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Annual Risk of Major Bleeding Among Persons Without Cardiovascular Disease Not Receiving Antiplatelet Therapy

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IMPORTANCE A decision to initiate aspirin therapy for primary prevention of cardiovascular disease (CVD) requires consideration of both treatment benefits and harms. The most significant harm associated with aspirin is major bleeding, yet there is a paucity of data on bleeding risk in suitable community populations.

OBJECTIVE To determine the risk of major bleeding among people without CVD who are not receiving antiplatelet therapy.

DESIGN, SETTING, AND PARTICIPANTS Prospective cohort study of 359 166 individuals aged 30 to 79 years receiving primary care in New Zealand who had CVD risk assessment between 2002 and 2015. Participants were censored at the earliest date on which they had a first major bleeding event, died, or met any baseline cohort exclusion criteria or the study end date of December 31, 2015. Analyses were repeated after excluding people with medical conditions associated with increased bleeding risk (non–high-risk cohort; n=305 057) and after further excluding people receiving other medications associated with increased bleeding risk (nonmedication cohort; n=240 254).

EXPOSURES Sex and age group in 10-year bands from 30 to 79 years.

MAIN OUTCOMES AND MEASURES Risk of a major bleeding event (hospitalization or death associated with bleeding); nonfatal gastrointestinal tract bleeding; and gastrointestinal tract bleeding–related case fatality.

RESULTS Mean participant age was 54 years (SD, 10 years), 44% were women, and 57% were European. Among the 359 166 individuals in the baseline cohort, 3976 had a major bleeding event during 1 281 896 person-years of follow-up. Most had gastrointestinal (GI) bleeding (n=2910 [73%]). There were 274 fatal bleeding events (7%), of which 153 were intracerebral. The risk of a nonfatal GI bleeding event per 1000 person-years was 2.19 (95% CI, 2.11-2.27), 1.77 (95% CI, 1.69-1.85) and 1.61 (95% CI, 1.52-1.69), in the baseline, non–high-risk, and nonmedication cohorts, respectively. Case fatality associated with GI bleeding was 3.4% (95% CI, 2.2%-4.1%), 4.0% (95% CI, 3.2%-5.1%), and 4.6% (95% CI, 3.6%-6.0%) in the baseline, non–high-risk, and nonmedication cohorts, respectively.

CONCLUSIONS AND RELEVANCE In a population not receiving antiplatelet therapy, the annual risk of major bleeding events and nonfatal major bleeding was estimated. These findings could inform population-level guidelines for primary prevention of CVD.

Supplemental content

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The decision to initiate treatment for primary prevention of cardiovascular disease (CVD) requires careful consideration of both absolute treatment benefits and harms.[1,2] The most significant harm associated with aspirin is major bleeding.[2,3] The magnitude of the CVD benefits and bleeding harms of aspirin depends primarily on baseline absolute rates of these outcomes.[4] Although absolute CVD risk among people in the community can be assessed using a number of risk equations,[5-8] there is a paucity of data on absolute bleeding risk from community cohorts.[2]

The US Preventive Services Task Force (USPSTF) published recommendations supporting the use of low-dose aspirin for primary prevention of CVD and cancer among adults aged 50 to 59 years who have a 10-year CVD risk of at least 10%.[9] Microsimulation model estimated rates of CVD, colorectal cancer, and major bleeding were used to determine the net balance of benefits and harms across individuals with varying baseline CVD risk.[9,10] Despite a comprehensive review of the relevant literature,[2] the task force was unable to find a suitable published study that directly measured bleeding risk in an untreated cohort for use in the simulation models. However, for the models, they derived estimates of baseline risk of gastrointestinal (GI) bleeding from an Italian cohort study that examined the risk of major bleeding in people who were taking aspirin and propensity-matched controls who were not taking aspirin.[11] They also used estimates of case fatality associated with GI bleeding from a UK cohort study published in 1995[12] in the simulation model.[10]

The aim of the current study was to estimate baseline (untreated) bleeding risk and case fatality in a large community cohort without CVD and not receiving antiplatelet therapy specifically to update US and other guidelines on use of aspirin for primary prevention of CVD.

Key Points

Question What is the risk of major bleeding among persons without cardiovascular disease who are not receiving antiplatelet therapy?

Findings In this prospective cohort study of 359 166 people without cardiovascular disease who were not receiving antiplatelet therapy, the risk of a nonfatal major bleeding event per 1000 person-years ranged from 1.8 in men aged 30 to 39 years to 6.4 in men aged 70 to 79 years and from 1.5 in women aged 30 to 39 years to 5.0 in women aged 70 to 79 years.

Meaning These findings provide baseline bleeding risk estimates that could inform decision making for prevention of cardiovascular disease.

Methods

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology)[13] and RECORD (Reporting of Studies Conducted Using Observational Routinely-Collected Health Data)[14] statements were used to report the methods and results of this study.

Ethics Approval

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.

Study Design, Setting, Entry, and Follow-up

This 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.[15] The program enables available clinical data in the medical record to auto-populate fields, and the data template has a number of compulsory fields and built-in range and validity checks at the point of data entry. These factors facilitated accurate and nearly complete (>99%) data collection for variables required in the CVD risk equation used in New Zealand at the time,[15] which was based on the Framingham risk equation with adjustments for groups whose CVD risk may be underestimated by that equation (eg, family history of premature CVD; Māori [New Zealand's indigenous population], Pacific, or South Asian ethnicity).[16]

Since 2003, New Zealand CVD risk management guidelines have recommended that men aged 45 years or older (10 years later for women; 10 years earlier for subpopulations at increased risk: those of Māori, Pacific, or South Asian ethnicity and individuals with known CVD risk factors) have a regular CVD risk assessment.[15] 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.[15]

Data up to 2015 indicate that approximately 80% of people eligible for CVD risk assessment (according to national guidelines[17]) in practices using the PREDICT program had their CVD risk assessed using this software.[15] This program is in use by 35% to 40% of New Zealand primary care practices, and these practices serve approximately 1.6 million people, approximately 35% of the New Zealand resident population.[15] The only exclusion criterion for the program is current pregnancy, and no decision support is provided for patients younger than 18 years.[15]

Study entry occurred between August 27, 2002, and June 30, 2015, and the study end date was December 31, 2015, to provide a minimum 6-month follow-up period across all data sources. People were censored at the earliest date on which they had a first major bleeding event, died, or met any of the baseline cohort exclusion criteria or the study end date.

Data Sources and Linkage

Data on cardiovascular risk factors (including age, sex, smoking status, diabetes status, blood pressure, body mass index, and cholesterol levels), history (including CVD, atrial fibrillation, and diabetes with renal disease), and medication use (including aspirin) were obtained during the index CVD risk assessment. 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 and regional databases. Further information on definitions of the risk factors is provided in eTables 1 through 4 in the Supplement.

National databases were used to obtain demographic data (age, sex, self-identified ethnicity, and socioeconomic deprivation),[18] deaths,[19] publicly funded hospitalizations (from 1988 onward),[20] and subsidized pharmaceutical dispensing (from 2005 onward).[21] Ethnicity data were included because people of Māori, Pacific, and South Asian ethnicity are at increased risk of CVD and were collected using an open-ended question. Laboratory test results were obtained from TestSafe, a regional laboratory repository for all tests undertaken among people in both the hospital and the community, with coverage of nearly all study cohort members since 2005.[15]

Participants

All people who had had a CVD risk assessment in primary care using the PREDICT program were considered for inclusion in this study. The main cohort for this study (baseline cohort) comprised persons who were not already receiving antiplatelet or anticoagulant therapy and who had no indication for and no absolute contraindication to these medications. In addition, the cohort was restricted to persons younger than 80 years to align with US guidelines for CVD risk assessment.[5]

Exclusion Criteria

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 CVD, congestive heart failure, atrial fibrillation, chronic kidney disease (estimated glomerular filtration rate <30 mL/min on at least 2 occasions at least 90 days apart), diabetes with renal disease, or intracerebral bleeding; and aspirin, antiplatelet, or anticoagulant medication use according to primary care records or 1 or more dispensing record in the preceding 6 months. Participants who met any of the exclusion criteria during follow-up (including being dispensed aspirin, antiplatelet, or anticoagulant medication) were censored from the study at the earliest date on which they met an exclusion criterion. Further information on definitions of exclusion criteria is provided in eTables 5 and 6 in the Supplement.

