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Rivaroxaban Is Associated With Higher Rates of Gastrointestinal Bleeding Than Other Direct Oral Anticoagulants

A Nationwide Propensity Score–Weighted Study

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Background: Gastrointestinal bleeding (GIB) rates for direct oral anticoagulants (DOACs) and warfarin have been extensively compared. However, population-based studies comparing GIB rates among different DOACs are limited.

Objective: To compare rates of GIB among apixaban, dabigatran, and rivaroxaban.

Design: Nationwide population-based cohort study.

Setting: Landspítali–The National University Hospital of Iceland and the 4 regional hospitals in Iceland.

Patients: New users of apixaban, dabigatran, and rivaroxaban from 2014 to 2019.

Measurements: Rates of GIB were compared using inverse probability weighting, Kaplan–Meier survival estimates, and Cox regression.

Results: In total, 2157 patients receiving apixaban, 494 patients receiving dabigatran, and 3217 patients receiving rivaroxaban were compared. For all patients, rivaroxaban had higher overall rates of GIB (3.2 vs. 2.5 events per 100 person-years; hazard ratio [HR], 1.42 [95% CI, 1.04 to 1.93]) and major GIB (1.9 vs. 1.4 events per 100 person-years; HR, 1.50 [CI, 1.00 to 2.24]) compared with apixaban. Rivaroxaban also had higher GIB rates than dabigatran, with similar point estimates, although the CIs were wider and included the possibility of a null effect. When only patients with atrial fibrillation were included, rivaroxaban was associated with higher rates of overall GIB than apixaban (HR, 1.40 [CI, 1.01 to 1.94]) or dabigatran (HR, 2.04 [CI, 1.17 to 3.55]). Dabigatran was associated with lower rates of upper GIB than rivaroxaban in both analyses.

Limitations: Unmeasured confounding and small subgroup analyses.

Conclusion: Rivaroxaban was associated with higher GIB rates than apixaban and dabigatran regardless of treatment indication.

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Gastrointestinal bleeding (GIB) is a common and potentially life-threatening adverse effect of oral anticoagulation (1). Initial, phase 3, randomized controlled trials demonstrated that warfarin was associated with lower rates of major GIB than rivaroxaban and high-dose dabigatran and edoxaban, whereas major GIB rates were similar compared with apixaban (2–5). Meta-analysis of these studies demonstrated higher GIB rates for direct oral anticoagulants (DOACs) compared with warfarin but lower rates of intracranial hemorrhage and all-cause mortality (6). However, results from real-world studies have been conflicting (7–12). Importantly, no randomized controlled trial has made direct comparisons of GIB rates between DOACs. Previous population-based studies have suggested that rivaroxaban has higher GIB rates than other DOACs (13–18). However, these studies have been based on information from administrative databases, which has an inherent risk for selection bias because of variables including insurance status, age, and comorbidities. Most such studies have been limited to patients with atrial fibrillation (AF) (13–16, 19, 20), with few studies comparing the risk for GIB between DOACs using a wider population (17, 18, 21). Whether rates of upper and lower GIB differ between DOACs is still unknown.

The aim of the current study was to evaluate the risk for GIB in patients receiving rivaroxaban compared with other DOACs in a nationwide cohort study.

Methods

This nationwide cohort study compared rates of GIB among new users of apixaban, dabigatran, and rivaroxaban, using propensity score weighting on baseline characteristics to account for indication bias (Appendix, available at Annals.org).

Data Source

Data on all patients in Iceland who received a prescription for oral anticoagulants (OACs) from 1 January 2008 to 28 February 2019 were collected using the Icelandic Medicine Registry, which contains records of all outpatient prescriptions in Iceland. The database has operated since 2002; about 3 500 000 prescriptions are added to it annually (22). The personal identification numbers of these patients were linked to the electronic medical record system of Landspítali–The National University Hospital of Iceland (Landspítali) and Iceland's 4 regional hospitals in Akranes, Akureyri, Ísafjörður, and Neskaupstaður. Appendix Figure 1 (available at Annals.org) shows the service area of each regional hospital.

Patient Selection and Follow-up

Patients who filled a prescription for apixaban, dabigatran, or rivaroxaban from 1 March 2014 to 28 February 2019 were included. Per their product monographs,

medication dosages were assumed to be twice daily for apixaban and dabigatran and once daily for rivaroxaban. Patients prescribed 20 mg of rivaroxaban, 5 mg of apixaban, or 150 mg of dabigatran were considered to be receiving a standard dose; other doses were considered low doses. For patients receiving rivaroxaban because of venous thromboembolism (VTE), the standard dose was considered to be 15 mg twice daily for the initial 21 days followed by 20 mg once daily. Patients were excluded from the study if they had filled an OAC prescription in the preceding 12 months; had end-stage renal disease, a mechanical heart valve, or mitral valve stenosis; had permanent residence outside Iceland; or were receiving 2.5 mg of rivaroxaban. Follow-up was started on the day the first prescription was filled and continued until 28 February 2019, or earlier if the primary outcome was achieved, death occurred, or treatment was ceased or switched to another OAC (**Appendix Figure 2**, available at Annals.org).

Exposure and Outcomes

The exposure of interest was treatment with apixaban, dabigatran, or rivaroxaban. The primary outcome was any clinically relevant GIB, defined as bleeding leading to medical intervention, unscheduled physician contact, or temporary treatment cessation (23). Secondary outcomes were any clinically relevant upper or lower GIB, differences in causes of upper and lower GIB, and major GIB. Major bleeding was defined, according to International Society on Thrombosis and Haemostasis criteria, as bleeding leading to a decrease in hemoglobin level of 20 g/L or more, transfusion of 2 or more units of red blood cells, symptomatic bleeding into a closed compartment such as the retroperitoneum, or death due to bleeding (24). Upper GIB was defined as hematemesis or confirmed upper GIB site on endoscopy; lower GIB was defined as hematochezia or confirmed lower GIB site on endoscopy.

Data Extraction

We identified GIB events using 3 separate routes. First, GIB events were identified using relevant International Classification of Diseases, 10th Revision (ICD-10) codes from Landspítali and the 4 regional hospitals (**Appendix Table 1**, available at Annals.org); ICD-10 codes were selected from previous studies (19, 25) and a priori. Second, GIB events were gathered by reviewing results from all endoscopic procedures performed on patients receiving DOACs at the Icelandic hospitals during their follow-up period. Third, data on fatal GIB events were collected from the Icelandic Cause of Death Registry. All GIB events were verified by manual chart review; the cause was identified, and each event was classified as either major or nonmajor. Whether the bleeding was from the upper or lower gastrointestinal tract was also determined.

For comparison, we also identified GIB events using only previously validated ICD-10 codes (19, 25) without manually reviewing each diagnosis. Compared with the more robust searching algorithm described herein, the sensitivity and specificity of this traditional method of identifying GIB events were calculated.

Prior GIB and VTE events were identified using ICD-10 codes (**Appendix Table 1**) and were limited to those occurring at or after the beginning of electronic data recording (that is, from 1 January 1996 or later). The Charlson Comorbidity Index (CCI) and the CHA_2DS_2-VASc score were used to evaluate the comorbidity burden of patients (26, 27). The ICD-10 codes used for the CCI were based on a previously verified algorithm (28). The diagnoses needed to calculate the CHA_2DS_2-VASc score are all included in the CCI, except for hypertension. Diagnosis of hypertension was defined by relevant ICD-10 code or prescription of at least 2 different antihypertensive medications (20, 29).

Treatment indication was collected using relevant ICD-10 codes from Landspítali; the 4 regional hospitals; and the primary health care databases from the capital area, Westfjords, and northern, western, and eastern Iceland (**Appendix Table 1**). Data on treatment indication were collected by manual chart review if a diagnosis was missing or ambiguous (that is, results from the ICD-10 code search suggested >1 possible indication). Indication for treatment was classified as AF, VTE, cryptogenic ischemic stroke (that is, without AF or other underlying processes), other, or unknown. Data on comorbidities and treatment indication were collected from the day of study entry or earlier (**Appendix Figure 2**).

In addition to OACs, data for the following drug prescriptions were collected: antihistamines, antihypertensives, antiplatelets, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), proton-pump inhibitors (PPIs), selective serotonin reuptake inhibitors, and statins. All drug prescriptions were collected from the Icelandic Medicine Registry using relevant Anatomical Therapeutic Chemical codes (**Appendix Table 2**, available at Annals.org). Concomitant drug use was defined as filling of a relevant drug prescription within the period of 6 months before study inclusion.

For the follow-up period, the Cause of Death Registry at The Directorate of Health was searched to collect information on date of death and whether it was due to GIB.

Statistical Analysis

All statistical analysis was performed in R, version 3.6.1 (R Foundation for Statistical Computing) using RStudio, version 1.2.1335. All statistical tests were 2-tailed, and all CIs were 95% CIs.

Rates of GIB were compared for patients receiving apixaban, dabigatran, and rivaroxaban using inverse probability weighting (IPW), Kaplan–Meier survival estimates, and Cox regression. The IPW method assigns weights to patients based on propensity scores calculated from potential confounders. The "twang" package in R was used to calculate propensity scores with gradient-boosted logistic regression. The following variables were included in the IPW model: age, sex, all variables in the CCI (except for AIDS, which was too sporadic), hypertension, bleeding or coagulation disorders, history of VTE or GIB, treatment indication, DOAC dosing (standard or low dose), concomitant drug use (antihistamines, antiplatelets, corticosteroids, NSAIDs, PPIs, selective serotonin reuptake inhibitors, and

statins), and region. Standardized mean differences were used to measure the balance between study groups; values below 0.1 indicated ideal balance, and values below 0.2 indicated acceptable balance (30, 31).

A sensitivity analysis that included patients with AF only was performed using the statistical methods described earlier. To account for potential unmeasured confounding, another sensitivity analysis was performed that included only patients with AF living in the greater capital area and events identified from Landspítali. To assess the effect of potential unmeasured confounders, we calculated the E-value for comparisons of GIB rates (32).

The proportional causes of upper and lower GIB between groups were compared using the Fisher exact test.

Role of the Funding Source

This study was funded by the Icelandic Centre for Research and by the Landspítali University Hospital Research Fund. The funding sources had no role in the design, conduct, or reporting of the study.

RESULTS

Study Population

Overall, 8892 patients who received DOACs from 1 March 2014 to 28 February 2019 were identified. Patients receiving edoxaban were excluded due to their low numbers (n = 153). Furthermore, 2819 patients who received an OAC prescription in the preceding 12 months, 32 patients whose permanent residence was outside of Iceland, 10 patients receiving 2.5 mg of rivaroxaban, 6 patients with end-stage renal disease, and 4 patients with a mechanical heart valve or mitral stenosis were excluded. This left 3217 patients receiving rivaroxaban, 2157 patients receiving apixaban, and 494 patients receiving dabigatran who were included in the study (**Figure 1**). The IPW method provided balanced baseline characteristics between the groups (**Table 1**; **Appendix Figures 3** to **7**, available at Annals.org). The mean follow-up time was 1.6 years for patients receiving rivaroxaban, 1.2 years for patients receiving apixaban, and 1.8 years for patients receiving dabigatran. Comparisons of baseline characteristics between study subgroups (patients with AF, and patients with AF living in the capital area) are provided in **Appendix Tables 3** and **4** (available at Annals.org).

