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RESEARCH ARTICLE

Comparison of the effectiveness and side effects of dofetilide and dronedarone in the treatment of atrial fibrillation during an indicated period in time with perceived equipoise [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Dronedarone is an anti-arrhythmic drug (AAD) originally approved for the treatment of atrial arrhythmias. The effectiveness and side effects of dronedarone have not been adequately compared to other commonly used AADs using observational data. We compared rates of recurrent atrial arrhythmias, incidence of side effects, and discontinuation rates of dronedarone to another class III AAD, dofetilide. We included patients from a single academic medical center between 2003 and 2010. Chart review was utilized to collect historical data of baseline clinical characteristics, side effects, arrhythmia recurrence, and drug discontinuation. Propensity score matching was used to balance baseline covariates. Cox-proportional hazard models were used to compare rates of recurrence between dronedarone and dofetilide. Patients were excluded if they failed to acutely achieve sinus rhythm, developed side effects leading to immediate discontinuation, or did not have sufficient follow-up. The final analysis included 127 dofetilide patients and 57 dronedarone patients. Fifty-nine patients (46.5%) experienced recurrence in the dofetilide group within the first year of treatment compared to 42 dronedarone patients (71.2%) (p<0.01). The adjusted hazard rate of recurrence was 2.42 times greater for dronedarone compared to dofetilide (95% CI: 1.44, 4.07; p-value<0.01). Side effects leading to drug discontinuation, including significant QT prolongation, developed more frequently with dofetilide (24.1% vs. 9.9%; p<0.01). Dronedarone is less effective than dofetilide in arrhythmia

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suppression. Our findings suggest dofetilide is associated with more
serious side effects and a higher rate of discontinuation.

Keywords
dofetilde , dronedarone , anti-arrhythmic , atrial fibrillation ,
arrhythmia , side effects

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Introduction

A variety of anti-arrhythmic drugs (AADs) are used to suppress arrhythmias encountered in clinical practice[1]. AADs exert their pharmacologic effect by blocking ion channel currents in myocardial cells. Specifically, class III AADs block the delayed potassium rectifier current (IKr) and prolong phase 3 repolarization of the individual cell action potential. While this mechanism of action is aimed at suppressing arrhythmias, it can also predispose to other, potentially more dangerous ones. AADs also have important non-cardiac side effects. Despite being generally safe and well tolerated in the majority of patients, AADs demonstrate various degrees of efficacy in controlling arrhythmias in the clinical setting. The clinical use of AADs has been somewhat disappointing due to limited effectiveness and the occurrence of cardiac and systemic side effects.

Dofetilide is a class III AAD in clinical use for over ten years for the treatment of atrial arrhythmias. It is especially useful in patients with structural heart disease, such as coronary artery disease and congestive heart failure[2]. This is supported by clinical trials comparing its efficacy and safety to placebo[3]. Initiation of dofetilide requires hospitalization to ensure rigorous observation and monitoring for long QT, Torsade de Pointes, or other side effects through the first six doses. Patients are then followed up on a routine basis where they are monitored for drug efficacy and side effects.

Dronedarone is an additional class III AAD used for the treatment of atrial arrhythmias. It is a non-iodinated derivative of amiodarone, and it was originally believed to have a more favorable side effect profile compared to the parent drug. Dronedarone's original approval was based on clinical trials demonstrating increased efficacy compared to placebo[4,5]. In the European and Australian-American-African trials EURIDIS and ADONIS respectively[5], dronedarone significantly prolonged the time to first recurrence in patients with paroxysmal and persistent atrial fibrillation and flutter. However, one placebo-controlled clinical trial, referred to as the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS), ended prematurely due to safety reasons, as the dronedarone arm showed significantly higher rates of major cardiovascular events[6]. A recent meta-analysis, comprised of seven placebo-controlled clinical trials, including the PALLAS trial, was implemented to better understand why the PALLAS trial's findings conflicted with other similar investigations. This analysis reported significant heterogeneity of dronedarone treatment effects and concluded that permanent AF may be the most important predictor of harmful effects potentially caused by dronedarone[7]. Furthermore, a recent subgroup analysis was performed using the PALLAS trial, and investigators observed a harmful interaction between dronedarone and digoxin in patients with permanent AF, which they felt was partly responsible for the higher death rate observed in the original clinical trial[8].

Currently, dronedarone is restricted or contraindicated in patients with symptomatic heart failure with New York Heart Association (NYHA) class II or III symptoms, recent heart failure hospitalization or left ventricular ejection fraction <40%, largely due to the results of the PALLAS trial[9]. However, dronedarone may still be an important treatment option for clinicians to consider when treating patients that do not meet these criteria and are subsequently experiencing paroxysmal or persistent AF. Strengthening the available evidence could potentially reduce the trial and error process clinicians maybe be following in prescribing AADs.

