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Original Article

Amiodarone vs Dronedarone for Atrial Fibrillation: A Retrospective Cohort Study

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ABSTRACT

Background: Atrial fibrillation is one of the most common arrhythmias, but the optimal drug choice for a rhythm-control strategy remains uncertain.

Methods: This article reports on a retrospective cohort claims database study conducted using the Truven Health Market Scan Commercial Claims and Encounters and Medicare Supplemental databases. Patients with a new diagnosis of atrial fibrillation, and a discharge date between 2011 and 2015, were included. The exposure variables of interest were a discharge prescription for amiodarone or

RÉSUMÉ

Contexte : La fibrillation auriculaire est l'une des arythmies les plus fréquentes, mais ce qui constitue un choix optimal en matière de médicament dans le cadre d'une stratégie de normalisation du rythme cardiaque demeure incertain.

Méthodologie : Cet article présente une étude de cohorte rétrospective menée à partir des renseignements accessibles dans les bases de données *MarketScan Commercial Claims and Encounters* et *Medicare Supplemental de Truven Health Analytics* à propos des réclamations. Les patients qui avaient reçu leur congé de l'hôpital

Atrial fibrillation is one of the most common arrhythmias, and a progressive worldwide increase in its incidence, prevalence, and burden of disease has been observed in the 21st century.[1] The rising incidence is likely multifactorial, due to increasing longevity, with an associated increase in comorbidities, as well as improved detection strategies, including the use of wearables. Atrial fibrillation may exist as paroxysmal, persistent, or permanent forms. Although some atrial fibrillation patients are asymptomatic, many do present to the hospital with symptoms of palpitations, dyspnea, or reduced exercise tolerance. Atrial fibrillation complications may include systemic or cerebral thromboembolism and heart failure, as well as an increase in overall mortality.[2] Numerous therapeutic options are available for the treatment of atrial fibrillation, including ablation techniques, but the majority of patients still receive some form of pharmacologic treatment as part of either a rhythm- or rate-control strategy. A recent large randomized study, the Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4),[3] showed that a rhythm-control therapy with either antiarrhythmic drugs or atrial fibrillation ablation was associated with a lower risk of adverse cardiovascular outcomes than usual care among patients with early atrial fibrillation and cardiovascular conditions. Although the choice of antiarrhythmic drug was not standardized in this study, and although debate about the optimal rhythm-control agent is longstanding, amiodarone has been a common choice despite its many known toxic side effects.

Dronedarone is a congener of amiodarone, with the omission of its iodine molecule, developed with the intention of reducing the likelihood of toxic side effects, and it is consequently a safer alternative to amiodarone and was also a popular choice in EAST-AFNET 4.[3] The only comparative randomized clinical trial (RCT) of these 2 drugs showed that dronedarone was better tolerated and had fewer side effects than amiodarone but was less effective in maintaining sinus rhythm.[4] However, the small sample size and relatively short 6-month follow-up period precluded any comparison of clinical outcomes, and hospitalizations were not recorded, with the primary endpoint being recurrent atrial fibrillation.[4] Moreover, placebo-controlled RCTs have shown an increased risk of death or hospitalization with dronedarone in patients with a low ejection fraction[5] or permanent atrial fibrillation.[6]

The increased tendency to pursue a rhythm-control strategy, coupled with the uncertainty regarding the optimal drug choice, due to a lack of randomized comparative trial data for meaningful patient outcomes with antiarrhythmic drugs, was the motivation for this observational study seeking to determine the comparative drug effectiveness of amiodarone and dronedarone in a real-world population of patients with an incident hospitalization for atrial fibrillation.

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Ethics Statement: The project received ethics approval from the McGill University Health Centre Research Ethics Board.

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dronedarone. The average treatment effect for the composite of total mortality or a repeat cardiovascular (CV)-related hospitalization was the primary outcome. Sensitivity analyses with other treatment effect metrics were performed. Baseline covariate imbalances between the groups were adjusted using propensity-score methods with inverse probability weighting.

