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Original Research

Real-World Polypharmacy and Drug-Drug Interactions in a Large Cohort of Direct Oral Anticoagulant Users With Atrial Fibrillation

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ABSTRACT

Purpose: Despite their promising safety profile, use of direct oral anticoagulants (DOACs) presents challenges, particularly concerning polypharmacy and potential drug-drug interactions (DDIs). This study aimed to investigate real-world effects of polypharmacy and DDIs among DOAC users, focusing on patients with atrial fibrillation (AF).

Methods: A retrospective cohort analysis was conducted using administrative health care data from the Caserta Local Health Unit (2012–2020). Incident DOAC users were categorized by type of anticoagulant (apixaban, dabigatran, rivaroxaban, and edoxaban). Polypharmacy and DDIs were analyzed before and after index date (ID), stratifying results by DOAC and therapeutic indication. The impact of DDIs on safety outcomes, particularly bleeding risk, was assessed. Bleeding outcomes were evaluated within 1 year after ID by multivariate regression models.

Findings: Among 16,367 incident DOAC users, 68.9% were treated for AF. The number of interacting drugs increased in 55.2% of patients, with a higher prevalence of 3+ interacting drugs in low-dose users (35% vs 29.2% in high-dose users; $P < 0.05$). Before ID, 35.6% of the overall cohort had 0 interacting drugs compared with 15.2% after ID. Dabigatran users had the highest increase in interacting drugs (61.8%) compared with anti-Xa agents (56%). Patients with 6+ interacting drugs exhibited a 2.5% incidence of major bleeding after ID. Dabigatran use and low-dose DOAC regimens were independently associated with increased bleeding risks.

Implications: Polypharmacy and DDIs are prevalent among real-world DOAC users, particularly in patients with AF. The observed association between DDIs and bleeding risk underscores the importance of personalized medication management strategies and routine DDI evaluations to optimize DOAC safety.

Introduction

The introduction of direct oral anticoagulants (DOACs) dramatically changed the clinical management of thromboembolic prophylaxis in view of the proved superiority in safety coupled with similar to better efficacy^{1–4} compared with vitamin K antagonists (VKAs). These drugs were developed to address the limitations associated with VKAs, includ-

ing unpredictable response, delayed onset of action, narrow therapeutic window, and frequent drug/food interactions. Despite these premises, the complex real-world scenario of candidates to thromboembolic prophylaxis frequently challenges the safety profile of DOACs. This is particularly true for patients with atrial fibrillation (AF) due to long-term prophylaxis and associated comorbidities that can evolve over time.^{5,6} Currently, all physicians prescribing DOACs are well aware of the in-

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teractions involving either pharmacokinetic (ie, P-glycoprotein and cytochrome P450 3A4, enzymes)⁷ or pharmacodynamic properties (ie, anticoagulants, antiplatelet agents, and nonsteroidal anti-inflammatory drugs),^{8–10} based on recommendations from expert and consensus documents.^{11–13} However, these tools usually focus on principal interactions limited to 2 agents, neglecting multiple drug-drug interactions (DDIs) and the impact of additional enzymes.

This study seeks to delve into the intricate patterns of multidrug therapy among DOAC users, analyzing, in a large real-world cohort of unselected patients, the types and prevalence of concomitant medications prescribed at baseline and within 1 year to provide valuable insights into safety in patients with AF. Specifically, the primary aim of this study was to quantify the prevalence and changes in DDIs before and after DOAC initiation. A secondary aim was to explore the association between polypharmacy, DDIs, and major bleeding events in real-world patients with AF receiving DOACs.

