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Concomitant Oral Anticoagulant and Nonsteroidal Anti-Inflammatory Drug Therapy in Patients With Atrial Fibrillation

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ABSTRACT

BACKGROUND Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used medications that can potentially increase the risk of bleeding and thrombosis.

OBJECTIVES This study quantified the effect of NSAIDs in the RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy) trial.

METHODS This was a post hoc analysis of NSAIDs in the RE-LY study, which compared dabigatran etexilate (DE) 150 and 110 mg twice daily (b.i.d.) with warfarin in patients with atrial fibrillation. Treatment-independent, multivariate-adjusted Cox regression analysis assessed clinical outcomes by comparing NSAID use with no NSAID use. Interaction analysis was obtained from treatment-dependent Cox regression modeling. Time-varying covariate analysis for NSAID use was applied to the Cox model.

RESULTS Among 18,113 patients in the RE-LY study, 2,279 patients used NSAIDs at least once during the trial. Major bleeding was significantly elevated with NSAID use (hazard ratio [HR]: 1.68; 95% confidence interval [CI]: 1.40 to 2.02; $p < 0.0001$). NSAID use did not significantly alter the risk of major bleeding for DE 150 or 110 mg b.i.d. relative to warfarin ($p_{interaction} = 0.63$ and 0.93, respectively). Gastrointestinal major bleeding was significantly elevated with NSAID use (HR: 1.81; 95% CI: 1.35 to 2.43; $p < 0.0001$). The rate of stroke or systemic embolism (stroke/SE) with NSAID use was significantly elevated (HR: 1.50; 95% CI: 1.12 to 2.01; $p = 0.007$). The use of NSAIDs did not significantly alter the relative efficacy on stroke/SE for DE 150 or 110 mg b.i.d. relative to warfarin ($p_{interaction} = 0.59$ and 0.54, respectively). Myocardial infarction rates were similar with NSAID use compared with no NSAID use (HR: 1.22; 95% CI: 0.77 to 1.93; $p = 0.40$). Patients were more frequently hospitalized if they used an NSAID (HR: 1.64; 95% CI: 1.51 to 1.77; $p < 0.0001$).

CONCLUSIONS The use of NSAIDs was associated with increased risk of major bleeding, stroke/SE, and hospitalization. The safety and efficacy of DE 150 and 110 mg b.i.d. relative to warfarin were not altered. (Randomized Evaluation of Long Term Anticoagulant Therapy [RE-LY]; NCT00262600) (J Am Coll Cardiol 2018;72:255–67)

The class of medications known as nonsteroidal anti-inflammatory drugs (NSAIDs) consists of a variety of agents with a common pathway of inhibiting the cyclooxygenase (COX) enzyme and reducing the synthesis of prostaglandins, thromboxane, and prostacyclin. The COX enzyme is subdivided into 2 isoenzymes: COX-1 and COX-2 (1). Examples of nonselective NSAIDs include ibuprofen,

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ABBREVIATIONS AND ACRONYMS

b.i.d. = twice daily

CI = confidence interval

COX = cyclooxygenase

DE = dabigatran etexilate

GI = gastrointestinal

HR = hazard ratio

NSAID = nonsteroidal anti-inflammatory drug

OAC = oral anticoagulation

SE = systemic embolism

naproxen, meloxicam, diclofenac, and ketorolac, whereas celecoxib is an example of a selective NSAID (selective COX-2 inhibitor) (2–4). Aspirin irreversibly inhibits COX, and preferentially, COX-1 at low doses, as well as both isoenzymes at higher doses. Clinically, NSAIDs are associated with an increased risk of bleeding and thrombosis (5–8), adverse effects on renal function (9), and worsening heart failure (10).

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NSAIDs are commonly used and easily accessible medications for patients, and are frequently self-used in the community in conflict with labeling information (11). For example, the use of NSAIDs for analgesia is prevalent among patients initiating dabigatran (12). Both the transient or prolonged combination of NSAIDs with direct oral anticoagulation (OAC) poses a serious risk of bleeding (13). Transient or prolonged use of NSAIDs occurs for a variety of reasons, including arthritis (osteoarthritis and rheumatoid arthritis). Importantly, the burden of arthritis is increasing, particularly among patients with heart disease (14), making the overlap use of NSAIDs and OAC more probable.

In the context of atrial fibrillation, concomitant administration of NSAIDs with vitamin K antagonists poses an elevated risk of thromboembolism and bleeding (7,15). Direct OACs, including the direct thrombin inhibitor dabigatran and factor X inhibitors rivaroxaban, apixaban, and edoxaban, are understudied with regard to NSAID use, with current reports based on venous thromboembolism prevention and treatment (16–23). The effect of NSAIDs on the safety and efficacy of dabigatran etexilate (DE), specifically in the context of patients with atrial fibrillation in the randomized, controlled RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy) trial, has not been previously reported.

The objective of this post hoc analysis of the RE-LY trial was to assess the effects of the combined use of NSAIDs with OAC therapy, specifically dabigatran or warfarin, in the context of patients with atrial fibrillation to quantify bleeding and thrombotic risks, respectively.

METHODS

The RE-LY trial was a prospective evaluation of DE (150 or 110 mg twice daily [b.i.d.]) in comparison to dose-adjusted warfarin (mean time in therapeutic range: 64%) among 18,113 patients with atrial fibrillation. The rationale and design of the RE-LY trial, as well as its primary outcomes were previously described (16,24).

This post hoc analysis of the RE-LY trial compared the group of patients who used nonselective NSAIDs at least once during the RE-LY trial (n = 2,279) with patients who never used NSAIDs during the trial (n = 15,834). Concomitant NSAID use was recorded at study randomization and during routine patient follow-up. The baseline characteristics and outcomes of patients were described according to NSAID use versus no NSAID use, and treatment-independent (OAC therapy) or with respect to treatment arm. The analysis of NSAID use excluded aspirin and selective COX-2 inhibitors. The concomitant use of antiplatelet therapy with DE in patients with atrial fibrillation was previously described (25). Clinical outcomes from the RE-LY trial were adjudicated for verification of the outcome event. The definition of major bleeding was published previously (24).

STATISTICAL ANALYSIS. Cox regression models were used to assess time to relevant outcome events, by providing hazard ratios (HRs), 95% confidence intervals (CIs), and p values for treatment-independent outcomes (**Table 1**). In the Cox model, patients were censored after their first event. Multivariate adjustment analysis was applied to all clinical outcomes data to correct for confounding variables. HRs were based on multivariate-adjusted analysis, which adjusted for

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17 total covariates as described in Table 1. Time-varying covariate analysis was applied to the Cox model to account for the variability in NSAID use over time, its duration of use, and its use before an outcome event (Table 2). Interaction analysis was performed to assess for any interaction of NSAIDs with dabigatran relative to warfarin with respect to clinical outcomes (Table 3). Interaction p values were generated based on the relative differences in the HRs for dabigatran compared with warfarin in the context of NSAID use versus no use according to clinical outcome.

RESULTS

PROPORTION OF NSAID USE. Of the 18,113 total patients randomized in the RE-LY trial to either dabigatran or warfarin, 12.6% of patients (n = 2,279) used NSAIDs at least once during the study period. There were a similar proportion of patients who used NSAIDs per OAC treatment group (dabigatran 110 mg b.i.d., 13.0%; dabigatran 150 mg b.i.d., 11.9%; and warfarin, 12.8%). Most patients never used an NSAID during the study period (87.4%; n = 15,834).

