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Direct oral anticoagulant and antiplatelet combination therapy: hemorrhagic events in coronary artery stent recipients

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Abstract

Direct oral anticoagulant (DOAC) use is growing as monotherapy and combined with platelet inhibitors. The safety of such combination therapy, especially in comparison to regimens including warfarin, in real world populations remains uncertain. We investigated hemorrhage associated with DOAC and antiplatelet combination therapy in a cohort of elderly coronary artery stent recipients. We employed Medicare data 2010 to 2013 for a 40% random sample of beneficiaries enrolled in inpatient, outpatient and prescription benefits. We used Cox proportional hazards models to examine the association of the combination anticoagulant (DOAC or warfarin) plus antiplatelets with major hemorrhage events (upper gastrointestinal or intracranial) in the 12 months following stent placement. We identified 70,900 stent recipients. 14.4% had atrial fibrillation (AF) diagnosis preoperatively. Among the 24.5 million observation days, exposure distribution was: 73.8% antiplatelets only, 4.7% antiplatelets plus warfarin, 0.6% antiplatelets plus DOAC, 2.2% warfarin only, 0.3% DOAC only and 18.4% no observed antiplatelets or anticoagulant. Overall, 8,029 patients (11.3%) experienced major hemorrhage. Among AF patients, compared to antiplatelets only, DOAC plus antiplatelets was associated with increased hemorrhage risk (HR, 1.94; 95%CI, 1.48–2.54); warfarin plus antiplatelets conferred comparable bleed risk (HR, 1.69; 95%CI, 1.47–1.94). In the non-AF group, compared to antiplatelets alone, combination DOAC plus antiplatelets (HR, 3.09; 95%CI, 2.15–4.46), and warfarin plus antiplatelets (HR, 2.21; 95%CI, 1.97–2.48) conferred greater bleed risk. Among elderly coronary artery stent recipients with AF, the two drug

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Conflicts of interest

The authors have no conflicts to disclose

combinations, DOAC plus antiplatelets and warfarin plus antiplatelets, were associated with similarly increased risk of major hemorrhage compared to antiplatelets alone.

Keywords

DOAC; antiplatelets; coronary stent; atrial fibrillation; intracranial hemorrhage; major hemorrhage; Medicare

INTRODUCTION

Since their 2010 market introduction, direct oral anticoagulants (DOACs) have grown in popularity.^{4-6,12,19,21} They address the unpredictable bioavailability, and requisite laboratory monitoring that make warfarin use challenging and inconvenient.²¹ The use of DOACs has seen rapid growth in atrial fibrillation (AF) patients, and in patients with acute coronary syndromes (ACS).^{4-6,12,19,21} In patients with multiple comorbidities¹⁴ who undergo coronary artery stenting, DOACs are increasingly used in combination with antiplatelets.^{2,3,17,18,22} The safety of this regimen and its association with hemorrhagic events remains uncertain.

Randomized trials have investigated the safety of DOAC plus antiplatelet therapy in patients with ACS.^{2,3,17,18,22} All phase II trials^{2,3,18,22} have demonstrated a definite increase in bleeding with the combination therapy in comparison to antiplatelet treatment alone. A phase III study³ with apixaban, in high-risk ACS patients, was terminated prematurely due to increased bleeding, without evidence for decreased major cardiovascular events. In contrast, a phase III study¹⁷ of rivaroxaban in ACS patients showed significant reductions in the composite endpoint of death, myocardial infarction, and stroke, but an increased rate of major bleeding. Safety examined in the context of these carefully controlled clinical trials, in select populations, is not always apparent when such products are used in real-world settings.⁷ No prior investigation explores the relative safety of the combined use of anticoagulant and antiplatelet treatment option in a large cohort from the community. The increasing use of DOACs especially in combination with antiplatelets, in our aging population, makes relative safety in real world settings especially important to clinicians.

To examine safety of DOAC and antiplatelet combination therapy outside of the clinical trial setting, we studied a cohort of Medicare patients undergoing cardiac stenting and examined major hemorrhagic events associated with receipt of medication combinations (antiplatelets plus DOAC or antiplatelets plus warfarin). Our models used time-varying exposure to reflect real-world prescription fill patterns; we controlled for diverse patient characteristics and comorbidities and stratified on atrial fibrillation diagnosis at time of stent placement.

