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Risk of upper gastrointestinal bleeding in patients on oral anticoagulant and proton pump inhibitor co-therapy

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Abstract

Background

Proton pump inhibitors (PPIs) are known to reduce the risk of upper gastrointestinal bleeding in patients on oral anticoagulants, and patients are increasingly on oral anticoagulants and PPI co-therapy. However, evidence is lacking on the safety and effectiveness of oral anticoagulants when co-administered with PPIs.

Methods

Among patients initiating oral anticoagulants (warfarin and non-vitamin K antagonist oral anticoagulants [NOACs], i.e. rivaroxaban, dabigatran, apixaban, and edoxaban) during 2013–2017, those concomitantly prescribed PPIs were identified (n = 19,851). The primary endpoint was hospitalization for major upper gastrointestinal bleeding, and secondary endpoints were death and ischemic stroke.

Results

During a mean 1.4 years of follow-up, the primary endpoint occurred in 512 (2.58%) patients. Overall, NOACs were associated with lower upper gastrointestinal bleeding risk after adjustment for age, sex, comorbidities and concomitant medications (adjusted hazard ratio 0.78, 95% confidence interval 0.65–0.94), compared to warfarin. There was no significant difference in upper gastrointestinal bleeding risk among the individual NOACs. This trend of reduced risk for upper gastrointestinal bleeding in NOACs compared to warfarin was consistent for both regular and reduced doses, throughout bleeding risk groups, and other subgroup analyses. NOACs were also associated with lower risk of death compared to warfarin. The risk for ischemic stroke was not significantly different among the oral anticoagulants in patients with atrial fibrillation.

Conclusion

In patients on oral anticoagulant and PPI co-therapy, NOACs were associated with lower risk of upper gastrointestinal bleeding and mortality compared to warfarin, while there was

no difference among the oral anticoagulants for stroke prevention. In patients on PPI therapy, NOACs may preferred over warfarin for decreasing risk of upper gastrointestinal bleeding and mortality.

Introduction

Age-related diseases including atrial fibrillation and cardiovascular diseases are on the rise worldwide with the progression of population aging [1, 2], and increasingly more people are on oral anticoagulants (OACs). Consequently, the bleeding risk associated with OACs is not negligible and attracts clinical attention. Proton pump inhibitors (PPIs) are recommended for OAC users on concomitant antiplatelet therapy to reduce upper gastrointestinal bleeding complications [3]. Previous observational studies and a randomized trial have also shown that PPIs are associated with reduced upper gastrointestinal bleeding risk in patients on OACs [4–6], suggesting that PPIs can be used to prevent upper gastrointestinal bleeding in OAC users. Meanwhile, there have also been concerns in pharmacodynamics and pharmacokinetic studies over possible drug interactions between PPIs and OACs, which are different for the individual OACs and are mostly related to dabigatran and warfarin [7–9]. While these interactions are presumed to have minor therapeutic effects [10], clinical outcomes data are hitherto lacking. Previous studies have reported differential risks in the gastrointestinal bleeding depending on the OACs [11–13]; however, no study has specifically focused on which OAC has the most favorable gastrointestinal safety profile in patients on OAC and PPI co-therapy.

We aimed to compare the upper gastrointestinal tract safety of OACs in a cohort of patients on OAC and PPI co-therapy. We also explored the effectiveness for stroke prevention and risk of death associated with OACs in these patients.

Materials and methods

Data source and study design

The study utilized the Korean National Health Insurance Service claims database covering the entire Korean population, the details of which have been described previously [14, 15]. This database is available for research on request at the National Health Insurance Sharing Service homepage (nhiss.nhis.or.kr), after study approval by the institutional review board approval and data provision review committee. We used a de-identified dataset conforming to the inclusion criteria detailed below (NHIS-2020-1-055), which is currently valid until August 19, 2021. The current study complied with the Declaration of Helsinki, and was approved by the Institutional Review Board of Seoul National University Hospital (E-1906-115-1041). Informed consent was waved due to the retrospective nature of the study and anonymized database.

