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# Impact of dronedarone on the risk of myocardial infarction and stroke in atrial fibrillation patients followed in general practices in Germany☆

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ABSTRACT

*Background:* The goal of this study was to analyze the impact of dronedarone on the risk of myocardial infarction and stroke in atrial fibrillation (AF) patients followed in general practices in Germany.
*Methods:* This study included patients who had received a first prescription of dronedarone, amiodarone, flecainide, propafenone, or sotalol in 1258 general and 62 cardiology practices between January 2010 and March 2017 (index date). The main outcomes of this study were the percentages of patients with myocardial infarction and stroke in the dronedarone group and in the group of individuals who had received other antiarrhythmic drugs within six years of the index date. Cox proportional regression models were used to estimate the relationship between dronedarone and myocardial infarction and stroke.
*Results:* This study included 3498 individuals who had received dronedarone and 17,724 individuals who had received other antiarrhythmic drugs. After six years of follow-up, 3.9% of patients who had received dronedarone and 5.2% of patients who had received other antiarrhythmic drugs had been diagnosed with myocardial infarction (log-rank $p$-value = 0.002). At the end of the follow-up period, 7.4% of individuals with dronedarone prescriptions and 8.3% of those who had been prescribed other antiarrhythmic drugs had been diagnosed with a stroke (log-rank $p$-value = 0.003). Dronedarone was associated with a significant decrease in the risk of developing myocardial infarction (HR = 0.78) and suffering a stroke (HR = 0.84) compared to other antiarrhythmics.
*Conclusions:* In our study, dronedarone was associated with a lower risk of myocardial infarction and stroke in patients with AF compared to other antiarrhythmics.


## 1. Introduction

In 2010, there were around 34 million people with atrial fibrillation (AF) in the world [1]. In Germany, AF affects approximately 2% of the population [2], and the average cost of treatment per patient exceeds €500 each year, which highlights the significant impact of this cardiovascular condition in this country [3].

The treatment of AF involves the use of antiarrhythmic drugs. The goal of antiarrhythmic therapy is to reduce the frequency and duration of arrhythmic episodes [4]. Commonly prescribed antiarrhythmic drugs include amiodarone, flecainide, propafenone, sotalol, and dronedarone. Dronedarone is a benzofuran derivative that was launched in 2009 after the completion of an extensive clinical trial. It has similar electropharmacologic properties to amiodarone (i.e. increase of RR and QT intervals, decrease of maximum upstroke velocity or decrease in sinoatrial node automaticity), but different relative effects on ion channels [5,6]. Dronedarone was synthesized with multiple molecular changes to reduce its volume of distribution via a decrease in lipophilicity [7] and to reduce the potential of thyroid and pulmonary side effects [6,8,9].

Based on the clinical practice guidelines developed by the European Society of Cardiology, dronedarone is recommended for the prevention of recurrences of paroxysmal or persistent AF [10,11]. Of particular importance is the fact that dronedarone can be prescribed to patients with coronary heart disease or other structural diseases, such as left ventricular hypertrophy or valvular heart disease. In contrast to other

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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antiarrhythmic drugs such as flecainide, which are associated with an increased risk of proarrhythmia and sudden cardiac death after a myocardial infarction and are therefore not recommended in patients with CAD [12], dronedarone has been shown to reduce cardiovascular hospitalizations and death in non-permanent AF patients [13] and to prevent microvascular flow alterations in the left ventricle during AF [14,15]. In addition, dronedarone has been found to reduce the size of myocardial infarctions in porcine models [16]. Furthermore, a recent meta-analysis demonstrated a reduced stroke rate with dronedarone that was not present with any other anti-arrhythmic agent (OR 0.66, 95% CI 0.46 to 0.95, $p = 0.02$) [17]. This effect was largely corroborated by the results of the ATHENA trial. Finally, in a post-hoc analysis of the ATHENA trial, the use of dronedarone in patients with AF and coronary heart disease (CHD) reduced cardiovascular mortality, cardiovascular hospitalization, and first acute coronary syndrome [18].

