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Safety of apixaban in combination with dronedarone in patients with atrial fibrillation

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ABSTRACT

Background: There have been concerns about bleeding risks for patients with atrial fibrillation treated with dronedarone in combination with new oral anticoagulants (NOACs). The aim of the study was to compare the bleeding risks with the apixaban + dronedarone and warfarin + dronedarone combinations.
Method: Retrospective study of Swedish nationwide health registers. All patients with atrial fibrillation who used dronedarone in combination with apixaban or warfarin during 2013–2016 were identified. Two propensity matched cohorts of each 1681 patients were compared. The main endpoint included intracranial bleeding, bleedings with hospitalization and fatal bleedings.
Results: Bleedings thus defined occurred at rates of 1.31 and 2.14 per 100 years at risk with the apixaban and warfarin combinations respectively ($p = 0.121$). The hazard ratio with the apixaban combination was 0.66 (CI 0.35–1.23) compared to the warfarin combination. No significant differences were seen regarding secondary endpoints.
Conclusion: Major bleedings were rare among patients with atrial fibrillation treated with dronedarone in combination with apixaban or warfarin. No significant differences in favour of either drug combination were found.

1. Introduction

Patients with non-permanent atrial fibrillation (AF) are frequently treated with dronedarone as a way to prevent or reduce recurrences of arrhythmia. Most AF patients also have an indication for an oral anticoagulant for stroke prevention. There have been concerns about increased bleeding risks when dronedarone is combined with the newer oral anticoagulants (NOACs). Dronedarone is a strong P-glycoprotein (PGP) inhibitor and also an inhibitor of CYP3A4. According to the summary of product characteristics (SmPC), apixaban should not be used together with drugs which are *strong* inhibitors of both PGP and CYP3A4 [1] because this could increase the bleeding risk due to increase in the apixaban concentration. As dronedarone only is a moderate inhibitor of CYP3A4 there is no formal contraindication or warning in the European SmPC [1] or the USA FDA label [2] against the combination. There are no published pharmacokinetic or pharmacodynamic data for the combination and hospitals in Sweden have interpreted the available information in different ways; some have used the apixaban combination while others have continued with warfarin.

The aim of this study was to compare the occurrence of major bleeding among patients treated with dronedarone in combination with either apixaban or warfarin in a real-life setting.

2. Methods

The study used retrospective data from population-wide Swedish health registers; the Dispensed Drug Register, the Patient Register and the Cause of Death register. Data was linked by civic identification numbers given to all permanent residents in Sweden irrespective of citizenship. The validity of these registers is high according to validation studies [3–8] and they are frequently used for epidemiological studies.

2.1. Study population

All individuals with a diagnosis of AF in the Patient register who received dronedarone, apixaban or warfarin between May 29, 2013, and December 31, 2016 were identified from the national registers. Periods with concomitant use of dronedarone + apixaban or dronedarone + warfarin were identified. The first day of co-treatment with either combination defined index date and start of follow-up. No exclusions were made (Fig. 1).

2.2. Drug exposure

The duration of dronedarone treatment was estimated from the number of dispensed tablets assuming 90% adherence to dosage instructions. The duration of warfarin treatment could not be assessed in the same way because dose requirements vary both between individuals and over time. Instead, warfarin exposure was approximated by the