Methods

Data Source

Fully anonymized data were extracted from the administrative databases of Caserta Local Health Unit (LHU), covering a total population of over 1 million people, during the years 2012–2020. Caserta LHU collects anonymized electronic data on DOAC dispensing to residents in the catchment area. For each DOAC prescription, specialists must fill out a therapeutic plan that specifies the exact drug name, number of dispensed packages, dosing regimen, and indication for use. These data can be linked through unique and anonymous patient identifiers to other claims databases, containing several types of information, including causes of hospitalization and reasons for health care service copayment exemptions. Drug dispensing is coded using the Anatomical Therapeutic Chemical (ATC) classification system and the Italian marketing authorization code, Autorizzazione all'Immissione in Commercio (AIC), whereas indications for use and causes of hospitalization are coded using the International Classification of Diseases, Ninth Revision, Clinical Modification.

Study Population

All 1,118,129 subjects residing in the catchment areas of Caserta LHU during the years 2012–2020 were considered. From the source population, all patients with at least 1 year of database history and receiving at least 1 DOAC dispensing during the observation period were identified. Among these, incident DOAC users (ie, no DOAC dispensing within 1 year prior to the first dispensing date, designated as the index date [ID]) were included in the cohort. The same patient could be included multiple times in the analysis if they discontinued DOAC treatment for at least 1 year and subsequently initiated a new DOAC treatment in the following period. A total of 500 patients (488 included twice and 12 included 3 times) were re-entered, representing 4.4% of the 11,283 patients with incident AF. This proportion was considered negligible for risk estimation purposes, and no further adjustment for repeated measures was considered necessary. Information about the indication for use was collected from the electronic therapeutic plan or hospital discharge diagnoses, when an electronic therapeutic plan was not available.

Exposure

During the observation period, the following DOACs were included in the analysis: dabigatran (ATC: B01AE07), rivaroxaban (ATC: B01AF01/B01AX06), apixaban (ATC: B01AF02), and edoxaban (ATC: B01AF03).

Data Analyses

Incident DOAC users were classified according to the type of DOAC (ie, dabigatran, apixaban, rivaroxaban, and edoxaban) dispensed at the ID. **Supplemental Table I** (in the online version at [doi:10.1016/j.clinthera.2025.08.007](https://doi.org/10.1016/j.clinthera.2025.08.007)) summarizes the main DDIs of DOACs (identified from Micromedex/SmPC, a comprehensive clinical decision support system provided by IBM Watson Health, Armonk, New York) and describes their effects on DOAC absorption (increase or decrease in the area under the curve) and pharmacodynamic effects. First, a baseline characterization of incident DOAC users was performed. Second, among incident DOAC users treated for AF, the distribution of low-dose and high-dose DOAC use was explored. Third, the comparison of the distribution (%) of the number of interacting drugs (0, 1, 2, 3–5, and 6–9) dispensed pre-ID (ie, within 3 months before the ID) and post-ID (ie, within 12 months after ID) was explored and stratified by individual DOAC. Only incident DOAC users with at least 12 months of observation after the ID were included in this analysis.

To avoid a biased higher number of interacting drugs before the ID compared with after the ID, due to use of bridging therapy from diagnosis to DOACs prescription, antithrombotic agents were excluded in the “Pre-ID” analysis. To evaluate potential DDIs over time, the median number and the frequency (%) of interacting drug use were compared pre-ID and post-ID, stratified by individual DOAC. The proportion (%) of incident DOAC users increasing the number of interacting drugs within 1 year after ID was calculated. Finally, to estimate the risk of major bleeding associated with DOACs use, the frequency of incident DOAC users with at least 1 hospitalization for major bleeding, distinguishing between intracranial and other types of major bleeding, within 1 year after ID was calculated and stratified by the number of DDIs (0, 1, 2, 3–5, 6–9).

Statistical Methods

Continuous variables with normal distribution were expressed as mean \pm SD, whereas other variables were summarized as percentage, median and interquartile range. Differences among groups were tested by using χ^2 test and Kruskal-Wallis test, as appropriate. To identify parameters significantly associated with major bleeding at 1 year after ID, univariate and multivariate conditional logistic regression models were performed. The multivariate model included all those covariates significantly ($P < 0.05$) associated with major bleeding risk in the univariate model. Results were reported as adjusted odds ratios with 95% CI and represented using forest plots. Statistical analyses were performed using the Statistical Package for the SPSS 28.0.1.1 (SPSS Inc, Chicago, Illinois) and SAS 9.2 (SAS Institute, Cary, North California).

