Direct oral anticoagulant- versus vitamin K antagonist-related gastrointestinal bleeding

Insights from a nationwide cohort

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Direct Oral Anticoagulant- versus Vitamin K Antagonist-related Gastrointestinal Bleeding: Insights from a nationwide cohort

Running title: *GI bleeding and in-hospital mortality in patients receiving OAC treatment*

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Abstract

Background: To examine the association between the type of preceding oral anticoagulant use (warfarin or direct oral anticoagulants [DOACs]) and in-hospital mortality among patients admitted with gastrointestinal bleeding.

Methods and Results: In this observational cohort study, all patients admitted with a first-time gastrointestinal bleeding from January 2011 to March 2017 while receiving any oral anticoagulant therapy prior to admission were identified using data from Danish nationwide registries. The risk of in-hospital mortality according to type of oral anticoagulation therapy was examined by multivariable logistic regression models. Among 5,774 patients admitted with gastrointestinal bleeding (median age, 78 years [25th-75th percentile, 71-85 years]; 56.8% men), 2,038 (35.3%) were receiving DOACs and 3,736 (64.7%) were receiving warfarin prior to admission. The unadjusted in-hospital mortality rates were 7.5% for DOAC (7.2% for dabigatran, 6.4% for rivaroxaban, and 10.1% for apixaban) and 6.5% for warfarin. After adjustment for baseline demographic and clinical characteristics, there was no statistically significant difference in in-hospital mortality between prior use of any DOAC and warfarin (unadjusted odds ratio [OR] 1.18 [95% confidence interval [CI],0.95-1.45], adjusted OR 0.97 [95%CI,0.77-1.24]). Similar results were found for each individual DOAC as compared with warfarin (dabigatran, unadjusted OR 1.12 [95%CI,0.84-1.49], adjusted OR 0.96 [95%CI,0.71-1.30]); rivaroxaban, unadjusted OR 0.98 [95%CI,0.71-1.37], adjusted OR 0.84 [95%CI,0.59-1.21]; and apixaban, unadjusted OR 1.62 [95%CI,0.84-1.49], adjusted OR 1.22 [95%CI, .83-1.79]).

Conclusions: Among patients admitted with gastrointestinal bleeding, there was no statistically significant difference in in-hospital mortality between prior use of DOAC and warfarin.

Key words: Epidemiology; oral anticoagulation therapy; gastrointestinal bleeding.

Introduction

During the last decade, direct oral anticoagulants (DOACs) have emerged as alternatives to vitamin K antagonists (VKA) for the prevention of stroke and systemic thromboembolism in high-risk patients with non-valvular atrial fibrillation (NVAF) and have been rapidly adopted into clinical practice.[1-5] Compared with warfarin, DOACs reduce the risk of stroke and systemic thromboembolism and have a favorable safety profile with respect to the risk of major and intracerebral hemorrhage.[6, 7] Despite their safety, DOACs increase the risk of bleeding complications, especially gastrointestinal (GI) bleeding.[6, 7] However, unlike warfarin, no antidote or reversal agent was available for any of the DOACs until the approval of Idarucizumab in October 2015 and Andexanet Alpha in May 2018. The lack of a reversal agent raises concern whether DOAC-related bleeding more frequently results in death compared with bleeding events associated with the use of warfarin, a medication whose effects can be rapidly reversed by vitamin K, plasma, and prothrombin complex concentrates. A recent study showed that prior use of DOACs was associated with lower risk of severe stroke and in-hospital mortality among patients with intracerebral hemorrhage compared with prior use of warfarin.[8] However, data regarding DOAC-related GI bleeding, which is the most common serious complication of oral anticoagulation, are limited. Whether the type of OAC treatment prior to admission may lead to differential severity of GI bleeding and subsequent adverse outcomes has been sparsely studied.[9-13] Thus, a better understanding of the outcomes among patients experiencing a GI bleeding according to the type of preceding anticoagulant use is necessary and warrants further investigation. This gap in knowledge prompted us to conduct a Danish nationwide retrospective cohort study to examine in-hospital mortality among patients admitted with GI bleeding according to the type of preceding anticoagulant use in an era where specific reversal agents for DOACs were largely unavailable.

Methods

Data sources

All residents in Denmark are assigned a unique and permanent civil registration number allowing accurate linkage of nationwide administrative registries at an individual level over time. For this study, data from the following nationwide administrative registries were collected: The Danish National Patient Registry holds information on all hospital admissions and outpatient contacts according to the International Classification of Diseases (ICD-8 until 1994 and ICD-10 from 1994) and all surgical procedures according to the NOMESCO Classification of Surgical Procedures (NCSP);[14] the Danish Registry of Medicinal Product Statistics (the Danish National Prescription Registry) contains detailed information on dispensing date, strength, and quantity on all claimed drug prescriptions in Denmark;[15] and the Danish Civil Registration System holds information on birth date, sex, and vital status (i.e. whether a person is alive and resident in Denmark, disappeared [persons whose residence is unknown to Danish authorities], emigrated, or dead, along with the date of these events).[16]

Study population

All Danish residents with a primary discharge diagnosis of GI bleeding between January 1, 2011 and June 30, 2017 were identified. Patients were included in the study if they had no history of GI bleeding (i.e. those who did not have a primary or secondary in-hospital or outpatient diagnosis of GI bleeding any time prior to admission until 1994) and had a prescription for OAC medication in the 3 months prior to admission. The study population was stratified into two groups, the warfarin and DOAC group (i.e. dabigatran, rivaroxaban, and apixaban), based on the most recent prescription for OAC medication prior to GI bleeding. Less than 5 patients admitted with GI

bleeding were in treatment with edoxaban. Therefore, these patients were excluded from the analyses.