Although the findings of the previous works on the topic are promising, the literature regarding the potential deleterious cardiovascular effects associated with the use of dronedarone has been conflicting

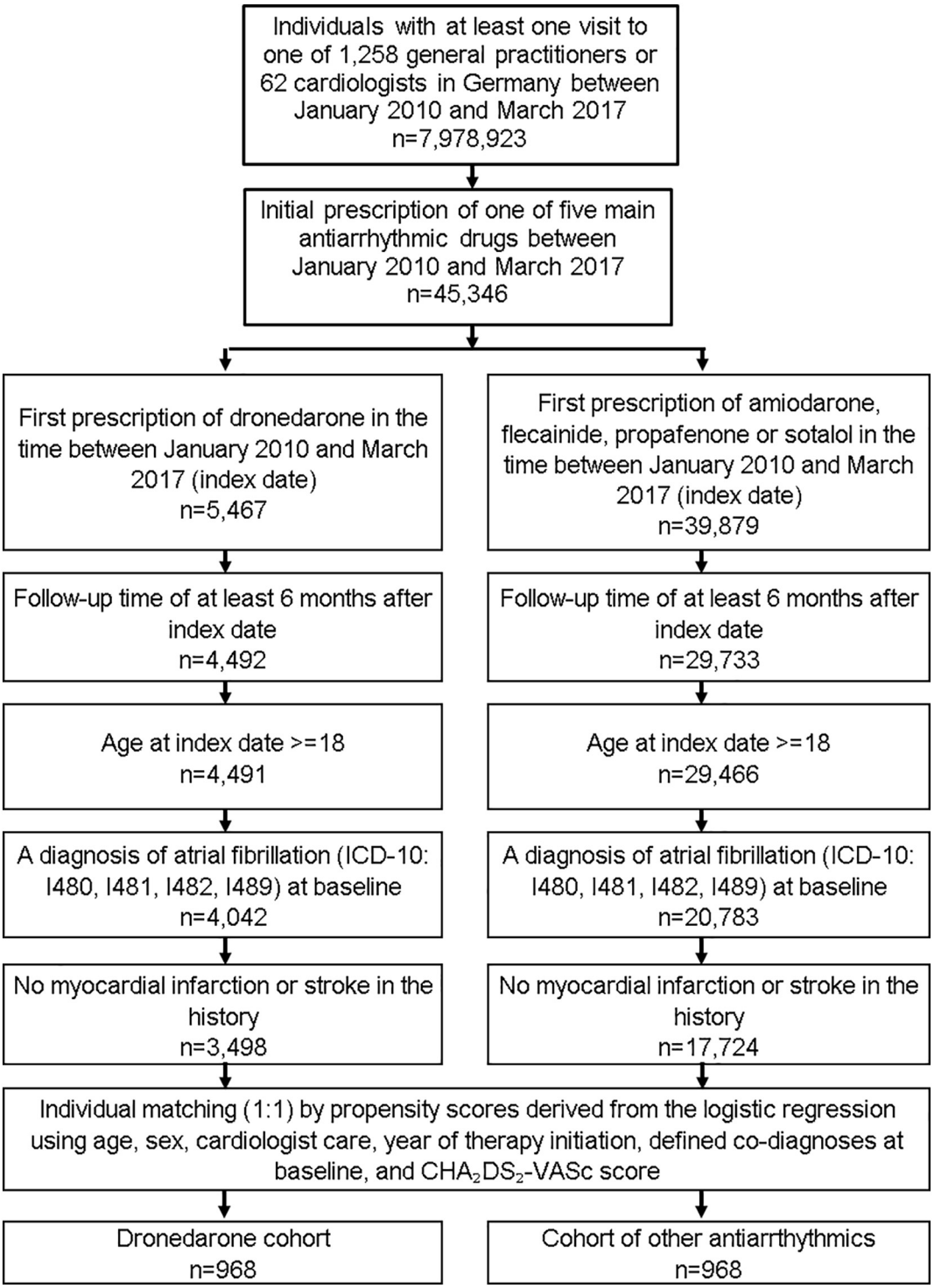


**Fig. 1.** Selection of study patients.

[19–23]. Of particular interest is a very recent analysis conducted by Friberg showing that major bleeding is rare among AF patients treated with dronedarone in combination with apixaban or warfarin [23]. Therefore, the goal of this study was to analyze the impact of dronedarone on the risk of myocardial infarction and stroke in atrial fibrillation patients followed in general and cardiology practices in Germany. Additionally, the incidence of the toxic liver disease was estimated.