To our knowledge only two observational studies have been implemented to compare the efficacy and safety of dronedarone to other anti-arrhythmic drugs[10,11]. However, only one of these studies was able to directly compare dronedarone and dofetilide. This study suggested the efficacy of dronedarone and dofetilide to be similar, with dronedarone being associated with a great risk of cardiac-related admissions. This evidence could benefit from replication, as the study was restricted to a patient cohort generated from a single university medical center. Thus, further investigation is warranted in improving the generalizability of such findings, further characterizing dronedarone treatment effects in a 'real world' clinical setting. In addition, further investigation may also assist in helping us to better understand why the PALLAS trial observed such serious adverse drug events.

Therefore, the goal of this study was to utilize a historical cohort to compare the effectiveness of dronedarone and dofetilide in maintaining normal rhythm. The results of the PALLAS trial were not known during the study period of our analysis and could not have influenced the recommendation or choice of anti-arrhythmic drugs. This study is comprised of a group of patients with comparable clinical characteristics in a large single center university hospital setting. We also compared the side effect profile and discontinuation rates of the two agents.

Methods

Design and setting

The University of Utah institutional review board (IRB) approved this study (IRB#39735) and a waiver of informed consent was granted. We employed a historical cohort design using an intention-to-treat analysis designed to compare rates of arrhythmia recurrence and side-effects between dronedarone and dofetilide. Patients dispensed dronedarone or dofetilide were identified from University of Utah's hospital pharmacy database from January 2003 to 2010. Clinical pharmacists reviewed all patient charts using a structured template to extract relevant clinical variables including patient characteristics, clinical course, and response to drug therapy. Cohort entry was defined as the time of drug initiation. Patients initiated on either dronedarone or dofetilide that met inclusion criteria were considered on treatment for the drug they were initiated on until the end of follow-up or if they experienced an adverse event that required discontinuation. Inclusion criteria included initiation and long term follow up for drug monitoring at the University of Utah. The time window used to compare the outcomes of atrial arrhythmia recurrence, side effects, and discontinuation rates was restricted to the first year of drug treatment for both groups. Patients were excluded from the analysis if they did not receive their long-term follow-up care at the University of Utah. They were also excluded if they failed to achieve sinus rhythm or experienced significant adverse events leading to drug discontinuation within the first six doses of the medication.

Outcomes

The primary outcome was arrhythmia recurrence within the first year of treatment. Secondary outcomes included a comparison of side effects and drug discontinuation rates. Each patient's experience on the drug was tracked through progress notes entered into the electronic medical records system. When arrhythmia recurrence was documented in progress notes, the patient was classified as having an event and censored from the recurrence analysis. Patients who did not achieve the primary outcome under drug exposure were censored at the end of the one-year follow-up period. Patients who developed a side effect from drug therapy but continued treatment without arrhythmia recurrence were not censored until the end of the one-year follow-up period. Patients who discontinued therapy due to adverse events were censored at the time of the adverse event.

Covariate selection

Covariates included in the analysis were selected based on patients' clinical characteristics and comorbidities. These included patient age, gender, prior diagnoses of diabetes, hypertension, coronary artery disease, kidney function, congestive heart failure, concomitant drug treatment, and left ventricular ejection fraction. In addition, arrhythmia history and severity were included with the type of AF (paroxysmal or persistent), prior treatment with other AADs, or catheter ablation.

Statistical analyses

Descriptive statistics were calculated and chi-square or t-tests for equality of means between treatment groups were computed before and after matching. One-to-one nearest neighbor propensity score matching was used to balance potential confounders between treatment groups. An analysis using propensity scores contains two steps: 1) Estimation of the probability of being treated (propensity score) using probit regression, and 2) Incorporation of the

propensity score as a matching variable in the outcome model. All statistical analyses, including propensity scores and 1:1 nearest neighbor matching were computed using STATA 11 (STATA corp, College Station, Tx)[12].

Propensity scores are typically used to model the probability of being treated, and for this reason, they are used to calculate the average treatment effect in the treated. Since we are comparing two treatments, we modeled the probability of being treated with dronedarone – the newer agent being compared to the older therapy, dofetilide. In propensity score matching, it has been argued that inference should be restricted to areas where propensity scores overlap between treatment groups. For this reason, results are reported with and without imposition of common support (Figure 1). When the common support option is used, treatment observations (in this case dronedarone users) whose propensity score is higher than the maximum or less than the minimum propensity score of dofetilide users are dropped. Crude, covariate adjusted, and propensity score matched Cox-Proportional Hazard models were used to estimate hazard ratios for the difference in recurrence rates between treatments. Missing values for continuous measures were imputed using individual-level regression equations. Analyses were performed with and without imputed values and leaving the variables out of the equations all together. The hazard ratios; nevertheless, were not impacted in any meaningful way, and for this reason, we reported analyses with imputed values.