METHODS

Data and Cohort

Using a 40% random sample of the Medicare beneficiaries enrolled in fee-for-service Medicare Parts A (inpatient), B (outpatient) and D (prescription) coverage, residing in the U.S., we identified a cohort of patients receiving inpatient coronary artery stents in 2010–

2012 (Table S1). The year 2010 was selected as the baseline year because DOACs appeared on the market in 2010. Each patient's first stent episode between 2010–2012 served as the index stent episode. Patients dying within 30 days of the index stent episode were excluded. Patients not enrolled Medicare Part D or not using prescription benefits (i.e. no prescription fill record) in the 120 days preceding index stent were also excluded. We also excluded cancer patients because of their potentially complicated anticoagulation profile.

Exposure

We used the Medicare Part D Prescription Drug Event file (PDE) to identify prescription fills prior to and following index stent episode. Pre-index prescription fills were used to ascertain prescription supply prior to stent. For each day in the observation period, following index stent receipt, a warfarin, DOAC (dabigatran, rivoroxaban), or antiplatelets exposure category was assigned to each patient for each day based on fill date and days supply dispensed. For each patient, exposure was allowed to vary over time based on prescription fill events. Exposure was assumed to begin on the date of the prescription fill event; overlapping supplies were carried forward (e.g. a 90 day supply filled 80 days after a previous 90 day supply resulted in a 10 day supply carried forward). Patients were considered to have stopped medication use if no repeat fill occurred after 120% of days supply had elapsed (e.g. no repeat fill within 108 of a 90 day fill was classified as discontinuation of the medication 108 days after last observed fill). Prescription fill events occurring in the 120 days prior to stent receipt were carried forward following index stent hospitalization when supply was sufficient to cover post discharge days. We assumed no consumption of home medication supply for the full length of index and subsequent hospitalizations; and we assumed medication use resumed after discharge.

Outcome

The primary outcome of interest was major hemorrhagic events (upper gastrointestinal and intracranial), identified from the Emergency Room visit or on an inpatient claim. Hemorrhages were classified as upper gastrointestinal, intracranial (traumatic, non-traumatic), and other (Table S1). Hemorrhages in the first 30 days after stenting were considered periprocedural morbidity and were conservatively excluded. In sensitivity analysis we additionally considered this time period as seven or 14 days. The direction and magnitude of observed associations in these sensitivity analyses were similar to those of the main analysis; these analyses are not reported further.

Covariates

From index episode (up to 10 diagnosis codes), patients were stratified based on their atrial fibrillation (AF) status (*International Classification of Disease* (ICD-9) diagnostic code 427.31). Covariates included in the models were age, gender, race (categorized as Black, Hispanic, and other based on Medicare denominator file variable), Medicare Part D low income subsidy (a marker for income 150% or less of federal poverty level, dichotomized),¹ and index drug-eluting stent placement (versus bare metal). The following comorbidities, present at the time of the index episode were also included: chronic obstructive lung disease and/or tobacco use (combined as “tobacco exposure” proxy variable), diabetes mellitus, hypertension, myocardial infarction, ischemic stroke, acute coronary syndrome (ACS),

congestive heart failure, chronic kidney disease, end-stage renal disease, peripheral vascular disease, liver disease, alcoholism, mechanical heart valve, long-term anticoagulation, pulmonary embolism/deep vein thrombosis, and hypercoagulable state (Table S1).

In addition, models adjusted for other time-varying drug exposure during observation due to their possible contribution to bleed risk: antibiotics, proton pump inhibitors, cyclooxygenase-2 (COX-2) inhibitors, oral glucocorticoids and prescription non-selective non-steroidal anti-inflammatories (NSAIDs).

We calculated bleed risk for each patient using the claims based “Anticoagulation and Risk Factors in Atrial Fibrillation” (ATRIA) score⁹ for the index episode; this is reported in Table 1 as a baseline characteristic but we did not include this score in the models, because we used other covariates listed above (due to the significant overlap).

Statistical analysis

The main analysis modeled primary outcome on current treatment (a time-dependent exposure) adjusted for the covariates listed above, using a Cox proportional hazards model. Data were structured as follows. The unit of analysis was a person day until death, first bleed event, disenrollment from fee for service Medicare Parts A, B or D coverage or end of 12-months post index observation time. The dependent variable was the major hemorrhagic event, and the exposure of interest was medication receipt status (DOAC only, warfarin only, DOAC plus antiplatelets, warfarin plus antiplatelets, or none of the above; antiplatelet receipt only was the reference exposure category).