Results: A total of 1735 patients were discharged on amiodarone, and 338 were discharged on dronedarone, with a median follow-up time of 357 days. A total of 43 (12.7%) CV-related hospitalizations occurred in the dronedarone group, and 146 (8.4%) occurred in the amiodarone group (risk difference 4.3%, 95% confidence interval [CI] 0.4%-8.3%, $P = 0.02$). A total of 4 (1.2%) deaths occurred in the dronedarone group, and 31 (1.8%) deaths occurred with amiodarone (risk difference -0.6%, 95% CI -2.1%-0.9%, $P = 0.6$). After adjusting for baseline covariates, the dronedarone hazard ratio for the composite endpoint was 1.47 (95% CI 1.01-2.12). This result was generally robust to sensitivity analyses.

Conclusion: In this incident cohort of patients hospitalized for atrial fibrillation, compared to those discharged on amiodarone, patients who received a dronedarone discharge prescription had an increase in the composite endpoint of recurrent CV-related hospitalization and death, over a median 1-year follow-up period.

entre 2011 et 2015 après un nouveau diagnostic de fibrillation auriculaire ont été inclus dans l'étude. La variable d'exposition d'intérêt était la prescription d'amiodarone ou de dronédarone à la sortie de l'hôpital. L'effet moyen du traitement sur la variable composite, soit la mortalité totale et la réhospitalisation d'origine cardiovasculaire (CV), constituait le paramètre d'évaluation principal. Des analyses de sensibilité fondées sur d'autres indicateurs de l'effet du traitement ont été effectuées. Les déséquilibres intergroupes touchant les covariables de base ont été corrigés par pondération de probabilité inverse selon l'indice de propension.

Résultats : À leur sortie de l'hôpital, 1 735 patients s'étaient vu prescrire de l'amiodarone et 338, de la dronédarone. Le temps de suivi médian était de 357 jours. Le nombre total d'hospitalisations d'origine CV atteignait 43 (12,7 %) sous dronédarone et 146 (8,4 %) sous amiodarone (différence de risque : 4,3 %; intervalle de confiance [IC] à 95 % : 0,4-8,3 %, $P = 0,02$). Par ailleurs, le nombre total de décès était de quatre (1,2 %) sous dronédarone et de 31 (1,8 %) sous amiodarone (différence de risque : -0,6 %; IC à 95 % : -2,1 %-0,9 %, $P = 0,6$). Après correction en fonction des covariables de base, le rapport des risques instantanés s'établissait à 1,47 (IC à 95 % : 1,01-2,12) au regard de la variable composite chez les patients sous dronédarone, et ce résultat s'est généralement maintenu dans les analyses de sensibilité.

Conclusion : Au sein de la cohorte incidente de patients hospitalisés pour cause de fibrillation auriculaire, une augmentation des cas de réhospitalisation d'origine CV et de la mortalité (variable composite à l'étude) a été notée au cours d'une période médiane de suivi de un an chez les patients qui s'étaient vu prescrire de la dronédarone plutôt que de l'amiodarone à leur sortie de l'hôpital.

