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Drug-drug interactions with direct oral anticoagulants in Belgian primary care patients with non-valvular atrial fibrillation

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TITLE PAGE

Drug-Drug Interactions with Direct Oral Anticoagulants in Belgian Primary Care: A Real-World Study in Patients with Non-Valvular Atrial Fibrillation

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ABSTRACT

Direct oral anticoagulants (DOACs) are widely prescribed in primary care, but co-prescription with interacting drugs may increase thromboembolic and major bleeding risks. We conducted a retrospective cohort study in Belgium in 2022-2023 using the real-world THIN database to evaluate the prevalence of DOAC-related drug-drug interactions (DDIs) in general

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practitioners' (GPs) prescriptions for patients with non-valvular atrial fibrillation (NVAF) and to assess factors associated with pharmacodynamic DDIs. DDIs were defined as the co-prescription of a DOAC and an interacting drug within the same week. Factors associated with pharmacodynamic DDIs were assessed using multivariable logistic regression. Among 5,637 patients receiving 13,334 DOAC prescriptions, 22.9% had at least one DDI during the year. Overall, 17.8% of GP-issued DOAC prescriptions involved a DDI, of which 91.5% were pharmacodynamic. The most frequently interacting drug classes were selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors (44.2%), antiplatelets (22.6%) and non-steroidal anti-inflammatory drugs (19.6%). Higher CHA_2DS_2-VASc score and receiving multiple DOAC types were associated with higher odds of pharmacodynamic DDIs, whereas edoxaban use and older age were associated with lower odds. Most DOAC-related interactions in primary care involved bleeding-risk drugs highlighting the need to prioritizing identification and review of these high-risk associations to support safer anticoagulation prescribing.

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MANUSCRIPT TEXT

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia [1–3], affecting approximately 2% of European adults [4]. Due to population aging, its prevalence is projected to more than double by 2060 [2,4]. To mitigate thromboembolism risk - particularly ischemic stroke - lifelong oral

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anticoagulation with either direct oral anticoagulants (DOACs) or vitamin K antagonists (VKAs) is recommended for eligible patients with non-valvular atrial fibrillation (NVAF) [1]. According to the 2024 European Society of Cardiology (ESC) guidelines, DOACs are now recommended as first-line therapy for patients with a CHA_2DS_2-VA score 2 [1]. They offer key advantages over VKAs: lower intracranial bleeding risk, rapid onset, fixed dosing, no need for regular monitoring, and fewer food-drug or drug-drug interactions [1].

Despite these benefits, DOACs may still be involved in clinically relevant drug-drug interactions (DDIs) [1,5], via pharmacokinetic (PK) and pharmacodynamic (PD) mechanisms [6–8]. All DOACs are substrates of P-glycoprotein (P-GP), and apixaban and rivaroxaban also undergo CYP3A4 metabolism, making them vulnerable to PK-DDIs [5,6,9–16]. CYP3A4 or P-GP inhibitors can elevate DOAC plasma levels, increasing bleeding and mortality risk [6,8,10,16], while inducers can lower concentrations, compromising efficacy and increasing thromboembolic risk [6,10,12,15–18]. PD interactions occur when DOACs are combined with other drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), or serotonin and norepinephrine reuptake inhibitors (SNRIs), leading to additive or synergistic effects on hemostasis and an increased risk of bleeding [5,7,9,10]. Real-world data underscore the magnitude of the DDI issue: up to 71% of NVAF patients in a six-country European study [19], and 34% in

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Belgian community pharmacies [9] were exposed to DDIs. These figures are concerning, as such patients may be at increased risk of adverse drug events [16]. Older adults, who represent the majority of DOAC users, are particularly vulnerable to iatrogenic harm due to frequent polypharmacy, frailty, multimorbidity, and age-related PK changes [20]. In Belgium, where general practitioners (GPs) frequently initiate and renew anticoagulant prescriptions, the evaluation of DOAC-related DDIs in primary care is critical. Yet, to our knowledge, no study has specifically examined Belgian GPs' prescribing practices.

Consequently, this study aimed to address this gap by assessing (1) the prevalence of DOAC-related DDIs and (2) factors associated with their occurrence in patients with NVAF, based on real-world prescription data from Belgian GPs.

Methods

This retrospective cohort study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [21] (Supplementary Table S1).

