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Original article

Comparative effectiveness of antiarrhythmic drugs for rhythm control of atrial fibrillation



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ABSTRACT

Introduction: Although there are many different antiarrhythmic drugs (AADs) approved for rhythm management of atrial fibrillation (AF), little comparative effectiveness data exist to guide drug selection. *Methods:* We followed 5952 consecutive AF patients who were prescribed amiodarone (N = 2266), dronedarone (N = 488), dofetilide (N = 539), sotalol (N = 1718), or class 1C agents (N = 941) to the primary end point of AF recurrence.

Results: Median follow-up time was 18.2 months (range 0.1–101.6 months). Patients who were prescribed amiodarone had the highest, while patients on class 1C agents had the lowest baseline CHA_2DS_2 -VASc score, Charlson comorbidity index, and burden of comorbid illnesses including coronary artery disease, congestive heart failure, diabetes mellitus, hyperlipidemia, chronic obstructive lung disease, chronic kidney disease, or cancer (p < 0.05 for all comparisons). After adjusting for baseline characteristics, using dronedarone as benchmark, amiodarone [hazard ratio (HR) 0.58, p < 0.001], class 1C agents (HR 0.70, p < 0.001), and sotalol (HR 0.79, p = 0.008), but not dofetilide (HR 0.87, p = 0.178) were associated with less AF recurrence. In addition, compared to dronedarone, amiodarone and class 1C agents were associated with lower rates of admissions for AF (HR 0.55, p < 0.001 for amiodarone; HR 0.71, p = 0.021 for class 1C agents) and all-cause mortality was lowest in patients treated with class 1C agents (HR 0.42, p = 0.018). The risk of stroke was similar among all groups.

Conclusion: Compared with dronedarone, amiodarone, class 1C agents, and sotalol are more effective for rhythm control, while dofetilide had similar efficacy. These findings have important implications for clinical practice.

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Introduction

Atrial fibrillation (AF) is the most common arrhythmic disorder in an aging population, leading to significant morbidity and mortality due to its associated thromboembolic complications and decompensation of cardiac function [1–6]. Based on estimates from the American Heart Association, there are more than 467,000 hospitalizations and 99,000 deaths due to AF in the USA each year [5]. Rhythm control is a desirable strategy for many patients with

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AF [7–10], and is often achieved using antiarrhythmic drugs (AAD) that alter the function of membrane channels in cardiac myocytes [11,12,7,13,14]. Published guidelines on rhythm management of AF allow the use of many AADs in most patients, but there is paucity of data on the relative efficacy of the various agents in maintaining sinus rhythm [14]. As a result, clinicians prescribe AADs for AF management on a trial and error basis or according to their personal preferences. Moreover, information on the efficacy of AADs in maintaining sinus rhythm is largely based on the results of clinical trial data, which may not reflect "real world" clinical practice [11,12,7].

This study was therefore designed to investigate the relative efficacy of AADs in preventing AF recurrence and their impact on other clinical outcomes, including cardiovascular and AF-related hospitalizations, stroke, and all-cause mortality.



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Methods

Study design

This is a retrospective cohort analysis comparing relative effectiveness of AADs in 5952 consecutive paroxysmal (58%) or persistent (42%) AF patients cared for at the hospitals and clinics of the University of Pittsburgh Medical Center (UPMC) from January 2006 to November 2013 with the goal of achieving rhythm control. The cohort was assembled via query of the UPMC electronic medical record for encounters in which International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis of AF (427.31) was assigned and by searching associated pharmacologic databases for a prescription of Vaughan Williams Class IC or Class III AAD [15,16]. The cohort was followed starting from the date of first AAD prescription through May 30th, 2014 with prospective review of outpatient and inpatient medical records. Patients who discontinued their first AAD, died, or were lost to follow-up during this period were censored at their date of discontinuation of first AAD, death, or last encounter. Patients with sustained AF were electrically cardioverted into normal sinus rhythm if they did not convert within 1 month of the initiation of AAD. The University of Pittsburgh Institutional Review Board approved this study.

Demographic data were obtained from the clinical records. Information on comorbidities was generated from ICD-9-CM codes in the clinical database with coding algorithms as described by Quan et al. [17]. The CHA₂DS₂-VASc score and Charlson comorbidity index were also calculated for each patient for risk stratification [18–20]. The initiation date and discontinuation date of AADs as well as information on other medications were ascertained via review of the institutional pharmacologic database and clinical notes and orders in the electronic medical record.

