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Angiotensin Receptor Blockers in Heart Failure: Meta-Analysis of Randomized Controlled Trials

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OBJECTIVES We sought to determine the effect of angiotensin receptor blockers (ARBs) on mortality and hospitalization in patients with heart failure (HF).

BACKGROUND There is uncertainty regarding the efficacy of ARBs as substitute or adjunctive therapy to angiotensin-converting enzyme inhibitors (ACEIs) in the treatment of HF.

METHODS We conducted a meta-analysis of all randomized controlled trials that compared ARBs with either placebo or ACEIs in patients with symptomatic HF. The pooled outcomes were all-cause mortality and hospitalization for HF.

RESULTS Seventeen trials involving 12,469 patients were included. Overall, ARBs were not superior to controls in the pooled rates of death (odds ratio: 0.96; 95% confidence interval: 0.75 to 1.23) or hospitalization (0.86; 0.69 to 1.06). Stratified analysis, however, showed a non-significant trend in benefit of ARBs over placebo in reducing mortality (0.68; 0.38 to 1.22) and hospitalization (0.67; 0.29 to 1.51) when given in the absence of background ACEI therapy. When compared directly with ACEIs, ARBs were not superior in reducing either mortality (1.09; 0.92 to 1.29) or hospitalization (0.95; 0.80 to 1.13). In contrast, the combination therapy of ARBs and ACEIs was superior to ACEIs alone in reducing hospitalization (0.74; 0.64 to 0.86) but not mortality (1.04; 0.91 to 1.20).

CONCLUSIONS This meta-analysis cannot confirm that ARBs are superior in reducing all-cause mortality or HF hospitalization in patients with symptomatic HF, particularly when compared with ACEIs. However, the use of ARBs as monotherapy in the absence of ACEIs or as combination therapy with ACEIs appears promising. (J Am Coll Cardiol 2002;39:463–70)

The use of angiotensin receptor blockers (ARBs) as substitute or adjunctive therapy to angiotensin-converting enzyme inhibitors (ACEIs) in the treatment of heart failure (HF) remains controversial. Although randomized controlled trials have shown conclusively that ACEIs reduce mortality and hospitalization in patients with HF (1), trials with ARBs in similar HF populations have qualitatively reached mixed conclusions. This is despite the theoretical superiority of ARBs over ACEIs in improving blockade of the renin-angiotensin-aldosterone system (2,3). A recent meta-analysis using data from six small studies has suggested a survival benefit with losartan when compared with either placebo or ACEIs in patients with HF (4). That meta-analysis, however, did not include data from the large Evaluation of Losartan in the Elderly II trial (5). This latter study, published subsequent to the meta-analysis, did not demonstrate a mortality benefit with losartan when compared with captopril in patients with HF. Furthermore, the meta-analysis did not include randomized trials that compared other ARBs with standard care. Given the limitations of existing data and their potential impact on the prescribing practices of these two drug classes in the HF population, we undertook a quantitative meta-analysis of all relevant randomized controlled trials to determine the effect of ARBs on the survival and hospitalization rates in patients with HF.

METHODS

Search strategy. The protocol of this study has been published elsewhere under the aegis of Cochrane Collaboration (6). In brief, we performed a systematic search (7,8) for randomized controlled trials published between 1966 and May 2001 from the following databases: MEDLINE, EMBASE, Biological Abstracts, International Pharmaceutical Abstracts, Cochrane Controlled Trials Database, McMaster Cardiovascular Randomized Clinical Trial Registry and Science Citation Index. We used the keywords of *heart* or *cardiac failure*, *cardiac insufficiency*, *cardiomyopathy*, *angiotensin receptor blockers*, *antagonists* or *inhibitors*, along with individual drug names and their registry numbers.

Selection criteria. We included only studies that met the following criteria: enrolment of patients with New York Heart Association (NYHA) functional class II to IV HF, comparison of ARBs with placebo or ACEIs, randomized

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Abbreviations and Acronyms

ACEI	= angiotensin-converting enzyme inhibitor
ADEPT	= Addition of the AT1 Receptor Antagonist Eprosartan to ACE Inhibitor Therapy in Chronic Heart Failure trial
ARB	= angiotensin receptor blocker
CHARM	= Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity trial
CI	= confidence interval
ELITE	= Evaluation of Losartan In The Elderly study
HF	= heart failure
NYHA	= New York Heart Association
OPTIMAAL	= Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan trial
OR	= odds ratio
RESOLVD	= Randomized Evaluation of Strategies for Left Ventricular Dysfunction pilot study
SPICE	= Study of Patients Intolerant of Converting Enzyme inhibitors
STRETCH	= Symptom, Tolerability, Response to Exercise Trial of Candesartan cilexetil in Heart failure
V-HeFT	= Vasodilator Heart Failure Trial
Val-HeFT	= Valsartan Heart Failure Trial
VALIANT	= Valsartan in Acute Myocardial Infarction

allocation, parallel-group design, blinded studies and treatment duration of at least four weeks. Included studies must report death or hospitalization as clinical efficacy or safety end points. Studies that required the co-administration of non-randomized investigational agents were excluded. We excluded studies that were published in non-peer reviewed journals or only as abstracts.