Results

Study Population

Among the overall population of 1,118,129 subjects registered in Caserta LHU, 21,045 (1.9%) subjects were prescribed DOAC; 20,491 (97.4%) were incident users, with AF as an indication in 13,182 (64.3%) (**Supplemental Table II**, in the online version at doi.org/10.1016/j.clinthera.2025.08.007). **Table 1** shows the clinical characteristics of the 11,283 (68.9%) patients with AF with at least 1 year of follow-up. Approximately 60% of the cohort received high-dose DOAC, except for dabigatran users, of whom 58% were treated with low-dose dabigatran. Unsurprisingly, the subgroup of patients receiving low-dose DOACs was more frequently female and older with a higher prevalence of comorbidities. No clinically relevant differences in the prevalence of interacting drugs were recorded according to different DOAC subgroups (**Table 2**).

Table 1
Baseline characterization of incident users of direct oral anticoagulants with atrial fibrillation.

AF DOAC Users	Apixaban		Dabigatran		Rivaroxaban		Edoxaban	
	Low Dose n = 1210	High Dose n = 2032	Low Dose n = 1365	High Dose n = 1087	Low Dose n = 1710	High Dose n = 2630	Low Dose n = 482	High Dose n = 767
Sex, n (%)								
Males	471 (38.9)	1,023 (50.3)	609 (44.6)	604 (55.6)	643 (37.6)	1,361 (51.7)	166 (34.4)	371 (48.4)
Females	739 (61.1)	1,009 (49.7)	756 (55.4)	483 (44.4)	1,067 (62.4)	1,269 (48.3)	316 (65.6)	396 (51.6)
Age (y), median (IQR)	83 (79–87)	73 (66–78)	80 (75–83)	69 (61–74)	81 (77–85)	72 (65–78)	82 (78–86)	72 (65–78)
Age groups, n (%)								
<65 y	24 (2.0)	396 (19.5)	88 (6.4)	374 (34.4)	54 (3.2)	607 (23.1)	8 (1.7)	184 (24.0)
65–79 y	334 (27.6)	1,228 (60.4)	561 (41.1)	665 (61.2)	596 (34.9)	1,599 (60.8)	153 (31.7)	452 (58.9)
≥80 y	852 (70.4)	408 (20.1)	716 (52.5)	48 (4.4)	1,060 (62.0)	424 (16.1)	321 (66.6)	131 (17.1)
Comorbidities,* n (%)								
Stroke/TIA	354 (29.3)	421 (20.7)	371 (27.2)	171 (15.7)	477 (27.9)	526 (20.0)	133 (27.6)	112 (14.6)
Heart failure	408 (33.7)	507 (25.0)	379 (27.8)	214 (19.7)	554 (32.4)	598 (22.7)	147 (30.5)	163 (21.3)
Myocardial infarction	154 (12.7)	204 (10.0)	214 (15.7)	105 (9.7)	203 (11.9)	251 (9.5)	59 (12.2)	66 (8.6)
Diabetes	440 (36.4)	651 (32.0)	473 (34.7)	315 (29.0)	588 (34.4)	741 (28.2)	174 (36.1)	228 (29.7)
Hypertension	764 (63.1)	1,189 (58.5)	876 (64.2)	558 (51.3)	1,116 (65.3)	1,501 (57.1)	304 (63.1)	439 (57.2)
Liver disease	112 (9.3)	178 (8.8)	122 (8.9)	105 (9.7)	156 (9.1)	246 (9.4)	39 (8.1)	56 (7.3)

AF = atrial fibrillation; DOAC = direct oral anticoagulant; IQR = interquartile range; TIA = transient ischemic attack.