## 2. Methods

### 2.1. Database

The Disease Analyzer database (IQVIA) compiles drug prescriptions, diagnoses, and basic medical and demographic data obtained directly and in anonymous format from computer systems used in the practices of general practitioners and specialists [24]. Diagnoses (ICD-10), prescriptions (Anatomical Therapeutic Chemical (ATC) Classification System), and the quality of reported data have been monitored by IQVIA based on a number of criteria (e.g., completeness of documentation, linkage between diagnoses and prescriptions). In Germany, the sampling methods used for the selection of physicians' practices were appropriate for obtaining a representative database of clinical practices [24]. Finally, the Disease Analyzer database has already been used in several studies focusing on cardiovascular diseases and cardiovascular drugs [25–27].

### 2.2. Study population

This study included patients who had received a first prescription of dronedarone, amiodarone, flecainide, propafenone, or sotalol in 1258 general and 62 cardiology practices between January 2010 and March 2017 (index date). Inclusion criteria were as follows: (i) follow-up of at least six months after the index date; (ii) age 18 or older on the index date; (iii) diagnosis of atrial fibrillation (ICD-10: I480, I481, I482, I489) on the index date; and (iv) no diagnosis of myocardial infarction (I21, I22, I23) or stroke (I63, I64, G45) in the patient's medical history. Patients were categorized into two different groups: the group of patients who had been prescribed dronedarone and the group of patients who had been prescribed other antiarrhythmic drugs (amiodarone, flecainide, propafenone, or sotalol; Fig. 1).

### 2.3. Study outcome and study covariables

The main outcomes of this study were the percentages of patients with myocardial infarction and stroke in the dronedarone group and in the group of patients who had received other antiarrhythmics within six years of the index date. Demographic variables included age, gender, and the period of therapy initiation (2010–2013 versus 2014–2016). Clinical variables included eight disorders diagnosed at baseline (other cardiac arrhythmias [I49], heart failure [I50], hyperlipidemia [E78], hypertension [I10], diabetes mellitus [E10, E11], renal insufficiency [N18, N19], peripheral artery disease [I73.9], and coronary heart disease [I25 with the exclusion of I25.2]), nine classes of drugs prescribed in the year prior to the index date (diuretics [EphMRA ATC: C03], beta blockers [C07], calcium channel blockers [C08], ACE inhibitors [C09A, C09B], angiotensin II antagonists [C09C, C09D], lipid-lowering drugs [C10], vitamin K antagonists [B01A], acetylsalicylic acid [B01C1], and non-vitamin K antagonist oral anticoagulants (NOAC) [B01E, B01F]), therapy duration in months, and the $CHA_2DS_2$-VASc score. The incidence of toxic liver disease (ICD 10: K71) was estimated and the changes in Gamma-GT values were calculated.

