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Outcomes in atrial fibrillation patients on combined warfarin & antiarrhythmic therapy

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ABSTRACT

Background: This retrospective cohort study compared rates of treatment persistence, incidences of de novo stroke, arterial embolism, and hemorrhage/bleeding, and healthcare resource use and costs between atrial fibrillation/flutter (AF/AFL) patients receiving concomitant warfarin (W) + amiodarone (A) or warfarin + other antiarrhythmic drug (OAAD) therapy in real-world practice.
Methods: The Ingenix IMPACT database (1997–2009) was used to identify patients with ≥1 diagnostic claim for AF/AFL and concurrent pharmacy claims (≥60 days' supply) for W and A ($n = 4238$) or W + OAAD ($n = 6332$) within the first 90 days of initiating therapy. Outcomes of interest were assessed over 12 months following initiation of dual therapy.
Results: The W + A cohort was older than the W + OAAD cohort (mean 66.5 vs. 61.9 years) and had greater baseline comorbidity. The W + A cohort had significantly 1) lower rates of treatment persistence; 2) higher incidences of de novo stroke (hazard ratio [HR] 1.24), arterial embolism (HR 1.48) and combined stroke/hemorrhage/bleeding/arterial embolism (HR 1.25); 3) more frequent inpatient (incidence rate ratio [IRR] 1.25), emergency room (IRR 1.16) and outpatient (IRR 1.07) admissions; and 4) higher incidences of cardiovascular- (IRR 1.35) and arterial embolism- (IRR 1.94) related healthcare use than the W + OAAD cohort. Incremental total healthcare costs over 12 months were $4114 ($2397 inpatient; $1171 outpatient).
Conclusions: Allowing for differences in prescribing practice, AF/AFL patients treated with W + A are at higher risk of stroke and arterial embolism, and have higher healthcare use and costs, than patients receiving W + OAAD.

1. Introduction

Current recommendations for the management of atrial fibrillation (AF) and atrial flutter (AFL) include the use of antiarrhythmic drugs for restoration and/or maintenance of sinus rhythm [1,2]. Potential benefits of a rhythm-control strategy in AF/AFL include slowing of disease progression and improvement in symptoms, cardiac hemodynamics, exercise tolerance, and quality-of-life [3,4]. However, antiarrhythmic therapy does not obviate the need for long-term anticoagulation in AF/AFL, since patients with apparently successful restoration of sinus rhythm remain at embolic risk [5–7]. Amiodarone, the most widely used rhythm control agent in the United States (US) [8], is recommended as a second-line agent in the long-term treatment of AF in patients with structural heart disease and in highly symptomatic patients without heart disease [1,2]. Warfarin is the most commonly used oral anticoagulant in AF, and is recommended for patients at intermediate or high risk of embolic stroke [9]. Concurrent use of amiodarone and warfarin is, however, complicated by a drug-interaction that may potentially lead to excessive anticoagulation and hemorrhage [10–13].

Several observational cohort studies have compared clinical outcomes with long-term amiodarone + warfarin combination therapy vs. warfarin monotherapy in cardiac arrhythmia [11,12,14]. However, the warfarin + amiodarone combination has not been compared directly with warfarin + other antiarrhythmic drug combinations. This observational cohort study, using data from the Ingenix Impact National Managed Care Database (IMPACT) (1997–2009), compared treatment adherence, clinical outcomes, and healthcare resource use and costs among AF/AFL patients receiving warfarin with either amiodarone or other Class I/III antiarrhythmics.

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2. Methods

2.1. Study design and patient selection

The IMPACT database contains claims from approximately 60 million patients, from all census regions of the US, and covers 46 commercial health plans. Available information includes patient demographics, enrollment history, medical and pharmacy claims, and laboratory data. All data collected from the database were de-identified in compliance with the patient confidentiality requirements of the Health Insurance Portability and Accountability Act (HIPAA).