* Comorbidities were evaluated any time prior to the index date.



Figure 1. Distribution (%) of the number of interacting drugs within 3 months before the index date (Pre-ID) and within 12 months after index date (Post-ID) among atrial fibrillation (AF) direct oral anticoagulant (DOAC) users. (A) Proportion (%) of AF DOAC users increasing the number of interacting drugs within 1 year after ID (B). Only incident DOAC users with at least 3 months of observation before the index date and 12 months of observation after the index date were included in this analysis. Antithrombotic agents were not included in “Pre-ID” analysis.

Prevalence of DDIs Before and After DOAC Prescription

The analysis of 11,283 patients with AF revealed that before DOACs prescription (pre-ID), approximately two-thirds of all the patients (64.4%) had at least 1 interacting drug (Figure 1), being 3 or more in 8.1%. This prevalence significantly increased in the post-ID assessment, reaching 84.8% of patients with at least 1 interacting drug, and 31.6% of patients with 3 or more interacting drugs ($P < 0.001$ for both ≥ 1 and ≥ 3 interacting drugs compared with pre-ID). In particular,

there was a reduction in the number of interacting drugs in 7.6% of cases, no change in 37.2%, and an increase in 55.2%.

Focusing on dose regimens of the prescribed DOAC, we found that patients with low-dose versus high-dose regimens presented a higher number of interacting drugs both pre-ID and post-ID (both $P < 0.001$; Figure 1B), with 3 or more interacting drugs increasing from 9.4% versus 7.2% to 34.9% versus 29.2%, respectively. The number of interacting drugs increased in 57.7% of low-dose cases compared with 55.2% for high-dose cases ($P = 0.025$).

Table 2
Distribution of interacting drugs use evaluated pre- and post-ID and stratified by individual DOAC in AF DOAC users.