Covariates

Comorbidity was obtained using in-hospital and outpatient diagnoses any time prior to admission for GI bleeding (eTable 1 for ICD-8 and ICD-10 codes) with the following exceptions: cancer was defined using hospital discharge diagnoses in the 3 years prior to admission; diabetes and hypertension were identified using claimed drug prescriptions, as done previously;[17, 18] and alcohol abuse was defined from related prescription fills and ICD-10 diagnosis codes. Concomitant pharmacotherapy was defined as filled prescriptions within 180 days prior to admission (eTable 2 for Anatomical Therapeutic Chemical Classification System codes). In-hospital endoscopic procedures were defined as procedures performed during admission (eTable 3 for NCSP codes). The duration of OAC therapy prior to admission for GI bleeding was estimated using claimed consecutive prescriptions, taking dosage and packing size into account, as done previously.[19, 20] The estimated risk of stroke (CHA_2DS_2-VASc-score) and bleeding (a modified HAS-BLED-score [international normalized ratio left out due to the lack of data]) was calculated as described previously.[21, 22]

Outcomes

The primary outcome was in-hospital mortality, defined as the date of death – retrieved from the Danish Civil Registration System – during admission for GI bleeding.

Statistics

Descriptive data were reported as frequencies and percentages or medians with 25^{th}-75^{th} percentile as appropriate. Differences in baseline characteristics according to type of OAC were examined by Chi-square test or Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables. Multivariable logistic regression models were used to estimate odds ratios (OR) with 95% confidence intervals (CI), adjusted for age, sex, comorbidity, concomitant pharmacotherapy, duration of OAC therapy, and year of admission. The warfarin group served as the reference group in all models. Prespecified subgroup analyses of the primary outcome were performed for the following variables: Age, sex, source of bleeding, atrial fibrillation, venous thromboembolism, cancer, and in-hospital endoscopic procedure. All statistical analyses were performed with SAS statistical software (SAS 9.4, SAS Institute, Cary, North Carolina, USA). A two-sided p-value <0.05 was considered statistically significant. **The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.**

Ethics

This study was approved by the Danish Data Protection Agency (No. 2007-58-0015; internal reference: *GEH-2014-013*, I-Suite no. 02731). In Denmark, ethical approval is not required for register-based studies in which individuals cannot be identified.

Sources of funding

No extramural funding was used to support this work.

Results

From January 1, 2011 to June 30, 2017, 40,812 patients admitted with GI bleeding with no history of GI bleeding any time prior to admission were identified. Of these, 5,774 (14.1%) patients received OAC therapy prior to admission and were included in the study (Figure 1). In total, 3,736 (64.7%) patients received warfarin prior to admission, while 892 (15.4%), 708 (12.3%), and 438 (7.6%) patients received dabigatran, rivaroxaban, and apixaban, respectively. The median age of the study population was 78 years (25^{th}-75^{th} percentile 71-85) and 56.8% were men. Baseline characteristics of the study population according to OAC therapy are summarized in Table 1. Compared with patients receiving warfarin, patients receiving DOACs were characterized by a higher proportion of females, older age, greater prevalence of atrial fibrillation, and lower proportion of congestive heart failure, ischemic heart disease, peripheral vascular disease, chronic kidney disease, diabetes, and venous thromboembolism. Further, a lower proportion of patients received antiplatelet therapy prior to admission in the DOAC group compared with the warfarin group.

Source of bleeding

The distribution of the source of bleeding is shown in Table 2. Compared with patients with prior use of warfarin, a significantly lower proportion of patients with prior use of DOAC were admitted with upper GI bleeding. In patients with prior use of DOAC, a higher proportion of patients receiving apixaban were admitted with upper GI bleeding compared with dabigatran and rivaroxaban.

Endoscopic procedures

During admission, 1,227 (60.2%) and 2,533 (67.8%) patients with prior use of DOAC and warfarin, respectively, underwent at least one endoscopic procedure. The distribution of endoscopic

procedures performed during admission is shown in Table 2. Compared with patients with prior use of warfarin, a significantly lower proportion of patients with prior use of DOAC underwent esophago-/gastro-/duodenoscopy, whereas a similar proportion of patients in both groups underwent sigmoido-/colonoscopy. In patients with prior use of DOAC, a numerically lower proportion of patients receiving apixaban underwent an endoscopic procedure compared with dabigatran and rivaroxaban. A numerically higher proportion of patients with prior use of rivaroxaban underwent esophago-/gastro-/duodenoscopy, while a significantly higher proportion of patients receiving dabigatran underwent sigmoido-/colonoscopy.

