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Association of type of oral anticoagulation with risk of bleeding in 45,114 patients with venous thromboembolism during initial and extended treatment—A nationwide register-based study

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Abstract. Glise Sandblad K, Schulman S, Rosengren A, Sörbo J, Philipson J, Hansson P-O. Association of type of oral anticoagulation with risk of bleeding in 45,114 patients with venous thromboembolism during initial and extended treatment—A nationwide register-based study. *J Intern Med.* 2023;**294**:743–760.

Background. Safety data for different anticoagulant medications in venous thromboembolism (VTE) are scarce, in particular for extended treatment.

Objectives. To compare major bleeding rates depending on the choice of anticoagulation during initial (first 6 months) and extended treatment (6 months up to 5 years).

Methods. A nationwide register-based study including cancer-free patients with a first-time VTE between 2014 and 2020. Cox proportional hazards models were used to compare bleeding rates.

Results. We included 6558 patients on warfarin, 18,196 on rivaroxaban, and 19,498 on apixaban. At 6 months, 4750 (72.4%) remained on warfarin, 11,366 (62.5%) on rivaroxaban, and 11,940 (61.2%) on apixaban. During initial treatment, major bleeding rates were 3.86 (95% CI 3.14–4.58), 2.93 (2.55–3.31), and 1.95 (1.65–2.25) per 100 patient-years for warfarin, rivaroxaban, and apixaban, respectively, yielding adjusted hazard ratios (aHRs) of 0.89 (95% CI 0.71–1.12) for rivaroxaban versus warfarin, 0.55 (0.43–0.71) for apixaban versus warfarin, and 0.62 (0.50–0.76) for apixaban versus rivaroxaban. During extended treatment, major bleeding rates were 1.55 (1.19–1.91), 1.05 (0.85–1.26), and 0.96 (0.78–1.15) per 100 patient-years for warfarin, rivaroxaban, and apixaban, respectively, with aHRs of 0.72 (0.53–0.99) for rivaroxaban versus warfarin, 0.60 (0.44–0.82) for apixaban versus warfarin, and 0.85 (0.64–1.12) for apixaban versus rivaroxaban. Previous bleeding and increasing age were risk factors for bleeding both during initial and extended treatment.

Conclusion. Apixaban had a lower bleeding risk than warfarin or rivaroxaban during initial treatment. During extended treatment, bleeding risk was similar for apixaban and rivaroxaban, and higher with warfarin.

Keywords: apixaban, anticoagulants, hemorrhage, rivaroxaban, venous thromboembolism, warfarin

Background

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common disease with an annual incidence rate of approximately 1 per 1000 inhabitants [1]. VTE has a high recurrence rate, particularly in cases without temporary

provoking factors [2]. Extended treatment with anticoagulation beyond the initial treatment phase (3–6 months) effectively reduces the number of recurrences compared with placebo during the duration of extended treatment but does not affect the risk of recurrence after ending treatment [3–5].

For initial treatment, direct oral anticoagulants (DOACs), as a group, have lower bleeding risk compared with vitamin K antagonists (VKA) according to pooled data from randomized controlled trials (RCTs) [6]. In individual studies, there are differences in the safety benefits of different DOACs, with possibly the largest benefit for apixaban [7–11]; however, without head-to-head studies, it is not possible to draw firm conclusions. In real-world data, a superior safety profile has been confirmed for apixaban versus warfarin [12–15], but there is conflicting evidence concerning the safety benefit of rivaroxaban versus warfarin [14, 16, 17]. Previous data from registry and medical claims databases also suggest that apixaban might have a more favorable safety profile than rivaroxaban during initial treatment [13, 14, 18]. This is currently being investigated in a randomized trial (NCT03266783) [19].

In accordance with international guidelines, many VTE patients receive extended anticoagulation [6, 20, 21]. In clinical practice, the decision for extended treatment for VTE requires balancing the risk of a recurrent event without treatment against the risk of bleeding during treatment in each patient. However, the bleeding risk during extended treatment with DOACs is largely unknown. Data on treatment beyond 1 year of extended treatment are lacking from RCTs and prospective cohort studies [22]. In registry data, most studies have addressed initial treatment with approximately 6 months of follow-up [12–14, 16, 18].

The aim of this study was to describe the risk of major bleeding depending on the choice of anticoagulant treatment, both during initial VTE treatment (0–6 months) and extended treatment (6 months up to 5 years) in patients with a first-time VTE. We also aimed to identify risk factors for predicting an increased risk of bleeding during initial and extended anticoagulant therapy. Patients with known cancers were excluded from the analysis because the risk of bleeding is considerably higher in this patient group, leading to difficulties in interpreting the data when the groups are not studied separately [23].

Methods

Study population

This was a cohort study based on nationwide data from the Swedish Patient Register, the Prescribed Drug Register, and the Cause of Death Register. The Swedish Patient Register includes diagnostic and procedural codes with complete coverage of inpatient and hospital-based outpatient care [1, 24]. The Prescribed Drug Register includes all dispensed prescription drugs in Sweden [25]. The Cause of Death Register includes data on main and contributing causes of death for all persons registered in Sweden [26].

We included patients who filled a prescription for an oral anticoagulant within 30 days (index treatment) of a first-time PE or DVT between January 2014 and December 2020. We excluded individuals with DVT or PE prior to the start of the study (registered in the Swedish Patient Register after 1987), patients with atrial fibrillation at any time point until the day of censoring, patients who were pregnant at inclusion (defined as within 9 months prior to childbirth), patients with a diagnosis of cancer within 1 year before or on the date of inclusion in the study (International Classification of Diseases [ICD] 10 codes, see Table S1), and patients who had filled a prescription for anticoagulant medication within 6 months prior to VTE (for Anatomical Therapeutic Chemical [ATC] codes see Table S2) (Fig. 1). Patients were followed until major bleeding, death, diagnosis of cancer, end of index treatment, 5 years after diagnosis of VTE, or the end of follow-up (December 31, 2020). The study was approved by the Swedish Ethical Review Authority (Dnr 2019-01956).

Definitions

Diagnosis of PE and DVT was defined according to ICD 10: PE (I26) and DVT (I80 except for I80.0). VTE was defined as a first inpatient or outpatient diagnosis of DVT or PE *and* at least one dispensed prescription of anticoagulant medication within 30 days of diagnosis (for inpatients after discharge). Diagnoses were accepted regardless of whether they were considered primary or secondary diagnoses.

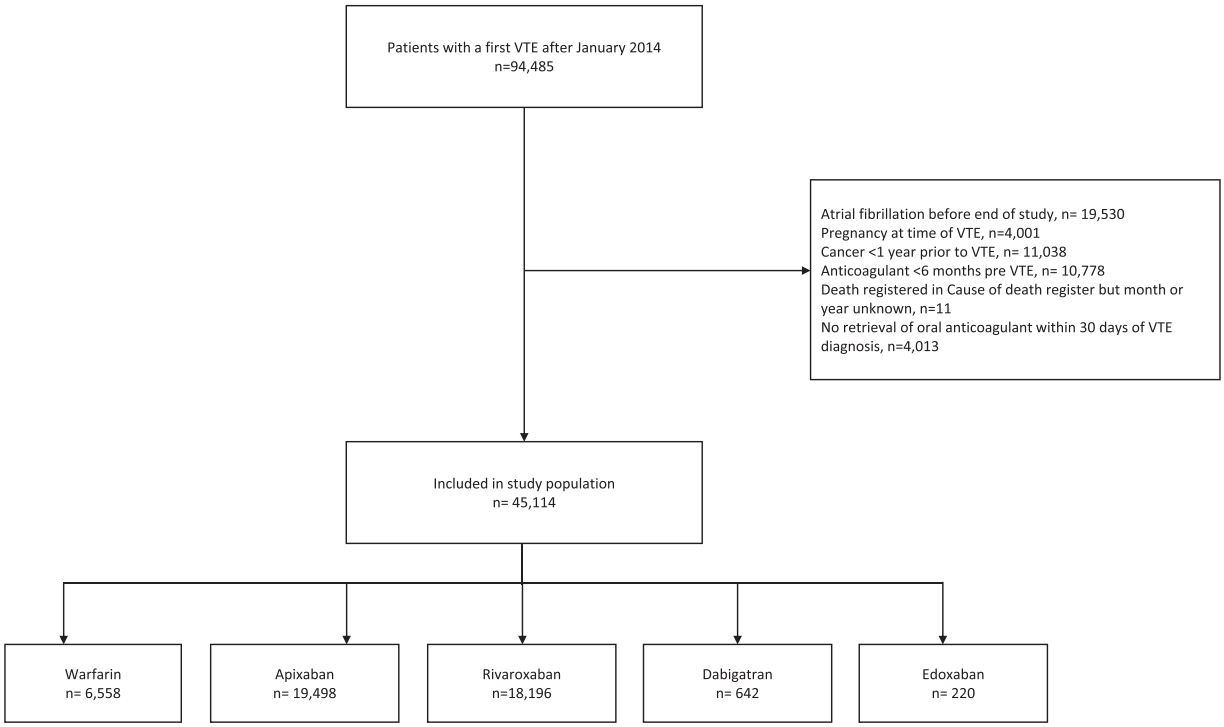

Fig. 1 *Flow chart for study inclusion and number of patients with a first venous thromboembolism (VTE) in each study group.*

Definition of ongoing treatment

Patients were considered on treatment for VTE if they filled a prescription of anticoagulant treatment within 30 days of a diagnosis of VTE. Continued treatment was defined as at least two dispenses of a prescription for an index anticoagulant treatment per 12 months. End of treatment was defined as 3 months after the last refill of a prescription, unless a new refill was carried out within 12 months. Change of dosage of the same anticoagulant medication was allowed within the same index treatment period, whereas a switch to another anticoagulant medication was considered end of treatment (for ATC codes for anticoagulant treatments, see Table S2).

