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# Gender differences in stroke, mortality, and hospitalization among patients with atrial fibrillation: A systematic review

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ABSTRACT

*Objective:* To conduct a systematic review of gender differences in stroke, mortality, and hospitalization for patients with atrial fibrillation and/or flutter (AF/Afl).
*Methods:* Full texts, published, peer-reviewed, English language articles from 1999 through July 2014 were examined. Articles with populations of patients with AF/Afl were included if they conducted longitudinal analysis of any of three outcomes: stroke, mortality, and hospitalization, and reported or compared at least one of the outcomes according to gender.
*Results:* Seventeen articles were included: sixteen on stroke, nine on mortality, and one on hospitalization. In nine articles women had more strokes (RRs 0.89–1.9). Findings about gender differences in mortality (RRs 0.69–2.8) and hospitalizations were equivocal.
*Conclusions:* Few articles examine differences in outcomes between men and women with AF/Afl. Given the prevalence of AF/Afl and health care costs it is vital to determine gender differences to evaluate appropriate therapies to decrease stroke, mortality, and hospitalizations.


## Introduction

Atrial fibrillation (AF) and atrial flutter (Afl) are major global health problems that are increasing in prevalence and affect more than 3 million Americans.[1,2] Atrial fibrillation is an atrial arrhythmia that results in rapid randomized contractions of small areas of the atrial myocardium, thereby causing an irregular, and often rapid, ventricular rate. In Afl the atria beat regularly and faster than the ventricles. Atrial flutter frequently precedes the onset of AF. These arrhythmias are associated with an increased risk of stroke, dementia, heart failure (HF), and mortality.[3–6] Estimated annual costs of managing AF/Afl is $6.65 billion, which includes $4.88 billion in hospitalization expenses and $1.53 billion in outpatient management costs.[7] Atrial fibrillation/Afl are primarily diseases of the elderly with the prevalence doubling with each decade of life after the age of 60 years and occurring in 11% of the population over 80 years old.[2,8] The high prevalence in the older population is anticipated to increase the burden of AF on the health-care system with an estimation of a 2.5 fold increase in patients with AF over the next 50 years.[9] Prevalence rates of AF are increasing not only because of an increase in the older population but also increasing incidence of AF. The reason for the increased incidence/prevalence is unclear and is postulated due to increased risk factors of diabetes and obesity, increased diagnosis of AF, and improvements in management of hypertension and stroke.[10]

The incidence of AF in men is slightly higher in all age groups. The lifetime risk for developing AF for men and women over 55 is 23.8% for men and 22.2% for women.[11] Though a great deal of attention is focused on gender differences in other cardiac diseases including coronary artery disease (CAD), much less attention is focused on gender differences in AF, the most common sustained cardiac arrhythmia.[12] Although many individuals with CAD develop AF/Afl they frequently exist independently of each other. In CAD, different presentation and management strategies are proposed for women and men. Women present more often than men with angina, have higher resting heart rates, higher systolic heart rates, and are less likely to have undergone cardiac investigations.[13] Women are more likely to receive calcium channel blockers but fewer angiotensin converting enzymes (ACE) inhibitors, and fewer lipid lowering drugs than men. However, women remain at higher risk for subsequent adverse events.[13] Women at high-risk for acute coronary syndrome (ACS) experience less coronary angiography, angioplasty and coronary artery bypass surgery compared to men. They do not have higher incidence of cardiovascular death,

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recurrent myocardial (MI) or stroke but do have increased numbers of refractory ischemia and rehospitalizations.[14] Women who have percutaneous coronary intervention for non-ST elevation ACS have increased risk of major adverse events compared to men.[15] The extensive research on gender differences in CAD has revealed significant clinical findings. The gender differences is AF/Afl have not been carefully examined.

In a multicenter study of 150 patients with AF/Afl, female gender emerged as an indicator of poor health related quality of life (HRQOL) for patients with AF/Afl.[16] In another study evaluating outcomes related to gender, limited-use data from the National Institutes of Health/National Heart, Lung, and Blood Institute Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) clinical trial provided a sample of 693 patients with AF, 262 women and 431 men.[17] Clinical status predicted mortality in women. However, for men, HRQOL and clinical status predicted mortality. Both clinical status and HRQOL predicted hospitalizations for men and women.[17]

The goal of this paper was to evaluate differences according to gender in predictors of stroke, mortality, and hospitalization in patients with AF/Afl. If differences in predictors according to gender are present in these outcomes, further evaluating these differences may lead to reduced costs, improved function or quality of life of patients with AF/Afl. If there are differences between men and women they will have important implications for disease management.