### 2.4. Statistical analysis

Descriptive statistics were obtained and differences in subject characteristics (dronedarone versus other anti-arrhythmic drugs) were assessed using Wilcoxon tests or chi-squared tests. Kaplan-Meier curves were performed to study the development of myocardial infarction and stroke in patients who had been prescribed dronedarone and those who had been prescribed other antiarrhythmic drugs within six years of the index date. As the two patient cohorts to be compared had different baseline characteristics, two methods were used to avoid confounding. In the first step, a multivariate Cox proportional regression model was used to estimate the relationship between defined antiarrhythmics and the risk of myocardial infarction and stroke in the original patient cohorts (3498 versus 17,724 patients). In the second step, each patient treated with dronedarone was matched (1:1) to a control (defined as a patient treated with dronedarone, flecainide, propafenone, or sotalol) based on propensity scores derived from the logistic regression using age, gender, cardiologist care, year of therapy initiation, defined co-diagnoses at baseline, and $CHA_2DS_2$-VASc score. A univariate cox regression analysis was then conducted for matched pairs. The main advantage of propensity score matching is that, after 1:1 matching, two very homogeneous cohorts can be compared. The disadvantage, however, is that, due to the large number of covariables, many patients are lost because no "partner" with the same characteristics for all variables can be found. The reduction in the number of patients leads to a loss of statistical power. Therefore, only 968 matched

**Table 1**
Baseline characteristics of study patients.

| Variable | Prior to 1:1 matching | | | After 1:1 matching | | |
|---|---|---|---|---|---|---|
| | Dronedarone | Others | *p*-Value | Dronedarone | Others | *p*-Value |
| N | 3498 | 17,724 | | 968 | 968 | |
| Age (mean, SD) | 68.9 (9.0) | 69.2 (11.2) | <0.001 | 69.6 (8.4) | 69.6 (8.4) | 1.000 |
| Age ≤50 (%) | 4.9 | 6.4 | 0.001 | 2.9 | 2.9 | 1.000 |
| Age 51–60 (%) | 14.6 | 14.5 | 0.855 | 12.5 | 12.5 | 1.000 |
| Age 61–70 (%) | 30.1 | 26.5 | <0.001 | 30.6 | 30.6 | 1.000 |
| Age 71–80 (%) | 40.6 | 39.1 | 0.102 | 47.7 | 47.7 | 1.000 |
| Age >80 (%) | 9.8 | 13.5 | <0.001 | 6.3 | 6.3 | 1.000 |
| Males (%) | 50.5 | 53.7 | <0.001 | 51.9 | 51.9 | 1.000 |
| Cardiologist care (%) | 34.2 | 25.3 | <0.001 | 38.0 | 38.0 | 1.000 |
| Therapy initiation between 2010 and 2013 | 73.8 | 57.2 | <0.001 | 73.9 | 73.9 | 1.000 |
| Therapy initiation between 2014 and 2016 | 26.2 | 42.8 | | 26.1 | 26.1 | |
| Co-diagnoses at baseline (%) | | | | | | 1.000 |
| Other cardiac arrhythmias (ICD 10: I49) | 34.8 | 35.3 | 0.559 | 34.6 | 34.6 | 1.000 |
| Heart failure (ICD 10: I50) | 29.9 | 35.1 | <0.001 | 19.3 | 19.3 | 1.000 |
| Hyperlipidemia (ICD 10: E78) | 34.5 | 32.3 | 0.016 | 31.1 | 31.1 | 1.000 |
| Hypertension (ICD 10: I10) | 66.6 | 64.1 | 0.005 | 60.4 | 60.4 | 1.000 |
| Diabetes (ICD 10: E10, E11) | 15.7 | 16.8 | 0.125 | 11.0 | 11.0 | 1.000 |
| Renal insufficiency (N18, N19) | 5.9 | 9.1 | <0.001 | 4.8 | 4.8 | 1.000 |
| Peripheral artery disease (I73.9) | 3.4 | 4.1 | 0.053 | 2.8 | 2.8 | 1.000 |
| Coronary heart disease (ICD 10: I25 excl. I252) | 27.5 | 27.5 | 0.966 | 23.6 | 23.6 | 1.000 |
| Therapy prescribed within 12 months prior to the index date (EphMRA ATC) (%) | | | | | | 1.000 |
| Diuretics (C03) | 22.6 | 34.2 | <0.001 | 14.1 | 14.1 | 1.000 |
| Beta blockers (C07) | 53.4 | 63.3 | <0.001 | 46.0 | 46.0 | 1.000 |
| Calcium channel blockers (C08) | 17.8 | 18.4 | 0.355 | 14.1 | 14.1 | 1.000 |
| ACE inhibitors (C09A, C09B) | 27.2 | 32.0 | <0.001 | 17.5 | 17.5 | 1.000 |
| Angiotensin II antagonists (C09C, C09D) | 20.1 | 20.4 | 0.705 | 15.3 | 15.3 | 1.000 |
| Lipid-lowering drugs (C10) | 23.0 | 24.5 | 0.031 | 18.6 | 18.6 | 1.000 |
| Vitamin K antagonists (B01A) | 30.2 | 26.6 | <0.001 | 20.7 | 20.7 | 1.000 |
| ASS (B01C1) | 15.0 | 15.0 | 0.904 | 12.4 | 12.4 | 1.000 |
| Non-vitamin K antagonist oral anticoagulants (NOAC) (B01E, B01F) | 16.0 | 24.5 | <0.001 | 11.1 | 11.1 | 1.000 |
| Therapy duration in months (mean, SD) | 24.6 (24.5) | 23.5 (23.1) | <0.001 | 25.5 (25.8) | 25.5 (25.8) | 1.000 |
| CHADs-VASc score (mean, SD) | 2.6 (1.7) | 2.7 (1.8) | 0.002 | 2.3 (1.7) | 2.3 (1.7) | 1.000 |