We identified adults (age ≥20 years) who initiated OACs between January 2013 and December 2017, for the clinical indications of non-valvular atrial fibrillation or venous thromboembolism. According to regulations of the National Health Insurance Service, this population was provided after 50% random sampling from the database. OACs included warfarin and the non-vitamin K antagonist oral anticoagulants (NOACs), i.e. rivaroxaban, dabigatran, apixaban, and edoxaban. The starting year was set as 2013 which was when NOACs were approved for use in Korea. We excluded patients with previous prescription of OACs or less than 1 month of OAC use, and patients with prosthetic heart valves, mitral stenosis, end-stage renal disease or liver cirrhosis. We also excluded patients with very high gastrointestinal
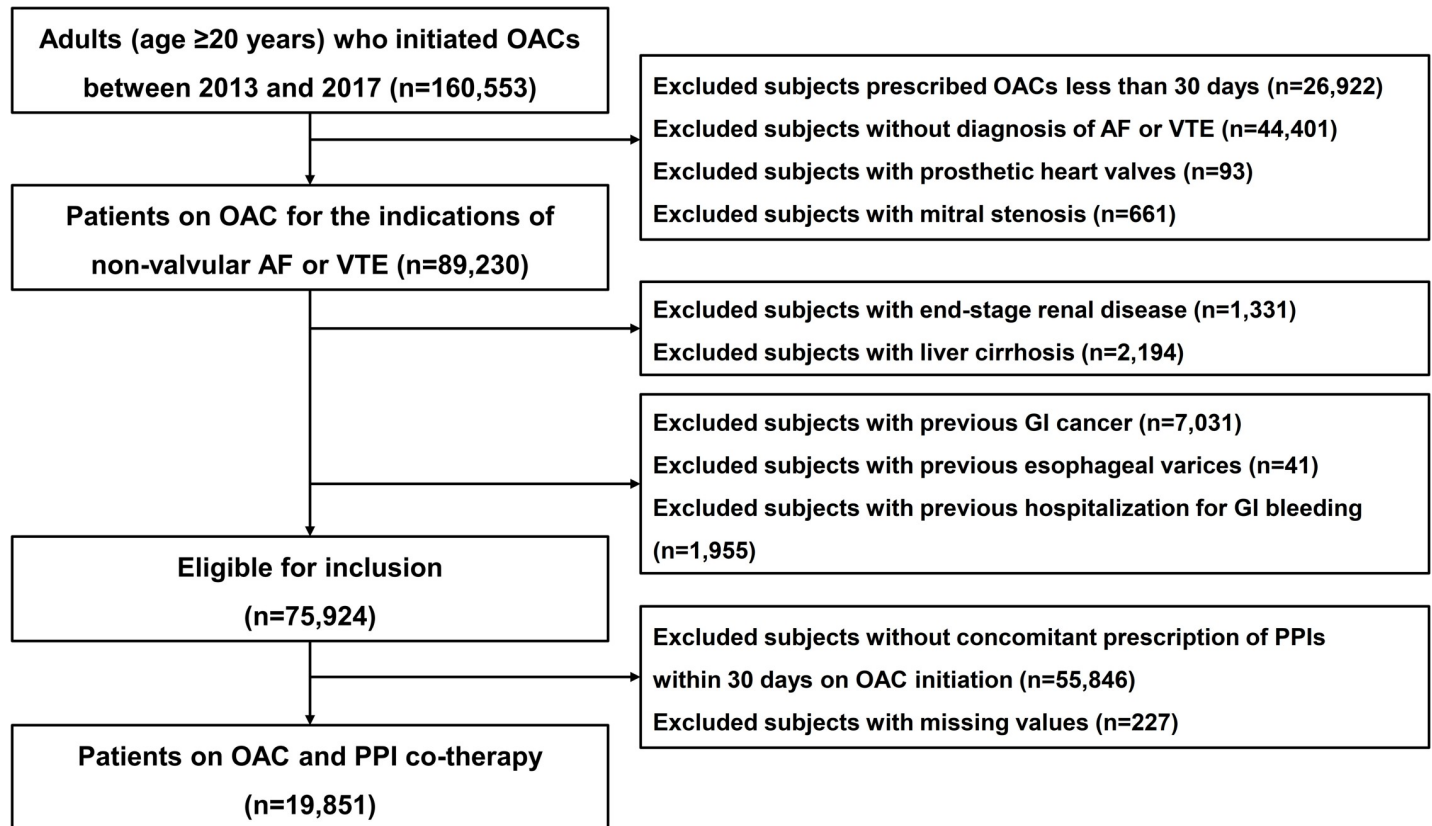
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┌──────────────────────────────────┐
│ Adults (age ≥20 years) who initiated OACs │
│ between 2013 and 2017 (n=160,553) │
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            │    ┌──────────────────────────────────────────────────────┐
            │    │ Excluded subjects prescribed OACs less than 30 days (n=26,922) │
            ├───▶│ Excluded subjects without diagnosis of AF or VTE (n=44,401) │
            │    │ Excluded subjects with prosthetic heart valves (n=93) │
            │    │ Excluded subjects with mitral stenosis (n=661) │
            │    └──────────────────────────────────────────────────────┘
            ▼
┌──────────────────────────────────┐
│ Patients on OAC for the indications of │
│ non-valvular AF or VTE (n=89,230) │
└──────────────────────────────────┘
            │    ┌──────────────────────────────────────────────────────┐
            ├───▶│ Excluded subjects with end-stage renal disease (n=1,331) │
            │    │ Excluded subjects with liver cirrhosis (n=2,194) │
            │    └──────────────────────────────────────────────────────┘
            │    ┌──────────────────────────────────────────────────────┐
            │    │ Excluded subjects with previous GI cancer (n=7,031) │
            ├───▶│ Excluded subjects with previous esophageal varices (n=41) │
            │    │ Excluded subjects with previous hospitalization for GI bleeding │
            │    │ (n=1,955) │
            │    └──────────────────────────────────────────────────────┘
            ▼
┌──────────────────────────────────┐
│ Eligible for inclusion │
│ (n=75,924) │
└──────────────────────────────────┘
            │    ┌──────────────────────────────────────────────────────┐
            ├───▶│ Excluded subjects without concomitant prescription of PPIs │
            │    │ within 30 days on OAC initiation (n=55,846) │
            │    │ Excluded subjects with missing values (n=227) │
            │    └──────────────────────────────────────────────────────┘
            ▼
┌──────────────────────────────────┐
│ Patients on OAC and PPI co-therapy │
│ (n=19,851) │
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Fig 1. Study inclusion flow. OAC, oral anticoagulant; AF, atrial fibrillation; VTE, venous thromboembolism; GI, gastrointestinal; PPI, proton pump inhibitor.

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bleeding risk, i.e. those with previous gastrointestinal cancer, esophageal varices, or history of gastrointestinal bleeding within 1 year prior to OACs prescription. Finally, we included patients who were concomitantly prescribed PPIs within 1 month of OAC initiation (**Fig 1**). Proton pump inhibitors included pantoprazole, lansoprazole, omeprazole, rabeprazole, esome-prazole, ilaprazole, and dexlansoprazole.

Covariates and study outcomes

Age, sex, and income level were ascertained from the database. Comorbidities were assessed for 1 year before the index OAC initiation. Diseases were defined using diagnostic codes, inpatient/outpatient hospital visits, and prescription codes (**S1 Table in S1 File**) [16, 17]. Concomitant antiplatelet and nonsteroidal anti-inflammatory drug (NSAID) use of at least 1 month or more during the study period was also identified. The HAS-BLED score was calculated as a measure of bleeding risk, by assessing the presence of hypertension (1 point), abnormal renal function (1 point; end-stage renal disease, chronic kidney disease, kidney transplantation), abnormal liver function (1 point; liver cirrhosis, liver disease), stroke (1 point; ischemic stroke), bleeding (1 point; previous hospitalization for gastrointestinal bleeding, peptic ulcer), old age (1 point; age >65 years), heavy alcohol drinking (1 point; >8 times/week), and antiplatelet or NSAID use (1 point) [18]. The CHA$_2$DS$_2$-VASc score was calculated as a measure of stroke risk in patients with atrial fibrillation, by assessing the presence of congestive heart failure (1 point), hypertension (1 point), old age (2 points if ≥75 years; 1 point if ≥65 years), diabetes mellitus (1 point), prior stroke or transient ischemic attack or systemic embolism (2

points), vascular disease (1 point; myocardial infarction or peripheral artery disease), and female sex (1 point) [17, 19] (**S1 Table in S1 File**).

The primary endpoint was major upper gastrointestinal bleeding, defined as hospitalization with red blood cell transfusion for bleeding related to gastric ulcers, duodenal ulcers, gastrojejunal ulcers, or hemorrhagic gastritis (**S1 Table in S1 File**). The secondary endpoint was death in the total study population, and the occurrence of ischemic stroke in the subpopulation of patients on OAC for non-valvular atrial fibrillation. The index date was the date of the OAC initiation and follow-up was until the occurrence of the endpoints, death, censoring due to discontinuation of OAC for more than 1 month or change of OAC type, or the end of the study (December 31, 2018).

Statistical analysis

Categorical variables are presented as numbers (%), and continuous variables are presented as mean ± standard deviation or median (interquartile ranges). Incidence rates were calculated by dividing the number of events by the total follow-up period (per 1000 person-years). The risks of the upper gastrointestinal bleeding associated with warfarin, pooled NOACs, and individual NOACs were assessed with Cox regression analysis, and the hazard ratio (HR) and corresponding 95% confidence interval (CI) were estimated. Multivariable models were adjusted for age, sex, atrial fibrillation, venous thromboembolism, comorbidities including hypertension, diabetes mellitus, chronic kidney disease, ischemic heart disease, heart failure, and peptic ulcer disease, and the concomitant use of aspirin, $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, ticagrelor), and NSAID. Weighted cumulative incidence curves were drawn by the Kaplan-Meier method and compared with the log-rank test. We also performed separate analyses for the primary endpoint stratified by the NOAC dose regimen (i.e., regular and reduced). Pre-specified subgroup analyses were performed according to age, sex, indication for OAC use, number of antiplatelet agents, use of NSAID, history of peptic ulcer disease, and bleeding risk. We also conducted multivariable Cox regression analyses for the secondary endpoints of death and ischemic stroke.