Outcomes

The primary outcome of the study was major bleeding, defined as any principal/first position inpatient diagnosis of bleeding (intracranial, gastrointestinal [GI], hematuria, airway bleeding, anemia because of bleeding or iron deficiency, hemopericardium, and gynecological bleeding) or bleeding on a death certificate (any position; for ICD codes, see Table S3). Fatal bleeding was defined as a diagnosis of bleeding in any position on a death certificate *or* bleeding requiring hospitalization (primary position inpatient diagnosis) and death within 30 days of discharge from the hospital.

Definition of comorbidities

The following comorbidities were defined as a registered diagnosis within 7 years prior to the VTE, on the same date as the VTE, or during follow-up: hypertension, heart failure, chronic obstructive pulmonary disease, diabetes, renal failure, liver disease, ischemic heart disease, peripheral arterial disease, ischemic stroke, hemorrhagic stroke, systemic connective tissue disease, inflammatory bowel disease, and dementia. In addition, previous bleeding was defined as a registered inpatient diagnosis within 7 years prior to or on the same date as the VTE, but not if diagnosed during follow-up (for ICD codes, see Table S4).

Concomitant pharmaceutical treatment

We captured concomitant medication with antiplatelet agents, proton pump inhibitors (PPI),

selective serotonin reuptake inhibitors, or statins if a prescription of these medications was filled in during anticoagulant treatment (for ATC codes, see Table S4). Patients were considered to be on concomitant treatment during 0–6 months from the date of filling a prescription of the concomitant medication. During 6 months to 5 years, patients were considered to be on the concomitant medication from the start of the period if they filled a prescription during months 3–6 of anticoagulant treatment. If the patient filled a prescription during 6 months to 5 years, the concomitant treatment was considered to start on the date of filling a prescription. When fulfilling these criteria, patients were considered to be on concomitant treatment for the entire remaining period studied (initial or extended treatment).

Statistical analysis

Categorical variables are presented as numbers with percentages. Continuous variables are presented as means and standard deviations and medians with first and third quartiles. Cumulative incidence functions of major bleeding, intracranial bleeding, and GI bleeding for different anticoagulant treatments were calculated with 95% confidence intervals (CI) with death, cancer, and other types of bleeding as competing risks. Event rates per 100 patient-years for all major bleeding, intracranial bleeding, and GI bleeding and their corresponding 95% CIs were calculated using Poisson models. In order to characterize the etiology of bleeding, we used cause-specific hazards in Cox proportional hazard models in which we additionally censored for death, cancer, and other types of bleeding [27]. We used multivariable Cox proportional hazards regression to estimate associations between choice of anticoagulant treatment and risk of bleeding during follow-up, adjusted for the following confounders: sex, age, and all previously mentioned comorbidities and concomitant pharmacological treatments in Table S4. We used a single model containing all three anticoagulant agents, parameterized using warfarin as the reference category for each of the other agents. In subanalyses with few events, the number of adjustment variables was reduced according to the number of events (see footnote for each figure with multivariable adjusted numbers). We also used time-dependent Cox proportional hazards regression (time-updated for anticoagulant treatment) to estimate associations between bleeding and various comorbidities in patients with VTE. The proportional hazards assumption was assessed graphically and with diagnostics based on the weighted Schoenfeld residuals for nonproportional hazards. The main results for the Cox regression models are hazard ratios (HR) with 95% CIs. All significance tests were two-sided and conducted at the 5% significance level. SAS Version 9.4 (SAS Institute, Cary, NC, USA) was used for calculations of all statistics.

Results

Patient characteristics

The study included 45,114 patients with a first-time VTE. The participants' median age was 68 years (54.7% men) and median follow-up after initiation of anticoagulation treatment was 0.60 years (mean 0.98 years). As shown in Table 1, a total of 6558 patients were treated with warfarin, 18,196 with rivaroxaban, and 19,498 with apixaban. Dabigatran treatment was initiated in 642 patients and edoxaban in 220 patients. Table 1 shows characteristics of individuals according to anticoagulant treatment, including data on comorbidities and concomitant pharmacological treatment.

Patients on rivaroxaban were slightly younger, more often men and had fewer comorbidities than patients on other medications. Patients on edoxaban or warfarin were slightly older, had more diabetes, hypertension, heart failure, renal failure, peripheral arterial disease, and systemic connective tissue disorder than patients on other anticoagulant medications. Patients on dabigatran more often had a history of bleeding, including hemorrhagic stroke, than patients on other treatments. Patients receiving dabigatran or edoxaban were excluded from the multivariable statistical analysis because of too few individuals and events. Event rates are shown in Table 2.

After 6 months, 28,056 patients remained on either warfarin (n = 4750), rivaroxaban (n = 11,366), or apixaban (n = 11,940). Among apixaban users, 917 (8%) were on reduced dosage (2.5 mg tablets) after 6 months, and 2269 (31%) patients switched from full dosage (5 mg tablets) to reduced dosage between 6 months and 5 years of treatment. Among rivaroxaban users, 125 (1%) were on reduced dosage (10 mg tablets) after 6 months, and 664 (11%) patients had a dose reduction from full dosage (20 mg) to reduced dosage between 6 months and 5 years of treatment.

Table 1. *Baseline characteristics of 45,114 patients on index anticoagulant treatment after a first-time venous thromboembolism (VTE) divided according to choice of treatment.*

Characteristics	Total ($n = 45,114$)	Warfarin ($n = 6558$)	Rivaroxaban ($n = 18,196$)	Apixaban ($n = 19,498$)	Edoxaban ($n = 220$)	Dabigatran ($n = 642$)
			Mean (SD), median (min; max)			
Follow-up from VTE, years	0.98 (1.09) 0.60 (0.00; 5.01)	1.14 (1.27) 0.69 (0.01; 5.00)	0.95 (1.10) 0.57 (0.00; 5.00)	0.97 (1.02) 0.63 (0.01; 5.01)	0.60 (0.53) 0.50 (0.03; 3.6)	0.85 (0.93) 0.52 (0.01; 5.01)
Demographics			Mean (SD), median (min; max)			
Age, years	65.4 (16.6) 68 (0; 104)	67.1 (16.4) 69 (0; 102)	64.5 (16.8) 67 (13; 103)	65.7 (16.4) 68 (12; 104)	68.8 (17.3) 73 (22; 100)	65.5 (16.9) 68 (15; 98)
Male *n* (%)	24,662 (54.7%)	3511 (53.5%)	10,142 (55.7%)	10,570 (54.2%)	106 (48.2%)	333 (51.9%)
Comorbidity			*n* (%)			
Bleeding	3911 (8.7%)	600 (9.1%)	1396 (7.7%)	1782 (9.1%)	34 (15.5%)	99 (15.4%)
Hypertension	14,646 (32.5%)	2560 (39.0%)	5380 (29.6%)	6363 (32.6%)	113 (51.4%)	230 (35.8%)
Heart failure	2322 (5.1%)	512 (7.8%)	760 (4.2%)	990 (5.1%)	21 (9.5%)	39 (6.1%)
Chronic obstructive pulmonary disease	2583 (5.7%)	426 (6.5%)	952 (5.2%)	1142 (5.9%)	16 (7.3%)	47 (7.3%)
Diabetes	4293 (9.5%)	818 (12.5%)	1496 (8.2%)	1883 (9.7%)	36 (16.4%)	60 (9.3%)
Renal disease	1777 (3.9%)	607 (9.3%)	439 (2.4%)	685 (3.5%)	24 (10.9%)	22 (3.4%)
Liver disease	337 (0.7%)	54 (0.8%)	129 (0.7%)	139 (0.7%)	2 (0.9%)	13 (2.0%)
Ischemic heart disease	3781 (8.4%)	750 (11.4%)	1345 (7.4%)	1587 (8.1%)	28 (12.7%)	71 (11.1%)
Peripheral arterial disease	700 (1.6%)	138 (2.1%)	258 (1.4%)	287 (1.5%)	8 (3.6%)	9 (1.4%)
Stroke (ischemic)	1918 (4.3%)	302 (4.6%)	700 (3.8%)	852 (4.4%)	13 (5.9%)	51 (7.9%)
Stroke (hemorrhagic)	348 (0.8%)	44 (0.7%)	118 (0.6%)	159 (0.8%)	2 (0.9%)	25 (3.9%)
Systemic connective tissue disorders	1678 (3.7%)	330 (5.0%)	584 (3.2%)	731 (3.7%)	14 (6.4%)	19 (3.0%)
Inflammatory bowel disease	1119 (2.5%)	176 (2.7%)	442 (2.4%)	476 (2.4%)	7 (3.2%)	18 (2.8%)
Dementia	1720 (3.8%)	218 (3.3%)	674 (3.7%)	783 (4.0%)	13 (5.9%)	32 (5.0%)
Medication-collected at least once during index treatment						
Antiplatelet treatment	4346 (9.6%)	797 (12.2%)	1375 (7.6%)	1663 (8.5%)	23 (10.5%)	71 (11.1%)
Proton pump inhibitor	11,937 (26.5%)	1888 (28.8%)	4413 (24.3%)	5218 (26.8%)	84 (38.2%)	212 (33.0%)
Selective serotonin reuptake inhibitors	4945 (11.0%)	772 (11.8%)	1996 (11.0%)	2019 (10.4%)	28 (12.7%)	88 (13.7%)
Statins	9004 (20.0%)	1529 (23.3%)	3252 (17.9%)	3964 (20.3%)	57 (25.9%)	142 (22.1%)