Methods

Design and population

To optimize the possibility of drawing causal inferences from these observational data, we have followed the target trial emulation approach of Hernan and colleagues.[7,8] This retrospective claims database study was conducted using the Truven Health Analytics MarketScan Research Databases (2011-2015) with US commercial and Medicare supplemental claims. The dataset included all inpatient medical claims and outpatient medical claims, plus enrollment information, all within this 5-year period, on individuals with a hospitalization for atrial fibrillation (inpatient medical claim with primary diagnosis using the International Classification of Diseases (ICD), 9th revision, Clinical Modification (ICD-9-CM), code 427.x or ICD, 10th revision (ICD-10) diagnosis codes I46, I47, I48, I49, I51.8, R00.1, R00.8, and R01.2. Subjects had to be continuously enrolled for at least 12 months before the index date, with no prior atrial fibrillation diagnosis. The discharge date of the first observed hospital claim was the assigned index date for this incident cohort. The cohort was restricted to patients who received a prescription for isolated dronedarone or amiodarone antiarrhythmic therapy within 2 days of discharge, thereby avoiding any potential immortal time bias.[8] Specifically, patients receiving concomitant therapy with additional atrial fibrillation drug therapies, including digoxin, sotalol, flecainide, propafenone, dofetilide, mexiletine, and disopyramide, were excluded. The primary outcome was a repeat cardiovascular hospitalization or within-hospital death occurring following the initial hospital discharge. The project received ethics approval from the McGill University Health Centre research ethics board.

Propensity-score methods

As patients have not been randomized to amiodarone or dronedarone, propensity scores with inverse probability of treatment weights were used to balance the baseline characteristics of the 2 groups. Propensity scores are the probability of being assigned to a certain treatment, conditional on baseline characteristics, and are estimated using logistic regression. The idea is to apply a weight to each propensity score to balance the dronedarone and amiodarone groups with regard to the propensity score and thereby, hopefully, balance the individual covariates. Essentially, this means that, for any given propensity score, the choice of drug is a random process, at least as far as the measured confounders are concerned. Ultimately, the propensity score will be used to estimate the treatment effect. An important point to note is that several treatment effects may be calculated and of interest. Also, to prevent individual measurements from assuming an over-sized importance in the pseudo-populations, observations with weights greater than 5 have been censored.

Treatment effects. (i) The **average treatment effect** (ATE) is the most common measure and what is estimated in a randomized study in which the target population is the whole population, both treated and controlled, and was the prespecified subject of the primary analysis. However, this population is not always the medically or scientifically appropriate

Table 1. Discharge medications for 52,164 patients hospitalized for atrial fibrillation

Exposure	Number
Beta blockers	12,723
Sotalol	1072
Amiodarone	1735
Dronedarone	338
Calcium channel blockers	5450
Digoxin	406
Other	546
None	29,894

population, as it assumes that every participant can be switched from their current treatment to the opposite, which is not always possible. Therefore, as sensitivity analyses, additional treatment effects were investigated. (ii) The **average treatment effect among the treated** (ATT) estimates the treatment effect with the treated population as the target population. (iii) The **average treatment effect among the controls** (ATC) estimates the treatment effect with the controlled population as the target population. (iv) The **average treatment effect among the evenly matchable** (ATM) estimates the treatment effect with a matched population as the target population. The estimated population is nearly equivalent to the cohort formed by one-to-one pair matching.

The weights for these different effect measures are calculated as follows, where the propensity score for participant i is defined as e_i, and the treatment assignment is Z_i, where $Z = 1$ indicates that the participant received the treatment (dronedarone), and $Z = 0$ indicates that they received the control (amiodarone):

$$\omega_{ATE} = \frac{Z_i}{e_i} + \frac{1 - Z_i}{1 - e_i}$$

$$\omega_{ATT} = \frac{e_i Z_i}{e_i} + \frac{e_i(1 - Z_i)}{1 - e_i}$$

$$\omega_{ATC} = \frac{(1 - e_i)Z_i}{e_i} + \frac{(1 - e_i)(1 - Z_i)}{1 - e_i}$$

$$\omega_{ATM} = \frac{min\{e_i, 1 - e_i\}}{Z_i e_i + (1 - Z_i)(1 - e_i)}$$

The success of the propensity-score methods was assessed by examining the standardized mean difference between the groups and by graphical inspection of the propensity-score histograms.