AF DOAC Users	Apixaban		Dabigatran		Rivaroxaban		Edoxaban	
	n = 3242 (%)		n = 2452 (%)		n = 4340 (%)		n = 1249 (%)	
	Pre-ID	Post-ID	Pre-ID	Post-ID	Pre-ID	Post-ID	Pre-ID	Post-ID
Number of interacting drugs, median (IQR)*	1 (0–2)	2 (1–3)	1 (0–2)	2 (1–3)	1 (0–2)	2 (1–3)	1 (0–2)	2 (1–3)
Interacting drugs, N (%)								
Antithrombotic agents								
Vitamin K antagonists	431 (13.3)	73 (2.3)	459 (18.7)	129 (5.3)	688 (15.9)	155 (3.6)	148 (11.8)	32 (2.6)
Heparin group	818 (25.2)	602 (18.6)	511 (20.8)	501 (20.4)	953 (22.0)	781 (18.0)	269 (21.5)	245 (19.6)
Platelet aggregation inhibitors	1227 (37.8)	626 (19.3)	846 (34.5)	520 (21.2)	1531 (35.3)	697 (16.1)	477 (38.2)	216 (17.3)
Other antithrombotic agents	34 (1.0)	22 (0.7)	22 (0.9)	12 (0.5)	44 (1.0)	24 (0.6)	6 (0.5)	8 (0.6)
Antiarrhythmic drugs								
Amiodarone	462 (14.3)	602 (18.6)	331 (13.5)	423 (17.3)	606 (14.0)	761 (17.5)	159 (12.7)	213 (17.1)
Digoxin	355 (11.0)	472 (14.6)	274 (11.2)	359 (14.6)	521 (12.0)	721 (16.6)	112 (9.0)	152 (12.2)
Diltiazem	27 (0.8)	30 (0.9)	28 (1.1)	23 (0.9)	39 (0.9)	36 (0.8)	7 (0.6)	10 (0.8)
Dronedaron	15 (0.5)	14 (0.4)	18 (0.7)	18 (0.7)	19 (0.4)	15 (0.3)	7 (0.6)	6 (0.5)
Verapamil	120 (3.7)	132 (4.1)	85 (3.5)	84 (3.4)	192 (4.4)	186 (4.3)	42 (3.4)	36 (2.9)
Antibiotics								
Clarithromycin	118 (3.6)	330 (10.2)	79 (3.2)	244 (10.0)	132 (3.0)	415 (9.6)	44 (3.5)	120 (9.6)
Erythromycin	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	2 (0.0)	5 (0.1)	0 (0.0)	0 (0.0)
Azithromycin	65 (2.0)	226 (7.0)	53 (2.2)	188 (7.7)	91 (2.1)	292 (6.7)	29 (2.3)	96 (7.7)
Rifampicin	3 (0.1)	3 (0.1)	6 (0.2)	9 (0.4)	6 (0.1)	9 (0.2)	0 (0.0)	1 (0.1)
Antifungals								
Fluconazole	23 (0.7)	60 (1.9)	16 (0.7)	67 (2.7)	29 (0.7)	114 (2.6)	5 (0.4)	28 (2.2)
Itraconazole	11 (0.3)	28 (0.9)	6 (0.2)	36 (1.5)	18 (0.4)	33 (0.8)	7 (0.6)	16 (1.3)
Voriconazole	1 (0.0)	—	0 (0.0)	—	1 (0.0)	—	0 (0.0)	—
Anti-inflammatory and antirheumatic products, nonsteroids								
NSAIDs	693 (21.4)	1297 (40.0)	498 (20.3)	952 (38.8)	856 (19.7)	1642 (37.8)	250 (20.0)	513 (41.1)
Statins								
Lovastatin	62 (1.9)	73 (2.3)	39 (1.6)	51 (2.1)	95 (2.2)	108 (2.5)	24 (1.9)	31 (2.5)
Simvastatin	328 (10.1)	360 (11.1)	247 (10.1)	280 (11.4)	448 (10.3)	503 (11.6)	129 (10.3)	128 (10.2)
Anticonvulsants								
Carbamazepine	12 (0.4)	18 (0.6)	8 (0.3)	9 (0.4)	18 (0.4)	20 (0.5)	1 (0.1)	1 (0.1)
Phenobarbital	21 (0.6)	25 (0.8)	9 (0.4)	14 (0.6)	23 (0.5)	32 (0.7)	2 (0.2)	2 (0.2)
Phenytoin	—	0 (0.0)	—	1 (0.0)	—	0 (0.0)	—	0 (0.0)
Oxcarbazepine	10 (0.3)	14 (0.4)	2 (0.1)	6 (0.2)	7 (0.2)	7 (0.2)	2 (0.2)	3 (0.2)
Primidone	2 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)	3 (0.1)	0 (0.0)	0 (0.0)
Antidepressants								
SSRI	229 (7.1)	338 (10.4)	173 (7.1)	273 (11.1)	356 (8.2)	535 (12.3)	81 (6.5)	144 (11.5)
SNRI	44 (1.4)	64 (2.0)	33 (1.3)	50 (2.0)	67 (1.5)	97 (2.2)	28 (2.2)	35 (2.8)
Trazodone	41 (1.3)	93 (2.9)	39 (1.6)	74 (3.0)	71 (1.6)	143 (3.3)	15 (1.2)	46 (3.7)
Vortioxetine	16 (0.5)	44 (1.4)	11 (0.4)	20 (0.8)	16 (0.4)	51 (1.2)	10 (0.8)	25 (2.0)
Anticancer drugs								
Enzalutamide	—	—	—	—	—	—	—	—
Other interacting drugs								
Anagrelide	—	—	—	—	—	—	—	—
Atenolol	159 (4.9)	151 (4.7)	102 (4.2)	123 (5.0)	195 (4.5)	227 (5.2)	45 (3.6)	46 (3.7)
Carvedilol	480 (14.8)	501 (15.5)	346 (14.1)	373 (15.2)	657 (15.1)	711 (16.4)	131 (10.5)	132 (10.6)
Cyclosporine	2 (0.1)	4 (0.1)	2 (0.1)	2 (0.1)	2 (0.0)	1 (0.0)	2 (0.2)	2 (0.2)
Ranolazine	39 (1.2)	62 (1.9)	29 (1.2)	53 (2.2)	55 (1.3)	81 (1.9)	22 (1.8)	29 (2.3)
Tibolone	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	2 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)