Pre-specified subgroup analyses were run, stratifying on AF diagnosis status (at time of index (stent placement) hospitalization). In addition, the models were repeated for the individual components of the primary outcome, specifically: upper gastrointestinal hemorrhage and intracranial hemorrhage. We also repeated the analyses including the “other hemorrhage” category in the composite hemorrhage outcome. Finally, the main analyses were repeating separating clopidogrel (dominant anti-platelet) from all other anti-coagulants.

All probability values were the result of two sided tests and the level of statistical significance was set at 0.05. SAS 9.4 (SAS Institute, Cary, North Carolina) was used for analysis. This study was approved by the Dartmouth Committee for Protection of Human Subjects.

RESULTS

Patient characteristics

From 2010–2012, we identified 70,900 Medicare patients in our sample who underwent inpatient coronary artery stenting, and met the inclusion and exclusion criteria for the study. The respective distribution of exposure stratified on AF status can be found in Table 1. Patients exhibited an average observation period of 11.5 months. Of these, 73.8% person days were characterized by exposure to antiplatelets only, 2.2% to warfarin only, 0.3% to DOAC only, and 4.7% to a combination of warfarin plus antiplatelets, whereas 0.6% to a combination of DOAC plus antiplatelets. Table 2 provides descriptive statistics on

anticoagulant and antiplatelet exposure for the duration of the 12-month observation period, stratified on baseline AF status.

Major hemorrhagic events

Overall, 8,029 (11.3%) patients experienced a major hemorrhagic complication (Table 2) during the 12 month post stent observation period. As demonstrated in Table 3, using a Cox proportional hazards model adjusted for patient covariates, combination therapy including antiplatelets plus DOAC (HR, 2.36; 95% CI 1.91–2.93), or warfarin plus antiplatelets (HR, 2.00; 95% CI 1.83–2.18) was associated with increased risk of major hemorrhage in comparison to antiplatelets only. Monotherapy with DOAC (HR, 1.57; 95% CI 1.09–2.27), or warfarin (HR, 1.46; 95% CI 1.27–1.68) was also associated with increased risk of hemorrhage in comparison to antiplatelets, but of lesser magnitude in comparison to combination treatment (Table 3, S2).

These results were similar in models stratified on index AF status (Table 3). Among patients with AF, combination therapy including antiplatelets plus DOAC (HR, 1.94; 95% CI 1.48–2.54), or antiplatelets plus warfarin (HR, 1.69; 95% CI 1.47–1.94) was associated with increased risk of major hemorrhage in comparison to antiplatelets only. Similar associations were observed in the non-AF group for combination therapy including antiplatelets plus DOAC (HR, 3.09; 95% CI 2.15–4.46), or antiplatelets plus warfarin (HR, 2.21; 95% CI 1.97–2.48), with higher point estimates (Table 3, S2).

Sensitivity analyses

In sensitivity analyses, we assessed hemorrhagic events in greater detail. Overall, 7,218 (10.2% patients had upper gastrointestinal hemorrhages, and 949 (1.3% had intracranial hemorrhages (Table 2). As demonstrated in Table S3, combination therapy with antiplatelets plus DOAC (HR, 2.44; 95% CI 1.95–3.06), or antiplatelets plus warfarin (HR, 1.99; 95% CI 1.81–2.18) was associated with increased risk of upper gastrointestinal hemorrhage in comparison to antiplatelets only. Similar associations were observed for intracranial hemorrhage among patients receiving combination therapy with antiplatelets plus DOAC (HR, 1.51; 95% CI 0.75–3.07), or antiplatelets plus warfarin (HR, 2.00; 95% CI 1.57–2.55), compared to antiplatelets alone. Combination treatment with DOAC was not statistically significant in the above analysis among a small group of patients (N=16).