In-hospital mortality

The unadjusted in-hospital mortality rates for patients with prior use of DOACs and warfarin were 7.5% (153/2,038) and 6.5% (241/3,736), respectively. In patients with prior use of dabigatran, rivaroxaban, and apixaban, the unadjusted in-hospital mortality rates were 7.2% (64/892), 6.4% (45/708), and 10.1% (44/438), respectively. The results from the multivariable adjusted logistic regression models are illustrated in Figure 2. Prior use of any DOAC was not associated with a statistically significant difference in in-hospital mortality compared with prior use of warfarin (unadjusted odds ratio [OR] 1.18 [95% confidence interval [CI], 0.95-1.45], adjusted OR 0.97 [95% CI, 0.77-1.24]). Likewise, compared with prior use of warfarin, prior use of dabigatran (unadjusted OR 1.12 [95% CI, 0.84-1.49], adjusted OR 0.96 [95% CI, 0.71-1.30]), rivaroxaban (unadjusted OR 0.98 [95% CI, 0.71-1.37], adjusted OR 0.84 [95% CI, 0.59-1.21]), and apixaban (unadjusted OR 1.62 [95% CI, 0.84-1.49], adjusted OR 1.22 [95% CI, 0.83-1.79]) were not associated with a statistically significant difference in in-hospital mortality.

The results of the prespecified subgroup analyses are displayed in Figure 3. There was no statistically significant interaction between the treatment group and each subgroup. As in the

main analysis, the subgroup analyses overall demonstrated that prior use of DOACs was not associated with a statistically significant difference in in-hospital mortality compared with prior use of warfarin.

Sensitivity analysis

A number of sensitivity analyses were performed to test the robustness of these findings.

1) To examine the association between preceding oral anticoagulant use and in-hospital mortality in an era, where reversal agents for DOACs were available, the inclusion period was restricted to December 1, 2015 and June 30, 2017. As in the main analysis, prior use of DOACs was not associated with a statistically significant difference in in-hospital mortality compared with prior use of warfarin (unadjusted OR 1.03 [95% CI, 0.70-1.50], adjusted OR 0.84 [95% CI, 0.57-1.26]).

2) Patients were included only if they had a prescription for OAC medication in the 30 days prior to admission. This analysis yielded similar findings as in the main analysis (unadjusted OR 1.20 [95% CI, 0.92-1.58], adjusted OR 0.88 [95% CI, 0.66-1.18]).

3) To account for differences in the duration of hospital stay, we compared the risk of 30-day mortality among patients receiving DOACs and warfarin, respectively. The unadjusted 30-day mortality rates for patients with prior use of DOACs and warfarin were 11.3% (231/2,038) and 8.6% (322/3,736), respectively. Prior use of any DOAC was not associated with a statistically significant difference in 30-day mortality compared with prior use of warfarin (unadjusted OR 1.36 [95% CI, 1.13-1.62], adjusted OR 1.04 [95% CI, 0.85-1.28]).

4) Propensity score stratification analysis was performed to account for differences in baseline characteristics. Propensity scores were calculated using logistic regression with OAC treatment as the dependent outcome and were generated from the covariates adjusted for in the primary logistic regression model. ORs were calculated using logistic regression stratified in five groups according

to the propensity to DOAC treatment. Stratification on propensity scores ensured comparison only within strata of propensity scores. The C-index of the propensity model was 0.67. As in the main analysis, prior use of DOACs was not associated with a statistically significant difference in in-hospital mortality compared with prior use of warfarin (OR 0.93 [95% CI, 0.80-1.07]).

Discussion

In this nationwide cohort study, we examined the association between type of preceding anticoagulant use and in-hospital mortality among patients admitted with GI bleeding. The main finding of this study is that there was no significant difference in the risk of in-hospital mortality between prior use of DOACs and warfarin among patients admitted with GI bleeding.

Although the efficacy of DOACs for the prevention of stroke and systemic thromboembolism is well-established, a major safety concern in clinical practice has been the lack of specific reversal agents or antidotes. Only recently, idarucizumab and andexanet alfa were approved for emergent reversal of dabigatran and factor Xa inhibitors, respectively. Several studies have compared case-fatality among patients who experience any bleeding while receiving DOAC and those who experience any bleeding while receiving warfarin, for which an established reversal strategy is available. Xu et al. found that in patients with oral anticoagulant-related bleeding (460 receiving DOACs and 1,542 receiving warfarin), in-hospital mortality was lower among DOAC-related bleeding events compared with warfarin-related bleeding events (9.8% vs 15.2%; adjusted relative risk, 0.66, 95% CI, 0.49-0.89) despite high rates of warfarin reversal with vitamin K and prothrombin complex concentrates in the warfarin group.[23] In a meta-analysis of 20 randomized trials including 1,976 major DOAC-related bleeding events and 2,080 major warfarin-related bleeding events, prior use of DOAC was associated with a lower risk of a fatal bleeding compared with prior use warfarin (OR, 0.65, 95% CI, 0.52-0.81).[24] Likewise, a meta-analysis of 12

randomized trials reported that in patients with major bleeding, prior use of DOACs was associated with lower case-fatality compared with prior use of warfarin.[25] A recent large study specifically addressed the association between preceding oral anticoagulant use and in-hospital mortality among patients with intracerebral hemorrhage and found that prior use of NOACs, compared with prior use of warfarin, was associated with lower risk of in-hospital mortality.[8] Thus, mounting evidence suggest that among patients admitted with bleeding or specifically intracerebral hemorrhage, prior use of DOACs is associated with at least similar, or even better, outcomes than warfarin use. However, studies specifically addressing in-hospital mortality among patients experiencing oral anticoagulant-related GI bleeding are scarce and limited by a small number of patients with DOAC-related bleeding. In a recent study including 143 patients with DOAC-related GI bleeding and 185 patients with VKA-related GI bleeding, in-hospital mortality was lower in patients with prior use of DOACs compared with prior use of VKAs (1.6% and 5.6%, respectively).[9] A second study did not find a significant difference in the 30-day mortality risk among groups in a cohort of 88 and 151 patients with DOAC- and warfarin-related GI bleeding, respectively (11% vs 7%; hazard ratio 1.76, 95% CI, 0.65-4.76).[11]

