Risk of Major Bleeding by Ethnicity and Socioeconomic Deprivation among 488,107 People in Primary Care: A Cohort Study

Wai Chung Tse

Monash University

Corina Grey

University of Auckland

Matire Harwood

University of Auckland

Rod Jackson

University of Auckland

Andrew Kerr

University of Auckland

Katrina Poppe

University of Auckland

Suneela Mehta

University of Auckland

Romana Pylypchuk

University of Auckland

Sue Wells

University of Auckland

Vanessa Selak (✉ v.selak@auckland.ac.nz)

University of Auckland <https://orcid.org/0000-0002-9824-8674>

Research

Keywords: Cardiovascular Disease, Bleeding Risk

Posted Date: October 29th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-98289/v1>

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Version of Record: A version of this preprint was published at BMC Cardiovascular Disorders on April 23rd, 2021. See the published version at <https://doi.org/10.1186/s12872-021-01993-9>.

Abstract

Background: Antithrombotic medication (antiplatelets and anticoagulants) reduce the risk of cardiovascular disease (CVD), but with the disadvantage of increasing bleeding risk. Ethnicity and socioeconomic deprivation are independent predictors of major bleeds among patients without CVD, but it is unclear whether they are also predictors of major bleeds among patients with CVD or atrial fibrillation (AF) after adjustment for clinical variables.

Methods: Prospective cohort study of 488,107 people in New Zealand Primary Care (including 64,420 Māori, the indigenous people of New Zealand) aged 30-79 years who had their CVD risk assessed between 2007 and 2016. Participants were divided into three mutually exclusive subgroups: (1) AF with or without CVD (n=15,212), (2) CVD and no AF (n=43,790), (3) no CVD or AF (n=429,105). Adjusted hazards ratios (adjHRs) were estimated from Cox proportional hazards models predicting major bleeding risk for each of the three subgroups to determine whether ethnicity and socioeconomic deprivation are independent predictors of major bleeds in different cardiovascular risk groups .

Results: In all three subgroups (AF, CVD, no CVD/AF), Māori (adjHR 1.63 [1.39-1.91], 1.24 [1.09-1.42], 1.57 [95% CI 1.45-1.70], respectively), Pacific people (adjHR 1.90 [1.58-2.28], 1.30 [1.12-1.51], 1.62 [95% CI 1.49-1.75], respectively) and Chinese people (adjHR 1.53 [1.08-2.16], 1.15 [0.90-1.47], 1.13 [95% CI 1.01-1.26], respectively) were at increased risk of a major bleed compared to Europeans, although for Chinese people the effect did not reach statistical significance in the CVD subgroup. Compared to Europeans, Māori and Pacific peoples were generally at increased risk of all bleed types (gastrointestinal, intracranial and other bleeds). An increased risk of intracranial bleeds was observed among Chinese and Other Asian people and, in the CVD and no CVD/AF subgroups, among Indian people. Increasing socioeconomic deprivation was also associated with increased risk of a major bleed in all three subgroups (adjHR 1.07 [95% CI 1.02-1.12], 1.07 [1.03-1.10], 1.10 [1.08-1.12], respectively, for each increase in socioeconomic deprivation quintile).

Conclusion: Ethnicity and socioeconomic status should be considered in bleeding risk assessments to guide the use of antithrombotic medication for the management of AF and CVD.

Primary Funding Source: The Health Research Council of New Zealand

Background

Antithrombotic medication (antiplatelets and anticoagulants) reduce the risk of cardiovascular disease (CVD), but with the disadvantage of increasing bleeding risk. Bleeding risk equations have been developed so that clinicians can balance the potential cardiovascular benefits of antithrombotic medication against their bleeding harms. We recently developed such an equation for people without CVD or atrial fibrillation (AF) to guide decision-making on the use of aspirin for the primary prevention of CVD (1, 2). We found that ethnicity and socioeconomic status, in addition to clinical variables, were important independent predictors of major bleeds among women and men.

Neither ethnicity nor socioeconomic status are specified as factors associated with increased bleeding risk in US guidelines for the secondary prevention of CVD (3) or management of atrial fibrillation (AF) (4). Bleeding risk is of particular importance among people with AF given the widespread use of anticoagulants to reduce the risk of thromboembolic disease, especially stroke, in this group. The purpose of this study was to determine whether ethnicity and/or socioeconomic status are also independent risk factors for a major bleed among people with a history of CVD or AF.