For study inclusion, adult patients (≥18 years) were required to have at least one diagnostic claim for AF (International Classification of Diseases, 9th Revision, Clinical Modification [*ICD-9-CM*]: 427.31) or AFL (*ICD-9-CM:* 427.32) within the 6-month period preceding initiation of dual warfarin/antiarrhythmic therapy, and pharmacy claims for at least 60 days' concomitant supply of warfarin and amiodarone or another Class I/III antiarrhythmic drug within the first 90 days of commencing co-therapy. Patients were required to be continuously enrolled in a health plan for ≥6 months before and ≥12 months after the date of initiation of dual warfarin/antiarrhythmic therapy ('index date'). Eligible patients were assigned to 1 of 2 mutually exclusive treatment cohorts: (1) the warfarin + amiodarone (W + A) cohort received these drugs concomitantly with no prior or on-study exposure to any other antiarrhythmic drug; and (2) the warfarin + other class I/III antiarrhythmic drug (W + OAAD) cohort received concomitant warfarin and either sotalol, propafenone, flecainide, dofetilide, quinidine, procainamide, disopyramide, or moricizine, with no prior or on-study exposure to amiodarone.

The analyses included two study populations: (1) the full study population, which included patients with or without prior stroke, hemorrhage/bleeding, or arterial embolism (used for assessment of treatment persistence, healthcare resource use, and costs); and (2) a sub-population which specifically excluded patients with baseline stroke, hemorrhage/bleeding, or arterial embolism (used for assessment of de novo clinical outcomes).

2.2. Study outcomes

Information on patient demographics (age, gender, geographic region) and baseline clinical characteristics (comorbidities, Charlson Comorbidity Index [CCI], cardiovascular-related surgery/treatment, and use of medications with potential for interaction with warfarin) were collected for both treatment cohorts, using claims data for the 6-month pre-index period.

Treatment persistence over the 12-month post-index follow-up period was defined as the time from treatment initiation to discontinuation of either index drug. Discontinuation was signified by a gap in prescription coverage of ≥60 consecutive days for either drug (the discontinuation date was the last day with drug supply before the 60-day gap). Patients were censored at first discontinuation of either index drug or on completion of the 12-month post-index follow-up period (whichever occurred first).

Clinical events of interest, comprising stroke (*ICD-9-CM*: 430, 431, 432.0–432.9, 434.01, 434.11, 434.91), hemorrhage/bleeding (*ICD-9-CM*: 459.0x), and arterial embolism (*ICD-9-CM*: 444.xx), were identified from medical claims with a diagnosis (*ICD-9-CM* code) of the relevant condition. Post-index follow-up was continued until either (1) first occurrence of the clinical event of interest; (2) 30 days after discontinuation of either index drug (for hemorrhage/bleeding only, since these events are unlikely to occur after treatment discontinuation); or (3) the end of patient eligibility or data availability (whichever occurred first). Event-related hospitalizations (inpatient stays with ≥1 diagnostic claim for the event of interest) and AF/AFL-related hospitalizations (inpatient stays with ≥1 cardioversion or intracardiac catheter ablation procedure) occurring during the 12-month post-index period were also identified, based on claims with a Current Procedural Technology (CPT), or *ICD-9* procedure code for cardioversion (CPT: 92960, 92961), or intracardiac catheter ablation (CPT: 93650–93652, 93799, 33250–33251, 33254–33259, 33261, 33265–33266; *ICD-9*: 37.34).

Healthcare resource utilization, including inpatient admissions, emergency room admissions, outpatient visits, and other medical services (laboratory, radiology, and other ancillary services), was estimated from claims data over the 12-month post-index period. In addition, total medical service resource utilization was separated into its constituent cardiovascular-, stroke-, AF/AFL-, hemorrhage/bleeding-, and arterial embolism-related components.

Healthcare costs for medical services and pharmacy prescriptions were measured over the 12-month post-index period from a managed care perspective and were expressed in 2009 US$ values. Costs were separately categorized as all-cause and condition-related medical costs (i.e. costs of medical services associated with a diagnosis code for the specific condition).