We conducted sensitivity analyses to test the robustness of the main results. Due to the increasing popularity of NOACs, the number of patients prescribed warfarin decreased steadily while that of NOACs increased throughout the study period (**S2 Table in S1 File**). Thus, we performed a sensitivity analysis censoring patient follow-up at 2 years to approximate the follow-up durations of OAC groups (**S3 Table in S1 File**). Second, as the mortality rate was high within the study population, we conducted a sensitivity analysis considering death as a competing risk using the Fine-Gray method. Third, we conducted a sensitivity analysis in patients not on antiplatelets or NSAIDs.

A p-value <0.05 was considered statistically significant. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

Results

Baseline characteristics

The study cohort included 19,851 patients on OAC and PPI co-therapy. There were 6,995 (35.2%), 6,468 (32.6%), 2,301 (11.6%), 2,613 (13.2%), and 1,474 (7.4%) patients initiating warfarin, rivaroxaban, dabigatran, apixaban, and edoxaban, respectively. Mean age was 71.0±12.7 years and 44.6% were men. Indication for OAC use was non-valvular atrial fibrillation in 63.5%, venous thromboembolism in 47.8%, and both in 11.3% of the patients. Approximately a third (31.2%) were on antiplatelet agents; 22.7% and 8.5% were on single and double antiplatelet therapy, respectively. NSAIDs were prescribed in 29.3% of the patients. Mean

Table 1. Baseline characteristics of the study population.

	Warfarin (n = 6995)	Rivaroxaban (n = 6468)	Dabigatran (n = 2301)	Apixaban (n = 2613)	Edoxaban (n = 1474)	p-value
Age (year)						
Mean±SD	68.9±13.31	71.0±12.9	71.9±11.5	74.23±10.9	73.16±11.05	<0.001
≥75	2809 (40.2)	3005 (46.5)	1079 (46.9)	1496 (57.3)	760 (51.6)	<0.001
Sex, male	3367 (48.1)	2561 (39.6)	1118 (48.6)	1149 (44.0)	657 (44.6)	<0.001
Income, low 20%	1693 (24.2)	1611 (24.9)	548 (23.8)	573 (21.9)	357 (24.2)	0.056
Comorbidities						
Non-valvular atrial fibrillation	4681 (66.9)	2798 (43.3)	1790 (77.8)	2136 (81.8)	1200 (81.4)	<0.001
Venous thromboembolism	3125 (44.7)	4417 (68.3)	761 (33.1)	770 (29.5)	419 (28.4)	<0.001
Hypertension	4607 (65.9)	4181 (64.6)	1613 (70.1)	1910 (73.1)	1043 (70.8)	<0.001
Diabetes mellitus	1594 (22.8)	1416 (21.9)	544 (23.6)	681 (26.1)	341 (23.1)	<0.001
Chronic kidney disease	438 (6.2)	280 (4.3)	87 (3.8)	169 (6.5)	69 (4.7)	<0.001
Ischemic heart disease	2050 (29.3)	1675 (25.9)	695 (30.2)	883 (33.8)	473 (32.1)	<0.001
Heart failure	1748 (25.0)	1536 (23.8)	625 (27.2)	867 (33.2)	472 (32.0)	<0.001
Peptic ulcer disease	2109 (30.2)	1994 (30.8)	629 (27.3)	741 (28.4)	399 (27.1)	0.001
Medications						
Aspirin	2215 (31.7)	1396 (21.6)	446 (19.4)	475 (18.2)	250 (17.0)	<0.001
$P2Y_{12}$ inhibitor	1347 (19.3)	829 (12.8)	320 (13.9)	383 (14.7)	207 (14.0)	<0.001
Number of antiplatelet agents						<0.001
0	4314 (61.7)	4627 (71.5)	1685 (73.2)	1932 (73.9)	1103 (74.8)	
1	1800 (25.7)	1457 (22.5)	466 (20.3)	504 (19.3)	285 (19.3)	
2	881 (12.6)	384 (5.9)	150 (6.5)	177 (6.8)	86 (5.8)	
NSAID	2026 (29.0)	2173 (33.6)	584 (25.4)	637 (24.4)	403 (27.3)	<0.001
Previous PPI use	3286 (47.0)	3705 (57.3)	1176 (51.1)	1408 (53.9)	861 (58.4)	<0.001
HAS-BLED score	2.50±1.31	2.51±1.29	2.49±1.22	2.63±1.22	2.53±1.21	0.001

NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

HAS-BLED score was 2.5±1.3, signifying that the study population had moderate bleeding risk.

Baseline characteristics according to the OAC groups are summarized in **Table 1**. Warfarin users were the youngest, while apixaban users were the oldest. Non-valvular atrial fibrillation was the main indication for OAC use except for rivaroxaban, the main indication of which was venous thromboembolism. Apixaban users had the highest proportion of comorbidities, with the only exception of previous history of peptic ulcer disease. Concomitant use of anti-platelet agents was highest in warfarin users (38.3%), while that of NSAIDs was highest in riv-aroxaban users (33.6%). HAS-BLED scores were mostly similar among the OAC users, with apixaban users having a slightly higher score.

Risk of upper gastrointestinal bleeding

During a mean 1.41±1.35 years of follow-up, 512 (2.58%) patients on OAC and PPI co-therapy were hospitalized for major upper gastrointestinal bleeding. The weighted cumulative incidence of upper gastrointestinal bleeding events was higher in patients on warfarin compared to those on NOAC (**Fig 2**, log-rank p = 0.024). Weighted event-free survival for warfarin and NOAC users were 85.4% and 87% at 1 year, and 80.3% and 81.1% at 2 years, respectively. Compared to patients on warfarin, patients on NOACs had 22% lower risk of developing major upper gastrointestinal bleeding, after adjustment for age, sex, comorbidities and
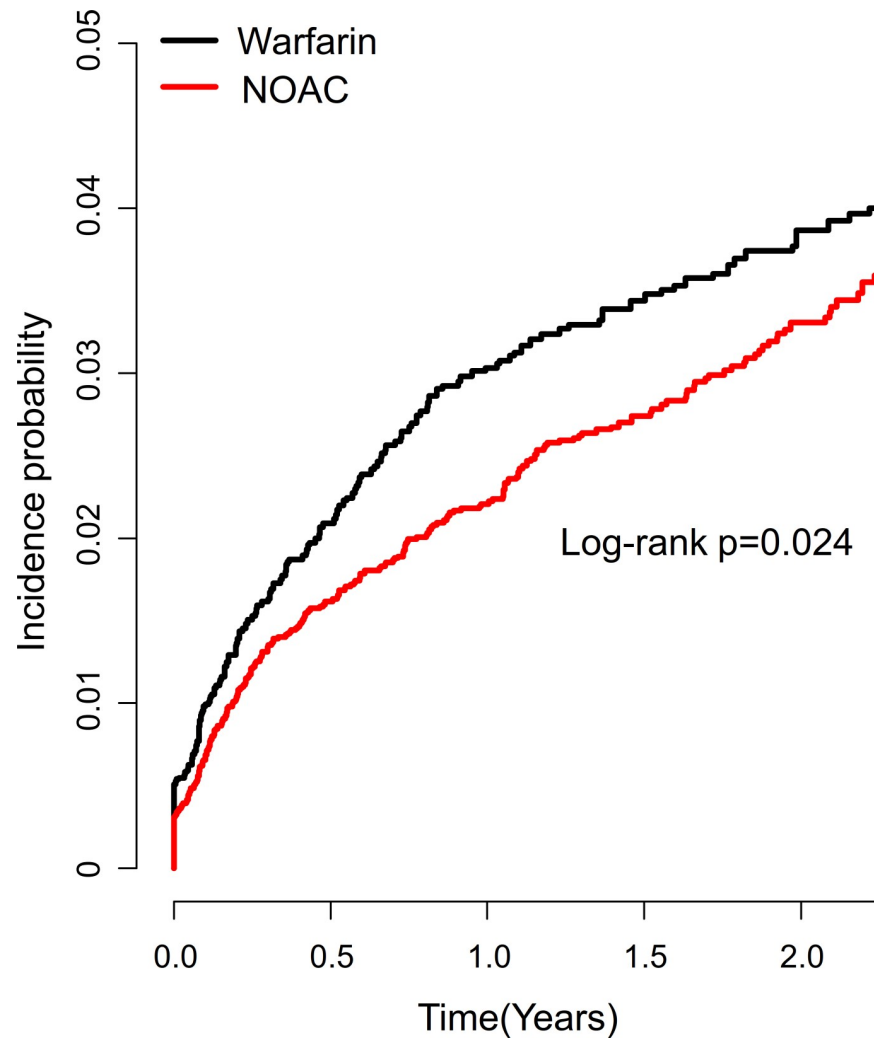
Fig 2. Weighted Kaplan-Meier curves for upper gastrointestinal bleeding events according to oral anticoagulants.
NOAC, non-vitamin K antagonist oral anticoagulant.