Results

Patient characteristics

During the period of January 2003 to September 2009, 162 patients were observed to have initiated dofetilide, while 71 patients were observed to have initiated dronedarone between September 2009 and September 2010. Direct comparison of baseline characteristics between the two drug groups described in Table 1 showed more
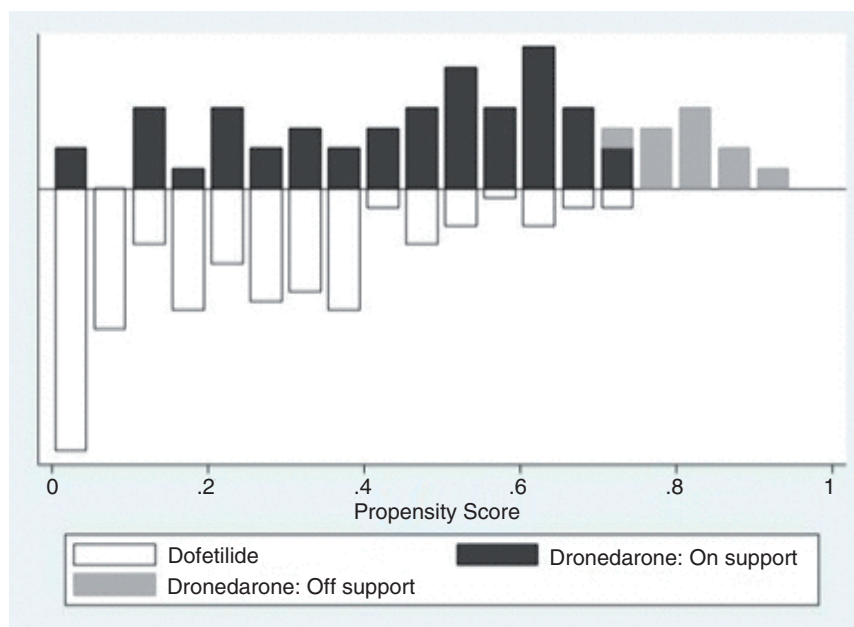

Figure 1. Distribution of propensity scores and illustration of common support.

females in the dronedarone group (40.9% vs. 25.9%, p=0.02). Dronedarone patients also had an older average age (68±12 vs. 62±13; p=0.001), a higher left ventricular ejection fraction (58±12 vs. 47±15; p<0.001), and were more likely to have undergone catheter ablation (53.5% vs. 24.1%; p<0.001). By contrast, a higher prevalence of congestive heart failure was seen in the dofetilide group (42.6% vs. 19.7%; p<0.001). An increased use of concomitant drug therapy was also observed in the dofetilide group with a higher use of beta-blockers, angiotensin-converting-enzyme inhibitors, aldosterone antagonists, and digoxin. The proportion of patients with paroxysmal atrial fibrillation was similar between the two groups (43.6% vs. 48.9%; p=0.48).

Acute effectiveness and side effects
Patients initiated on either drug had to achieve normal sinus rhythm in order to be maintained on long-term treatment and be included in the evaluation of recurrence. Sinus rhythm was present upon drug initiation in 70 dofetilide patients (43.2%) compared to 37 dronedarone patients (55.2%; p=0.09). Forty-five patients (27.8%) converted to sinus rhythm with dofetilide loading compared to 15 dronedarone patients (21.3%; p=0.32). Direct current cardioversion was used to achieve sinus rhythm, when drug loading failed to achieve this, in 19 dofetilide patients (11.7%) compared to 7 dronedarone patients (9.9%; p=0.67). In total, sinus rhythm was achieved in 134 dofetilide patients (82.7% of initial cohort) and 59 dronedarone patients (83.1% of initial cohort; p=0.94). In addition, if patients developed significant side effects upon drug initiation, the drugs were discontinued and not used for long-term

Table 1. Baseline characteristics of treatment groups before restriction to inclusion criteria.