AF = atrial fibrillation; DOAC = direct oral anticoagulant; ID = index date; IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin and norepinephrine reuptake inhibitor.

Moving to the different DOACs, we found a lower number of interacting drugs for edoxaban at pre-ID assessment, with respect to the other interacting drugs ($P = 0.002$) without any significant difference at post-ID (Figure 1). Notably, considering the variation in the number of interacting drugs, dabigatran presented the highest increase in the number of interacting drugs, being 59.6% ($P = 0.007$).

DDIs and Clinical Outcomes

After 1 year of follow-up, we recorded 16 hospitalizations for intracranial bleeding (0.14%) and 190 hospitalizations (1.7%) for any other major bleeding (eg, gastrointestinal bleeding, postmenopausal bleeding, hemoptysis, hematuria, metrorrhagia, epistaxis, and acute posthemorrhagic anemia). We found a strong association of overall major bleedings with the increasing number of interacting drugs post-ID ($P < 0.001$ at univariate logistic regression analysis), as shown in Figure 2.

Among the included variables, 2 other parameters were found independently associated with the occurrence of overall major bleedings: use of dabigatran and low DOAC dose. In particular, an increased incidence of overall major bleedings in patients receiving dabigatran versus subjects treated with anti-X agents was found, whereas no statistical difference was present within the latter subgroup (Figure 3). A sensitivity analysis stratifying logistic regression models by individual DOAC did not reveal statistically significant associations between the number of interacting drugs and major bleeding events within each DOAC subgroup (also in view of the limited number of events).

Discussion

Our results underscore the importance of vigilance in managing polypharmacy among patients receiving DOACs. Direct oral anticoagulants currently represent the standard of care for prevention of throm-