Statistical analyses

Multivariate logistic regression was used to model the propensity-score treatment model. Cox proportional hazards regression was used to model the time to the composite outcome using the datasets created by the inverse probability of treatment-weighted propensity scores described above. All

Table 2. Demographic and baseline characteristics

Characteristic	Amiodarone (n = 1735)	Dronedarone (n = 338)	Overall (N = 2073)
Age, y			
Mean (SD)	67.0 (11.3)	63.9 (11.4)	66.5 (11.4)
Median [min, max]	65.0 [40.0, 89.0]	63.0 [40.0, 89.0]	65.0 [40.0, 89.0]
Sex			
Male	1069 (61.6)	191 (56.5)	1260 (60.8)
Female	666 (38.4)	147 (43.5)	813 (39.2)
Previous AMI	154 (8.9)	15 (4.4)	169 (8.2)
Congestive heart failure	335 (19.3)	20 (5.9)	355 (17.1)
Peripheral vascular disease	90 (5.2)	7 (2.1)	97 (4.7)
Chronic obstructive lung disease	324 (18.7)	48 (14.2)	372 (17.9)
CHA_2DS_2_VASc			
Mean (SD)	2.22 (1.48)	1.84 (1.44)	2.16 (1.48)
Median [min, max]	2.00 [0, 7.00]	2.00 [0, 6.00]	2.00 [0, 7.00]
Renal disease	93 (5.4)	16 (4.7)	109 (5.3)
Cancer	213 (12.3)	20 (5.9)	233 (11.2)
Diabetes	261 (15.0)	46 (13.6)	307 (14.8)
Cerebrovascular disease	150 (8.6)	21 (6.2)	171 (8.2)
Charlson Index			
0	551 (31.8)	196 (58.0)	747 (36.0)
1	514 (29.6)	82 (24.3)	596 (28.8)
2	311 (17.9)	30 (8.9)	341 (16.4)
3	155 (8.9)	18 (5.3)	173 (8.3)
4	54 (3.1)	4 (1.2)	58 (2.8)
5+	150 (8.6)	8 (2.4)	158 (7.6)
ACE-Is	334 (19.3)	67 (19.8)	401 (19.3)
ARBs	249 (14.4)	40 (11.8)	289 (13.9)
Statins	565 (32.6)	91 (26.9)	656 (31.6)
OACs admission	67 (3.9)	9 (2.7)	76 (3.7)
OACs on discharge	628 (36.2)	155 (45.9)	783 (37.8)

Values are n (%), unless otherwise indicated.

AMI, acute myocardial infarction; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; max, maximum; min, minimum; OAC, oral anticoagulant; SD, standard deviation.

Table 3. Outcome data on repeat hospitalizations and deaths

Measure	Amiodarone (n = 1735)	Drondarone (n = 338)	Overall (N = 2073)
Outcomes			
None	1558 (89.8)	291 (86.1)	1849 (89.2)
CV-related hospitalization	146 (8.4)	43 (12.7)	189 (9.1)
Deaths	31 (1.8)	4 (1.2)	35 (1.7)
Follow-up time			
Mean (SD)	465 (387)	492 (405)	470 (390)
Median [min, max]	356 [3.00, 1450]	363 [4.00, 1460]	357 [3.00, 1460]

Values are n (%), unless otherwise indicated.
CV, cardiovascular; max, maximum; min, minimum; SD, standard deviation.

analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, 52,164 hospitalizations for atrial fibrillation occurred, with 1735 patients discharged on amiodarone, and 338 discharged on dronedarone (Table 1). None of these patients received other antiarrhythmic drugs on discharge. Table 2 compares their baseline characteristics. In general, the amiodarone group was older (mean age: 67.0 years [standard deviation: 11.3] vs 63.9 years (standard deviation: 11.4]) and had more comorbidities. The low rate of baseline anticoagulants is to be expected, as this was an incident cohort of new atrial fibrillation cases. The rate of discharge on oral anticoagulants was increased approximately 10-fold (Table 2).

