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Gastrointestinal bleeding with direct oral anticoagulants in patients with atrial fibrillation and anaemia

Nour Al-Hussainy [a,b,*], Kristian Hay Kragholm [b,c], Søren Lundbye-Christensen [a,c], Christian Torp-Pedersen [d,e], Manan Pareek [d,f], Susette Krohn Therkelsen [g], Gregory Y.H. Lip [a,h], Sam Riahi [a,b]

[a] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
[b] Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark
[c] Unit of Clinical Biostatistics and Epidemiology, Aalborg University Hospital, Aalborg, Denmark
[d] Department of Cardiology, North Zealand Hospital, Hillerød, Denmark
[e] Department of Public Health, University of Copenhagen, Denmark
[f] Center for Translational Cardiology and Pragmatic Randomized Trials, Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark
[g] Department of Medicine, Holbæk Hospital, Holbæk, Denmark
[h] Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom

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ABSTRACT

Introduction: A high risk of gastrointestinal bleeding has been reported with the use of some direct oral anticoagulants (DOACs). This risk may be of particular concern in individuals with associated anaemia. The aim of this study is to investigate potential differences in the risks of gastrointestinal bleeding and stroke among the four available DOACs in patients with atrial fibrillation (AF) and moderate or severe anaemia.

Materials and methods: All Danish patients diagnosed with incident AF who had a baseline haemoglobin measurement and subsequently initiated DOAC therapy between 2012 and 2021 were identified through administrative registries. Only patients with moderate or severe anaemia ($N = 7269$) were included and evaluated regarding the risk of hospitalization for gastrointestinal bleeding and stroke. Standardized absolute 1-year risks of stroke and gastrointestinal bleeding were calculated from multivariable Cox regression analyses. DOACs were compared pairwise

Results: Compared with apixaban, both dabigatran and rivaroxaban were associated with a significantly increased risk of gastrointestinal bleeding with standardized 1-year risk ratios of 1.73 (95 % confidence interval [CI], 1.10–2.35) and 1.56 (95 % CI, 1.18–1.93), respectively, while no significant difference was seen in the comparison of apixaban with edoxaban 1.32 (95 % CI, 0.41–2.32). No significant differences in gastrointestinal bleeding were observed with pairwise comparisons of dabigatran, rivaroxaban and edoxaban. Finally, no significant difference in stroke risk among the four DOACs was observed.

Conclusion: In AF patients with moderate or severe anaemia, apixaban was associated with a significantly lower risk of gastrointestinal bleeding than dabigatran and rivaroxaban. No significant difference in stroke risk was observed across all four available DOACs.

1. Introduction

Direct oral anticoagulants (DOACs) are recommended for stroke prevention in patients with nonvalvular atrial fibrillation (AF) [1,2] with no specific recommendation for a specific DOAC type for anaemic patients. However, the presence of anaemia might challenge prescription of DOACs due to fear of bleeding complications [3,4]. Indeed, we previously reported an increased risk of gastrointestinal (GI) bleeding in AF patients with moderate or severe anaemia compared with patients with a normal haemoglobin (hb) level [5]. However, patients with mild

* Corresponding author at: Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.
E-mail address: dr.radha@hotmail.com (N. Al-Hussainy).

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anaemia did not experience increased bleeding compared with patients without anaemia. In our previous study, all DOACs were grouped together. However, these medications have differences in mechanism of action, dosing, extent of renal clearance, half-life, etc. As no randomized head-to-head comparison of DOACs exist, it is difficult to choose between DOACs for anaemic AF patients. Therefore, we conducted a nationwide, retrospective, register-based cohort study to investigate whether there was a difference among DOACs with respect to the risk of GI bleeding and stroke in patients with AF and concomitant moderate or severe anaemia.

2. Methods

2.1. Data sources

The Danish National Patient Register [6] includes data on all hospital admissions and discharges since 1977 and outpatient contacts since 1995. Diagnostic codes used are based on the International Classification of Disease (ICD) system; ICD-8 was used for coding until 1993, while ICD-10 has been used since 1994.

The Danish National Prescription Register [7] holds information on prescriptions medications dispensed from all Danish pharmacies since 1995. Drugs are classified according to the Anatomical Therapeutical Chemical (ATC) system. The register includes information on the name of the drug dispensed, date of filling and quantity filled.

The Danish Civil Registration System [8] was used to obtain information on patients' vital status, date of birth and date of death.

The Clinical Laboratory Information System (LABKA) [9] was used to obtain information on laboratory tests. Denmark is divided into five healthcare regions, and we had laboratory data available from four of the regions, covering approximately 78 % of the Danish population.

A unique and permanent civil registration number is assigned to every person upon birth in, or immigration to, Denmark. This number is used by all abovementioned registries. By using an encrypted form of this civil registration number, we cross-linked all registries.