Data source and ethics

We used data from The Health Improvement Network (THIN) [22], a Belgian primary care database marketed by GERS DATA. THIN collects anonymized longitudinal real-world data through CrossWay® prescription assistance software. The database includes about 300 GPs and over 625,000 patients annually who constitute a representative sample of the Belgian

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population in terms of sex, age, geographic region, and language. For each patient, demographic and diagnostic information as well as GP-issued prescriptions were extracted [23]. THIN complies with all current European data protection laws (General Data Protection Regulation) and as we only used anonymized data, no additional ethical approval was required.

Study population

We extracted from the Belgian THIN database all patients with an AF diagnosis [International Classification of Diseases, 10th revision (ICD-10) code: I48] during the study period, i.e. from August 1, 2022, to July 31, 2023 (the most recent time period available at data extraction) (Figure 1). We selected patients with at least one DOAC prescription (rivaroxaban, apixaban, edoxaban or dabigatran [Anatomical Therapeutic Chemical (ATC)-code: B01AF01, B01AF02, B01AF03, B01AE07]) during the study period. The index date was defined as the date of the first DOAC prescription within the study period.

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We included patients who met the following criteria: (1) age ≥18 years at the index date; and (2) a diagnosis of AF prior to the index date. Then, we excluded patients with: (1) a diagnosis of valvular heart disease or valvular replacement recorded at any time prior to the index date (Supplementary Table S2), ensuring DOAC use for stroke prevention in NVAF; or (2) a record of deep vein thrombosis, cardiac catheterization, pulmonary embolism, or hip/knee surgery within 6 months before the index

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date (Supplementary Table S2), to avoid competing indications for DOAC therapy.

Patients with identical sex, age, AF diagnosis date, first GP contact date, and first DOAC prescription date during the study period were considered duplicates and excluded from the study population.

Assessment of drugs involved in DDIs with DOACs

A comprehensive list of drugs involved in DDIs with their severity when co-administered with DOACs was compiled (Supplementary Table S3) using data from the Pharmaceutical Information Library (Phil), managed by the Belgian Pharmaceutical Association (APB) [24]. Phil collaborates with the Federal Union of German Associations of Pharmacist (ABDA), which identifies DDIs based on Summaries of Product Characteristics (SmPC) and, when available, peer-reviewed literature, case reports or clinical studies. This source of information was selected because it is integrated into the prescription software promoted by GERS DATA and routinely used by Belgian GPs, ensuring clinical relevance and consistency with local prescribing practices.

Due to database anonymization, the exact prescription date was unavailable; instead, the recorded date corresponded to the Monday following the actual prescription. Therefore, a DDI was defined as the co-prescription of a DOAC and an interacting drug by the same GP within the same calendar week.

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Finally, we decided a posteriori to assess proton pump inhibitor (PPI) use in patients with a HAS-BLED score ≥ 3 when DDIs involved NSAIDs, antiplatelet agents, or SSRIs/SNRIs, given the high prevalence of these DDIs and the common PPI co-prescription to reduce the risk of gastrointestinal (GI) bleeding [25]. Concomitant use was defined in this case as a PPI prescription within 3 months before or 1 month after the DDI prescription. All medications were identified using 5th-level ATC codes.

Covariates

Baseline covariates included sex, age, and comorbidities identified using ICD-10 codes (Supplementary Table S4). Renal impairment was defined using both ICD-10 codes and laboratory results from the year preceding the study; patients with at least one estimated Glomerular Filtration Rate (eGFR) < 60 mL/min/1.73 m² within one year before baseline were classified as having renal impairment. The age-adjusted Charlson Comorbidity Index was then calculated (Supplementary Table S4). Regarding thromboembolic and bleeding risk assessment, the 2024 ESC guidelines have refined stroke risk stratification by adopting the CHA_2DS_2-VA score, which excludes sex as it is considered an age-dependent risk modifier rather than an independent risk factor, thereby simplifying clinical decision-making. In addition, the HAS-BLED score is no longer recommended as a standalone tool; instead, a structured and individualized assessment of both modifiable and non-modifiable bleeding risk factors is encouraged [1]. However, in the present study, we chose to use the ESC

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guidelines in force at the time of the study period, namely the 2020 recommendations [25], to ensure methodological consistency. Accordingly, thromboembolic and bleeding risks were assessed using the CHA_2DS_2-VASc and HAS-BLED scores, respectively (Supplementary Table S4). To avoid potential collinearity in the statistical models, a modified HAS-BLED score was calculated by excluding the "drugs" item (i.e., NSAID or antiplatelet use). Concomitant medications were identified from GP prescriptions using 5^{th}-level ATC codes and were considered if prescribed within the 3 months preceding the index date (when no end-of-use date was identifiable), or beyond the index date when an end-of-use date could be inferred (Supplementary Table S4).