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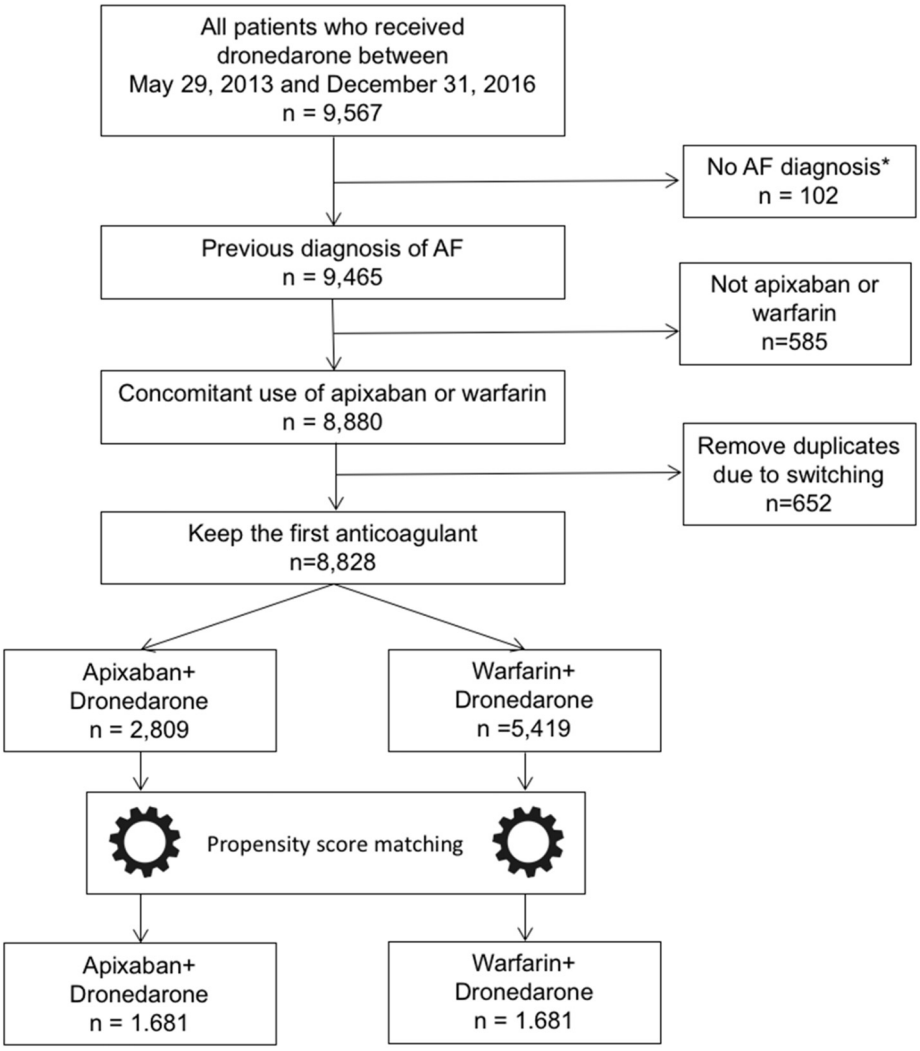

Fig. 1. Inclusions/exclusions.

frequency of refill dispenses. All days between refills were counted as days on treatment as long as the interval did not exceed 6 months. This was because the only available packet size of warfarin in Sweden could last up to 6 months in occasional low-dose patients [9]. If there was no refill within 6 months, or if there were no further refills, treatment was assumed to have stopped after three months. Dispensation of an oral anticoagulant other than the index drug was also considered as a marker of discontinuation. All days considered as treatment days were added up and used to estimate the date when treatment ended. This method was derived in a database of over 25,000 patients with known individual warfarin dosages and has previously been validated in the Swedish registries [9]. The refill based method was used for apixaban as well, although it meant a loss of detail regarding apixaban exposure. The reason for doing so was that the groups have to be assessed in the same way if comparisons are to be made. As a sensitivity analysis, apixaban exposure was assessed from dispensed quantities and dosage instructions. The results with the two methods turned out to be almost identical. The sensitivity analysis will therefore not be discussed further, but has been included in the online appendix.

2.3. Endpoints

Endpoint events were extracted from the Patient register and the Cause of Death register. The main bleeding endpoint was a composite of intracranial bleeds, fatal bleeds and hospitalization with a diagnosis of bleeding. The codes used to identify bleeds are listed in Appendix A. A previous validation study of the Swedish registers has shown that these codes confer a high positive predictive value for major bleedings [8]. Secondary bleeding endpoints were intracranial bleeds, fatal bleeds, any hospitalization with bleeding diagnosis, gastrointestinal bleeding with hospitalization, urogenital bleeding with hospitalization, other bleeding with hospitalization, open care visit with bleeding diagnosis and death from any cause.

2.4. Time at risk and censoring

Time at risk was counted from day 1 after index. The observation period ended December 31, 2016. Censoring was made at the specified bleeding endpoints, death, emigration, end of follow-up or drug discontinuation, whichever came first. Patients who switched treatment during the study remained in their original cohort but were censored at the switch. Analyses according to the drug combination at baseline without consideration of later changes (in analogy with the intention to treat principle) have also been made and are presented in the appendix.

2.5. Covariates

A list of covariates with definitions according to the ICD-10 coding system has been included in Appendix B and C. Medication before