2.2. Study population

The diagnosis of AF in the Danish National Patient Register has been shown to be very high [10]. We therefore used the Danish National Patient Register to identify all patients discharged alive with a first-time diagnosis of AF. Of these, we then selected patients who initiated DOAC treatment between 2012 and 2021, based on information from the Danish National Prescription Register. The index date was defined as day 30 after DOAC initiation. ICD and ATC codes used in this study are listed in Supplemental Table S1. Only patients with a registered Hb measurement within 30 days prior to DOAC initiation were included. Patients with DOAC treatment <30 days, no Hb measured within 30 days before initiation of DOAC, or no records of estimated glomerular filtration rate (eGFR) prior to DOAC initiation were excluded. Fig. 1 shows the flowchart for patient inclusion and exclusion.

2.3. Baseline comorbidities and medications

Drug prescriptions claimed during the 180 days prior to inclusion were defined as baseline medications. Comorbidities were defined by diagnoses recorded during hospital contacts prior to the first-time diagnosis of AF. However, hypertension was defined as the use of at least two antihypertensive drugs defined by ATC codes [11].

Only patients with moderate or severe anaemia were included. The definition of anaemia was based on the World Health Organization (WHO) definition [12], where moderate anaemia is defined as Hb 4.9–6.8 mmol/L and severe anaemia as Hb ≤4.9 mmol/L. Patients were then stratified into four groups according to the DOAC prescribed (dabigatran, rivaroxaban, apixaban and edoxaban).

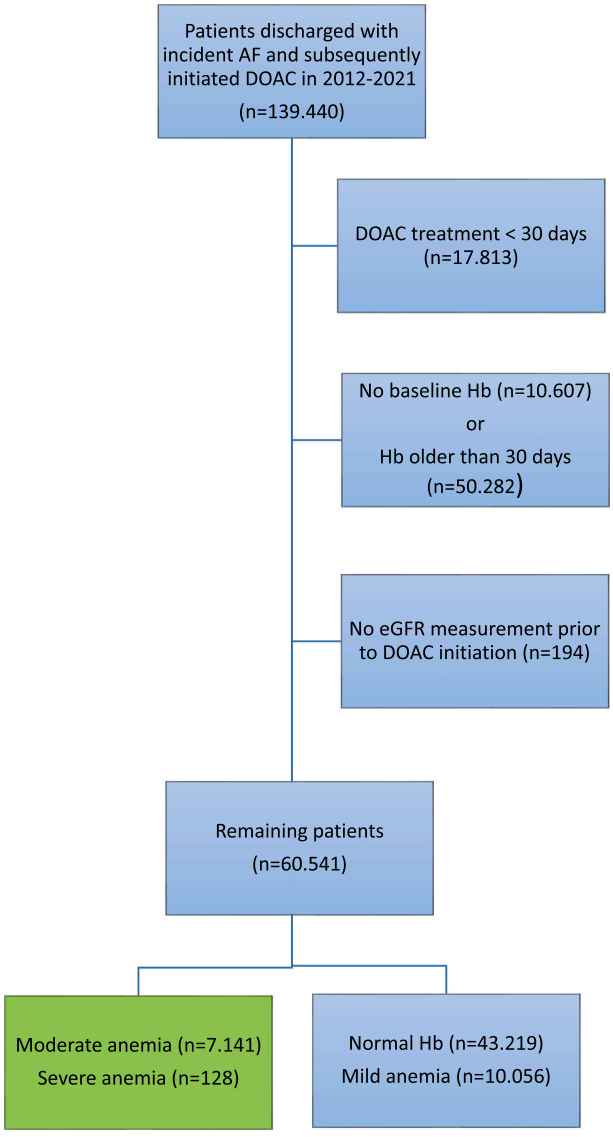

Fig. 1. Flow-chart showing selection of the study population (green box). AF, atrial fibrillation. DOAC, direct oral anticoagulants. Hb, haemoglobin. eGFR, estimated glomerular filtration rate. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.4. Study outcomes

Outcomes investigated were GI bleeding and stroke at 1 year. Both outcomes were based on ICD codes in the Danish National Patient Register. The validities for both outcomes have been shown to be very high in the Danish registries [13,14]. GI bleeding was defined as serious GI bleeding requiring hospital visit or admission. Stroke was defined as the composite of ischaemic stroke or transient ischaemic attack (TIA). ICD codes used for both outcomes are listed in Supplemental Table S1. We performed a falsification endpoint analysis using “erysipelas” (irrelevant outcome). ICD codes used are listed in Supplemental Table S1. There was no difference in standardized 1-year risk ratio between the four DOACs. Results are shown in Supplementary Fig. 2.

Patients were followed from day 30 after initiation of DOAC treatment until the occurrence of an outcome, discontinuation of DOAC or switching to another DOAC, death, or one year of follow-up, whichever occurred first.

2.5. Statistical analysis

Medians with 1st to 3rd quartiles (Q1-Q3) or means with standard deviations were used to present continuous variables, and the Kruskal–Wallis test or one-way analysis of variance (ANOVA) was used for comparison of the different groups as appropriate. Numbers and percentages were used to present categorical data, which were compared using the chi-squared test.