Two additional cohorts were generated to align with the recommendations of the USPSTF by censoring people with relative contraindications to use of aspirin either because they had conditions known to increase risk of bleeding (non-high-risk cohort) or because they were taking medication known to increase risk of bleeding (nonmedication cohort). Exclusion criteria for the non-high-risk cohort were those for the baseline cohort plus history of peptic ulcer disease, bleeding (GI or other; people with prior intracerebral bleeding had already been excluded), chronic liver disease, pancreatitis, chronic alcohol-related disease, and thrombocytopenia. Definitions of these conditions are provided in eTable 1 in the Supplement. Exclusion criteria for the nonmedication cohort were those for the non-high-risk cohort plus dispensing in the preceding 6 months of any nonsteroidal anti-inflammatory drugs (people taking aspirin had already been excluded), corticosteroids, or selective serotonin reuptake inhibitors. Medications included within these categories are described in eTable 2 in the Supplement.

Outcomes

The primary outcome in this study was a first major bleeding event after study entry (hospitalization or death associated with bleeding). Hospitalizations associated with bleeding were defined as those in which an *International Statistical Classification of Diseases and Related Health Problems* code for a bleeding event was assigned as a diagnosis for the admission, either on its own if it was the principal diagnosis (ie, the main reason for the admission) or, if the bleed was not the principal diagnosis, when there was also a blood transfusion of whole blood (code 1370601 in the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification* [*ICD-10-AM*]; code 9903 in the Australian version of the *International Classification of Diseases, 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]).

Potential *ICD* codes for a major bleeding event were identified by a review of *ICD* code sets used by other studies to identify bleeding events[22-25] and a review (by V.S.) of all *ICD-9-CM-A* and *ICD-10-AM* codes for any additional potentially relevant codes. The final set of *ICD-9-CM-A* and *ICD-10-AM* codes for a major bleeding event (eTable 3 in the Supplement) was compiled following a review of all potential *ICD* codes by V.S. and A.K. Major bleeding events were classified into 3 types: GI, intracerebral, and other. Other types were respiratory (including epistaxis and hemoptysis), ocular (vitreous and retinal), bleeding into a joint, and bleeding into the pericardium or peritoneum. Major bleeding associated with trauma or procedures was excluded. Major bleeding events were classified as nonfatal (hospitalization only; patient still alive 28 days after admission) or fatal (death in which the underlying cause of death was a bleeding event or any death up to 28 days after admission).

Statistical Analyses

Continuous variables were summarized as means with standard deviations and medians with interquartile ranges and categorical data as frequencies with percentages. Ninety-five percent confidence intervals for rates (using person-time as the denominator) were calculated using the Wald interval and for proportions were calculated using the inverted score test. Bleeding risk was plotted over time using Kaplan-Meier analyses by bleeding type, sex, and age group for nonfatal bleeding events. To assess whether the risk of a nonfatal bleeding event was constant, the proportions of at-risk

Table 1. Patient Characteristics[a]

Characteristics	Baseline Cohort (n=359 166)	Non-High-Risk Cohort (n=305 057)	Nonmedication Cohort (n=240 254)
Exclusion criteria	Aged <30 or >80 y; history of cardiovascular disease, congestive heart failure, atrial fibrillation, or chronic kidney disease; prior intracerebral bleeding; aspirin, antiplatelet, or anticoagulant use in preceding 6 mo	Same as baseline cohort plus prior gastrointestinal or other bleeding; history of peptic ulcer disease, chronic liver disease, pancreatitis, or alcohol-related disease; thrombocytopenia	Same as non-high-risk cohort plus nonaspirin NSAID, corticosteroid, or SSRI use in preceding 6 mo
Year of cohort entry, No. (%)			
2002-2006	24 142 (6.7)	22 073 (7.2)	20 582 (8.6)
2007-2010	95 564 (26.6)	80 235 (26.3)	61 652 (25.7)
2011-2015	239 460 (66.7)	202 749 (66.5)	158 020 (65.8)
Male, No. (%)	201 459 (56.1)	172 316 (56.5)	137 005 (57.0)
Age, y			
Mean (SD)	53.5 (10.0)	53.1 (9.9)	53.4 (9.8)
Median (IQR)	53.0 (46.0-61.0)	53.0 (46.0-60.0)	53.0 (46.0-60.0)
Ethnicity, No. (%)[b]			
Māori	45 560 (12.7)	39 855 (13.1)	29 527 (12.3)
Pacific	43 751 (12.2)	38 951 (12.8)	28 111 (11.7)
South Asian	29 464 (8.2)	24 191 (7.9)	18 660 (7.8)
Chinese	36 763 (10.2)	30 841 (10.1)	26 696 (11.1)
European	203 628 (56.7)	171 219 (56.1)	137 260 (57.1)
New Zealand Index of Deprivation quintile, No. (%)[c]			
9 or 10	92 910 (25.9)	78 557 (25.8)	58 258 (24.2)
7 or 8	65 631 (18.3)	54 988 (18)	42 836 (17.8)
5 or 6	69 032 (19.2)	58 570 (19.2)	46 830 (19.5)
3 or 4	59 759 (16.6)	51 271 (16.8)	41 738 (17.4)
1 or 2	71 320 (19.9)	61 220 (20.1)	50 226 (20.9)
Cardiovascular risk factors			
Diabetes, No. (%)	40 797 (11.4)	33 025 (10.8)	25 572 (10.6)
Smoker (current or former), No. (%)	109 080 (30.4)	90 943 (29.8)	68 257 (28.4)
Systolic blood pressure, mm Hg			
Mean (SD)	128.8 (15.6)	128.7 (15.7)	128.8 (15.8)
Median (IQR)	128.0 (120.0-138.0)	127.5 (119.5-138.0)	127.5 (119.5-138.0)
Ratio of total cholesterol to high-density lipoprotein cholesterol, mmol/L			
Mean (SD)	4.11 (1.24)	4.11 (1.24)	4.09 (1.23)
Median (IQR)	4.00 (3.20-4.80)	4.00 (3.20-4.80)	3.90 (3.20-4.80)
Body mass index[d]			
Mean (SD)	29.1 (6.6)	29.1 (6.6)	28.7 (6.4)
Median (IQR)	27.9 (24.7-32.1)	27.9 (24.7-32.1)	27.6 (24.5-31.6)
Medical history, No. (%)			
Peptic ulcer disease	45 820 (12.8)	0	0
Gastrointestinal bleeding	6710 (1.9)	0	0
Other bleeding[e]	2216 (0.6)	0	0
Thrombocytopenia	4697 (1.3)	0	0
Chronic liver disease	599 (0.2)	0	0
Chronic pancreatitis	214 (0.1)	0	0
Alcohol-related disease	2542 (0.7)	0	0
Medication use in preceding 6 mo, No. (%)			
Corticosteroids	18 235 (5.1)	12 846 (4.2)	0
Nonaspirin NSAIDs	60 897 (17)	45 722 (15)	0
SSRIs	17 698 (4.9)	12 777 (4.2)	0

(continued)

Table 1. Patient Characteristics[a] (continued)

Characteristics	Baseline Cohort (n=359 166)	Non-High-Risk Cohort (n=305 057)	Nonmedication Cohort (n=240 254)
Follow-up duration			
Total person-years	1 281 896	1 102 418	883 901
Median (IQR), y	2.78 (1.8-4.8)	2.78 (1.8-4.9)	2.78 (1.8-5.0)

Abbreviations: IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

[a] Data complete or near complete (>99% of values available) unless otherwise specified.

[b] People with Middle Eastern, Latin American, African, other, or unknown ethnicity were excluded from the analysis because of small numbers.

[c] The New Zealand Index of Deprivation (2006) is constructed from 9 census-derived variables representing 8 dimensions of deprivation. Deciles range from 1 (least deprived) to 10 (most deprived).

[d] Calculated as weight in kilograms divided by height in meters squared. Data were missing for 23% of the baseline and non-high-risk cohorts and for 24% of the nonmedication cohort.

[e] Other bleeding included respiratory (including epistaxis and hemoptysis), ocular (vitreous and retinal), bleeding into a joint, and bleeding into the pericardium or peritoneum.

individuals experiencing a bleeding event were compared between years 1 and 5 using the χ^2 test (or the Fisher test if there were fewer than 5 events in a stratum), for each bleeding event type, sex, and age group (all $P > .05$). Because there was no evidence of a statistically significant difference in the annual risk of a nonfatal bleeding event over a 5-year period, risk of a bleeding event (per 1000 person-years) was calculated by dividing the number of events by person-years of follow-up within each stratum. Survival curves for men and women for each fatal and nonfatal bleeding event type were compared using the log-rank test with statistical significance set at $P < .05$ (2-sided). Data analysis was performed using R software, version 3.3.1 (https://cran.r-project.org/), which included the "survival" package.

In a sensitivity analysis, nonfatal bleeding rates were assessed when patients who initiated antiplatelet or antithrombotic therapy during follow-up were retained rather than excluded because of the potential risk of upward bias in study estimates.