2.3. Statistical analysis

Baseline demographics and clinical characteristics were summarized with descriptive statistics, and inter-group differences were assessed using Wilcoxon rank-sum test (continuous variables) and chi-square test (categorical variables). Kaplan–Meier survival analysis was used to generate treatment persistence curves, and inter-cohort comparisons were performed using Log-ranks tests. Unadjusted and adjusted risks of clinical events were evaluated using Cox proportional hazards regression models, and results were reported as hazard ratios (HRs) and 95% confidence intervals (CIs). Adjusted incidence rate ratios (IRR) and 95% CIs for each type of healthcare resource use were estimated using Poisson regression models. Adjusted incremental medical and pharmacy costs were estimated using generalized linear models (GLM) with log link and gamma distribution or two-part models for cost components with more than 5% of patients with zero costs. Multivariate regression analysis was conducted to control for differences in demographics (age, gender, region of residence) and baseline clinical characteristics (comorbidities, cardiovascular surgery, number of days of warfarin and antiarrhythmic drug use during the baseline period, use of medication showing major interaction with warfarin, and baseline resource utilization and costs) between the study cohorts.

3. Results

3.1. Patient selection and baseline characteristics

Of 307,443 patients identified in the database with a diagnosis of AF or AFL and at least one warfarin or amiodarone prescription, 10,570 patients met the study inclusion criteria (4238 in the W + A cohort; 6332 in the W + OAAD cohort) ('Full Study Population') (Fig. 1). A sub-group of 9947 patients with no prior history of stroke, hemorrhage/bleeding, or arterial embolism at baseline (3919 in the W + A cohort; 6028 in the W + OAAD cohort) was used for the clinical events analysis ('Clinical Events Group') (Fig. 1).

Demographic and baseline (pre-index) clinical characteristics of the two treatment cohorts are detailed in Table 1. For the full study population, the W + A cohort was significantly older (mean 66.5 vs. 61.9 years), had higher baseline CCI and $CHADS_2$ (Congestive heart failure, history of Hypertension, Age ≥75 years, Diabetes mellitus, and past history of Stroke or TIA) scores, and higher rates of cardiovascular comorbidity than the W + OAAD cohort, (Table 1). The W + A cohort had also experienced significantly shorter exposure to warfarin and antiarrhythmic drugs during the pre-index period (Table 1). Durations of follow-up (index date to end of eligibility) were similar for the W + A and W + OAAD cohorts (mean ± SD: 138.1 ± 81.6 vs. 136.1 ± 77.6 weeks, respectively). The Clinical Events sub-population mirrored the full study population in demographic and baseline clinical characteristics and pre-index drug exposure (Table 1). For both study populations, the most commonly administered antiarrhythmics (W + OAAD cohort) were sotalol (51% of patients), propafenone (20%), flecainide (19%), and dofetilide (6.0%).

3.2. Treatment persistence

Among the full study population, persistence rates with dual therapy (i.e. both index drugs) were higher in the W + OAAD cohort than the W + A cohort at 3 months (86.0% vs. 80.9%), 6 months (63.4% vs. 51.5%), and 12 months (41.7% vs. 27.3%; $p<0.0001$) post-index (Fig. 2). Similarly, the W + OAAD cohort showed significantly ($p<0.0001$) higher persistence rates with W (56.6% vs. 48.3%) and antiarrhythmic drug therapy (67.1% vs. 46.9%) than the W + A cohort over the 12-month post-index period.

After adjustment for inter-cohort differences in demographic and clinical variables, the W + A cohort was at significantly ($p<0.0001$) higher risk of discontinuation of dual therapy [HR 1.54, 95% CI: 1.46–1.62], antiarrhythmic drug therapy (HR 1.92, 95% CI: 1.80–2.06) and warfarin therapy (HR 1.33, 95% CI: 1.25–1.42) than the W + OAAD cohort.

3.3. Clinical events

Among the 'Clinical Events Group', the W + A cohort had significantly ($p<0.0001$) higher incidences of stroke (6.6% vs. 4.2%, unadjusted HR 1.59), arterial embolism (2.4% vs. 1.1%, unadjusted HR 2.12) and combined stroke, hemorrhage/bleeding, and/or arterial embolism (9.3% vs. 5.7%, unadjusted HR 1.67) than the W + OAAD cohort, but the difference in hemorrhage/bleeding rates was not statistically significant (0.8% vs. 0.6%, unadjusted HR 1.54, $p=0.0761$)