We used Cox proportional-hazards regression models in which time after first DOAC prescription following discharge, was used as the underlying time scale. The Cox models with GI bleeding as outcome were adjusted for age at DOAC initiation (categorized into four groups: <65, 65–74, 75–84 and ≥85 years), sex, hypertension, previous ischaemic stroke/thromboembolism (TE), chronic kidney disease (CKD), prior bleeding requiring hospitalization, chronic liver disease, alcohol abuse, use of aspirin, use of $P2Y_{12}$-receptor inhibitors, use of non-steroidal anti-inflammatory drugs (NSAIDs) and use of proton pump inhibitors (PPIs). The Cox models with stroke as outcome were adjusted for age at DOAC initiation (categorized into 4 groups: <65, 65–74, 75–84 and ≥85 years), sex, hypertension, previous ischaemic stroke/TE, CKD, heart failure (HF), diabetes, vascular disease, use of aspirin, and use of $P2Y_{12}$-inhibitors.

Cumulative incidence of events was estimated using the Aalen-Johansen method, which takes into account the competing risk of death from other causes. G-formula was used to calculate the average treatment effect (ATE) [15] as standardized absolute 1-year risks, for comparisons of the four DOACs. For this purpose, the R package "riskRegression" [16] was used. All six pairwise comparisons were calculated. The standardized absolute 1-year risks of GI bleeding and stroke were computed by using a cause-specific Cox regression model, considering death from other causes as a competing risk. Results are presented as standardized absolute risks and standardized risk ratios at 1 year, according to the DOAC used. A two-sided p-value < 0.05 was considered significant. All statistical analyses were performed using R, version 4.0.3.

2.6. Ethics

The data responsible unit in the Capital Region of Denmark approved the study, reference number P-2019-395. According to Danish regulations, retrospective register-based studies do not require ethical approval.

3. Results

From January 1st 2012 through August 9th 2021, 139,440 patients

Table 1
Characteristics of the Study Population.

	Apixaban (n = 3551)	Rivaroxaban (n = 2890)	Edoxaban (n = 204)	Dabigatran (n = 624)	Total (n = 7269)	p-Value
Male sex, n (%)	1656 (46.6)	1346 (46.6)	96 (47.1)	321 (51.4)	3419 (47.0)	0.1485
Age at DOAC index, mean (SD)	80.9 (9.1)	79.7 (9.4)	81 (8.5)	78.9 (9.3)	80.2 (9.2)	<0.001
Age category, n (%)						
Age < 65 years	165 (4.6)	181 (6.3)	7 (3.4)	50 (8.0)	403 (5.5)	<0.001
Age 65–74 years	722 (20.3)	642 (22.2)	45 (22.1)	159 (25.5)	1568 (21.6)	
Age 75–84 years	1388 (39.1)	1175 (40.7)	83 (40.7)	255 (40.9)	2901 (39.9)	
Age ≥ 85 years	1276 (35.9)	892 (30.9)	69 (33.8)	160 (25.6)	2397 (33.0)	
Total exposure time (days), mean (SD)	137.8 (157.1)	225.3 (213.7)	162.5 (161.6)	196.1 (257.4)	178.3 (195.8)	<0.001
CHA_2DS_2-VASc, (median, 25th - 75th percentiles)	5 (4–6)	5 (3–6)	5 (3–6)	5 (3–6)	5 (4–6)	0.0016
HASBLED, (median, 25th - 75th percentiles)	4 (4–6)	4 (3–6)	4 (3–6)	4 (3–6)	4 (4–6)	<0.001
Baseline Hb (g/dL), mean (SD)	6.1 (0.5)	6.1 (0.5)	6.1 (0.5)	6.1 (0.5)	6.1 (0.5)	0.5249
eGFR mL/min/1.73 m^2, mean (SD)	60.8 (21.8)	64.3 (21.5)	60.4 (22.5)	67.6 (21.5)	62.7 (21.8)	<0.001
Heart failure, n (%)	1143 (32.2)	829 (28.7)	56 (27.5)	195 (31.2)	2223 (30.6)	0.0162
Hypertension, n (%)	2467 (69.5)	1971 (68.2)	140 (68.6)	429 (68.8)	5007 (68.9)	0.7490
Previous stroke or TE, n (%)	1261 (35.5)	986 (34.1)	57 (27.9)	223 (35.7)	2527 (34.8)	0.1189
Vascular disease, n (%)	1023 (28.8)	739 (25.6)	56 (27.5)	189 (30.3)	2007 (27.6)	0.0128
Diabetes, n (%)	2294 (64.6)	1740 (60.2)	123 (60.3)	381 (61.1)	4538 (62.4)	0.0027
Chronic kidney disease, n (%)	446 (12.6)	285 (9.9)	18 (8.8)	51 (8.2)	800 (11.0)	0.0003
COPD, n (%)	668 (18.8)	538 (18.6)	36 (17.6)	99 (15.9)	1341 (18.4)	0.3589
Any malignancy, n (%)	916 (25.8)	697 (24.1)	54 (26.5)	130 (20.8)	1797 (24.7)	0.0425
Previous urogenital bleeding, n (%)	357 (10.1)	247 (8.5)	18 (8.8)	46 (7.4)	668 (9.2)	0.0684
Previous cerebral bleeding, n (%)	45 (1.3)	34 (1.2)	NA	11 (1.8)	NA	0.6705
Previous GI bleeding, n (%)	350 (9.9)	285 (9.9)	24 (11.8)	47 (7.5)	706 (9.7)	0.2105
Previous epistaxis, n (%)	131 (3.7)	101 (3.5)	5 (2.5)	29 (4.6)	266 (3.7)	0.4228
Previous peptic ulcer, n (%)	587 (16.5)	463 (16.0)	47 (23.0)	93 (14.9)	1190 (16.4)	0.0474
Hemiparesis, n (%)	15 (0.4)	10 (0.3)	NA	6 (1.0)	NA	0.1309
Mild liver disease, n (%)	70 (2.0)	45 (1.6)	NA	9 (1.4)	NA	0.4408
Severe liver disease, n (%)	19 (0.5)	15 (0.5)	NA	NA	NA	0.6709
Medication in use at baseline, n (%)						
Beta blockers	2381 (67.1)	1932 (66.9)	143 (70.1)	426 (68.3)	4882 (67.2)	0.7314
ACE-inhibitors/AT-2 blockers	1632 (46.0)	1324 (45.8)	77 (37.7)	290 (46.5)	3323 (45.7)	0.1408
Amiodarone	264 (7.4)	255 (8.8)	22 (10.8)	42 (6.7)	583 (8.0)	0.0526
Ticagrelor	39 (1.1)	30 (1.0)	NA	NA	NA	0.2425
Clopidogrel	533 (15.0)	403 (13.9)	33 (16.2)	67 (10.7)	1036 (14.3)	0.0318
Aspirin	1100 (31.0)	823 (28.5)	52 (25.5)	238 (38.1)	2213 (30.4)	<0.001
NSAID	518 (14.6)	488 (16.9)	22 (10.8)	123 (19.7)	1151 (15.8)	0.0005
PPI	2013 (56.7)	1673 (57.9)	111 (54.4)	340 (54.5)	4137 (56.9)	0.3597
Previous vitamin-K antagonist users	1007 (28.4)	838 (29.0)	55 (27.0)	239 (38.3)	2139 (29.4)	<0.001