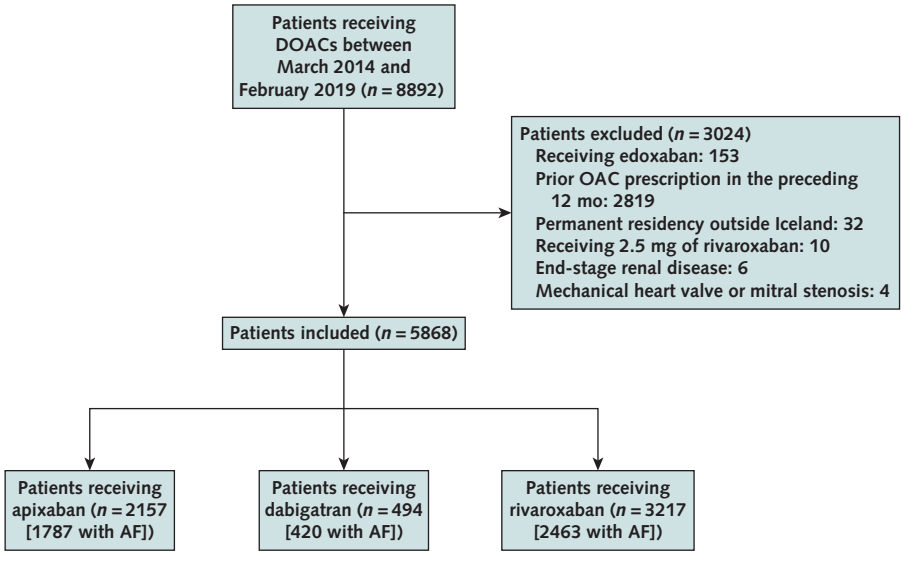
For the overall study population, 241 total GIB events were identified: 190 by manual review of ICD-10 codes (79%), 49 by review of endoscopic procedures (20%), and 2 from the death registry (1%). When only previously validated ICD-10 codes were used to identify cases without manually confirming the validity of the diagnoses, 130 GIB events were identified; this method had 99.9% specificity and 53% sensitivity compared with the selected method.

Of the 241 GIB events, 135 originated from the lower gastrointestinal tract (56%), 72 originated from the upper gastrointestinal tract (30%), and 34 could not be classified (14%). Overall, 146 GIB events were classified as major bleeding (61%) according to the predetermined criteria (24).

Rates of GIB With Rivaroxaban Versus Apixaban and Dabigatran

Compared with apixaban, rivaroxaban was associated with higher rates of overall GIB (3.2 vs. 2.5 events per 100 person-years; hazard ratio [HR], 1.42 [95% CI, 1.04 to 1.93]) and major GIB (1.9 vs. 1.4 events per 100 person-years; HR, 1.50 [CI, 1.00 to 2.24]) (**Figure 2**).

Figure 1. Flowchart for cohort selection.



AF = atrial fibrillation; DOAC = direct oral anticoagulant; OAC = oral anticoagulant.

Table 1. Baseline Characteristics of the Study Population

Characteristics	Apixaban (*n* = 2157)	Dabigatran (*n* = 494)	Rivaroxaban (*n* = 3217)	SMD*	
				Before IPW	After IPW
Mean age (SD), *y*	72 (13)	70 (14)	69 (13)	0.191	0.044
Male sex, *n (%)*	1153 (53.5)	279 (56.5)	1905 (59.2)	0.078	0.062
Mean CHA_2DS_2-VASc score (SD)	2.3 (1.6)	2.1 (1.5)	1.8 (1.4)	0.228	0.052
Mean CCI score (SD)	0.9 (1.4)	0.7 (1.2)	0.6 (1.1)	0.154	0.071
Comorbidities, *n (%)*					
Ischemic heart disease	162 (7.5)	38 (7.7)	224 (7.0)	0.019	0.004
Congestive heart failure	176 (8.2)	40 (8.1)	184 (5.7)	0.064	0.024
Peripheral vascular disease	96 (4.5)	24 (4.9)	108 (3.4)	0.051	0.012
Cerebrovascular disease	272 (12.6)	37 (7.5)	169 (5.3)	0.174	0.035
Hemiplegia	22 (1.0)	4 (0.8)	16 (0.5)	0.040	0.052
Diabetes mellitus	102 (4.7)	22 (4.5)	101 (3.1)	0.055	0.015
Diabetes mellitus with end-organ damage	64 (3.0)	12 (2.4)	68 (2.1)	0.036	0.019
Chronic lung disease	125 (5.8)	25 (5.1)	122 (3.8)	0.063	0.040
Moderate/severe renal disease	74 (3.4)	11 (2.2)	72 (2.2)	0.048	0.074
Liver disease	17 (0.8)	2 (0.4)	17 (0.5)	0.033	0.055
Peptic ulcer disease	48 (2.2)	11 (2.2)	36 (1.1)	0.058	0.026
Connective tissue disease	49 (2.3)	8 (1.6)	58 (1.8)	0.032	0.059
Dementia	54 (2.5)	6 (1.2)	37 (1.2)	0.068	0.085
Any tumor	255 (11.8)	51 (10.3)	279 (8.7)	0.069	0.034
Metastatic solid tumor	11 (0.5)	1 (0.2)	24 (0.7)	0.054	0.058
Hypertension	1415 (65.6)	326 (66.0)	1898 (59.0)	0.097	0.027
Bleeding disease	14 (0.6)	1 (0.2)	15 (0.5)	0.046	0.047
Prior GIB	97 (4.5)	24 (4.9)	86 (2.7)	0.077	0.017
Prior VTE	265 (12.3)	46 (9.3)	672 (20.9)	0.219	0.145
Concomitant drug use, *n (%)*					
Antihistamines	12 (0.6)	5 (1.0)	18 (0.6)	0.034	0.018
Antiplatelets	584 (27.1)	134 (27.1)	643 (20.0)	0.113	0.022
Corticosteroids	444 (20.6)	98 (19.8)	625 (19.4)	0.019	0.045
NSAIDs	482 (22.3)	102 (20.6)	823 (25.6)	0.078	0.079
PPIs	885 (41.0)	186 (37.7)	1190 (37.0)	0.055	0.012
SSRIs	402 (18.6)	58 (11.7)	464 (14.4)	0.129	0.113
Statins	964 (44.7)	223 (45.1)	1289 (40.1)	0.068	0.022
Dosing, *n (%)*	–	–	–	0.391	0.039
Standard dose	1699 (78.8)	269 (54.5)	2601 (80.9)	–	–
Low dose	458 (21.2)	225 (45.5)	616 (19.1)	–	–
Treatment indication, *n (%)*	–	–	–	0.239	0.148
AF	1787 (82.8)	420 (85.0)	2463 (76.6)	–	–
VTE	236 (10.9)	41 (8.3)	605 (18.8)	–	–
Ischemic stroke	75 (3.5)	13 (2.6)	38 (1.2)	–	–
Other	51 (2.4)	17 (3.4)	93 (2.9)	–	–
Unknown	8 (0.4)	3 (0.6)	18 (0.6)	–	–
Area of residence, *n (%)*	–	–	–	0.316	0.117
Capital area	1512 (70.1)	310 (62.8)	1960 (60.9)	–	–
Eastern	73 (3.4)	17 (3.4)	90 (2.8)	–	
Northern	144 (6.7)	55 (11.1)	495 (15.4)	–	–
Southern	267 (12.4)	99 (20.0)	438 (13.6)	–	–
Western	116 (5.4)	12 (2.4)	179 (5.6)	–	–
Westfjords	45 (2.1)	1 (0.2)	55 (1.7)	–	–

AF = atrial fibrillation; CCI = Charlson Comorbidity Index; GIB = gastrointestinal bleeding; IPW = inverse probability weighting; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton-pump inhibitor; SMD = standardized mean difference; SSRI = selective serotonin reuptake inhibitor; VTE = venous thromboembolism.
* An SMD below 0.1 indicated ideal balance, and an SMD below 0.2 indicated acceptable balance.

Rivaroxaban also had higher rates of overall GIB and major GIB than dabigatran with similar point estimates, although the CIs were wider and included the possibility of a null effect (Table 2).

To estimate the effect of potential confounding, we calculated the E-value for the comparison of overall GIB rates between apixaban and rivaroxaban. The E-value was 2.19 for the point estimate and 1.26 for the lower

limit of the CI. This means that the sum of all unmeasured confounders unrelated to the included covariates would have to be 119% more common in the rivaroxaban group and increase the risk for GIB by 119% to explain away the observed difference, or be 26% more common in the rivaroxaban group and increase the risk for GIB by 26%, for the CI to include the possibility of a null effect. The E-value for dabigatran versus rivaroxaban was 2.64.

In analyses of upper and lower GIB, dabigatran was associated with approximately 3 times fewer upper GIB events than apixaban and rivaroxaban, although this must be interpreted in the context of wide CIs (Table 2; Appendix Figure 8, available at Annals.org). Similarly, apixaban was associated with lower rates of lower GIB than rivaroxaban.

