Direct oral anticoagulant– versus vitamin K antagonist–related gastrointestinal bleeding: Insights from a nationwide cohort

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Background The purpose of the study was 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 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.

Results 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% 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 0.83-1.79]).

Conclusions Among patients admitted with gastrointestinal bleeding, there was no statistically significant difference in in-hospital mortality between prior use of DOAC and warfarin. (Am Heart J 2019;216:117-124.)

During the last decade, direct oral anticoagulants (DOACs) have emerged as alternatives to vitamin K antagonists (VKAs) for the prevention of stroke and systemic thromboembolism in high-risk patients with nonvalvular atrial fibrillation 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 alfa 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

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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[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 (ie, 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 (ie, 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 2 groups, the warfarin and DOAC group (ie, 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 I 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 II for Anatomical Therapeutic Chemical Classification System codes). *In-hospital endoscopic procedures* were defined as procedures performed during admission (eTable III for NOMESCO Classification of Surgical Procedures 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 25th-75th percentile as appropriate. Differences in baseline characteristics according to type of OAC were examined by χ^2 test or Fisher exact test for categorical variables and Kruskal–Wallis test for continuous variables. Multivariable logistic regression models were used to estimate odds ratios (ORs) with 95% CIs, 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, NC). A 2-sided P value $< .05$ 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, whereas 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 (25th-75th percentile 71-85), and 56.8% were men. Baseline characteristics of the study population according to OAC therapy are summarized in Table I. 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. Furthermore, 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 II. 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.

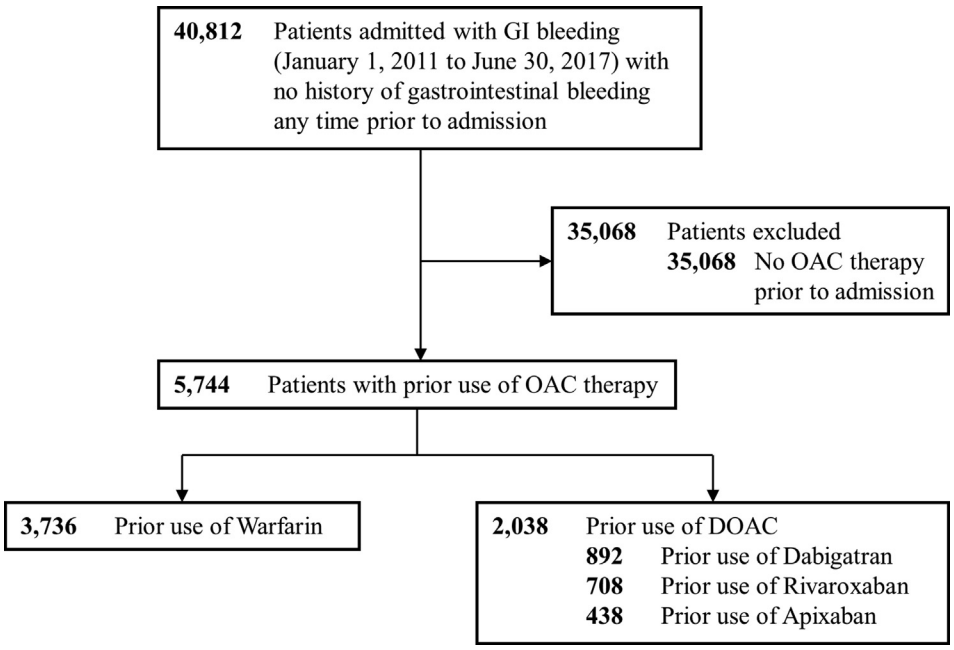
Endoscopic procedures

During admission, 1,227 (60.2%) and 2,533 (67.8%) patients with prior use of DOAC and warfarin, respectively, underwent at least 1 endoscopic procedure. The distribution of endoscopic procedures performed during admission is shown in Table II. 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, whereas 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/

Figure 1



Flowchart of the study population selection process.