Statistical analysis

Categorical variables were reported as counts and percentages, and continuous variables were reported as means ± standard deviations (SD) and medians with interquartile ranges.

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Since over 90% of identified DDIs were PD-DDIs, we specifically focused on factors associated with having at least one PD-DDI, which were assessed using binary logistic regression. Potential associated factors that were evaluated included sex, age, DOAC type, CHA_2DS_2-VASc score, and modified HAS-BLED score. First, a univariate logistic regression was performed to evaluate individual associations. Subsequently, a multivariable model incorporating all aforementioned factors was performed. Collinearity was assessed using the variance inflation factor (VIF), and variables with

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VIF>5 were removed from the model. Results of the multivariable model are presented as adjusted OR (aORs) with their corresponding 95% CIs. All statistical tests were two-sided, and a $p<0.05$ was considered statistically significant. No missing data was present for the included variables. Statistical analyses were performed using R software (version 4.4.1).

Results

A total of 5,637 adults with NVAF who received at least one DOAC prescription from a GP between August 1, 2022, and July 31, 2023, were included (Figure 1). Mean age was 77.0 ± 9.7 years and 53.4% were men (Table 1). Baseline patient characteristics are summarized in Table 1.

Prevalence and Characteristics of DDIs

a. At the patient level

Overall, 22.9% of patients had at least one DDI in their DOAC prescriptions during the study year. The highest proportion was observed among dabigatran users (26.3%), followed by rivaroxaban (25.0%), apixaban (23.7%), and edoxaban (18.3%) (Table 2). Patients were prescribed different DOACs; for this reason, results are presented separately for each DOAC (Table 2, Supplementary Table S5).

All DOACs presented comparable proportions of PK and PD-DDIs, with one exception: dabigatran users exhibited a higher proportion of PK-DDIs compared with other DOACs (Table 2). This elevated PK-DDI proportion was primarily driven by P-GP inhibitors (2.9%) (Table 2).

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Among patients with a HAS-BLED score ≥ 3 who had DDIs involving NSAIDs, antiplatelets, or SSRIs/SNRIs (n=425), 48.7% had a PPI co-prescription (Supplementary Table S6).

b. At the prescription level

A total of 13,334 individual DOAC prescriptions issued by GPs were identified. Apixaban accounted for the largest proportion (n=5,389, 40.4%), followed by rivaroxaban (n=3,382, 25.4%), edoxaban (n=3,143, 23.6%), and dabigatran (n=1,420, 10.6%).

Among these prescriptions, 2,379 (17.8%) included at least one DDI, with 16.3% (n=2,174) involving PD-DDIs and 1.5% (n=205) involving PK-DDIs (Table 3). Notably, 9.1% (n=198) of DDI-containing prescriptions included multiple DDIs within the same prescription (Supplementary Table S7), resulting in a total of 2,449 identified DDIs. The large majority of DDIs were classified as severe (n=2,236/2,449 - 91.3%) and predominantly involved PD interactions (n=2,240/2,449 - 91.5%) (Table 3). The most frequently implicated drug classes were SSRIs or SNRIs (44.2%), antiplatelets (22.6%), and NSAIDs (19.6%) (Table 3). Escitalopram was the most prescribed interacting drug (n=390/2,449 - 15.9%), followed by acetylsalicylic acid (n=379/2,449 - 15.5%), and sertraline (n=187/2,449 - 7.6%). Regarding PK-DDIs, these more often involved CYP3A4 and/or P-GP inhibitors (5.5%) than CYP3A4 and/or P-GP inducers (3.0%) (Table 3). Detailed results for each DOAC are available in Supplementary Table S8. Finally, among DDIs involving NSAIDs, antiplatelets, or SSRIs/SNRIs in

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high-bleeding-risk patients, 52.5% (n=439/836) included a PPI co-prescription (Supplementary Table S6).

Factors associated with having at least one PD-DDI

Given that over 90% of identified DDIs were PD-DDIs, our analysis focused specifically on factors associated with having at least one PD-DDIs.