Methods

Setting

This study was a prospective open cohort study. People were entered into the cohort the first time their primary care physician or nurse entered their CVD risk assessment data into PREDICT, a web-based decision support program integrated with electronic primary care practice management systems in New Zealand (5). 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 (6)) had their risk assessed using this software (5). Participants were recruited between 1 January 2007 and 31 December 2016. The study end date was 31 December 2017, which provided at least 12 months of follow-up across all data sources. Participants were censored on the earliest of the following dates: death, 5 years follow up or the study end date.

Since 2003, New Zealand CVD risk management guidelines have recommended a regular CVD risk assessment for men aged 45 years or older, women aged 55 years or older (and 10 years earlier for subpopulations at increased risk: those of Māori, Pacific, or Indian ethnicity) (7). Whether a person visiting the primary care clinic has his or her CVD risk assessed, and therefore whether he or she enters the cohort, is at the discretion of the primary care clinician. Most primary care physicians receive alerts advising them of individual patient eligibility for CVD risk assessment (5).

Data sources and Linkage

During CVD risk assessment, an electronic risk profile is stored both in the practice management system and anonymously on a central database. With the permission of clinicians, this profile is linked to an encrypted National Health Index number, which is used to anonymously link the profile to national (mortality, hospitalisation and medication dispensing) and regional (laboratory result) databases.

Inclusion and Exclusion Criteria

All people who had a first CVD risk assessment in primary care using the PREDICT program between 1 January 2007 and 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 age 80 years or older, history of intracranial haemorrhage (ICH, as antithrombotic therapy is generally contraindicated in this group), or with ethnicity of MELAA (Middle Eastern/Latin American/African) or Other (due to the small numbers in these ethnic groups in New Zealand). Participants were divided into three mutually exclusive

subgroups: AF (whether or not they had CVD), CVD (without AF), and without either AF or CVD. Definitions of AF, CVD, intracranial bleeding and ethnicity are provided in eTable 1.

Outcome

The primary outcome in this study was time to a first major bleeding event (hospitalization or death associated with bleeding) during follow up (any, or for sensitivity analyses by type: gastrointestinal, intracranial, other). Hospitalizations with bleeding were defined as those in which an International Statistical Classification of Diseases and Related Health Problems (ICD) code for a bleeding event (eTable 2) was assigned as a diagnosis for the admission, either on its own if it was the principal diagnosis (i.e., the main reason for the admission) or, if the bleed was not the principal diagnosis, when there was also a transfusion of whole blood (code 1370601 in the ICD, Tenth Revision, Australian Modification [ICD-10-AM]; code 9903 in the Australian version of the ICD, 9th Revision, Clinical Modification [ICD-9-CM-A]) or a blood transfusion of packed cells [ICD-10-AM code 1370602; ICD-9-CM-A code 9904]). Deaths with bleeding were defined as those in which an ICD code for a bleeding event (eTable 2) was the underlying cause of death. Major bleeding associated with trauma or procedures was excluded.

Variables

To classify ethnicity, we used self-reported ethnicity categorised using the prioritised output method of national ethnicity data protocols (8) with the Indian population (who comprise 90% of the South Asian population in New Zealand (9)) separated out from the Asian category as they are known to have elevated CVD risk. Non-Indian South Asians cannot currently be distinguished from other Asians in New Zealand administrative health data. This classified the population into Māori (the indigenous people of New Zealand), Pacific, Indian, Chinese, Other Asian, European, MELAA and Other ethnicity.

Socioeconomic deprivation was measured using an area-based measure, the New Zealand Index of Deprivation (NZDep) (10). The NZDep was constructed from nine census derived variables representing eight dimensions of deprivation. In this study, deprivation quintiles (1 = least deprived, 5 = most deprived) were used rather than the conventional NZDep deciles.

The following predictors were also included in the analysis: age, sex, systolic blood pressure (SBP), total cholesterol to high density lipoprotein cholesterol ratio (TC:HDL), medical history (smoking, diabetes, CVD, heart failure, cancer, bleeding, peptic ulcer disease, thrombocytopaenia, anaemia, chronic kidney disease, liver disease, pancreatitis or alcohol-related conditions) and medication use (antiplatelet, anticoagulant, antihypertensive, lipid lowering, non-steroidal anti-inflammatory, corticosteroid, selective serotonin reuptake inhibitor).

Definitions of all predictors are provided in eTable 1.

