6.4)	4852 (7.7)	4572 (3.5)	3369 (4.2)

BMI = body mass index; CVD = cardiovascular disease; HDL = high-density lipoprotein; IQR = interquartile range; NZDep = New Zealand Index of Deprivation; SBP = systolic blood pressure.
* Data are numbers (percentages) of the sex-specific derivation or validation cohort unless otherwise specified. Data are complete or nearly complete (>99% of values available) unless otherwise specified. 2729 women (1%) and 3962 men (1%) were not in either the derivation or validation cohort because they did not live in the districts of the Auckland, Counties Manukau, Northland, or Waitemata district health boards. The derivation cohorts had lower proportions of European (49%–50% vs. 64%–66%) and Māori (11%–12% vs. 15%–17%) people and higher proportions of Pacific (16%–17% vs. 6%), Indian (11%–12% vs. 4%), and Chinese or other Asian (11%–13% vs. 9%–10%) people compared with the validation cohorts. Approximately 24%–25% of the derivation cohorts were in the highest deprivation quintile, compared with only 15%–16% of the validation cohorts. There was a greater proportion of people with diabetes in the derivation than in the validation cohorts, whereas the proportion of smokers (current or former); those with a family history of premature CVD; and those with unrecorded BMI, hemoglobin levels, or platelet counts were higher in the validation than in the derivation cohorts.
† Mid-P exact test, calculated using www.openepi.com/PersonTime1/PersonTime1.htm.

Appendix Table 9. Adjusted Hazard Ratios for Major Bleeding Events in Total and Derivation Cohorts

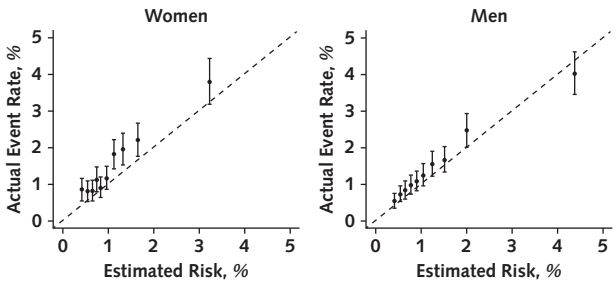
Characteristic	Adjusted Hazard Ratio (95% CI)*			
	Women		Men	
	Derivation (*n* = 101 935)	Full Cohort (*n* = 167 646)	Derivation (*n* = 130 670)	Full Cohort (*n* = 214 539)
Age, per year	1.04 (1.03–1.05)	1.04 (1.03–1.04)	1.04 (1.03–1.04)	1.04 (1.03–1.04)
Self-identified ethnicity				
European	1	1	1	1
Māori	1.40 (1.14–1.72)	1.37 (1.18–1.57)	1.84 (1.55–2.18)	1.51 (1.33–1.71)
Pacific	1.47 (1.21–1.80)	1.34 (1.15–1.56)	1.86 (1.59–2.18)	1.69 (1.49–1.92)
Indian	0.98 (0.75–1.28)	0.84 (0.67–1.06)	1.08 (0.87–1.34)	0.98 (0.82–1.18)
Chinese or other Asian	1.22 (0.98–1.52)	1.05 (0.88–1.24)	1.48 (1.24–1.76)	1.46 (1.28–1.67)
NZDep quintile, per 1 quintile	1.11 (1.06–1.17)	1.10 (1.07–1.14)	1.13 (1.09–1.18)	1.10 (1.06–1.13)
Smoking				
Never-smoker	1	1	1	1
Former smoker	1.26 (1.04–1.53)	1.16 (1.01–1.32)	1.13 (0.98–1.31)	1.17 (1.05–1.30)
Current smoker	1.67 (1.40–1.99)	1.64 (1.44–1.87)	1.48 (1.31–1.69)	1.47 (1.33–1.62)
Family history of premature CVD	0.98 (0.80–1.21)	1.06 (0.92–1.22)	1.20 (1.00–1.43)	1.05 (0.92–1.20)
Diabetes	1.23 (1.01–1.51)	1.20 (1.03–1.40)	1.29 (1.09–1.54)	1.19 (1.04–1.37)
Cancer	1.46 (1.19–1.80)	1.35 (1.16–1.57)	1.93 (1.59–2.34)	1.76 (1.52–2.04)
Prior bleeding event	2.97 (2.35–3.76)	3.18 (2.70–3.75)	3.11 (2.60–3.72)	3.13 (2.73–3.59)
Peptic ulcer disease (nonbleeding)	1.54 (0.95–2.50)	1.53 (1.08–2.17)	1.19 (0.85–1.66)	1.25 (0.97–1.61)
Alcohol-related condition	3.13 (1.97–4.99)	2.59 (1.81–3.70)	2.11 (1.56–2.86)	1.96 (1.54–2.51)
Chronic liver disease or pancreatitis	2.60 (1.36–4.94)	2.66 (1.66–4.27)	1.78 (1.11–2.84)	2.17 (1.54–3.06)
SBP, per mm Hg	1.01 (1.00–1.01)	1.01 (1.00–1.01)	1.00 (1.00–1.01)	1.00 (1.00–1.01)
Ratio of total–HDL cholesterol, per 1 unit	1.01 (0.95–1.07)	1.00 (0.96–1.05)	0.96 (0.92–1.00)	0.95 (0.92–0.98)
Medications in 6 mo before index assessment				
Blood pressure–lowering	1.12 (0.95–1.30)	1.15 (1.03–1.29)	1.33 (1.15–1.53)	1.23 (1.10–1.37)
Lipid-lowering	0.99 (0.82–1.20)	1.01 (0.88–1.16)	0.92 (0.78–1.09)	0.95 (0.84–1.09)
Peptic ulcer disease	1.42 (1.21–1.67)	1.45 (1.29–1.63)	1.53 (1.33–1.76)	1.44 (1.29–1.60)
Nonsteroidal anti-inflammatory	1.14 (0.97–1.33)	1.11 (0.99–1.25)	1.14 (1.01–1.29)	1.19 (1.08–1.31)
Corticosteroid	1.24 (0.99–1.54)	1.39 (1.19–1.62)	1.40 (1.16–1.68)	1.42 (1.23–1.64)
Selective serotonin reuptake inhibitor	1.20 (0.95–1.52)	1.18 (1.00–1.39)	1.16 (0.89–1.51)	1.34 (1.12–1.60)