In univariate logistic regression, variables associated with having at least one PD–DDI in GP prescriptions included being a woman [OR (95% CI): 1.15 (1.02, 1.31)], having a higher CHA_2DS_2-VASc score [OR (95% CI): 1.06 (1.02, 1.11)], and using multiple DOAC types during the year compared with apixaban alone [OR (95% CI): 2.21 (1.12, 4.24)] (Supplementary Table S9). Conversely, factors associated with lower odds of having at least one PD-DDI were: the use of edoxaban (vs apixaban) [OR (95% CI): 0.71 (0.60, 0.84)] and age ≥85 years compared with age <65 years [OR (95% CI): 0.72 (0.57, 0.92)] (Supplementary Table S9).

After adjustment in the multivariable analysis, being a woman was no longer associated with having at least one PD–DDI, whereas age groups 65–74 [aOR (95% CI): 0.73 (0.57, 0.93)], and 75–85 [aOR (95% CI): 0.64 (0.50, 0.83)] became significantly associated (Supplementary Table S9, Figure 2). Other factors associated with higher odds of having at least one PD-DDI in GP prescriptions were a higher CHA_2DS_2-VASc score [aOR (95% CI): 1.13 (1.06, 1.20)], and the use of multiple DOAC types over the year compared with apixaban alone [aOR (95% CI): 2.21 (1.12, 4.24)] (Figure 2). Conversely, taking edoxaban alone was associated with lower odds of

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having at least one PD-DDI as compared to apixaban alone [aOR (95% CI): 0.70 (0.59, 0.83)] (Figure 2).

Discussion

In this real-world cohort of 5,637 NVAF patients, DOAC-related DDIs were common in primary care, concerning 17.8% of GP-issued prescriptions and affecting nearly one quarter of patients over the one-year study period.

When comparing the proportion of patients with DDIs to findings from neighboring European countries, our results were broadly consistent with those reported in the Netherlands (20.4%) and the United Kingdom (25.8%), but were substantially lower than figures reported in Germany (48.7% and 52.7%) and France (70.5%) [19]. However, it is important to note differences in data sources: our study, like those in the Netherlands and the UK, considered only GP prescriptions, whereas the German and French databases included both GP and specialist prescriptions, which may partly explain the higher DDI rates observed. Another study conducted in Belgian community pharmacies reported findings closely aligned with ours regarding the types of DDIs and the drug classes most frequently involved [9].

After accounting for comorbidities and risk factors - the cornerstone of AF patient management in the 2024 ESC guidelines - stroke prevention through oral anticoagulation remains a critical priority [1]. These guidelines emphasize the need for healthcare professionals to maintain vigilance regarding potential DDIs with DOACs [1]. Our real-world data applicable to

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general practice suggest that DDIs may be underestimated in primary care despite their clinical relevance.

Evidence suggests that healthcare professionals, especially in ambulatory care settings, may lack sufficient knowledge to effectively identify and manage DDIs [1,26–28], underscoring the critical need for targeted GP training and education [1]. Raising awareness of DOAC-related DDIs is essential to ensure safe DOAC prescribing [1,10]. However, while targeted training can improve knowledge and prescribing practices, its long-term behavioral impact remains limited [1]. Sustainable improvements in DDI management may require additional tools. Clinical decision support systems (CDSS) integrated into electronic prescribing software can help GPs in identifying relevant DDIs [1,26,29]. In our study, GPs had access to a CDSS with a default alert for “contraindications in the presence of risk factors”, although alert exposure and deactivation could not be assessed. The effectiveness of CDSS in practice remains constrained by the overload of less relevant alerts contributing to alert fatigue and systematic overrides, even in clinically relevant situations [26,29–31]. Future strategies should focus on optimizing CDSS design, including targeting high-quality DDI alerts [30–32] and creating ergonomic interfaces that minimize click burden, thereby reducing cognitive overload [31].

Regarding the three most frequently implicated drug classes - SSRIs/SNRIs, antiplatelets, and NSAIDs – several observations emerge from our results. Firstly, one-third of DDIs in our cohort involved SSRIs, and 11%