Statistical Analyses

Continuous variables were summarized as means with standard deviations and medians with interquartile ranges (IQR) and categorical data as frequencies with percentages. Adjusted hazards ratio

(adjHR) for time to a first major bleed during follow up were obtained using Cox proportional hazards models. All variables noted above were included. Separate models were developed in each of the three subgroups for all bleeds. In sensitivity analyses, separate models were developed in each of the three subgroups for three bleed types: gastrointestinal, intracranial, other. Time in the study was the time scale and was calculated from index assessment to the earliest of the following dates: first major bleed during follow up, death, 5 years follow up or the study end date (31 December 2017). Reference groups for categorical variables are shown in bold and underlined in eTable 1. The proportionality assumption in each model was assessed by using the global Schoenfeld test (11) and plotting $\log[-\log(\text{survival})]$ versus $\log(\text{time})$. The linearity of the association between continuous variables (age, SBP and TC:HDL) and the outcome was assessed by visual inspection of LOWESS smoothed plots of martingale residuals (12). Data analysis was performed using R software, version 3.5.1 (<https://cran.r-project.org/>), which included the “survival” package.

Results

A total of 523,064 people who had a PREDICT CVD risk assessment were considered for the analysis (Fig. 1). Of these, 6,903 people were excluded because their first risk assessment was prior to 2007. Among the remaining 516,161 people, 28,054 were excluded because they met at least one of the exclusion criteria.

Among the remaining cohort of 488,107 people, 56.4% were men and the median age was 55 years (IQR 47–63). Although the majority were European (272,499, 55.8%), there were large numbers in the other ethnic groups: 64,420 (13.2%) Māori, 60,905 (12.5%) Pacific, 41,505 (8.5%) Indian, 28,948 (5.9%) Chinese and 19,830 (4.1%) Other Asian. There was a higher proportion of people living in areas of the highest (22.3%) and lowest (21.6%) quintiles of socioeconomic deprivation, than those living in intermediate quintiles (second quintile 19.4%, third quintile 18.0%, fourth quintile 18.7%).

We identified a total of 15,212 (3.1%), 43,790 (9.0%), and 429,105 (87.9%) people with AF (+/- CVD), CVD (no AF), and no CVD or AF, respectively (Table 1). There was a greater proportion of men, Europeans and Māori in those with AF or CVD compared with those without either. Those with AF or CVD were also older and more likely to be in the most deprived quintile of socioeconomic deprivation than those without either. The median follow-up (5.0 years, IQR 3.8 to 5.0) was similar across subgroups. During follow up there were a total of 9,873 bleeds (AF 1,218, CVD 2,105, no CVD/AF 6,550), of which 6,736 were gastrointestinal, 1,384 were intracranial and 2,024 were other bleeds.

Table 1
Baseline characteristics, follow up duration and bleeds during follow up, by subgroup

Variables		Atrial fibrillation	Cardiovascular disease	No atrial fibrillation or cardiovascular disease
n (% of total)		15212 (3.1%)	43790 (9.0%)	429105 (87.9%)
Male		9857 (64.8%)	25704 (58.7%)	239552 (55.8%)
Age, years		64 ± 10 (66, 58 to 72)	62 ± 910 (64, 56 to 70)	54 ± 10 (54, 46 to 61)
Ethnicity (self- identified and prioritised)	Māori	2885 (19%)	6452 (14.7%)	55083 (12.8%)
	Pacific	1578 (10.4%)	4671 (10.7%)	54656 (12.7%)
	Indian	340 (2.2%)	3226 (7.4%)	37939 (8.8%)
	Chinese	428 (2.8%)	1526 (3.5%)	26994 (6.3%)
	Other Asian	158 (1%)	909 (2.1%)	18763 (4.4%)
	European	9823 (64.6%)	27006 (61.7%)	235670 (54.9%)
Socioeconomic deprivation*	Quintile 1 (least deprived)	2953 (19.4%)	7815 (17.8%)	94741 (22.1%)
	Quintile 2	2735 (18%)	7585 (17.3%)	84564 (19.7%)
	Quintile 3	2697 (17.7%)	7832 (17.9%)	77327 (18%)
	Quintile 4	2956 (19.4%)	9046 (20.7%)	79204 (18.5%)
	Quintile 5 (most deprived)	3871 (25.4%)	11512 (26.3%)	93269 (21.7%)
HDL = high density lipoprotein, TC = total cholesterol				
Categorical data are n (%) of subgroup, unless indicated otherwise.				
Continuous data are mean ± standard deviation (median, interquartile range), unless indicated otherwise.				
Data complete or near complete (> 99% of values available).				
*Socioeconomic deprivation measured by the New Zealand Deprivation Index (2006), an area-based measure constructed from 9 census derived variables representing 8 dimensions of deprivation.				
†Other bleeds were respiratory bleeds (including epistaxis and haemoptysis), ocular bleeds (vitreous and retinal), bleeds into a joint and bleeds into the pericardium or peritoneum				