To our knowledge, our study is the first to examine in-hospital mortality in a large nationwide, unselected cohort of patients specifically admitted with GI bleeding according to the type of preceding anticoagulant use. In line with previous studies, we found that prior use of DOACs was not associated with a significant difference in in-hospital mortality among patients admitted with GI bleeding as compared with prior use of warfarin. This finding is reassuring in light of the absence of specific reversal agents for DOACs during the study period and the availability of a well-established reversal strategy for warfarin-related bleedings with vitamin K, plasma, and prothrombin complex concentrates. Our findings may be partly explained by be the short half-life of DOACs **and possibly that DOAC patients may have had less severe bleedings**~~, efficacy of~~

~~endoscopic or other interventional therapy, and the fact that anticoagulant-related GI bleeding is a marker of generalized illness~~. In any case, our data support the safety of DOACs in routine clinical practice, even in an era where specific reversal agents for DOACs were largely unavailable.

In an additional analysis, we compared each of the DOACs with warfarin with regards to the risk of in-hospital mortality. As in the main analysis, there was no significant difference in in-hospital mortality between each of the DOACs and warfarin. Despite the fact that both randomized trials and observational data have raised concern on the risk of GI bleeding associated with DOACs, especially dabigatran, [6, 7] these findings suggest that DOAC-related GI bleeding regardless of type of DOAC is not associated with worse outcomes than warfarin-related GI bleeding. These findings, however, should be interpreted with caution as our study was not powered to detect a significant difference in in-hospital mortality between each of the DOACs and warfarin.

An interesting observation in this study was that a higher proportion of patients receiving warfarin underwent in-hospital endoscopic procedures compared with those receiving DOACs. Although speculative, a possible explanation may be that a lower proportion of patients receiving DOACs had an upper gastrointestinal bleeding and that DOAC patients may have had less severe bleedings **and thus were less likely to receive endoscopic treatment** than those receiving warfarin**. This**~~, which~~ is also supported by the shorter hospital stay in the DOAC group. Importantly, there was no significant difference in in-hospital mortality among patients receiving DOACs and warfarin when restricting the study population to those who underwent in-hospital endoscopic procedures.

Strengths and limitations

The main strength of this study is the completeness of data in a large nationwide unselected cohort of patients admitted with GI bleeding. The Danish healthcare system, funded by taxes, provides

equal access to healthcare services for all residents regardless of socioeconomic or insurance status. Since 1871, it has been mandatory by law to complete a death certificate in any case of death occurring in Denmark. In Denmark, OACs can be purchased only through prescription. Due to partial reimbursement of drug expenses by the Danish healthcare system, pharmacies are required to register all redeemed prescriptions ensuring complete and accurate registration. The findings of this study should be viewed in the context of a number of limitations. The observational nature of this study precludes the assessment of cause-effect relationships. Instead, we examined the association between in-hospital mortality and prior use of DOACs or warfarin in OAC-related GI bleeding. The possibility of residual confounding cannot be excluded despite adjustment for potential confounders in the logistic regression models. Data on important clinical variables such as hemoglobin levels, creatinine levels, international normalized ratios, blood transfusions, subsequent thrombotic events, and intensive care unit admissions were not available. Although patients with warfarin-related GI bleeding presumably had the benefit of the availability of an established reversal strategy, data on actual use of reversal strategies, including the use of vitamin K, plasma, prothrombin complex concentrates, and idarucizumab were not available. However, only 20% of patients with dabigatran-related GI bleeding were admitted after the approval of idarucizumab in Denmark (December 2015). Finally, we did not have information on the specific type and severity of bleeding besides the location and endoscopic interventions.

Conclusions

In a large nationwide, unselected cohort of patients admitted with GI bleeding, prior use of a DOAC was not associated with a significant difference in in-hospital mortality compared with prior use of warfarin, even in an era where specific reversal agents for DOACs were largely unavailable. These findings further underline the safety of DOACs in routine care.

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Disclosures

None.

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Figure legends

Figure 1. Flow chart of the study population selection process

Figure 2. Adjusted odds ratios of in-hospital mortality in patients admitted with GI bleeding according to prior anticoagulant therapy

The warfarin group served as the reference group in all models

**Adjusted for age, sex, arterial thromboembolism (ischemic stroke, transient ischemic attack, or peripheral thromboembolism), venous thromboembolism, a history of ischemic heart disease, atrial fibrillation, peripheral vascular disease, congestive heart failure, hypertension, diabetes, alcohol abuse, chronic kidney disease, chronic obstructive pulmonary disease, liver disease, malignancy, peptic ulcer, use of NSAID and antiplatelet therapy, duration of OAC therapy, and year of admission*

Figure 3. Adjusted odds ratios of in-hospital mortality in patients admitted with GI bleeding for prior DOAC versus warfarin use within subgroups

The warfarin group served as the reference group in all models

**Adjusted for age, sex, arterial thromboembolism (ischemic stroke, transient ischemic attack, or peripheral thromboembolism), venous thromboembolism, a history of ischemic heart disease, atrial fibrillation, peripheral vascular disease, congestive heart failure, hypertension, diabetes, alcohol abuse, chronic kidney disease, chronic obstructive pulmonary disease, liver disease, malignancy, peptic ulcer, use of NSAID and antiplatelet therapy, duration of OAC therapy, and year of admission. The Cox model for each subgroup analysis was not adjusted for the variable that was used to define the specific subgroup.*