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concomitant antiplatelets and NSAIDs (adjusted HR 0.78, 95% CI 0.65–0.94, p = 0.007) (**Fig 3**, **Table 2**). The largest risk reduction in upper gastrointestinal bleeding was observed in apixaban (adjusted HR 0.69, 95% CI 0.51–0.93, p = 0.014) and edoxaban users (adjusted HR 0.61, 95% CI 0.41–0.92, p = 0.019). There was no significant difference in upper gastrointestinal bleeding risk among the individual NOACs (p = 0.332), although adjusted HRs showed a progressively decreasing trend of events from rivaroxaban, dabigatran, apixaban, to edoxaban (**S4 Table in S1 File**).

Sensitivity analysis censoring follow-up at 2 years showed similar results (**S5, S6 Tables in S1 File**). In brief, patients on NOACs had lower upper gastrointestinal bleeding risk compared to those on warfarin (adjusted HR 0.78, 95% CI 0.64–0.94, p = 0.011). Sensitivity analysis accounting for the competing risk of death also showed consistent results (adjusted HR 0.77, 95% CI 0.64–0.92, p = 0.004; **S7, S8 Tables in S1 File**). Sensitivity analysis excluding patients on antiplatelet agents or NSAIDs also showed that the use of NOAC was associated with lower upper gastrointestinal bleeding risk compared to use of warfarin (adjusted HR 0.74, 95% CI 0.58–0.95, p = 0.020; **S9, S10 Tables in S1 File**). In all the sensitivity analyses as well, upper

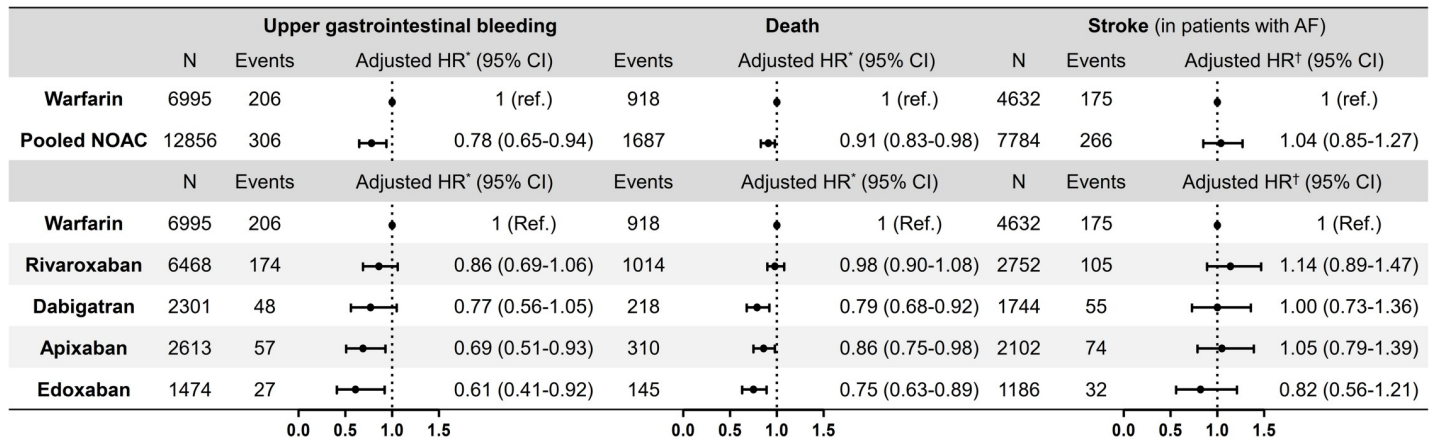|		Upper gastrointestinal bleeding			Death			Stroke (in patients with AF)	
	N	Events	Adjusted HR* (95% CI)	Events	Adjusted HR* (95% CI)	N	Events	Adjusted HR† (95% CI)	
Warfarin	6995	206	1 (ref.)	918	1 (ref.)	4632	175	1 (ref.)	
Pooled NOAC	12856	306	0.78 (0.65-0.94)	1687	0.91 (0.83-0.98)	7784	266	1.04 (0.85-1.27)	
	N	Events	Adjusted HR* (95% CI)	Events	Adjusted HR* (95% CI)	N	Events	Adjusted HR† (95% CI)	
Warfarin	6995	206	1 (Ref.)	918	1 (Ref.)	4632	175	1 (Ref.)	
Rivaroxaban	6468	174	0.86 (0.69-1.06)	1014	0.98 (0.90-1.08)	2752	105	1.14 (0.89-1.47)	
Dabigatran	2301	48	0.77 (0.56-1.05)	218	0.79 (0.68-0.92)	1744	55	1.00 (0.73-1.36)	
Apixaban	2613	57	0.69 (0.51-0.93)	310	0.86 (0.75-0.98)	2102	74	1.05 (0.79-1.39)	
Edoxaban	1474	27	0.61 (0.41-0.92)	145	0.75 (0.63-0.89)	1186	32	0.82 (0.56-1.21)	

Fig 3. Differential risk of upper gastrointestinal bleeding, death, and ischemic stroke in users of warfarin and 4 NOACs. In patients on combined proton pump inhibitor and oral anticoagulant therapy, NOACs were associated with lower risk of upper gastrointestinal bleeding and mortality compared to warfarin, while there was no significant difference among the OACs in risk of stroke. *Adjusted for age, sex, atrial fibrillation, venous thromboembolism, comorbidities (hypertension, diabetes mellitus, chronic kidney disease, ischemic heart disease, heart failure, peptic ulcer disease), and concomitant use of aspirin, $P2Y_{12}$ inhibitor, and nonsteroidal anti-inflammatory drug. †Additionally adjusted for the CHA_2DS_2-VASc score. NOAC, non-vitamin K antagonist oral anticoagulant; AF, atrial fibrillation.