Overall, 10,224 (14.4%) patients experienced other hemorrhages (Table 2). Including other hemorrhages in the composite outcome did not change our principal findings (Table S4); the combination therapy including antiplatelets plus DOAC (HR, 2.10; 95% CI 1.79–2.46), or antiplatelets plus warfarin (HR, 2.02; 95% CI 1.90–2.16) was associated with increased risk of any hemorrhage compared to antiplatelets only. Separating clopidogrel from all other anticoagulants did not change the direction of the observed associations. (Table S5)

DISCUSSION

In a cohort of elderly Medicare beneficiaries undergoing coronary artery stenting, we found combination treatment with antiplatelets plus DOAC associated with risk of major hemorrhagic events, compared to antiplatelets alone. This effect was comparable to the risk

associated with combination treatment with antiplatelets plus warfarin. This was also found in analysis stratified on index AF status. Compared to antiplatelet therapy alone, the excess bleed risk conferred by combination therapy is substantial, but it is reassuring to find, in this real world application, that the risk associated with the more convenient DOACs is similar to warfarin. This finding suggests that choice of combination therapy, in these complex patients, might safely be determined by patient preference, individual needs, concern for reversibility, and perhaps prescription drug costs balanced against the cost and inconvenience of laboratory monitoring.

Prior randomized trials have compared the rate of hemorrhagic events between DOACs and warfarin.^{6,11,12,19} DOACs significantly reduced the relative risk of intracranial hemorrhage for AF patients in comparison to warfarin in all RCTs.^{6,11,12,19} Several of these researchers have found a trend towards lower rates of other major bleeding associated with DOACs,^{6,12} whereas some have shown no such association.¹⁹ A meta-analysis of these trials indicated that different products are associated with different bleeding sites.¹¹ Our analysis focusing on the elderly identified similar rates of hemorrhagic events among patients receiving DOACs or warfarin.

Oral anticoagulants are often administered in combination with antiplatelets especially following coronary artery stent placement. Previous phase II and III trials failed to demonstrate a significant reduction in major cardiovascular events with such combination therapy among ACS patients.^{2,3,17,18,22} Combination therapy was associated with a higher rate of clinically significant bleeding compared to antiplatelets only.^{2,3,17,18,22} In a meta-analysis of all prior such trials, including 26,731 ACS patients, combination therapy of DOACs and antiplatelets was associated with a hazard ratio for clinically significant bleeding of 2.34 (95% CI, 2.06–2.66), in comparison to antiplatelets only.²⁰ Although these studies included a highly selected patient group with ACS, the observed association is remarkably similar to our findings. Our cohort included all elderly patients undergoing coronary artery stenting (including elective procedures). We considered all observed treatment regimens including comparison groups treated with warfarin.

Our study examines the safety of DOACs in a real-world cohort of elderly patients undergoing coronary artery stenting. The increased hemorrhagic events associated with combination treatments of DOACs and antiplatelets are consistent with prior RCTs. However, the similar rates of hemorrhagic events of warfarin and DOACs are conflicting with the results of some RCTs demonstrating the superior safety of DOACs.^{6,11,12,19} Although well designed, these studies do not reflect all age and comorbidity profiles. In addition, the differences might be explained by our patient population, focusing on all cases of coronary artery stenting, which is different from prior investigations focusing solely on AF patients.^{6,11,12,19} Our cohort is the largest studied to date and gives a picture of national prescribing practice in elderly stent recipients. Dosing regimens, appropriate administration, and drug interactions can affect the safety profile of new medications in the community.

Our study has several limitations. First, this is a retrospective cohort study based on claims data, and is subject to limitations common to this research approach, including uncontrolled confounders and a reliance of the accuracy and completeness of diagnostic codes. The

coding for intra-cranial hemorrhage used in this study has been validated through medical record review in prior studies.^{15,24} Potential indication bias (careful selection of patients for each exposure group based on factors we cannot observe) would bias our results towards the null and weaken observed differences. Second, our definition of AF based on the index episode might misclassify some of our patients with intermittent AF, patients who later develop AF, and patients successfully cardioverted to sinus rhythm. This would bias our results towards the null, highlighting the importance of the observed differences. The difference in the hemorrhage risk among patients with and without AF might indicate the presence of unmeasured confounders.

Findings among this older population may not be generalizable to younger or otherwise dissimilar populations. Our measure of medication use was derived from prescription fill records. Prescription fill records have been shown a good proxy measure of prescription use,^{13,16,23} but poor adherence could result in misclassification of exposure and bias our findings toward the null.^{16,23} Some of our patients were not on any products of interest despite undergoing coronary artery stenting. This raises concerns about potential selection bias, care quality, and missed fill events occurring independent of Part D plan. We also have no data on use or recommendation for use of aspirin,^{8,10} which is available over the counter and thus not apparent in prescription fill records. The combination of an anticoagulant and dual antiplatelet therapy (such as clopidogrel and aspirin) is recommended for some patients.²⁰ Patients on warfarin or DOACs may be differentially advised to use aspirin. While we are aware of no clinical indication for such practice, if occurring this would bias our findings and conclusions regarding the bleeding risk of these products. Finally, we focused our analysis on the initial DOACs commercially available. Subgroup analyses based on specific products should be pursued in future studies examining this question.