Table 1. Baseline characteristics of the study population

Characteristics	Full study population			Study population with prior use of DOAC			
	DOAC N=2,038	Warfarin N=3,736	P-value	Dabigatran N=892	Rivaroxaban N=708	Apixaban N=438	P-value
Demographics							
Age, median (25^{th}-75^{th} percentile)	80 (73-86)	78 (70-84)	<0.001	80 (74-86)	79 (72-86)	81 (73-88)	0.007
Male, N (%)	997 (48.9)	2,285 (61.2)	<0.001	414 (46.4)	369 (52.1)	214 (48.9)	0.08
Comorbidities, N (%)							
Ischemic heart disease	737 (36.2)	1,556 (41.7)	<0.001	331 (37.1)	250 (35.3)	156 (35.6)	0.73
Atrial fibrillation	1,545 (75.8)	2,701 (72.3)	0.004	724 (81.2)	468 (66.1)	353 (80.6)	<0.001
Heart failure	594 (29.2)	1,232 (33.0)	0.003	274 (30.7)	194 (27.4)	126 (28.8)	0.34
Arterial thromboembolism[a]	529 (26.0)	928 (24.8)	0.35	218 (24.4)	167 (23.6)	144 (32.9)	<0.001
Peripheral vascular disease	185 (9.1)	420 (11.2)	0.01	87 (9.8)	63 (8.9)	35 (8.0)	0.56
Hypertension	1,452 (71.3)	2,703 (73.4)	0.37	670 (75.1)	480 (67.8)	302 (69.0)	0.003
Diabetes	324 (15.9)	700 (18.7)	0.007	150 (16.8)	102 (14.4)	72 (16.4)	0.40
Venous thromboembolism	311 (15.3)	766 (20.5)	<0.001	63 (7.1)	185 (26.1)	63 (14.4)	<0.001
Malignancy	301 (14.8)	529 (14.2)	0.53	127 (14.2)	111 (15.7)	63 (14.4)	0.70
Chronic renal disease	113 (5.5)	365 (9.8)	<0.001	29 (3.3)	51 (7.2)	33 (7.5)	<0.001
Chronic obstructive pulmonary disease	406 (19.9)	696 (18.6)	0.23	176 (19.7)	145 (20.5)	85 (19.4)	0.89
Peptic ulcer	214 (10.5)	458 (12.3)	0.05	85 (9.5)	81 (11.4)	48 (11.0)	0.44
Liver disease	71 (3.5)	135 (3.6)	0.80	21 (2.4)	30 (4.2)	20 (4.6)	0.05
Alcohol abuse	147 (7.2)	254 (6.8)	0.55	52 (5.8)	59 (8.3)	36 (8.2)	0.10
Risk scores, mean (standard deviation)							

CHA2DS2-VASc	4.2 (1.7)	4.1 (1.7)	0.02	4.4 (1.6)	4.0 (1.7)	4.4 (1.7)	<0.001
HAS-BLED	2.6 (1.0)	2.7 (1.1)	<0.001	2.6 (1.0)	2.5 (1.0)	2.6 (1.1)	0.33
Concomitant medical treatment, N (%)							
Antiplatelets			<0.001				0.009
Single	344 (16.9)	1,030 (27.6)		167 (18.7)	127 (17.9)	50 (11.4)	
Dual	54 (2.7)	130 (3.5)		19 (2.1)	20 (2.8)	15 (3.4)	
Nonsteroidal anti-inflammatory drugs	343 (16.8)	582 (15.6)	0.22	162 (18.2)	109 (15.4)	72 (16.4)	0.33
Duration of oral anticoagulant treatment, days (median [25th-75th percentile])	157 (34-484)	354 (93-968)	<0.001	241 (46-607)	108 (28-358)	139 (32-400)	<0.001

[a]*Ischemic stroke, transient ischemic attack, or peripheral thromboembolism*

CHA2DS2-VASc: Congestive heart failure, hypertension, age ≥75 years (2 points), diabetes, history of stroke/transient ischemic attack/systemic thromboembolism (2 points), vascular disease, age 65–74 years, and female sex.

HAS-BLED: Hypertension, abnormal renal/liver function, history of stroke, history of bleeding, labile International Normalized Ratio (left out due to missing data), age > 65 years, and drug consumption with antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse.

Table 2. Length of hospital stay, sSource of GI bleeding and in-hospital endoscopic procedures

	Full study population			Study population with prior use of DOAC			
	DOAC N=2,038	**Warfarin N=3,736**	**P-value**	**Dabigatran N=892**	**Rivaroxaban N=708**	**Apixaban N=438**	**P-value**
Hospital stay (days), median (25th-75th percentile)	3 (1-6)	4 (2-7)	0.003	3 (1-6)	3 (1-6)	4 (1-6)	0.65
Source of GI bleeding			<0.001				<0.001
Upper	786 (38.6)	1,881 (50.4)		290 (32.5)	294 (41.5)	202 (46.1)	
Lower	849 (41.7)	1,201 (32.2)		428 (45.0)	261 (36.9)	160 (36.5)	
Unspecified	403 (19.8)	654 (17.5)		174 (19.5)	153 (21.6)	76 (17.4)	
Endoscopy							
Any endoscopy*	1,227 (60.2)	2,533 (67.8)	<0.001	545 (61.1)	432 (61.0)	250 (57.1)	0.32
Esophago-/gastro-/duodenoscopy	973 (47.7)	2,120 (56.8)	<0.001	405 (45.4)	358 (50.6)	210 (48.0)	0.12
Colonoscopy/sigmoidoscopy	472 (23.2)	810 (21.7)	0.19	259 (29.0)	145 (20.5)	68 (15.3)	<0.001
Proctoscopy/anoscopy	23 (1.1)	22 (0.6)	0.03	14 (1.6)	5 (0.7)	4 (0.9)	0.24
Enteroscopy	6 (0.3)	18 (0.5)	0.29	1 (0.1)	5 (0.7)	0 (0.0)	0.07
Capsule	12 (0.6)	16 (0.4)	0.40	5 (0.6)	6 (0.9)	1 (0.2)	0.45