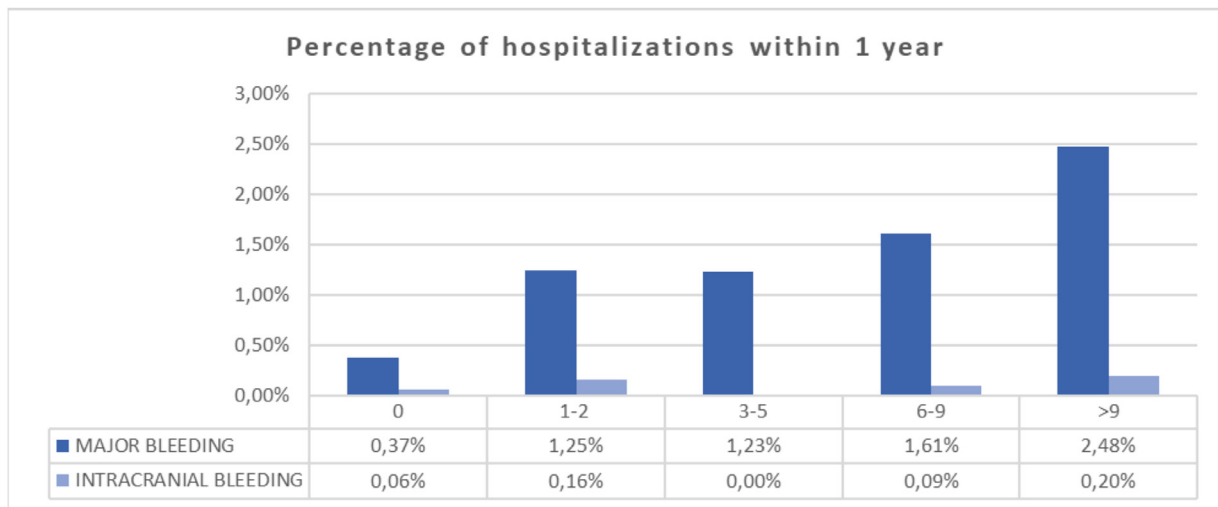


Figure 2. Frequency of incident direct oral anticoagulant users, treated for atrial fibrillation, with at least 1 hospitalization for major bleeding or intracranial bleeding within 1 year after index date, stratified by the number of drug-drug interactions.

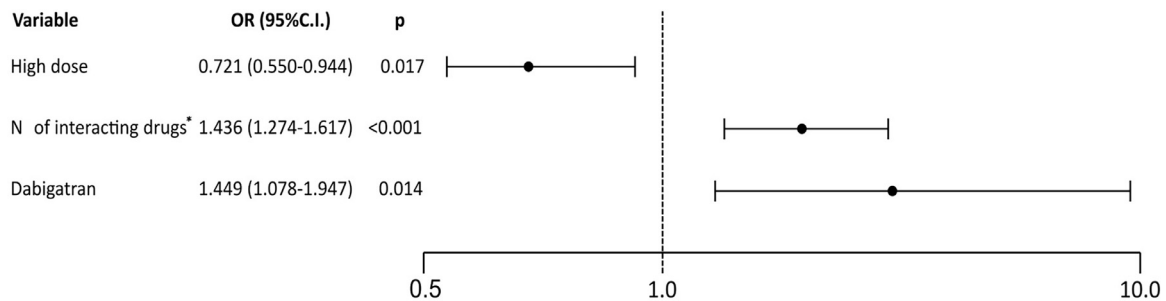


Figure 3. Forest plot showing variables associated with major bleedings at multivariate logistic regression analysis including: intracranial bleeding, gastrointestinal bleeding, other major bleeding (eg, postmenopausal bleeding, hemoptysis, hematuria, excessive or frequent menses, metrorrhagia, epistaxis, and acute posthemorrhagic anemia). *The number of interacting drugs was considered aggregated as in Figure 2. OR = odds ratio.

boembolic events in patients with AF due to a better safety profile compared with VKAs.^{1–4} Despite the promising safety profile shown by the pivotal randomized controlled trials, real-world clinical scenarios present challenges related to polypharmacy, potentially hampering the safety profile of drugs, including DOACs. In particular, there are several potential pharmacokinetic (involving P-glycoprotein, breast cancer resistance protein, organic anion transporting polypeptides, and different isoforms of cytochrome P450) and pharmacodynamic (eg, concomitant use of antiplatelet agents) properties, that frequently cluster among the same patient,¹³ limiting the possibility to estimate the real impact of multiple interactions despite the available indications provided by the Summary of Product Characteristics and clinical guidelines.¹⁴ Notably, although several analyses focused on specific interacting drugs, such as antiarrhythmic (eg, dronedarone and amiodarone), anticonvulsant, antibiotic, and chemotherapy agents, there are frequently used drugs in patients with AF that are less considered for their interaction potential. This is the case for selective serotonin reuptake inhibitors/selective norepinephrine reuptake inhibitors, which inhibit the accumulation of serotonin within the platelets, hampering their aggregation and potentially increasing the hemorrhagic risk of DOACs, especially when combined chronically or acutely with other agents, which can be almost “unsuspected” such as beta-blockers (eg, carvedilol), statins, and digoxin.^{14–16} This phenomenon parallels what happens with the risk of torsade de pointes, claiming for a sort of “preventing bleeding” reserve similar to the well-known “repolarization reserve,” which, however, in this case, cannot be estimated with easy parameters like corrected QT interval.^{17,18} Notably, according to our analysis, both the number of