Variables		Atrial fibrillation	Cardiovascular disease	No atrial fibrillation or cardiovascular disease
Measurements	Systolic blood pressure, mm Hg	130 ± 16 (130, 120 to 140)	132 ± 16 (130, 122 to 141)	129 ± 16 (128, 120 to 138)
	TC:HDL, mmol/L	3.8 ± 1.2 (3.6, 3.0 to 4.5)	3.8 ± 1.2 (3.6, 3.0 to 4.5)	4.1 ± 1.2 (3.9, 3.2 to 4.8)
Medical history	Smoker (current or former)	6011 (39.5%)	18725 (42.8%)	134420 (31.3%)
	Diabetes	3942 (25.9%)	13594 (31%)	51497 (12%)
	Coronary heart disease	5598 (36.8%)	28219 (64.4%)	0 (0%)
	Cerebrovascular disease	2070 (13.6%)	9894 (22.6%)	0 (0%)
	Peripheral vascular disease	1588 (10.4%)	6387 (14.6%)	0 (0%)
	Heart failure	4889 (32.1%)	9777 (22.3%)	0 (0%)
	Atrial fibrillation	15212 (100%)	0 (0%)	0 (0%)
	Cancer	1899 (12.5%)	4517 (10.3%)	22330 (5.2%)
	Gastrointestinal bleed	1373 (9%)	2726 (6.2%)	8173 (1.9%)
	Other [†] bleed	895 (5.9%)	1278 (2.9%)	2921 (0.7%)

HDL = high density lipoprotein, TC = total cholesterol

Categorical data are n (%) of subgroup, unless indicated otherwise.

Continuous data are mean ± standard deviation (median, interquartile range), unless indicated otherwise.

Data complete or near complete (> 99% of values available).

*Socioeconomic deprivation measured by the New Zealand Deprivation Index (2006), an area-based measure constructed from 9 census derived variables representing 8 dimensions of deprivation.

[†]Other bleeds were respiratory bleeds (including epistaxis and haemoptysis), ocular bleeds (vitreous and retinal), bleeds into a joint and bleeds into the pericardium or peritoneum

Variables		Atrial fibrillation	Cardiovascular disease	No atrial fibrillation or cardiovascular disease
	Peptic ulcer disease	4749 (31.2%)	14499 (33.1%)	56353 (13.1%)
	Thrombocytopenia	854 (5.6%)	1610 (3.7%)	6694 (1.6%)
	Anaemia	1794 (11.8%)	4566 (10.4%)	14352 (3.3%)
	Chronic kidney disease	666 (4.4%)	1885 (4.3%)	2148 (0.5%)
	Chronic liver disease	94 (0.6%)	286 (0.7%)	752 (0.2%)
	Chronic pancreatitis	33 (0.2%)	82 (0.2%)	270 (0.1%)
	Chronic alcohol- related disease	467 (3.1%)	901 (2.1%)	2931 (0.7%)
Medication (preceding 6 months)	Antiplatelet	6928 (45.5%)	29329 (67%)	41743 (9.7%)
	Anticoagulant	6265 (41.2%)	1207 (2.8%)	1244 (0.3%)
	Blood pressure- lowering	12089 (79.5%)	33027 (75.4%)	101896 (23.7%)
	Lipid-lowering	7861 (51.7%)	30072 (68.7%)	71831 (16.7%)
	Non-steroidal anti- inflammatory	2011 (13.2%)	7710 (17.6%)	77586 (18.1%)
	Steroid	1813 (11.9%)	4585 (10.5%)	23505 (5.5%)
HDL = high density lipoprotein, TC = total cholesterol				
Categorical data are n (%) of subgroup, unless indicated otherwise.				
Continuous data are mean $\pm$ standard deviation (median, interquartile range), unless indicated otherwise.				
Data complete or near complete (> 99% of values available).				
*Socioeconomic deprivation measured by the New Zealand Deprivation Index (2006), an area-based measure constructed from 9 census derived variables representing 8 dimensions of deprivation.				
†Other bleeds were respiratory bleeds (including epistaxis and haemoptysis), ocular bleeds (vitreous and retinal), bleeds into a joint and bleeds into the pericardium or peritoneum				

