Gender Related Differences in Gastrointestinal Bleeding With Oral Anticoagulation in Atrial Fibrillation

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Abstract

Background: DOACs are characterized by a higher incidence of gastrointestinal bleeding and this may be different among males and females. Female patients were underrepresented in the DOAC pivotal trials. We aimed to assess real-world differences in gastrointestinal bleeding with oral anticoagulants (DOACs and VKAs) among males and females with atrial fibrillation.

Methods: We performed a population-based retrospective analysis on linked administrative claims. Atrial fibrillation patients of 65 years and above were considered. Bleeding risk factors were assessed through HASBED and previous history of gastrointestinal disease. A time-to-event analysis compared gastrointestinal bleeding between males and females.

Results: The overall cohort consisted of 15338 (55% female) DOAC and 44542 (50% female) VKA users. Most of the patients showed HASBED ≥2. Incidence rate of GI bleeding was higher in females as compared to males among DOAC users (0.90% vs 0.59%), and significant gender difference in GI bleeding was found, after adjustment, in the Cox regression analysis (HR 1.48, 95%CI 1.02-2.16). In the VKA group, no significant difference among genders was found in the time-to-event analysis.

Conclusions: Our data suggest that female patients treated with DOACs have a higher risk of GI bleeding versus male patients; this difference is not observed in VKA patients.

Keywords

DOACs, GI bleeding, gender differences, atrial fibrillation, real-life

Introduction

There is an increasing body of literature showing that gender differences exist in anticoagulation therapy response in the setting of atrial fibrillation (AF).¹⁻⁸ Female gender per se is an independent risk factor for stroke in AF patients, albeit only in the presence of other risk factors.⁹,¹⁰ There is uncertainty whether women are at higher risk of adverse events from oral anticoagulation with respect to men,¹¹⁻¹⁴ although this evidence derives mostly from studies in the pre-DOAC era.¹⁵⁻¹⁸

There is perception that women have a higher risk of bleeding complications with warfarin,¹⁵ possibly due to pharmacodynamics, pharmacokinetics,¹⁶,¹⁷ and difficulties in maintaining an adequate percentage of time in therapeutic range (TTR).¹⁶ The introduction of direct oral anticoagulants (DOACs), has revolutionized anticoagulation in atrial fibrillation, but how this translates in gender related outcomes remains uncertain.⁷

DOACs, have different pharmacologic properties with respect to vitamin K antagonists (VKAs), and theoretically offer a more stable anticoagulant effect, the TTR issue has been scattered, but other gender related issues might come to play.¹

DOACs in AF seem to be associated with less major bleeding or intracranial bleeding in both genders,¹⁹ at the cost of an increased risk of gastrointestinal bleeding.²⁰ The safety benefit is retained in women⁷ while the risk of gastrointestinal bleeding with DOACs versus VKAs is comparable between both sexes.⁵

Data on gender differences with DOACs mainly come from post-hoc ancillary analyses of randomized trials.⁷ There is consolidated evidence that DOACs have a higher risk of gastrointestinal (GI) bleeding,¹⁹ however, whether this risk is different in male and female is less clear.⁵,²⁰,²¹
The aim of this population-based cohort study is to provide real-world evidence on gender differences in the gastrointestinal bleeding of DOACs and well-managed warfarin treatment.

**Methods**

We performed a population-based retrospective analysis on linked administrative claims in the Veneto Region, Italy, using regional health information systems including the drug prescription database and the regional inpatients register. The drug prescription database stores information on drug Anatomical Therapeutic Chemical (ATC) classification, forms and quantities dispensed. The regional inpatients register stores data on all hospital admissions and discharge dates (both from private and public hospitals), and discharge diagnoses coded according to the International Classification of Disease, 9th Revision, Clinical Modification (ICD9-CM).

**Patient Identification and Exposure**

We enrolled patients receiving oral anticoagulants, VKAs (ATC B01Axx) or DOACs (dabigatran B01AE07, rivaroxaban B01AF01, apixaban B01AF02, edoxaban B01AF03), in the period July 1, 2013 to September 30, 2017. The first prescription of oral anticoagulants (DOACs or VKAs), or index date, identified the date of enrolment in the cohort. We excluded from enrolment individuals with any dispensed prescription of OACs in the 12 months preceding the index date. Patients with mechanical heart valves, mitral stenosis, venous thromboembolism and other indications different from atrial fibrillation were excluded using diagnoses from hospital discharge records. We adopted the as treated (AS) approach, where exposure was calculated from the index date until the absence of a new prescription by the end of a 60-day period from the last identified index medication fill (grace time), occurrence of an endpoint, or the end of follow up, whichever came first. In this setting, we measured drug exposure in terms of defined daily doses (DDD). The number of DDD was converted to the number of days the patient was treated, counting 1 DDD per day and distributing all available DDDs to days of follow-up (including the days covered by the last prescription). All analyses were performed on routinely collected health records by previous anonymization process that allowed linkage of archives but without any possibility of identification of individuals. There was no direct patient involvement in this study.