incidents of DOAC users receiving interacting drugs and the average number of interacting drugs increased in the first year after DOAC dispensation, underlying this issue. This was confirmed by the independent association we found between the number of interacting drugs and the occurrence of major bleeding. Two strategies can be theoretically adopted to prevent the occurrence of bleedings: the use of a reduced DOAC dose and laboratory assay for DOAC assessment. However, despite the nonrandomized design of our study, we found that a low DOAC dose was associated with a 1.38 times higher risk of bleeding when compared with the standard dose. This finding is not completely unexpected, since many factors promoting bleeding are associated with the parameters used for selecting a reduced dose of DOAC (ie, age, body weight, and renal function). Notably, these parameters affect the pharmacodynamic properties of several interacting drugs, leading to a sort of chain reaction. Regarding the use of laboratory assays for DOAC assessment, only very limited unrandomized data are available reporting significant variability in plasma concentrations, largely influenced by patient-specific factors such as age and renal function. Despite their predictable profile, DOACs are given in fixed doses without linking drug levels to clinical outcomes. As a result, there are no standardized guidelines for laboratory monitoring, assay standardization, or therapeutic targets.^{19–22}

Finally, our results suggest a potential increase in bleeding associated with the use of dabigatran. The unrandomized design of the study limits the possibility to generalize our findings, but the evidence that most of the interactions we found in our large population involved the inhibition of P-glycoprotein provides a plausible explanation, in view of the low bioavailability of this agent compared with anti-Xa agents.

This is supported by a recent paper showing that interacting drugs frequently prescribed in our population (eg, amiodarone and digoxin) are specifically associated with increased bleeding when coprescribed with dabigatran.²³ This study was based on data extracted from specific time windows. Due to ethical and technical constraints, the analysis could not capture real-time changes in treatment or interactions. Future research with longitudinal data will be necessary to explore these aspects more comprehensively.

All these considerations call for caution when prescribing multiple drugs in patients treated with DOAC for AF and underline the need to develop integrated software to estimate the bleeding risk in candidates for DOAC treatment to improve personalized management. Notably, the approval of bioequivalent agents for DOACs should be carefully evaluated by regulatory authorities, as the parameters currently adopted do not estimate the real net clinical benefit of DOACs or consider possible specific interactions, as observed with dabigatran.²³

Conclusion

Our study showed a frequent use of multiple interacting drugs in a large real-world population of patients treated with DOACs, which increases after drug dispensation. The number of interacting drugs is strongly associated with the occurrence of major bleeding independently of the use of low DOAC doses. These findings emphasize the need for a personalized approach to medication management in DOAC users that could benefit from the development of dedicated tools aimed at estimating bleeding and interaction risk.

Declaration of competing interest

Igor Diemberger reports speaker fees from Daiichi Sankyo, Pfizer, Philips, Biotronik, and Medtronic. Ylenia Ingrasciotta is the Chief Executive Officer of the academic spin-off “INSPIRE s.r.l.,” which has received funding for conducting observational studies from contract research organizations (RTI Health Solutions and Pharmo Institute N.V.) and from pharmaceutical Companies (Chiesi Italia, Kyowa Kirin s.r.l., and Daiichi Sankyo Italia S.p.A.).

CRediT authorship contribution statement

Veronica De Angelis: Writing – review & editing, Writing – original draft, Data curation. **Ylenia Ingrasciotta:** Writing – review & editing, Investigation, Conceptualization. **Maria Carelli:** Writing – review & editing, Software, Data curation. **Alberto Spadotto:** Writing – review & editing, Data curation. **Martina Amadori:** Writing – review & editing. **Claudia Pagliaro:** Data curation. **Annalisa Di Giorgio:** Data curation. **Valentina Isgro:** Data curation. **Saveria Serena Foti:** Data curation. **Michele Tari:** Investigation, Data curation. **Igor Diemberger:** Writing – review & editing, Supervision, Software, Methodology, Investigation, Data curation, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2025.08.007.

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