	Dofetilide (N=162)	Dronedarone (N=71)	P value
Age (yrs)	62±13	68±12	0.001
Gender (%female)	25.9%	40.9%	0.02
Diabetes	19.8%	14.1%	0.46
Hypertension	59.3%	59.2%	0.99
Coronary Disease	32.1%	43.7%	0.20
Congestive heart failure	42.6%	19.7%	0.003
LV ejection fraction	47±15	58±12	<0.001
Serum Creatinine	1.04±0.24	1.00±0.27	0.27
Prior AAD	43.8%	49.3%	0.44
Paroxysmal AF (%)	43.6%	48.9%	0.48
Prior ablation	24.1%	53.5%	<0.01
Beta blockers	61.1%	56.5%	0.04
Calcium channel blockers	21.0%	19.7%	0.85
ACE-inhibitors	47.5%	26.8%	0.003
ARBs	16.1%	19.7%	0.49
Diuretics	39.5%	35.2%	0.54
Aldosterone antagonists	6.8%	12.7%	0.004
Digoxin	6.8%	12.7%	0.004

arrhythmia suppression. Gastrointestinal side effects were significantly higher in the dronedarone group (11.3% vs. 1.9%; p<0.01) while QT prolongation was significantly increased in the dofetilide group (13% vs. 1.4%; p<0.001).

Long-term effectiveness
Adequate follow-up information was available on 127 of 162 patients in the dofetilide group, and 59 of 71 patients treated in the dronedarone group. The average number of office visits during the first year of drug treatment was 4.5±1.2 for dofetilide patients compared to 4.2±1.7 for dronedarone patients (p=0.17). Fifty-nine patients (46.5%) experienced recurrence in the dofetilide group within the first year of treatment compared to 42 patients (71.2%) of dronedarone patients (Figure 2). A Kaplan Meier survival curve showing the difference in arrhythmia recurrence over the first year of treatment visually illustrates the difference in recurrence rates between dronedarone and dofetilide (Figure 3). Recurrence rates per 1000-days are reported in Table 2. A Cox proportional hazard model with the treatment drug assignment as the predictor variable was used to compare the two agents (Table 3). The hazard for one-year recurrence with dronedarone was 2.7 (95% CI: 1.79, 3.99; p-value<0.01) times larger than the hazard for dofetilide. The findings for the traditional covariate-adjusted model were similar, where the hazard ratio was 2.9 (95% CI: 1.74, 4.88; p-value<0.001).

Propensity score matching was also used to adjust for potential confounders. As seen in Supplementary material Table 1, significant differences existed in baseline characteristics between the 127 dofetilide and 59 dronedarone patients. The matching procedures were able to balance these covariates. This table also presents post-matching means and p-values when matches were restricted to regions of common support or not. The propensity score matched survival models produced similar hazard ratios to the crude and standard regression approaches. Shown in Table 3, the hazard for one-year recurrence in the dronedarone group was 2.9 (95% CI: 1.78, 4.84; p-value<0.00) times larger than the hazard for the dofetilide group when matching was not restricted to areas of common support and 2.4 (95% CI: 1.44, 4.07; p-value<0.00), when matching was restricted to areas of common support.

Drug tolerability and discontinuation
During long-term follow-up, drug discontinuation due to concern with side effects was observed significantly more frequently in dofetilide patients compared to dronedarone patients (31 patients (24.4%) vs. 5 patients (8.5%); p<0.01). QT interval prolongation and ventricular arrhythmias (ventricular premature beats, sustained, and non-sustained ventricular tachycardia) were the most frequent causes of drug discontinuation in the dofetilide group (16 patients (10.2%), compared to 2 patients (3.4%) in the dronedarone group (p=0.11)). One patient in the dronedarone group demonstrated polymorphic ventricular tachycardia suggesting Torsade de Pointes. Gastrointestinal side effects were more frequent in the dronedarone group (6 patients (10.2%)) compared to the dofetilide group (2 patients (1.5%); p=0.03).