BASELINE CHARACTERISTICS. The baseline characteristics of patients at randomization to treatment group (dabigatran 110 mg b.i.d., dabigatran 150 mg b.i.d., or warfarin) in the RE-LY study are described according to NSAID use versus no NSAID use (Table 4).

At randomization into RE-LY, the mean CHA_2DS_2-VASc score was the same for patients who took NSAIDs (3.6) compared with patients who did not take NSAIDs (3.6). Renal function was similar between the NSAID use and never used groups. There was a smaller proportion of patients with a history of myocardial infarction (13.1% vs. 17.1%; p < 0.0001) and a smaller proportion with a history of heart failure (30.1% vs. 32.3%; p = 0.0349) among those who took NSAIDs compared with patients who did not take NSAIDs. The proportion of patients with valvular heart disease was greater among patients who used NSAIDs (24.3%) compared with patients who did not use NSAIDs (21.4%) (p < 0.0001).

Aspirin, clopidogrel, or dipyridamole were used in slightly greater proportion among patients who took NSAIDs at least once during the RE-LY (44.9%) trial than among patients who never took NSAIDs (41.2%) (p = 0.0007). The NSAID use group had a moderately higher proportion of patients who took proton-pump inhibitors compared with patients who did not take NSAIDs (16.5% vs. 13.8%; p = 0.0008). Multivariate-adjusted analysis was performed for all outcomes to adjust for differences in baseline characteristics.

TABLE 1 Outcomes of NSAID Use Versus Never Used NSAID in RE-LY*

	NSAID	No NSAID	HR (95% CI)	p Value†
Patient-yrs	4,584	31,143		
Major bleeding	206 (4.5)	976 (3.1)	1.39 (1.20–1.63)	<0.0001
GI major bleeding	83 (1.8)	371 (1.2)	1.48 (1.16–1.89)	0.0018
ICH	24 (0.5)	133 (0.4)	1.20 (0.77–1.86)	0.42
Any bleeding	1,045 (22.8)	4,880 (15.7)	1.60 (1.50–1.71)	<0.0001
Stroke/SE	81 (1.8)	440 (1.4)	1.27 (0.99–1.61)	0.0553
Ischemic stroke	61 (1.3)	329 (1.1)	1.27 (0.96–1.67)	0.10
Hemorrhagic stroke	11 (0.2)	60 (0.2)	1.22 (0.64–2.35)	0.54
SE	12 (0.3)	37 (0.1)	2.31 (1.19–4.47)	0.01
Myocardial infarction	32 (0.7)	210 (0.7)	1.07 (0.73–1.57)	0.73
Hospitalization	1,152 (25.1)	6,048 (19.4)	1.41 (1.32–1.50)	<0.0001
All-cause mortality	161 (3.5)	1,210 (3.9)	0.88 (0.75–1.05)	0.15

Values are n (% per year) unless otherwise indicated. *Treatment independent (dabigatran 110 mg b.i.d., dabigatran 150 mg b.i.d., or warfarin). †HRs and p values calculated using Cox regression model and multivariate adjusted analysis. Multivariate analysis adjusted for: continuous variables: age, body mass index, and creatinine clearance; and discrete variables: sex, type of atrial fibrillation, history of heart failure, hypertension, previous stroke, coronary artery disease, previous myocardial infarction, diabetes mellitus, valvular heart disease, and baseline medication: proton-pump inhibitor, beta-blocker, statin, aspirin/clopidogrel/dipyridamole, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

b.i.d. = twice a day; CI = confidence interval; GI = gastrointestinal; HR = hazard ratio; ICH = intracranial hemorrhage; NSAID = nonsteroidal anti-inflammatory drug; RE-LY = Randomized Evaluation of Long Term Anticoagulant Therapy; SE = systemic embolism.

OUTCOMES. The annualized rate of major bleeding when NSAIDs were used at least once in combination with OAC therapy was significantly elevated compared with patients who did not use NSAIDs (Cox model: HR: 1.39; p < 0.0001; time-varying covariate analysis: HR: 1.68; p < 0.0001) (Tables 1 and 2, Figure 1). The rates of major bleeding for each OAC treatment arm, dabigatran 110 mg b.i.d., dabigatran 150 mg b.i.d., and warfarin, were elevated with NSAID use (Table 5, Figure 2). Major bleeding rates with dabigatran 110 and 150 mg b.i.d.

TABLE 2 Outcomes of NSAID Use Versus Never Used NSAID in RE-LY by Time-Varying Covariate Analysis*

	NSAID	No NSAID	HR (95% CI)	p Value†
Patient-yrs	2,525	33,202		
Major bleeding	136 (5.4)	1046 (3.2)	1.68 (1.40–2.02)	<0.0001
GI major bleeding	56 (2.2)	398 (1.2)	1.81 (1.35–2.43)	<0.0001
ICH	15 (0.6)	142 (0.4)	1.41 (0.83–2.41)	0.21
Any bleeding	569 (22.5)	5,356 (16.1)	1.63 (1.50–1.78)	<0.0001
Stroke/SE	51 (2.0)	470 (1.4)	1.50 (1.12–2.01)	0.007
Ischemic stroke	40 (1.6)	350 (1.1)	1.55 (1.11–2.16)	0.01
Hemorrhagic stroke	5 (0.2)	66 (0.2)	1.08 (0.43–2.70)	0.86
SE	7 (0.3)	42 (0.1)	2.43 (1.08–5.46)	0.03
Myocardial infarction	20 (0.8)	222 (0.7)	1.22 (0.77–1.93)	0.40
Hospitalization	740 (29.3)	6,460 (19.5)	1.64 (1.51–1.77)	<0.0001
All-cause mortality	95 (3.8)	1,276 (3.8)	1.00 (0.81–1.24)	0.97

Values are n (% per year) unless otherwise indicated. *Treatment independent (dabigatran 110 mg b.i.d., dabigatran 150 mg b.i.d., or warfarin). †HRs and p values calculated using Cox regression model.

Abbreviations as in Table 1

TABLE 3 Interaction Analysis for NSAID and Dabigatran Etexilate Relative to Warfarin

	Dabigatran 110 mg b.i.d.			Dabigatran 150 mg b.i.d.		
	NSAID at Least Once	Never NSAID		NSAID at Least Once	Never NSAID	
	HR vs. Warfarin (95% CI)	HR vs. Warfarin (95% CI)	Interaction p Value*	HR vs. Warfarin (95% CI)	HR vs. Warfarin (95% CI)	Interaction p Value*
Major bleeding	0.81 (0.59–1.13)	0.80 (0.68–0.94)	0.93	0.88 (0.63–1.23)	0.96 (0.83–1.11)	0.63
GI major bleeding	1.00 (0.58–1.73)	1.05 (0.80–1.37)	0.89	1.32 (0.78–2.24)	1.53 (1.19–1.95)	0.63
ICH	0.40 (0.14–1.14)	0.28 (0.17–0.44)	0.53	0.59 (0.23–1.51)	0.39 (0.26–0.59)	0.43
Any bleeding	0.72 (0.62–0.84)	0.79 (0.74–0.85)	0.27	0.89 (0.77–1.03)	0.91 (0.85–0.98)	0.78
Stroke/SE	1.03 (0.63–1.69)	0.87 (0.70–1.08)	0.54	0.56 (0.31–1.01)	0.67 (0.53–0.84)	0.59
Ischemic stroke	1.38 (0.77–2.49)	1.08 (0.84–1.40)	0.47	0.81 (0.41–1.59)	0.75 (0.57–0.99)	0.85
Hemorrhagic stroke	0.12 (0.02–0.97)	0.35 (0.18–0.65)	0.33	0.26 (0.05–1.21)	0.26 (0.13–0.53)	0.97
SE	1.66 (0.48–5.66)	0.47 (0.20–1.09)	0.09	0.25 (0.03–2.27)	0.69 (0.33–1.45)	0.40
MI	1.38 (0.59–3.24)	1.29 (0.91–1.83)	0.88	1.14 (0.46–2.81)	1.35 (0.96–1.90)	0.72
Hospitalization	0.98 (0.85–1.13)	0.91 (0.85–0.96)	0.30	1.07 (0.93–1.23)	0.96 (0.90–1.02)	0.16
All-cause mortality	1.12 (0.77–1.63)	0.88 (0.77–1.01)	0.22	1.05 (0.71–1.54)	0.86 (0.75–0.98)	0.32

*p values for treatment-by-subgroup interaction calculated by using Cox regression model.
MI = myocardial infarction; other abbreviation as in Table 1.

were not altered relative to warfarin with NSAID use ($p_{interaction}$ = 0.93 and 0.63, respectively) (Table 3).