**Some patients have undergone different endoscopic procedures. Thus, these patients count in more than one category of endoscopic procedures.*

Credit author statement

Study concept and design: Butt, Li, Xian, Peterson, Garcia, Torp-Pedersen, Køber, Fosbøl.

Acquisition, analysis, or interpretation of data: Butt, Li, Xian, Peterson, Garcia, Torp-Pedersen, Køber, Fosbøl.

Drafting of the manuscript: Butt.

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Statistical analysis: Butt, Fosbøl.

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Study supervision: Li, Køber, Fosbøl.

Online-only supplement

Association of Preceding Oral Anticoagulant Treatment With In-Hospital Mortality Among Patients Admitted With Gastrointestinal Bleeding: Insights from a nationwide cohort

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Contents

eTable 1. ICD-8 and -10 codes

Comorbidity	ICD-8 and ICD-10 codes
Gastrointestinal bleeding	ICD-10: Upper: K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K298A, K920, K921 Lower: K625 Unspecified: K922, K638B, K638C
Ischemic heart disease	ICD-10: I20-I25 ICD-8: 410-414
Heart failure	ICD-10: I42, I50, J81, I110, I130, I132 ICD-8: 425, 428, 4270, 4271
Atrial fibrillation	ICD-10: I48 ICD-8: 4274
Ischemic stroke	ICD-10: I63, I64 ICD-8: 433, 434
Transient cerebral ischemia	ICD-10: G45 ICD-8: 435
Thrombosis or embolism in peripheral arteries	ICD-10: I74 ICD-8: 444
Peripheral vascular disease	ICD-10: I70 ICD-8: 440
Coagulopathy	ICD-10: D66-D69 ICD-8: 286
Deep vein thrombosis	ICD-10: I801-I803, I808, I809, I821-I823, I828, I829 ICD-8: 45100, 45108, 45109, 45190, 45199, 45300,

	45302, 45303, 45304, 45309
Pulmonary embolism	ICD-10: I26 ICD-8: 450
Malignancy	ICD-10: C00-C97 (if not C44) ICD-8: 140-209 (if not 173)
Chronic renal disease	ICD-10: E102, E112, E132, E142, I120, N02-N08, N11, N12, N14, N18, N19, N26, N158-N160, N162-N164, N168, M300, M313, M319, M321B, Q612, Q613, Q615, Q619, T858, T859, Z992 ICD-8: 403, 404, 581-584, 25002, 40039, 59009, 59320, 75310, 75311, 75319
Chronic obstructive pulmonary disease	ICD-10: J42-J44 ICD-8: 490-492
Liver disease	ICD-10: B15-B19, K70-K77, C22, I982, Z944, D684C, Q618A ICD-8: 070, 155, 571-573
Alcohol abuse	ICD-10: E244, E52, F10, G312, G621, G721, I426, K292, K70, K860, L27A, O354, T51, Z714, Z721 ICD-8: 291, 303, 57109, 57110, 57710

ICD, International Classification of Diseases

eTable 2. ATC classification codes

Pharmacotherapy	ATC codes
Beta-blockers	C07, C09BX
Calcium channel blockers	C08, C07F, C09BB, C09DB
Renin-angiotensin-system inhibitors	C09
Vasodilator drugs	C02DB, C02DD, C02DG
Antiadrenergic drugs	C02A, C02B, C02C
Thiazides	C03A, C07B, C07D, C09XA52, C03EA01
Loop diuretics	C03C, C03EB01, C03EB02
Spironolactone	C03DA01
Anti-diabetics	A10
Aspirin	B01AC06, N02BA01
ADP-receptor inhibitors	B01AC04, B01AC22, B01AC24
Dipyridamole	B01AC07
Vitamin K antagonists	B01AA03, B01AA04
Non-vitamin K antagonists	B01AE07, B01AF01, B01AF02
Drugs used in alcohol dependence	N07BB
Non-steroidal anti-inflammatory drugs	M01A

ATC, Anatomical Therapeutic Chemical; ADP, adenosine diphosphate

eTable 3. NCSP codes

Endoscopic procedure	NCSP codes
Esophago-/gastro-/duodenoscopy	KUJC, KUJD, KJCA05, KJCA22, KJCA32, KJCA35, KJCA42, KJDA05, KJDA22, KJDA32, KJDA35, KJDA38, KJDA42, KJDH05, KJDH15, KJDH18, KJDH22, KJDH25
Colonoscopy/sigmoidoscopy	KUJF3, KUJF4, KJFA15, KJFA42, KJFA45, KJFA48, KJFA52, KJGA05, KJGA22, KJGA28, KJGA32, KJGA35
Proctoscopy/anoscopy	KUJG, KUJH
Enteroscopy	KUJF0, KUJF1, KUJF2, KUJF8
Capsule	KUJF9