Table I. Baseline characteristics of the study population

Characteristics	Full study population			Study population with prior use of DOAC			
	DOAC n = 2038	Warfarin n = 3736	*P* value	Dabigatran n = 892	Rivaroxaban n = 708	Apixaban n = 438	*P* value
Demographics							
Age, median (25th-75th percentile)	80 (73-86)	78 (70-84)	<.001	80 (74-86)	79 (72-86)	81 (73-88)	.007
Male, n (%)	997 (48.9)	2285 (61.2)	<.001	414 (46.4)	369 (52.1)	214 (48.9)	.08
Comorbidities, n (%)							
Ischemic heart disease	737 (36.2)	1556 (41.7)	<.001	331 (37.1)	250 (35.3)	156 (35.6)	.73
Atrial fibrillation	1545 (75.8)	2701 (72.3)	.004	724 (81.2)	468 (66.1)	353 (80.6)	<.001
Heart failure	594 (29.2)	1232 (33.0)	.003	274 (30.7)	194 (27.4)	126 (28.8)	.34
Arterial thromboembolism	529 (26.0)	928 (24.8)	.35	218 (24.4)	167 (23.6)	144 (32.9)	<.001
Peripheral vascular disease	185 (9.1)	420 (11.2)	.01	87 (9.8)	63 (8.9)	35 (8.0)	.56
Hypertension	1452 (71.3)	2703 (73.4)	.37	670 (75.1)	480 (67.8)	302 (69.0)	.003
Diabetes	324 (15.9)	700 (18.7)	.007	150 (16.8)	102 (14.4)	72 (16.4)	.40
Venous thromboembolism	311 (15.3)	766 (20.5)	<.001	63 (7.1)	185 (26.1)	63 (14.4)	<.001
Malignancy	301 (14.8)	529 (14.2)	.53	127 (14.2)	111 (15.7)	63 (14.4)	.70
Chronic renal disease	113 (5.5)	365 (9.8)	<.001	29 (3.3)	51 (7.2)	33 (7.5)	<.001
Chronic obstructive pulmonary disease	406 (19.9)	696 (18.6)	.23	176 (19.7)	145 (20.5)	85 (19.4)	.89
Peptic ulcer	214 (10.5)	458 (12.3)	.05	85 (9.5)	81 (11.4)	48 (11.0)	.44
Liver disease	71 (3.5)	135 (3.6)	.80	21 (2.4)	30 (4.2)	20 (4.6)	.05
Alcohol abuse	147 (7.2)	254 (6.8)	.55	52 (5.8)	59 (8.3)	36 (8.2)	.10
Risk scores, mean (standard deviation)							
CHA2DS2-VASc	4.2 (1.7)	4.1 (1.7)	.02	4.4 (1.6)	4.0 (1.7)	4.4 (1.7)	<.001
HAS-BLED	2.6 (1.0)	2.7 (1.1)	<.001	2.6 (1.0)	2.5 (1.0)	2.6 (1.1)	.33
Concomitant medical treatment, n (%)							
Antiplatelets			<.001				.009
Single	344 (16.9)	1030 (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)	.22	162 (18.2)	109 (15.4)	72 (16.4)	.33
Duration of oral anticoagulant treatment, days (median [25th-75th percentile])	157 (34-484)	354 (93-968)	<.001	241 (46-607)	108 (28-358)	139 (32-400)	<.001

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 because of missing data), age >65 years, and drug consumption with antiplatelet agents, nonsteroidal anti-inflammatory drugs, or alcohol abuse.
Ischemic stroke, transient ischemic attack, or peripheral thromboembolism.

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 OR 1.18 [95% 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]) was 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.