Discussion
Our study compares the effectiveness and side effect profile of two class III anti-arrhythmic agents dronedarone and dofetilide. We demonstrate that dronedarone is associated with a significantly
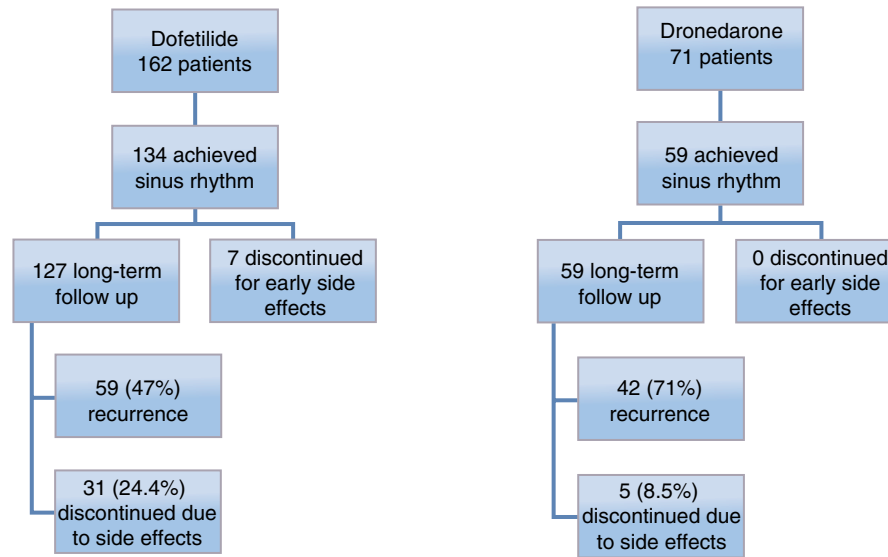
Figure 2. Diagram of patients included in the study illustrating initial and long-term effectiveness and discontinuation.
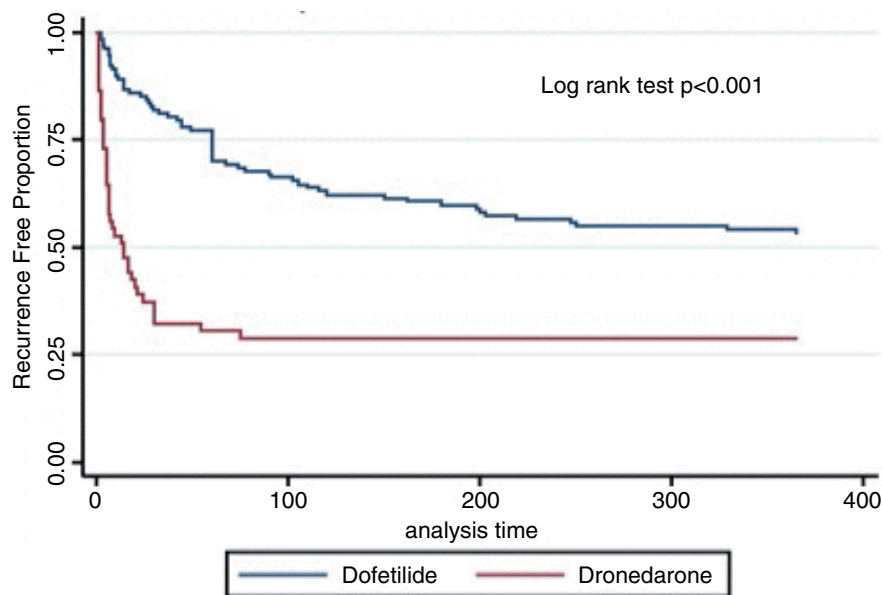

Figure 3. Difference in arrhythmia recurrence over the first year of treatment between dronedarone and dofetilide.

Table 2. Arrhythmia recurrence rates per 1000-days.

	Dofetilide	Dronedarone
Patients with recurrence	61	42
Time to recurrence (days)	28631	6681
Incident rate	0.0021	0.0063
Incident per 1000 days	2.1	6.3

Table 3. Cox Proportional Hazard ratios comparing recurrence rates between dronedarone and dofetilide.

	Hazard Ratio	Standard Error	z	P>z	95% confidence interval	
Crude	2.67	0.55	4.82	0.00	1.79	3.99
Standard adjusted	2.91	0.77	4.05	0.00	1.74	4.88
PS[j] matched, No CS[k]	2.94	0.75	4.22	0.00	1.78	4.84
PS[j] matched, CS[k]	2.42	0.64	3.34	0.00	1.44	4.07

[j]PS = Propensity Score
[k]CS = Common Support

higher arrhythmia recurrence rate compared to dofetilide after one year of usage. However, we observed dofetilide to be associated with a significantly higher rate of serious side effects, specifically QT interval prolongation and ventricular arrhythmia.

Rational for observational design

The ideal way to compare the efficacy and tolerability of these two agents is a prospective randomized controlled trial, where all clinical covariates would be balanced through randomization and any patient would have an equal probability of being assigned to receive one of the two agents. The majority of current literature that has examined the efficacy and tolerability of dronedarone are placebo-controlled clinical trials. Due to the premature ending of the PALLAS trial, coupled with difficulties in the patient enrollment process surrounding cost and monitored care, an observational study design utilizing historical data is a reasonable and ethically appropriate alternative in comparing these agents. In addition, such a design can better reflect treatment effects that may occur in a 'real world' clinical setting, as clinical trials are performed in a highly controlled environment, often comprised of choice patient candidates.

Current evidence comparisons

Our findings do not fully reflect the findings from the aforementioned University of Pittsburgh Medical Center (UPMC) observational investigation. This may be in part due to the fact that our measures of drug tolerability and safety differed. In addition, our sample sizes were not comparable and we did not examine multiple AADs, such as amiodarone and sotalol. Our lack of comparisons and subsequent smaller sample sizes are two notable limitations of our design. However, some may argue that UPMC design may be susceptible to chance statistical associations due to the multiple comparisons being made in their multivariate analyses. Furthermore, we attempted to handle statistical differences in baseline patient characteristics differently than the UPMC study: by means of the nearest neighbor one-to-one propensity score, which assisted us in reducing the effects of potential selection biases.