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gastrointestinal bleeding risks among the individual NOACs were not significantly different (p = 0.216, p = 0.334, and p = 0.268, respectively), though there was a trend for decreasing adjusted HRs in the order of rivaroxaban, dabigatran, apixaban, and edoxaban (**S6, S8, and S10 Tables in S1 File**).

Among NOAC users, 65.8% (n = 8,460) were prescribed reduced dose of NOACs. Reduced doses of NOACs were defined as 15 or 10 mg rivaroxaban once daily, 110 mg dabigatran twice daily, 2.5 mg apixaban twice daily, and 30 mg edoxaban once daily, while regular doses of NOACs were defined as 20 mg rivaroxaban once daily, 150 mg dabigatran twice daily, 5 mg apixaban twice daily, and 60 mg edoxaban once daily. Compared to patients on warfarin, there was a tendency for reduced upper gastrointestinal bleeding risk in patients on both standard dose and reduced dose of NOACs, which was statistically significant in standard dose of NOACs and was of borderline significance in reduced dose of NOACs (**Fig 4**). This trend of reduced upper gastrointestinal bleeding risk compared to warfarin was consistent for both regular and reduced dose regimens of all individual NOACs.

Table 2. Upper gastrointestinal bleeding risk according to OAC treatment.

	N	Events	IR*	Crude HR (95% CI)	p-value		Adjusted HR† (95% CI)	p-value	
Warfarin	6995	206	17.6	1 (reference)			1 (reference)		
NOACs	12856	306	18.8	0.91 (0.76–1.09)	0.324		0.78 (0.65–0.94)	0.007	
	N	Events	IR*	Crude HR (95% CI)	p-value	Overall p-value	Adjusted HR† (95% CI)	p-value	Overall p-value
Warfarin	6995	206	17.6	1 (reference)		0.467	1 (reference)		0.032
Rivaroxaban	6468	174	19.1	0.98 (0.80–1.20)	0.858		0.86 (0.69–1.06)	0.145	
Dabigatran	2301	48	18.7	0.86 (0.63–1.18)	0.360		0.77 (0.56–1.05)	0.100	
Apixaban	2613	57	19.3	0.88 (0.65–1.18)	0.379		0.69 (0.51–0.93)	0.014	
Edoxaban	1474	27	16.6	0.72 (0.48–1.08)	0.109		0.61 (0.41–0.92)	0.019	

*IR: incidence rate per 1000 person-years.

†Adjusted for age, sex, atrial fibrillation, venous thromboembolism, hypertension, diabetes mellitus, chronic kidney disease, ischemic heart disease, heart failure, peptic ulcer disease, concomitant use of aspirin, $P2Y_{12}$ inhibitor, and nonsteroidal anti-inflammatory drug.

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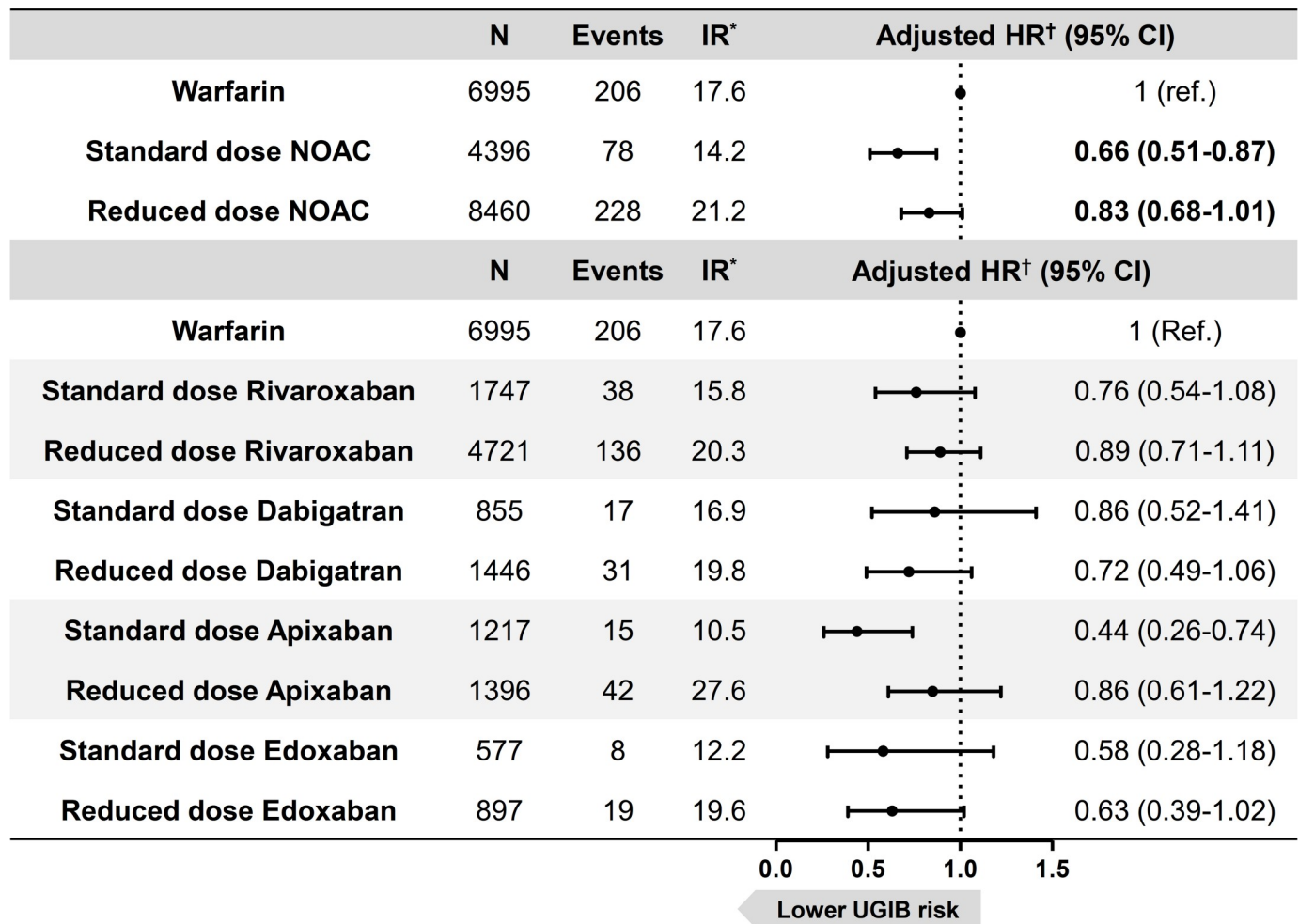|	N	Events	IR*	Adjusted HR† (95% CI)	
Warfarin	6995	206	17.6		1 (ref.)
Standard dose NOAC	4396	78	14.2		**0.66 (0.51-0.87)**
Reduced dose NOAC	8460	228	21.2		**0.83 (0.68-1.01)**
	N	**Events**	**IR***	**Adjusted HR† (95% CI)**	
Warfarin	6995	206	17.6		1 (Ref.)
Standard dose Rivaroxaban	1747	38	15.8		0.76 (0.54-1.08)
Reduced dose Rivaroxaban	4721	136	20.3		0.89 (0.71-1.11)
Standard dose Dabigatran	855	17	16.9		0.86 (0.52-1.41)
Reduced dose Dabigatran	1446	31	19.8		0.72 (0.49-1.06)
Standard dose Apixaban	1217	15	10.5		0.44 (0.26-0.74)
Reduced dose Apixaban	1396	42	27.6		0.86 (0.61-1.22)
Standard dose Edoxaban	577	8	12.2		0.58 (0.28-1.18)
Reduced dose Edoxaban	897	19	19.6		0.63 (0.39-1.02)