Table 2. *Event rate for major bleeding, intracranial bleeding, gastrointestinal bleeding, and major bleeding for patients aged <65 years and ≥65 years depending on the choice of anticoagulant treatment for 0–6 months and 6 months to 5 years.*

Treatment	Events	Patient-years	Rate n/100 years (95% CI)
Major bleeding, 0–6 months			
Warfarin	111	2877	3.86 (3.14–4.58)
Rivaroxaban	223	7610	2.93 (2.55–3.31)
Apixaban	160	8214	1.95 (1.65–2.25)
Edoxaban	2	83	2.41 (0.00–5.75)
Dabigatran	12	258	4.65 (2.02–7.27)
Major bleeding, 6 months to 5 years			
Warfarin	71	4583	1.55 (1.19–1.91)
Rivaroxaban	102	9689	1.05 (0.85–1.26)
Apixaban	103	10,710	0.96 (0.78–1.15)
Edoxaban	1	49	2.03 (0.00–6.01)
Dabigatran	5	290	1.72 (0.21–3.23)
Intracranial bleeding, 0–6 months			
Warfarin	9	2877	0.31 (0.11–0.52)
Rivaroxaban	22	7610	0.29 (0.17–0.41)
Apixaban	22	8214	0.27 (0.16–0.38)
Edoxaban	0	83	0
Dabigatran	1	258	0.39 (0.00–1.15)
Intracranial bleeding, 6 months to 5 years			
Warfarin	14	4583	0.31 (0.15–0.47)
Rivaroxaban	13	9689	0.13 (0.06–0.21)
Apixaban	21	10,710	0.20 (0.11–0.28)
Edoxaban	1	49	2.03 (0.00–6.01)
Dabigatran	0	290	0
Gastrointestinal bleeding, 0–6 months			
Warfarin	55	2877	1.91 (1.41–2.42)
Rivaroxaban	112	7610	1.47 (1.20–1.74)
Apixaban	65	8214	0.79 (0.60–0.98)
Edoxaban	1	83	1.21 (0.00–3.57)
Dabigatran	7	258	2.71 (0.70–4.72)
Gastrointestinal bleeding, 6 months to 5 years			
Warfarin	19	4583	0.41 (0.23–0.60)
Rivaroxaban	41	9689	0.42 (0.29–0.55)
Apixaban	35	10,710	0.33 (0.22–0.44)
Edoxaban	0	49	0
Dabigatran	3	290	1.03 (0.00–2.20)
Major bleeding, patient aged <65 years, 0–6 months			
Warfarin	24	1079	2.22 (1.33–3.11)
Rivaroxaban	45	3316	1.36 (0.96–1.75)
Apixaban	33	3303	1.00 (0.66–1.34)
Major bleeding, patient aged <65 years, 6 months to 5 years			
Warfarin	12	1714	0.70 (0.30–1.10)
Rivaroxaban	14	3879	0.36 (0.17–0.55)
Apixaban	17	3925	0.43 (0.23–0.64)
Major bleeding, patient aged ≥65 years, 0–6 months			
Warfarin	87	1797	4.84 (3.82–5.86)
Rivaroxaban	178	4294	4.14 (3.54–4.75)
Apixaban	127	4911	2.59 (2.14–3.04)
Major bleeding, patient aged ≥65 years, 6 months to 5 years			
Warfarin	59	2868	2.06 (1.53–2.58)
Rivaroxaban	88	5810	1.51 (1.20–1.83)
Apixaban	86	6785	1.27 (1.00–1.54)

Abbreviation: CI, confidence interval.

Major bleeding

During the first 6 months of treatment with warfarin, rivaroxaban, or apixaban, 494 patients (1.1% of patients starting anticoagulant treatment) experienced major bleeding. Patients on warfarin, rivaroxaban, or apixaban had major bleeding rates (per 100 patient-years at risk) of 3.86 (95% CI 3.14–4.58), 2.93 (95% CI 2.55–3.31), and 1.95 (95% CI 1.65–2.25), respectively. Cumulative incidence is shown in Fig. 2A1. After multivariable adjustment, patients on apixaban, but not rivaroxaban, had a significantly lower risk of major bleeding than those on warfarin: adjusted HR (aHR) 0.55 (95% CI 0.43–0.71) for apixaban and aHR 0.89 (95% CI 0.71–1.12) for rivaroxaban (Fig. 3A1). Furthermore, there was a significantly lower rate of major bleeding for patients on apixaban compared with those on rivaroxaban (aHR 0.62; 95% CI 0.50–0.76). In a subanalysis of the first month of treatment, 44 patients on apixaban and 98 patients on rivaroxaban experienced major bleeding. The event rate was 2.79 (95% CI 1.97–3.61) for apixaban and 6.66 (95% CI 5.34–7.89) for rivaroxaban, yielding an aHR of 0.40 (95% CI 0.28–0.57). During months 1–6, 116 patients on apixaban and 126 patients on rivaroxaban experienced major bleeding, resulting in event rates of 1.76 (95% CI 1.44–2.08) for apixaban and 2.05 (95% CI 1.69–2.41) for rivaroxaban. The difference was not significant, aHR 0.79 (95% CI 0.61–1.02).