Table II. Length of hospital stay, source of GI bleeding, and in-hospital endoscopic procedures

	Full study population			Study population with prior use of DOAC			
	DOAC n = 2038	Warfarin n = 3736	*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)	.003	3 (1-6)	3 (1-6)	4 (1-6)	.65
Source of GI bleeding			<.001				<.001
Upper	786 (38.6)	1881 (50.4)		290 (32.5)	294 (41.5)	202 (46.1)	
Lower	849 (41.7)	1201 (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	1227 (60.2)	2533 (67.8)	<.001	545 (61.1)	432 (61.0)	250 (57.1)	.32
Esophago-/gastro-/duodenoscopy	973 (47.7)	2120 (56.8)	<.001	405 (45.4)	358 (50.6)	210 (48.0)	.12
Colonoscopy/sigmoidoscopy	472 (23.2)	810 (21.7)	.19	259 (29.0)	145 (20.5)	68 (15.3)	<.001
Proctoscopy/anoscopy	23 (1.1)	22 (0.6)	.03	14 (1.6)	5 (0.7)	4 (0.9)	.24
Enteroscopy	6 (0.3)	18 (0.5)	.29	1 (0.1)	5 (0.7)	0 (0.0)	.07
Capsule	12 (0.6)	16 (0.4)	.40	5 (0.6)	6 (0.9)	1 (0.2)	.45

Some patients have undergone different endoscopic procedures. Thus, these patients count in more than 1 category of endoscopic procedures.

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]).

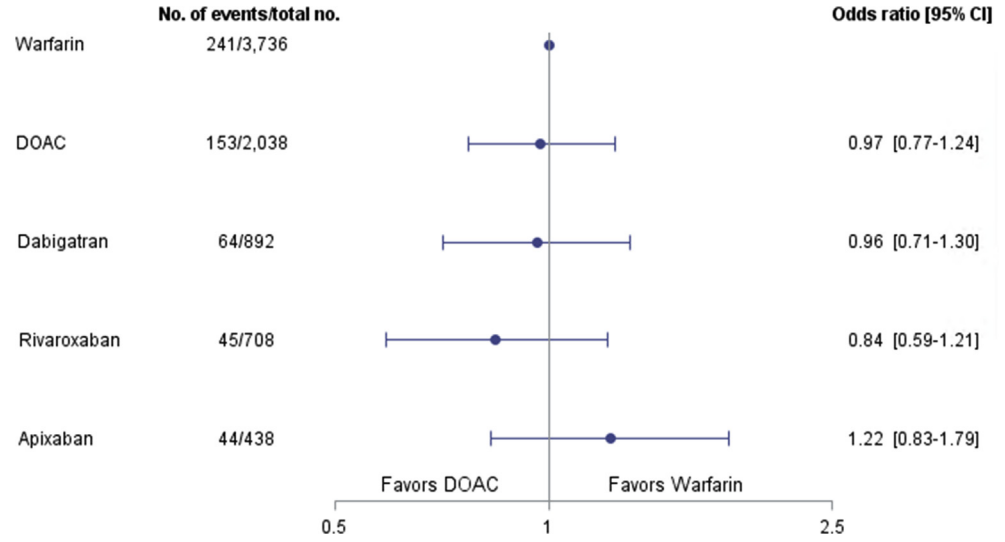
4. Propensity score stratification analysis was performed to account for differences in baseline characteristics. Propensity scores were calculated using logistic regression with OAC treatment as the dependent outcome and were generated from the covariates adjusted for in the primary logistic regression model. ORs were calculated using logistic regression stratified in 5 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 of 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 DOACs, 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

Figure 2



Adjusted ORs 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 nonsteroidal anti-inflammatory drug and antiplatelet therapy, duration of OAC therapy, and year of admission.

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 by the fact that DOAC patients may have had less severe bleedings. 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.