Table 3 shows the outcomes according to discharge drug exposure. More repeat cardiovascular (CV)-related hospitalizations occurred in the dronedarone group (146 [8.4%] vs 43 [12.7%], risk difference = 4.3%, 95% confidence interval [CI] 0.3%-8.3%) but with no statistically significant difference in total mortality (31 [1.8%] vs 4 [1.2%], risk difference = 0.6%, 95% CI −0.9%-2.1%). Although not prespecified in our protocol, in a *post hoc* analysis, we examined individual CV-related hospitalization causes. The majority of the recurrent hospitalizations had atrial fibrillation as the primary diagnosis (89 [5.13%] with amiodarone vs 39 [11.54%] with dronedarone, risk ratio [RR] 2.25, 95% CI 1.57-3.22). No statistically significant differences were found between the drugs for other CV-related hospitalizations, including acute coronary syndromes (19 [1.09%] with amiodarone vs 1 [0.30%] with dronedarone, RR 0.27, 95% CI 0.04-2.01) and congestive heart failure (39 [2.25%] with amiodarone vs 3 [0.89%] with dronedarone, RR 0.39, 95% CI 0.12-1.27).

The Kaplan-Meier survival curves for the composite endpoint are shown in Figure 1. These 2 curves are not significantly different statistically (log rank test, $P = 0.1$) for this unadjusted analysis. However, given the baseline imbalances observed in Table 2, adjusted time-to-event analyses are required.

The success of the propensity-score model in adjusting for the baseline imbalances is shown in Figure 2, in which the standardized mean differences, judged to be acceptable (standardized mean differences < 0.1), are displayed. The pseudo-populations created by the inverse probability weighting are shown graphically to have very similar propensity-score distributions for all measured confounders (Fig. 3).

The Cox proportional model for these pseudo populations revealed a dronedarone hazard ratio of 1.47 (95% CI 1.01-2.12) for the average treatment effect for the primary outcome of recurrent CV-related hospitalization or death. Table 4 shows that evaluation of other average treatment effects indicates a consistently increased dronedarone risk.

Discussion

In this cohort of patients with an incident hospitalization for atrial fibrillation, an increased risk for recurrent CV-related hospitalizations or death was observed in patients receiving a discharge prescription for dronedarone, compared to amiodarone. This increased risk was observed even after adjusting for baseline imbalances between the 2 groups in this nonrandomized study. These results were robust to different average treatment effect measures.

Although RCTs remain the gold standard for evaluating drug efficacy, only one small study of 504 patients[4] directly compared dronedarone use to amiodarone use; with a combined 7 deaths and no data reported on recurrent hospitalizations, this provides only minimal information as to the

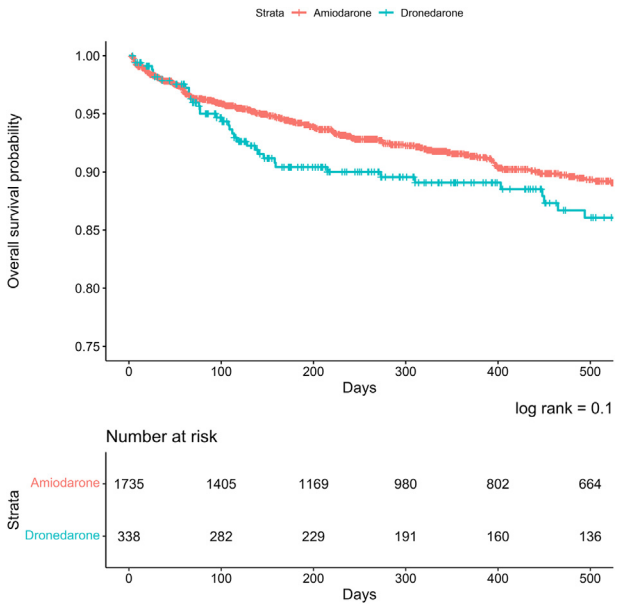

Figure 1. Kaplan-Meier curves.