Variables		Atrial fibrillation	Cardiovascular disease	No atrial fibrillation or cardiovascular disease
	Selective serotonin re-uptake inhibitor	1017 (6.7%)	3586 (8.2%)	22192 (5.2%)
Follow-up duration	Total, person-years	62657	189336	1822153
	Median (interquartile range), years	5.0 (3.6 to 5.0)	5.0 (4.1 to 5.0)	4.9 (3.7 to 5.0)
Major bleeds during follow up	Any	1218 (8.0%)	2105 (4.8%)	6550 (1.5%)
	Gastrointestinal	734 (4.8%)	1476 (3.4%)	4526 (1.1%)
	Intracranial	172 (1.1%)	273 (0.6%)	939 (0.2%)
	Other [†]	384 (2.5%)	428 (1.0%)	1212 (0.3%)
HDL = high density lipoprotein, TC = total cholesterol				
Categorical data are n (%) of subgroup, unless indicated otherwise.				
Continuous data are mean $\pm$ standard deviation (median, interquartile range), unless indicated otherwise.				
Data complete or near complete (> 99% of values available).				
*Socioeconomic deprivation measured by the New Zealand Deprivation Index (2006), an area-based measure constructed from 9 census derived variables representing 8 dimensions of deprivation.				
[†] Other bleeds were respiratory bleeds (including epistaxis and haemoptysis), ocular bleeds (vitreous and retinal), bleeds into a joint and bleeds into the pericardium or peritoneum				

The proportionality assumption and linearity of the association between continuous variables (age, SBP, TC:HDL) and the outcomes were assessed for the three main models (outcome = all bleeds) and the nine models in the sensitivity analysis (outcome = gastrointestinal bleeds, intracranial bleeds, other bleeds). The proportionality assumption largely held for all variables across each of the models. While the association between age and TC:HDL and the outcomes was largely linear, there was some non-linearity in the association between SBP and the outcomes in some of the models at 140 mmHg, and therefore SBP was dichotomised for all models (< 140, $\geq$ 140 mmHg).

The adjHRs for ethnicity and socioeconomic deprivation in all of the models (main and sensitivity) are provided in Tables 2 and 3, respectively, and the adjHRs for all variables in each of the subgroups are provided in eTable 4 (main) and eTables 5–7 (sensitivity).

Table 2
Adjusted hazard ratios for ethnicity, by subgroup and bleed type

Ethnicity (self-identified and prioritised; comparator European)	Atrial fibrillation	Cardiovascular disease	No atrial fibrillation or cardiovascular disease
<i>Any bleed</i>			
Māori	1.63 (1.39– 1.91)	1.24 (1.09– 1.42)	1.57 (1.45–1.70)
Pacific	1.90 (1.58– 2.28)	1.30 (1.12– 1.51)	1.62 (1.49–1.75)
Indian	0.75 (0.48– 1.19)	0.98 (0.82– 1.19)	0.95 (0.85–1.06)
Chinese	1.53 (1.08– 2.16)	1.15 (0.90– 1.47)	1.13 (1.01–1.26)
Other Asian	1.22 (0.65– 2.29)	1.05 (0.75– 1.46)	1.34 (1.17–1.52)
<i>Gastrointestinal bleed</i>			
Māori	1.48 (1.21– 1.82)	1.17 (1.00– 1.38)	1.47 (1.34–1.62)
Pacific	1.64 (1.29– 2.08)	1.08 (0.90– 1.30)	1.51 (1.37–1.66)

Hazard ratios are adjusted for all of the following variables: age, sex, ethnicity, socioeconomic deprivation, systolic blood pressure ($\geq$ or $<$ 140 mm Hg), ratio of total cholesterol to high density lipoprotein cholesterol (mmol/L), medical history (smoking, diabetes, cardiovascular disease, heart failure, cancer, bleeding, peptic ulcer disease, thrombocytopaenia, anaemia, chronic kidney disease, liver disease, pancreatitis or alcohol-related condition) and medication use in the preceding 6 months (antiplatelet, anticoagulant, BP-lowering, lipid-lowering, non-steroidal anti-inflammatory, steroid, selective serotonin re-uptake inhibitor).

The total number of people included (and excluded due to a missing value) in the models for atrial fibrillation, cardiovascular disease and no atrial fibrillation or cardiovascular disease were: 15097 (115), 43437 (353) and 425668 (3437), respectively.

For the atrial fibrillation subgroup, the number of bleeds in the models were: any (1202), gastrointestinal (723), intracranial (172), other (379). For the cardiovascular disease subgroup, the number of bleeds in the models were: any (2092), gastrointestinal (1470), intracranial (270), other (423). For the no atrial fibrillation or cardiovascular disease subgroup, the number of bleeds in the models were: any (6478), gastrointestinal (4482), intracranial (926), other (1196).