NCSP, NOMESCO Classification of Surgical Procedures

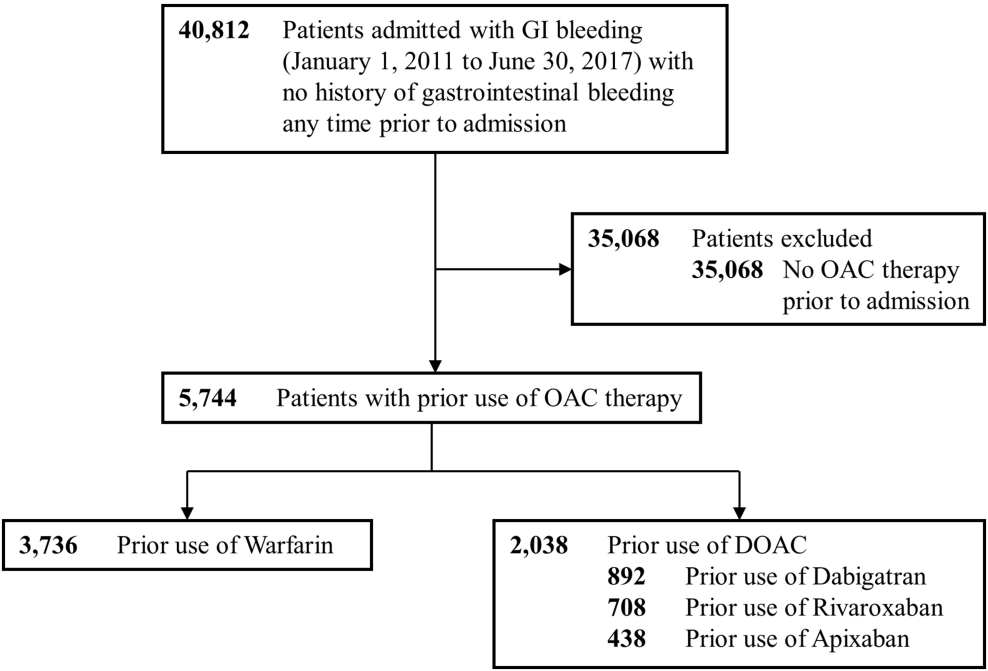
40,812 Patients admitted with GI bleeding (January 1, 2011 to June 30, 2017) with no history of gastrointestinal bleeding any time prior to admission
35,068 Patients excluded
35,068 No OAC therapy prior to admission
5,744 Patients with prior use of OAC therapy
3,736 Prior use of Warfarin
2,038 Prior use of DOAC
892 Prior use of Dabigatran
708 Prior use of Rivaroxaban
438 Prior use of Apixaban

Figure 1

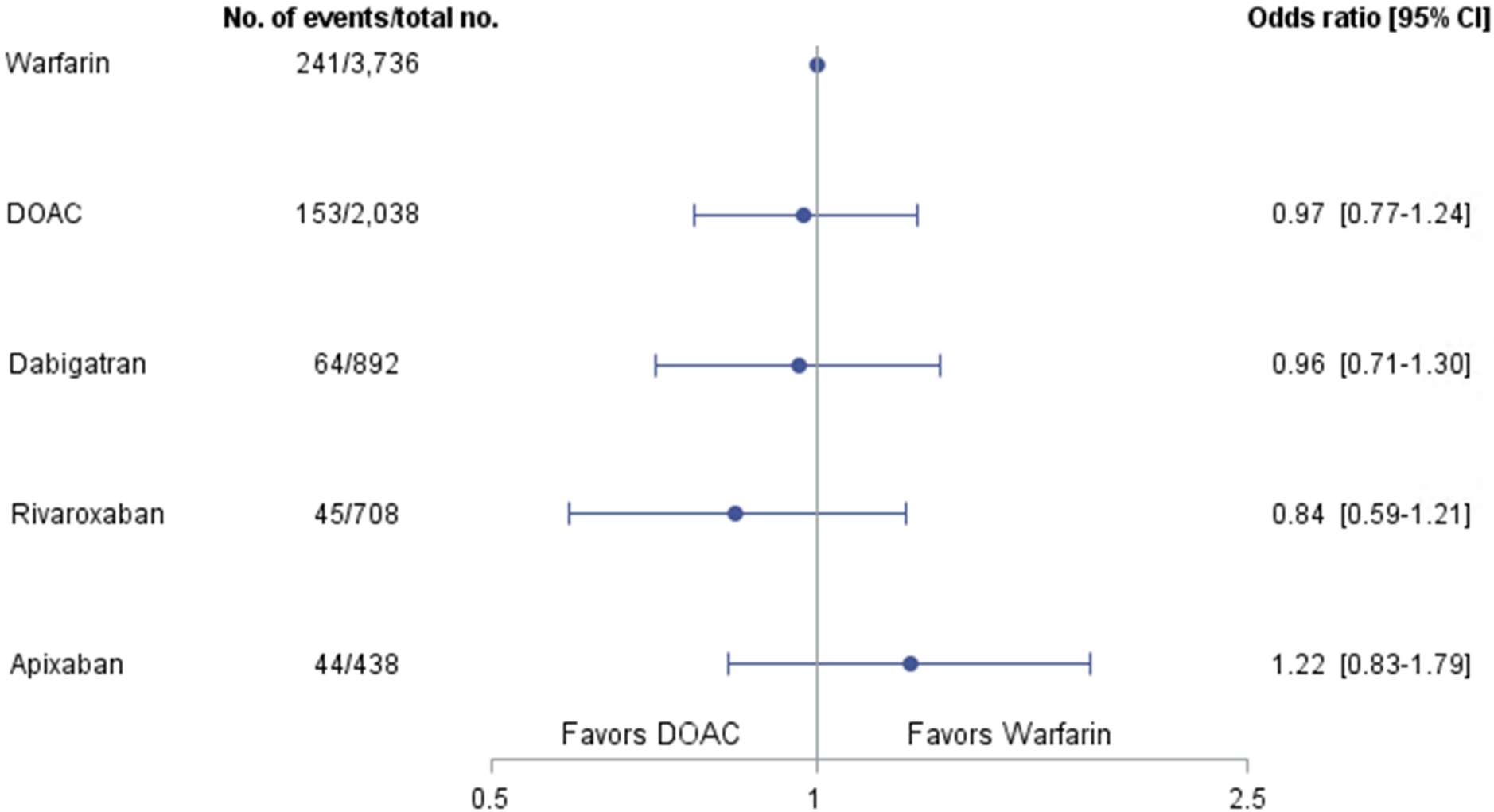
No. of events/total no.
Odds ratio [95% CI]
Warfarin
241/3,736
DOAC
153/2,038
0.97 [0.77-1.24]
Dabigatran
64/892
0.96 [0.71-1.30]
Rivaroxaban
45/708
0.84 [0.59-1.21]
Apixaban
44/438
1.22 [0.83-1.79]
Favors DOAC
Favors Warfarin
0.5
1
2.5