Gastrointestinal (GI) major bleeding occurred significantly more often in patients who took NSAIDs at least once with OAC therapy than in patients who did not take NSAIDs (Cox model: HR: 1.48; p = 0.0018; time-varying covariate analysis: HR: 1.81; p < 0.0001) (Tables 1 and 2, Figure 3). GI bleeding also occurred significantly more frequently in the NSAID group despite a higher proportion of patients on a proton-pump inhibitor in the unadjusted analysis. GI major bleeding was elevated across all OAC treatment arms with NSAID use (Table 5, Figure 4). NSAID use did not alter the rate of GI major bleeding with dabigatran 110 and 150 mg b.i.d. relative to warfarin (Table 3).

In the basic Cox model, without the time-varying covariate analysis, there was a trend toward significance for stroke or systemic embolism (stroke/SE) with NSAID use (HR: 1.27; p = 0.0553), and ischemic stroke and hemorrhagic stroke did not show a significant difference with NSAID use (Table 1). In the time-varying covariate analysis of the Cox model, stroke/SE was significantly elevated among patients taking NSAIDs in combination with OAC therapy (2.0%/year vs. 1.4%/year; HR: 1.50; 95% CI: 1.12 to 2.01; p = 0.007) (Table 2, Figure 5). Notably, ischemic stroke was significantly elevated with NSAID use (HR: 1.55; p = 0.0102). Hemorrhagic stroke rates were similar with NSAID use or nonuse (HR: 1.08; p = 0.8631). Rates of stroke/SE were elevated with dabigatran 110 mg b.i.d., dabigatran 150 mg b.i.d., or warfarin combined with NSAID use (Table 5, Figure 6). In the interaction analysis, the efficacy of dabigatran 110 and 150 mg b.i.d. in preventing stroke/SE relative to warfarin was not significantly altered by the use of NSAIDs (Table 3).

Myocardial infarction rates were low and occurred at a similar rate (0.70%/year) among patients who took an NSAID at least once during the study period in combination with OAC therapy compared with patients who did not take an NSAID (0.67%/year), which was consistent with the time-varying covariate analysis (Tables 1 and 2). With respect to the OAC treatment arm (dabigatran 110 or 150 mg b.i.d., or warfarin), the rates of myocardial infarction were similar with or without NSAID use (Table 5). The use of NSAIDs did not interact with dabigatran 110 or 150 mg b.i.d. to alter the rates of myocardial infarction relative to warfarin (Table 3).

Patients were more frequently hospitalized if they used an NSAID with OAC therapy compared with patients who did not take an NSAID (p < 0.0001) (Tables 1 and 2, Figure 7). Hospitalizations were more frequently associated with NSAID use in combination with each treatment arm, dabigatran 110 mg b.i.d., dabigatran 150 mg b.i.d., and warfarin, compared with patients who did not take an NSAID with the respective anticoagulant (Table 5, Figure 8).

All-cause mortality among patients who used NSAIDs with dabigatran or warfarin was not significantly different compared with patients who did not use NSAIDs (Tables 1 and 2). Mortality with NSAID use

TABLE 4 Baseline Characteristics of Patients According to NSAID Use in RE-LY

	NSAID Used at Least Once				Never Used NSAID				
	D110 (n = 784)	D150 (n = 726)	W (n = 769)	Total (n = 2,279)	D110 (n = 5,231)	D150 (n = 5,350)	W (n = 5,253)	Total (N = 15,834)	p Value*
Age, yrs	71.3 ± 8.6	71.6 ± 8.7	71.7 ± 8.3	71.5 ± 8.5	71.4 ± 8.7	71.5 ± 8.9	71.5 ± 8.6	71.5 ± 8.7	0.85
Men	492 (62.8)	441 (60.7)	458 (59.6)	1391 (61.0)	3,373 (64.5)	3,399 (63.5)	3,351 (63.8)	10,123 (63.9)	0.007
BMI, kg/m^2	29.0 ± 6.2	29.1 ± 6.5	29.2 ± 6.4	29.1 ± 6.4	28.7 ± 5.8	28.6 ± 5.6	28.7 ± 5.7	28.7 ± 5.7	0.004
CrCl, ml/min	73.6 ± 30.6	71.6 ± 27.8	72.6 ± 29.1	72.7 ± 29.2	72.9 ± 27.3	72.9 ± 28.3	73.0 ± 27.1	72.9 ± 27.6	0.68
Type of AF									0.0005†
Paroxysmal	231 (29.5)	218 (30.1)	258 (33.6)	707 (31.0)	1,698 (32.5)	1,760 (32.9)	1,778 (33.9)	5,236 (33.1)	
Persistent	294 (37.5)	252 (34.8)	263 (34.2)	809 (35.5)	1,656 (31.7)	1,657 (31.0)	1,667 (31.7)	4,980 (31.5)	
Permanent	258 (33.0)	255 (35.2)	248 (32.3)	761 (33.4)	1,874 (35.8)	1,933 (36.1)	1,807 (34.4)	5,614 (35.5)	
$CHADS_2$ score	2.2 ± 1.1	2.2 ± 1.2	2.1 ± 1.1	2.2 ± 1.1	2.1 ± 1.1	2.1 ± 1.1	2.1 ± 1.1	2.1 ± 1.1	0.22†
0 or 1	250 (31.9)	218 (30.0)	224 (29.1)	692 (30.4)	1,710 (32.7)	1,743 (32.6)	1,638 (31.2)	5,091 (32.2)	
2	273 (34.8)	259 (35.7)	300 (39.0)	832 (36.5)	1,815 (34.7)	1,877 (35.1)	1,929 (36.7)	5,621 (35.5)	
≥3	261 (33.3)	249 (34.3)	245 (31.9)	755 (33.1)	1,705 (32.6)	1,730 (32.3)	1,686 (32.1)	5,121 (32.3)	
$CHADS_2$-VASc score	3.6 ± 1.4	3.7 ± 1.5	3.6 ± 1.3	3.6 ± 1.4	3.6 ± 1.4	3.6 ± 1.4	3.6 ± 1.4	3.6 ± 1.4	0.54†
0 or 1	25 (3.2)	24 (3.3)	20 (2.6)	69 (3.0)	205 (3.9)	176 (3.3)	186 (3.5)	567 (3.6)	
2	149 (19.0)	130 (17.9)	129 (16.8)	408 (17.9)	949 (18.1)	1,055 (19.7)	996 (19.0)	3,000 (18.9)	
≥3	610 (77.8)	572 (78.8)	620 (80.6)	1,802 (79.1)	4,077 (77.9)	4,119 (77.0)	4,071 (77.5)	12,267 (77.5)	
Medical history									
Hypertension	625 (79.7)	584 (80.4)	610 (79.3)	1,819 (79.8)	4,113 (78.6)	4,211 (78.7)	4,140 (78.8)	12,464 (78.7)	0.23
Diabetes mellitus	201 (25.6)	174 (24.0)	188 (24.4)	563 (24.7)	1,208 (23.1)	1,228 (23.0)	1,222 (23.3)	3,658 (23.1)	0.09
Coronary artery disease	199 (25.4)	203 (28.0)	210 (27.3)	612 (26.9)	1,462 (28.0)	1,507 (28.2)	1,453 (27.7)	4,422 (27.9)	0.28
MI	91 (11.6)	112 (15.4)	95 (12.4)	298 (13.1)	917 (17.5)	917 (17.1)	873 (16.6)	2,707 (17.1)	<0.0001
Heart failure	234 (29.8)	228 (31.4)	223 (29.0)	685 (30.1)	1,703 (32.6)	1,706 (31.9)	1,699 (32.3)	5,108 (32.3)	0.03
Stroke	108 (13.8)	95 (13.1)	106 (13.8)	309 (13.6)	653 (12.5)	661 (12.4)	650 (12.4)	1,964 (12.4)	0.12
Valvular heart disease	194 (24.7)	176 (24.2)	183 (23.8)	553 (24.3)	1,094 (20.9)	1,177 (22.0)	1,120 (21.3)	3,391 (21.4)	<0.0001
Cigarette smoking	66 (8.4)	52 (7.2)	43 (5.6)	161 (7.1)	374 (7.2)	395 (7.4)	405 (7.7)	1,174 (7.4)	0.55
Alcohol	274 (34.9)	236 (32.5)	256 (33.3)	766 (33.6)	1,722 (32.9)	1,763 (33.0)	1,725 (32.8)	5,210 (32.9)	0.51
Medication use at entry									
Aspirin, clopidogrel or dipyridamole	347 (44.3)	319 (43.9)	357 (46.4)	1,023 (44.9)	2,165 (41.4)	2,154 (40.3)	2,197 (41.8)	6,516 (41.2)	0.0007
Proton-pump inhibitor	136 (17.3)	121 (16.7)	118 (15.3)	375 (16.5)	711 (13.6)	757 (14.1)	724 (13.8)	2,192 (13.8)	0.0008