pairs were available for analysis. A $p$-value of <0.05 was considered statistically significant. All analyses were carried out using SAS 9.4 (SAS Institute, Cary, USA).

## 3. Results

### 3.1. Patient characteristics

The baseline characteristics of the study patients are displayed in Table 1. In total, 3498 individuals had received dronedarone and 17,724 individuals had received other antiarrhythmic drugs. The mean age was 68.9 years (SD = 9.0 years) in the dronedarone group and 69.2 years (SD = 11.2 years) in the group of patients who had been prescribed other anti-arrhythmic drugs. The proportions of men in the two groups were 50.5% and 53.7% respectively. The most frequent co-diagnosis at baseline was hypertension both in patients who had been prescribed dronedarone (66.6%) and in those who had been prescribed amiodarone, flecainide, propafenone, or sotalol (64.1%). In both groups, the drugs most commonly prescribed in the year prior to the index date were beta blockers (dronedarone: 53.4%; others: 63.3%).

### 3.2. Impact of dronedarone on myocardial infarction and stroke

Kaplan-Meier curves are shown in Fig. 2. After six years of follow-up, 3.9% of patients prescribed dronedarone and 5.2% of patients prescribed other antiarrhythmic drugs had been diagnosed with myocardial infarction (log-rank $p$-value = 0.002). By the end of the follow-up period, stroke had been diagnosed in 7.4% of individuals prescribed dronedarone and in 8.3% of those prescribed other molecules (log-rank $p$-value = 0.003). Table 2 shows the results of the Cox regression analyses. Dronedarone was associated with a significant decrease in the risk of developing myocardial infarction (HR = 0.78). Older age (age 71–80: HR = 1.76; age > 80: HR = 1.89), male gender (HR = 1.62), heart failure (HR = 1.76), peripheral artery disease (HR = 1.40), diabetes (HR = 1.26), coronary heart disease (HR = 1.75),