## Methods

### *Design*

A systematic review was conducted guided by processes recommended by the Evidence Based Practice Centers funded by the Agency for Healthcare Research and Quality. Processes were developed to identify and select relevant articles, review and rate the individual articles, and then synthesize results and grade the evidence. No meta-analysis was planned as considerable heterogeneity across articles was anticipated with regard to patient samples, definitions of outcomes, length of follow-up, and settings.

### *Literature search*

A literature search was conducted as recommended by the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement*[18,19] Study eligibility criteria were established a priori. Inclusion criteria were full text, published, peer-reviewed, English language and human articles originating from any country. Articles about populations with AF/Afl were included if they conducted longitudinal analysis of three outcomes: stroke, mortality, and hospitalization reported or compared at least one of the outcomes according to gender, and included only participants over 18 years old. Case studies, qualitative studies, cross-sectional studies, dissertations or reviews were excluded. Studies of interventions or outcomes for caregivers or providers of patients with AF/Afl also were excluded.

Search strategies were adapted from Cochrane[16] and the National Institute for Health and Clinical Excellence[17] protocols to systematically search MEDLINE (OVID), CINAHL (EBSCOHost), and Cochrane Libraries of Systematic Reviews and Clinical Trials (OVID) databases from 1999 through July, 2014. The searches were designed for high sensitivity to locate any study of patients with AF/Afl that examined gender as a predictor of stroke, mortality, or hospitalization or provided data about the rates of these outcomes for the two genders separately. Limiting the search to the last 15 years was chosen to capture a timely body of research that occurred after the AFFIRM study which set standards for treatment.[4] Search selection strategies were conducted in a stepwise fashion: two reviewers independently examined all titles for inclusion criteria. Consensus was reached and abstracts reviewed. Finally, selected full text articles were randomly assigned to three reviewers. Each article was examined by two reviewers. Bibliographies of full-text articles were searched to locate additional articles and eight were found.

### *Data extraction*

Two reviewers who were part of the research team with both clinical and methodological expertise extracted data from each study to complete detailed evidence tables. Data were rechecked against the original articles for accuracy. If discrepancies were discovered, these were discussed by the team, resolved and corrected.

### *Quality assessment*

The Qualitative Assessment Tool for Quantitative Studies (QATQS) was used to rate study quality.[20] This tool evaluates study bias in eight areas including: sample selection, study design, confounding, blinding, data collection methods, withdrawals and dropouts, intervention integrity and analysis. The first six areas are scored and result in an overall methodological rating of study quality as strong, moderate, or weak. The QATQS is well validated for use in public health nursing and randomized and non-randomized trials.[21,22] Two reviewers independently rated the quality with an agreement rate of 100%.

### *Article evaluation*

The results of all analyses included in each article that were directly relevant to the specified outcomes were summarized along with study details and presented in tables for each outcome. An additional table (Table 1) was created that used the raw numbers of male and female participants and the raw number of participants of each gender who experienced each outcome to create an unadjusted risk ratio. This provides a standard metric to facilitate comparison of all articles within and between outcomes.

## Results

The literature searches of the databases located 489 records and examination of references within the articles evaluated located eight additional articles (Fig. 1). Ninety four articles were duplicates. Title evaluation eliminated 235 articles. Abstract evaluation eliminated 120 articles. Full text review eliminated 31 articles. Two articles[23,24] included the same sample. Only the article that focused directly on gender differences was retained.[24] The final list included 17 articles.[12,24–39] Ten of them included multiple outcomes.[12,24–27,33,35–38] Sixteen articles included the outcome of stroke,[12,24,26–39] nine articles included the outcome of mortality,[24–27,33,35–38] and one article included the outcome of hospitalization.[12] Specific numbers of women and men could not be ascertained from one article which included 229,530 individuals with AF/Afl and provided age and gender standardized rates but did not provide raw data about rates according to gender.[12] The sixteen remaining articles included 122,795 women and 128,010 men with AF/Afl.

### *Stroke*

Sixteen articles either included data that provided differences between men and women in rates of stroke or provided the data in