Values are mean ± SD or n (%). *p value for comparison of totals (Student's *t*-test). †Chi-square test. $CHADS_2$-VASc score modeling: congestive heart failure; left ventricular ejection fraction ≤40% or history of heart failure; stroke/transient ischemic attack, includes history of non-central nervous system SE; vascular disease, history of myocardial infarction or peripheral arterial disease.

AF = atrial fibrillation; BMI = body mass index; CrCl = creatinine clearance; D110 = dabigatran 110 mg b.i.d.; D150 = dabigatran 150 mg b.i.d.; W = warfarin; other abbreviations as in Tables 1 and 3.

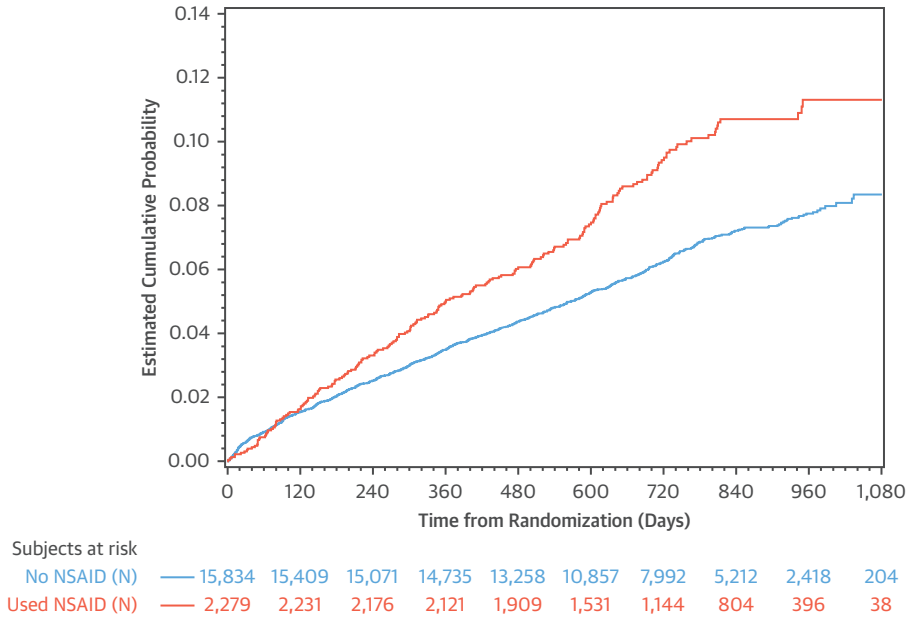
and warfarin (3.3%/year) was notably lower compared with warfarin use without NSAID use (4.3%/year) (Table 5).

DISCUSSION

The present analysis was the first to evaluate NSAID use with DE in the context of atrial fibrillation. The rates of major bleeding, GI major bleeding, stroke/SE, ischemic stroke, and hospitalization when NSAID was used in combination with OAC therapy (dabigatran 110 or 150 mg b.i.d., or warfarin) were significantly elevated compared with patients who did not use NSAID. The rates of myocardial infarction with NSAID use in combination with OAC therapy were similar compared with not taking NSAIDs (Central Illustration). The use of NSAIDs did not significantly alter the relative efficacy or safety for DE 110 mg b.i.d. or DE 150 mg b.i.d., respectively, relative to warfarin.

The mechanism for the observed bleeding associated with NSAIDs was likely a result of its antiplatelet effects and a reduction in gastric mucosal protection. Non-GI bleeding represented 60% and GI bleeding represented 40% of major bleeding events among the NSAID group. NSAIDs are known to reduce the glomerular filtration rate (9), and DE is excreted approximately 80% via glomerular filtration. Despite the potential renal effects of NSAIDs, the interaction analysis did not show that NSAIDs had any direct interaction with DE to alter its bleeding profile relative to warfarin.

FIGURE 1 Major Bleeding, Treatment Independent



Major bleeding among patients who used nonsteroidal anti-inflammatory drugs (NSAIDs) compared with patients who did not use NSAIDs with oral anticoagulation (OAC). Kaplan-Meier curves estimate the cumulative probability of major bleeding events based on time to first event, over a period of 1,080 days (3 years). Cox regression modeling, including multivariate adjustment analysis, assessed annualized rates of major bleeding for NSAID use compared with no NSAID use (4.5%/year vs. 3.1%/year; hazard ratio [HR]: 1.39; 95% confidence interval [CI]: 1.20 to 1.63, $p < 0.0001$; time-varying covariate analysis: 5.4%/year vs. 3.2%/year; HR: 1.68; 95% CI: 1.40 to 2.02; $p < 0.0001$). NSAID use with concomitant OAC therapy was associated with a significantly higher rate of major bleeding compared with no NSAID use.