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involved SNRIs. Combined SSRIs/SNRIs and DOAC use has been associated with up to a 50% overall increase in bleeding risk [7,11,33,34] and a 70% increase in major bleeding requiring hospitalization [35]. GPs should therefore reassess the necessity of these antidepressants, consider deprescribing or safer alternatives for high-risk patients [33,35,36], and exercise caution by addressing modifiable bleeding risk factors [34] and considering DOAC dose reduction, as recommended by the European Heart Rhythm Association (EHRA) practical guide [6]. Although we could not assess prescription appropriateness, the high prevalence of SSRI/SNRI-related DDIs observed in our study, together with evidence of antidepressant overuse reported in the literature [37], highlight the need for greater vigilance and improved risk management by GPs. Secondly, antiplatelets accounted for 23% of all DDIs. Evidence shows that adding an antiplatelet to a DOAC doubles bleeding risk, without any clear benefit in terms of stroke prevention or mortality [1,7,35]. Current guidelines restrict dual therapy to up to 12 months only in selected AF patients, with acute coronary syndrome (ACS) or undergoing uncomplicated percutaneous coronary intervention (PCI), to minimize major bleeding [1]. Although our data did not capture clinical indications for antiplatelet use, one study found that only 8% of AF patients on DOAC-antiplatelet therapy had guideline-consistent indications [38]. Thirdly, NSAIDs represented one in five DDIs, reflecting ongoing misconceptions about DOAC safety [39,40]. Their concomitant use has been associated with higher bleeding risk beyond GI

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bleeding [7,38–42]. Before prescribing NSAIDs, GPs should carefully weigh benefit-risk and consider safer alternatives such as paracetamol [27]. When NSAIDs are unavoidable, the lowest effective dose for the shortest duration is recommended [6,27,28]. Given their over-the-counter (OTC) availability, reinforcing warnings to prescribers and patients is critical [27,40]. Finally, in our study, nearly half of high-bleeding-risk patients (i.e., HAS-BLED score ≥ 3) did not receive PPI co-prescriptions when a DDI involved SSRIs/SNRIs, antiplatelets, or NSAIDs to reduce the risk of GI bleeding, although this does not fully eliminate risk [43]. However, these results should be interpreted with caution, given the variability in recommendations. Some guidelines [6,43], expert consensus statements [28], and observational studies [28,39] recommend PPI use in the presence of these PD-DDIs to provide gastric protection and reduce GI bleeding risk, whereas the 2024 ESC guidelines emphasize that PPI use should be tailored to individual bleeding risk rather than applied universally [1].

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Regarding logistic regression analyses, differences between univariate and multivariable analyses were observed. Although sex was associated with having at least one PD–DDI in univariate analysis, this association was no longer observed after adjustment in the multivariable model. This change is likely explained by confounding with age, as women were disproportionately represented in older age groups, particularly among patients aged ≥85 years (13.0% vs 9.9% in men; $p<0.001$), whereas they were less represented in younger age categories (<74 years: 13.1% vs

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22.7% in men; p<0.001). Furthermore, adjustment for the CHA_2DS_2-VASc score, which incorporates both age and sex, may have further attenuated any independent effect of sex. These findings are consistent with the rationale underlying the 2024 ESC guidelines [1], which no longer consider female sex as an independent risk factor but rather as an age-dependent risk modifier. In this context, the disappearance of the association after adjustment supports the notion that the observed effect of sex is largely driven by its interaction with age and comorbidity burden, rather than reflecting an independent contribution.

After multivariable adjustment, factors associated with higher odds of having at least one PD-DDIs in GP-issued prescriptions were a higher CHA_2DS_2-VASc score, receiving multiple DOAC types over the year as compared to apixaban, and age <65 years whereas the use of edoxaban as compared to apixaban was associated with lower odds.

This association observed for edoxaban compared with apixaban remains difficult to explain, as no differences in patient characteristics were identified and pharmacodynamic interaction profiles are expected to be similar across DOACs. Unmeasured patient- or prescriber-related factors may therefore partly account for this finding.

The use of multiple DOACs, compared with apixaban alone, was associated with higher odds of having at least one PD-DDI. Patients who switched between different DOACs may represent a subgroup at higher risk of DDIs. Although one possible explanation could be higher clinical

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complexity, we specifically explored whether these patients differed from non-switchers in terms of baseline characteristics. No meaningful differences were observed regarding comorbidities or risk profiles, including CHA_2DS_2-VASc score, history of bleeding or stroke, HAS-BLED score, sex, or age, nor in terms of co-medication burden or polypharmacy. This suggests that the increased risk of DDIs is unlikely to be solely explained by differences in patient profiles. Instead, DOAC switching may reflect periods of therapeutic transition or instability, during which treatment regimens are adjusted and the risk of overlapping or interacting prescriptions may be higher. In addition, switching may occur in response to prior adverse events or suspected interactions [44,45], raising the possibility of reverse causation. Finally, transitions between treatments may also increase the risk of fragmented prescribing, particularly when multiple prescribers are involved, thereby contributing to a higher likelihood of DDIs.