Results

Study Population and Characteristics

There were 359 166, 305 057, and 240 254 people in the baseline, non-high-risk, and nonmedication cohorts, respectively. Approximately 43% to 44% of participants were women; the mean age was between 53 and 54 years; the cohorts were ethnically diverse (12%-13% Māori, 12%-13% Pacific, 8% South Asian, and 10%-11% Chinese/East Asian), and median follow-up was 2.8 years (interquartile range, 1.8-4.8 years for the baseline cohort). Demographics, cardiovascular risk factors, medical history, medication use, and follow-up duration for each of the cohorts are described in **Table 1**.

Major Bleeding

The total numbers of people experiencing a first major bleeding event during follow-up were 3976 (1.1%), 2808 (0.9%), and 2090 (0.9%) in the baseline, non-high-risk, and nonmedication cohorts, respectively. Most events were GI bleeding (n = 2910 [73%], n = 2014 [72%], and n = 1473 [70%] in the 3 cohorts, respectively), and there were similar numbers of intracerebral bleeding events (518 [13%], 407 [14%], and 322 [15%]) and other bleeding events (548 [14%], 387 [14%], and 295 [14%]) in the baseline, non-high-risk, and nonmedication cohorts, respectively. In the baseline cohort, only 274 (7%) of these events were fatal, and the majority (56%) of fatal events were intracerebral; similar patterns were observed in the non-high-risk and nonmedication cohorts. The number of bleeding events by type and whether they were fatal are shown by age and sex groups for each of the cohorts in **Table 2**.

Bleeding Risk

Generally, the risk of a nonfatal bleeding event increased with age for each type of nonfatal bleeding event, but particularly for GI bleeding (**Figure**). Although the risk of a nonfatal GI bleeding event was greater among men than women (log-rank $P < .001$), the risk of intracerebral bleeding ($P = .14$) or other bleeding ($P = .05$) was not statistically significantly different by sex. There were no statistically significant differences in the risk of a fatal bleeding event by sex (log-rank $P = .13$ for GI bleeding, $P = .31$ for intracerebral bleeding, and $P = .36$ for other fatal bleeding events). There was no statistically significant difference in the annual risk of a nonfatal bleeding event over a 5-year period within each bleeding type, sex, and age group stratum.

In the baseline cohort, the risk of nonfatal GI bleeding among men ranged from 1.4 (95% CI, 1.2-1.7) per 1000 person-years in the youngest age group (30-39 years) to 5.1 (95% CI, 4.3-5.9) per 1000 person-years in the oldest age group (70-79 years) (**Table 3**). For women, nonfatal GI bleeding risk ranged from 1.1 (95% CI, 0.7-1.6) per 1000 person-years among ages 30 to 39 years to 3.5 (95% CI, 3.0-4.1) per 1000 person-years among ages 70 to 79 years. The point estimates for the risk of nonfatal GI bleeding were lower in the non-high-risk cohort and even lower in the nonmedication cohort compared with the baseline cohort within each sex and age group stratum.

In the baseline cohort, among men, the risk of a fatal GI bleeding event per 1000 person-years ranged from 0.01 (95% CI, −0.01 to 0.03) among ages 30 to 39 years to 0.40 (95% CI, 0.17-0.63) among ages 70 to 79 years. Among women, the risk of a fatal GI bleeding event per 1000 person-years ranged from

Table 2. Patients Experiencing a First Bleeding Event by Bleeding Type, Sex, and Age Group in Each of the 3 Cohorts[a]

	No. (%) of Patients								
	Baseline Cohort			Non–High-Risk Cohort			Nonmedication Cohort		
Bleeding Events	Nonfatal[b]	Fatal[c]	Total	Nonfatal[b]	Fatal[c]	Total	Nonfatal[b]	Fatal[c]	Total
Gastrointestinal Bleeding									
Men									
Aged 70-79 y	153 (1.49)	12 (0.12)	165/10 244 (1.61)	91 (1.19)	4 (0.05)	95/7665 (1.24)	70 (1.10)	4 (0.06)	74/6383 (1.16)
Aged 60-69 y	380 (1.10)	21 (0.06)	401/34 613 (1.16)	243 (0.87)	14 (0.05)	257/28 020 (0.92)	183 (0.80)	12 (0.05)	195/22 814 (0.85)
Aged 50-59 y	522 (0.84)	19 (0.03)	541/62 402 (0.87)	359 (0.67)	13 (0.02)	372/53 429 (0.70)	261 (0.60)	11 (0.03)	272/43 275 (0.63)
Aged 40-49 y	463 (0.67)	9 (0.01)	472/69 269 (0.68)	342 (0.56)	4 (0.01)	346/60 918 (0.57)	242 (0.50)	4 (0.01)	246/48 045 (0.51)
Aged 30-39 y	137 (0.55)	1 (<0.01)	138/24 931 (0.55)	117 (0.53)	1 (<0.01)	118/22 284 (0.53)	82 (0.50)	1 (0.01)	83/16 488 (0.50)
Subtotal	1655 (0.82)	62 (0.03)	1717/201 459 (0.85)	1152 (0.67)	36 (0.02)	1188/172 316 (0.69)	838 (0.61)	32 (0.02)	870/137 005 (0.64)
Women									
Aged 70-79 y	155 (1.14)	10 (0.07)	165/13 639 (1.21)	100 (0.98)	5 (0.05)	105/10 185 (1.03)	81 (0.98)	4 (0.05)	85/8281 (1.03)
Aged 60-69 y	378 (0.90)	11 (0.03)	389/41 897 (0.93)	244 (0.72)	10 (0.03)	254/34 069 (0.75)	192 (0.70)	8 (0.03)	200/27 253 (0.73)
Aged 50-59 y	386 (0.62)	10 (0.02)	396/61 932 (0.64)	282 (0.53)	8 (0.02)	290/52 838 (0.55)	201 (0.49)	6 (0.01)	207/41 167 (0.50)
Aged 40-49 y	212 (0.61)	4 (0.01)	216/35 013 (0.62)	153 (0.49)	3 (0.01)	156/31 008 (0.50)	93 (0.40)	1 (<0.01)	94/23 107 (0.41)
Aged 30-39 y	26 (0.50)	1 (0.02)	27/5226 (0.52)	20 (0.43)	1 (0.02)	21/4641 (0.45)	16 (0.46)	1 (0.03)	17/3441 (0.49)
Subtotal	1157 (0.73)	36 (0.02)	1193/157 707 (0.76)	799 (0.60)	27 (0.02)	826/132 741 (0.62)	583 (0.56)	20 (0.02)	603/103 249 (0.58)
Total	2812 (0.78)	98 (0.03)	2910/359 166 (0.81)	1951 (0.64)	63 (0.02)	2014/305 057 (0.66)	1421 (0.59)	52 (0.02)	1473/240 254 (0.61)
Intracerebral Bleeding									
Men									
Aged 70-79 y	20 (0.20)	10 (0.10)	30/10 244 (0.29)	14 (0.18)	5 (0.07)	19/7665 (0.25)	12 (0.19)	3 (0.05)	15/6383 (0.23)
Aged 60-69 y	55 (0.16)	18 (0.05)	73/34 613 (0.21)	44 (0.16)	10 (0.04)	54/28 020 (0.19)	37 (0.16)	8 (0.04)	45/22 814 (0.20)
Aged 50-59 y	70 (0.11)	26 (0.04)	96/62 402 (0.15)	59 (0.11)	17 (0.03)	76/53 429 (0.14)	52 (0.12)	13 (0.03)	65/43 275 (0.15)
Aged 40-49 y	29 (0.04)	21 (0.03)	50/69 269 (0.07)	27 (0.04)	17 (0.03)	44/60 918 (0.07)	20 (0.04)	15 (0.03)	35/48 045 (0.07)
Aged 30-39 y	15 (0.06)	4 (0.02)	19/24 931 (0.08)	11 (0.05)	4 (0.02)	15/22 284 (0.07)	9 (0.05)	3 (0.02)	12/16 488 (0.07)
Subtotal	189 (0.09)	79 (0.04)	268/201 459 (0.13)	155 (0.09)	53 (0.03)	208/172 316 (0.12)	130 (0.09)	42 (0.03)	172/137 005 (0.13)
Women									
Aged 70-79 y	27 (0.20)	24 (0.18)	51/13 639 (0.37)	20 (0.20)	17 (0.17)	37/10 185 (0.36)	18 (0.22)	12 (0.14)	30/8281 (0.36)
Aged 60-69 y	50 (0.12)	23 (0.05)	73/41 897 (0.17)	35 (0.10)	17 (0.05)	52/34 069 (0.15)	26 (0.10)	14 (0.05)	40/27 253 (0.15)
Aged 50-59 y	69 (0.11)	16 (0.03)	85/61 932 (0.14)	60 (0.11)	15 (0.03)	75/52 838 (0.14)	43 (0.10)	10 (0.02)	53/41 167 (0.13)
Aged 40-49 y	28 (0.08)	11 (0.03)	39/35 013 (0.11)	22 (0.07)	11 (0.04)	33/31 008 (0.11)	18 (0.08)	7 (0.03)	25/23 107 (0.11)
30-39 y	2 (0.04)	0	2/5226 (0.04)	2 (0.04)	0	2/4641 (0.04)	2 (0.06)	0	2/3441 (0.06)
Subtotal	176 (0.11)	74 (0.05)	250/157 707 (0.16)	139 (0.10)	60 (0.05)	199/132 741 (0.15)	107 (0.10)	43 (0.04)	150/103 249 (0.15)
Total	365 (0.10)	153 (0.04)	518/359 166 (0.14)	294 (0.10)	113 (0.04)	407/305 057 (0.13)	237 (0.10)	85 (0.04)	322/240 254 (0.13)