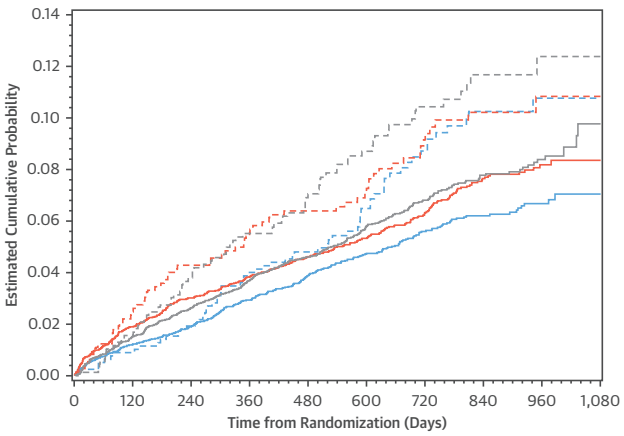
Previous studies demonstrated a thrombotic risk associated with NSAIDs (5–8). The present analysis demonstrated a significantly elevated stroke/SE rate, specifically, ischemic stroke, with NSAID use. The time-varying covariate analysis of the Cox model accounted for the duration of NSAID use and its use before an outcome event compared with the basic Cox model. The present analysis did not include celecoxib or other selective COX-2 inhibitors due to the small sample size (~160 per

TABLE 5 Outcomes of NSAID Use Versus Never Used NSAID by Treatment in RE-LY

	NSAID			No NSAID		
	D110 (n = 784)	D150 (n = 726)	W (n = 769)	D110 (n = 5,231)	D150 (n = 5,350)	W (n = 5,253)
Major bleeding	65 (4.1)	65 (4.4)	76 (5.0)	282 (2.7)	344 (3.3)	350 (3.4)
GI major bleeding	26 (1.7)	32 (2.2)	25 (1.7)	108 (1.1)	160 (1.5)	103 (1.0)
ICH	5 (0.3)	7 (0.5)	12 (0.8)	22 (0.2)	32 (0.3)	79 (0.8)
Any bleeding	314 (19.8)	339 (22.8)	392 (25.8)	1445 (14.0)	1658 (15.7)	1777 (17.3)
Stroke/SE	33 (2.1)	17 (1.2)	31 (2.0)	150 (1.5)	118 (1.1)	172 (1.7)
Ischemic stroke	27 (1.7)	15 (1.0)	19 (1.3)	125 (1.2)	89 (0.8)	115 (1.1)
Hemorrhagic stroke	1 (0.06)	2 (0.13)	8 (0.53)	13 (0.13)	10 (0.09)	37 (0.36)
SE	7 (0.44)	1 (0.07)	4 (0.26)	8 (0.08)	12 (0.11)	17 (0.17)
Myocardial infarction	13 (0.82)	10 (0.67)	9 (0.59)	74 (0.72)	79 (0.75)	57 (0.55)
Hospitalization	389 (24.6)	380 (25.6)	383 (25.2)	1923 (18.6)	2050 (19.4)	2075 (20.2)
All-cause mortality	59 (3.7)	52 (3.5)	50 (3.3)	387 (3.8)	386 (3.7)	437 (4.3)

Values are n (% per year).
Abbreviations as in Table 1.

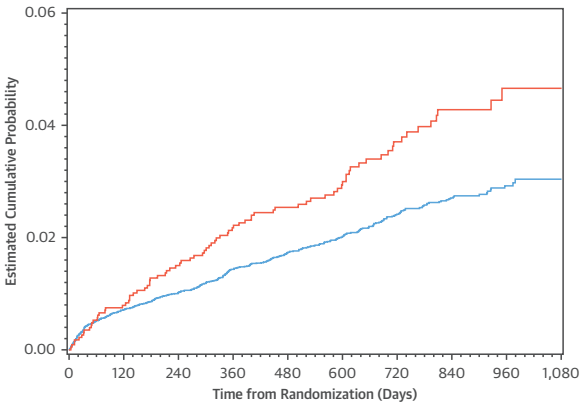
FIGURE 2 **Major Bleeding, Treatment Dependent**



Subjects at risk										
DE110 No NSAID (N)	5,231	5,105	5,011	4,892	4,422	3,633	2,641	1,757	822	69
DE150 No NSAID (N)	5,350	5,196	5,070	4,960	4,474	3,677	2,728	1,756	837	74
Warf No NSAID (N)	5,253	5,108	4,990	4,883	4,362	3,547	2,623	1,699	759	61
DE110 Used NSAID (N)	784	772	759	734	664	524	402	282	148	14
DE150 Used NSAID (N)	726	705	688	675	616	506	380	272	128	12
Warf Used NSAID (N)	769	754	729	712	629	501	362	250	120	12

Major bleeding among patients who used NSAIDs compared with patients who did not use NSAIDs according to OAC treatment. Kaplan-Meier curves estimate the cumulative probability of major bleeding events based on time to first event, over a period of 1,080 days (3 years). The annualized rates of major bleeding associated with NSAID use were elevated with each OAC treatment group compared with no NSAID use. DE110 = dabigatran etexilate 110 mg twice daily (b.i.d.); DE150, dabigatran etexilate 150 mg b.i.d.; Warf, warfarin; other abbreviations as in Figure 1.

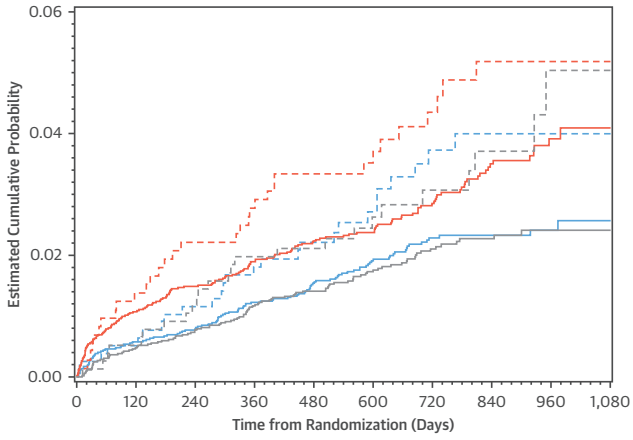
FIGURE 3 **Major GI Bleeding, Treatment Independent**



Subjects at risk										
No NSAID (N)	15,834	15,519	15,262	14,985	13,537	11,142	8,247	5,419	2,513	212
Used NSAID (N)	2,279	2,249	2,210	2,174	1,964	1,587	1,199	848	419	41

Major gastrointestinal (GI) bleeding among patients who used NSAIDs compared with patients who did not use NSAIDs with OAC. Kaplan-Meier curves estimate the cumulative probability of major GI bleeding events based on time to first event, over a period of 1,080 days (3 years). Cox regression modeling, including multivariate adjustment analysis, assessed annualized rates of major GI bleeding for NSAID use compared with no NSAID use (1.85%/year vs. 1.2%/year; HR: 1.48; 95% CI: 1.16 to 1.89; $p = 0.0018$; time-varying covariate analysis: 2.2%/year vs. 1.2%/year; HR: 1.81; 95% CI: 1.35 to 2.43; $p < 0.0001$). Concomitant NSAID use with OAC therapy was associated with a significantly higher rate of major GI bleeding compared with no NSAID use. Abbreviations as in Figure 1.

