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Prevention of Atrial Fibrillation With Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

A Meta-Analysis

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OBJECTIVES This study was designed to identify all randomized clinical trial data evaluating angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for the prevention of atrial fibrillation (AF), to estimate the magnitude of this effect and to identify patient subgroups most likely to benefit.

BACKGROUND Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) reduce morbidity and mortality in patients with heart failure, vascular disease, and hypertension. Several reports suggest that they may also prevent the development of AF.

METHODS A systematic review of the literature was performed to identify all reports of the effect of ACEIs or ARBs on the development of AF. Eligible studies had to be randomized, controlled, parallel-design human trials of an ACEI or ARB that collected data on the development of AF.

RESULTS A total of 11 studies, which included 56,308 patients, were identified: 4 in heart failure, 3 in hypertension, 2 in patients following cardioversion for AF, and 2 in patients following myocardial infarction. Overall, ACEIs and ARBs reduced the relative risk of AF by 28% (95% confidence interval [CI] 15% to 40%, $p = 0.0002$). Reduction in AF was similar between the two classes of drugs (ACEI: 28%, $p = 0.01$; ARB: 29%, $p = 0.00002$) and was greatest in patients with heart failure (relative risk reduction [RRR] = 44%, $p = 0.007$). Overall, there was no significant reduction in AF in patients with hypertension (RRR = 12%, $p = 0.4$), although one trial found a significant 29% reduction in patients with left ventricular (LV) hypertrophy. In patients following cardioversion, there appears to be a large effect (48% RRR), but the confidence limits are wide (95% CI 21% to 65%).

CONCLUSIONS Both ACEIs and ARBs appear to be effective in the prevention of AF. This benefit appears to be limited to patients with systolic left ventricular dysfunction or LV hypertrophy. The use of these drugs following cardioversion appears promising but requires further study. (J Am Coll Cardiol 2005;45:1832–9) © 2005 by the American College of Cardiology Foundation

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-II receptor blockers (ARBs) reduce morbidity and mortality in patients with heart failure (HF) (1,2) or systolic dysfunction after myocardial infarction (MI) (3–5) and are effective in the treatment of hypertension (6). Retrospective analyses of some of these trials suggest that these medications may prevent the development or recurrence of atrial fibrillation (AF) (7–14). Atrial fibrillation is associated with a higher risk of stroke, death, and HF. It is therefore important to understand the effect of these agents on the occurrence of AF (15,16).

There are several potential mechanisms by which inhibition of the renin-angiotensin-aldosterone system (RAAS) with ACEIs and ARBs may reduce AF. Although certain drugs may possess direct anti-arrhythmic properties (17), in animal models ACEIs and ARBs appear to prevent AF by attenuating changes in cardiac structure and function (18–22). In these studies, these drugs prevented left atrial dilation, atrial fibrosis, and conduction velocity slowing, and these changes were associated with a lower rate of AF induction with atrial pacing (18,22–24). One study demonstrated that these benefits were not seen in animals treated to identical hemodynamic targets with hydralazine and isosorbide mononitrate, suggesting that the beneficial effect is specifically related to RAAS inhibition (23).

There have been few prospectively designed clinical trials to test whether ACEIs and ARBs prevent AF (7,12). Several secondary analyses of large randomized trials suggest a benefit. A systematic review of published and unpublished data is timely and provides the best way to estimate of the effectiveness of ACEIs and ARBs and identify patient subgroups who may be most likely to benefit.

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Abbreviations and Acronyms

AF = atrial fibrillation
ACEI = angiotensin-converting enzyme inhibitor
ARB = angiotensin-II receptor blocker
CI = confidence interval
HF = heart failure
LVEF = left ventricular ejection fraction
MI = myocardial infarction
RAAS = renin-angiotensin-aldosterone system
RRR = relative risk reduction