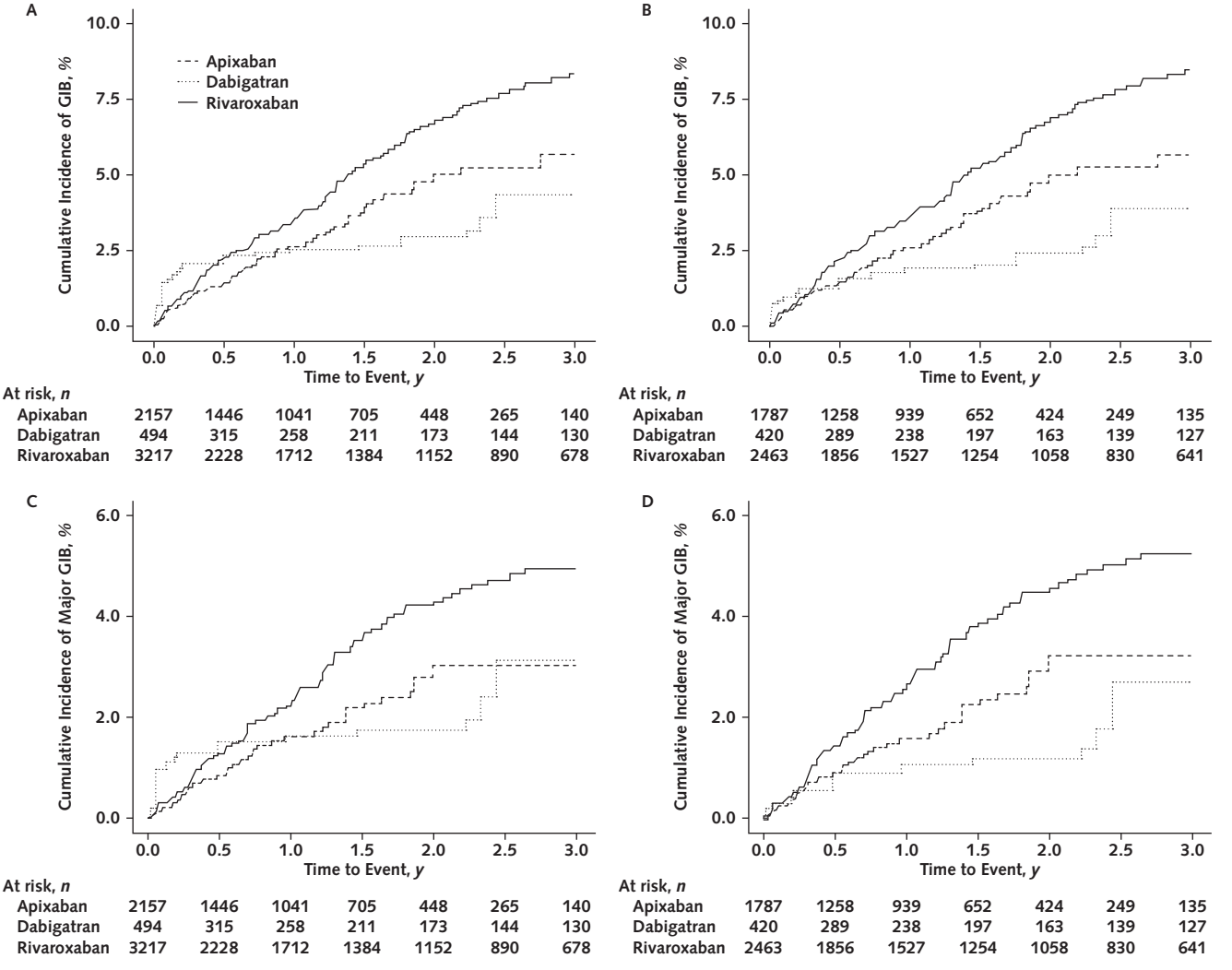
The cause of GIB was similar among the drugs (Appendix Table 5, available at Annals.org).

Sensitivity Analysis

When only patients with AF were analyzed, rivaroxaban had higher rates of overall GIB than apixaban (HR, 1.40 [CI, 1.01 to 1.94]) or dabigatran (HR, 2.04 [CI, 1.17 to 3.55]) (Table 3; Figure 2). Rivaroxaban also had higher rates of major GIB than either apixaban or dabigatran, with point estimates similar to the overall GIB rates, although the CIs included the possibility of a null effect for the former comparison (Table 3). Similar to the primary analysis, rivaroxaban had higher rates of upper GIB than dabigatran (HR, 2.85 [CI, 1.01 to 8.04]).

In the sensitivity analysis restricted to patients with AF living in the greater capital area and events identified

Figure 2. Kaplan–Meier plots comparing the cumulative incidence of GIB events.



GIB = gastrointestinal bleeding. A and B. Comparison of the cumulative incidence of any clinically relevant GIB with apixaban, dabigatran, and rivaroxaban for all patients and patients with AF only, respectively. C and D. Comparison of the cumulative incidence of major GIB with apixaban, dabigatran, and rivaroxaban for all patients and patients with AF only, respectively.

Table 2. Comparison of GIB Rates Among Patients Receiving Rivaroxaban, Apixaban, or Dabigatran: All Patients

OAC	GIB Events per 100 Person-Years	HR (95% CI)		
		Compared With Apixaban	Compared With Dabigatran	Compared With Rivaroxaban
Overall GIB*				
Apixaban	2.5	–	1.15 (0.61–2.17)	0.71 (0.52–0.96)
Dabigatran	1.9	0.87 (0.46–1.65)	–	0.61 (0.34–1.10)
Rivaroxaban	3.2	1.42 (1.04–1.93)	1.63 (0.91–2.92)	–
Major GIB				
Apixaban	1.4	–	0.93 (0.42–2.08)	0.67 (0.45–1.00)
Dabigatran	1.4	1.08 (0.48–2.40)	–	0.72 (0.35–1.48)
Rivaroxaban	1.9	1.50 (1.00–2.24)	1.39 (0.67–2.88)	–
Upper GIB				
Apixaban	0.8	–	2.90 (0.98–8.55)	0.77 (0.44–1.35)
Dabigatran	0.3	0.35 (0.12–1.02)	–	0.27 (0.09–0.76)
Rivaroxaban	1.0	1.30 (0.74–2.27)	3.75 (1.32–10.71)	–
Lower GIB				
Apixaban	1.2	–	0.65 (0.31–1.39)	0.65 (0.43–1.00)
Dabigatran	1.7	1.53 (0.72–3.24)	–	1.00 (0.51–1.95)
Rivaroxaban	1.7	1.53 (1.00–2.33)	1.00 (0.51–1.96)	–

GIB = gastrointestinal bleeding; HR = hazard ratio; OAC = oral anticoagulant.
* Upper and lower GIB rates do not equate to the overall GIB rate because some GIB events could not be classified as either upper or lower.

from Landspítali, results were similar to those of the other 2 analyses (Appendix Table 6, available at Annals.org).

DISCUSSION

In this nationwide population-based study, GIB rates were compared for new users of rivaroxaban, apixaban, and dabigatran. The results showed that rivaroxaban was associated with 40% to 42% higher overall risk for GIB and 49% to 50% higher risk for major GIB compared with apixaban. Similarly, rivaroxaban was associated with 63% to 104% higher overall risk for GIB and 39% to 95% higher risk for major GIB compared with dabigatran. This association must be interpreted in the context of relatively wide CIs, especially for the smaller dabigatran group.

The findings of this study are supported by similar results from previous population-based registry studies (13–18). In a U.S. study of claims data from privately insured patients and Medicare enrollees (obtained from the Optum database), rivaroxaban users had higher GIB rates than apixaban and dabigatran users (17). Another study using the Medicare database showed similar results (13). Both studies used administrative insurance databases, which have inherent limitations and possible selection bias due to variables including insurance status, age, and employment. For example, both studies included data from the Medicare database, which includes only patients aged 65 years or older and patients with certain disabilities and/or end-stage renal disease (13, 17). In addition, the Optum database primarily includes data from employer-sponsored insurance (14, 17). Rivaroxaban has also been associated with higher GIB rates than apixaban and/or dabigatran in studies from the United Kingdom and Taiwan (15, 16, 18). To our knowledge, the current study is the first population-based study in which all GIB events were manually confirmed by chart review, increasing the accuracy of the results.

In this study, the incidence of GIB was 1.9 to 3.2 events per 100 person-years, including 1.4 to 1.9 major GIB events per 100 person-years. This is relatively high compared with previous observational studies that showed incidence rates of 0.8 to 2.7 events per 100 person-years (14, 15, 17–19) but is similar to the incidence in randomized controlled trials (33, 34). In comparison, GIB rates of 1.0 to 3.1 events per 100 person-years have been reported for warfarin in previous observational studies (12, 18, 19). The high incidence is most likely explained by our robust search algorithm, which used a thorough "catch-all" ICD-10 code search to identify cases, reviewed all endoscopic procedures undergone by participants during the study period, and searched the national death registry for fatal GIB events. Each GIB event was confirmed by manual chart review, increasing the accuracy of the results and potentially providing a better estimate of the real-world incidence of OAC-related GIB. Supporting this, we also analyzed the data using only previously validated ICD-10 codes to detect GIB events without manually reviewing GIB events. Although this method was highly specific, the sensitivity was only 53%, meaning that compared with the initial analysis, half of all GIB events would have been missed. Previous registry studies relying only on ICD-10 codes have probably had low sensitivity of detection of GIB events (12–21). Thus, the current study is likely to give a more accurate picture of the real-world outcome in patients receiving OACs than studies based on registry or administrative data only, without verification of diagnoses and less detailed phenotypic data (12–21).

In previous registry studies, information about the location and cause of GIB has not been available. In this study, dabigatran was associated with markedly lower rates of upper GIB than either apixaban or rivaroxaban, albeit with wide CIs. In addition, rivaroxaban was associated with higher rates of lower GIB than apixaban. In

comparison, a study by Vinogradova and colleagues demonstrated that apixaban was associated with lower rates of major upper GIB than rivaroxaban and dabigatran; however, rivaroxaban and dabigatran were not directly compared (18). Other population-based registry studies have not distinguished between upper and lower GIB (13–17, 19–21). This knowledge gap is likely explained by the fact that without manually reviewing events, classification into upper or lower GIB is difficult. For example, in previous observational studies examining GIB in the general population, the incidence of upper and lower GIB has been similar (35–37); however, in the study by Vinogradova and colleagues, the incidence of major upper GIB was more than 7-fold higher compared with major lower GIB (18), suggesting low detection of lower GIB events given that the origin of the GIB events was not validated. In contrast, the ratio of upper to lower GIB was 1:2 in the current study.

Because AF is the most common indication for OACs, most observational studies have included only new users with AF (13–16, 19, 20), thus providing more homogeneous study groups but reducing generalizability. To increase generalizability, the current study included all patients regardless of treatment indication and accounted for this factor using IPW. To account for potential unmeasured confounding, sensitivity analyses restricted to patients with AF and patients with AF living in the greater capital area were performed. Compared with the main analysis, the sensitivity analyses reassuringly yielded similar point estimates for most comparisons, indicating that IPW adequately accounted for differences in patients with various indications.

Why the risk for GIB increased for patients receiving rivaroxaban is not clear, but this may at least partly be due to the different pharmacokinetics of rivaroxaban, which is administered once daily, as opposed to the other 2 drugs, which are given twice daily. Supporting this, 2 crossover treatment studies have demonstrated that rivaroxaban has a peak plasma concentration almost twice as high as that of apixaban (38, 39). The anti-Xa activity of the drugs was highly correlated to the plasma concentration, with rivaroxaban having higher maximal anti-Xa activity and a higher 24-hour area under the curve for anti-Xa activity (38, 39).

Alternatively, the increased bleeding risk associated with rivaroxaban may be due to better adherence compared with the other 2 drugs, leading to more bleeding events and potentially fewer thromboembolic events. Indeed, once-daily dosing has been associated with better adherence than twice-daily dosing for chronic cardiovascular diseases (40); in support of this, dabigatran has been associated with lower adherence compared with other DOACs (41–49), perhaps due to its frequent gastrointestinal side effects (50). During the RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) trial, 12% of patients receiving dabigatran reported dyspepsia, and more than 3 times as many patients discontinued dabigatran due to gastrointestinal upset compared with warfarin (2). In contrast, adherence to apixaban has generally been similar to or better than adherence to rivaroxaban (41–49).