TE, thromboembolism; COPD, Chronic pulmonary disease; GI, gastrointestinal; ACE-inhibitors, Angiotensin Converting Enzyme; AT-2 blockers, Angiotensin II receptor blockers; NSAID, Non-steroid-anti-inflammatory drugs; PPI, Proton pump inhibitors; eGFR, estimated glomerular filtration rate; Hb, haemoglobin.

were registered with an incident AF diagnosis and were subsequently prescribed a DOAC. Only patients with moderate (7141 patients) or severe (128 patients) anaemia were included, yielding a total of 7269 patients (mean age 80.2 (SD ± 9.2) years; 53 % female). Details of cohort selection and exclusions made are shown in Fig. 1.

The vast majority of patients continued DOAC therapy the majority of the year of focus where 6.389 (87.9 %) patients picked up a second prescription and 4.893 (67.3 %) patients picked up a prescription 6 months after initiation of DOAC therapy. Only 635 (8.9 %) patients switched from one DOAC type to another DOAC type, where most of the switches were to apixaban 404 (5.6 %) from one of the other DOAC types.

In general, patients in the apixaban group were on average older than those on other DOACs. The apixaban group also included more patients with diabetes and CKD. Patients on dabigatran and rivaroxaban had longer treatment exposure time than those on apixaban and edoxaban. Patients on dabigatran had also a higher proportion of concomitant use of aspirin and NSAIDs, while patients on apixaban and edoxaban had a higher proportion of concomitant use of clopidogrel. Baseline characteristics of the study population are shown in Table 1.

3.1. Cumulative incidence rates of stroke and GI bleeding

Event rates per 100 patient-years are presented in Table 2. Cumulative incidence rates of GI bleeding and stroke are depicted as Aalen-Johansen plots, with pairwise comparison of DOACs with HRs depicted on same plots in Figs. 2 and 3 respectively. Mortality stratified by type of DOAC are depicted as Kaplan-Meier plots in Supplementary Fig. 1.

3.2. GI bleeding

Within 1 year after initiation of DOAC therapy, 294 (4.0 %) patients experienced a first serious GI bleeding event, corresponding to event rates of 9.38 (95 % CI, 9.36–9.40), 9.09 (95 % CI, 9.02–9.16), 13.30 (95 % CI, 13.25–13.34) and 10.42 (95 % CI, 10.40–10.44) per 100 patient years for patients on apixaban, edoxaban, dabigatran and rivaroxaban, respectively.