0.0   0.5   1.0   1.5

Lower UGIB risk

Fig 4. Comparison of upper gastrointestinal bleeding risk in users of warfarin and 4 NOACs with consideration of dose regimens. *IR: incidence rate per 1000 person-years. †Adjusted for age, sex, atrial fibrillation, venous thromboembolism, comorbidities (hypertension, diabetes mellitus, chronic kidney disease, ischemic heart disease, heart failure, peptic ulcer disease), and concomitant use of aspirin, $P2Y_{12}$ inhibitor, and nonsteroidal anti-inflammatory drug. NOAC, non-vitamin K antagonist oral anticoagulant; UGIB, upper gastrointestinal bleeding.

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In subgroup analyses according to age (<75, ≥75), sex, indication for OAC use (i.e. non-valvular atrial fibrillation or venous thromboembolism), number of antiplatelet agents (0, 1, or 2), NSAID use, history of peptic ulcer disease, and bleeding risk according to the HAS-BLED scores (0, 1–2, ≥3), tests for interaction showed no significant subgroup differences in the treatment effects of OACs (**Fig 5**). There was a general trend for reduced upper gastrointestinal bleeding risk in NOAC users compared to warfarin users, which was consistent throughout the subgroups, except for similar risks in patients on 2 antiplatelet agents or NSAIDs. Notably, the trend of lower gastrointestinal bleeding risk associated with NOACs compared to warfarin was consistent throughout patients with low (0), moderate (1–2), or high bleeding risk (≥3) by HAS-BLED scores; this trend was also consistent for individual NOACs (**S1 Fig in S1 File**).

Risk of death

During a mean 1.43±1.35 years of follow-up, 2605 (13.1%) deaths occurred in patients on OAC and PPI co-therapy. Compared to patients on warfarin, patients on NOACs had a small
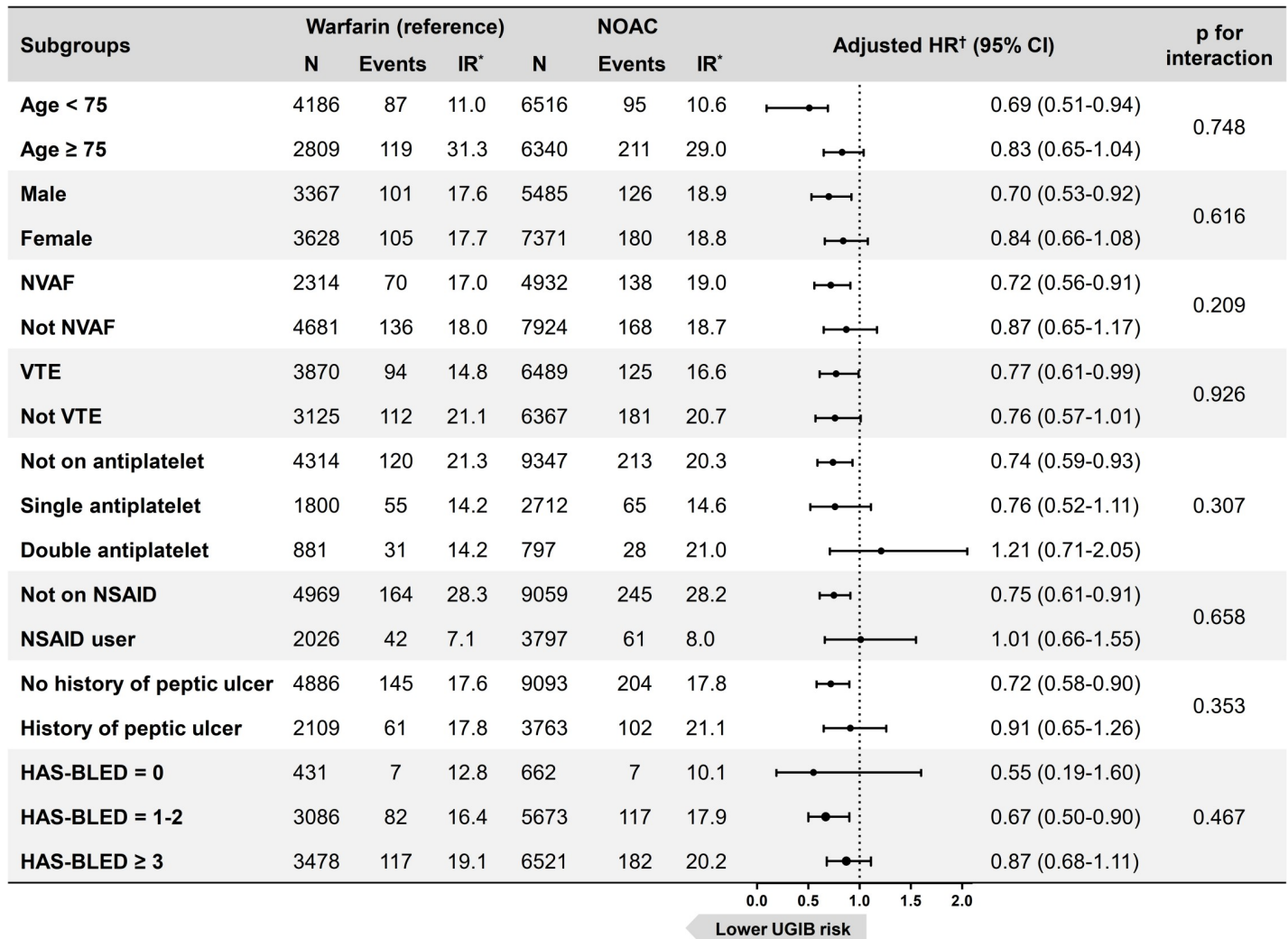
Subgroups	Warfarin (reference)			NOAC			Adjusted HR† (95% CI)	p for interaction
	N	Events	IR*	N	Events	IR*		
Age < 75	4186	87	11.0	6516	95	10.6	0.69 (0.51-0.94)	0.748
Age ≥ 75	2809	119	31.3	6340	211	29.0	0.83 (0.65-1.04)	
Male	3367	101	17.6	5485	126	18.9	0.70 (0.53-0.92)	0.616
Female	3628	105	17.7	7371	180	18.8	0.84 (0.66-1.08)	
NVAF	2314	70	17.0	4932	138	19.0	0.72 (0.56-0.91)	0.209
Not NVAF	4681	136	18.0	7924	168	18.7	0.87 (0.65-1.17)	
VTE	3870	94	14.8	6489	125	16.6	0.77 (0.61-0.99)	0.926
Not VTE	3125	112	21.1	6367	181	20.7	0.76 (0.57-1.01)	
Not on antiplatelet	4314	120	21.3	9347	213	20.3	0.74 (0.59-0.93)	
Single antiplatelet	1800	55	14.2	2712	65	14.6	0.76 (0.52-1.11)	0.307
Double antiplatelet	881	31	14.2	797	28	21.0	1.21 (0.71-2.05)	
Not on NSAID	4969	164	28.3	9059	245	28.2	0.75 (0.61-0.91)	0.658
NSAID user	2026	42	7.1	3797	61	8.0	1.01 (0.66-1.55)	
No history of peptic ulcer	4886	145	17.6	9093	204	17.8	0.72 (0.58-0.90)	0.353
History of peptic ulcer	2109	61	17.8	3763	102	21.1	0.91 (0.65-1.26)	
HAS-BLED = 0	431	7	12.8	662	7	10.1	0.55 (0.19-1.60)	
HAS-BLED = 1-2	3086	82	16.4	5673	117	17.9	0.67 (0.50-0.90)	0.467
HAS-BLED ≥ 3	3478	117	19.1	6521	182	20.2	0.87 (0.68-1.11)	