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The observation that patients over 65 years of age exhibit fewer PD-DDIs than younger individuals may seem counterintuitive. A plausible explanation includes the increased GP vigilance in older people who are often polymedicated and could reflect more frequent medication reviews. Conversely, a less favorable hypothesis might involve a survival effect: older patients with fewer PD-DDIs, and consequently fewer adverse drug events, are more likely to remain in the population.

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Regarding CHA_2DS_2-VASc, one explanation could be that higher scores reflect more comorbidities including coronary artery disease (present in 16.4% of our cohort), for which antiplatelets tend to be prescribed.

Our study has several strengths and limitations. The main strength lies in the use of real-world primary care data. Firstly, the THIN database includes data from a representative panel of the Belgian population, enabling nationwide extrapolation. Secondly, our NVAF population was not limited to a specific subgroup (e.g. patients at high thromboembolic risk, new DOAC users, or older people). Thirdly, to our knowledge, this is the first study to evaluate GPs' prescriptions of DOACs in Belgium. Fourth, given that the definition of DDIs relies on the DOAC and the interacting medication being prescribed within the same week — and therefore simultaneously — we can be confident that the same GP is responsible for the DDI. However, this study has several limitations. Drug identification relied on GP prescription data; therefore, there was no possibility to check actual medication intake. Some patients may not have collected their prescriptions or adhered to their treatment, potentially leading to some degree of misclassification, a common problem in all observational studies. Moreover, because prescriptions from specialists and OTC medications were not available, DDIs may be underestimated. Furthermore, we had no information on the DDI alert level configured by GPs in the prescription software, and therefore we cannot determine whether alerts were ignored, acknowledged, or not received. Finally, as community pharmacists actively detect and

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manage DDIs in the outpatient setting [9], the identified DDIs are only potential and may have already been addressed, and therefore may no longer be present.

Conclusion

Among GPs' prescriptions involving DOAC, about 18% included at least one DDI with one in five patients affected. Notably, around 90% of the DDIs identified were pharmacodynamic in nature. The drug classes most frequently implicated were SSRIs/SNRIs, followed by antiplatelet agents and NSAIDs. Prioritizing the identification and review of these high-risk associations may support safer anticoagulation prescribing in primary care.

DATA AVAILABILITY

The data of this study are available from GERS DATA but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data is, however, available from authors upon reasonable request and with permission of GERS DATA.

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AUTHOR CONTRIBUTIONS

VF and SH contributed to the conception and design of the study. VF performed the data analysis and wrote the first draft of the manuscript. SH, LZ and AS provided a critical review of the manuscript. All authors have read and approved the final manuscript.

ADDITIONAL INFORMATION

Conflicts of interest: The authors have no competing interests to declare that are relevant to the content of this article.

LEGENDS FOR TABLE AND FIGURES

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Table 1. Baseline characteristics of direct oral anticoagulant (DOAC) users (N=5,637).
Table 2. Distribution of drug-drug interactions (DDIs) involving direct oral anticoagulants (DOACs) by drug classes among patients with a DOAC prescription issued by general practitioners.
Table 3. Distribution of drug-drug interactions (DDIs) involving direct oral anticoagulants (DOACs) by drug classes, as identified on all prescriptions issued by general practitioners (N= 13,334) and among all DDI found in prescriptions (N=2,449).
Figure 1. Flow chart describing the sample selection.
AF: atrial fibrillation; DOAC: direct oral anticoagulants; NVAF: non-valvular atrial fibrillation; THIN: The Health Improvement Network

Figure 2. Factors associated with having at least one pharmacodynamic interaction with direct oral anticoagulants (DOAC) among patients with non-valvular atrial fibrillation in multivariable logistic regression (N=5,637).
*Mixed: patients who took several types of DOAC during the year
aOR: adjusted odds ratio; DOAC: direct oral anticoagulant; PD-DDI: pharmacodynamic drug-drug interaction

TABLES

Table 1:

Patient characteristics	**DOAC users, n (%) or mean ± SD and median [P25, P75]**
	(N = 5,637)
Male	3,011 (53.4)
Age at baseline	77.0 ± 9.7 78 [71, 84]
<65 years	554 (9.8)
65-74 years	1,462 (25.9)
75-84 years	2,330 (41.3)
≥ 85 years	1,291 (22.9)
Comorbidities at baseline	
Cancer	550 (9.8)
Chronic pulmonary disease	2,045 (36.3)
Congestive heart failure	1,476 (26.2)
Coronary heart disease	924 (16.4)
Dementia	182 (3.2)
Diabetes	1,388 (24.6)
Epilepsy	145 (2.6)
Inflammatory Bowel Disease	57 (1.0)
Acid-related gastrointestinal disease	1999 (35.5)
History of bleeding	301 (5.3)
History of ischemic stroke, TIA, arterial systemic embolism	584 (10.4)
Hypertension	4,406 (78.2)
Liver disease	103 (1.8)
Peripheral vascular disease	157 (2.8)
Psychiatric disorders except dementia	1,374 (24.4)