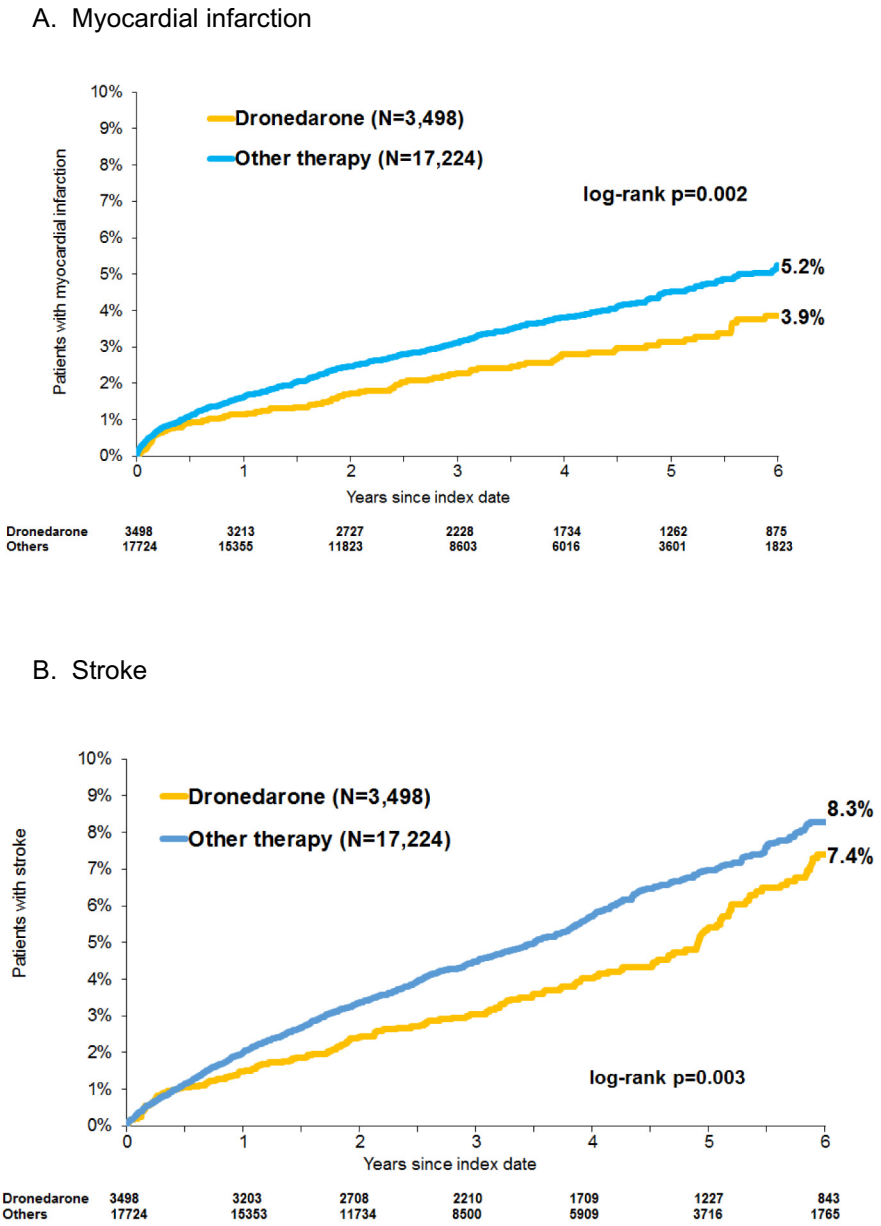


**Fig. 2.** Kaplan-Meier curves for time to diagnosis of myocardial infarction and stroke in patients treated with dronedarone and those treated with other antiarrhythmic drugs.

**Table 2**
Association between dronedarone therapy and myocardial infarction/stroke (Cox regression model).

| Variable | Hazard ratio (95% CI)[a] | *p*-Value |
|---|---|---|
| *Myocardial infarction* | | |
| Dronedarone versus other therapy | 0.78 (0.63–0.96) | 0.020 |
| Age 51–60 vs. age ≤50 | 1.26 (0.79–1.99) | 0.330 |
| Age 61–70 vs. age ≤50 | 1.42 (0.92–2.20) | 0.109 |
| Age 71–80 vs. age ≤50 | 1.76 (1.15–2.68) | 0.009 |
| Age >80 vs. age ≤50 | 1.89 (1.20–2.98) | 0.006 |
| Males versus females | 1.62 (1.38–1.91) | <0.001 |
| Heart failure | 1.76 (1.50–2.05) | <0.001 |
| Peripheral artery disease | 1.40 (1.06–1.84) | 0.017 |
| Diabetes | 1.26 (1.05–1.51) | 0.014 |
| Coronary heart disease | 1.75 (1.49–2.07) | <0.001 |
| Hyperlipidemia | 1.34 (1.09–1.64) | 0.006 |
| VKA therapy | 0.78 (0.66–0.92) | 0.004 |
| NOACs | 0.64 (0.46–0.88) | 0.007 |
| *Stroke* | | |
| Dronedarone versus other therapy | 0.84 (0.71–0.99) | 0.043 |
| Age 51–60 vs. age ≤50 | 1.67 (1.10–2.54) | 0.016 |
| Age 61–70 vs. age ≤50 | 2.02 (1.36–3.00) | <0.001 |
| Age 71–80 vs. age ≤50 | 2.70 (1.84–3.97) | <0.001 |
| Age >80 vs. age ≤50 | 3.91 (2.62–5.83) | <0.001 |
| Heart failure | 1.22 (1.07–1.38) | 0.003 |
| Beta blockers | 0.83 (0.72–0.95) | 0.008 |
| VKA | 0.82 (0.71–0.94) | 0.006 |
| NOACs | 0.79 (0.66–0.96) | 0.016 |