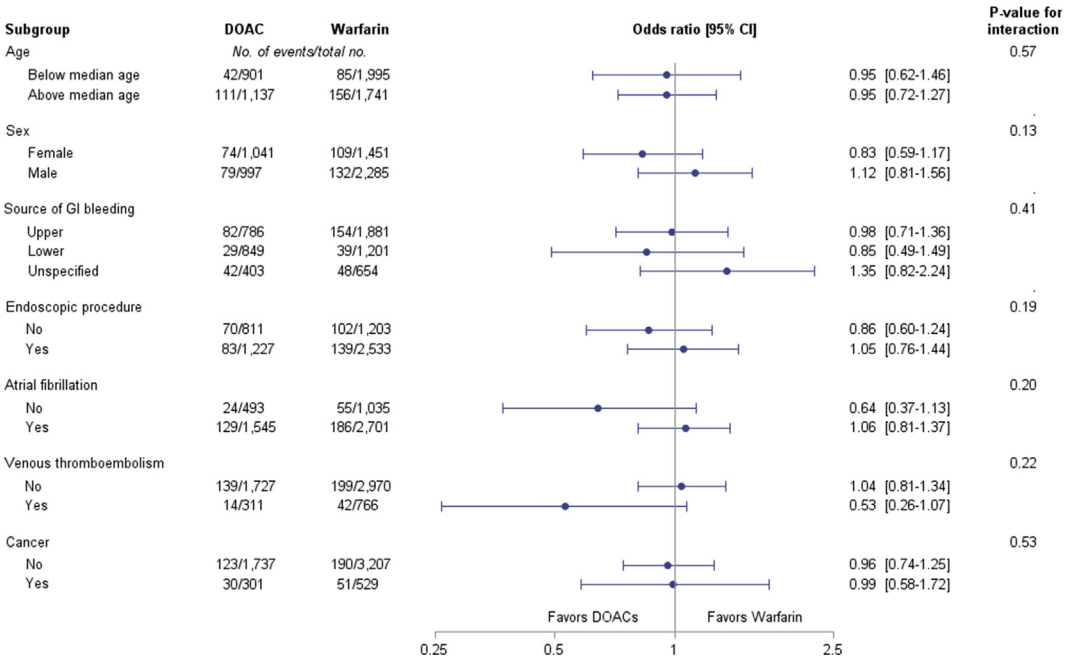
In an additional analysis, we compared each of the DOACs with warfarin with regard to the risk of in-hospital mortality. As in the main analysis, there was no significant difference in in-hospital mortality between each of the DOACs and warfarin. Despite the fact that both randomized trials and observational 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 because 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 GI 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 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

Figure 3



Adjusted ORs of in-hospital mortality in patients admitted with GI bleeding for prior DOAC versus warfarin use within 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 nonsteroidal anti-inflammatory drug 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.

admitted with GI bleeding. The Danish health care system, funded by taxes, provides equal access to health care 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. Because of partial reimbursement of drug expenses by the Danish health care 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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.07.012.