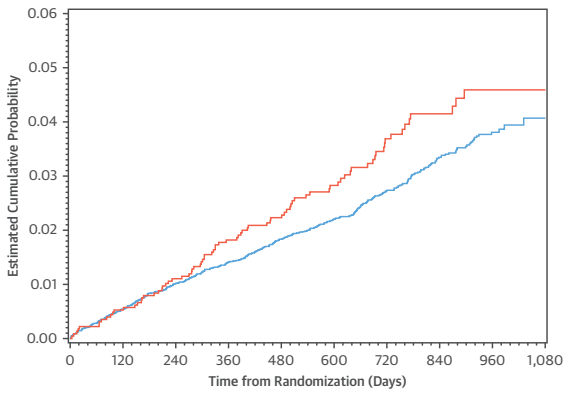
FIGURE 4 Major GI Bleeding, Treatment Dependent



Subjects at risk										
DE110 No NSAID (N)	5,231	5,131	5,058	4,962	4,508	3,714	2,711	1,820	855	71
DE150 No NSAID (N)	5,350	5,234	5,134	5,040	4,558	3,763	2,811	1,821	865	76
Warf No NSAID (N)	5,253	5,154	5,070	4,983	4,471	3,665	2,725	1,778	793	65
DE110 Used NSAID (N)	784	774	763	748	679	541	422	299	157	15
DE150 Used NSAID (N)	726	713	701	692	629	519	393	283	135	13
Warf Used NSAID (N)	769	762	746	734	656	527	384	266	127	13

Major GI bleeding among patients who used NSAIDs compared with patients who did not use NSAIDs according to OAC treatment group. Kaplan-Meier curves estimate the cumulative probability of major GI bleeding events based on time to first event, over a period of 1,080 days (3 years). NSAID use was associated with higher annualized rates of major GI bleeding compared with no NSAID use in each OAC treatment group. Abbreviations as in Figures 1 to 3.

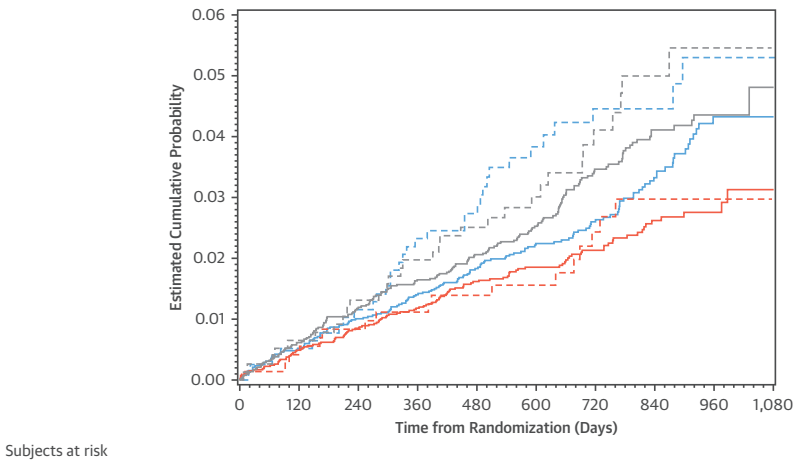
FIGURE 5 Stroke or Systemic Embolism, Treatment Independent



Subjects at risk										
No NSAID (N)	15,834	15,556	15,282	15,022	13,554	11,153	8,254	5,421	2,504	214
Used NSAID (N)	2,279	2,255	2,223	2,192	1,982	1,603	1,207	855	422	39

Stroke or systemic embolism (stroke/SE) among patients who used NSAIDs compared with patients who did not use NSAIDs with OAC. Kaplan-Meier curves estimate the cumulative probability of stroke/SE events based on time to first event, over a period of 1,080 days (3 years). Cox regression modeling, including multivariate adjustment, assessed annualized rates of stroke/SE for NSAID use compared with no NSAID use (1.8%/year vs. 1.4%/year; HR: 1.27; 95% CI: 0.99 to 1.61; $p = 0.0553$; time-varying covariate analysis: 2.0%/year vs 1.4%/year; HR: 1.50; 95% CI: 1.12 to 2.01; $p = 0.007$). Concomitant NSAID use with OAC therapy was associated with a significantly elevated rate of stroke/SE. Other abbreviations as in Figure 1.

FIGURE 6 Stroke/SE, Treatment Dependent



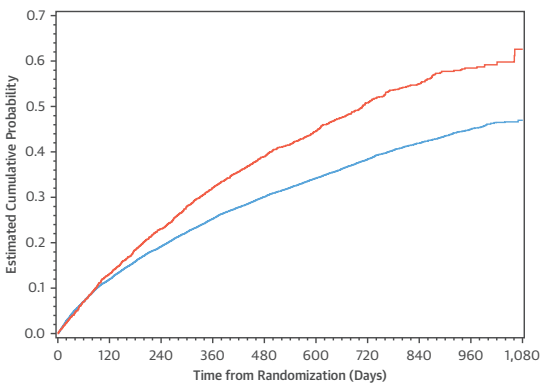
Subjects at risk										
DE110 No NSAID (N)	5,231	5,135	5,051	4,964	4,508	3,719	2,716	1,819	847	73
DE150 No NSAID (N)	5,350	5,266	5,171	5,078	4,589	3,784	2,835	1,842	876	77
Warf No NSAID (N)	5,253	5,155	5,060	4,980	4,457	3,650	2,703	1,760	781	64
DE110 Used NSAID (N)	784	775	764	749	678	536	416	295	155	14
DE150 Used NSAID (N)	726	719	711	704	642	532	403	290	137	13
Warf Used NSAID (N)	769	761	748	739	662	535	388	270	130	12

Stroke/SE among patients who used NSAIDs compared with patients who did not use NSAIDs according to OAC treatment group. Kaplan-Meier curves estimate the cumulative probability of stroke/SE events based on time to first event, over a period of 1,080 days (3 years). NSAID use was associated with an elevated annualized rate of stroke/SE compared with no NSAID use in each OAC treatment group. Abbreviations as in **Figures 1, 2, and 5**.

treatment arm), and the cardiovascular risk associated with COX-2 inhibitors does not necessarily make them a safe alternative to nonselective NSAIDs (26,27).

Hospitalization was common (~20%/year) among a patient population with atrial fibrillation on OAC without NSAID use, and was significantly elevated with NSAID use (~29%/year). In addition to atrial

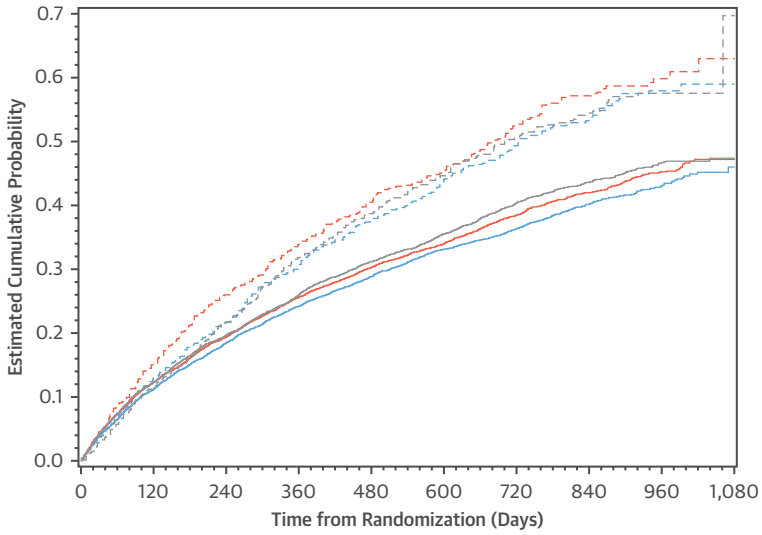
FIGURE 7 Hospitalization, Treatment Independent



Subjects at risk										
No NSAID (N)	15,834	13,845	12,604	11,566	9,874	7,776	5,434	3,431	1,578	124
Used NSAID (N)	2,279	1,975	1,738	1,532	1,268	927	636	423	198	13

Hospitalization among patients who used NSAIDs compared with patients who did not use NSAIDs with OAC. Kaplan-Meier curves estimate the cumulative probability of hospitalization events based on time to first event, over a period of 1,080 days (3 years). Cox regression modeling, including multivariate adjustment analysis, assessed annualized rates of hospitalization for NSAID use compared with no NSAID use (25.1%/year vs. 19.4%/year; HR: 1.41; 95% CI: 1.32 to 1.50; $p < 0.0001$; time-varying covariate analysis: 29.3%/year vs. 19.5%/year; HR: 1.64; 95% CI: 1.51 to 1.77; $p < 0.0001$). Concomitant NSAID use with OAC therapy was associated with a significantly higher rate of hospitalization compared with no NSAID use. Abbreviations as in **Figure 1**.