(continued)

Table 2. Patients Experiencing a First Bleeding Event by Bleeding Type, Sex, and Age Group in Each of the 3 Cohorts[a] (continued)

Bleeding Events	No. (%) of Patients								
	Baseline Cohort			Non-High-Risk Cohort			Nonmedication Cohort		
	Nonfatal[b]	Fatal[c]	Total	Nonfatal[b]	Fatal[c]	Total	Nonfatal[b]	Fatal[c]	Total
Other Bleeding[d]									
Men									
Aged 70-79 y	19 (0.19)	1 (0.01)	20/10 244 (0.20)	8 (0.10)	1 (0.01)	9/7665 (0.12)	7 (0.11)	0	7/6383 (0.11)
Aged 60-69 y	63 (0.18)	4 (0.01)	67/34 613 (0.19)	43 (0.15)	1 (<0.01)	44/28 020 (0.16)	32 (0.14)	1 (<0.01)	33/22 814 (0.14)
Aged 50-59 y	97 (0.16)	6 (0.01)	103/62 402 (0.17)	73 (0.14)	3 (0.01)	76/53 429 (0.14)	56 (0.13)	2 (<0.01)	58/43 275 (0.13)
Aged 40-49 y	73 (0.11)	4 (0.01)	77/69 269 (0.11)	48 (0.08)	3 (<0.01)	51/60 918 (0.08)	36 (0.07)	1 (<0.01)	37/48 045 (0.08)
Aged 30-39 y	18 (0.07)	0	18/24 931 (0.07)	17 (0.08)	0	17/22 284 (0.08)	14 (0.08)	0	14/16 488 (0.08)
Subtotal	270 (0.13)	15 (0.01)	285/201 459 (0.14)	189 (0.11)	8 (<0.01)	197/172 316 (0.11)	145 (0.11)	4 (<0.01)	149/137 005 (0.11)
Women									
Aged 70-79 y	38 (0.28)	0	38/13 639 (0.28)	20 (0.20)	0	20/10 185 (0.20)	17 (0.21)	0	17/8281 (0.21)
Aged 60-69 y	64 (0.15)	4 (0.01)	68/41 897 (0.16)	51 (0.15)	2 (0.01)	53/34 069 (0.16)	44 (0.16)	2 (0.01)	46/27 253 (0.17)
Aged 50-59 y	92 (0.15)	2 (<0.01)	94/61 932 (0.15)	68 (0.13)	2 (<0.01)	70/52 838 (0.13)	49 (0.12)	2 (<0.01)	51/41 167 (0.12)
Aged 40-49 y	56 (0.16)	2 (0.01)	58/35 013 (0.17)	41 (0.13)	2 (0.01)	43/31 008 (0.14)	26 (0.11)	2 (0.01)	28/23 107 (0.12)
Aged 30-39 y	5 (0.10)	0	5/5226 (0.10)	4 (0.09)	0	4/4641 (0.09)	4 (0.12)	0	4/3441 (0.12)
Subtotal	255 (0.16)	8 (0.01)	263/157 707 (0.17)	184 (0.14)	6 (<0.01)	190/132 741 (0.14)	140 (0.14)	6 (0.01)	146/103 249 (0.14)
Total	525 (0.15)	23 (0.01)	548/359 166 (0.15)	373 (0.12)	14 (<0.01)	387/305 057 (0.13)	285 (0.12)	10 (<0.01)	295/240 254 (0.12)
Any Bleeding									
Men									
Aged 70-79 y	192 (1.87)	23 (0.22)	215/10 244 (2.10)	113 (1.47)	10 (0.13)	123/7665 (1.60)	89 (1.39)	7 (0.11)	96/6383 (1.50)
Aged 60-69 y	498 (1.44)	43 (0.12)	541/34 613 (1.56)	330 (1.18)	25 (0.09)	355/28 020 (1.27)	252 (1.10)	21 (0.09)	273/22 814 (1.20)
Aged 50-59 y	689 (1.10)	51 (0.08)	740/62 402 (1.19)	491 (0.92)	33 (0.06)	524/53 429 (0.98)	369 (0.85)	26 (0.06)	395/43 275 (0.91)
Aged 40-49 y	565 (0.82)	34 (0.05)	599/69 269 (0.86)	417 (0.68)	24 (0.04)	441/60 918 (0.72)	298 (0.62)	20 (0.04)	318/48 045 (0.66)
Aged 30-39 y	170 (0.68)	5 (0.02)	175/24 931 (0.70)	145 (0.65)	5 (0.02)	150/22 284 (0.67)	105 (0.64)	4 (0.02)	109/16 488 (0.66)
Subtotal	2114 (1.05)	156 (0.08)	2270/201 459 (1.13)	1496 (0.87)	97 (0.06)	1593/172 316 (0.92)	1113 (0.81)	78 (0.06)	1191/137 005 (0.87)
Women									
Aged 70-79 y	220 (1.61)	34 (0.25)	254/13 639 (1.86)	140 (1.37)	22 (0.22)	162/10 185 (1.59)	116 (1.40)	16 (0.19)	132/8281 (1.59)
Aged 60-69 y	492 (1.17)	38 (0.09)	530/41 897 (1.27)	330 (0.97)	29 (0.09)	359/34 069 (1.05)	262 (0.96)	24 (0.09)	286/27 253 (1.05)
Aged 50-59 y	547 (0.88)	28 (0.05)	575/61 932 (0.93)	410 (0.78)	25 (0.05)	435/52 838 (0.82)	293 (0.71)	18 (0.04)	311/41 167 (0.76)
40-49 y	296 (0.85)	17 (0.05)	313/35 013 (0.89)	216 (0.70)	16 (0.05)	232/31 008 (0.75)	137 (0.59)	10 (0.04)	147/23 107 (0.64)
Aged 30-39 y	33 (0.63)	1 (0.02)	34/5226 (0.65)	26 (0.56)	1 (0.02)	27/4641 (0.58)	22 (0.64)	1 (0.03)	23/3441 (0.67)
Subtotal	1588 (1.01)	118 (0.07)	1706/157 707 (1.08)	1122 (0.85)	93 (0.07)	1215/132 741 (0.92)	830 (0.80)	69 (0.07)	899/103 249 (0.87)
Total	3702 (1.03)	274 (0.08)	3976/359 166 (1.11)	2618 (0.86)	190 (0.06)	2808/305 057 (0.92)	1943 (0.81)	147 (0.06)	2090/240 254 (0.87)