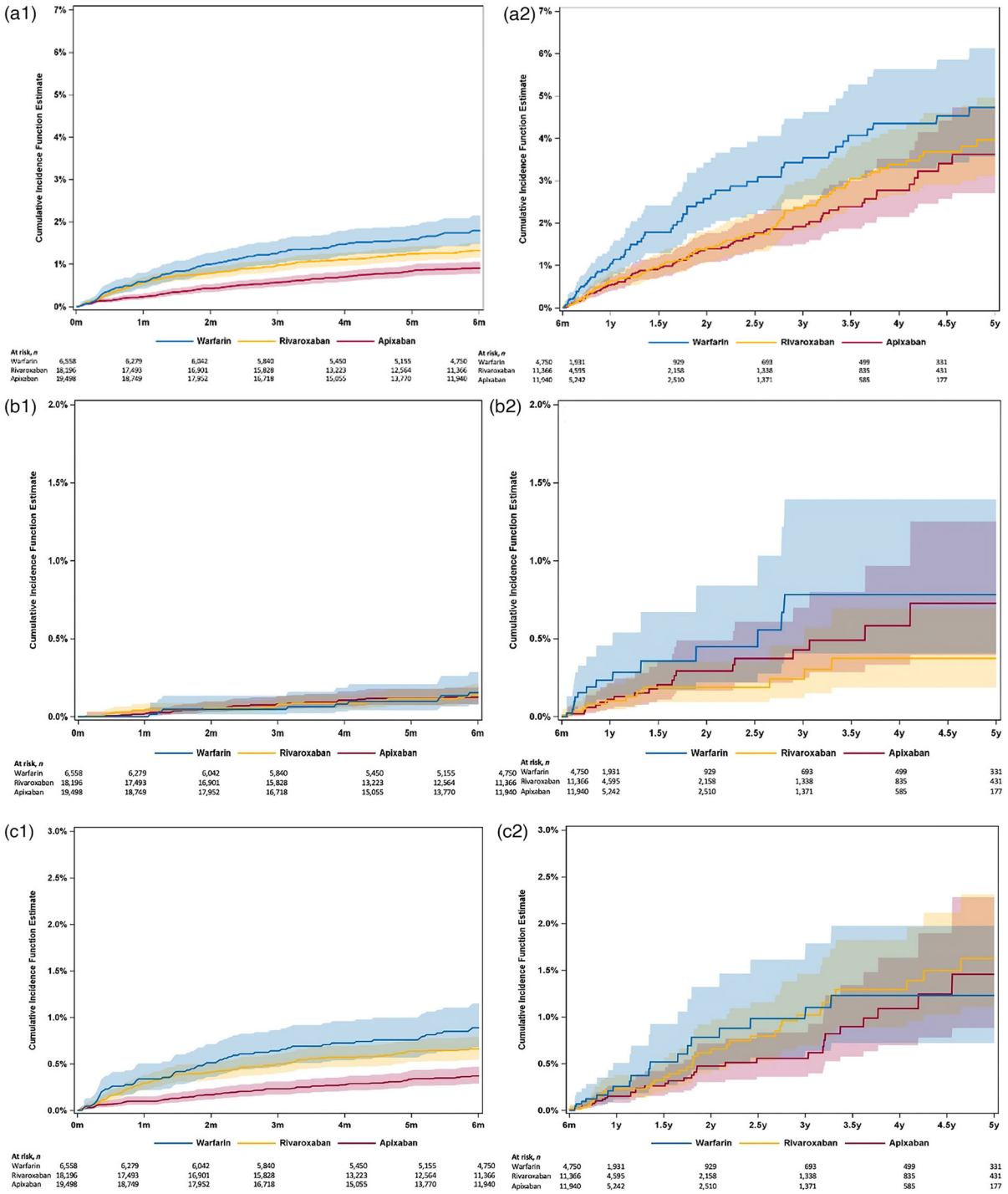

Fig. 2 *Cumulative incidence graphs for the initial 6 months of treatment (1) and extended treatment after 6 months up to 5 years (2) for major bleeding (A1 + A2), intracranial bleeding (B1 + B2), and gastrointestinal (GI)-bleeding (C1 + C2). Major bleeding for patients aged <65 years (D1 + D2) and ≥65 years (E1 + E2).*

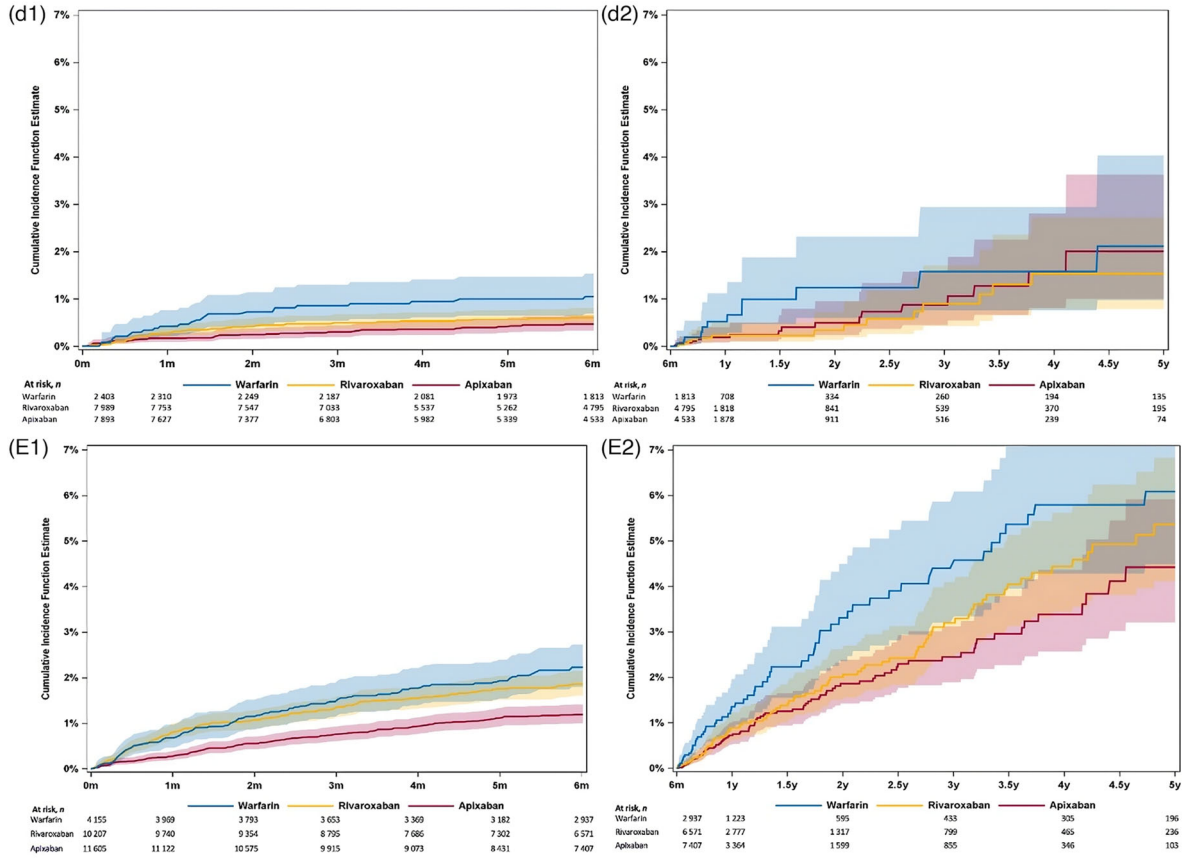

Fig. 2 *Continued*

Patients who continued treatment with the index anticoagulant for more than 6 months after the VTE event were followed up to 5 years. During this time, 276 patients (0.98% of patients who remained on anticoagulant treatment at 6 months) experienced major bleeding. The rates of major bleeding per 100 patient-years for warfarin, rivaroxaban, or apixaban were 1.55 (1.19–1.91), 1.05 (0.85–1.26), and 0.96 (0.78–1.15), respectively. The cumulative incidence is shown in Fig. 2A2. After multivariable adjustment, both rivaroxaban (aHR 0.72; 0.53–0.99) and apixaban (aHR 0.60; 0.44–0.82) carried a lower bleeding risk than warfarin (Fig. 3A2). Apixaban had an aHR of 0.85 (0.64–1.12) when compared with rivaroxaban.

Intracranial bleeding

During the first 6 months of treatment, 53 patients (0.12% of patients starting anticoagulant treatment) experienced intracranial bleeding. The bleeding rate during the initial 6 months was 0.31 (0.11–0.52) per 100 patient-years for warfarin. The corresponding event rate was 0.29 (0.17–0.41) for rivaroxaban and 0.27 (0.16–0.38) for apixaban (Table 2). The cumulative incidence of intracranial bleeding is shown in Fig. 2B1. During extended treatment between 6 months and 5 years, 48 patients (0.21% of patients who remained on anticoagulant treatment at 6 months) had an intracranial bleed. The bleeding rate per 100 patient-years during extended treatment was 0.31 (0.15–0.47) for warfarin, 0.13 (0.06–0.21) for rivaroxaban, and 0.20 (0.11–0.28) for apixaban (Table 2); the cumulative incidence is presented in Fig. 2B2. After multivariable adjustment for comorbidities and concomitant medications, there was no difference in the HRs of intracranial bleeding in patients on rivaroxaban or apixaban compared with patients on warfarin during initial treatment (up to 6 months). For extended treatment (6 months to 5 years), rivaroxaban, but not apixaban, carried a