Ethnicity (self-identified and prioritised; comparator European)	Atrial fibrillation	Cardiovascular disease	No atrial fibrillation or cardiovascular disease
Indian	0.59 (0.31– 1.11)	0.93 (0.75– 1.16)	0.93 (0.81–1.06)
Chinese	1.43 (0.92– 2.22)	1.06 (0.78– 1.43)	1.03 (0.90–1.17)
Other Asian	1.00 (0.41– 2.43)	0.93 (0.62– 1.41)	1.24 (1.06–1.45)
<i>Intracranial bleed</i>			
Māori	1.49 (0.97– 2.30)	0.96 (0.63– 1.47)	1.44 (1.16–1.78)
Pacific	1.97 (1.23– 3.16)	2.09 (1.43– 3.05)	1.73 (1.40–2.14)
Indian	1.00 (0.36– 2.79)	1.67 (1.05– 2.64)	1.38 (1.05–1.82)
Chinese	3.51 (1.79– 6.87)	1.77 (0.99– 3.16)	1.45 (1.12–1.89)
Other Asian	2.60 (0.81– 8.32)	2.08 (1.01– 4.29)	1.67 (1.21–2.30)
<i>Other bleed</i>			

Hazard ratios are adjusted for all of the following variables: age, sex, ethnicity, socioeconomic deprivation, systolic blood pressure ($\geq$ or $<$ 140 mm Hg), ratio of total cholesterol to high density lipoprotein cholesterol (mmol/L), medical history (smoking, diabetes, cardiovascular disease, heart failure, cancer, bleeding, peptic ulcer disease, thrombocytopaenia, anaemia, chronic kidney disease, liver disease, pancreatitis or alcohol-related condition) and medication use in the preceding 6 months (antiplatelet, anticoagulant, BP-lowering, lipid-lowering, non-steroidal anti-inflammatory, steroid, selective serotonin re-uptake inhibitor).

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Ethnicity (self-identified and prioritised; comparator European)	Atrial fibrillation	Cardiovascular disease	No atrial fibrillation or cardiovascular disease
Māori	1.98 (1.50– 2.61)	1.52 (1.15– 2.03)	2.28 (1.92–2.70)
Pacific	2.35 (1.71– 3.24)	1.65 (1.22– 2.24)	2.05 (1.71–2.46)
Indian	0.94 (0.44– 2.04)	0.86 (0.55– 1.34)	0.73 (0.54–0.98)
Chinese	0.75 (0.31– 1.82)	1.17 (0.67– 2.07)	1.33 (1.03–1.71)
Other Asian	0.78 (0.19– 3.17)	0.62 (0.23– 1.68)	1.47 (1.09–1.99)
Hazard ratios are adjusted for all of the following variables: age, sex, ethnicity, socioeconomic deprivation, systolic blood pressure ($\geq$ or $<$ 140 mm Hg), ratio of total cholesterol to high density lipoprotein cholesterol (mmol/L), medical history (smoking, diabetes, cardiovascular disease, heart failure, cancer, bleeding, peptic ulcer disease, thrombocytopaenia, anaemia, chronic kidney disease, liver disease, pancreatitis or alcohol-related condition) and medication use in the preceding 6 months (antiplatelet, anticoagulant, BP-lowering, lipid-lowering, non-steroidal anti-inflammatory, steroid, selective serotonin re-uptake inhibitor).			
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Table 3
Adjusted hazard ratios for socioeconomic deprivation, by subgroup and bleed type

Socioeconomic deprivation	Atrial fibrillation	Cardiovascular disease	No atrial fibrillation or cardiovascular disease
Area-based, per quintile of increasing deprivation, compared with those living in the quintile of least deprivation	<i>Any bleed</i>		
	1.07 (1.02–1.12)	1.07 (1.03–1.10)	1.10 (1.08–1.12)
	<i>Gastrointestinal bleed</i>		
	1.07 (1.01–1.13)	1.09 (1.04–1.13)	1.11 (1.08–1.13)
	<i>Intracranial bleed</i>		
	1.23 (1.09–1.40)	1.00 (0.91–1.10)	1.07 (1.02–1.12)
	<i>Other bleed</i>		
	1.01 (0.93–1.09)	1.04 (0.96–1.12)	1.08 (1.03–1.13)
Hazard ratios are adjusted for all of the following variables: age, sex, ethnicity, socioeconomic deprivation, systolic blood pressure ($\geq$ or $<$ 140 mm Hg), ratio of total cholesterol to high density lipoprotein cholesterol (mmol/L), medical history (smoking, diabetes, cardiovascular disease, heart failure, cancer, bleeding, peptic ulcer disease, thrombocytopaenia, anaemia, chronic kidney disease, liver disease, pancreatitis or alcohol-related condition) and medication use in the preceding 6 months (antiplatelet, anticoagulant, BP-lowering, lipid-lowering, non-steroidal anti-inflammatory, steroid, selective serotonin re-uptake inhibitor).			
The total number of people included (and excluded due to a missing value) in the models for atrial fibrillation, cardiovascular disease and no atrial fibrillation or cardiovascular disease were: 15097 (115), 43437 (353) and 425668 (3437), respectively.			
For the atrial fibrillation subgroup, the number of bleeds in the models were: any (1202), gastrointestinal (723), intracranial (172), other (379). For the cardiovascular disease subgroup, the number of bleeds in the models were: any (2092), gastrointestinal (1470), intracranial (270), other (423). For the no atrial fibrillation or cardiovascular disease subgroup, the number of bleeds in the models were: any (6478), gastrointestinal (4482), intracranial (926), other (1196).			