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Renal disease	1,525 (27.1)
Risk scores at baseline	
CHA_2DS_2-VASc score	3.7 ± 1.5 4 [3, 5]
0-1	393 (7.0)
2	804 (14.3)
3	1,397 (24.8)
≥4	3,043 (54.0)
HAS-BLED score	2.2 ± 0.9 2 [2, 3]
0-1	1,085 (19.2)
2	2,492 (44.2)
≥3	2,060 (36.5)
Charlson Comorbidity Index Score	5.2 ± 2.1 5 [4, 6]
0-2	410 (7.3)
3-4	1,854 (32.9)
5-6	1,967 (34.9)
≥7	1,406 (24.9)
Medication history at baseline	
Number of medications	5.7 ± 3.0 5 [4, 7]
Polypharmacy (≥5 drugs)	3,497 (62.0)
Lipid modifying agents	2,563 (45.5)
Antihypertensive drugs	4,525 (80.3)
Proton pump inhibitors	1,793 (31.8)
NSAIDs	185 (3.3)
Antiplatelet agents	428 (7.6)
Antidiabetic drugs	1,133 (20.1)
Antiarrhythmics	1,422 (25.2)
Antiepileptics	157 (2.8)
Psychotropic drugs	1,735 (30.8)

The term “at baseline” corresponds to the patient's index date. Details of the ICD-10 codes used for diagnostics and ATC codes used for drugs are presented in *Supplementary Table S4.*

DOAC: direct oral anticoagulant; NSAIDs: non-steroidal anti-inflammatory drug; TIA: transient ischemic attack.

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Drug classes at patient level	Among patients prescribed apixaban (N= 2,254)	Among patients prescribed edoxaban (N= 1,407)	Among patients prescribed rivaroxaban (N= 1,436)	Among patients prescribed dabigatran (N= 578)
	n (%)	n (%)	n (%)	n (%)
Overall DDIs rate	535 (23.7)	257 (18.3)	359 (25.0)	152 (26.3)
Pharmacokinetic interactions				
Overall PK-DDIs	37 (1.6)	20 (1.4)	37 (2.6)	18 (3.1)
CYP3A4 and/or P-GP inhibitors	25 (1.1)	12 (0.9)	23 (1.6)	17 (2.9)
CYP3A4 and/or P-GP inducers	12 (0.5)	8 (0.6)	14 (1.0)	1 (0.2)
Pharmacodynamic interactions				
Overall PD-DDIs	512 (22.7)	243 (17.3)	328 (22.8)	143 (24.7)
SSRI	197 (8.7)	89 (5.9)	129 (9.0)	51 (8.8)
SNRI	49 (2.2)	22 (1.6)	40 (2.8)	27 (4.7)
Platelet aggregation inhibitors (heparin excluded)	154 (6.8)	68 (4.8)	83 (5.8)	37 (6.4)
NSAID	134 (5.9)	78 (5.5)	96 (6.7)	44 (7.6)
Direct thrombin inhibitors	2 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Direct Factor Xa inhibitors	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Heparin group	11 (0.5)	7 (0.5)	8 (0.6)	4 (0.7)
Hypnotics and sedatives	14 (0.6)	9 (0.6)	6 (0.4)	0 (0.0)
Enzymes (bromelain, pepsin, protease, peptidase)	4 (0.2)	4 (0.3)	3 (0.2)	2 (0.3)
Prostaglandins	3 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
VKA	2 (0.1)	1 (0.1)	3 (0.2)	0 (0.0)

Table 2:
One patient can have several DDIs among the same prescription.
The co-prescription of a DOAC with a VKA, heparin, direct thrombin inhibitors, or direct factor Xa inhibitors most likely reflects a transitional prescribing period, such as a switch from a VKA to a DOAC.
Details of the ATC codes used for drug interactions are presented in *Supplementary Table S3.*
CYP3A4: cytochrome P450 3A4; DDI: drug-drug interactions; DDIs: drug-drug interactions; DOAC: direct oral anticoagulant; NSAID: non-steroidal anti-inflammatory drug; P-GP: permeability-glycoprotein; PD-DDIs: pharmacodynamic drug-drug interactions; PK: pharmacokinetic drug-drug interactions; SNRI: serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; VKA: vitamin K antagonist