Study outcomes. Relevant trials were identified by consensus. Outcome data were independently extracted by two reviewers, and disagreements were resolved by consensus or a third reviewer. Adequacies of random allocation, blinding and descriptions of withdrawals and dropouts were individually judged for each trial. Study authors and pharmaceutical companies were contacted to clarify insufficiencies of the published data.

Our primary outcome was all-cause mortality. Our secondary outcome was hospitalization for HF. We defined hospitalization for HF as a hospital admission for worsening signs or symptoms of HF or for complications relating to the treatment of HF or for syncope or arrhythmias related to acute exacerbations of HF.

Statistical analysis. All analyses were based on the intention-to-treat principle. Crude treatment effects for each study were reported as standard odds ratios (ORs). Pooled ORs and the 95% confidence intervals (CIs) were calculated based on the Mantel-Haenszel method (9) for fixed effects models and the methods of DerSimonian and Laird (10) for random effects models. A continuity correction factor (11) was added in order to avoid division by zero. The chi-square test for heterogeneity was used to test for the assumption of a fixed effects model ($p > 0.10$).

In our primary analysis, all ARBs were combined regardless of dosages, assuming a class effect and analyzed regardless of the types of controls (placebo or ACEI). Combination therapy with ARBs and ACEIs were analyzed as the ARB arm and compared with controls. For studies with more than one control arm (such as both placebo and ACEI), all controls were combined to form one "mixed" control arm and compared with the ARB arm. Random effects models were used to report the primary analysis.

Secondary stratified analyses were conducted to refine the types of treatment comparison. Three treatment comparisons were made: 1) ARBs versus placebo, without background ACEI therapy; 2) ARBs versus ACEIs; and 3) combination therapy of ARBs and ACEIs versus ACEIs alone. The latter comparison included trials that compared ARBs with placebo where background open-label ACEI therapy was given. Fixed effects models were used to report all stratified analyses.

To determine the robustness of our pooled effects, we compared our primary analysis with fixed effects and random effects models. We also compared our stratified analyses with our primary analysis to determine whether any observed heterogeneity in the treatment effects of ARBs was partly due to differences in the types of controls with which ARBs were compared. We recalculated the pooled effect estimates using Peto OR (12) and then compared them with those calculated using the methods of DerSimonian and Laird (10). Pooled estimates were also recalculated after excluding either: 1) studies that included only ACEI-intolerant patients; or 2) studies that lasted less than six months. We defined a pooled treatment effect to be qualitatively robust if the upper and lower confidence bounds for the pooled effect would remain unchanged in direction with respect to unity. A funnel plot (13) of all included trials was used to check for the presence of publication bias. Power calculations (14) were used to determine the minimal effect sizes detectable by our analysis. All analyses were conducted using the RevMan 4.1 (7) and SAS 8.0 (Cary, North Carolina) statistical packages.

RESULTS

Literature search. Our search identified 17 relevant trials (Table 1). Twenty-six studies were excluded for the following reasons: data published as abstracts only (n = 6); crossover trials (n = 4), singe-dose study (n = 5); inappropriate study population (n = 3), lack of appropriate controls (n = 2); non-randomized study (n = 2); failure to report clinical events (n = 2); and duplicated study (n = 2). Three trials (Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity trial [CHARM] [15], Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan trial [OPTIMAAL] [16] and

Table 1. Characteristics of Randomized Trials on ARBs in HF That Were Included in the Meta-analysis