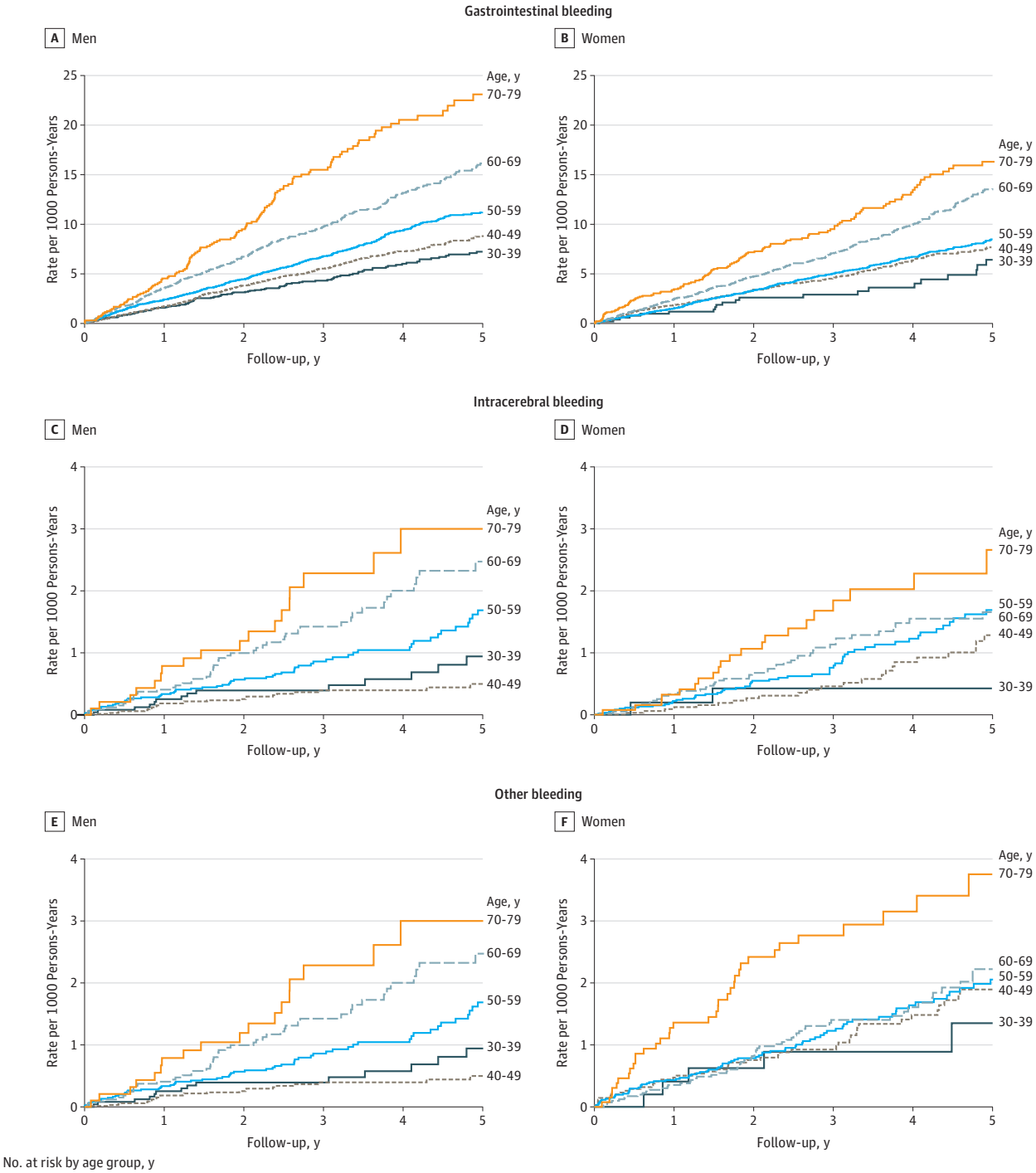
[a] See Methods section of text for descriptions of baseline, non–high-risk, and nonmedication cohorts.

[b] People who did not die within 28 days of a hospital admission associated with a major bleeding event were classified as having had a nonfatal bleeding event.

[c] People who died within 28 days of a hospital admission associated with a major bleeding event were classified as having had a fatal bleeding event.

[d] Other bleeding included respiratory (including epistaxis and hemoptysis), ocular (vitreous and retinal), bleeding into a joint, and bleeding into the pericardium or peritoneum.

Figure. Rates Per 1000 Person-Years of First Nonfatal Major Bleeding Events by Bleeding Type, Sex, and Age Group



No. at risk by age group, y

30-39	24931	22573	17396	11796	9235	7074	5226	4723	3895	3026	2443	1898
40-49	69269	62871	49307	31851	23746	17193	35013	31601	25090	17833	13701	10325
50-59	62402	56430	46268	29432	20973	14639	61932	55503	43959	28308	20267	14346
60-69	34613	29803	24192	15017	10039	6569	41897	37690	31625	20205	13908	9122
70-79	10244	8336	6602	3962	2547	1555	13639	11698	9603	5975	3970	2549

Median follow-up time: men aged 30 to 39 years, 2.8 (interquartile range [IQR], 1.7-5.4) years; men aged 40-49 years, 2.8 (IQR, 1.8-5.0) years; men aged 50 to 59 years, 2.8 (IQR, 1.9-4.8) years; men aged 60 to 69 years, 2.7 (IQR, 1.7-4.3) years; men aged 70 to 79 years, 2.6 (IQR, 1.5-4.0) years; women aged 30 to 39 years, 3.7 (IQR, 2.0-6.4) years; women aged 40 to 49 years, 3.1 (IQR, 1.8-5.5) years; women aged 50 to 59 years, 2.8 (IQR, 1.8-4.7) years; women aged 60 to 69 years, 2.9 (IQR, 2.0-4.6) years; women aged 70 to 79 years, 2.7 (IQR, 1.7-4.3) years.

Table 3. Rates Per 1000 Person-Years of Nonfatal First Bleeding Event by Type, Sex, and Age Group for Each of the 3 Cohorts[a]

	Baseline Cohort		Non-High-Risk Cohort		Nonmedication Cohort	
Bleeding Events	Person-Years, No.	Rate (95% CI)	Person-Years, No.	Rate (95% CI)	Person-Years, No.	Rate (95% CI)
Gastrointestinal Bleeding						
Men						
Aged 70-79 y	29 835	5.13 (4.32-5.94)	22 741	4.00 (3.18-4.82)	19 192	3.65 (2.79-4.50)
Aged 60-69 y	112 189	3.39 (3.05-3.73)	92 188	2.64 (2.30-2.97)	76 179	2.40 (2.05-2.75)
Aged 50-59 y	224 014	2.33 (2.13-2.53)	193 684	1.85 (1.66-2.05)	159 054	1.64 (1.44-1.84)
Aged 40-49 y	252 575	1.83 (1.67-2.00)	223 802	1.53 (1.37-1.69)	179 601	1.35 (1.18-1.52)
Aged 30-39 y	95 015	1.44 (1.20-1.68)	85 611	1.37 (1.12-1.61)	65 463	1.25 (0.98-1.52)
Subtotal	713 628	2.32 (2.21-2.43)	618 026	1.86 (1.76-1.97)	499 489	1.68 (1.56-1.79)
Women						
Aged 70-79 y	43 990	3.52 (2.97-4.08)	33 308	3.00 (2.41-3.59)	27 573	2.94 (2.30-3.58)
Aged 60-69 y	147 086	2.57 (2.31-2.83)	120 763	2.02 (1.77-2.27)	97 880	1.96 (1.68-2.24)
Aged 50-59 y	219 208	1.76 (1.59-1.94)	188 872	1.49 (1.32-1.67)	150 264	1.34 (1.15-1.52)
Aged 40-49 y	135 163	1.57 (1.36-1.78)	120 931	1.27 (1.06-1.47)	92 541	1.00 (0.80-1.21)
Aged 30-39 y	22 820	1.14 (0.70-1.58)	20 518	0.97 (0.55-1.40)	16 154	0.99 (0.51-1.48)
Subtotal	568 267	2.04 (1.92-2.15)	484 392	1.65 (1.54-1.76	384 412	1.52 (1.39-1.64)
Total	1 281 895	2.19 (2.11-2.27)	1 102 418	1.77 (1.69-1.85)	883 901	1.61 (1.52-1.69)
Intracerebral Bleeding						
Men						
Aged 70-79 y	29 835	0.67 (0.38-0.96)	22 741	0.62 (0.29-0.94)	19 192	0.63 (0.27-0.98)
Aged 60-69 y	112 189	0.49 (0.36-0.62)	92 188	0.48 (0.34-0.62)	76 179	0.49 (0.33-0.64)
Aged 50-59 y	224 014	0.31 (0.24-0.39)	193 684	0.30 (0.23-0.38)	159 054	0.33 (0.24-0.42)
Aged 40-49 y	252 575	0.11 (0.07-0.16)	223 802	0.12 (0.08-0.17)	179 601	0.11 (0.06-0.16)
Aged 30-39 y	95 015	0.16 (0.08-0.24)	85 611	0.13 (0.05-0.20)	65 463	0.14 (0.05-0.23)
Subtotal	713 628	0.26 (0.23-0.30)	618 026	0.25 (0.21-0.29)	499 489	0.26 (0.22-0.31)
Women						
Aged 70-79 y	43 990	0.61 (0.38-0.85)	33 308	0.60 (0.34-0.86)	27 573	0.65 (0.35-0.95)
Aged 60-69 y	147 086	0.34 (0.25-0.43)	12 763	0.29 (0.19-0.39)	97 880	0.27 (0.16-0.37)
Aged 50-59 y	219 208	0.31 (0.24-0.39)	188 872	0.32 (0.24-0.40)	150 264	0.29 (0.20-0.37)
Aged 40-49 y	135 163	0.21 (0.13-0.28)	120 931	0.18 (0.11-0.26)	92 541	0.19 (0.10-0.28)
Aged 30-39 y	22 820	0.09 (−0.03 to 0.21)	20 518	0.10 (−0.04 to 0.23)	16 154	0.12 (−0.05 to 0.30)
Subtotal	568 267	0.31 (0.26-0.36)	484 392	0.29 (0.24-0.33)	384 412	0.28 (0.23-0.33)
Total	1 281 895	0.28 (0.26-0.31)	1 102 418	0.27 (0.24-0.30)	883 901	0.27 (0.23-0.30)
Other Bleeding						
Men						
Aged 70-79 y	29 835	0.64 (0.35-0.92)	22 741	0.35 (0.11-0.60)	19 192	0.36 (0.09-0.63)
Aged 60-69 y	112 189	0.56 (0.42-0.70)	92 188	0.47 (0.33-0.61)	76 179	0.42 (0.27-0.57)
Aged 50-59 y	224 014	0.43 (0.35-0.52)	193 684	0.38 (0.29-0.46)	159 054	0.35 (0.26-0.44)
Aged 40-49 y	252 575	0.29 (0.22-0.36)	223 802	0.21 (0.15-0.28)	179 601	0.20 (0.13-0.27)
Aged 30-39 y	95 015	0.19 (0.10-0.28)	85 611	0.20 (0.10-0.29)	65 463	0.21 (0.10-0.33)
Subtotal	713 628	0.38 (0.33-0.42)	618 026	0.31 (0.26-0.35)	499 489	0.29 (0.24-0.34)
Women						
Aged 70-79 y	43 990	0.86 (0.59-1.14)	33 308	0.60 (0.34-0.86)	27 573	0.62 (0.32-0.91)
Aged 60-69 y	147 086	0.44 (0.33-0.54)	120 763	0.42 (0.31-0.54)	97 880	0.45 (0.32-0.58)
Aged 50-59 y	219 208	0.42 (0.33-0.51)	188 872	0.36 (0.27-0.45)	150 264	0.33 (0.23-0.42)
Aged 40-49 y	135 163	0.41 (0.31-0.52)	120 931	0.34 (0.24-0.44)	92 541	0.28 (0.17-0.39)
Aged 30-39 y	22 820	0.22 (0.03-0.41)	20 518	0.19 (0.00-0.39)	16 154	0.25 (0.00-0.49)
Subtotal	568 267	0.45 (0.39-0.50)	484 392	0.38 (0.32-0.43)	384 412	0.36 (0.30-0.42)
Total	1 281 895	0.41 (0.37-0.44)	1 102 418	0.34 (0.30-0.37)	883 901	0.32 (0.29-0.36)