Conclusions

In a cohort of elderly Medicare beneficiaries undergoing coronary artery stenting, we found combination treatment with DOAC and antiplatelets associated with risk of major hemorrhagic events, in comparison to antiplatelets alone. This effect was comparable to the risk associated with combination treatment including antiplatelets and warfarin. Compared to antiplatelets alone, the excess bleed risk conferred by combination therapy is substantial, but it is reassuring to find, in this real world application, that the risk associated with the more convenient DOACs is similar to warfarin. Our finding underlines that choice of combination therapy should be tailored to individual patient characteristics, needs, and cost.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

1. In a cohort of elderly Medicare beneficiaries undergoing coronary artery stenting, we found combination treatment with DOAC and antiplatelets associated with risk of major hemorrhagic events, in comparison to antiplatelets alone. This effect was comparable to the risk associated with combination treatment including antiplatelets and warfarin.
2. Compared to antiplatelets alone, the excess bleed risk conferred by combination therapy is substantial, but it is reassuring to find, in this real world application, that the risk associated with the more convenient DOACs is similar to warfarin.
3. Our finding underlines that choice of combination therapy should be tailored to individual patient characteristics, needs, and cost.

Table 1

Patient characteristics overall and stratified on atrial fibrillation status

	Overall		AF		Non-AF	
	N	%	N	%	N	%
Overall	70,900		10,238	14.4	60,662	85.6
Year of stent						
2010	26,193	36.9	3,599	35.2	22,594	37.2
2011	22,936	32.3	3,422	33.4	19,514	32.2
2012	21,771	30.7	3,217	31.4	18,554	30.6
Age, years						
65–69	17,480	24.7	1,612	15.7	15,868	26.2
70–74	18,362	25.9	2,197	21.5	16,165	26.6
75–79	15,195	21.4	2,348	22.9	12,847	21.2
80–84	11,877	16.8	2,286	22.3	9,591	15.8
Over 85	7,986	11.3	1,795	17.5	6,191	10.2
Male	36,194	51.0	5,334	52.1	30,860	50.9
Race/Ethnicity						
White	58,837	83.0	9,112	89.0	49,725	82.0
Black	4,693	6.6	390	3.8	4,303	7.1
Hispanic	4,654	6.6	453	4.4	4,201	6.9
Other	2,716	3.8	283	2.8	2,433	4.0
Low income subsidy[*]	24,215	34.2	3,129	30.6	21,086	34.8
Drug eluting stent[*]	53,363	75.3	6,562	64.1	46,801	77.2
ATRIA Bleed risk score[*]						
Low (0–3)	63,647	89.8	9,038	88.3	54,609	90.0
Intermediate (4)	804	1.1	122	1.2	682	1.1
High (5–10)	6,449	9.1	1,078	10.5	5,371	8.9
Prior Hemorrhage[*]						
Upper Gastrointestinal	1,170	1.7	175	1.7	995	1.6

	Overall		AF		Non-AF	
	N	%	N	%	N	%
Intracranial	49	0.1	0	0	39	0.1
Other	994	1.4	163	1.6	831	1.4
Any	2,163	3.1	341	3.3	1,822	3.0
Baseline Comorbidities[*]						
Diabetes	25,030	35.3	3,106	30.3	21,924	36.1
PVD	8,683	12.2	1,093	10.7	7,590	12.5
COPD	20,578	29.0	2,807	27.4	17,771	29.3
Liver disease	291	0.4	22	0.2	269	0.4
Chronic kidney disease	8,174	11.5	1,154	11.3	7,020	11.6
ESRD	2,542	3.6	335	3.3	2,207	3.6
CHF	17,198	24.3	3,694	36.1	13,504	22.3
Myocardial infarction	50,245	70.9	6,941	67.8	43,304	71.4
Ischemic stroke	2,649	3.7	358	3.5	2,291	3.8
Hypertension	41,515	58.6	5,508	53.8	36,007	59.4
Alcoholism	220	0.3	27	0.3	193	0.3
Mechanical heart valve	26	0.0	0	0	18	0.0
PE/DVT	1,102	1.6	154	1.5	948	1.6
Acute Coronary Syndrome	47,404	66.9	6,573	64.2	40,831	67.3
Long-term Anticoagulation	1,480	2.1	946	9.2	534	0.9
Hypercoagulable state	87	0.1	12	0.1	75	0.1