FIGURE 8 Hospitalization, Treatment Dependent



Subjects at risk										
DE110 No NSAID (N)	5,231	4,609	4,200	3,879	3,343	2,651	1,867	1,201	561	44
DE150 No NSAID (N)	5,350	4,663	4,246	3,881	3,314	2,629	1,843	1,134	528	48
Warf No NSAID (N)	5,253	4,573	4,158	3,806	3,217	2,496	1,724	1,096	489	32
DE110 Used NSAID (N)	784	682	611	541	443	321	235	153	78	5
DE150 Used NSAID (N)	726	615	532	476	398	297	200	132	53	4
Warf Used NSAID (N)	769	678	595	515	427	309	201	138	67	4

Hospitalization among patients who used NSAIDs compared with patients who did not use NSAIDs according to OAC treatment group. Kaplan-Meier curves estimate the cumulative probability of hospitalization events based on time to first event, over a period of 1,080 days (3 years). NSAID use was associated with an elevated annualized rate of hospitalization for each OAC treatment group compared with no NSAID use. Abbreviations as in Figures 1 and 2.

fibrillation, there was a prominent comorbid burden among patients, which was highlighted by the mean CHA_2DS_2-VASc score of 3.6 for both the NSAID and no NSAID use groups.

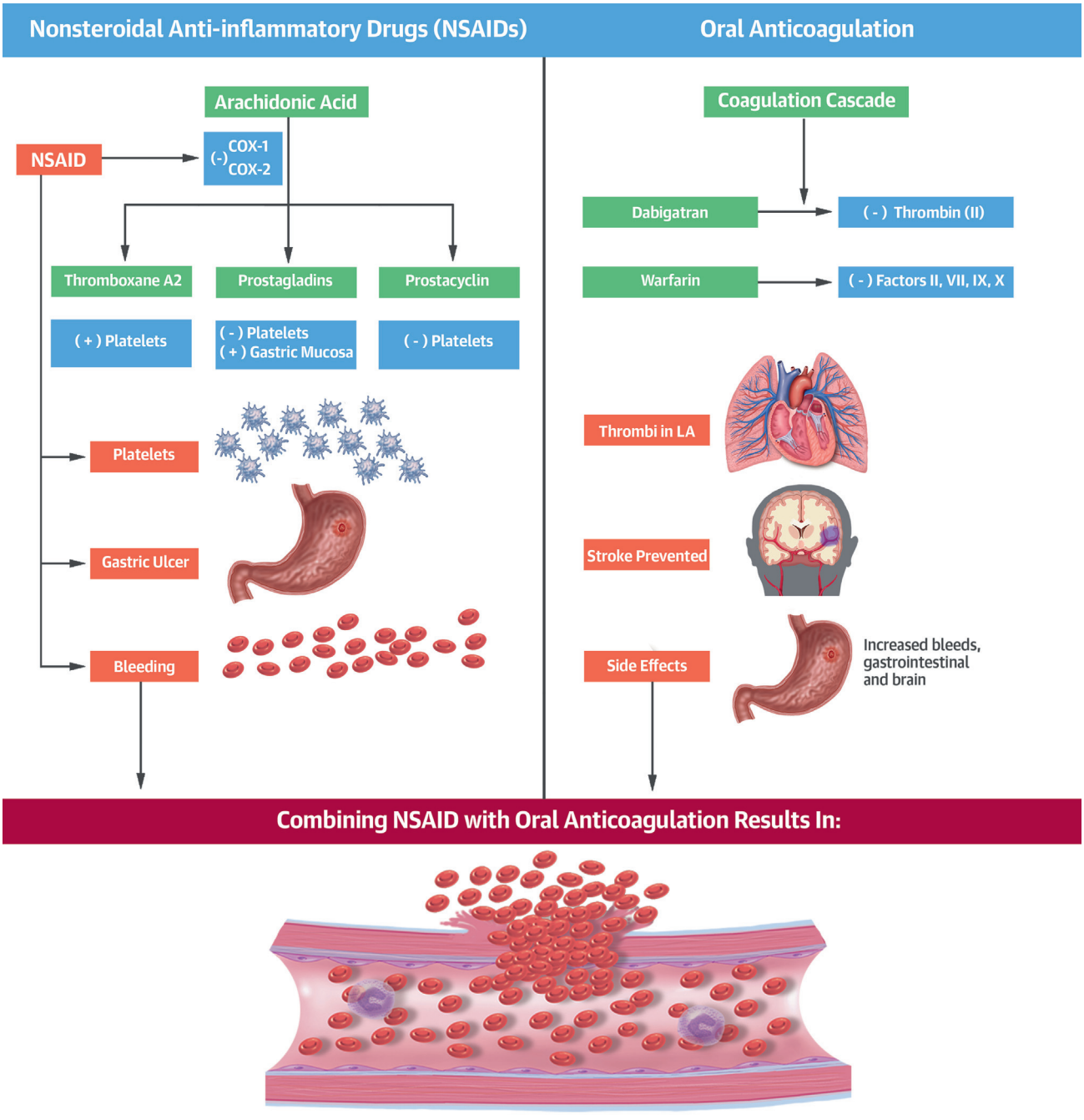
Seeking safer alternatives to NSAIDs for patients with atrial fibrillation who receive OAC therapy is recommended from this study. Atrial fibrillation is an epidemic with an estimated burden of 2.7 to 6.1 million people in the United States (28), and >30 million people worldwide (29). Notably, >2 million people in the United States are addicted to prescription opioids (30). Safer alternatives beyond NSAIDs and opioids are available (31). Updated guidelines and better therapeutic interventions (nonpharmacological and pharmacological) are needed to address analgesia in patients with heart disease because current approaches with NSAIDs and opioids pose a risk to patients (32).

The present analysis was consistent with a previous study of NSAID use in combination with warfarin in patients with atrial fibrillation that demonstrated an elevated rate of bleeding and stroke with NSAID use (7,15). In previous studies, the use of NSAIDs with dabigatran 150 mg b.i.d. in the context of venous thromboembolism did not significantly effect the rate of bleeding (20,21), which was in contrast to the present analysis, and potentially due to the different populations studied.

The present analysis adds to the body of literature that have investigated the safety of NSAIDs and reinforces the evidence that NSAIDs are not innocuous medications (26,33-39). Thus, there is a need for careful clinical review of NSAID use in patients with atrial fibrillation who are receiving OAC therapy. Further analysis is required to investigate the effects of NSAIDs when used concomitantly with direct OACs in patients with atrial fibrillation.

STUDY LIMITATIONS. The study was a post hoc analysis. It was limited by the lack of data regarding the specific type of nonselective NSAIDs, the dosage of NSAIDs, and the reasons for NSAIDs use, which were not captured in the standardized case report form used during the RE-LY trial follow-up visits. Patients were allowed to stop and start NSAIDs

CENTRAL ILLUSTRATION **Mechanisms of Action for Nonselective NSAIDs and OAC Therapy**



Kent, A.P. et al. J Am Coll Cardiol. 2018;72(3):255–67.