In all three subgroups (AF, CVD, no CVD or AF), Māori (adjHR 1.63 [1.39–1.91], 1.24 [1.09–1.42], 1.57 [95% CI 1.45–1.70], respectively), Pacific people (adjHR 1.90 [1.58–2.28], 1.30 [1.12–1.51], 1.62 [95% CI 1.49–1.75], respectively) and Chinese people (adjHR 1.53 [1.08–2.16], 1.15 [0.90–1.47], 1.13 [95% CI 1.01–1.26], respectively) were at increased risk of a major bleed compared to Europeans, although for Chinese people the effect did not reach statistical significance in the CVD subgroup (Table 2). For Māori and

Pacific people there was a fairly consistent increase in bleeding risk compared with Europeans across the three subgroups for each of the three bleed types. In contrast, for Chinese people the increase in bleeding risk in the three subgroups was mainly due to an increased risk of intracranial bleeds compared with Europeans. There was also an increased risk of intracranial bleeds among Other Asian people and, in the CVD and no CVD/AF subgroups, among Indian people.

Increasing socioeconomic deprivation was associated with increased risk of a major bleed in all three subgroups (adjHR 1.07 [1.02–1.12], 1.07 [1.03–1.10], 1.10 [95% CI 1.08–1.12], respectively, for each increase in socioeconomic deprivation quintile) (Table 3). There was a fairly consistent increase in bleeding risk with increasing socioeconomic deprivation across the three subgroups for each of the three bleed types.

Discussion

We found that, after adjusting for multiple clinical variables, ethnicity and socioeconomic deprivation were independent predictors of major bleeds in those with AF, CVD and without either condition. Māori and Pacific people were at increased risk compared with Europeans across most bleed types / subgroups, whereas Indian, Chinese and Other Asians were at increased risk of intracranial bleeds compared with Europeans across most subgroups. Increasing socioeconomic deprivation was also associated with a higher risk of a major bleed across most bleed types / subgroups.

Strengths of this study are its considerable size overall, the substantial size of the included ethnic and socioeconomic groups, and the ability to adjust for multiple clinical variables. While a limitation of the study is its reliance on coded diagnoses to identify major bleeds, this limitation is unlikely to have a substantive effect on our findings unless there are differences in coding by ethnicity or socioeconomic deprivation. Another limitation of the study is that it was restricted to patients who had their CVD risk assessed. However, in included practices, data up to 2015 indicate that a CVD risk assessment had been conducted in approximately 90% of eligible persons (5).

Our findings are largely consistent with those of other New Zealand (13–15) and international (16–35) studies that have also found higher rates of major bleeds (total, gastrointestinal or intracranial) in non-Whites compared with Whites and with increasing socioeconomic deprivation. In these studies, populations were not defined according to their history of CVD and AF, and there was adjustment for a limited number of variables, if any. Studies of people with AF have shown this group to have increased risk of major bleeds with more deprived socioeconomic status (36), and increased risk of intracranial haemorrhage if they were Asian, Hispanic or Black (compared with White people) (37).

We identified two studies with findings inconsistent with our study (38) (39). A systematic review of population-based studies of intracranial haemorrhage that pooled incidences in a random-effects binomial meta-analysis found that the incidence of intracranial haemorrhage was greater for East and Southeast Asian people than for White people, whereas there was no statistically significant differences in incidence for Black, Hispanic, Indian or Māori compared with White people (38). There are a number of

significant limitations to this study, including inconsistency in case definition and ascertainment across included studies and the inability to adjust for individual participant characteristics such as age because of a reliance on aggregated data (38).