Our study shows that dofetilide is more effective than dronedarone in preventing atrial arrhythmia recurrence in a 'real world' clinical setting. The probability of maintaining sinus rhythm with dofetilide at one year was 53.5% in our cohort. This is comparable to the reported probability of around 60% at 2 years in the DIAMOND-CHF trial, which successfully studied patients with congestive heart failure, in addition to their atrial fibrillation. Our rate of atrial fibrillation recurrence in the dronedarone group was comparable to that observed in the DIONYSOS trial [71.2% (n=71) vs. 63.5% (n=249); two sample test of proportions p=0.18][13]. On the contrary, the University of Pittsburgh Medical Center (UPMC) retrospective cohort analysis reported dofetilide and dronedarone to have similar efficacy[10]. It is important to note that the DIONYSOS study findings are also in agreement with a portion of the findings from the UPMC study, suggesting amiodarone to be superior to dronedarone in preventing arrhythmia recurrence.

We also have demonstrated that dronedarone is better tolerated than dofetilide, which would appear to be contrary to what the PALLAS trial would suggest. This may in part be due to the multiple differences in baseline characteristics between patients in the PALLAS trial and those in our analysis, most notably in age, gender, and

heart failure status. Moreover, unlike the PALLAS trial, none of our patients had permanent AF when drug therapy was initiated. Furthermore, despite the higher incidence of gastrointestinal side effects observed in our dronedarone group, this did not lead to higher rates of discontinuation. In our particular cohort, dronedarone was most likely continued because prescribing providers at the time were less concerned about life threatening side effects with this agent. Ventricular arrhythmias associated with long-term use of dofetilide were estimated at 10.2%, which is very similar to the rate observed in the DIAMOND-CHF trial (7.0%, including ventricular fibrillation, Torsade de Pointes, monomorphic, and polymorphic ventricular tachycardia). Side effects associated with dofetilide, specifically QT interval prolongation and subsequent pro-arrhythmia, led to a higher rate of drug discontinuation.

Conclusion

The findings in our study fill an important gap in the medical literature and demonstrate the comparative effectiveness of dronedarone to anti-arrhythmic agents other than amiodarone using observational data. Amiodarone is known as the most effective agent available, but other agents are often needed when long-term amiodarone use leads to subsequent side effects[13,14]. Furthermore, these findings suggest that dronedarone may actually be a well-tolerated treatment regimen for those with paroxysmal or persistent AF, after normal sinus rhythm has been achieved. However, clinicians should take into consideration patient-specific characteristics in order to reduce the risk of adverse events and complications. Despite the relatively small sample size of patients included in our study, our results are robust and provide important clinical evidence that will aid providers in managing patients with atrial fibrillation. Randomized prospective trials designed to compare the two agents may be difficult to conduct at this time and further observational studies, possibly from multiple centers, will continue to strengthen the evidence generated from this study.

Data availability

Raw datasets are not available due to the regulations surrounding patient data; University of Utah IRB approval and agreement to all related data use policies is required. This data can be obtained by contacting the authors, University of Utah IRB, and Department of Internal Medicine, with the University of Utah. Instructions for applying for IRB approval are available on the following University of Utah ERICA website (http://irb.utah.edu/guidelines/erica-assistance/access-instructions.php). An individual must first obtain a University of Utah ID (uNID) number as outlined and instructed on the ERICA website. The Department of Internal Medicine, within the University of Utah, will then approve the request for issuing an individual with a uNID. Once a uNID is obtained, the individual can then create a UU IRB ERICA account. Upon completion of self-registering in ERICA, the individual can be granted access to the study and de-identified data via the University of Utah IRB number that can be obtained from the authors.

Author contributions

NA conceived the study, carried out the research, and prepared initial drafts of the manuscript. FB assisted in designing the study, provided critical review, and participated in editing the manuscript. MG and DS assisted with the data collection, provided critical

review, and participated in editing the manuscript. ZB polished initial manuscript drafts, added critical epidemiologic review, and prepared the manuscript for submission. BS provided oversight and critical review of the study design prior to implementation, assisted in carrying out the research and analysis, and participated in drafting sections of the manuscript relevant to his expertise.

Supplementary material

Table 1. The distribution of baseline covariates before and after 1:1 nearest neighbor matching. The distributions have been summarized with and without restricting matching to areas of common support.