**Baseline Demographics and Clinical Features of Patients**

Demographics were recorded at the time of enrolment in the cohort using data stored on the health information systems. Comorbidities of interest were diabetes, congestive heart failure, cerebrovascular disease, peripheral and carotid artery diseases, hypertension, myocardial infarction, coronary bypass graft and percutaneous coronary intervention, chronic renal disease, chronic liver disease, history of prior major bleeding, previous hospitalization for GI disease and diagnosis of cancer. Assessed drugs of interest included concomitant prescription of antiplatelet agents, nonsteroidal anti-inflammatory drugs, and antihypertensive drugs. Patients were stratified in 2 categories according to a modified bleeding score (HAS-BED), since the value of INR was not available.

**Endpoint Definition**

Study endpoints were gender differences for major GI bleeding with DOACs and VKAs. GI bleeding identified from hospital discharge records using the Cunningham algorithm for automated database definition of serious bleeding related to oral anticoagulant use. Endpoints were identified by inpatient hospital relevant primary and secondary discharge diagnoses that included ICD codes of interest.

**Statistical Analysis**

We assessed the incidence of endpoints on the NOACs and VKAs cohorts. The rate of events for the assessed endpoints is expressed as number per 100 patient-years. A time-to-event analysis was performed for gastrointestinal bleeding and analyses were expressed as Kaplan-Meier curves, with significance assessed by means of the log-rank test. Cox regression was used to compare event rates by gender with results expressed as hazard ratios (HR) with 95% confidence intervals (CI). We performed a univariate analysis to identify those variables significantly correlated to the outcome to be included in the model. We performed a goodness of fit assessment by the Groenneby and Borgan test. Furthermore, we also performed the test for the proportional-hazards assumption.

**Results**

During the study period, we identified 59880 naïve to anticoagulation patients with non-valvular AF. Of these, 15338 were on DOACs (dabigatran, rivaroxaban, apixaban, edoxaban) and 44542 on VKAs. Female population represented 51.8% of the DOACs group and 47.5% of the VKAs group. Baseline and clinical characteristics of the study population stratified by gender and by anticoagulant use are shown in Table 1.

The mean age of the cohort was 77.8 for male and 80.3 for female in the DOACs group and 77.1 for male and 79.4 for female in the VKAs group. Most patients of both genders and among DOAC and VKA belonged to the 75-84 age group. HASBED score was higher among female patients in both DOAC and VKAs group.

As all the selected patients have a HASBED score of at least 1 being all older than 65 years of age, we decided to select patients with HASBED of 2 or above as our study population.

At univariate analysis in the DOACs group (Table 2), the variables significantly associated to GI bleeding were: age >85 years, gender, history of GI disease, congestive heart
failure, history of bleeding, myocardial infarction and peripheral artery disease.

Follow up for females in the VKAs and DOACs groups was 16277 and 10888 patient-years, respectively; in males 20609 and 10246 patient-years in the VKAs and DOACs groups, respectively. GI bleeding was more frequent among females as compared to males in DOAC users (0.90 per 100 patient-years vs 0.59 per 100 patient-years, HR 1.51, 95% CI 1.05-2.19).

These results can be appreciated in the Kaplan-Meir curves in which female DOAC users show higher GI bleeding with respect to males (Figure 1 panel A). Furthermore, this finding was statistically significant after adjustment for the variables found correlated with the outcome at univariate analysis: HR 1.48, 95% CI 1.02-2.16. We performed the goodness-of-fit test that yielded a chi-square = 4.617 (P = 0.33); therefore, the predictions from the model were close to observed data. Furthermore, we performed a test for the proportional-hazards assumption that yielded a chi-square = 10.2 (P = 0.25); therefore, the Cox model was properly applied.

In the VKAs group, GI bleeding was more frequent among males as compared to females (0.61 per 100 patient-years vs 0.50 per 100 patient-years, HR 0.82, 95% CI 0.67-1.01), although the finding was not statistically significant (Figure 1, panel B).