The current study has several strengths. It is both population-based and nationwide and includes all major hospitals in Iceland (**Appendix Table 7**, available at Annals.org). A robust search algorithm was used to identify GIB events: ICD-10 codes were extensively searched, all endoscopies performed in these patients were scrutinized, and data from the national death registry were reviewed. In contrast to other registry and administrative studies, all diagnoses were verified and validated; only a small minority were lost to follow-up. Phenotypic details were also obtained on the severity of bleeding, as well as the location and cause of GIB. Furthermore, the Icelandic Medicine Registry includes all outpatient prescriptions in

Table 3. Comparison of GIB Rates Among Patients Receiving Rivaroxaban, Apixaban, or Dabigatran: Patients With AF Only

OAC	GIB Events per 100 Person-Years	HR (95% CI)		
		Compared With Apixaban	Compared With Dabigatran	Compared With Rivaroxaban
Overall GIB*				
Apixaban	2.4	–	1.46 (0.80–2.64)	0.71 (0.52–0.99)
Dabigatran	1.6	0.69 (0.38–1.24)	–	0.49 (0.28–0.86)
Rivaroxaban	3.2	1.40 (1.01–1.94)	2.04 (1.17–3.55)	–
Major GIB				
Apixaban	1.4	–	1.31 (0.66–2.58)	0.67 (0.44–1.02)
Dabigatran	1.1	0.77 (0.39–1.51)	–	0.51 (0.27–0.98)
Rivaroxaban	2.0	1.49 (0.98–2.28)	1.95 (1.02–3.73)	–
Upper GIB				
Apixaban	0.8	–	2.19 (0.72–6.63)	0.77 (0.43–1.36)
Dabigatran	0.4	0.46 (0.15–1.39)	–	0.35 (0.12–0.99)
Rivaroxaban	1.0	1.30 (0.73–2.32)	2.85 (1.01–8.04)	–
Lower GIB				
Apixaban	1.3	–	1.04 (0.51–2.12)	0.78 (0.50–1.21)
Dabigatran	1.2	0.96 (0.47–1.95)	–	0.75 (0.39–1.44)
Rivaroxaban	1.6	1.28 (0.83–1.99)	1.34 (0.69–2.59)	–

AF = atrial fibrillation; GIB = gastrointestinal bleeding; HR = hazard ratio; OAC = oral anticoagulant.
* Upper and lower GIB rates do not equate to the overall GIB rate because some GIB events could not be classified as either upper or lower.

the country; as such, data on all patients who received DOACs were retrieved during the study period, with information on treatment indication for more than 99% of all patients.

The study also has several limitations. First, although a robust method was used to account for potential confounders, the existence of residual confounding factors cannot be excluded. For example, the study did not account for socioeconomic status or lifestyle (for example, smoking and alcohol consumption). However, because the cost of all DOACs is similar in Iceland, selection bias due to socioeconomic status is unlikely. Second, the analysis was based on small numbers compared with previous registry studies, especially for comparisons with dabigatran. Third, although the study period spanned 5 years, the follow-up period averaged only 1.2 to 1.8 years, in large part due to the high number of patients starting DOAC treatment at the end of the study period. Fourth, the Icelandic population is relatively homogeneous; as such, the results may not be generalizable to other more diverse populations. Fifth, the study did not include data on baseline laboratory values such as serum creatinine and hemoglobin levels; however, it did account for moderate to severe renal disease and history of GIB. Sixth, the study did not include data on over-the-counter medication, which is important because both NSAIDs and PPIs are available in Iceland without a prescription. However, preweighted comparisons of the groups showed no difference in prescribed NSAIDs or PPIs, making potential differences in over-the-counter use less likely. Seventh, although our study cohort included almost all new users of apixaban, dabigatran, and rivaroxaban in Iceland, we did not have data on patients who were eligible for treatment but did not receive OACs. This population may differ from the treated population, and, as such, the observed average treatment effect among the treated population in the current study may not precisely represent the average treatment effect. Finally, although the results of the study suggest higher GIB rates for rivaroxaban, data on thromboembolic or other bleeding events have not yet been obtained.

In conclusion, rivaroxaban was associated with higher rates of GIB than apixaban and dabigatran. This may help guide oral anticoagulant selection, especially for patients at high risk for GIB.

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Appendix: The Icelandic Health Care System

Iceland has a single public health care system. Landspítali–The National University Hospital of Iceland is the only hospital in the capital area (which includes 64% of the total population) and serves as the only tertiary hospital in the country. Four regional hospitals serve as the primary hospital for each region (apart from the capital area and southern region in which patients would be primarily referred straight to Landspítali). **Appendix Figure 1** shows the location of each regional hospital and its service area.

The venues for OAC prescriptions are primarily a) Landspítali/regional hospital, b) clinic, and c) primary health care. Follow-up of patients receiving OACs is often done at clinics outside the regional hospitals or less commonly at a primary health care center. However, these centers only have ambulant service, and as such patients presenting to these centers with acute GIB would typically be referred to the emergency department at Landspítali or the nearest regional hospital for treatment.

Appendix Table 1. ICD-10 Codes

Variables	ICD-10 Codes
Outcomes	
Gastrointestinal bleeding (specific search)	K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K92.0, K92.1, K92.2, I85.0, I98.3
Gastrointestinal bleeding (sensitive search)	C15, C15.3, C15.4, C15.5, C15.8, C15.9, C16, C16.0, C16.1, C16.2, C16.3, C16.4, C16.5, C16.6, C16.8, C16.9, C17, C17.0, C17.1, C17.2, C17.3, C17.8, C17.9, C18, C18.0, C18.1, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C18.9, C19, C20, C21, C21.0, C21.1, C21.2, C21.8, D37.1, D37.2, D37.3, D37.4, D37.5, K29, K29.2, K29.3, K29.4, K29.5, K29.6, K29.7, K29.8, K29.9, K50, K50.0, K50.1, K50.8, K50.9, K51, K51.0, K51.2, K51.3, K51.4, K51.5, K51.8, K51.9, K55.0, K55.1, K55.8 K55.9, K57.1, K57.3, K57.5, K57.9, K22.1, K22.3, K22.6, K25, K25.0, K25.1, K25.2, K25.3, K25.4, K25.5, K25.6, K25.7, K25.9, K26, K26.0, K26.1, K26.2, K26.3, K26.4, K26.5, K26.6, K26.7, K26.9, K27, K27.0, K27.1, K27.2, K27.3, K27.4, K27.5, K27.6, K27.7, K27.9, K28, K28.0, K28.1, K28.2, K28.3, K28.4, K28.5, K28.6, K28.7, K28.9, K29.0, K55.2, K62.5, K62.6, K63.1, K63.3, K92.0, K92.1, K92.2, I85, I85.0, I85.1, I98.3
Treatment indication	
Atrial fibrillation	I48, I48.0, I48.1, I48.2, I48.3, I48.4, I48.9
Venous thromboembolism	I26, I26.0, I26.9, I80.2, I80.3, I80.8, I80.9, I82, I82.2, I82.3, I82.4, I82.6, I82.8, I82.9
Ischemic stroke	G46, G46.0, G46.1, G46.2, G46.3, G46.4, G46.5, G46.6, G46.7, G46.8, I63, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I64, I64.0, I64.1, I64.2, I64.3, I64.4, I64.5, I64.6, I64.8, I64.9, I69, I69.3, I69.8, 169.9
Mechanical heart valve	Z95.2, Z95.3, Z95.4
Comorbidities	
History of gastrointestinal bleeding	K22.1, K22.3, K22.6, K25, K25.0, K25.1, K25.2, K25.3, K25.4, K25.5, K25.6, K25.7, K25.9, K26, K26.0, K26.1, K26.2, K26.3, K26.4, K26.5, K26.6, K26.7, K26.9, K27, K27.0, K27.1, K27.2, K27.3, K27.4, K27.5, K27.6, K27.7, K27.9, K28, K28.0, K28.1, K28.2, K28.3, K28.4, K28.5, K28.6, K28.7, K28.9, K29.0, K55.2, K62.5, K62.6, K63.1, K63.3, K92.0, K92.1, K92.2, I85.0, I98.3
Venous thromboembolism	I26, I26.0, I26.9, I80.2, I80.3, I80.8, I80.9, I82, I82.2, I82.3, I82.4, I82.6, I82.8, I82.9
Ischemic heart disease	I21, I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22, I22.0, I22.1, I22.2, I22.8, I22.9, I23, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.7, I23.8
Heart failure	I11.0, I13.0, I13.2, I50, I50.1, I50.2, I50.3, I50.4, I50.8, I50.9
Peripheral vascular disease	I70, I70.0, I70.1, I70.2, I70.8, I70.9, I71, I71.0, I71.1, I71.2, I71.3, I71.4, I71.5, I71.6, I71.8, I71.9, I72, I72.0, I72.1, I72.2, I72.3, I72.4, I72.8, I72.9, I73.0, I73.1, I73.8, I73.9, I74, I74.0, I74.1, I74.2, I74.3, I74.4, I74.5, I74.8, I74.9, I77, I77.0, I77.1, I77.2, I77.3, I77.4, I77.5, I77.6, I77.8, I77.9
Cerebral accident	G45, G45.0, G45.1, G45.2, G45.3, G45.4, G45.8, G45.9, G46, G46.0, G46.1, G46.2, G46.3, G46.4, G46.5, G46.6, G46.7, G46.8, I60, I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9, I61, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.7, I61.8, I61.9, I62, I62.0, I62.1, I62.9, I63, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6,I63.8, I63.9, I64, I64.0, I64.1, I64.2, I64.3, I64.4, I64.5, I64.6, I64.8, I64.9
Hemiplegia	G81, G81.0, G81.1, G81.9, G82, G82.0, G82.1, G82.2, G82.3, G82.4, G82.5
Dementia	F00, F00.0, F00.1, F00.2, F00.39, F01, F01.0, F01.1, F01.2, F01.3, F01.8, F01.9, F02, F02.0, F02.1, F02.2, F02.3, F02.4, F02.8, F03, F05, F05.0, F05.1, F05.8, F05.9, G30, G30.0, G30.1, G30.8, G30.9
Chronic lung disease	J40, J41, J41.0, J41.1, J41.8, J42, J43, J43.0, J43.1, J43.2, J43.8, J43.9, J44, J44.0, J44.1, J44.8, J44.9, J45, J45.0, J45.1, J45.8, J45.9, J46, J47, J60, J61, J62, J62.0, J62.8, J63, J63.0, J63.1, J63.2, J63.3, J63.4, J63.5, J63.8, J64, J65, J66, J66.0, J66.1, J66.2, J66.8, J67, J67.0, J67.1, J67.2, J67.3, J67.4, J67.5, J67.6, J67.7, J67.8, J67.9, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Connective tissue disease	D86, D86.0, D86.1, D86.2, D86.3, D86.8, D86.9, M05, M05.0, M05.1, M05.2, M05.3, M05.8, M05.9, M06, M06.0, M06.1, M06.2, M06.3, M06.4, M06.8, M06.9, M08, M08.0, M08.1, M08.2, M08.3, M08.4, M08.8, M08.9, M09, M09.0, M09.1, M09.2, M09.8, M30, M30.0, M30.1, M30.2, M30.3, M30.8, M31, M31.0, M31.1, M31.2, M31.3, M31.4, M31.5, M31.6, M31.7, M31.8, M31.9, M32, M32.0, M32.1, M32.2, M32.8, M32.9, M33, M33.0, M33.1, M33.8, M33.9, M34, M34.0, M34.1, M34.2, M34.8, M34.9, M35, M35.0, M35.1, M35.2, M35.3, M35.4, M35.5, M35.6, M35.7, M35.8, M35.9, M36, M36.0, M36.1, M36.2, M36.3, M36.4, M36.8
Peptic ulcer disease	K22.1, K25, K25.0, K25.1, K25.2, K25.3, K25.4, K25.5, K25.6, K25.7, K25.9, K26, K26.0, K26.1, K26.2, K26.3, K26.4, K26.5, K26.6, K26.7, K26.9, K27, K27.0, K27.1, K27.2, K27.3, K27.4, K27.5, K27.6, K27.7, K27.9, K28, K28.0, K28.1, K28.2, K28.3, K28.4, K28.5, K28.6, K28.7, K28.9
Mild liver disease	B18, B18.0, B18.1, B18.2, B18.8, B18.9, K70.0, K70.1, K70.2, 70.3, K70.9, K71, K71.0, K71.1, K71.2, K71.3, K71.4, K71.5, K71.6, K71.7, K71.8, K71.9, K73, K73.0, K73.1, K73.2, K73.8, K73.9, K74, K74.0, K74.1, K74.2, K74.3, K74.4, K74.5, K74.6, K76.1, K76.2, K76.3, K76.4, K76.8, K76.9

Continued on following page

Appendix Table 1–Continued

Variables	ICD-10 Codes
Moderate or severe liver disease	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K72.0, K72.1, K72.9, K76.6, I85, I85.0, I85.9, I86.4, I98.2
Moderate or severe renal disease	I12, I12.0, I12.9, I13, I13.0, I13.1, I13.2, I13.9, N00, N00.0, N00.1, N00.2, N00.3, N00.4, N00.5, N00.6, N00.7, N00.8, N00.9, N1, N01.0, N01.1, N01.2, N01.3, N01.4, N01.5, N01.6, N01.7, N01.8, N01.9, N02, N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, N03, N03.0, N03.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N03.8, N03.9, N04, N04.0, N04.1, N04.2, N04.3, N04.4, N04.5, N04.6, N04.7, N04.8, N04.9, N05, N05.0, N05.1, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N05.8, N05.9, N07, N07.0, N07.1, N07.2, N07.3, N07.4, N07.5, N07.6, N07.7, N07.8, N07.9, N11, N11.0, N11.1, N11.8, N11.9, N14, N14.0, N14.1, N14.2, N14.3, N14.4, N17, N17.0, N17.1, N17.2, N17.8, N17.9, N18, N18.0, N18.8, N18.9, N19, Q61, Q61.0, Q61.1, Q61.2, Q61.3, Q61.4, Q61.5, Q61.8, Q61.9
Diabetes mellitus without signs of end-organ damage	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9
Diabetes mellitus with end-organ damage	E10.2, E10.3, E10.4, E10.5, E10.6, E10.7, E10.8, E11.2, E11.3, E11.4, E11.5, E11.6, E11.7, E11.8
Tumor	C00-C75, C81-C85, C88, C90-C96
Metastasis	C76-C80
HIV/AIDS	B20, B20.0, B20.1, B20.2, B20.3, B20.4, B20.5, B20.6, B20.7, B20.8, B20.9, B21, B21.0, B21.1, B21.2, B21.3, B21.7, B21.8, B21.9, B22, B22.0, B22.1, B22.2, B22.7, B23, B23.0, B23.1, B23.2, B23.8, B24
Hypertension	I10, I11, I11.0, I11.9, I12, I12.0, I12.9, I13, I13.0, I13.1, I13.2, I13.9, I15, I15.0, I15.1, I15.2, I15.8, I15.9
Bleeding or coagulation disorders	D65, D66, D67, D68.0, D68.1, D68.2, D68.3, D68.4, D68.5, D68.6, D68.8, D68.9, D69.1, D69.3, D69.4, D69.5, D69.6

ICD-10 = International Classification of Diseases, 10th Revision.

Appendix Table 2. ATC Codes for Concomitant Drug Use

Drug Class	ATC Codes
Antihistamines	A02BA
Antiplatelets	B01AC
Corticosteroids	H02AB
NSAIDs	M01A
PPIs	A02BC
SSRIs	N06AB
Statins	C10AA
Antihypertensive medications	
α-Adrenergic blockers	C02A, C02B, C02C
β-Blockers	C07A, C07B
Calcium-channel blockers	C08, C09BB, C09DB, C07FB
Medications affecting the RAAS	C09
Thiazides	C03A, C09BA, C09DA, C07B, C07D, C08G
Other diuretics	C02L, C03B, C03D, C03EA, C03X, C07C, C07D
Vasodilators	C02D, C04, C05, C07E

ATC = Anatomical Therapeutic Chemical; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton-pump inhibitor; RAAS = renin–angiotensin–aldosterone system; SSRI = selective serotonin reuptake inhibitor.

Appendix Table 3. Baseline Characteristics of the Study Population: Patients With AF Only

Characteristic	Apixaban (*n* = 1787)	Dabigatran (*n* = 420)	Rivaroxaban (*n* = 2463)	SMD*	
				Before IPW	After IPW
Mean age (SD), *y*	74 (12)	71 (12)	71 (11)	0.175	0.067
Male sex, *n (%)*	976 (54.6)	245 (58.3)	1526 (62.0)	0.099	0.083
Mean CHA_2DS_2-VASc score (SD)	2.3 (1.6)	2.1 (1.4)	1.9 (1.4)	0.211	0.078
Mean CCI score (SD)	0.9 (1.4)	0.7 (1.1)	0.6 (1.1)	0.156	0.090
Comorbidities, *n (%)*					
Ischemic heart disease	142 (7.9)	34 (8.1)	187 (7.6)	0.012	0.013
Congestive heart failure	158 (8.8)	34 (8.1)	156 (6.3)	0.063	0.033
Peripheral vascular disease	81 (4.5)	16 (3.8)	91 (3.7)	0.028	0.028
Cerebrovascular disease	207 (11.6)	25 (6.0)	125 (5.1)	0.159	0.039
Hemiplegia	15 (0.8)	2 (0.5)	8 (0.3)	0.046	0.018
Diabetes mellitus	84 (4.7)	22 (5.2)	84 (3.4)	0.060	0.035
Diabetes mellitus with end-organ damage	50 (2.8)	12 (2.9)	57 (2.3)	0.023	0.045
Chronic lung disease	105 (5.9)	20 (4.8)	90 (3.7)	0.070	0.031
Moderate/severe renal disease	61 (3.4)	9 (2.1)	59 (2.4)	0.052	0.077
Liver disease	17 (1.0)	0 (0.0)	13 (0.5)	0.097	0.084
Peptic ulcer disease	42 (2.4)	9 (2.1)	27 (1.1)	0.064	0.014
Connective tissue disease	35 (2.0)	8 (1.9)	45 (1.8)	0.006	0.026
Dementia	45 (2.5)	6 (1.4)	25 (1.0)	0.077	0.066
Any tumor	207 (11.6)	38 (9.0)	191 (7.8)	0.087	0.053
Metastatic solid tumor	8 (0.4)	1 (0.2)	12 (0.5)	0.028	0.034
Hypertension	1245 (69.7)	298 (71.0)	1613 (65.5)	0.078	0.023
Bleeding disease	13 (0.7)	1 (0.2)	10 (0.4)	0.048	0.049
Prior GIB	80 (4.5)	19 (4.5)	68 (2.8)	0.063	0.031
Prior VTE	27 (1.5)	4 (1.0)	59 (2.4)	0.076	0.029
Concomitant drug use, *n (%)*					
Antihistamines	9 (0.5)	5 (1.2)	16 (0.6)	0.050	0.022
Antiplatelets	488 (27.3)	114 (27.1)	532 (21.6)	0.089	0.021
Corticosteroids	356 (19.9)	82 (19.5)	455 (18.5)	0.025	0.031
NSAIDs	384 (21.5)	87 (20.7)	586 (23.8)	0.049	0.042
PPIs	735 (41.1)	158 (37.6)	882 (35.8)	0.073	0.018
SSRIs	313 (17.5)	46 (11.0)	322 (13.1)	0.126	0.124
Statins	829 (46.4)	198 (47.1)	1088 (44.2)	0.040	0.019
Dosing, *n (%)*	–	–	–	0.356	0.030
Standard dose	1393 (78.0)	230 (54.8)	1948 (79.1)	–	–
Low dose	394 (22.0)	190 (45.2)	515 (20.9)	–	–
Area of residence, *n (%)*	–	–	–	0.319	0.126
Capital area	1269 (71.0)	258 (61.4)	1529 (62.1)	–	–
Eastern	58 (3.2)	15 (3.6)	58 (2.4)	–	–
Northern	120 (6.7)	46 (11.0)	361 (14.7)	–	–
Southern	220 (12.3)	90 (21.4)	335 (13.6)	–	–
Western	87 (4.9)	10 (2.4)	135 (5.5)	–	–
Westfjords	33 (1.8)	1 (0.2)	45 (1.8)	–	–

AF = atrial fibrillation; CCI = Charlson Comorbidity Index; GIB = gastrointestinal bleeding; IPW = inverse probability weighting; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton-pump inhibitor; SMD = standardized mean difference; SSRI = selective serotonin reuptake inhibitor; VTE = venous thromboembolism.

* An SMD below 0.1 indicated ideal balance, and an SMD below 0.2 indicated acceptable balance.

Appendix Table 4. Baseline Characteristics of the Study Population: Patients With AF Living in the Capital Area Only

Characteristic	Apixaban (*n* = 1269)	Dabigatran (*n* = 258)	Rivaroxaban (*n* = 1529)	SMD*	
				Before IPW	After IPW
Mean age (SD), *y*	74 (12)	71 (12)	70 (11)	0.199	0.112
Male sex, *n (%)*	685 (54.0)	143 (55.4)	969 (63.4)	0.128	0.048
Mean CHA_2DS_2-VASc score (SD)	2.4 (1.6)	2.1 (1.6)	1.9 (1.5)	0.219	0.095
Mean CCI score (SD)	1.0 (1.4)	0.7 (1.1)	0.7 (1.2)	0.151	0.130
Comorbidities, *n (%)*					
Ischemic heart disease	104 (8.2)	14 (5.4)	120 (7.8)	0.073	0.032
Congestive heart failure	130 (10.2)	17 (6.6)	113 (7.4)	0.088	0.088
Peripheral vascular disease	61 (4.8)	10 (3.9)	58 (3.8)	0.033	0.036
Cerebrovascular disease	163 (12.8)	22 (8.5)	92 (6.0)	0.157	0.040
Hemiplegia	11 (0.9)	0 (0.0)	6 (0.4)	0.094	0.089
Diabetes mellitus	63 (5.0)	8 (3.1)	62 (4.1)	0.063	0.011
Diabetes mellitus with end-organ damage	37 (2.9)	7 (2.7)	44 (2.9)	0.008	0.031
Chronic lung disease	89 (7.0)	13 (5.0)	71 (4.6)	0.068	0.019
Moderate/severe renal disease	49 (3.9)	7 (2.7)	45 (2.9)	0.043	0.074
Liver disease	15 (1.2)	0 (0.0)	12 (0.8)	0.107	0.103
Peptic ulcer disease	35 (2.8)	6 (2.3)	21 (1.4)	0.065	0.022
Connective tissue disease	32 (2.5)	5 (1.9)	35 (2.3)	0.026	0.064
Dementia	40 (3.2)	4 (1.6)	22 (1.4)	0.077	0.090
Any tumor	159 (12.5)	27 (10.5)	131 (8.6)	0.086	0.054
Metastatic solid tumor	7 (0.6)	1 (0.4)	8 (0.5)	0.016	0.025
Hypertension	865 (68.2)	184 (71.3)	997 (65.2)	0.088	0.015
Bleeding disease	11 (0.9)	1 (0.4)	9 (0.6)	0.041	0.037
Prior GIB	70 (5.5)	13 (5.0)	53 (3.5)	0.066	0.021
Prior VTE	22 (1.7)	3 (1.2)	44 (2.9)	0.082	0.069
Concomitant drug use, *n (%)*					
Antihistamines	5 (0.4)	1 (0.4)	8 (0.5)	0.013	0.049
Antiplatelets	344 (27.1)	64 (24.8)	327 (21.4)	0.089	0.049
Corticosteroids	242 (19.1)	43 (16.7)	263 (17.2)	0.042	0.103
NSAIDs	242 (19.1)	52 (20.2)	332 (21.7)	0.044	0.019
PPIs	515 (40.6)	98 (38.0)	513 (33.6)	0.097	0.023
SSRIs	227 (17.9)	25 (9.7)	196 (12.8)	0.160	0.172
Statins	584 (46.0)	118 (45.7)	696 (45.5)	0.007	0.032
Dosing, *n (%)*				0.353	0.056
Standard dose	985 (77.6)	139 (53.9)	1195 (78.2)	–	–
Low dose	284 (22.4)	119 (46.1)	334 (21.8)	–	–

AF = atrial fibrillation; CCI = Charlson Comorbidity Index; GIB = gastrointestinal bleeding; IPW = inverse probability weighting; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton-pump inhibitor; SMD = standardized mean difference; SSRI = selective serotonin reuptake inhibitor; VTE = venous thromboembolism.

* An SMD below 0.1 indicated ideal balance, and an SMD below 0.2 indicated acceptable balance.

Appendix Table 5. Comparison of Causes for Upper and Lower GIB in Patients Receiving Rivaroxaban, Apixaban, and Dabigatran

Cause of GIB	Rivaroxaban, *n* (%)	Apixaban, *n* (%)	Dabigatran, *n* (%)	OR (95% CI)	
				Rivaroxaban vs. Apixaban	Rivaroxaban vs. Dabigatran*
Upper GIB					
Peptic ulcer	20 (44.4)	8 (34.8)	0 (0)	1.49 (0.48–4.94)	–
Mucosal erosion	10 (22.2)	5 (21.7)	3 (75.0)	1.03 (0.27–4.44)	0.10 (0.002–1.41)
Angiodysplasia	10 (22.2)	5 (21.7)	1 (25.0)	1.03 (0.27–4.44)	0.86 (0.06–49.44)
Esophageal ulcer	0 (0)	3 (13.0)	0 (0)	0 (0–1.18)	–
Postpapillotomy bleeding	1 (2.2)	0 (0)	0 (0)	∞ (0.13–∞)	–
Unexplained	4 (8.9)	2 (8.7)	0 (0)	1.02 (0.13–12.19)	–
Lower GIB					
Diverticulosis	20 (24.1)	8 (22.9)	2 (11.8)	1.07 (0.39–3.17)	2.36 (0.48–23.08)
Hemorrhoid	13 (15.7)	6 (17.1)	0 (0)	0.90 (0.28–3.17)	–
Colorectal cancer	11 (13.3)	5 (14.3)	4 (23.5)	0.92 (0.26–3.67)	0.50 (0.12–2.49)
Angiodysplasia	8 (9.6)	4 (11.4)	3 (17.6)	0.83 (0.20–4.04)	0.50 (0.10–3.29)
Polyp	8 (9.6)	1 (2.9)	3 (17.6)	3.60 (0.45–165.47)	0.50 (0.10–3.29)
Rectal ulcer	5 (6.0)	1 (2.9)	1 (5.9)	2.17 (0.23–106.02)	1.03 (0.10–51.50)
Colitis	3 (3.6)	1 (2.9)	0 (0)	1.27 (0.10–65.85)	–
Postoperative bleeding†	2 (2.4)	2 (5.7)	0 (0)	0.41 (0.29–5.89)	–
Bowel ulcer	2 (2.4)	1 (2.9)	0 (0)	0.84 (0.04–50.97)	–
Ischemic colitis	1 (1.2)	1 (2.9)	1 (5.9)	0.42 (0.005–33.50)	0.20 (0.002–16.27)
Colon erosion	0 (0)	1 (2.9)	0 (0)	0 (0–16.45)	–
Unexplained	10 (12.0)	4 (11.4)	3 (17.6)	1.06 (0.28–4.99)	0.64 (0.14–4.09)

GIB = gastrointestinal bleeding; OR = odds ratio.
* OR was not calculated if dabigatran recipients had no events.
† Includes bleeding from anastomosis (2 cases) and postpolypectomy bleeding (2 cases).

Appendix Table 6. Comparison of GIB Rates Among Patients Receiving Rivaroxaban, Apixaban, or Dabigatran: Patients With AF Living in the Greater Capital Area

OAC	GIB Events per 100 Person-Years	HR (95% CI)		
		Compared With Apixaban	Compared With Dabigatran	Compared With Rivaroxaban
Overall GIB*				
Apixaban	2.7	–	1.44 (0.73–2.84)	0.76 (0.52–1.10)
Dabigatran	1.9	0.69 (0.35–1.36)	–	0.52 (0.28–0.99)
Rivaroxaban	3.4	1.32 (0.91–1.92)	1.91 (1.01–3.63)	–
Major GIB				
Apixaban	1.7	–	1.42 (0.67–3.01)	0.73 (0.46–1.17)
Dabigatran	1.3	0.70 (0.33–1.49)	–	0.51 (0.25–1.07)
Rivaroxaban	2.3	1.36 (0.85–2.18)	1.94 (0.93–4.04)	–
Upper GIB				
Apixaban	1.0	–	1.83 (0.59–5.68)	0.81 (0.43–1.53)
Dabigatran	0.6	0.55 (0.18–1.70)	–	0.44 (0.15–1.28)
Rivaroxaban	1.2	1.23 (0.65–2.33)	2.26 (0.78–6.49)	–
Lower GIB				
Apixaban	1.5	–	1.16 (0.50–2.69)	0.90 (0.54–1.49)
Dabigatran	1.3	0.87 (0.37–2.02)	–	0.78 (0.35–1.74)
Rivaroxaban	1.6	1.12 (0.67–1.86)	1.29 (0.57–2.90)	–

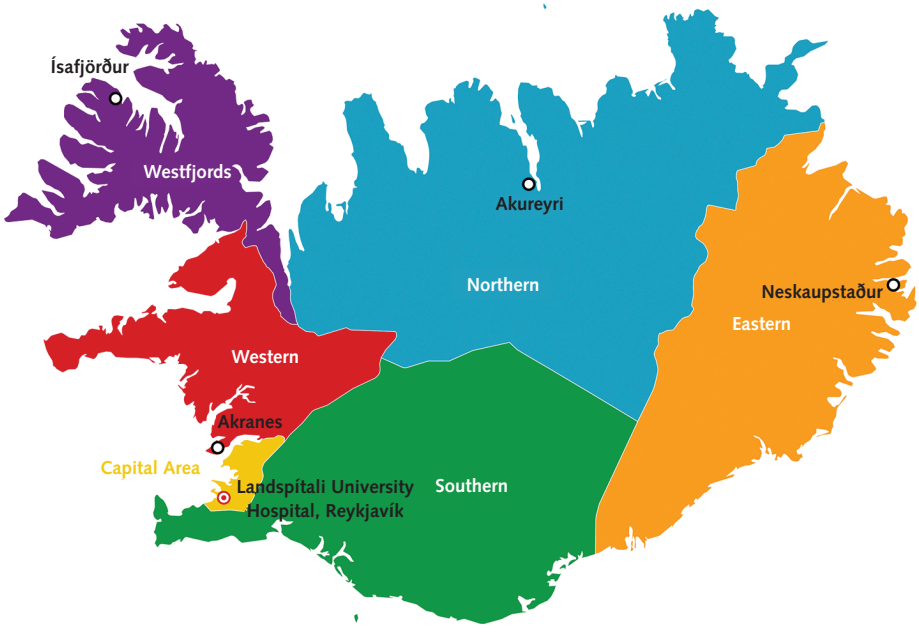
AF = atrial fibrillation; GIB = gastrointestinal bleeding; HR = hazard ratio; OAC = oral anticoagulant.
* Upper and lower GIB rates do not equate to the overall GIB rate because some GIB events could not be classified as either upper or lower.

Appendix Table 7. Study Groups Stratified by Area of Residence*

Region	Apixaban	Dabigatran	Rivaroxaban
Capital area	1512 (40)	310 (8)	1960 (52)
Eastern	73 (41)	17 (9)	90 (50)
Northern	144 (21)	55 (8)	495 (71)
Southern	267 (33)	99 (12)	438 (54)
Western	116 (38)	12 (4)	179 (58)
Westfjords	45 (45)	1 (1)	55 (54)

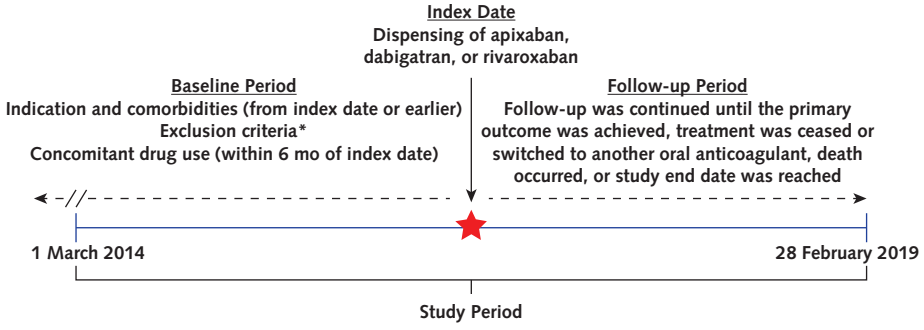
* Data are presented as numbers (percentages).

Appendix Figure 1. The division of Iceland by the service area of each regional hospital.



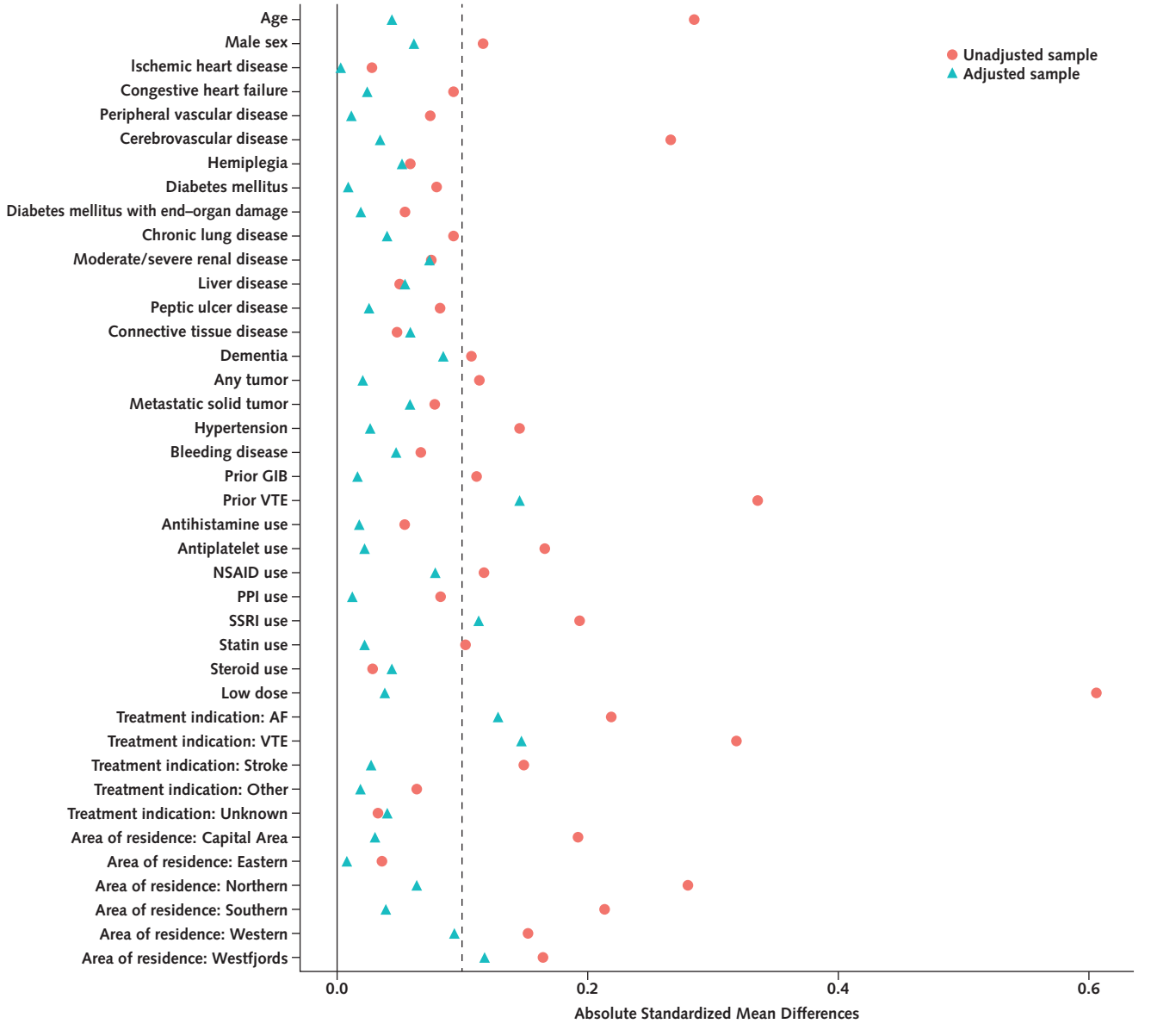
The location of each regional hospital is shown on the map. Landspítali, the only tertiary hospital in the country, serves as a regional hospital for both the capital area and southern Iceland.

Appendix Figure 2. Cohort creation diagram.



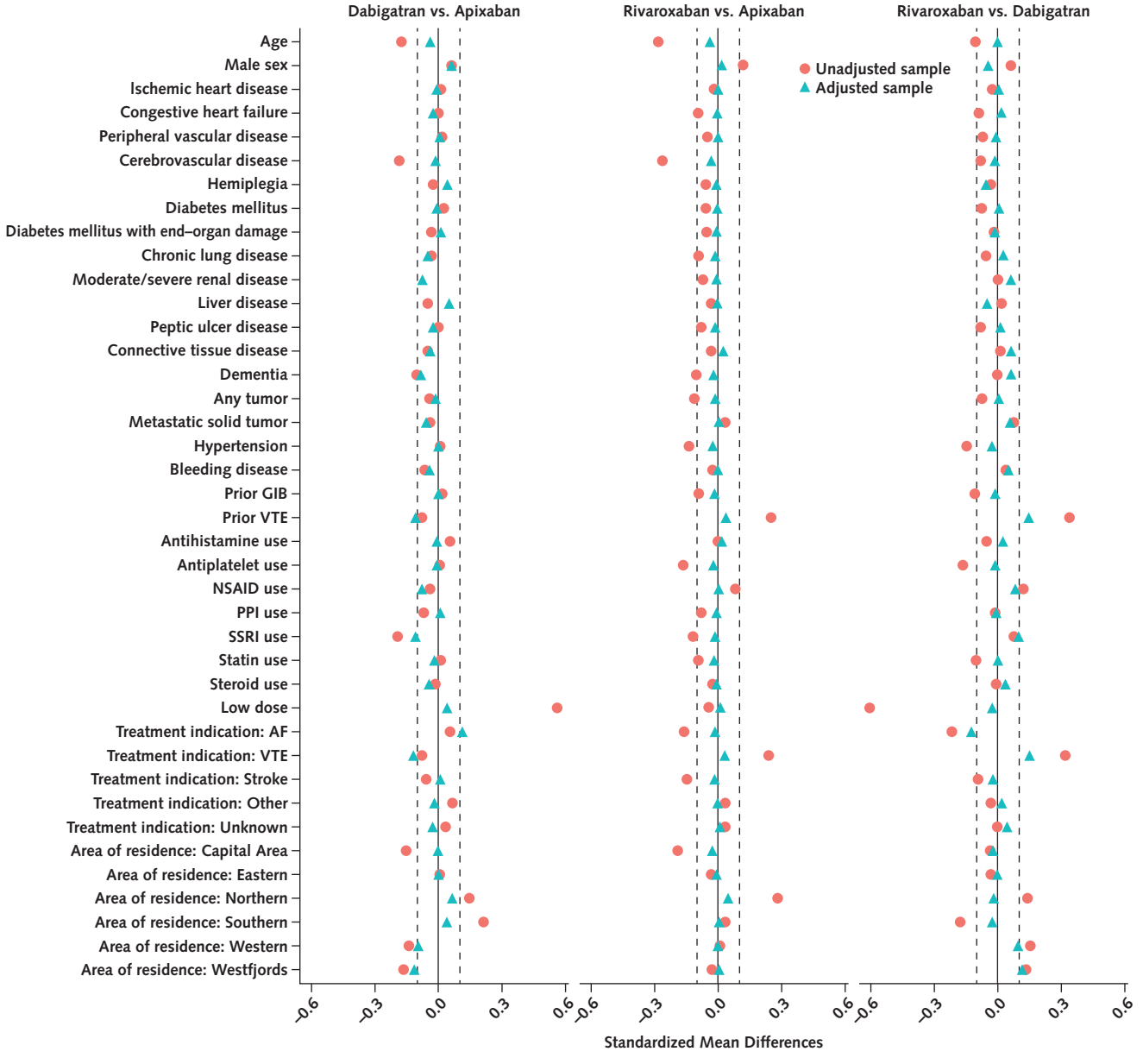
*The exclusion criteria were residence outside of Iceland at the index date, prior use of oral anticoagulants within 12 months of the index date, prescription of 2.5 mg of rivaroxaban at the index date, and diagnosis of end-stage renal disease, a mechanical heart valve, or mitral stenosis from the index date or earlier.

Appendix Figure 3. Love plot comparing maximal standardized mean difference in the study population before and after inverse probability weighting.



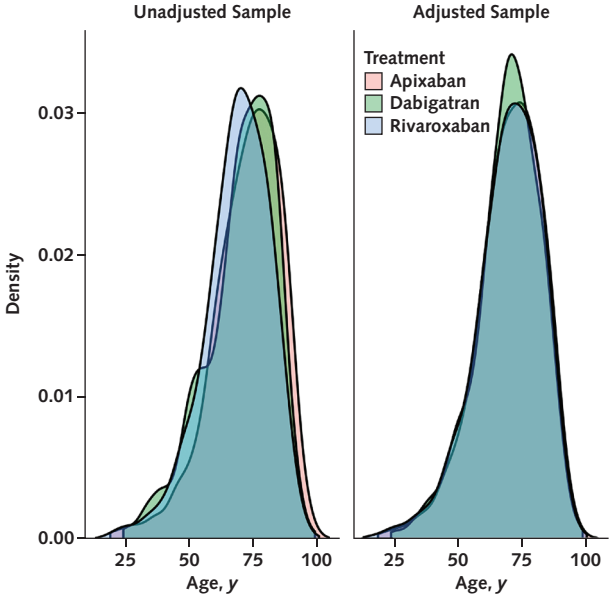
AF = atrial fibrillation; GIB = gastrointestinal bleeding; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton-pump inhibitor; SSRI = selective serotonin reuptake inhibitor; VTE = venous thromboembolism.

Appendix Figure 4. Love plot comparing standardized mean difference between individual study groups before and after inverse probability weighting.

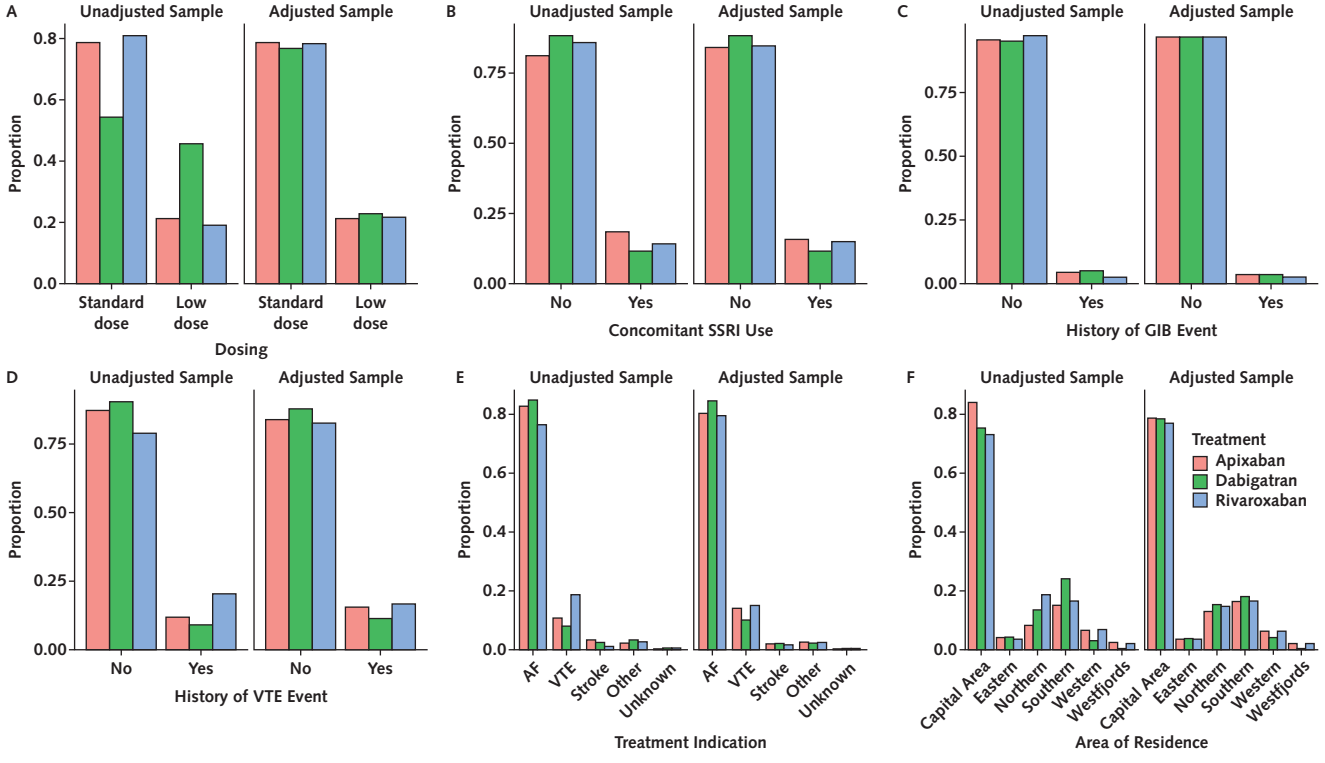


AF = atrial fibrillation; GIB = gastrointestinal bleeding; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton-pump inhibitor; SSRI = selective serotonin reuptake inhibitor; VTE = venous thromboembolism.

Appendix Figure 5. Density plot comparing the distribution of age across study groups before and after inverse probability weighting.

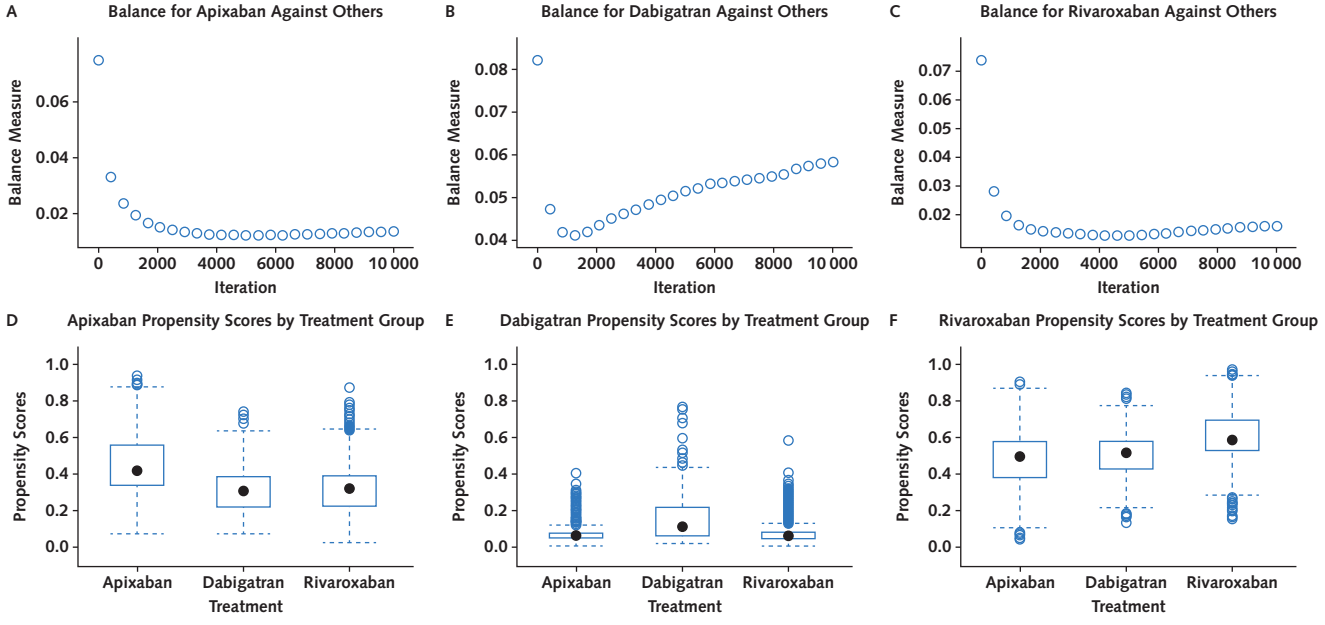


Appendix Figure 6. Bar graphs comparing the distribution of chosen categorical variables across study groups before and after inverse probability weighting.



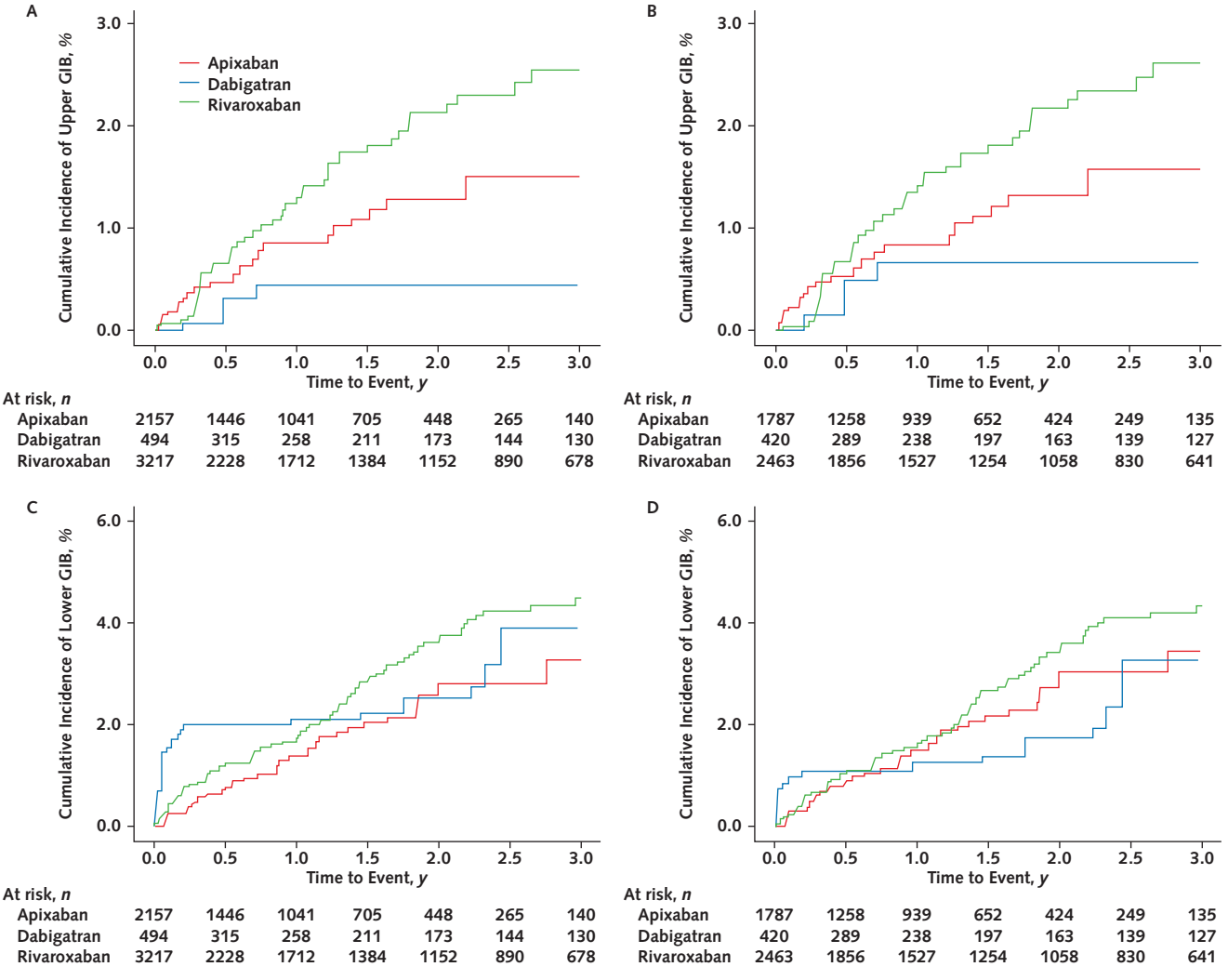
AF = atrial fibrillation; GIB = gastrointestinal bleeding; SSRI = selective serotonin reuptake inhibitor; VTE = venous thromboembolism.

Appendix Figure 7. Plots comparing balance between study groups after inverse probability weighting.



A to C. Balance measures of the inverse probability weighting model calculated with mean standardized effect size and average treatment effect. The plots show the mean change in the absolute mean standardized difference across study variables by the number of iterations used in the construction of the inverse probability weighting model. The final model used 10 000 iterations. D to F. Box plots comparing the distribution of propensity scores between groups after weighting.

Appendix Figure 8. Kaplan–Meier plots comparing the cumulative incidence of GIB events.



GIB = gastrointestinal bleeding. **A and B.** Comparison of the cumulative incidence of upper GIB with apixaban, dabigatran, and rivaroxaban for all patients and patients with AF only, respectively. **C and D.** Comparison of the cumulative incidence of lower GIB with apixaban, dabigatran, and rivaroxaban for all patients and patients with AF only, respectively.