The standardized absolute 1-year risks of GI bleeding were 3.55 % (95 % CI, 2.88–4.12) for patients on apixaban, 4.69 % (95 % CI, 1.57–7.82) for those on edoxaban, 6.14 % (95 % CI, 4.22–8.06) for dabigatran and 5.54 % (95 % CI, 4.66–6.41) for rivaroxaban, Table 3. Compared with apixaban, both dabigatran and rivaroxaban were associated with a significantly increased risk of GI bleeding with standardized 1-year risk ratios of 1.73 (95 % CI, 1.10–2.35) and 1.56 (95 % CI, 1.18–1.93), respectively. No significant difference was seen when comparing apixaban with edoxaban 1.32 (95 % CI, 0.41–2.32). No significant differences in GI bleeding were observed with pairwise comparisons of dabigatran, rivaroxaban and edoxaban, Fig. 4.

Table 2
Event rates per 100 patient-years.

	No. of events within 1st year, n	No. of patient years (1 year follow-up), years	Event rate per 100 years, (95 % CI)
GI bleeding			
Apixaban	108	1.152	9.38 (9.36–9.40)
Edoxaban	7	77	9.09 (9.02–9.16)
Dabigatran	33	248	13.30 (13.25–13.34)
Rivaroxaban	146	1401	10.42 (10.40–10.44)
Stroke			
Apixaban	125	1141	10.95 (10.93–10.97)
Edoxaban	4	77	5.19 (5.14–5.24)
Dabigatran	21	250	8.40 (8.36–8.44)
Rivaroxaban	93	1412	6.59 (6.58–6.60)

GI bleeding: gastrointestinal bleeding.

3.3. Stroke

Within one year after initiation of DOAC therapy, 243 (3.3 %) patients experienced a stroke, corresponding to event rates of 10.95 (95 % CI, 10.93–10.97), 5.19 (95 % CI, 5.14–5.24), 8.40 (95 % CI, 8.36–8.44) and 6.59 (95 % CI, 6.58–6.60) per 100 patient years for patients on apixaban, edoxaban, dabigatran and rivaroxaban respectively.

The standardized absolute 1-year risk for stroke with apixaban was 4.17 % (95 % CI, 3.44–4.90), edoxaban 3.05 % (95 % CI, 0.49–5.61), dabigatran 3.62 % (95 % CI, 2.13–5.11) and rivaroxaban 3.69 % (95 % CI, 2.98–4.40), Table 3. There were no significant differences in the standardized 1-year risk ratios for stroke between the four DOACs, Fig. 4.

4. Discussion

In this large, nationwide study, we compared the risks of GI bleeding and stroke associated with apixaban, edoxaban, dabigatran and rivaroxaban in patients with AF and moderate or severe anaemia. Apixaban was associated with a significantly lower GI bleeding risk when compared with dabigatran and rivaroxaban in this patient population. Conversely, the risk of stroke did not differ between the four DOACs.

To our knowledge, this is the first study to compare DOACs regarding stroke and GI bleeding risk in patients with AF and moderate or severe anaemia. Our study has implications for the appropriate assessment and mitigation of bleeding risks in patients with AF [18] as part of the holistic approach recommended in current guidelines [2].

Previous studies have shown that anaemia is associated with an increased risk of GI bleeding in AF patients [19,20]. Use of DOACs in AF patients has also been suggested to increase GI bleeding risk compared to warfarin [21,22]. Thus, choosing a DOAC that gives the desired protection against stroke without increasing GI bleeding risk even further in AF patients with anaemia is desirable.

Several register-based studies have compared the risk of bleeding in AF patients receiving DOACs and found that apixaban was associated with a lower risk of composite bleeding compared with other DOACs [23–28]. Although GI bleeding was included in the assessment of these composite bleeding endpoints, studies specifically investigating GI bleeding are sparse. Furthermore, only few studies included edoxaban.

Several observational studies [27,29,30] and meta-analysis [31,32] have shown a significantly increased risk of GI bleeding with dabigatran compared with apixaban in the general AF population as well as in elderly AF patients [30]. When comparing apixaban with rivaroxaban, the majority of observational studies [29,30,33,34] and network meta-analyses [31,32,35] found that apixaban was associated with a lower risk of GI bleeding compared with rivaroxaban in the general population of AF patients. Whereas, comparing dabigatran and rivaroxaban, there are no significant difference in the risk of GI bleeding [27,29,30,32,34–36]. A network meta-analysis [32] compared edoxaban with other DOACs and did not find any significant difference between edoxaban and other DOACs with respect to GI bleeding risk, while another meta-analysis [35] found that compared with rivaroxaban, edoxaban showed a significantly lower risk of GI bleeding. Only a limited number of observational studies [37–40] from Asia included edoxaban when comparing DOACs with respect to GI bleeding. However, as Asian patients have increased bleeding risk during antithrombotic therapies compared with Caucasian patients due to differences in thrombogenicity with low hypercoagulability, [41] the implication of these studies for Caucasian patients might be limited.