0.0 0.5 1.0 1.5 2.0

◄ Lower UGIB risk

Fig 5. Upper gastrointestinal bleeding risk of NOACs with reference to warfarin in various subgroups. *IR: incidence rate per 1000 person-years. †Adjusted for age, sex, atrial fibrillation, venous thromboembolism, comorbidities (hypertension, diabetes mellitus, chronic kidney disease, ischemic heart disease, heart failure, peptic ulcer disease), and concomitant use of aspirin, P2Y12 inhibitor, and nonsteroidal anti-inflammatory drug. NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drug; NVAF, non-valvular atrial fibrillation; UGIB, upper gastrointestinal bleeding; VTE, venous thromboembolism.

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but significant reduction in the risk of death, after adjustment for age, sex, comorbidities and concomitant medication (adjusted HR 0.91, 95% CI 0.83–0.98, p = 0.020) (**Table 3**). The lower risk of death was significant in dabigatran (adjusted HR 0.79, 95% CI 0.68–0.92, p = 0.002), apixaban (adjusted HR 0.86, 95% CI 0.75–0.98, p = 0.023), and edoxaban (adjusted HR 0.75, 95% CI 0.63–0.89, p = 0.001) users. Among individual NOACs, patients on dabigatran (adjusted HR 0.83, 95% CI 0.71–0. 97, p = 0.016) and edoxaban (adjusted HR 0.81, 95% CI 0.67–0.96, p = 0.019) had lower risk of death compared to patients on rivaroxaban (**S11 Table in S1 File**).

Risk of stroke

To compare the effectiveness of OACs when administered concomitantly with PPIs, the risk of ischemic stroke was compared in the subpopulation of patients on OAC for the indication of non-valvular atrial fibrillation (n = 12,416). Baseline characteristics according to the OAC

Table 3. Risk of death according to OAC treatment.

	N	Events	IR*	Crude HR (95% CI)	p-value		Adjusted HR† (95% CI)	p-value	
Warfarin	6995	918	77.3	1 (reference)			1 (reference)		
NOACs	12856	1687	102.4	1.19 (1.10–1.29)	<0.001		0.91 (0.83–0.98)	0.020	
	N	Events	IR*	Crude HR (95% CI)	p-value	Overall p-value	Adjusted HR† (95% CI)	p-value	Overall p-value
Warfarin	6995	918	77.3	1 (reference)		<0.001	1 (reference)		<0.001
Rivaroxaban	6468	1014	109.4	1.32 (1.21–1.45)	<0.001		0.98 (0.90–1.08)	0.720	
Dabigatran	2301	218	83.9	0.95 (0.82–1.10)	0.471		0.79 (0.68–0.92)	0.002	
Apixaban	2613	310	104.3	1.15 (1.01–1.31)	0.040		0.86 (0.75–0.98)	0.023	
Edoxaban	1474	145	88.4	0.93 (0.78–1.10)	0.390		0.75 (0.63–0.89)	0.001	

Footnotes same as Table 2.

used in this subpopulation are summarized in **S12 Table in S1 File**, and were similar to those of the total study population. The mean CHA_2DS_2-VASc score was 3.6±2.1, and was highest in apixaban users (3.9±2.0) and lowest in warfarin users (3.3±2.1). Ischemic stroke occurred in 441 (3.6%) patients. There was no significant difference in the risk of ischemic stroke between patients on warfarin and those on NOAC, after adjustment for age, sex, comorbidities, concomitant medication, and the CHA_2DS_2-VASc score (p = 0.719; **Table 4**). There was no significant difference among the individual NOACs, as well (p = 0.374; **S13 Table in S1 File**).

Discussion

In a large cohort of patients on OAC and PPI co-therapy, significant differences were clinically observed in upper gastrointestinal bleeding risk according to the OACs used. Specifically, NOACs were associated with lower risk of upper gastrointestinal bleeding compared to warfarin, after multivariable adjustment for age, sex, baseline comorbidities, and concomitant medication including antiplatelet agents and NSAIDs. The largest reduction in upper gastrointestinal bleeding risk was noted with apixaban and edoxaban, as compared to warfarin. Among four individual NOACs, the difference in upper gastrointestinal bleeding risk was not statistically significant. The trend of reduced risk for upper gastrointestinal bleeding in NOACs compared to warfarin was consistent for both regular and reduced dose NOAC regimens, and in subgroup analyses stratified by age, sex, indication for OAC use, number of

Table 4. Risk of stroke according to OAC treatment in patients with atrial fibrillation.

	N	Events	IR*	Crude HR (95% CI)	p-value		Adjusted HR† (95% CI)	p-value	
Warfarin	4632	175	23.3	1 (reference)			1 (reference)		
NOAC	7784	266	29.7	1.07 (0.88–1.30)	0.494		1.04 (0.85–1.27)	0.719	
	N	Events	IR*	Crude HR (95% CI)	p-value	Overall p-value	Adjusted HR† (95% CI)	p-value	Overall p-value
Warfarin	4632	175	23.3	1 (reference)		0.458	1 (reference)		0.560
Rivaroxaban	2752	105	31.8	1.17 (0.92–1.50)	0.203		1.14 (0.89–1.47)	0.295	
Dabigatran	1744	55	28.4	1.01 (0.75–1.38)	0.932		1.00 (0.73–1.36)	0.983	
Apixaban	2102	74	31.3	1.11 (0.84–1.46)	0.455		1.05 (0.79–1.39)	0.769	
Edoxaban	1186	32	23.8	0.84 (0.57–1.22)	0.358		0.82 (0.56–1.21)	0.315	

*IR: incidence rate per 1000 person-years.