Trials	Participants	n	Drugs	Controls	Mean Follow-up	Background ACEI	Outcomes
ADEPT 2001 (20)	NYHA II–IV, LV EF ≤35%	36	Eprosartan 400 mg BID	Placebo	8 weeks	Yes	Primary: EF; secondary; hemodynamics, neurohormones
Crozier 1995 (19)	NYHA II–IV, LV EF <40%, PCWP ≥13 mm Hg	134	1) Losartan 2.5 mg OD; 2) losartan 10 mg OD; 3) losartan 25 mg OD; 4) losartan 50 mg OD	Placebo	12 weeks	No	Primary: PCWP; secondary; clinical status, tolerability
Dickstein 1995 (27)	NYHA III–IV, LV EF ≤35%	166	1) Losartan 25 mg OD, 2) losartan 50 mg OD	Enalapril 10 mg BID	8 weeks	No	Primary: exercise capacity, clinical status, neurohumoral activation
ELITE 1997 (28)	NYHA II–IV, LV EF ≤40%, no prior ACEI, age ≥65	722	Losartan 50 mg OD	Captopril 50 mg TID	48 weeks	No	Primary: renal dysfunction; secondary: all-cause mortality, HF hospitalization
ELITE II 2000 (5)	NYHA II–IV, LV EF ≤40%	3,152	Losartan 50 mg OD	Captopril 50 mg TID	1.5 years	No	Primary: all-cause mortality; secondary: composite of sudden cardiac death or resuscitated cardiac arrest
Hamroff 1999 (21)	NYHA III–IV	33	Losartan 50 mg OD	Placebo	6 months	Yes	Primary: peak aerobic capacity, NYHA functional class; secondary: laboratory safety parameters, doses of concomitant background medications
Lang 1997 (29)	NYHA II–IV, LV EF ≤45%	116	1) Losartan 25 mg OD; 2) losartan 50 mg OD	Enalapril 10 mg BID	12 weeks	No	Primary: exercise tolerance, clinical status; secondary: EF
Mazayev 1998 (30)	NYHA II–IV, PCWP ≥15 mm Hg	116	1) Valsartan 40 mg BID; 2) valsartan 80 mg BID; 3) valsartan 160 mg BID	1) Placebo; 2) Iisinopril 10 mg OD	4 weeks	No	Primary: PCWP, adverse events; secondary: CO, SVR
Phase III Int'l 1996 (4)	NYHA II–IV, EF ≤40%	385	Losartan 50 mg OD	Placebo	12 weeks	No	Primary: exercise capacity
Phase III US 1995 (4)	NYHA II–IV, EF ≤40%	351	Losartan 50 mg OD	Placebo	12 weeks	No	Primary: exercise capacity
RESOLVD 1999 (31)	NYHA II–IV, LV EF <40%, 6-min walk distance <500 m	768	1) Candesartan 4 mg OD; 2) candesartan 8 mg OD; 3) candesartan 16 mg OD	1) Enalapril 10 mg BID; 2) placebo	43 weeks	No	Primary: 6-min walk distance, EF, ventricular volume, neurohormone level, QOL, NYHA
SPICE 2000 (22)	NYHA II–IV, LV EF <35%	270	Candesartan 16 mg OD	Placebo	12 weeks	No	Primary: tolerability; secondary: adverse events, clinical events, QOL, functional status
STRETCH 1999 (23)	NYHA II–III, LV EF 30%–45%	844	1) Candesartan 4 mg OD; 2) candesartan 8 mg OD; 3) candesartan 16 mg OD	Placebo	12 weeks	No	Primary: exercise time; secondary: clinical status, cardiothoracic ratio, neuroendocrine parameters
Tonkon 2000 (24)	NYHA II–III, LV EF ≤40%	109	Irbesartan 150 mg OD	Placebo	12 weeks	Yes	Primary: ETT; secondary: LV EF, clinical status, safety
V-HeFT 1999 (25)	NYHA II–IV, PCWP ≥15 mm Hg	83	1) Valsartan 80 mg BID; 2) valsartan 160 mg BID	Placebo	4 weeks	Yes	Primary: PCWP; secondary: hemodynamics, neurohormones
Val-HeFT 2001 (18)	NYHA II–IV, LV EF ≤40%	5,010	Valsartan 160 mg BID	Placebo	23 months	Yes	Primary: all-cause mortality, combined all-cause mortality and morbidity (hospitalization, resuscitated sudden death, IV inotropic or vasodilator support)
Weber 1997 (26)	NYHA II–IV	154	Losartan 2.5–50 mg OD	Placebo	12 weeks	No	Primary: safety

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BID = twice a day; CO = cardiac output; EF = ejection fraction; ETT = exercise tolerance time; HF = heart failure; IV = intravenous; LV = left ventricle; NYHA = New York Heart Association; OD = once daily; PCWP = pulmonary capillary wedge pressure; QOL = quality of life; SVR = systemic vascular resistance; TID = three times a day.

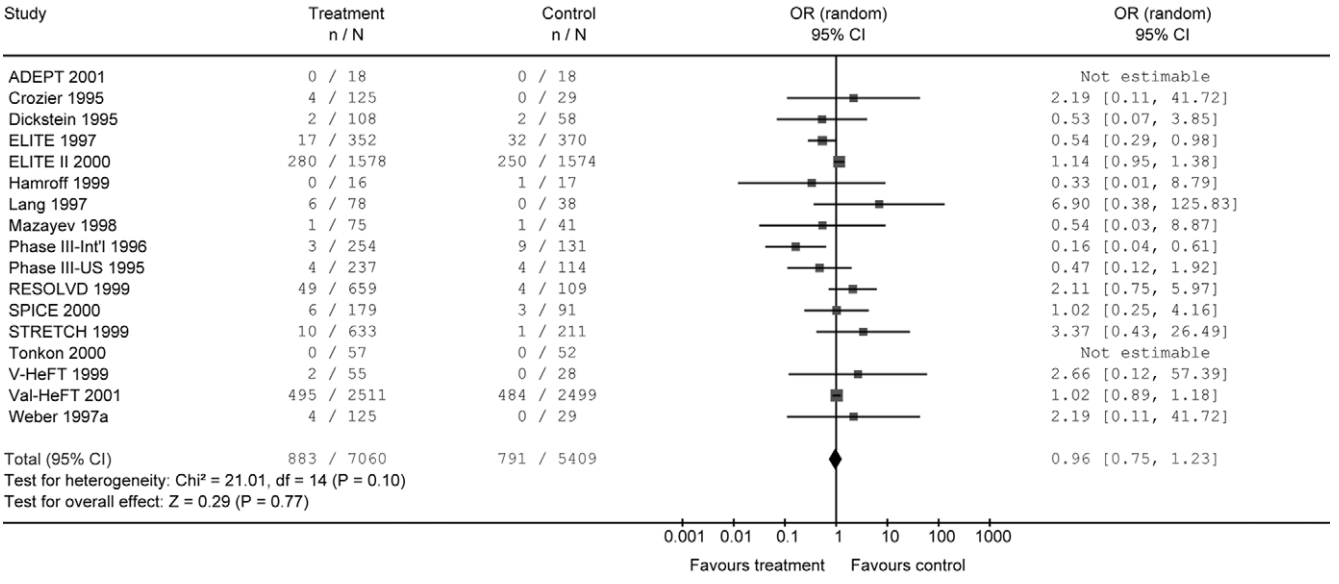

Figure 1. Comparison of angiotensin receptor blockers versus controls on all-cause mortality. Controls were either placebo or angiotensin-converting enzyme inhibitor (ACEI). Odds ratios (OR) and the 95% confidence intervals (CI) are shown on a logarithmic scale, with box size proportional to the sample size. The **diamond** represents the pooled effect. Acronyms as in Abbreviations and Acronyms box.

Valsartan in Acute Myocardial Infarction [VALIANT] [17]) are ongoing.

Study characteristics. All were randomized, double-blind, controlled trials. A total of 12,469 patients were randomized: 7,060 to ARBs and 5,409 to controls (placebo or ACEIs). Eleven trials (4,18–26) used placebo as controls. Four trials (5,27–29) used ACEIs as controls. Two trials (30,31) included both a placebo and an ACEI arm as controls. Background open-label ACEI therapy was mandatory or recommended in five of the 11 placebo-controlled trials (18,20,21,24,25). This was in contrast to one trial (22) that enrolled only ACEI-intolerant patients. Ten trials (5,18,20,22–25,27–30) employed a placebo or drug-free run-in period, whereas two trials (21,31) employed an active therapy run-in period. All but two trials (21,26) required objective documentation of left ventricular systolic dysfunction. The proportions of NYHA IV HF subjects across the studies were small (2% to 15%). The mean age of participants ranged between 56 and 73 years. Male subjects comprised 48% to 100% of the enrollees. The studies were dominated by whites (59% to 100%).

Five ARBs were tested in this meta-analysis: losartan (in nine trials), candesartan (in three trials), valsartan (in three trials), irbesartan (in one trial) and eprosartan (in one trial). Mean duration of treatment varied from four weeks to 1.5 years.

Methodological quality. Only one trial (23) gave explicit description of the randomization method. Given, however, all but two trials (20,21) were multicenter in design, it would be unlikely that the allocation method was flawed to such an extent as to influence the outcome of our analysis. Five trials (19,21,25,26,29) did not disclose methods of double blinding to judge their adequacies. Two trials (4) did not disclose any information on withdrawals or dropouts.

Mortality. All-cause mortality was reported in all trials. A total of 1,674 deaths were recorded. Overall, there was no statistical difference in the pooled mortality rate between the ARB and control group (OR: 0.96; 95% CI: 0.75 to 1.23; n = 7,060 vs. n = 5,409; Fig. 1). Heterogeneity of borderline significance was observed in the pooled estimate across the trials (p = 0.10). This heterogeneity was reduced when the analysis was stratified into one of the three ARB-ACEI-placebo treatment comparisons (Fig. 2). Among trials where background ACEIs were not given, the pooled estimate favored ARBs over placebo in improving survival (OR: 0.68; n = 1,628 vs. n = 631), albeit limited sample size prevented it from attaining statistical significance (95% CI: 0.38 to 1.22). In contrast, among trials that directly compared ARBs with ACEIs, ARBs were not superior in improving survival (1.09; 0.92 to 1.29; n = 2,518 vs. n = 2,164). When the combination therapy of ARBs and ACEIs was compared with ACEIs alone, the risks of death were virtually identical (1.04; 0.91 to 1.20; n = 2,989 vs. n = 2,723).

Hospitalization. Hospitalization for HF was reported in only six trials. A total of 1,515 hospitalizations (first event) were recorded. Overall, there was no statistical difference in the pooled rate of hospitalization between the ARB and control groups (0.86; 0.69 to 1.06; n = 5,336 vs. n = 4,695; Fig. 3). Once again, heterogeneity of borderline significance was observed in the pooled estimate across the trials (p = 0.11). This heterogeneity was reduced when the analysis was stratified by specific treatment comparisons (Fig. 4). Only one trial that compared ARBs with placebo without background ACEI therapy reported on hospitalization; it

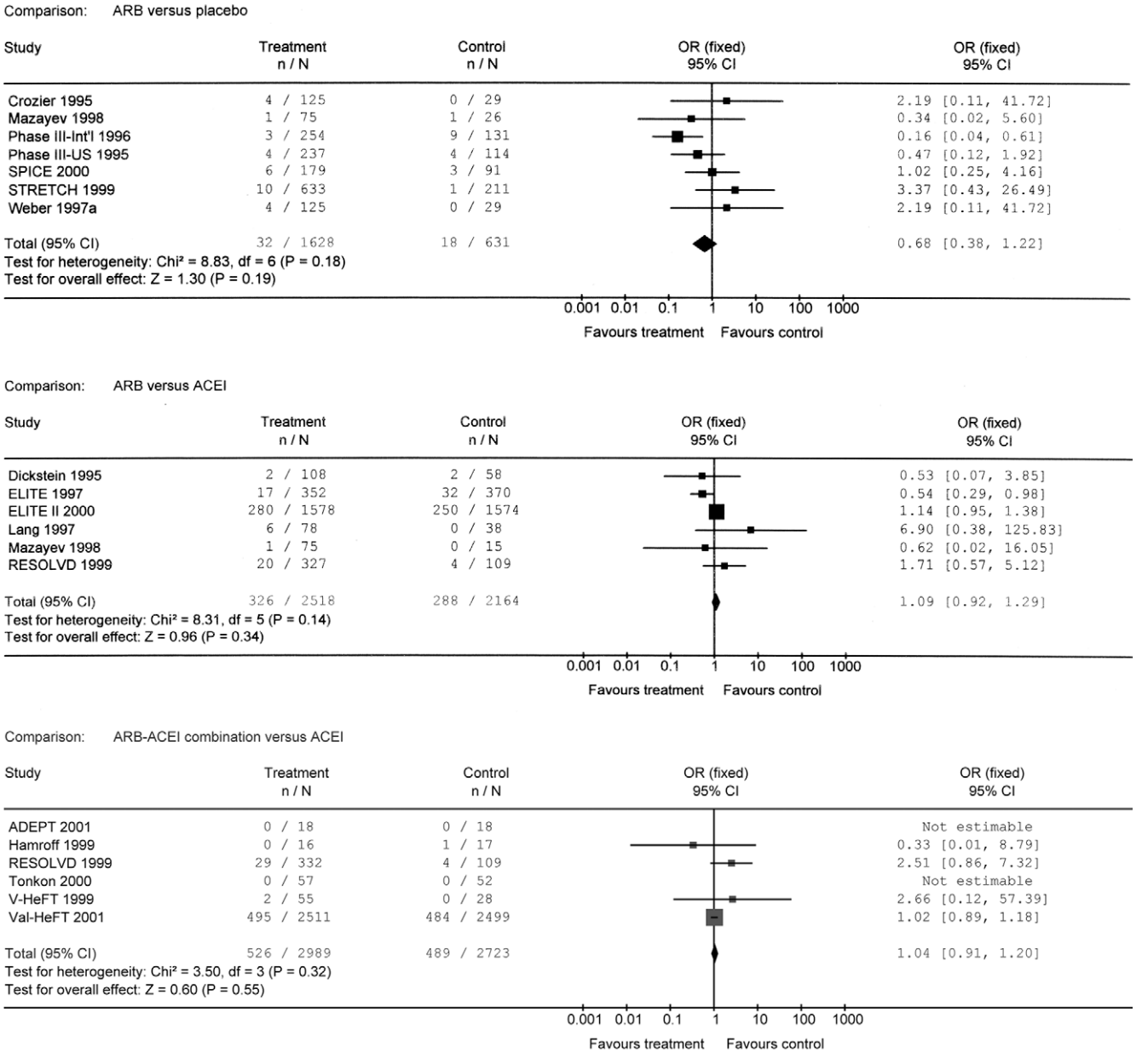

Figure 2. Stratified comparisons of angiotensin receptor blockers (ARB) on all-cause mortality: ARB versus placebo, ARB versus angiotensin-converting enzyme inhibitors (ACEI) and ARB-ACEI combination versus ACEI. Odds ratios (OR) and the 95% confidence intervals (CI) are shown on a logarithmic scale, with box size proportional to the sample size. In each stratum, the **diamond** represents the pooled effect. Acronyms as in Abbreviations and Acronyms box.

showed a non-significant trend in benefit favoring the ARB group (0.67; 0.29 to 1.51; n = 179 vs. n = 91). In the stratified comparison of ARBs with ACEIs, no difference in the rate of hospitalization was seen (0.95; 0.80 to 1.13; n = 2,257 vs. n = 2,053). In contrast, the combination therapy of ARBs and ACEIs showed a statistically significant benefit in reducing hospitalization over ACEIs alone (0.74; 0.64 to 0.86; n = 2,900 vs. n = 2,660).

Sensitivity analyses. Our analyses were largely robust, with a few exceptions, in both the choices of models and the statistical methods. The substitution of a fixed model for a random effects model did not change our initial qualitative interpretation of the pooled treatment effect on mortality, but it resulted in a statistically significant benefit of reduced hospitalization in favor of ARBs. Likewise, using pooled ORs obtained by the Peto method instead of the methods of DerSimonian and Laird (10) did not change our initial qualitative interpretation in the pooled treatment effect on mortality but resulted in a statistically significant benefit in reducing hospitalization now seen in favor of ARBs. Neither the exclusion of the one study that enrolled only ACEI-intolerant patients nor the exclusion of trials that lasted less than six months changed the qualitative interpretation of the pooled treatment effect on mortality or

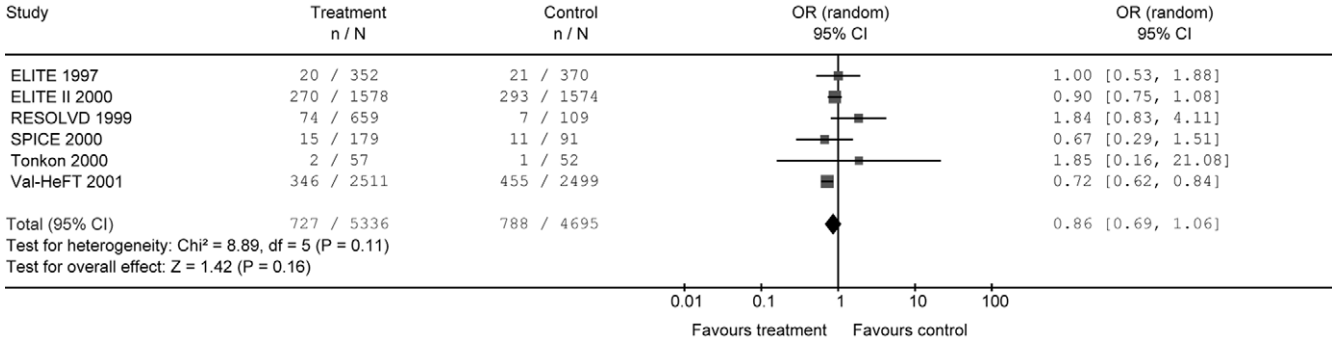

Figure 3. Comparison of angiotensin receptor blockers versus controls on hospitalization for HF. Controls were either placebo or angiotensin-converting enzyme inhibitors. Odds ratios (OR) and the 95% confidence intervals (CI) are shown on a logarithmic scale, with box size proportional to the sample size. The **diamond** represents the pooled effect. Acronyms as in Abbreviations and Acronyms box.

hospitalization. A funnel plot for mortality showed no obvious publication bias.

Study power. Post-hoc power calculations showed that our meta-analysis had adequate power to detect at least a moderate effect in favor of ARBs if ARBs were truly efficacious over controls. At 90% power and a type I error rate of 5%, our study was powered to detect an absolute risk reduction of 2.0% or a relative risk reduction of 13.7% in all-cause mortality in favor of ARBs when compared with either placebo or ACEIs. For hospitalization for HF, our

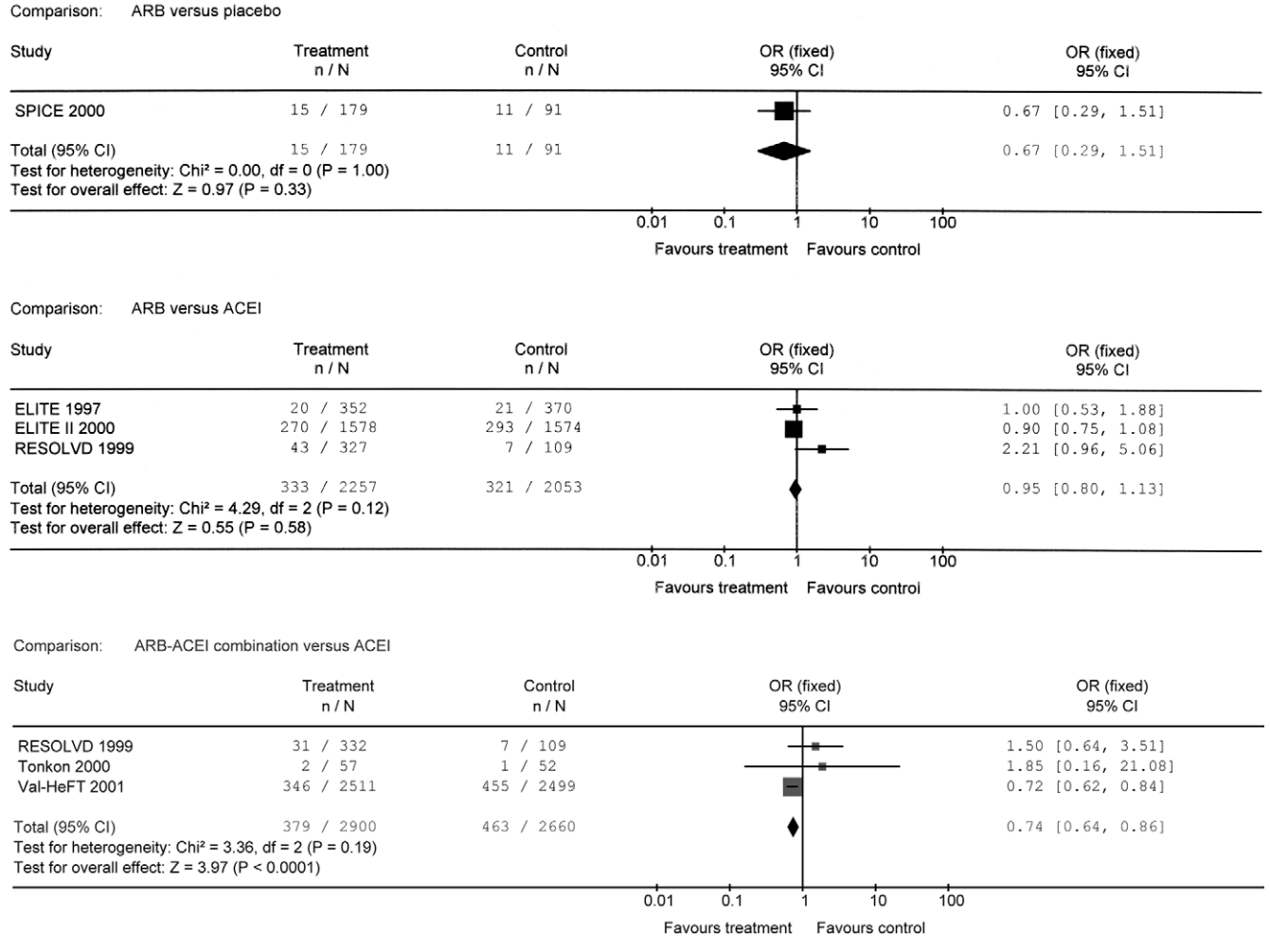

Figure 4. Stratified comparisons of angiotensin receptor blockers (ARB) on hospitalization for HF: ARB versus placebo, ARB versus angiotensin-converting enzyme inhibitor (ACEI) and ARB-ACEI combination versus ACEI. Odds ratios (OR) and the 95% confidence intervals (CI) are shown on a logarithmic scale, with box size proportional to the sample size. In each stratum, the **diamond** represents the pooled effect. Acronyms as in Abbreviations and Acronyms box.

study was powered to detect an absolute risk reduction of 2.4% or a relative risk reduction of 13.9% from ARBs over controls.

DISCUSSION

Evidence of benefit. Accumulated data to date cannot confirm a clear-cut superiority of ARBs in reducing either mortality or hospitalization when compared with controls. Our primary analysis, however, may be considered conservative given that 12 of the 17 trials had included ACEIs as either controls or background therapy. The inclusion of ACEIs, with a confirmed mortality and morbidity benefit, thus tends to underestimate the true treatment benefit of ARBs when compared with placebo controls alone. In fact, when we considered only the trials in which ARBs were compared with placebo without background ACEI therapy, the direction of the observed benefits was in favor of ARBs. Such a trend is reassurance to the use of ARBs as monotherapy in patients who are intolerant to ACEIs. In contrast, the virtually identical observed risks of both ARBs and ACEIs in the stratified analysis is compatible with, though not proof of, the hypothesis that ARBs and ACEIs may be interchangeable when clinically warranted.

The absence of a clear benefit in favor of ARBs cannot be solely attributed to a lack of power in our study. Pogue and Yusuf (32) have argued that most interventions in contemporary cardiovascular medicine that are clinically important reduce the relative risk of major outcomes by at least 15%. Any observed reduction below this threshold may simply be a result of statistical aberration and not truly represent a biologically plausible or clinically reliable change. We have shown that even if ARBs were truly efficacious, our meta-analysis was unlikely to miss a relative risk reduction as large as 13.9% in favor of ARBs. Our study is thus reliable in excluding any favorable effect from ARBs—particularly over ACEIs—that is of at least moderate size.

Heterogeneity of effect. The heterogeneity observed in the pooled estimates in our primary analysis may be explained by the trial designs—difference in the types of controls used, inclusion of different ARBs and variation in the duration of treatment. Analyses stratified by the types of controls indeed reduced the observed heterogeneity. Similarly, readers should be cautioned against the assumption that all ARBs exert a similar "class" effect upon which this meta-analysis is based. However, despite the known pharmacologic differences between the various ARBs (33), there is currently no definitive data to indicate that these differences have impact on major clinical end points. Finally, our present analysis cannot fully adjust for differences in the duration of treatment between trials. Although it is possible that some benefits of ARBs that were not detected in the early stages would emerge over time, it should be noted that trials with longer treatment periods did not show more favorable pooled effects with ARBs than the remaining trials with shorter treatment periods.

Sensitivity of effect. The observed pooled treatment effect of ARBs on mortality was qualitatively robust. We viewed the apparent sensitivity of the pooled treatment effect of ARBs on hospitalization with particular caution. This is because both the use of a fixed effects model and the use of Peto OR (which inherently assumes a fixed effects model) ignore the statistical and clinical heterogeneity we observed in such a comparison. The Peto method also tends to yield biased estimates when applied to unbalanced data such as those in this meta-analysis (34).

Improvements over previous meta-analyses. Results of our meta-analysis thus disagree with a previous meta-analysis (4) that suggested an overall survival benefit with losartan in HF. One source for this difference is the addition of the results from the Evaluation of Losartan in the Elderly (ELITE) II trial (5) to our analysis. ELITE II, published subsequent to the previous meta-analysis, contradicted the results of that meta-analysis and did not demonstrate a survival benefit of losartan over captopril. The large weight of that trial thus negated the favorable pooled effect demonstrated in that meta-analysis. Furthermore, the aforementioned meta-analysis pooled exclusively trials that used only losartan. In contrast, our analysis included trials with other ARBs such as Randomized Evaluation of Strategies for Left Ventricular Dysfunction pilot study (RESOLVD) (31) (candesartan) and Val-HeFT (18) (valsartan), both of which involved a significant cohort of patients.

Study limitations. Of all trials included in this meta-analysis, only ELITE II and Val-HeFT were powered to evaluate the mortality effect of ARBs as a primary outcome. In addition, the limited sample sizes in other trials limited the power of our stratified analyses to detect smaller, but potentially clinically meaningful, benefits of ARBs when compared with specific controls. On the other hand, the lack of "mega-trials" dominating the stratified comparison between ARBs and placebo reinforces the value of this meta-analysis to succinctly summarize data from existing smaller trials.

Inconsistent reports of other outcomes among the included studies also prevented us from pooling other clinically important end points. Although data from the ongoing CHARM, OPTIMAAL and VALIANT trials may refine our current conclusions in subsequent updates of this meta-analysis, the results of all three trials are not expected to be available until 2003, before which time this meta-analysis will remain as the best overview of the current evidence regarding the use of ARBs in the HF population.

Clinical implications. Our meta-analysis of 17 randomized controlled trials involving 12,649 patients with symptomatic HF cannot confirm the superiority of ARBs in reducing either all-cause mortality or hospitalization for HF, particularly when compared with ACEIs. Current evidence-based practice guidelines should continue to emphasize ACEIs as the primary pharmacologic therapy for patients with HF. However, in patients whom ACEIs cannot be given because of contraindications or intolerance,

ARBs may be a reasonable substitute. Ongoing clinical trials should help to resolve the definitive role of ARBs in the treatment of HF—in particular as monotherapy in the absence of ACEIs or as combination therapy with ACEIs.

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