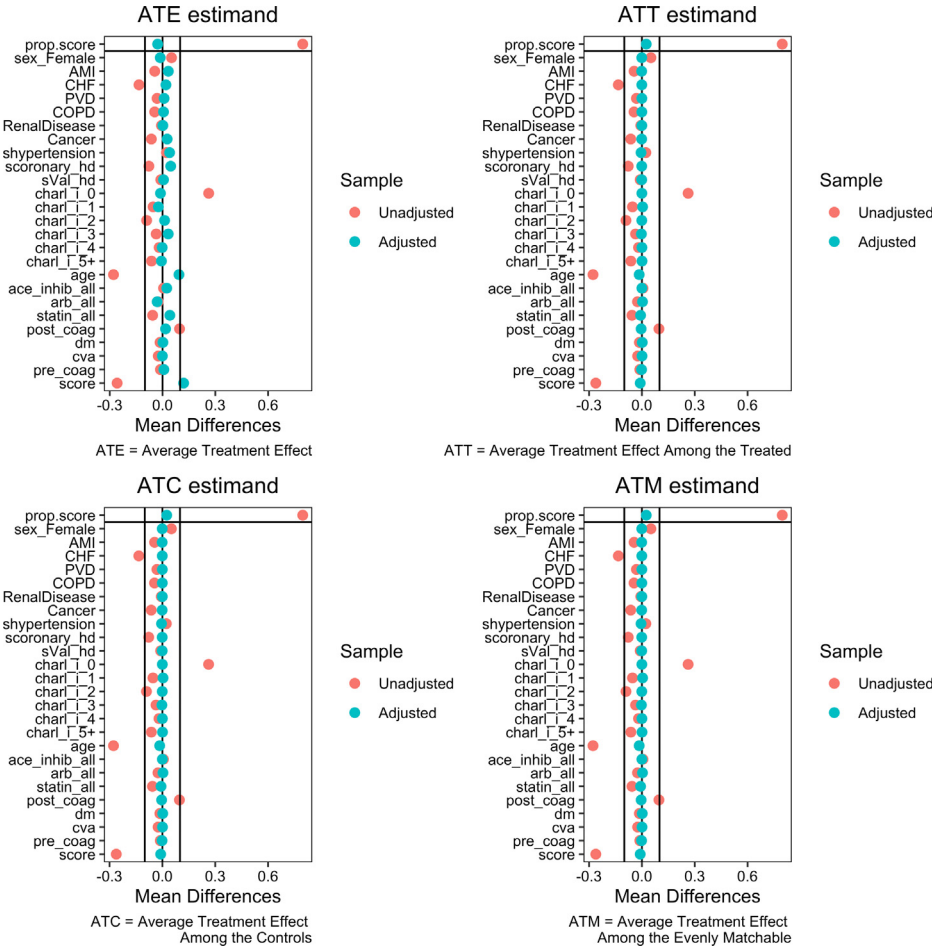

Figure 2. Standardized mean differences from models with different treatment effect estimands. ace_inhib, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; arb, angiotensin receptor blocker; ATC, average treatment effect among the controls; ATE, average treatment effect; ATM, average treatment effect among the evenly matchable; ATT, average treatment effect among the treated; CHF, congestive heart failure; coag, coagulant; COPD, chronic obstructive pulmonary disease; coronary_hd, coronary heart disease; cva, cerebral vascular disease; dm, diabetes; prop., propensity; PVD, peripheral vascular disease; shypertension, hypertension; sval_hd, valvular heart diseases.

relative safety and efficacy of these 2 drugs. In an attempt to overcome this limitation, a mixed treatment comparison including an additional 10 placebo-controlled RCTs has provided an indirect comparison of clinical outcomes between dronedarone and amiodarone.[9] This study found no statistically significant difference in mortality between amiodarone and dronedarone (odds ratio 2.52, 95% CI 0.72-8.90). Notwithstanding the limitations of the indirect comparisons in a mixed treatment comparison, the data for mortality remain very limited, as reflected by the wide CIs. Although recurrences of atrial fibrillation were less frequent with amiodarone (odds ratio 0.41, 95% CI 0.29-0.57) compared to dronedarone, repeat hospitalizations were not systematically recorded in these trials, and therefore, a mixed treatment effect for our composite endpoint cannot be estimated. In this context, data from well performed nonexperimental designs may be helpful. A general rule for minimizing bias from observational studies is to try to design them to emulate an RCT[7,8] and our study has followed these principles.