[a] Stepwise selection; only variables with a significant effect are displayed.

and hyperlipidemia (HR = 1.34) were found to be risk factors for myocardial infarction, whereas being followed in cardiology practices (HR = 0.50) and the prescription of vitamin K antagonists (HR = 0.78) and NOAC (HR = 0.64) were protective factors. Dronedarone was also associated with a decrease in the odds of developing myocardial infarction in different subgroups.

There was also a negative association between dronedarone and the risk of stroke (HR = 0.84). Risk factors for the development of stroke included older age (age 51–60: HR = 1.67; age 61–70: HR = 2.02; age 71–80: HR = 2.70; age > 80: HR = 3.91) and heart failure (HR = 1.22). By contrast, the use of beta blockers (HR = 0.83), vitamin K antagonists (HR = 0.82), and NOAC (HR = 0.79) were found to be protective factors. The negative association between dronedarone and the risk of stroke was subsequently shown in the subgroup analyses in 1906 matched pairs.

The reduced rate of stroke was evident despite a lower proportion of patients using NOAC therapy in the group of patients receiving non-vitamin K antagonist oral anticoagulants (NOAC) (16.0% vs. 24.5%, $p < 0.001$).

### 3.3. Incidence of toxic liver disease

There were no documented cases of toxic liver disease in patients prescribed dronedarone or other antiarrhythmic drugs. In 373 dronedarone patients and in 1855 patients treated with other antiarrhythmic drugs, Gamma-GT values were available within 6 months prior to and six months after the index date. In dronedarone patients Gamma-GT changed from 45.5 to 41.6 IU/L and in patients treated with other antiarrhythmic drugs from 52.2 to 48.1 IU/L. There was no significant difference between the value changes prior to versus after the index date between the two groups ($p = 0.185$).

## 4. Discussion

To the best of our knowledge, this is the first study that focuses on the incidence of myocardial infarction and stroke with dronedarone use in real-world clinical practice. This study, including >21,000 AF patients followed in general and cardiology practices in Germany, showed a negative association between dronedarone therapy and myocardial infarction, as well as between dronedarone therapy and stroke, after up to six years of follow-up. Our findings are consistent with those of a post hoc analysis conducted within the context of the ATHENA study, in which it was shown that the prescription of dronedarone was associated with a reduction in the risk of stroke [28]. Moreover, no toxic liver disease was documented in study patients.

There are major differences in patient characteristics between clinical trials [6,18,29–31] and real-world analyses [19,32], as clinical trials are designed to evaluate the efficacy and safety of a drug under ideal conditions. For example, clinical trials have specific inclusion or exclusion criteria, and ensure that patients have continuous follow-up and good compliance. In clinical practice, however, all patients can be analyzed, including patients with poor treatment compliance, and there is no need for specific exclusion criteria. Therefore, real-world analyses are of great importance for the study of the efficacy and safety of dronedarone.