(continued)

Table 3. Rates Per 1000 Person-Years of Nonfatal First Bleeding Event by Type, Sex, and Age Group for Each of the 3 Cohorts[a] (continued)

	Baseline Cohort		Non-High-Risk Cohort		Nonmedication Cohort	
Bleeding Events	Person-Years, No.	Rate (95% CI)	Person-Years, No.	Rate (95% CI)	Person-Years, No.	Rate (95% CI)
Any Bleeding						
Men						
Aged 70-79 y	29 835	6.44 (5.53-7.34)	22 741	4.97 (4.06-5.88)	19 192	4.64 (3.68-5.60)
Aged 60-69 y	112 189	4.44 (4.05-4.83)	92 188	3.58 (3.19-3.97)	76 179	3.31 (2.90-3.72)
Aged 50-59 y	224 014	3.08 (2.85-3.31)	193 684	2.54 (2.31-2.76)	159 054	2.32 (2.08-2.56)
Aged 40-49 y	252 575	2.24 (2.05-2.42)	223 802	1.86 (1.68-2.04)	179 601	1.66 (1.47-1.85)
Aged 30-39 y	95 015	1.79 (1.52-2.06)	85 611	1.69 (1.42-1.97)	65 463	1.60 (1.30-1.91)
Subtotal	713 628	2.96 (2.84-3.09)	618 026	2.42 (2.30-2.54)	499 489	2.23 (2.10-2.36)
Women						
Aged 70-79 y	43 990	5.00 (4.34-5.66)	33 308	4.20 (3.51-4.90)	27 573	4.21 (3.44-4.97)
Aged 60-69 y	147 086	3.34 (3.05-3.64)	120 763	2.73 (2.44-3.03)	97 880	2.68 (2.35-3.00)
Aged 50-59 y	219 208	2.50 (2.29-2.70)	188 872	2.17 (1.96-2.38)	150 264	1.95 (1.73-2.17)
Aged 40-49 y	135 163	2.19 (1.94-2.44)	120 931	1.79 (1.55-2.02)	92 541	1.48 (1.23-1.73)
Aged 30-39 y	22 820	1.45 (0.95-1.94)	20 518	1.27 (0.78-1.75)	16 154	1.36 (0.79-1.93)
Subtotal	568 267	2.79 (2.66-2.93)	484 392	2.32 (2.18-2.45)	384 412	2.16 (2.01-2.31)
Total	1 281 895	2.89 (2.80-2.98)	1 102 418	2.37 (2.28-2.47)	883 901	2.20 (2.10-2.30)

[a] People who did not die within 28 days of a hospital admission associated with a major bleeding event were classified as having had a nonfatal bleeding event. See Methods section of text for descriptions of baseline, non–high-risk, and nonmedication cohorts.

0.04 (95% CI, −0.04 to 0.13) among ages 30 to 39 years to 0.23 (95% CI, 0.09-0.37) among ages 70 to 79 years (eTable 6). The point estimates for the risk of fatal GI bleeding were predominantly lower in the non–high-risk cohort and the nonmedication cohort compared with the baseline cohort within each sex and age group stratum, but the number of fatal GI bleeding events within each stratum was low.

In the baseline cohort, case fatality associated with GI bleeding ranged from 0.7% (95% CI, 0.1%-4.0%) among ages 30 to 39 years to 7.3% (95% CI, 4.2%-8.1%) among ages 70 to 79 years in men and from 3.7% (95% CI, 0.7%-18.3%) among ages 30 to 39 years to 6.1% (95% CI, 3.3%-10.8%) among ages 70 to 79 years in women (**Table 4**). The case fatality for intracerebral bleeding was much higher (29.5%; 95% CI, 25.8%-33.6%) than for GI bleeding (3.4%; 95% CI, 2.8%-4.1%) or for other types of bleeding (4.2%; 95% CI, 2.8%-6.2%). Similar patterns were observed in the non–high-risk and nonmedication cohorts. Case fatality for all bleeding events was similar across the 3 cohorts (baseline: 6.9% [95% CI, 5.9%-8.0%]; non–high-risk: 6.1% [95% CI, 5.0%-7.4%]; nonmedication: 6.5% [95% CI, 5.3%-8.1%]).

In analyses retaining persons who initiated medication use during follow-up, nonfatal bleeding event rates were similar to or higher than those in the main analysis across bleeding type, sex, and age group (eFigure in the Supplement).

Discussion

The risk of a nonfatal GI bleeding event and case fatality associated with GI bleeding among people without CVD who were not receiving antiplatelet therapy were both higher in this study compared with estimates derived by the USPSTF for their recommendations on use of aspirin for primary prevention of CVD and colorectal cancer[9,10] (**Table 5**). The difference in nonfatal GI bleeding risk was evident across all age groups in both men and women and was most marked in people aged 40 to 49 years, although it was attenuated after exclusion of people with conditions and those who were taking additional medication that increased the risk of bleeding (nonmedication cohort, in alignment with the recommendations of the USPSTF). The higher case fatality associated with GI bleeding in this study compared with that derived by the USPSTF was evident across all age groups in both men and women and was not attenuated in the nonmedication cohort.

If data from this study were used, the net benefit of aspirin for primary prevention would be lower than that estimated by the USPSTF. The magnitude of the reduction in net benefit of aspirin, and hence the likely effect on current USPSTF recommendations, is difficult to predict without updating the simulation modeling using these inputs for both GI bleeding risk and case fatality. As noted by the USPSTF, there is a paucity of data on absolute bleeding risk from community cohorts,[2] and this is the first large-scale study that, to our knowledge, has directly measured the risk of major bleeding by sex and age group in a contemporary community cohort of people without CVD and not receiving antiplatelet therapy.