Our study has several strengths, including its incident design, which avoids any prevalence bias. The low anticoagulation rates on admission are a testament to our incident cohort design. Discharge anticoagulation rates were 10 times those observed on admission, but they were still lower than expected given current guidelines.[10] The reasons for this low rate are beyond the scope of the current research question, but the rate may reflect patient delays in filling prescriptions. Nevertheless, the rate of discharge anticoagulant use was statistically higher in the dronedarone group (46% vs 36%, $P = 0.001$), so this imbalance cannot readily explain the observed outcome differences in the 2 exposure groups. Limiting our study to the population of patients prescribed dronedarone or amiodarone, in isolation from other antiarrhythmic drugs, should provide a sharper exposure contrast. Care taken in creating our study design has eliminated possible immortal time bias.[8] Our propensity-score methods suggest that measured confounding variables have been appropriately adjusted. Propensity-score methods also separate the exposure and outcome models, minimizing false-positive errors from researcher degrees of freedom in the model selection process. Our results are also concordant with those of published RCTs that suggest concerns with dronedarone's

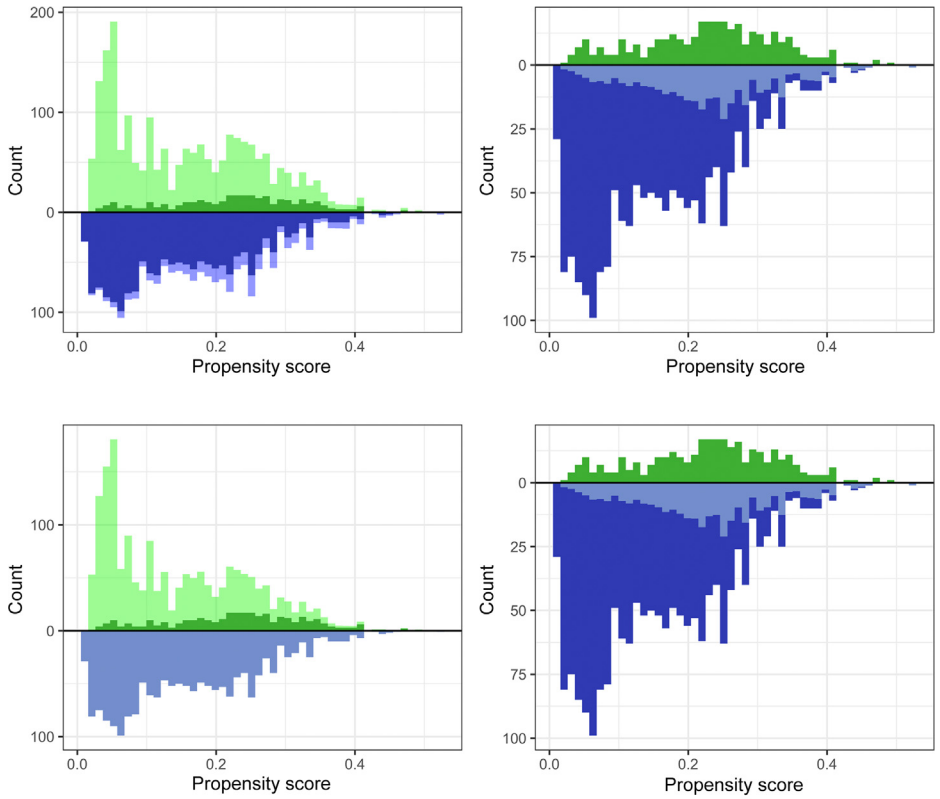

Figure 3. Histogram of propensity scores according to treatment received (dronedarone in **dark green** and amiodarone in **dark blue**). The weighted pseudo-population that is shown in the **light colors,** and the propensity-score histograms, are similar for both treatment arms in these pseudo-populations. ATC, average treatment effect among the controls; ATE, average treatment effect; ATM, average treatment effect among the evenly matchable; ATT, average treatment effect among the treated.

safety profile in patients with heart failure and permanent atrial fibrillation.[5,6]

Of note, in contrast to our findings, a comparative effectiveness study of dronedarone published in 2020[11] reported a decreased hazard ratio (HR = 0.86, 95% CI 0.78-0.95) for the composite outcome of CV-related hospitalization and death. However, this cohort is substantially different from ours in that it was derived from an earlier time period, involved older patients with more comorbidities, was not an incident atrial fibrillation cohort (50% were on anticoagulants on admission), and most importantly, the comparative group was a mixture of multiple different antiarrhythmic drugs, including not only amiodarone but also sotalol, flecainide, propafenone, and dofetilide. Another comparative effectiveness study from Germany[12] reported a lower risk of myocardial infarction and stroke in atrial fibrillation patients taking dronedarone, but again, the comparative group was taking a heterogeneous mixture of multiple antiarrhythmic drugs. These group and exposure differences may well explain these discordant findings.