	Variable	Mean		P value
		Dronedarone	Dofetilide	
Age	Unmatched	67.61	61.17	0.001
	No Common Matched	67.61	65.61	0.316
	Common Matched	65.44	64.83	0.791
Prior ablation	Unmatched	0.53	0.24	0.000
	No Common Matched	0.53	0.58	0.583
	Common Matched	0.44	0.48	0.686
Prior AAD	Unmatched	0.47	0.46	0.821
	No Common Matched	0.47	0.51	0.716
	Common Matched	0.50	0.40	0.310
Gender	Unmatched	0.42	0.29	0.075
	No Common Matched	0.42	0.34	0.348
	Common Matched	0.40	0.42	0.837
HTN	Unmatched	0.63	0.58	0.568
	No Common Matched	0.63	0.75	0.168
	Common Matched	0.60	0.69	0.399
Diabetes	Unmatched	0.12	0.23	0.347
	No Common Matched	0.12	0.22	0.528
	Common Matched	0.15	0.27	0.527
CAD	Unmatched	0.47	0.39	0.480
	No Common Matched	0.47	0.68	0.236
	Common Matched	0.40	0.60	0.312
CHF	Unmatched	0.19	0.41	0.003
	No Common Matched	0.19	0.12	0.310
	Common Matched	0.21	0.15	0.428

	Variable	Mean		P value
		Dronedarone	Dofetilide	
Beta Blockers	Unmatched	0.47	0.60	0.115
	No Common Matched	0.47	0.41	0.463
	Common Matched	0.48	0.50	0.840
Calcium Channel Blockers	Unmatched	0.24	0.22	0.800
	No Common Matched	0.24	0.39	0.075
	Common Matched	0.25	0.25	1.000
ACE-inhibitors	Unmatched	0.27	0.46	0.016
	No Common Matched	0.27	0.37	0.241
	Common Matched	0.31	0.46	0.145
ARBs	Unmatched	0.20	0.17	0.623
	No Common Matched	0.20	0.10	0.127
	Common Matched	0.15	0.13	0.768
Diuretics	Unmatched	0.41	0.39	0.787
	No Common Matched	0.41	0.54	0.143
	Common Matched	0.40	0.44	0.683
Digoxin	Unmatched	0.02	0.18	0.002
	No Common Matched	0.02	0.02	1.000
	Common Matched	0.02	0.02	1.000
Serum Creatinine	Unmatched	1.00	1.04	0.233
	No Common Matched	1.00	1.06	0.160
	Common Matched	1.00	1.02	0.658
LV ejection fraction	Unmatched	58.58	49.14	0.000
	No Common Matched	58.58	59.19	0.752
	Common Matched	57.51	58.44	0.691
TSH	Unmatched	2.35	2.24	0.566
	No Common Matched	2.35	2.12	0.237
	Common Matched	2.38	1.96	0.060

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Reviewer Report 30 August 2016

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❓ **Mohammad Shenasa**

Department of Cardiovascular Sciences, O'Connor Hospital, San Jose, CA, USA

This study is well designed and written during a long period of 7 years from 2003-2010. The study is a retrospective chart review and not a randomized trial as acknowledged by the authors.

- It is not clear how follow-up and recurrence rates were identified (i.e. Holter monitoring, phone calls to patients, etc.).

- Did any patients in each group have an implantable rhythm management device (i.e. pacemaker or implantable cardioverter-defibrillator)? Were there any crossovers from dofetilide to dronedarone or vice versa?

- Table one shows almost 20% (19.7%) of patients with congenital heart failure were on dronedarone. The PALLAS trial demonstrated that the drug increased mortality; therefore, dronedarone should not be prescribed to such patients.

- The authors should mention and further discuss that this data implied that dofetilide is more effective than dronedarone is in preventing recurrence of atrial arrhythmia.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

> Author Response 18 Sep 2016
>
> **Nazem Akoum**, University of Washington, Seattle, USA
>
> We thank Dr Mohammad Shenasa for reviewing our work and providing valuable commentary. We would like to answer the question he raised.

1. Follow up was through outpatient clinic visits every 3 months and additional visit as clinically indicated based on patient symptoms. The average number of visits during the first year of treatment was 4.5±1.2 for dofetilide patients and 4.2±1.7 for dronedarone patients.

2. 12 patients in the dofetilide group (7.4%) and 5 patients in the dronedarone (7.0%) had implantable rhythm management devices (p=0.91). This did not influence arrhythmia ascertainment for recurrence as arrhythmia episodes were detected at the scheduled clinic visits as described in point number 1 above. Remote rhythm monitoring through implantable rhythm devices was not available during the study period.

3. Patients were censored from the recurrence analysis at the time of arrhythmia recurrence and therefore cross over, if it occurred, did not affect the study endpoints.