Baseline echocardiogram results were reviewed via clinical records and were available for 5581 patients (93.8%). Left ventricular function was measured by ejection fraction and was classified according to two cut-off values: <30% vs. $\geq 30\%$ and <50% vs. $\geq 50\%$. Severe left ventricular hypertrophy was defined as left ventricular septal thickness of at least 1.5 cm. Left atrial enlargement was identified through left atrial diameter measurements and classified into mild to moderate (left atrial diameter ≥ 41 and <52 mm for men; ≥ 39 and <46 mm for women) and severe (left atrial diameter ≥ 52 mm for men; ≥ 47 mm for women). Mitral regurgitation was classified into mild, moderate, or severe.

Study end points

The primary outcome was the time to first AF recurrence. The secondary outcome measures included first cardiac admission, first AF admission, stroke, and all-cause mortality. Dates of AF recurrence were ascertained from clinical notes documenting recurrence of AF by electrocardiogram, electrocardiographic monitors, or recurrence of AF symptoms. Causes for admission to the hospital were adjudicated by review of admission notes.

Statistical analysis

Baseline characteristics are presented as means (standard deviation) for continuous variables and as occurrence rates for dichotomous variables and were compared using the Student's *t* and Chi-square tests, respectively. A two-sided *p*-value <0.05 was considered statistically significant. Nelson–Aalen cumulative hazard curves were constructed for AF recurrence. Cox proportional-hazard models were constructed for each clinical outcome to adjust for any unbalanced (p < 0.10) covariates affecting the

outcome of interest. These included, after adjusting for possible interactions between covariates, age, gender, CHA₂DS₂-VASc score, Charlson comorbidity index, congestive heart failure, coronary artery disease, hypertension, hyperlipidemia, chronic obstructive lung disease, chronic kidney disease, left ventricular ejection fraction, severe left ventricular hypertrophy, left atrial enlargement, and mitral regurgitation. Dronedarone was used as benchmark for comparing relative effectiveness with other AADs as it is the newest drug approved in the USA for AF management. Further, after adjusting for baseline characteristics, subgroup analysis was performed for the primary outcome among patients with or without coronary artery disease, history of congestive heart failure, reduced left ventricular ejection fraction, and left atrial enlargement.

Results

Study population

The study cohort comprised 5952 patients with AF, of whom 488 patients (8.2%) were prescribed dronedarone, 2266 patients (38.1%) amiodarone, 539 patients (9.1%) dofetilide, 1718 sotalol (28.9%), and 941 (15.8%) class 1C agents (flecainide, *n* = 545 and propafenone, n = 396) as first line AAD. Table 1 compares the baseline characteristics of patients according to the AAD group. Patients on amiodarone had the highest while patients on class 1C agents had the lowest CHA2DS2-VASc scores, Charlson comorbidity indices, and burden of comorbid illnesses, including history of coronary artery disease, congestive heart failure, reduced left ventricular ejection fraction, severe left ventricular hypertrophy. left atrial enlargement, mitral regurgitation, diabetes mellitus, hyperlipidemia, chronic obstructive lung disease, chronic kidney disease, or cancer (p < 0.05 for all). Rates of anticoagulation were highest among patients prescribed dofetilide and lowest in patients prescribed class 1C agents (91.7% vs. 67.0%, p < 0.001). Patients prescribed amiodarone had higher rates of receiving aspirin (74.2%) and clopidogrel (19.5%) compared with other AAD groups (p < 0.001).

Clinical outcomes

During a mean follow-up of 26.1 months (95% CI 25.5-26.8), 1989 (33.3%) patients had AF recurrence. After adjusting for differences in baseline characteristics using dronedarone as benchmark, amiodarone (HR 0.59, p < 0.001), class 1C agents (HR 0.70, p < 0.001), and sotalol (HR 0.79, p = 0.009) were associated with less AF recurrence, while no significant difference was noted in patients treated with dofetilide (HR 0.86, p = 0.152) (Figs. 1 and 2). In addition, compared with dronedarone, amiodarone, and class 1C agents were associated with fewer hospital admissions for AF (HR 0.55, p < 0.001 for amiodarone; HR 0.71, p = 0.020 for class 1C agents) and dofetilide and class 1C agents were associated with fewer cardiac admissions (HR 0.74, p = 0.027 for dofetilide; HR 0.74, p = 0.020 for class 1C agents) (Fig. 2). All-cause mortality was significantly lower in the class 1C agents group compared with dronedarone group (HR 0.42, p = 0.018) (Fig. 2). The risk of stroke was similar among all AADs (Fig. 2).

In subgroup analysis, amiodarone showed superior efficacy in all predetermined subgroups, including the groups with or without coronary artery disease, congestive heart failure, reduced left ventricular ejection fraction, or left atrial enlargement (Fig. 3). The efficacy of sotalol, on the other hand, was better demonstrated in patients without history of congestive heart failure (Fig. 3). Dofetilide had similar efficacy to dronedarone in all subgroups (Fig. 3). Download English Version:

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