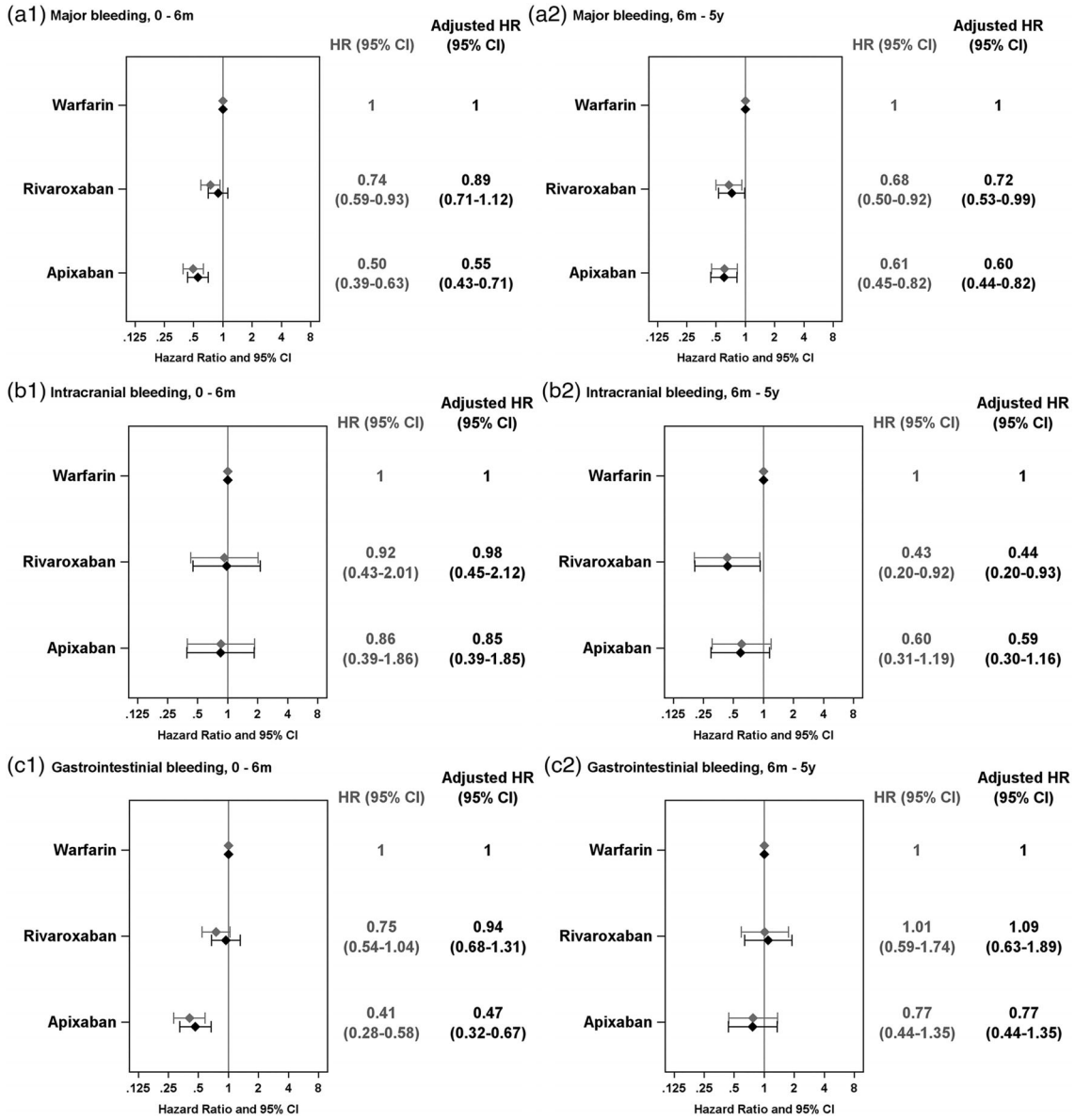

Fig. 3 *Unadjusted and multivariable adjusted hazard[1] ratios for major bleeding (A), intracranial bleeding (B), gastrointestinal bleeding (C), and major bleeding in patients aged <65 years (D) and ≥65 years (E). Section 1 during the initial 6 months of treatment and section 2 during extended treatment after 6 months up to 5 years. [1]Multivariable adjustment for A1,A2 and E1,E2 was made for age, sex, previous bleeding (inpatient diagnosis within 7 years prior to or on the same date as the venous thromboembolism [VTE], not during follow-up) and inpatient diagnosis within 7 years prior to or during follow-up after VTE of hypertension, heart failure, chronic obstructive pulmonary disease, diabetes, renal failure, liver disease, ischemic heart disease, peripheral arterial disease, ischemic stroke, hemorrhagic stroke, systemic connective tissue disease, inflammatory bowel disease, and dementia. Adjustment was also made for concomitant use of antiplatelet treatment, proton pump inhibitors (PPI), selective serotonin reuptake inhibitors or statins during anticoagulant treatment. No hazard ratios (HRs) were calculated for edoxaban or dabigatran owing to low event numbers. Multivariable adjustment for B1 was made for age and dementia. For B2, adjustment was made for age and ischemic stroke. For C1, adjustment was made for age, previous bleeding, heart failure, kidney failure, liver disease, inflammatory bowel syndrome, and PPI. For C2, adjustment was made for age, systemic connective tissue disorder, and antiplatelet treatment. For D1, adjustment was made for age, previous bleeding, liver disease, and PPI. For D2, adjustment was made for age and ischemic stroke.*

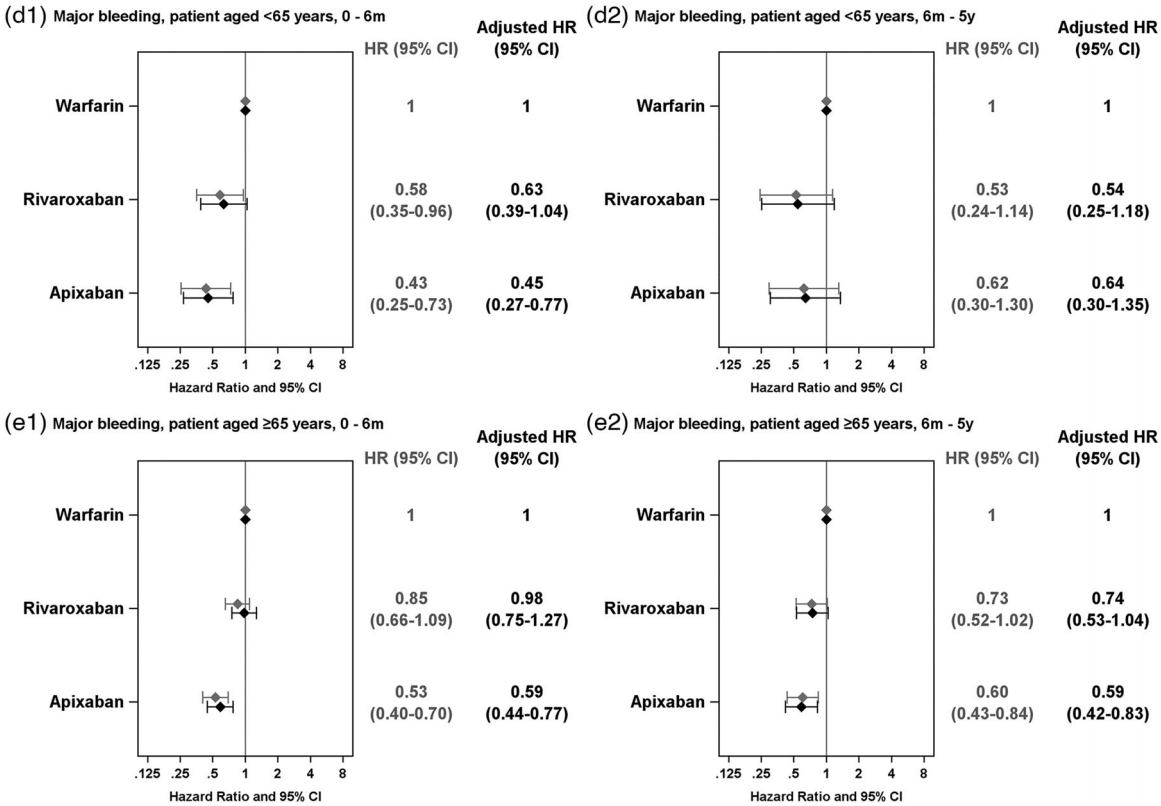

Fig. 3 *Continued*

statistically significant lower risk of intracranial bleeding compared with warfarin (Fig. 3B1,B2).

GI bleeding

A total of 232 patients (0.52% of patients starting anticoagulant treatment) had a GI bleed during the initial 6 months of anticoagulant treatment and 95 patients experienced a GI bleed during extended treatment after 6 months up to 5 years (0.34% of patients remaining on anticoagulant treatment at 6 months). The bleeding rates per 100 patient-years for the initial treatment were 1.91 (1.41–2.42), 1.47 (1.20–1.74), and 0.79 (0.60–0.98) for warfarin, rivaroxaban, and apixaban, respectively. During extended treatment, the bleeding rate was 0.41 (0.23–0.60) for warfarin, 0.42 (0.29–0.55) for rivaroxaban, and 0.33 (0.22–0.44) for apixaban (Table 2). Cumulative incidences are shown in Fig. 2C1,C2. After multivariable adjustment, the bleeding risk was lower for apixaban than warfarin during the initial 6 months of treatment but not for extended treatment (Fig. 3C1,C2). No significant difference was found between rivaroxaban and warfarin during initial or extended treatment (Fig. 3C1,C2).

Fatal bleeding

A total of 135 patients (0.3%) had a fatal bleed. Of these, 20 patients were on warfarin (0.3% of all warfarin-treated patients), 57 (0.3%) were on rivaroxaban, and 53 (0.3%) were on apixaban. The number and percentage of patients in each treatment group who were censored or followed to major bleeding, intracranial bleeding, GI bleeding, fatal bleeding, death, or diagnosis of cancer are specified in Table S5.