The USPSTF simulation model estimated that the net lifetime quality-adjusted life-years (QALYs) gained from taking aspirin among 10 000 persons with a 10-year CVD risk of at least 10% was 588 for men (using a GI bleeding risk of 1.2 per 1000 person-years) and 621 for women (GI bleeding risk of 0.7 per 1000 person-years) aged 50 to 59 years (grade B recommendation) and 180 for men (GI bleeding risk of 2.1 per 1000 person-years) and 284 for women (GI bleeding risk of 1.3 per 1000 person-years) aged 60 to 69 years (grade C recommendation).[9]

Table 4. Case Fatality of First Bleeding Event by Bleeding Type, Sex, and Age Group for Each of the 3 Cohorts[a]

Bleeding Events	Baseline Cohort		Non-High-Risk Cohort		Nonmedication Cohort	
	No. With Fatal Event/Total No. of Events	Case Fatality, % (95% CI)	No. With Fatal Event/Total No. of Events	Case Fatality, % (95% CI)	No. With Fatal Event/Total No. of Events	Case Fatality, % (95% CI)
Gastrointestinal Bleeding						
Men						
Aged 70-79 y	12/165	7.3 (4.2-12.3)	4/95	4.2 (1.6-10.3)	4/74	5.4 (2.1-13.1)
Aged 60-69 y	21/401	5.2 (3.5-7.9)	14/257	5.4 (3.3-8.9)	12/195	6.2 (3.6-10.4)
Aged 50-59 y	19/541	3.5 (2.3-5.4)	13/372	3.5 (2.1-5.9)	11/272	4.0 (2.3-7.1)
Aged 40-49 y	9/472	1.9 (1.0-3.6)	4/346	1.2 (0.5-2.9)	4/246	1.6 (0.6-4.1)
Aged 30-39 y	1/138	0.7 (0.1-4.0)	1/118	0.8 (0.1-4.6)	1/83	1.2 (0.2-6.5)
Subtotal	62/1717	3.6 (2.8-4.6)	36/1188	3.0 (2.2-4.2)	32/870	3.7 (2.6-5.1)
Women						
Aged 70-79 y	10/165	6.1 (3.3-10.8)	5/105	4.8 (2.1-10.7)	4/85	4.7 (1.8-11.5)
Aged 60-69 y	11/389	2.8 (1.6-5.0)	10/254	3.9 (2.2-7.1)	8/200	4.0 (2.0-7.7)
Aged 50-59 y	10/396	2.5 (1.4-4.6)	8/290	2.8 (1.4-5.3)	6/207	2.9 (1.3-6.2)
Aged 40-49 y	4/216	1.9 (0.7-4.7)	3/156	1.9 (0.7-5.5)	1/94	1.1 (0.2-5.8)
Aged 30-39 y	1/27	3.7 (0.7-18.3)	1/27	3.7 (0.7-18.3)	1/17	5.9 (1.0-27.0)
Subtotal	36/1193	3.0 (2.2-4.1)	27/832	3.2 (2.2-4.7)	20/603	3.3 (2.2-5.1)
Total	98/2910	3.4 (2.8-4.1)	63/1559	4.0 (3.2-5.1)	52/1121	4.6 (3.6-6.0)
Intracerebral Bleeding						
Men						
Aged 70-79 y	10/30	33.3 (19.2-51.2)	5/19	26.3 (11.8-48.8)	3/15	20.0 (7.0-45.2)
Aged 60-69 y	18/73	24.7 (16.2-35.6)	10/54	18.5 (10.4-30.8)	8/45	17.8 (9.3-31.3)
Aged 50-59 y	26/96	27.1 (19.2-36.7)	17/76	22.4 (14.5-32.9)	13/65	20.0 (12.1-31.3)
Aged 40-49 y	21/50	42.0 (29.4-55.8)	17/44	38.6 (25.7-53.4)	15/35	42.9 (28.0-59.1)
Aged 30-39 y	4/19	21.1 (8.5-43.3)	4/15	26.7 (10.9-52.0)	3/12	25.0 (8.9-53.2)
Subtotal	79/268	29.5 (24.3-35.2)	53/208	25.5 (20.0-31.8)	42/172	24.4 (18.6-31.4)
Women						
Aged 70-79 y	24/51	47.1 (34.1-60.5)	17/37	45.9 (31.0-61.6)	12/30	40.0 (24.6-57.7)
Aged 60-69 y	23/73	31.5 (22.0-42.9)	17/52	32.7 (21.5-46.2)	14/40	35.0 (22.1-50.5)
Aged 50-59 y	16/85	18.8 (11.9-28.4)	15/75	20.0 (12.5-30.4)	10/53	18.9 (10.6-31.4)
Aged 40-49 y	11/39	28.2 (16.5-43.8)	11/33	33.3 (19.8-50.4)	7/25	28.0 (14.3-47.6)
Aged 30-39 y	0/2	0.0 (0.0-65.8)	0/2	0.0 (0.0-65.8)	0/2	0.0 (0.0-65.8)
Subtotal	74/250	29.6 (24.3-35.5)	60/199	30.2 (24.2-36.9)	43/150	28.7 (22.0-36.4)
Total	153/518	29.5 (25.8-33.6)	113/361	31.3 (26.7-36.3)	85/270	31.5 (26.2-37.2)
Other Bleeding						
Men						
Aged 70-79 y	1/20	5.0 (0.9-23.6)	1/9	11.1 (2.0-43.5)	0/7	0.0 (0.0-35.4)
Aged 60-69 y	4/67	6.0 (2.3-14.4)	1/44	2.3 (0.4-11.8)	1/33	3.0 (0.5-15.3)
Aged 50-59 y	6/103	5.8 (2.7-12.1)	3/76	3.9 (1.4-11.0)	2/58	3.4 (1.0-11.7)
Aged 40-49 y	4/77	5.2 (2.0-12.6)	3/51	5.9 (2.0-15.9)	1/37	2.7 (0.5-13.8)
Aged 30-39 y	0/18	0.0 (0.0-17.6)	0/17	0.0 (0.0-18.4)	0/14	0.0 (0.0-21.5)
Subtotal	15/285	5.3 (3.2-8.5)	8/197	4.1 (2.1-7.8)	4/149	2.7 (1.0-6.7)
Women						
Aged 70-79 y	0/38	0.0 (0.0-9.2)	0/20	0.0 (0.0-16.1)	0/17	0.0 (0.0-18.4)
Aged 60-69 y	4/68	5.9 (2.3-14.2)	2/53	3.8 (1.0-12.8)	2/46	4.3 (1.2-14.5)
Aged 50-59 y	2/94	2.1 (0.6-7.4)	2/70	2.9 (0.8-9.8)	2/51	3.9 (1.1-13.2)
Aged 40-49 y	2/58	3.4 (1.0-11.7)	2/43	4.7 (1.3-15.5)	2/28	7.1 (2.0-22.6)
Aged 30-39 y	0/5	0.0 (0.0-43.4)	0/4	0.0 (0.0-49.0)	0/4	0.0 (0.0-49.0)
Subtotal	8/263	3.0 (1.5-5.9)	6/190	3.2 (1.5-6.7)	6/146	4.1 (1.9-8.7)
Total	23/548	4.2 (2.8-6.2)	14/360	3.9 (2.3-6.4)	10/275	3.6 (2.0-6.6)

(continued)

Table 4. Case Fatality of First Bleeding Event by Bleeding Type, Sex, and Age Group for Each of the 3 Cohorts[a] (continued)

Bleeding Events	Baseline Cohort		Non-High-Risk Cohort		Nonmedication Cohort	
	No. With Fatal Event/Total No. of Events	Case Fatality, % (95% CI)	No. With Fatal Event/Total No. of Events	Case Fatality, % (95% CI)	No. With Fatal Event/Total No. of Events	Case Fatality, % (95% CI)
Any Bleeding						
Men						
Aged 70-79 y	23/215	10.7 (7.2-15.5)	10/123	8.1 (4.5-14.3)	7/96	7.3 (3.6-14.3)
Aged 60-69 y	43/541	7.9 (6.0-10.5)	25/355	7.0 (4.8-10.2)	21/273	7.7 (5.1-11.5)
Aged 50-59 y	51/740	6.9 (5.3-8.9)	33/524	6.3 (4.5-8.7)	26/395	6.6 (4.5-9.5)
Aged 40-49 y	34/599	5.7 (4.1-7.8)	24/441	5.4 (3.7-8.0)	20/318	6.3 (4.1-9.5)
Aged 30-39 y	5/175	2.9 (1.2-6.5)	5/150	3.3 (1.4-7.6)	4/109	3.7 (1.4-9.1)
Subtotal	156/2270	6.9 (5.9-8.0)	97/1593	6.1 (5.0-7.4)	78/1191	6.5 (5.3-8.1)
Women						
Aged 70-79 y	34/254	13.4 (9.7-18.1)	22/162	13.6 (9.1-19.7)	16/132	12.1 (7.6-18.8)
Aged 60-69 y	38/530	7.2 (5.3-9.7)	29/359	8.1 (5.7-11.4)	24/286	8.4 (5.7-12.2)
Aged 50-59 y	28/575	4.9 (3.4-6.9)	25/435	5.7 (3.9-8.3)	18/311	5.8 (3.7-9.0)
Aged 40-49 y	17/313	5.4 (3.4-8.5)	16/232	6.9 (4.3-10.9)	10/147	6.8 (3.7-12.1)
Aged 30-39 y	1/34	2.9 (0.5-14.9)	1/27	3.7 (0.7-18.3)	1/23	4.3 (0.8-21.0)
Subtotal	118/1706	6.9 (5.8-8.2)	93/1215	7.7 (6.3-9.3)	69/899	7.7 (6.1-9.6)
Total	274/3976	6.9 (6.1-7.7)	190/2268	8.4 (7.3-9.6)	147/1666	8.8 (7.6-10.3)

[a] See Methods section of text for descriptions of baseline, non–high-risk, and nonmedication cohorts.