Figure 2

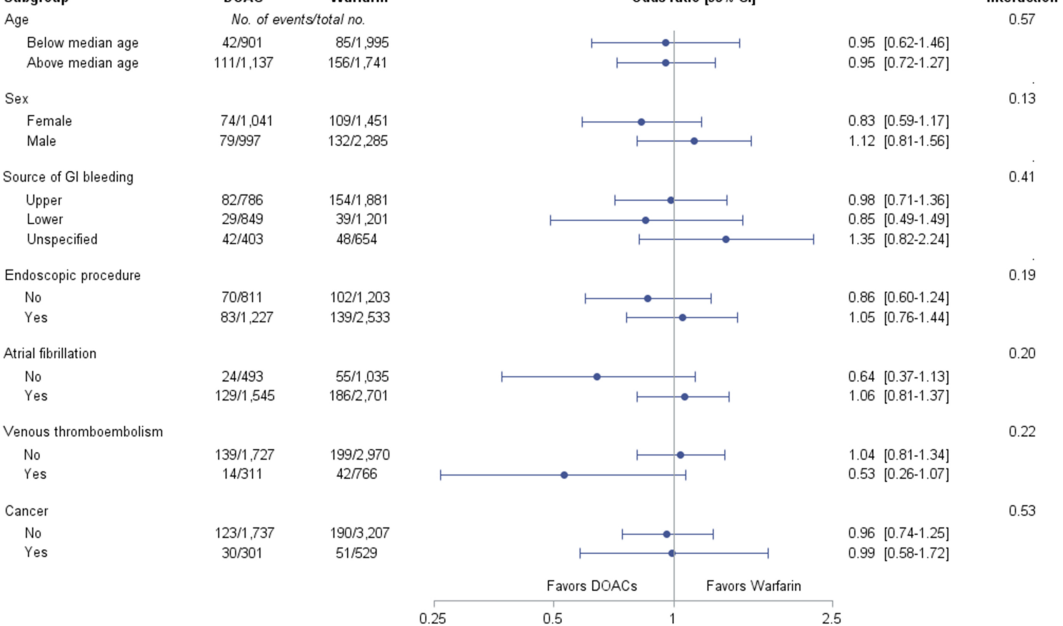
Subgroup
DOAC
Warfarin
Odds ratio [95% CI]
P-value for interaction
Age
No. of events/total no.
0.57
Below median age
42/901
85/1,995
0.95 [0.62-1.46]
Above median age
111/1,137
156/1,741
0.95 [0.72-1.27]
Sex
0.13
Female
74/1,041
109/1,451
0.83 [0.59-1.17]
Male
79/997
132/2,285
1.12 [0.81-1.56]
Source of GI bleeding
0.41
Upper
82/786
154/1,881
0.98 [0.71-1.36]
Lower
29/849
39/1,201
0.85 [0.49-1.49]
Unspecified
42/403
48/654
1.35 [0.82-2.24]
Endoscopic procedure
0.19
No
70/811
102/1,203
0.86 [0.60-1.24]
Yes
83/1,227
139/2,533
1.05 [0.76-1.44]
Atrial fibrillation
0.20
No
24/493
55/1,035
0.64 [0.37-1.13]
Yes
129/1,545
186/2,701
1.06 [0.81-1.37]
Venous thromboembolism
0.22
No
139/1,727
199/2,970
1.04 [0.81-1.34]
Yes
14/311
42/766
0.53 [0.26-1.07]
Cancer
0.53
No
123/1,737
190/3,207
0.96 [0.74-1.25]
Yes
30/301
51/529
0.99 [0.58-1.72]
Favors DOACs
Favors Warfarin
0.25
0.5
1
2.5

Figure 3