CVD = cardiovascular disease; HDL = high-density lipoprotein; NZDep = New Zealand Index of Deprivation; SBP = systolic blood pressure.
* Adjusted for all other variables in the model. Excluded because of a missing value: 1088 women in the derivation model, 1407 women in the full cohort model, 1132 men in the derivation model, and 1599 men in the full cohort model.

Appendix Table 10. Model Performance (Derivation Versus Full Cohort)

Statistic	Point Estimate			
	Women		Men	
	Derivation	Full Cohort	Derivation	Full Cohort
R^2, %				
Nagelkerke	2.30	2.16	3.25	2.65
Discrimination				
c (Harrell) (95% CI)	0.68 (0.66–0.70)	0.68 (0.66–0.69)	0.72 (0.70–0.73)	0.70 (0.69–0.71)
K (Gönen and Heller) (95% CI)	0.64 (0.63–0.65)	0.64 (0.63–0.65)	0.66 (0.57–0.75)	0.65 (0.63–0.67)

Appendix Figure 1. Calibration plot: estimated (derivation model) vs. observed (validation population) 5-year bleeding risk.



The diagonal lines represent perfect calibration.

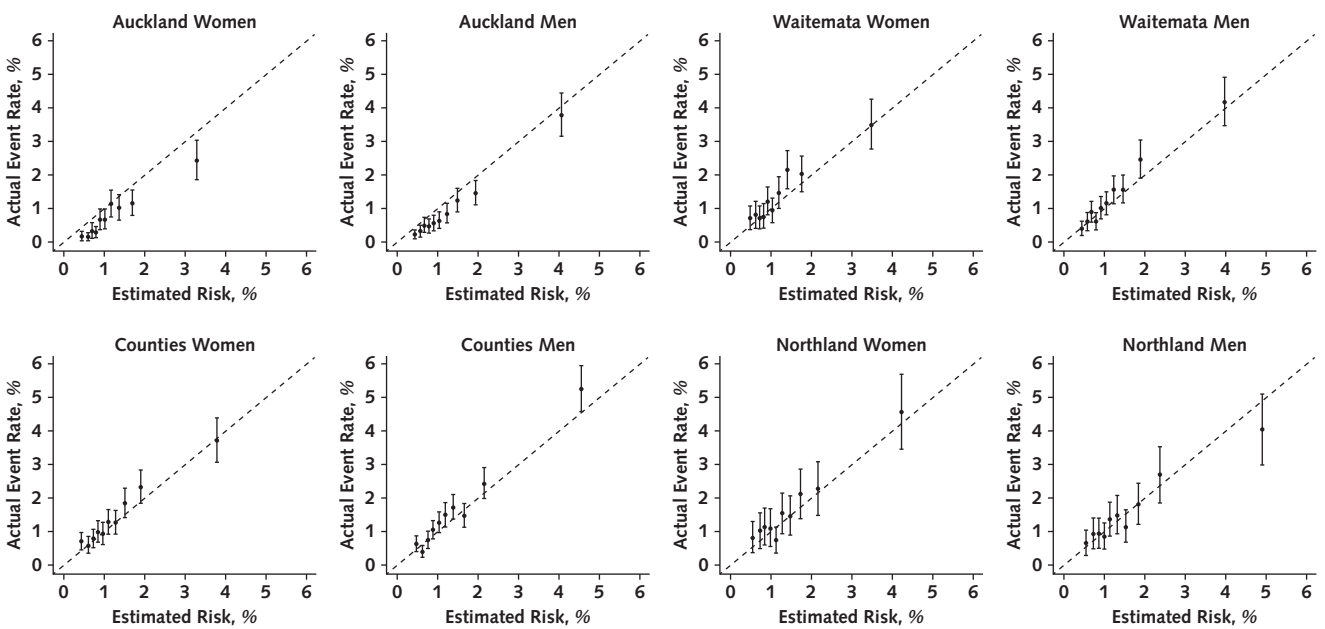
Web-Only References

47. **Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group.** KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013;3:1-150.

48. **Ministry of Health.** Managing chronic kidney disease in primary care: national consensus statement. Wellington: Ministry of Health; 2015.

49. **Johnson DW, Jones GR, Mathew TH, Ludlow MJ, Doogue MP, Jose MD, et al; Australasian Creatinine Consensus Working Group.** Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: new developments and revised recommendations. Med J Aust. 2012;197:224-5. [PMID: 22900871]

Appendix Figure 2. Calibration plot: estimated (full model) vs. observed (geographic subpopulations) 5-year bleeding risk.



The diagonal lines represent perfect calibration.