Table 5. Comparison of Gastrointestinal Bleeding Events in the Current Study With Estimates Used by the US Preventive Services Task Force (USPSTF)[a]

	Current Study, Estimate (95% CI)			USPSTF[10] Estimate for Modeling, Base Case (Sensitivity Value)
	Baseline Cohort	Non-High-Risk Cohort	Nonmedication Cohort	
No. of nonfatal bleeding events per 1000 person-years[b]				
Men				
Aged 70-79 y	5.13 (4.32-5.94)	4.00 (3.18-4.82)	3.65 (2.79-4.50)	3.9 (7.8)
Aged 60-69 y	3.39 (3.05-3.73)	2.64 (2.30-2.97)	2.40 (2.05-2.75)	2.1 (4.2)
Aged 50-59 y	2.33 (2.13-2.53)	1.85 (1.66-2.05)	1.64 (1.44-1.84)	1.2 (2.4)
Aged 40-49 y	1.83 (1.67-2.00)	1.53 (1.37-1.69)	1.35 (1.18-1.52)	0.5 (1.0)
Women				
Aged 70-79 y	3.52 (2.97-4.08)	3.00 (2.41-3.59)	2.94 (2.30-3.58)	2.3 (4.6)
Aged 60-69 y	2.57 (2.31-2.83)	2.02 (1.77-2.27)	1.96 (1.68-2.24)	1.3 (2.6)
Aged 50-59 y	1.76 (1.59-1.94)	1.49 (1.32-1.67)	1.34 (1.15-1.52)	0.7 (1.4)
Aged 40-49 y	1.57 (1.36-1.78)	1.27 (1.06-1.47)	1.00 (0.80-1.21)	0.3 (0.6)
Case fatality, %[c]				
Men				
Aged 60-79 y	5.8 (4.2-8.1)	5.1 (3.3-7.9)	5.9 (3.7-9.4)	3 (0-1.5)
Aged 40-59 y	2.8 (1.9-4.0)	2.4 (1.5-3.8)	2.9 (1.8-4.7)	1 (0-0.5)
Women				
Aged 60-79 y	3.8 (2.5-5.7)	4.2 (2.5-6.8)	4.2 (2.4-7.2)	3 (0-1.5)
Aged 40-59 y	2.3 (1.4-3.8)	2.5 (1.4-4.4)	2.3 (1.1-4.7)	1 (0-0.5)

[a] See Methods section of text for descriptions of baseline, non–high-risk, and nonmedication cohorts.

[b] USPSTF estimate based on De Berardis et al.[11]

[c] USPSTF estimate based on Rockall et al.[12]

Sensitivity analyses conducted by the USPSTF, which doubled base-case GI bleeding risks, suggested that the net lifetime QALYs gained from taking aspirin among 10 000 persons with a 10-year CVD risk of at least 10% was reduced to 426 for men (using a GI bleeding risk of 2.4 per 1000 person-years) and 468 for women (GI bleeding risk of 1.4 per 1000 person-years) aged 50 to 59 years and to −22 (a net loss) for men (GI bleeding risk of 4.2 per 1000 person-years) and 102 for women (GI bleeding risk of 2.6 per 1000 person-years) aged 60 to 69 years.[9,10] This is because given that the proportional increase in the risk of bleeding with aspirin is consistent across subgroups,[4] the higher the baseline bleeding risk, the higher the absolute bleeding risk associated with aspirin. These sensitivity analyses included GI bleeding risks in the range of those

identified by the nonmedication cohort of the present study (among ages 50-59 years, 1.64 [95% CI, 1.44-1.84] per 1000 person-years for men and 1.34 95% CI, 1.15-1.52] per 1000 person-years for women; among ages 60-69 years, 2.40 95% CI, 2.05-2.75] for men and 1.96 [95% CI, 1.68-2.24] for women). Gastrointestinal case fatality was halved or assumed to be zero in USPSTF sensitivity analyses, whereas in this study, case fatality approximately doubled. Although it is likely that there is still a net benefit (albeit smaller) of aspirin for people aged 50 to 59 years, this is less certain for people aged 60 to 69 years, particularly men. Hence, these findings do not necessarily invalidate the USPSTF recommendations.

The USPSTF estimate of the proportional effect of aspirin on GI bleeding risk (odds ratio, 1.59; 95% CI, 1.32-1.91)[2] was based on a meta-analysis of randomized clinical trials, which may also benefit from updating once the results of upcoming randomized clinical trials comparing aspirin with control for primary prevention, such as ARRIVE (clinicaltrials.gov identifier: NCT00501059), are fully reported. If the proportional effect of aspirin on GI bleeding risk is different from that observed in previous trials, this could change the net lifetime QALYs gained from taking aspirin in either direction.

Participants were recruited when their CVD risk was assessed using PREDICT software, which facilitates accurate and nearly complete data collection for variables required in New Zealand's CVD risk equation.[15,26] Encrypted linkage (using the National Health Index, a unique identifier available for >98% of New Zealanders[15]) to national health data sets enabled almost complete ascertainment of deaths, hospitalizations, and dispensing of government-subsidized medications. For example, more than 98% of cases of acute CVD events in New Zealand are managed by public health services and are hence available through the national hospitalization data set.[15] Bleeding-associated deaths were captured in this study, including deaths in which bleeding was the underlying cause of death and hospitalizations associated with major bleeding events in which the patients died within 28 days of admission. This approach provides a more sensitive definition of fatal bleeding events than solely relying on hospitalization data, which is clinically appropriate given that the purpose of the data from this study are to inform an assessment of the balance of benefits and harms of aspirin.

Cardiovascular disease prevention guidelines need to be based on robust baseline absolute rates of both CVD and bleeding events, as these rates are the main determinants of the magnitude of the benefits and harms of aspirin for primary prevention.[4] While this study excluded people with medical conditions or who were taking medications that increased their risk of bleeding, the Antithrombotic Trialists' Collaboration individual participant data meta-analysis of primary prevention trials found that a number of independent risk factors for CVD were also independent risk factors for major bleeding: age, sex, diabetes status, smoking status, blood pressure, and body mass index.[4] The assumption that absolute bleeding risk remains approximately constant irrespective of absolute CVD risk is therefore unlikely to be appropriate.[4] This study presents age- and sex-specific data, which could support the development of population-level guidelines. However, validated risk algorithms are required to take into account multiple risk factors at the same time, as with CVD itself, among people without CVD, to optimize the individualized assessment of the balance of absolute benefits and harms of aspirin for primary prevention of CVD.

Limitations

This study has several limitations. First, unlike other CVD medications, aspirin is available over the counter and without a prescription. However, there is some evidence that aspirin use can be assessed reasonably accurately from dispensing data in New Zealand (probably because it is less costly by prescription than over the counter),[27] and dispensing data were supplemented with data collected during CVD risk assessment. Second, although the cohort is largely representative of New Zealanders eligible for CVD risk assessment,[17] the study was restricted to primary care practices with PREDICT software and assessment. Third, this study relied on coded hospitalization data to identify bleeding events, which were found to miss 37% of people with bleeding in the Oxford Vascular Study.[28] Although it is likely that some major bleed events were missed in this cohort because of reliance on coded data, the primary purpose of the bleeding rate data in this study are to provide a basis of comparison with estimated CVD rates, which are often themselves based on coded data (eg, SCORE[7]).

Conclusions

In a population not receiving antiplatelet therapy, the annual risk of major bleeding events and nonfatal major bleeding was estimated. These findings could inform population-level guidelines for primary prevention of cardiovascular disease.

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Acquisition, analysis, or interpretation of data: Selak, Kerr, Poppe, Wu, Grey, Jackson, Wells.
Drafting of the manuscript: Selak, Kerr, Jackson.
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Statistical analysis: Selak, Kerr.
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