Based on our study results, apixaban might exert a favorable effect in AF patients with moderate or severe anaemia, as it was associated with lower GI bleeding risk compared with both rivaroxaban and dabigatran. Our results are thus in line with previous studies confirming less GI bleeding risk with apixaban, also in AF patients with moderate or severe

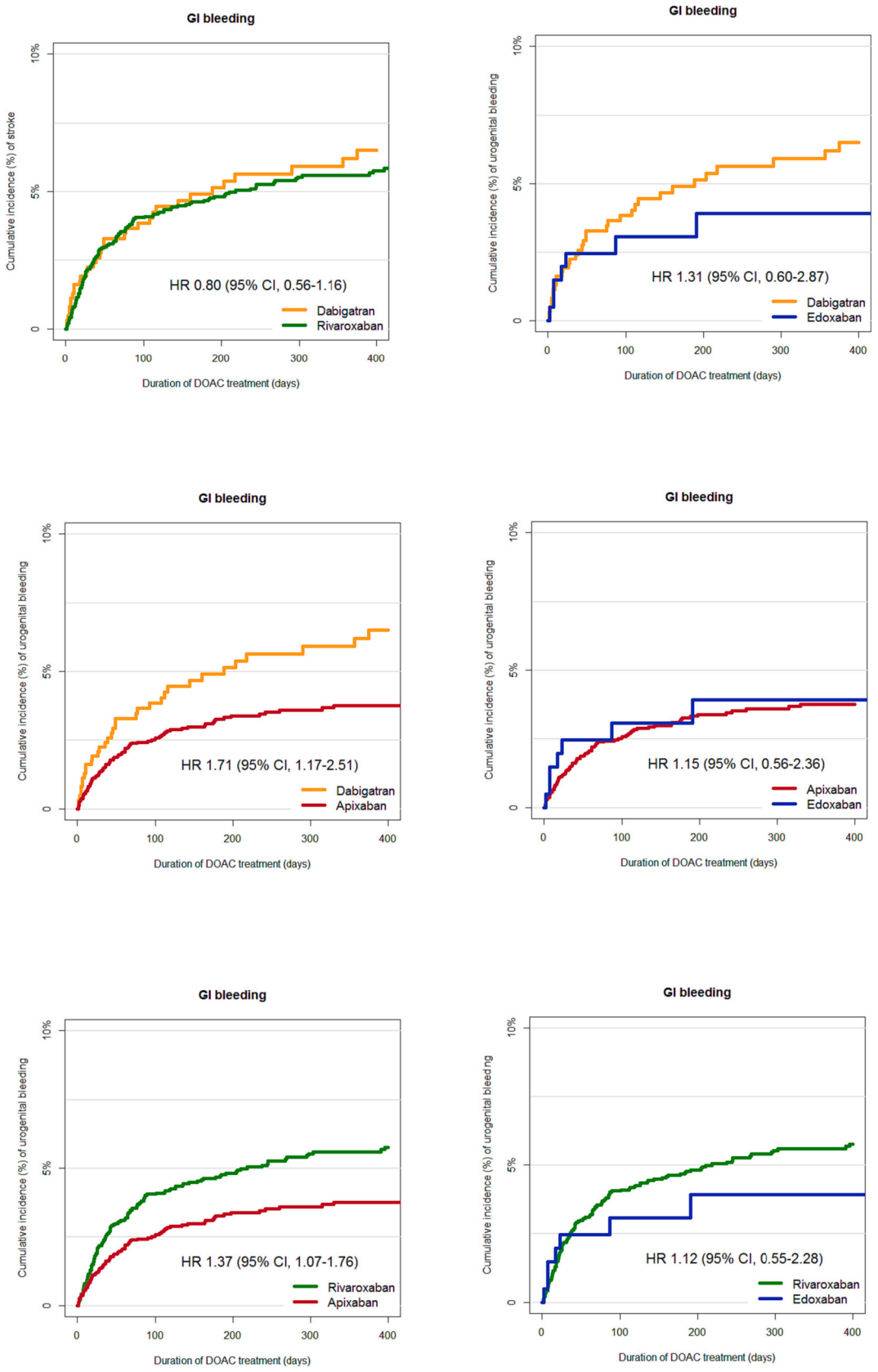

Fig. 2. Cumulative incidence rates of GI bleeding depicted as Aalen-Johansen plots, with pairwise comparison of DOACs with HRs depicted on same plots. HR, hazard ratio; CI, confidence interval.