†Adjusted for age, sex, hypertension, diabetes mellitus, chronic kidney disease, ischemic heart disease, heart failure, peptic ulcer disease, concomitant use of aspirin, $P2Y_{12}$ inhibitor, nonsteroidal anti-inflammatory drug, and CHA_2DS_2-VASc score.

antiplatelet agents or NSAID use, and history of peptic ulcer disease. In addition, NOACs were associated with lower risk of death compared to warfarin. Meanwhile, there was no significant difference in risk of ischemic stroke among the OACs in patients with atrial fibrillation. To our knowledge, this is the first study comparing the clinical outcomes of patients on OAC and PPI co-therapy.

PPIs have been associated with reduced risk of upper gastrointestinal bleeding in patients on OACs, especially in high-risk patients [4–6]. Guidelines also recommend co-administration of PPIs in OAC users on concomitant antiplatelet therapy [3]. Age-related cardiovascular diseases and atrial fibrillation are on the rise in the aging society [1, 2], while aging itself also predisposes to higher risk of gastrointestinal bleeding complications associated with antithrombotic therapy [20]. Thus, we can expect that PPIs will be prescribed more frequently to prevent upper gastrointestinal bleeding in OAC users, especially in those with higher bleeding risk. However, there is a lack of data on the optimal OAC choice considering the gastrointestinal safety and effectiveness of individual OACs in patients on OAC and PPI co-therapy. Although previous studies have shown that there are differences in gastrointestinal bleeding risk among the OACs without considering PPI use [11–13], it is unclear whether we can extrapolate these clinical observations that compared gastrointestinal safety in general OAC users to the subpopulation of patients on OAC and PPI co-therapy.

Some evidence suggests that the gastrointestinal safety of OACs may be altered with the concomitant use of PPIs. According to a previous study showing that PPI use was associated with reduced upper gastrointestinal bleeding events for all OACs, this risk reduction was most pronounced in dabigatran [5]. Dabigatran has a tartaric acid core that may cause dyspepsia and characteristic upper gastrointestinal tract mucosal injury [21, 22], and theoretically PPIs could prevent upper gastrointestinal bleeding events related to these lesions. Meanwhile, other NOACs such as rivaroxaban, apixaban, and edoxaban do not have a tartaric acid core and have not been linked to such mucosal erosions, except for one case report with rivaroxaban [23]. Also, co-administration of PPIs was reported to decrease the bioavailability of dabigatran around 12~24% [9, 10, 24, 25], which may be related to lower gastrointestinal bleeding risk but also potentially reduced effectiveness for preventing stroke or venous thromboembolism. The absorption of dabigatran is enhanced by a low pH [26], and thus can be hindered by PPI co-administration. On the other hand, the pharmacokinetics of rivaroxaban, apixaban, and edoxaban are not affected by gastric pH modifiers [8, 27, 28]. PPIs have also been suggested to potentiate the anticoagulant effects of warfarin, and caution should be taken to carefully monitor patients on warfarin and PPI co-therapy [7]. This may be related to the increased absorption of warfarin in a higher pH, and reduced metabolism of warfarin due to altered cytochrome P activity by the PPIs [29, 30]. However, drug interactions may differ according to PPI type [30], and some studies suggest that there are no clinically meaningful interactions between PPIs and warfarin [31, 32]. Fortunately, laboratory monitoring with prothrombin time makes it possible to adjust the level of anticoagulation in patients on warfarin, which is not possible in those on NOACs. Meanwhile, there is a lack of data on whether expected drug interactions between PPIs and OACs translate into clinically significant differences in patient outcome.

Previous studies have shown differences in the gastrointestinal bleeding risk of OACs [11–13]. In a meta-analysis using the landmark NOAC clinical trials, NOACs reduced ischemic stroke or systemic embolism, but were associated with increased gastrointestinal bleeding compared to warfarin [11]. In another meta-analysis including 43 randomized clinical trials, pooled NOACs and warfarin showed no differences in upper gastrointestinal bleeding, and rivaroxaban and dabigatran were associated with increased risk of major gastrointestinal bleeding, which was not true for apixaban and edoxaban [12]. Meanwhile, another meta-analysis of the landmark trials suggested that NOACs increased gastrointestinal bleeding compared

to warfarin in non-Asians, but not in Asians [33]. In observational studies comparing individual NOACs, apixaban had the lowest gastrointestinal bleeding risk, and was significantly lower than that of rivaroxaban or dabigatran [13, 34, 35]. In Asians, NOACs were associated with lower risks of gastrointestinal bleeding and ischemic stroke compared to warfarin, with apixaban showing the lowest rates of gastrointestinal bleeding [13]. Our study showed that in patients on OAC and PPI co-therapy, warfarin was related to a higher upper gastrointestinal bleeding risk compared to those on NOACs. Although the difference among the individual NOACs were not statistically significant, there was a trend for the lowest gastrointestinal bleeding risk in apixaban and edoxaban. Moreover, NOACs were associated with reduced mortality compared to warfarin. In contrary to the previous studies that showed lower risk of stroke with NOACs compared to warfarin [11, 13, 33], we found no significant difference in risk for ischemic stroke between the NOACs and warfarin when PPI was co-administrated. In the case of dabigatran, this may be related to lower bioavailability due to PPI co-therapy, while the same can be prevented by prothrombin time monitoring in warfarin, as described above. There is a possibility that the co-administration of PPI may reduce the effectiveness of other NOACs as well, through yet unknown mechanisms. To note, another study suggested that the effectiveness of NOACs for stroke prevention may be decreased compared with warfarin in patients with increasing polypharmacy, especially that of apixaban [36].

This study has several limitations that need to be addressed. First, possible differences with individual PPIs could not be analyzed due to the reduction in statistical power. Second, we excluded patients with gastrointestinal cancer, esophageal varices, or recent history of gastrointestinal bleeding, and this may limit generalization of the study results to these patients at very high risk for bleeding. Third, the time in therapeutic range in warfarin users could not be evaluated, as prothrombin time was unavailable in this database. Fourth, information on concomitant steroid use was unavailable. Also, possible drug interaction with other drugs were not considered in analysis. Fifth, while we performed multivariable adjustment for differences in observed covariates, there may be residual confounding related to unmeasured covariates. Finally, this is a retrospective study with inherent limitations and while demonstrating association, it does not prove causality.

In conclusion, in patients on OAC and PPI co-therapy, NOACs were associated with reduced upper gastrointestinal bleeding compared to warfarin, especially apixaban and edoxaban. NOACs were also associated with lower mortality compared to warfarin. There was no significant difference in risk for ischemic stroke among the OACs in patients with non-valvular atrial fibrillation. Results from observational studies suggest that PPIs can reduce gastrointestinal bleeding in patients on oral anticoagulation, especially in high-risk patients. If these results are confirmed in randomized controlled trials, the combined use of OAC and PPI may become a part of routine clinical practice. However, it is yet unclear which OAC regimen is optimal in patients on PPI therapy. The results of this study suggest that NOACs may be preferred to warfarin for better safety issues without difference in effectiveness. Further prospective studies are needed to confirm these results.

Supporting information

S1 File. Supplemental materials. S1 Fig, S1-S13 Tables.
(PDF)

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