4. As mentioned in the discussion section, the time period analyzed preceded the publication of the PALLAS trial, so excluding patients with heart failure from dronedarone use was not the standard of care at the time period analyzed.

5. Our study shows that dofetilide is more effective than dronedarone in preventing recurrent atrial arrhythmia and this is clearly mentioned in the discussion. We acknowledge that prospective randomized studies are needed to further strengthen the evidence for this outcome.

Competing Interests: No competing interests were disclosed.

Reviewer Report 13 July 2016

https://doi.org/10.5256/f1000research.8512.r14713

✔ **Richard Wyss**
Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

This study implements a historical cohort design to compare the effectiveness of dronedarone vs dofetilide with respect to arrhythmia recurrence and side effects within the first year of treatment using the University of Utah's hospital pharmacy database. This study addresses an important topic as there is little empirical evidence comparing the real world effectiveness of dofetilide vs dronedarone. I believe that the paper would benefit, however, if a few methodological aspects of the study were described in greater detail:

1. The authors mention that follow-up started at the time of drug-initiation (dofetilide or dronedarone). It would be helpful if the authors explicitly mentioned if this was the first initiation of these specific drugs for each subject, or if there was a washout period prior to the initiation of either dofetilide or dronedarone where subjects were required to have no pharmacy claim of either drug (new-user design)?

2. It would be helpful if the authors explicitly defined in the Methods section what side effects and adverse events are being considered.

3. The authors mention that they performed PS matched analyses with and without imposition of common support (i.e., trimming of the non-overlapping regions of the PS distributions). It is unclear why this is necessary. 1-1 PS matching should automatically restrict the analysis to individuals where there is common overlap as individuals with no common support would not be matched. It would be helpful if the authors explained why PS matched analyses with and without the common support region defined prior to matching would be expected to change the matched population and give different answers.

4. The authors do a nice job of highlighting the small sample size of the study as a limitation in the analysis. I think that it would be important for the authors to also highlight the potential for unmeasured confounding in this study as well as residual confounding caused by the measured baseline covariates even after PS adjustment.

    1. Table 1 and Figure 1 show strong differences in baseline covariates and strong separation in PS distributions across treatment groups. This often implies strong differences in unmeasured factors as well. The potential for unmeasured confounding should at least be mentioned as a limitation in the Discussion.

    2. Even after PS adjustment, Supplemental Table 1 shows that there are still some strong differences in baseline covariates. None of these differences are reported as significant according to the P-value, but the P-value is highly affected by sample size and is not the best metric for assessing whether or not balance is achieved. When just looking at absolute mean differences in the baseline covariates, some of the differences do not improve after matching (e.g., Diabetes, CAD, HTN). Consequently, I think the potential for residual confounding should be mentioned as a limitation.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 03 Aug 2016
Brian Sauer, Salt Lake City VA Medical Center, USA

We want to thank Dr. Richard Wyss for his outstanding review our our manuscript and we would like to clarify some of the points and issues he raised.
1. Unfortunately, this was not an inception cohort and patients may have had a previous exposure at the time they were indexed into our study. We will clarify this in the

manuscript. It is possible that patients indexed on Dronedarone may have had a previous AAD. If they had a previous exposure to an AAD and failed they may be more likely to fail on dronedarone, which would produce some selection bias. That said, we don't believe the lack of effectiveness is driven by this form of selection bias because, at the time, the cardiology program essentially switched practice to use dronedarone whenever indicated.

2. We will review and revise the methods section on ADEs abstracted from clinical notes.

3. Because the PS matching was based on nearest neighbor and not a caliper distance it is possible to match a dofetilide subject to a dronedarone patient who is not an ideal counterfactual substitute. We currently prefer the use of caliper distance or matched weights but at the time we conducted this study we were using a nearest neighbor matching algorithm. The findings are very robust and the matching algorithm is not expected to qualitatively change the results of this study.

4. We do agree that unmeasured confounding and residual confounding are of concern. It is important to understand that the prescribing practices of this institution changed from using dofetilide to dronedarone for indicated patients. This means providers for the most part were prescribing based on preference instead of patient risk. As a result, there could be historical bias where diagnostic or other care processes changed over time. We had much discussion on this issue and didn't believe there were substantial historical forms of bias, but this cannot be ruled out.

5. Dr Wyss rightfully is concerned with residual confounding, especially because some of the covariate may have clinically meaningful unbalance between groups. I don't believe any of the post-matching (common support) comparisons remained statistically significant. Nevertheless, we should have presented the standardize difference score instead of the p-value, which is not the best way of evaluating balance especially with the smaller sample size. Even though residual confounding is likely the findings were consistent with clinical experience and remained stable across various statistical treatment.

Competing Interests: No competing interests were disclosed.

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