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Table 3:

Drug classes at prescription level	Among all DOAC prescriptions* n (%)	Among all DDI found in prescriptions n (%)
	N= 13,334	**N=2,449**
Pharmacokinetic interactions	*205 (1.5)*	*209 (8.5)*
CYP3A4 and/or P-GP inhibitors	135 (1.0)	135 (5.5)
CYP3A4 and/or P-GP inducers	70 (0.5)	74 (3.0)
Pharmacodynamic interactions	*2,174 (16.3)*	*2,240 (91.5)*
SSRI	823 (6.2)	826 (33.7)
SNRI	256 (1.9)	256 (10.5)
Platelet aggregation inhibitors (heparin excluded)	540 (4.0)	554 (22.6)
NSAID	430 (3.2)	479 (19.6)
Hypnotics and sedatives	48 (0.4)	48 (2.0)
Heparin group	33 (0.2)	33 (1.3)
Enzymes (bromelain, pepsin, protease, peptidase)	25 (0.2)	25 (1.0)
VKA	8 (0.1)	8 (0.3)
Prostaglandins	5 (<0.1)	5 (0.2)
Direct thrombin inhibitors	3 (<0.1)	3 (0.1)
Direct Factor Xa inhibitors	3 (<0.1)	3 (0.1)

*One prescription may contain several DDIs

Details of the ATC codes used for drug interactions are presented in *Supplementary Table S3.*

CYP3A4: cytochrome P450 3A4; DDI: drug-drug interactions; DOAC: direct oral anticoagulant; NSAID: non-steroidal anti-inflammatory drug; P-GP: permeability-glycoprotein; SNRI: serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; VKA: vitamin K antagonist

FIGURES

Figure 1:

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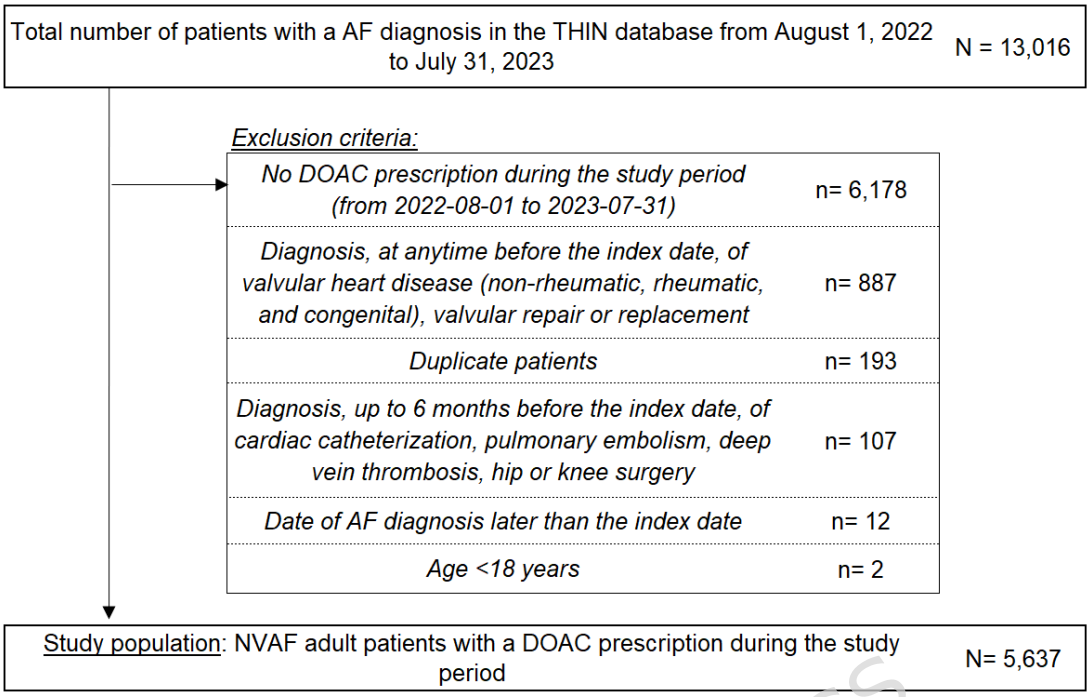


Figure 2:

