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ORIGINAL ARTICLE

Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers in Patients Without Heart Failure? Insights From 254,301 Patients From Randomized Trials

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Abstract

Objectives: To compare the efficacy and safety of angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) in patients without heart failure.

Patients and Methods: Meta-analysis of randomized trials identified using PubMed, Embase, and Cochrane Central Register of Controlled Trials searches from January 1, 1980, through April 13, 2015, of ACEis and ARBs compared with placebo or active controls and corroborated with head-to-head trials of ARBs vs ACEis. Outcomes were all-cause mortality, cardiovascular death, myocardial infarction (MI), angina, stroke, heart failure, revascularization, and new-onset diabetes.

Results: Our search yielded 106 randomized trials that enrolled 254,301 patients. Compared with placebo, ACEis but not ARBs reduced the outcomes of all-cause mortality (ACEis vs placebo: relative risk [RR], 0.89; 95% CI, 0.80-1.00; ARBs vs placebo: RR, 1.01; 95% CI, 0.96-1.06; $P_{interaction}$=.04), cardiovascular death (RR, 0.83; 95% CI, 0.70-0.99 and RR, 1.02; 95% CI, 0.92-1.14; $P_{interaction}$=.05), and MI (RR, 0.83; 95% CI, 0.78-0.90 and RR, 0.93; 95% CI, 0.85-1.03; $P_{interaction}$=.06). The meta-regression analysis revealed that the difference between ACEis and ARBs compared with placebo was due to a higher placebo event rate in the ACEis trials (most of these trials were conducted a decade earlier than the ARB trials) for the outcome of all-cause mortality (P=.001), cardiovascular death (P<.001), and MI (P=.02). Sensitivity analyses restricted to trials published after 2000 revealed similar outcomes with ACEis vs placebo and ARBs vs placebo ($P_{interaction}$>.05). Head-to-head comparison trials of ARBs vs ACEis exhibited no difference in outcomes except for a lower risk of drug withdrawal due to adverse effects with ARBs (RR, 0.72; 95% CI, 0.65-0.81).

Conclusion: In patients without heart failure, evidence from placebo-controlled trials (restricted to trials after 2000), active controlled trials, and head-to-head randomized trials all suggest ARBs to be as efficacious and safe as ACEis, with the added advantage of better tolerability.

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Angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) are treatment options for patients with cardiovascular disease (CVD) or those with cardiovascular risk factors. The comparative efficacy and safety of ACEis and ARBs have been much debated. Randomized trials of ACEi predominantly conducted from 1990 to 2000 exhibited a marked benefit of ACEis, including reduction in morbidity and mortality, compared with placebo.[1,2] However, randomized trials of ARBs conducted from 2000 to 2010 did not consistently exhibit a mortality benefit of ARBs compared with placebo.[3,4] Not surprisingly, this has led to the conclusion that ACEis are more cardioprotective than ARBs[5] and to the endorsement of ACEis over ARBs by guideline committees.[6,7] However, this indirect inference assumes that the placebo groups for comparisons in the 2 sets of trials are similar. The trials of ACEi were largely conducted before 2000, whereas the trials of ARBs were conducted after 2000. With more aggressive use of primary and secondary prevention strategies, changes in the guideline recommended primary and secondary prevention

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targets for blood pressure and cholesterol,[8,9] and better management of diabetes,[10] much has changed in the management of patients with CVD between those time frames. Conceivably these preventive strategies vastly affected the underlying risk of patients enrolled in trials almost a decade apart. Moreover, head-to-head randomized trials of ACEis vs ARBs do not suggest substantial differences between the 2 drug classes for efficacy outcomes.[11]

The objective of the present study was to evaluate the comparative effectiveness of ACEis and ARBs in patients without heart failure.

PATIENTS AND METHODS

Eligibility Criteria

We conducted PubMed, Embase, and Cochrane Central Register of Controlled Trials searches, without language restrictions, for randomized controlled trials using the MeSH terms for ACEis and ARBs (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org), from January 1, 1980, through April 13, 2015. In addition to the above databases, we searched the bibliography of original trials, meta-analyses, and review articles identified to find other eligible trials. The search was kept up-to-date by weekly reminders from PubMed.

Eligible trials had to fulfill the following criteria: (1) randomized controlled trials comparing ACEis or ARBs vs placebo or active controls or against each other (ie, ACEis vs ARBs); (2) trials with a sample size of at least 100 patients with follow-up of at least 1 year (to minimize the small-study effect); (3) trials with a cohort without heart failure; and (4) trials evaluating the outcomes of interest (below). Studies were excluded if the enrolled cohort were children (mean age, <18 years) or patients with cancer and if the study was redacted for any reason or randomized to a combination of an ACEi and an ARB.

Trial Selection and Bias Assessment

Three authors (R.F., B.T., and S.B.) independently assessed trial eligibility and trial bias risk and extracted data. Disagreements were resolved by consensus. The bias risk of trials was assessed using the components recommended by the Cochrane Collaboration[12] for randomized trials. This includes allocation sequence generation, allocation concealment, and blinding of outcome assessors. For each component, trials were categorized as low, high, or unclear risk of bias. We considered trials with high or unclear risk of bias for any one of the above components as trials with a high risk of bias.

Three groups of evidence were assessed: (1) comparisons of ACEis or ARBs vs placebo; (2) comparisons of ACEis or ARBs vs active controls; and (3) comparisons of ACEis vs ARBs (head-to-head trials). Our hypothesis was that if ACEis are superior to placebo but ARBs are not, a similar difference between ACEis and ARBs would also be evident in comparisons 2 (ACEis are superior to active controls, but ARBs are not) and in comparison 3 (ACEis are superior to ARBs).

Outcomes

The outcomes evaluated were all-cause mortality, cardiovascular death, myocardial infarction (MI), angina, stroke, heart failure, revascularization, new-onset diabetes, end-stage renal disease (ESRD), doubling of serum creatinine, hyperkalemia, and drug withdrawal due to adverse events.

Statistical Analyses

The meta-analysis was performed using an intention-to-treat approach and in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[12,13] The meta-analytic summary estimates (relative risk [RR]) were calculated using the fixed effect model and the random effects model of DerSimonian and Laird.[14] Heterogeneity, which is the proportion of total variation observed between the trials attributable to differences between trials rather than sampling error (chance), was assessed using the I^2 statistic,[15] with $I^2<25\%$ considered low and $I^2>75\%$ high. The small-study effect was assessed using the Begg test and the Egger test and by visual evaluation of the funnel plots for asymmetry. A test for interaction was used to compare the magnitude and direction of the effect size for ACEi and ARB trial analyses, with $P_{\text{interaction}}<.05$ considered statistically significant.

A meta-regression analysis was performed to evaluate the effect of the baseline risk of the enrolled cohort on the outcomes. The baseline risk was computed by calculating the event rate per year in the placebo arm of the trial. The placebo event rate is a good