In 2013, Gao et al., using data from 10,455 adults with AF or atrial flutter, observed that the use of dronedarone led to a decrease in the risk of cardiovascular events (HR = 0.59) and stroke (HR = 0.50) in the overall population, and consequently in patients without a history of congestive heart failure (cardiovascular events: HR = 0.42; stroke: HR = 0.45) [33]. In a study of 174,995 AF patients in 2014, Friberg showed that the annual mortality rate was lower in dronedarone users than in non-users (1.3% versus 14.0%) [19]. The fact that no sudden cardiac death and no liver failure-related death occurred in the group receiving dronedarone was particularly noteworthy. Finally, using regression analyses, it was estimated that the prescription of this antiarrhythmic drug was associated with a decrease in the risk of death (HR = 0.41), and this result was corroborated in a subgroup consisting of patients diagnosed with heart failure (HR = 0.40).

Diemberger et al. performed a meta-analysis of 12 randomized controlled trials and 7 observational studies that aimed to identify the differences between real-world practices and clinical trials in terms of any outcomes associated with dronedarone [21]. The authors found that dronedarone was not associated with increased all-cause mortality or cardiovascular mortality in randomized controlled trials, although there was significant heterogeneity in the sample studied. Observational studies also found that there was a trend toward a better survival rate with dronedarone, and the result became significant when the analysis was restricted to cardiovascular mortality. Finally, it was estimated that the heterogeneity found in randomized controlled trials was eliminated when the co-administration of digoxin and the prevalence of non-permanent atrial fibrillation were taken into consideration. These findings suggest that, although dronedarone should not be used in combination with digoxin, its prescription is not associated with an increased risk of death. In line with these studies, we found that the risk of myocardial infarction and stroke was significantly lower in patients prescribed dronedarone than in those prescribed amiodarone, flecainide, propafenone, or sotalol.

In addition, corroborating findings in the literature [34–38], the present study showed that older age, male gender, and medical comorbidities (i.e. heart failure, peripheral artery disease, diabetes, coronary heart disease, and hyperlipidemia) were risk factors for the development of myocardial infarction or stroke, whereas the prescription of vitamin K antagonists and NOAC protected against this risk. The fact that people followed in general practices were more likely to be diagnosed with myocardial infarction or stroke than those followed in cardiology practices is particularly significant. However, the higher incidence rate in general practices may be traced back to a better documentation of events in hospital reports as compared to cardiology practices. Another recent study that included over 150,000 patients in Germany with a new diagnosis of myocardial infarction found that outpatient follow-up care provided by a cardiologist, in combination with

consultations with general and internal practitioners, reduced the risk of death in such patients [39]. It is also noteworthy that NOAC users were prescribed dronedarone less frequently than NOAC non-users. Nonetheless, a recent study by Escobar et al. showed that concomitant administration of dronedarone and rivaroxaban is safe and not associated with significant adverse events [40].

The present retrospective study was subject to several limitations. First, the diagnosis of myocardial infarction and stroke relied solely on ICD-10 codes, and no information on mortality was available. However, the mortality rate should not differ between cohorts. Second, there was no information on well-known risk factors (i.e. familial history, dietary behavior, and smoking status), although these factors may have had an important impact on the association between dronedarone therapy and myocardial infarction and stroke. Third, there was no data regarding the reasons for the prescription of dronedarone instead of other antiarrhythmics, although the existence of potential contraindications in patients may indirectly reflect their cardiovascular profile. Moreover, the baseline characteristics of dronedarone patients are different from those of other patients. This suggests that dronedarone was not used in, for example, patients with advanced heart failure. This difference in baseline characteristics could lead to a bias in the outcomes. Finally, it is well known that observational studies are not an appropriate method for assessing causal relationships, and can only reveal associations.

The major strengths of this work are the number of patients available for analysis and the length of the follow-up period.

Overall, there was a negative association between dronedarone and the risk of myocardial infarction and stroke in patients with atrial fibrillation in Germany. Other studies using real-world data should be conducted in order to gain a better understanding of the positive cardiovascular effects of dronedarone therapy.

## Declaration of conflicts of interest

The authors declare that they have no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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