References

1. Gadsboll K, Staerk L, Fosbol EL, et al. Increased use of oral anticoagulants in patients with atrial fibrillation: temporal trends from 2005 to 2015 in Denmark. Eur Heart J 2017;38(12):899-906.
2. Marzec LN, Wang J, Shah ND, et al. Influence of direct oral anticoagulants on rates of oral anticoagulation for atrial fibrillation. J Am Coll Cardiol 2017;69(20):2475-84.
3. Barnes GD, Lucas E, Alexander GC, et al. National trends in ambulatory oral anticoagulant use. Am J Med 2015;128(12):1300-5 e2.
4. Loo SY, DellAniello S, Huiart L, et al. Trends in the prescription of novel oral anticoagulants in UK primary care. Br J Clin Pharmacol 2017;83(9):2096-106.
5. Huiart L, Ferdynus C, Renoux C, et al. Trends in initiation of direct oral anticoagulant therapies for atrial fibrillation in a national population-based cross-sectional study in the French health insurance databases. BMJ Open 2018;8(3)e018180.
6. Lopez-Lopez JA, Sterne JAC, Thom HHZ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ (Clinical research ed) 2017;j5058:359.
7. Ntaios G, Papavasileiou V, Makaritsis K, et al. Real-world setting comparison of nonvitamin-K antagonist oral anticoagulants versus vitamin-K antagonists for stroke prevention in atrial fibrillation: a systematic review and meta-analysis. Stroke 2017;48(9):2494-503.
8. Inohara T, Xian Y, Liang L, et al. Association of intracerebral hemorrhage among patients taking non–vitamin K antagonist vs vitamin K antagonist oral anticoagulants with in-hospital mortality. JAMA 2018;319(5):463-73.
9. Pannach S, Goetze J, Marten S, et al. Management and outcome of gastrointestinal bleeding in patients taking oral anticoagulants or antiplatelet drugs. J Gastroenterol 2017;52(12):1211-20.
10. Brodie MM, Newman JC, Smith T, et al. Severity of gastrointestinal bleeding in patients treated with direct-acting oral anticoagulants. Am J Med 2018;131(5):573.e9-573.e15, https://doi.org/10.1016/j.amjmed.2017.11.007 Epub 2017 Nov 22.
11. Becattini C, Franco L, Beyer-Westendorf J, et al. Major bleeding with vitamin K antagonists or direct oral anticoagulants in real-life. Int J Cardiol 2017;227:261-6.
12. Singer AJ, Quinn A, Dasgupta N, et al. Management and outcomes of bleeding events in patients in the emergency department taking warfarin or a non–vitamin K antagonist oral anticoagulant. The Journal of emergency medicine 2017;52(1):1-7 e1.
13. Majeed A, Hwang HG, Eikelboom JW, et al. Effectiveness and outcome of management strategies for dabigatran- or warfarin-related major bleeding events. Thromb Res 2016;140:81-8.
14. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health 2011;39(7):30-3 Suppl.
15. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health 2011;39(7):38-41 Suppl.
16. Pedersen CB. The Danish Civil Registration System. Scand J Public Health 2011;39(7):22-5 Suppl.
17. Schramm TK, Gislason GH, Kober L, et al. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. Circulation 2008;117(15):1945-54.
18. Olesen JB, Lip GY, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ (Clinical research ed) 2011;342:d124.
19. Gislason GH, Jacobsen S, Rasmussen JN, et al. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. Circulation 2006;113(25):2906-13.
20. Schjerning Olsen AM, Gislason GH, McGettigan P, et al. Association of NSAID use with risk of bleeding and cardiovascular events in patients receiving antithrombotic therapy after myocardial infarction. JAMA 2015;313(8):805-14.
21. Olesen JB, Sorensen R, Hansen ML, et al. Non–vitamin K antagonist oral anticoagulation agents in anticoagulant naive atrial fibrillation patients: Danish nationwide descriptive data 2011-2013. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of. Cardiology 2015;17(2):187-93.
22. Staerk L, Fosbøl EL, Gadsbøll K, et al. Non–vitamin K antagonist oral anticoagulation usage according to age among patients with atrial fibrillation: Temporal trends 2011–2015 in Denmark. Sci Rep 2016;631477.
23. Xu Y, Schulman S, Dowlatshahi D, et al. Direct oral anticoagulant- or warfarin-related major bleeding: characteristics, reversal strategies, and outcomes from a multicenter observational study. Chest 2017;152(1):81-91.
24. Skaistis J, Tagami T. Risk of fatal bleeding in episodes of major bleeding with new oral anticoagulants and vitamin K antagonists: a systematic review and meta-analysis. PloS one 2015;10(9)e0137444.
25. Chai-Adisaksopha C, Hillis C, Isayama T, et al. Mortality outcomes in patients receiving direct oral anticoagulants: a systematic review and meta-analysis of randomized controlled trials. Journal of thrombosis and haemostasis : JTH 2015;13(11):2012-20.