Patients aged <65 years or ≥65 years

In a subanalysis, we analyzed patients aged <65 years and ≥65 years separately. During initial treatment (0–6 months), patients aged <65 years had bleeding rates per 100 patient-years of 2.22 (1.33–3.11), 1.36 (0.96–1.75), and 1.00 (0.66–1.34) for warfarin, rivaroxaban, and apixaban, respectively. The corresponding numbers for patients

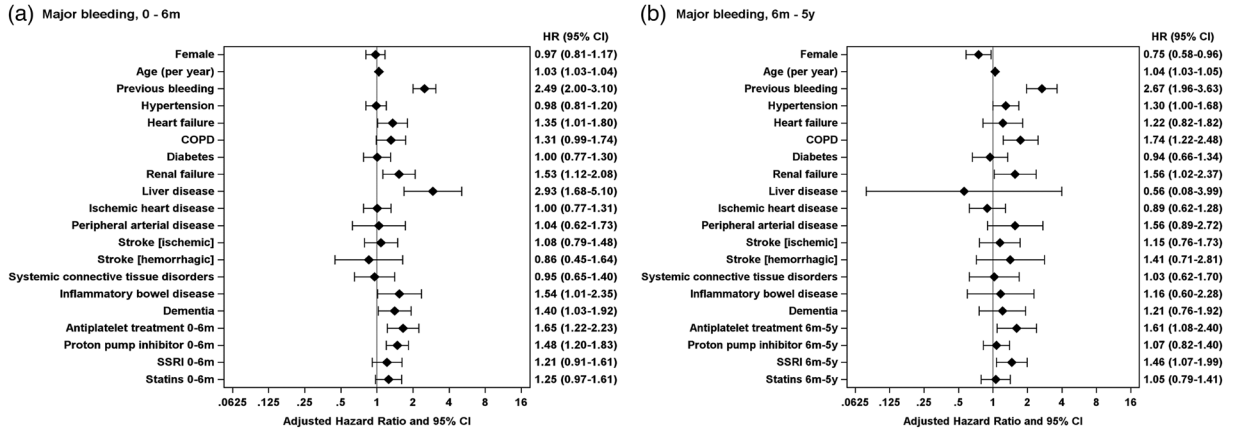

Fig. 4 *Multivariable adjusted[1] hazard ratios for major bleeding during the initial 6 months of treatment (A) and extended treatment after 6 months up to 5 years (B). [1]Multivariable adjustment was made for age, sex, previous bleeding (inpatient diagnosis within 7 years prior to or on the same date as the venous thromboembolism [VTE], not during follow-up) and inpatient diagnosis within 7 years prior to or during follow-up after VTE of hypertension, heart failure, chronic obstructive pulmonary disease (COPD), diabetes, renal failure, liver disease, ischemic heart disease, peripheral arterial disease, ischemic stroke, hemorrhagic stroke, systemic connective tissue disease, inflammatory bowel disease, and dementia. Adjustment was also made for concomitant use of antiplatelet treatment, proton pump inhibitors, selective serotonin reuptake inhibitors (SSRI), or statins during anticoagulant treatment.*

≥65 years were 4.84 (3.82–5.86) for warfarin, 4.14 (3.54–4.75) for rivaroxaban and 2.59 (2.14–3.04) for apixaban (Table 2). Figure 2D1,E1 shows the cumulative incidence. In both patients <65 years and ≥65 years of age after multivariable adjustment, bleeding risk during initial treatment was lower for apixaban than warfarin, but not for rivaroxaban compared with warfarin (Fig. 3D1,E1).

During extended treatment (6 months to 5 years), patients aged <65 years had bleeding rates per 100 patient-years of 0.70 (0.30–1.10), 0.36 (0.17–0.55), and 0.43 (0.23–0.64) for warfarin, rivaroxaban, and apixaban, respectively. Patients ≥65 years had bleeding rates of 2.06 (1.53–2.58), 1.51 (1.20–1.83), and 1.27 (1.00–1.54) for warfarin, rivaroxaban, and apixaban, respectively (Table 2). Cumulative incidence is shown in Fig. 2D2,E2. The risk of bleeding during extended treatment did not differ depending on the choice of treatment in patients <65 years (Fig. 3D2). For patients ≥65 years, the risk of bleeding was lower for apixaban, but not rivaroxaban, compared with warfarin after multivariable adjustment (Fig. 3E2).

Risk factors for bleeding

After multivariable adjustment, risk factors with significantly increased aHRs for major bleeding during the initial 6 months were age, previous bleeding, heart failure, renal failure, liver disease, inflammatory bowel disease, dementia, and concomitant medication with antiplatelet treatment or PPI (Fig. 4A). Risk factors with significantly increased aHRs for major bleeding during extended treatment (6 months to 5 years) were increasing age, previous bleeding, chronic obstructive pulmonary disease, renal failure, and concomitant medication with antiplatelet treatment and selective serotonin reuptake inhibitors. By contrast, female sex seemed to be a slightly protective factor (Fig. 4B). Unadjusted HRs are shown in Table 3.

After multivariable adjustment, comorbidities that significantly increased the aHR of intracranial bleeding during the initial 6 months of treatment were increasing age, previous hemorrhagic stroke, and dementia (Table 3A). During extended treatment, increasing age, and hemorrhagic and ischemic stroke were risk factors for intracranial bleeding after multivariable adjustment (Table 3B).

Increasing age, previous bleeding, heart failure, renal failure, liver disease, inflammatory bowel disease, and PPI all increased the risk of GI bleeding during the first 6 months of treatment in the multivariable model (Table 3A). During extended treatment, increasing age, previous bleeding, systemic connective tissue disorders, and antiplatelet treatment all increased the risk of GI bleeding

Table 3. (A and B) Univariable hazard ratios for major bleeding and univariable and multivariable hazard ratios[a] with 95% confidence intervals for intracranial bleeding and gastrointestinal bleeding for comorbidities and concomitant pharmaceutical medications for all included patients.

A. 0–6 months	Major bleeding	Intracranial bleeding		Gastrointestinal bleeding	
Characteristic	Univariable	Univariable	Multivariable	Univariable	Multivariable
Female	1.35 (1.13–1.61)	1.40 (0.82–2.39)	0.86 (0.49–1.51)	1.69 (1.31–2.19)	1.08 (0.82–1.41)
Age (per year)	1.04 (1.04–1.05)	1.07 (1.04–1.09)	1.05 (1.02–1.08)*	1.06 (1.05–1.07)	1.05 (1.04–1.06)*
Previous bleeding	3.30 (2.69–4.05)	4.18 (2.31–7.59)	1.87 (0.87–4.03)	3.05 (2.25–4.14)	2.30 (1.68–3.15)*
Hypertension	1.93 (1.62–2.30)	3.00 (1.74–5.15)	1.47 (0.82–2.61)	2.29 (1.78–2.95)	1.09 (0.82–1.44)
Heart failure	2.91 (2.25–3.76)	2.88 (1.30–6.37)	1.38 (0.61–3.11)	3.49 (2.46–4.95)	1.50 (1.01–2.21)*
Chronic obstructive pulmonary disease	2.13 (1.61–2.80)	1.72 (0.69–4.33)	1.19 (0.47–3.01)	2.49 (1.71–3.64)	1.40 (0.95–2.07)
Diabetes	1.74 (1.36–2.21)	1.42 (0.64–3.15)	0.83 (0.37–1.87)	1.58 (1.10–2.27)	0.80 (0.54–1.19)
Renal failure	2.84 (2.13–3.79)	2.01 (0.72–5.55)	1.19 (0.42–3.35)	3.56 (2.43–5.22)	1.75 (1.16–2.64)*
Liver disease	3.66 (2.11–6.35)	2.67 (0.37–19.29)	2.35 (0.32–17.11)	5.43 (2.79–10.57)	4.33 (2.21–8.49)*
Ischemic heart disease	2.32 (1.85–2.92)	2.52 (1.27–5.02)	1.19 (0.58–2.42)	2.28 (1.63–3.20)	0.88 (0.60—1.29)
Peripheral arterial disease	2.14 (1.30–3.52)	3.92 (1.22–12.57)	2.31 (0.71–7.48)	2.26 (1.12–4.58)	1.03 (0.50–2.11)
Ischemic stroke	2.31 (1.71–3.12)	4.53 (2.21–9.26)	1.73 (0.81–3.70)	2.18 (1.39–3.41)	0.98 (0.61–1.56)
Hemorrhagic stroke	2.61 (1.40–4.89)	19.37 (8.76–42.84)	5.94 (2.12–16.64)*	0.27 (0.02–4.37)	0.07 (0.00–1.58)
Systemic connective tissue disorder	1.51 (1.03–2.22)	0.49 (0.07–3.52)	0.32 (0.04–2.30)	1.85 (1.12–3.08)	1.03 (0.62–1.73)
Inflammatory bowel disease	1.89 (1.24–2.87)	0.75 (0.10–5.45)	0.75 (0.10–5.40)	2.84 (1.71–4.72)	2.30 (1.37–3.84)*
Dementia	2.71 (2.01–3.65)	8.26 (4.43–15.42)	3.59 (1.85–6.96)*	3.02 (2.00–4.57)	1.40 (0.91–2.17)
Antiplatelet treatment	3.46 (2.64–4.52)	3.77 (1.77–8.02)	1.88 (0.85–4.12)	3.12 (2.07–4.71)	1.30 (0.83–2.04)
Proton pump inhibitor	2.41 (1.98–2.94)	1.49 (0.79–2.81)	0.94 (0.50–1.79)	3.07 (2.33–4.06)	1.78 (1.32–2.40)*
Selective serotonin reuptake inhibitors	1.97 (1.50–2.58)	2.44 (1.19–5.03)	1.19 (0.56–2.51)	2.23 (1.52–3.27)	1.31 (0.88–1.95)
Statins	2.05 (1.64–2.57)	2.60 (1.41–4.78)	1.72 (0.91–3.25)	2.13 (1.53–2.95)	1.34 (0.94–1.92)