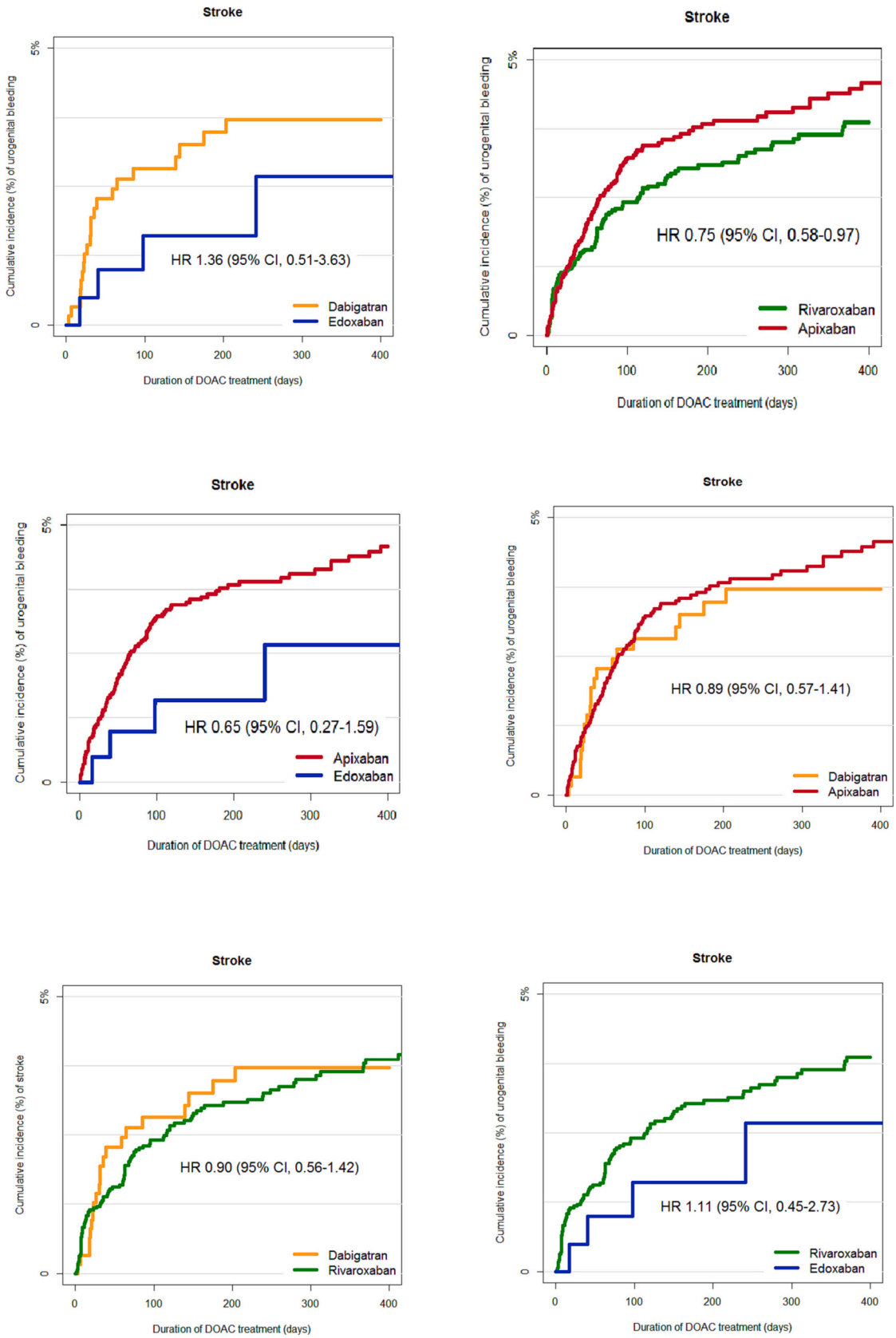

Fig. 3. Cumulative incidence rates of stroke depicted as Aalen-Johansen plots, with pairwise comparison of DOACs with HRs depicted on same plots. HR, hazard ratio; CI, confidence interval.

Table 3
Standardized absolute 1-year risks of Gastro-Intestinal (GI) bleeding and stroke.

	GI-bleeding	Stroke
Apixaban	3.55 (2.88–4.23)	4.17 (3.44–4.90)
Edoxaban	4.69 (1.57–7.82)	3.05 (0.49–5.61)
Dabigatran	6.14 (4.22–8.06)	3.62 (2.13–5.11)
Rivaroxaban	5.54 (4.66–6.41)	3.69 (2.98–4.40)

anaemia.

Differences between DOACs regarding pathophysiological mechanism can potentially explain the observed favorable effect of apixaban compared with rivaroxaban and dabigatran, including the two-dose regime and less dependency on renal clearance. However, pathophysiological comparison of mechanisms needs more dedicated investigations, which is beyond the scope of this study.

With respect to stroke, several observational studies [23,29,34,42] and a meta-analysis [32] compared apixaban, dabigatran and rivaroxaban in AF patients regarding stroke risk, and the majority of them found no significant difference in stroke protection between these DOACs. Similar findings were noted when accounting for standard and reduced doses separately [36,43]. These results are in line with our study that showed no significant differences in the risk of ischaemic stroke/TIA among the four DOACs in AF patients with moderate or severe anaemia.

4.1. Strengths and limitations

A major strength of our study is its use of a nationwide cohort of AF patients with no mentionable loss to follow-up. The validities for the diagnosis of AF, stroke and GI bleeding have been shown to be very high in the Danish registries [10,13,14]. Also, our study is the first observational study comparing edoxaban with other DOACs with respect to GI bleeding risk in a relatively homogeneous Caucasian population.