The mechanistic effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on platelet aggregation and gastric mucosa, as well as the action of the direct thrombin inhibitor dabigatran, and the inhibitory effects of warfarin on vitamin-K dependent clotting factors are shown. Independently, each mechanism carries an increased risk of bleeding, which is potentiated by the combination of NSAID with oral anticoagulation (OAC). COX = cyclooxygenase.

periodically. The basic Cox model evaluated NSAID use versus nonuse, irrespective of the duration and timing of NSAID use. Baseline characteristic data did not capture the prevalence of osteoarthritis, rheumatoid arthritis or other inflammatory conditions that might have partially explained NSAID use and might have added to the investigators' understanding of the patient population that used NSAIDs during RE-LY. Treatment-dependent outcomes for NSAID use versus no use were not analyzed with the Cox model due to small sample sizes per OAC treatment arm among patients using NSAIDs.

CONCLUSIONS

The use of NSAIDs in combination with OAC therapy (DE 110 or 150 mg b.i.d., or warfarin) in patients with atrial fibrillation was associated with an increased risk of major bleeding, GI major bleeding, stroke/SE, ischemic stroke, and hospitalization, compared with patients who did not use NSAIDs. No significant difference in myocardial infarction or mortality was observed with NSAID use. The safety and efficacy of DE 110 and 150 mg b.i.d. relative to warfarin was not significantly altered by the use of NSAIDs.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In anticoagulated patients with atrial fibrillation, concurrent use of NSAIDs was associated with a higher risk of major bleeding, thromboembolism, and hospitalization, but the safety and efficacy of dabigatran 150 and 110 mg b.i.d. relative to warfarin were not altered.

TRANSLATIONAL OUTLOOK: The effects on clinical outcomes of anti-inflammatory drugs, and selective COX-2 inhibitors in particular, should be evaluated in patients managed with target-specific OACs, including apixaban, rivaroxaban, and edoxaban.

REFERENCES

1. Rouzer CA, Marnett LJ. Cyclooxygenases: structural and functional insights. J Lipid Res 2009;50 Suppl:S29–34.

2. Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005;352:1071–80.

3. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N Engl J Med 2016;375:2519–29.

4. Solomon DH, Husni ME, Libby PA, et al. The risk of major NSAID toxicity with celecoxib, ibuprofen or naproxen: a secondary analysis of the PRECISION randomized controlled clinical trial. Am J Med 2017;130:1415–22.e4.

5. Chang CH, Shau WY, Kuo CW, Chen ST, Lai MS. Increased risk of stroke associated with nonsteroidal anti-inflammatory drugs: a nationwide case crossover study. Stroke 2010;41:1884–90.

6. Fosbøl EL, Olsen AM, Olesen JB, et al. Use of nonsteroidal anti-inflammatory drugs among healthy people and specific cerebrovascular safety. Int J Stroke 2014;9:943–5.

7. Lamberts M, Lip GY, Hansen ML, et al. Relation of nonsteroidal anti-inflammatory drugs to serious bleeding and thromboembolism risk in patients with atrial fibrillation receiving antithrombotic therapy: a nationwide cohort study. Ann Intern Med 2014;161:690–8.

8. Schjerning OAM, 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;313:805–14.

9. Harirforoosh S, Jamali F. Renal adverse effects of nonsteroidal anti-inflammatory drugs. Expert Opin Drug Saf 2009;8:669–81.

10. Arfè A, Scotti L, Varas-Lorenzo C, et al. Nonsteroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study. BMJ 2016;354:i4857.

11. Adams RJ, Appleton SL, Gill TK, Taylor AW, Wilson DH, Hill CL. Cause for concern in the use of non-steroidal anti-inflammatory medications in the community–a population-based study. BMC Fam Pract 2011;12:70.

12. Ilomäki J, Helin-Salmivaara A, Huupponen R, Rikala M, Kirkpatrick CM, Korhonen MJ. Analgesic use before and after oral anticoagulant initiation–a population-based study in Finland. Eur J Clin Pharmacol 2015;71:723–32.

13. Davidson BL, Verheijen S, Lensing AW, et al. Bleeding risk of patients with acute venous thromboembolism taking nonsteroidal anti-inflammatory drugs or aspirin. JAMA Intern Med 2014;174:947–53.

14. U.S. Department of Health and Human Services. CDC Vital Signs: Arthritis in America. Atlanta, GA: Centers for Disease Control and Prevention, 2017. Available at: www.cdc.gov/vitalsigns/arthritis. Accessed March 11, 2017.

15. Lip GY. Nonsteroidal anti-inflammatory drugs and bleeding risk in anticoagulated patients with atrial fibrillation. Expert Rev Cardiovasc Ther 2015;13:963–5.

16. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51; erratum, N Engl J Med 2010;363:1877.

17. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–91.

18. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–92.

19. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093–104.

20. Friedman RJ, Kurth A, Clemens A, Noack H, Eriksson BI, Caprini JA. Dabigatran etexilate and concomitant use of non-steroidal anti-inflammatory drugs or acetylsalicylic acid in patients undergoing total hip and total knee arthroplasty: no increased risk of bleeding. Thromb Haemost 2012;108:183–90.

21. Schulman S, Eriksson H, Goldhaber SZ, et al. Influence of concomitant NSAID or ASA on the efficacy and safety of dabigatran versus warfarin for the treatment of acute venous thromboembolism: a pooled analysis from RE-Cover and RE-Cover II. Poster presented at: 55th Annual Meeting of the American Society of Hematology. New Orleans, LA; December 7–10, 2013.

22. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499–510.

23. EINSTEIN-PE Investigators, Büller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287–97.

24. Ezekowitz MD, Connolly S, Parekh A, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. Am Heart J 2009;157:805–10, 810.e1-2.

25. Dans AL, Connolly SJ, Wallentin L, et al. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. Circulation 2013;127:634–40.

26. Gislason GH, Torp-Pedersen C. NSAIDs and the failing heart. BMJ 2016;354:i5163.

27. Brophy JM, Lévesque LE, Zhang B. The coronary risk of cyclo-oxygenase-2 inhibitors in patients with a previous myocardial infarction. Heart 2007;93:189–94.

28. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics–2015 update: a report from the American Heart Association. Circulation 2015;131:e29–322.

29. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. Circulation 2014;129:837–47.

30. Prescription drug use and misuse in the United States: results from the 2015 National Survey on Drug Use and Health. NSDUH Data Review. Available at: https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR2-2015/NSDUH-FFR2-2015.htm#topofpage. Accessed June 5, 2018.

31. Murthy VH. Ending the opioid epidemic - a call to action. N Engl J Med 2016;375:2413–5.

32. Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. Circulation 2007;115:1634–42.

33. 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 anti-inflammatory drugs after acute myocardial infarction. Circulation 2006;113:2906–13.

34. Schjerning Olsen AM, Fosbøl EL, Lindhardsen J, et al. Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study. Circulation 2011;123:2226–35.

35. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. PLoS Med 2011;8:e1001098.

36. Felson DT. Safety of nonsteroidal antiinflammatory drugs. N Engl J Med 2016;375:2595–6.

37. Grosser T, Ricciotti E, FitzGerald GA. The cardiovascular pharmacology of nonsteroidal anti-inflammatory drugs. Trends Pharmacol Sci 2017;38:733–48.

38. Coxib and Traditional NSAID Trialists' (CNT) Collaboration, Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013;382:769–79.

39. Bally M, Dendukuri N, Rich B, et al. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. BMJ 2017;357:j1909.

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