^{*} Baseline comorbidities appeared at time of discharge from index stent placement hospitalization. Bleed risk score is based on the ATRIA score (Anticoagulation Risk in Atrial Fibrillation) Fang et al. 2011

AF: Atrial Fibrillation; PVD: Peripheral Vascular Disease; COPD: Chronic Obstructive Pulmonary Disease; ESRD: End Stage Renal Disease; CHF: Congestive Heart Failure; PE/DVT: Pulmonary Embolism/Deep Venous Thrombosis

0 Suppressed to comply with Medicare reporting rules

Table 2

Exposure and crude outcomes overall and stratified by atrial fibrillation status

	Overall	AF	Non-AF
Number of patients	70,900	10,238	60,662
Total observed days	24,470,270	3,470,928	20,999,342
Average observed months	11.5	11.3	11.5
% Patients with bleed outcomes			
% Major hemorrhagic events	11.3	14.6	10.8
% Gastrointestinal hemorrhagic events	10.2	13.0	9.7
% Intracranial hemorrhagic events	1.3	2.0	1.2
% Other hemorrhagic events	14.4	19.5	13.6
% Any hemorrhagic events	21.8	28.4	20.7
% Days of use			
% Antiplatelets only	73.8	50.8	77.6
% Antiplatelets + Warfarin	4.7	18.9	2.4
% Antiplatelets +DOAC	0.6	2.9	0.2
% Warfarin only	2.2	9.3	1.1
% DOAC only	0.3	1.4	0.1
% No use Antiplatelets, Warfarin, or DOAC [§]	18.4	16.7	18.7

AF: Atrial Fibrillation; DOAC: Direct Oral Anticoagulant

[§]Possibly a consequence of patients switching from one agent to the other

Table 3

Association between treatment regimen major hemorrhagic events (gastrointestinal and intracranial) with, overall and stratified on atrial fibrillation

	HR*	L9 5	U9 5	P-value	HR*	L9 5	U9 5	P-value	HR*	L9 5	U9 5	P-value
	Overall (Reference)				AF (Reference)				Non-AF (Reference)			
Antiplatelets												
Antiplatelets and warfarin	2.00	1.83	2.18	<0.001	1.69	1.47	1.94	<0.001	2.21	1.97	2.48	<0.001
Antiplatelets and DOAC	2.36	1.91	2.93	<0.001	1.94	1.48	2.54	<0.001	3.09	2.15	4.46	<0.001
Warfarin only	1.46	1.27	1.68	<0.001	1.23	1.00	1.52	0.0479	1.71	1.41	2.08	<0.001
DOAC only	1.57	1.09	2.27	0.0162	1.34	0.85	2.10	0.2029	2.13	1.11	4.11	0.0234
No observed anticoagulation or antiplatelet[§]	1.18	1.10	1.25	<0.001	1.31	1.11	1.54	0.0011	1.15	1.08	1.23	<0.001

* Analyzed using a Cox proportional hazards model additionally controlling for age, gender, race, low income subsidy, drug-eluting stent, baseline comorbidities: atrial fibrillation, diabetes, peripheral vascular disease, chronic obstructive pulmonary disease, liver, chronic kidney disease, end stage renal disease, congestive heart failure, myocardial infarction, stroke, hypertension, alcoholism, mechanical heart valve, pulmonary embolism/deep vein thrombosis, acute coronary syndrome, hypercoagulable state, long-term anticoagulation, and time-varying drug exposure: antibiotics, proton pump inhibitors, cyclooxygenase-2 inhibitors, glucocorticoids, non-steroidal anti-inflammatory drugs

[§] Possibly a consequence of patients switching from one agent to the other

HR: Hazard Ratio; L95: Lower 95% Confidence Interval; U95: Upper 95% Confidence Interval; AF: Atrial Fibrillation; DOAC: Direct Oral Anticoagulant