On the other hand, our study is limited by not considering the etiology of anaemia and only including events requiring hospital contact. Thus, the etiology behind anaemia could also affect the risk of GI-bleeding, which is not accounted for in our study. Another important limitation is the nature of retrospective observational studies, meaning there could be still confounding factors (measured and unmeasured) not accounted for in our study, and we are thus unable to establish causality. Moreover, as the number of events was small low statistical power might have influenced our results. Particularly for patients on edoxaban, the calculated risk ratios could potentially reach statistically significance if the sample size was bigger (and thus event rates were higher). The findings should therefore be interpreted with caution. A larger, adequately powered randomized trial is needed to accurately address differences in events in relation to DOACs. Finally, differentiating between DOAC doses would have yielded a more comprehensive comparison of DOACs, however data for differentiating between doses is not available in our data source, and thus no differentiation between doses of the four DOACs was done.

5. Conclusions

In this study of AF patients with moderate or severe anaemia, no significant differences in the risk of stroke were observed between the four DOACs, but apixaban was associated with a significantly reduced risk of GI bleeding compared with both dabigatran and rivaroxaban. We cautiously suggest that apixaban might have a better safety profile with respect to GI bleeding in AF patients with moderate or severe anaemia. However, as our results are based on observational data, the results of this study should be interpreted with caution.

Declaration of competing interest

This study was funded by the AF-study Group, Aalborg University Hospital. Conflict of Interest: none declared.

Dr. Manan Pareek reports the following disclosures – Advisory Board: AstraZeneca, Janssen-Cilag; Speaker Fee: AstraZeneca, Bayer, Boehringer Ingelheim, Janssen-Cilag. Dr. Christian Torp-Pedersen has received a grant for a randomized study from "Bayer", which is outside the submitted work. Dr. Lip reports consultancy and speaker fees from BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo outside the submitted work. No personal fees received.

Data availability

Data are stored and accessed on secure servers at Statistics Denmark and cannot be shared. According to Statistics Denmark regulations, data cannot be exported but may be accessed in collaboration with an authorized research group.

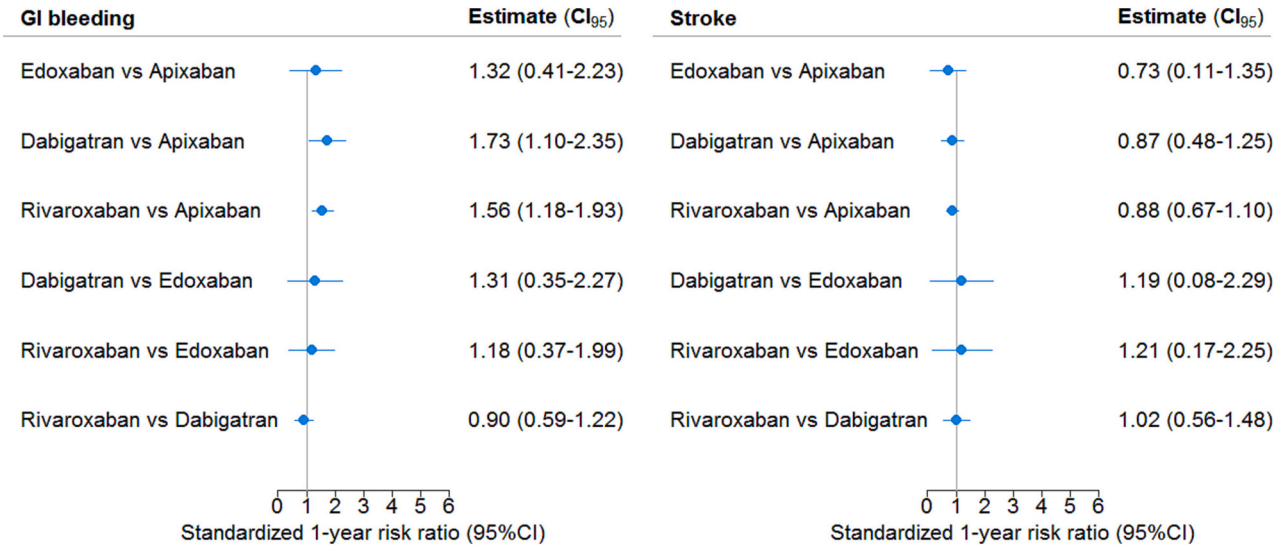

Fig. 4. The standardized absolute 1-year risks of GI bleeding and stroke, presented as pairwise comparisons of DOAC types. Compared with apixaban, both dabigatran and rivaroxaban were associated with a significantly increased risk of GI bleeding. Otherwise, no significant difference in GI bleeding was observed by pairwise comparisons of other DOAC types. No significant differences in the standardized 1-year risk ratios for stroke between the four DOACs were observed. CI, confidence interval.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2023.10.013.

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