The QBleed sex-specific risk equations for upper gastrointestinal and intracranial bleeds were developed among people in primary care irrespective of their history of CVD or AF, using multiple variables from routinely collected data from general practices in the United Kingdom (39). Increasing socioeconomic deprivation was associated with an increase in bleeds, both upper gastrointestinal and intracranial. In QBleed there was no statistically significant difference in the risk of upper gastrointestinal bleeds between those in any of the ethnic groups (Indian, Pakistani, Bangladeshi, Other Asian, Caribbean, Black African, Chinese, Other [including mixed]) compared with the reference group (Whites or people in whom ethnicity was not recorded), with the exception of Black African men who were at lower risk of an upper gastrointestinal bleed than the reference group (39). The following ethnic groups were at increased risk of an intracranial bleed: Bangladeshi women, Other Asian men, Caribbean men and Black African men. Chinese people were at increased risk of an intracranial bleed but the difference was not statistically significant. There are a number of reasons that might explain why differences by ethnicity were more consistently observed in our study than in QBleed. Ethnicity was missing from 26% of the QBleed participants, the reference ethnic group in QBleed combined Whites and those in whom ethnicity was missing, and the proportions in the non-reference groups was low (Indian 2.1%, Pakistani 1.0%, Bangladeshi 0.8%, Other Asian 1.4%, Caribbean 1.0%, Black African 1.8%, Chinese 1.1% and other or multiple 2.3%).

We consider that a plausible explanation for the finding of higher rates of major bleeds in non-Whites compared with Whites and with increasing socioeconomic deprivation to be that ethnicity and socioeconomic deprivation are surrogate markers for longitudinal, lifetime exposure to risk factors that are not able to be captured by other predictors either because these are cross sectional or not measured at all. Ethnicity itself has been directly associated with adverse health outcomes through racism.(40, 41)

US guidelines for the secondary prevention of CVD recommend antiplatelet therapy in specific groups, largely irrespective of bleeding risk (3). More recent US and European post-acute coronary syndrome guidelines (42, 43), have moved towards the use of multivariable equations to estimate the risk of bleeds, but none of these equations include ethnicity or socioeconomic status (44–46). Similarly, while US guidelines for the management of AF (4) recommend a multivariable equation to estimate the risk of bleeds, that Eq. (47) also does not include ethnicity or socioeconomic status.

Given the significant independent effects of socioeconomic status and ethnicity on major bleeds, it would be appropriate for future guidelines to consider both factors in bleeding risk assessments, ideally using multivariable equations, to guide the use of antithrombotic medication for the management of AF and CVD.

List Of Abbreviations

cardiovascular disease (CVD)

atrial fibrillation (AF)

Adjusted hazards ratios (adjHRs)

MELAA (Middle Eastern/Latin American/African)

International Statistical Classification of Diseases and Related Health Problems (ICD)

New Zealand Index of Deprivation (NZDep)

Systolic blood pressure (SBP)

Total cholesterol to high density lipoprotein cholesterol ratio (TC:HDL)

interquartile ranges (IQR)

Declarations

Ethics approval and consent to participate

The PREDICT study (under which this research was conducted) was approved by the New Zealand Northern Region Ethics Committee Y in 2003 (AKY/03/12/314), with subsequent annual approval by the New Zealand National Multi Region Ethics Committee since 2007 (MEC07/19/EXP). Participant informed consent was not obtained, consistent with a waiver granted by the ethics committee, because the study involved secondary use of patient data that was anonymized prior to being received by the research team.

Consent for publication

Not applicable

Competing Interests

This research was funded by a project grant (15/165) from the Health Research Council of New Zealand (HRC). CG, MH, RJ, AK, SM, KP and SW are receiving funding from the HRC for programme, project and Clinical Research Training grants for CVD research. KP is the recipient of a Heart Foundation of New Zealand Hynds Senior Fellowship and CG was the recipient of a National Heart Foundation of New Zealand Research Fellowship. SW was the recipient of a Fellowship in Health Innovation and Quality Improvement, funded by the Stevenson Foundation. Outside of this research, SW and KP have received funding from the Heart Foundation of New Zealand (project grant for quality improvement and structural heart disease, respectively) and SW from Roche Diagnostics Ltd (project grant for point of care testing trial).

Funding

This research was funded by a project grant (15/165) from the Health Research Council of New Zealand (HRC). AK, CG, KP, MH, RJ, SM and SW are receiving funding from the HRC for programme, project and Clinical Research Training grants for CVD research. KP is the recipient of a Heart Foundation of New Zealand Hynds Senior Fellowship and CG was the recipient of a National Heart Foundation of New Zealand Research Fellowship. Funding organizations 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.

Authors' contributions

VS, RJ, AK and SW conceptualised and designed the study. RJ, AK, KP and SW were involved in the data collection and management process. WCT and VS analysed the data with input from KP. All authors were involved in data interpretation. WCT and VS drafted the manuscript and all authors revised the manuscript. All authors approved the final submitted version and agreed to be accountable for the report.

Acknowledgements

The authors would like to thank the primary health care organisations, affiliated primary care physicians, nurses and patients for their contributions to this study.

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Figures

Figure 1

Cohort enrolment, exclusions

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