(Continued)

Table 3. *(Continued)*

B. 6 months to 5 years	Major bleeding	Intracranial bleeding		Gastrointestinal bleeding	
	Univariable	Univariable	Multivariable	Univariable	Multivariable
Female	1.10 (0.87–1.40)	1.08 (0.62–1.90)	0.76 (0.42–1.36)	1.35 (0.91–2.00)	0.86 (0.57–1.31)
Age (per year)	1.05 (1.04–1.06)	1.06 (1.03–1.08)	1.05 (1.02–1.08)*	1.06 (1.04–1.08)	1.05 (1.03–1.07)*
Previous bleeding	3.69 (2.80–4.87)	3.09 (1.54–6.20)	1.67 (0.70–3.97)	3.60 (2.24–5.79)	2.80 (1.72–4.56)*
Hypertension	2.27 (1.79–2.87)	2.03 (1.16—3.56)	1.07 (0.59–1.97)	2.22 (1.49–3.30)	1.15 (0.74–1.78)
Heart failure	2.39 (1.65–3.45)	1.62 (0.58–4.50)	0.97 (0.34–2.76)	2.86 (1.59–5.13)	1.35 (0.72–2.51)
Chronic obstructive pulmonary disease	2.64 (1.89–3.69)	1.80 (0.72–4.55)	1.22 (0.47–3.17)	2.66 (1.51–4.68)	1.78 (0.99–3.19)
Diabetes	1.55 (1.11–2.15)	1.25 (0.53–2.94)	0.88 (0.37–2.12)	1.27 (0.70–2.33)	0.75 (0.40–1.42)
Renal failure	2.82 (1.90–4.19)	2.33 (0.84–6.47)	1.50 (0.53–4.27)	3.38 (1.80–6.32)	1.78 (0.92–3.46)
Liver disease	0.69 (0.10–4.88)	1.87 (0.11–31.31)	1.92 (0.12–32.05)	2.02 (0.28–14.49)	1.49 (0.21–10.85)
Ischemic heart disease	2.02 (1.46–2.78)	2.10 (0.99–4.49)	1.18 (0.54–2.59)	1.67 (0.93–3.00)	0.70 (0.37–1.34)
Peripheral arterial disease	3.38 (1.97–5.78)	4.19 (1.30–13.46)	2.29 (0.70–7.56)	2.04 (0.65–6.42)	0.91 (0.28–2.94)
Ischemic stroke	2.44 (1.66–3.58)	4.73 (2.29–9.74)	2.58 (1.19–5.58)*	2.41 (1.25–4.64)	1.18 (0.60–2.35)
Hemorrhagic stroke	4.71 (2.51–8.86)	11.30 (4.06–31.41)	4.54 (1.26–16.30)*	4.08 (1.29–12.87)	1.37 (0.40–4.67)
Systemic connective tissue disorder	1.44 (0.88–2.35)	0.23 (0.01–3.77)	0.16 (0.01–2.65)	3.13 (1.71–5.72)	2.14 (1.16–3.95)*
Inflammatory bowel disease	1.38 (0.71–2.68)	0.41 (0.02–6.92)	0.42 (0.03–6.98)	2.26 (0.92–5.55)	2.02 (0.82–5.02)
Dementia	2.21 (1.41–3.44)	3.01 (1.19–7.61)	1.49 (0.57–3.87)	2.80 (1.41–5.57)	1.54 (0.76–3.13)
Antiplatelet treatment	2.33 (1.61–3.39)	1.72 (0.62–4.80)	1.09 (0.38–3.10)	2.61 (1.43–4.79)	1.96 (1.04–3.70)*
Proton pump inhibitor	1.60 (1.25–2.05)	1.37 (0.74–2.55)	1.01 (0.54–1.89)	1.77 (1.17–2.69)	1.08 (0.70–1.68)
Selective serotonin reuptake inhibitors	1.96 (1.46–2.64)	1.39 (0.62–3.09)	0.98 (0.44–2.22)	2.17 (1.33–3.53)	1.51 (0.92–2.50)
Statins	1.64 (1.27–2.12)	1.41 (0.74–2.68)	0.91 (0.46–1.81)	1.52 (0.98–2.36)	0.98 (0.61–1.59)

Note: (A) Time frame 0–6 months after venous thromboembolism; (B) 6 months to 5 years after venous thromboembolism.
"*" Indicates hazard ratios after multivariable adjustment with a statistically significant difference.
[a]Multivariable adjustment for intracranial bleeding 0–6 months was made for age, previous bleeding, hypertension, ischemic stroke, hemorrhagic stroke, and dementia. For intracranial bleeding 6 months to 5 years, adjustment was made for age, previous bleeding, hypertension, peripheral arterial disease, ischemic stroke, and hemorrhagic stroke. For gastrointestinal bleeding 0–6 months, adjustment was made for all factors except sex. For gastrointestinal bleeding 6 months to 5 years, adjustment was made for age, previous bleeding hypertension, heart failure, chronic obstructive pulmonary disease, renal failure, liver failure, ischemic stroke, systemic connective tissue disorder, dementia, antiplatelet treatment, and statins.

(Table 3B). Table S6A–F shows detailed information on the presence or absence of all analyzed comorbidities in all patients with major, intracranial, and GI bleeding, event rates, and univariable HRs.

Discussion

In this nationwide, register-based cohort study of patients with a first-time VTE without any diagnosed cancer, the main finding was the low overall bleeding risk for patients on apixaban and rivaroxaban during extended anticoagulant treatment (beyond 6 months), with bleeding rates comparable to those in clinical trials [22]. Treatment with either apixaban and rivaroxaban carried a lower multivariable-adjusted risk of bleeding than that with warfarin, with no difference between apixaban and rivaroxaban. During the initial 6 months of treatment, patients on apixaban had a lower bleeding risk than patients on warfarin or rivaroxaban. Among the most important risk factors for major bleeding during both initial and extended treatment were increasing age and previous bleeding.

Previously reported rates of major bleeding from clinical practice vary [12–14, 16, 18, 28], with event rates from 2.0 [16] to 6.4 [13] per 100 patient-years for warfarin, 1.7 [13] to 7.2 [18] per 100 patient-years for apixaban, and 2.4 [16] to 11.0 [18] per 100 patient-years for rivaroxaban. Inclusion of differing proportions of cancer patients within these studies might have contributed to these discrepancies because cancer patients are known to have an increased risk of bleeding [23]. In line with this, previous studies that included patients with cancer reported a high rate of major bleeding [13, 15, 18, 28]. Duration of follow-up is also an important factor, as the risk of bleeding is higher at the beginning of anticoagulant treatment. To our knowledge, the current study is the first to specifically address bleeding risk divided by initial and extended treatment in a VTE population without diagnosed cancer, in clinical practice.

Initial treatment up to 6 months

We found three previous studies on bleeding risk during initial anticoagulant treatment in VTE patients that either excluded or had a low proportion of cancer patients. These included one nationwide Danish study comparing rivaroxaban and warfarin treatment in patients with unprovoked VTE (excluding patients with recent surgery, trauma, or hospitalization) [16], one nationwide French study comparing treatment with rivaroxaban or apixaban to warfarin [14] and a private health care claims database from the USA comparing treatment with apixaban or warfarin [12].