METHODS

A comprehensive search was conducted to identify all human randomized controlled trials of ACEIs or ARBs that recorded new or recurrent AF as an outcome. Medline and Embase were searched for any relevant human randomized controlled trials or reviews published since 1980, using the terms "angiotensin-converting enzyme inhibitor," "angiotensin receptor blockers," the individual names of all drugs in these classes, and "atrial fibrillation." The search was limited to English-language publications. Two reviewers then independently evaluated identified titles, and manuscripts were retrieved for any publication that either reviewer felt was potentially relevant. Additional publications were sought using the reference lists of identified papers; published reviews on the topic; and a manual search of abstracts from the scientific sessions of the American College of Cardiology, the American Heart Association, the European Society of Cardiology, and the North American Society of Pacing and Electrophysiology during the past four years. Finally, a second Medline search was done without the term "atrial fibrillation" to identify additional randomized controlled trials of ACEIs and ARBs that might contain data on AF. The results sections and tables of these studies were then examined to see if data on AF were reported. Attempts were made to contact authors of ACEI or ARB trials that did not report on AF.

Two blinded reviewers re-evaluated all of the abstracts and manuscripts identified as potentially relevant, and publications were selected for this review if both reviewers felt that they met the following criteria: 1) randomized controlled human trials with parallel design, 2) comparing an ACEI or ARB to an alternative therapy, and 3) collecting data on AF during follow-up. Studies were included in this review if both authors felt they were relevant. Any discordance between reviewers was resolved by consensus.

Relevant study data were independently abstracted, in duplicate, using a standardized form. Any discrepancies during data abstraction were resolved by consensus. For studies using a factorial design, data on all patients were used in this analysis. Data analysis was performed with Review Manager 4.1 using the random-effects model. Effect sizes were weighted by the sample size to calculate a weighted mean effect size using the Dersimonian and Laird method (25), and the chi-square test was used to assess for heterogeneity between studies. The effect of treatment was presented using the relative risk.

Identified studies. Our database search identified a total of 1,021 randomized controlled human trials of ACEIs or ARBs, 85 of which included the term "atrial fibrillation." An additional 14 studies were identified from conference proceedings. These 99 manuscripts and abstracts were blindly reviewed by two investigators who identified 10 relevant studies: 6 from the literature search and 4 from the review of conference proceedings. There was 100% agreement between the two reviewers in the identification of studies. Next, the titles of studies identified in the database search that did not contain the term "atrial fibrillation" were reviewed, and 95 were searched for data on AF. This yielded another two relevant studies with data on AF (26,27). Authors of ACEI and ARB trials that did not present data on AF were contacted to determine if unpublished data existed. No additional available data were identified in this fashion; however, at least two large trials of ACEIs had collected data on AF but have not yet analyzed or presented the results: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (28) and Heart Outcomes Prevention Evaluation (HOPE) study (29). In total, 12 relevant publications were identified, including two reports from the Studies Of Left Ventricular Dysfunction (SOLVD), one examining the incidence of AF at a single large center (11) and the other describing hospital admissions for atrial tachyarrhythmias for the entire study population (30). Despite a smaller number of outcome events (55 of 374 vs. 158 of 6,797), the single-center data were used for this analysis because its primary outcome, the occurrence of AF, was selected as the outcome event for this meta-analysis. Hospitalization for AF, the primary outcome of the other report (30), captured too many other variables and did not directly answer the primary question of this meta-analysis. A sensitivity analysis using the data from this alternative publication (30) was performed.

RESULTS

Of the identified studies, eight were published in manuscript form and three as abstracts. The characteristics of included studies are summarized in Tables 1 and 2. Study populations and trial design were quite different. There were 56,308 patients in the identified studies: 26,403 in three hypertension trials (13,26,27), 17,711 in a trial of patients following MI (14), 1,577 in a second post-MI trial that enrolled only patients with left ventricular (LV) dysfunction (9), 10,319 in four trials of HF (8,11,28,31), and 299 in two post-AF cardioversion trials (7,12). Angiotensin-converting enzyme inhibitors were studied in seven trials and ARBs in four (Table 1). The definition of AF (new vs. all) and the methods used to document AF were different between studies (Table 2) but were similar enough to permit pooled analysis.

Overall, the use of ACEIs or ARBs reduced the relative risk of developing AF by 28% (95% confidence interval [CI]