Our study does have limitations. First, although we have more outcomes than have been reported in the clinical trials, the sample size nevertheless lacks the statistical power to examine mortality as a separate outcome. Although our propensity-score adjustments have successfully taken into consideration 16 baseline risk factors, no guarantee ensures that unmeasured potential confounders, such a smoking, obesity, and socioeconomic determinants, are equally distributed between the groups. However, in order for these non-measured variables to be confounders, physicians must be basing their choice of antiarrhythmic drug on these characteristics. Although this type of confounding may be unlikely for some lifestyle variables, it may be an issue for financial/insurance or other socioeconomic variables that can also influence outcomes. Another limitation is the unexpectedly large number of patients who did not fill a prescription upon discharge. Although an additional 9248 patients did eventually fill an antiarrhythmic drug prescription at a later date,

Table 4. Cox proportional hazards for varying treatment effect estimands

Group	HR	95% CI	*P*
ATE	1.41	0.97, 2.05	0.075
ATT	1.52	1.08, 2.15	0.018
ATC	1.25	0.86, 1.82	0.2
ATM	1.52	1.08, 2.15	0.018

Values are for dronedarone vs amiodarone.

ATC, average treatment effect among the controls; ATE, average treatment effect; ATM, average treatment effect among the evenly matchable; ATT, average treatment effect among the treated; CI, confidence interval; HR, hazard ratio.

they are not included, as their introduction would introduce an immortal time bias. We have no means of knowing how many other patients received but elected not to fill their prescription, possibly introducing a selection bias. Also, this analysis follows an intention-to-treat paradigm in which group assignment is determined at hospital discharge, and exposure misclassification may occur over time if patients do not follow the same treatments. Therefore, although these data sources have been used extensively in clinical research,[13,14] exposure, covariate, and outcome misclassifications remain a possibility. This possibility is perhaps especially likely for mortality, for which the data set records only deaths that occur during a hospitalization. Also worth recalling is that our median follow-up time is only 1 year, and the observed hazard rates may change with a longer follow-up period.

Conclusion

In conclusion, this study demonstrated that dronedarone, compared to amiodarone, treatment following a hospitalization for incident atrial fibrillation is associated with worse outcomes. Given the large burden of disease with atrial fibrillation, a pressing need remains to reproduce and expand these research findings in different settings.

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Disclosures

The authors have no conflicts of interest to disclose.

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