**Discussion**

In this population-based study we found that there are gender related differences in the risk of GI bleeding with DOACs and VKAs. Female patients treated with DOACs showed higher rates of GI bleeding as compared to male patients. This was
not the case among patients treated with VKAs where male patients had higher incidence rate of GI bleeding. There is conflicting data with gender related bleeding with oral anticoagulation in the setting of atrial fibrillation. In the VKA era, data suggested that the risk of major bleeding among male and female patients was comparable. Poli et al. also reported no difference between genders in bleeding risk in VKA-treated patients with atrial fibrillation. On the other hand, Penttilä et al. found lower risk of bleeding among AF females treated with proper warfarin therapy. The introduction of direct oral anticoagulants (DOACs) has changed the anticoagulation scenario in atrial fibrillation patients. They have shown to be at least as effective as warfarin but safer than warfarin with respect to intracranial hemorrhage (ICH) and, in most cases, in reference to all major bleeding in randomized controlled trials and in the real-life setting. GI bleeding has been reported to be more frequent with DOACs in both registration trials and real-world data. All major trials of DOACs were not designed or statistically powered to conduct sex-specific analyses. Moreover, in the DOAC registration trials, only 36% of all participants were female, thus gender differences in the outcomes might have been overlooked. The gap of gender representation in trials translates in difficulties in optimization of gender-specific oral anticoagulation therapy in real-world practice. Pancholy et al. found a lower risk of major bleeding in women when compared with men in the DOAC patients. Conversely, women on warfarin had a similar risk of major bleeding. Of note, major bleeding was a composite of multiple types of bleeding outcomes, thus, no conclusions can be drawn for GI bleeding. Proietti et al. pooled the results from the DOAC groups of different trials and found that women were more protected from major bleeding. Once again, major bleeding was a composite of bleeding sub-types.

In the present real-world study, we concentrated on gender differences in the GI bleeding with DOACs and VKAs. We found a higher risk among female patients as compared to male patients treated with DOACs, with an inverted trend among VKA users. Similar results were reported by Shantha et al., that found GI bleeding to be higher among women treated with DOACs versus men. The reasons for gender related effects of DOACs remain unknown. Fluctuations of anticoagulation levels have been proposed as a mechanism with VKAs, however, this does not translate in gender related differences in bleeding. In our study, by comparing gender differences among drug-classes (DOACs vs VKAs), INR fluctuations do not influence the final results.

A real-life study reported that HASBLED score has a good predictive power not only with major bleeding, but also in discriminating GI bleeding. Other than HASBLED, we assessed variables that showed to be significantly related to GI bleeding were age >85 years, history of GI disease, history of bleeding, peripheral artery disease and myocardial infarction. Others have reported that risk factors for bleeding other than those assessed by the HASBLED score might also come to play, but further research is needed for confirmation. The gender effect was not found to interact with bleeding outcomes when HASBLED ≥4 while age attenuated the benefit of DOACs over warfarin. Our data, are in line with those from other studies and reflect the fact that the risk of major bleeding is higher in patients with more comorbidities. What we add to the present evidence is that the risk of GI bleeding is higher in more comorbid women treated with DOACs. Possibly the history of GI bleeding should be assessed alongside the history of major bleeding. Furthermore, no differences with PPIs were observed possibly due to the fact that clinicians have perceived the recommendations on the use of PPIs with oral anticoagulation especially in high-risk populations.

Our study has limitations largely shared by all real-world studies. Potential selection bias and risk of confounding that are overcome only by randomization. However, we ran a goodness of fit analysis that found no impact on the overall results. Some studies of administrative data have reported a high proportion of false positives for VTE, but this is less the case for AF. Furthermore, in our study, we started selection from oral anticoagulation prescription, thus reducing the risk of unreported AF diagnosis in the hospital discharge records. Our
enrollment began in 2013 and practice changes with oral anticoagulation might have occurred. However, VKA reported adherence is similar to that of DOAC in the same cohort.

Finally, we treated DOACs as a class of drugs to increase the statistical power and thus balance for the known differences among individual DOACs in terms of mechanisms of action and pharmacokinetics including sensitivity to weight, renal function, and drug interactions.

**Conclusion**

Our data suggest that female patients treated with DOACs have a higher risk of GI bleeding versus male patients; this difference is not observed in VKA patients. When treated with DOACs, female patients with multiple comorbid conditions should be actively followed with frequent complete blood cell count and stool tests. While our study might help clinicians tailor their choice of anticoagulants in men and women, further studies exploring possible mechanisms and predictors are warranted.

**Author Contributions**

Eliana Ferroni and Gentian Denas contributed equally to this work. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

**Declaration of Conflicting Interests**

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