Our bleeding rates were similar to the crude rates of bleeding for apixaban [14] and rivaroxaban [14, 16] in the two European studies, but lower than the bleeding rate for apixaban in the US study [12]. Our bleeding rates for warfarin were also lower than those in the French and US studies [12, 14], but higher than those in the Danish study [16]. Our results on DOACs versus warfarin are in line with those of previous studies, with a lower risk of bleeding with apixaban [12, 14], but not rivaroxaban [14, 16], compared with warfarin. We found no previous real-life data study that excluded cancer patients and compared bleeding risk for apixaban versus rivaroxaban during initial treatment. Studies including both patients with and without cancer reported a lower risk of bleeding for apixaban compared with rivaroxaban, in line with our data [13, 18].

The reason for the difference in bleeding rates between DOACs is unknown. A subanalysis of the first month of treatment showed that the difference in bleeding risk was large during this treatment phase, but not from 1 to 6 months after VTE event. One possible reason for the difference could be that patients on rivaroxaban receive increased dosage for 21 days, whereas patients on apixaban receive 7 days of increased dosage. Other possible explanations include differences in anti-factor Xa activity, with higher peak activity for rivaroxaban compared with apixaban [29].

There was a low rate of intracranial bleeding without any difference between the treatment groups during the initial 6 months of treatment, whereas there was a lower risk for GI bleeding for apixaban, but not rivaroxaban, compared with warfarin during the initial 6 months of treatment. Our results on intracranial bleeding are in line with those of previous US data on apixaban versus warfarin [12], but differ from French data, which have shown a lower risk of intracranial bleeding for both rivaroxaban and apixaban compared with warfarin. Our data on GI bleeding align with the previous French and US studies [12, 14]. The Danish study did not report different types of bleeding [16].

Extended treatment for 6 months to 5 years

During extended treatment, we found a low rate of major bleeding and no difference between rivarox-

aban and apixaban. We found no previous studies on extended treatment in registry data in patients without a diagnosis of cancer for comparison. One previous study on extended treatment (beyond 90 days) in which 26% of patients had a recent diagnosis of cancer showed no difference in risk of bleeding among warfarin, rivaroxaban, and apixaban [28]. One meta-analysis of RCTs and prospective cohort studies comparing DOACs (as a group) with VKA showed a major bleeding rate (per 100 person-years) during extended treatment of 1.74 for VKA and 1.12 for DOACs, in line with our results. However, data were insufficient for calculation of DOAC-related bleeding incidence beyond 12 months of extended treatment [22]. In an earlier meta-analysis of data on extended treatment, DOACs were analyzed individually. In this study, apixaban had a lower composite outcome of major and clinically relevant nonmajor bleeding risk than all other oral anticoagulants. Furthermore, both apixaban and dabigatran, but not rivaroxaban, had a lower risk compared with warfarin [30].

Here, we reported a lower risk of intracranial bleeding for patients on rivaroxaban than warfarin during extended treatment, whereas there was no difference in the risk of GI bleeding between different anticoagulation treatments. However, the event numbers were low; therefore, the findings need to be interpreted with caution.

Stratification for age <65 or ≥65 years

The bleeding rate was low for patients aged <65 years, regardless of treatment duration. Compared with data from a meta-analysis of controlled treatment trials, our reported bleeding rate for 6 months up to 5 years was lower for patients aged <65 years. The bleeding rates reported in our study for patients aged ≥65 years receiving extended treatment were similar for VKA but lower than for DOAC treatment, when compared with the findings in the meta-analysis comparing VKA and DOACs [22].

Risk factors for bleeding

Our data on other risk factors for bleeding during the initial 6 months of treatment are largely in line with those in the European Society of Cardiology guidelines. This guideline also lists active cancer (excluded in our study), ischemic stroke (not a risk factor in our study) or hemorrhagic stroke (a risk factor for intracranial bleeding, but not for major bleeding in our study), nonsteroidal anti-inflammatory drugs, other serious acute or chronic diseases, and poor anticoagulation control [20]. The American College of Chest Physicians and American Society of Hematology guidelines list similar risk factors as those of the European Society of Cardiology, adding thrombocytopenia, diabetes (not a risk factor in our study), reduced functional capacity, recent surgery, frequent falls, and alcohol abuse [6, 21]. Unexpectedly, our study showed an increased risk for patients on PPI. This result is not in accordance with previous data from the Cardiovascular Outcomes for People Using Anticoagulation Strategies trial [31]. Our results could be caused by unaccounted residual confounding, as patients with an increased risk of GI bleeding are highly likely to receive PPI. Inflammatory bowel disease and dementia, which we listed as risk factors, are not specified in guidelines. We had no data on thrombocytopenia, functional capacity, frequent falls, alcohol abuse, or anticoagulant control. Nonsteroidal anti-inflammatory drugs are often sold without prescription and were therefore not included in analyzed medications. Our study did not show an increased risk of any major bleeding in patients with previous stroke or hypertension during initial treatment.

Increased age, previous bleeding, chronic obstructive pulmonary disease, renal failure, and treatment with antiplatelets or selective serotonin reuptake inhibitors were risk factors for bleeding during extended treatment after multivariable adjustment. To our knowledge, this has not previously been reported. Differences in bleeding risk factors in initial and extended treatment are not obvious but might be because of the types of patients for whom treatment is extended.

Strengths and limitations

The major strength of this study is the large study population, with a national coverage of VTE cases in Sweden and prescription dispenses of anticoagulants. Sweden has universal health care, and the registries cover patients of all socioeconomic backgrounds, thereby avoiding potential selection bias related to data from private health care insurance databases. Another strength is the exclusion of patients with cancer, who are known to have high recurrence and bleeding rates [23], making combined data on patients with and without cancer difficult to interpret.

The main limitation of this study is the risk of residual confounding based on the lack of information

on the reason for the treating physician to choose one treatment over another for a specific patient. Another limitation of the study is the validity of VTE diagnoses in Swedish patient registries, which have been questioned, in particular, in terms of outpatient diagnoses [32, 33]. However, all VTE diagnoses were confirmed by the patients filling a prescription of anticoagulant medication, a method previously suggested to increase the accuracy of VTE diagnosis [33]. In addition, we excluded all patients with atrial fibrillation and patients who had filled a prescription for anticoagulant medication within 6 months prior to the VTE. This minimized the risk of incorrect VTE diagnosis followed by patients filling a prescription for anticoagulant treatment for another diagnosis. Only 4013 of 94,485 patients with a VTE diagnosis were excluded due to a lack of filling of a prescription of anticoagulant treatment following diagnoses (Fig. 1), indicating a good positive predictive value of the VTE diagnoses in our data. Another limitation is the lack of information on clinical data such as the results from laboratory tests, frequent falls, body mass index, or blood pressure levels, which could introduce unaccounted confounding. It is also reasonable to assume that many diseases that are mainly treated in primary care, such as hypertension, depression, and chronic kidney failure in old patients are underreported in our registers. We did not have data on the quality of warfarin management; however, warfarin treatment in Sweden holds a high standard [34].

The results of this study are likely to be generalizable to populations with similar thrombotic risk and access to health care as the Swedish population. However, the generalizability to other groups is unknown. It is important to keep in mind that patients included in the analysis on extended treatment were free of major bleeding during initial treatment, which could contribute to the low bleeding incidence. This limits the generalizability to other groups of patients.

Conclusion

The most important finding of our study is the low bleeding rate for patients on apixaban or rivaroxaban during extended treatment, similar to the findings from RCTs. Apixaban was associated with the lowest bleeding risk during initial treatment, but thereafter the bleeding risk was similar for apixaban and rivaroxaban, and both carried lower bleeding risk than warfarin. When deciding on extended treatment, it is important to consider age, previous bleeding and concomitant diseases with increased bleeding risk.

Author Contributions

Katarina Glise Sandblad received the idea for the study. All authors made important contributions to the design of the study, in particular Sam Schulman, Per-Olof Hansson, and Katarina Glise Sandblad. Katarina Glise Sandblad wrote the first draft of the manuscript. Katarina Glise Sandblad, Per-Olof Hansson, Sam Schulman, Jacob Philipson, and Jan Sörbo provided clinical input at all stages of the project. All authors were involved in critical revision of the manuscript. All authors were involved in the interpretation of data and approved the final draft. Katarina Glise Sandblad had final responsibility for the submission of the article. Per-Olof Hansson, Annika Rosengren, and Katarina Glise Sandblad provided funds for the project.

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Conflict of interest statement

KGS has received speaker's honoraria from Bristol-Myers Squibb, Pfizer, Bayer, and Leo Pharma. SS has received a research grant from Octapharma and honoraria from Alexion, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Octapharma, Sanofi, Servier, Bristol-Myers Squibb, Pfizer, and Hemostasis Reference Library. JP has received speaker's honoraria from Pfizer. JS, AR, and POH report no conflicts of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supplementary appendix ■