REVIEW ARTICLE

Adverse Effects of Combination Angiotensin II Receptor Blockers Plus Angiotensin-Converting Enzyme Inhibitors for Left Ventricular Dysfunction

A Quantitative Review of Data From Randomized Clinical Trials

Christopher O. Phillips, MD, MPH; Amir Kashani, MS, MD; Dennis K. Ko, MD; Gary Francis, MD; Harlan M. Krumholz, MD, SM

Background: We performed a meta-analysis of randomized controlled trials to assess ongoing concerns about the safety profile of combination angiotensin II receptor blockers (ARBs) plus angiotensin-converting enzyme (ACE) inhibitors in symptomatic left ventricular dysfunction.

Methods: MEDLINE (January 1966–December 2006) and Web sites for the National Institute of Health Clinical Trials and the Food and Drug Administration were searched for eligible RCTs that included 500 or more subjects, had a follow-up of 3 months or longer, and reported adverse effects. We used a random effects model to calculate the relative risk (RR) and 95% confidence interval (CI) for the following outcome measures: medication discontinuations because of adverse effects, worsening renal function (an increase in serum creatinine level of >0.5 mg/dL [to convert to micromoles per liter, multiply by 88.4]), hyperkalemia (serum potassium level >5.5 mEq/L [to convert to millimoles per liter, multiply by 1]), and symptomatic hypotension.

Results: Four studies (N=17 337; mean follow-up, 25 months [range, 11-41 months]) were selected. Combination ARB plus ACE inhibitor vs control treatment that included ACE inhibitors was associated with significant increases in medication discontinuations because of adverse effects in patients with chronic heart failure (RR, 1.38 [95% CI, 1.22-1.55]) or in patients with acute myocardial infarction with symptomatic left ventricular dysfunction (RR, 1.17 [95% CI, 1.03-1.34]), and for both conditions there were significant increases in worsening renal function (RR, 2.17 [95% CI, 1.59-2.97] and RR, 1.61 [95% CI, 1.31-1.98], respectively), hyperkalemia (RR, 4.87 [95% CI, 2.39-9.94] and RR, 1.33 [95% CI, 0.90-1.98], respectively; the latter was not significant), and symptomatic hypotension (RR, 1.50 [95% CI, 1.09-2.07], and RR, 1.48 [95% CI, 1.33-3.18], respectively).

Conclusion: Combination ARB plus ACE inhibitor therapy in subjects with symptomatic left ventricular dysfunction was accompanied by marked increases in adverse effects.

Arch Intern Med. 2007;167(18):1930-1936

Author Affiliations:
Department of General Internal Medicine and Section of Hospital Medicine, The Cleveland Clinic Lerner College of Medicine, Cleveland, Ohio (Dr Phillips); Yale University School of Medicine and Yale–New Haven Hospital Center for Outcomes Research and Evaluation, New Haven, Connecticut (Drs Kashani and Krumholz); Division of Cardiology, The Cleveland Clinic (Dr Francis); and Division of Cardiology, Schulich Hearth Center, Sunnybrook Health Sciences Centre, Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada (Dr Ko).

DUAL SUPPRESSION OF THE renin angiotensin aldosterone system with combination therapy that includes angiotensin II type I receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors is gaining interest among heart failure (HF) experts.[1-13] However, current guidelines for recommended pharmacotherapy in patients with HF have not endorsed this approach.[14,15] This strategy could be very important given the continuing high mortality and morbidity among patients with HF. Prior reviews of this strategy suggested that there was no conclusive evidence for a survival advantage from combination ARB plus ACE inhibitor therapy; however, there were significant reductions in HF hospitalizations in subjects with chronic HF.[16-19] Recently, an additional large clinical trial investigating the efficacy of combination ARB plus ACE inhibitor therapy vs background treatment that includes ACE inhibitors in subjects with acute myocardial infarction (AMI) and symptomatic left ventricular (LV) dysfunction has been published,[20] and the results lend further support for the combination strategy in reducing HF hospitalizations but not overall mortality. Despite

the initial enthusiasm for combination ARBs plus ACE inhibitors as a viable therapeutic option for subsets of patients with symptomatic LV dysfunction, concerns about adverse effects including severe or life-threatening hyperkalemia[21-31] persist and may limit the application of this strategy.

Accordingly, we conducted a systematic review to quantify the magnitude of risk of adverse effects in association with combination ARB plus ACE inhibitor therapy. We compared changes in medication nonadherence as assessed by the overall risk of discontinuation of therapy because of adverse effects and the incidence and severity of worsening renal function (including elevations in serum creatinine level >0.5 mg/dL [to convert to micromoles per liter, multiply by 88.4] and hyperkalemia [serum potassium level >5.5 mEq/L {to convert to millimoles per liter, multiply by 1}]), and symptomatic hypotension. We also evaluated whether the occurrence of these end points differed among patients with chronic HF vs patients with AMI and symptomatic LV dysfunction.

METHODS

SELECTION OF RANDOMIZED TRIALS

We performed this review in accordance with the Quality of Reporting of Meta-analysis (QUOROM) statement and the Consolidated Standards of Reporting Trials (CONSORT) Group recommendations.[32,33] Eligible studies were identified by searching MEDLINE (January 1966–December 2006), EMBASE (January 1980–December 2006), the Cochrane Library (Controlled Trials Register and Database of Systematic Reviews, all years), the National Institute of Health Clinical Trials (http://www.clinicaltrials.gov) and the US Food and Drug Administration (FDA) Web sites (http://www.FDA.gov), and relevant bibliographies. Because terminology for HF is standardized, we used mostly the following medical subject headings (MeSH) for our search: *congestive heart failure*, *chronic heart failure*, *heart failure*, *left ventricular systolic dysfunction*, *angiotensin-converting enzyme inhibitors*, *angiotensin-II receptor blockers*, *angiotensin receptor blockers*, *combination angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers (or angiotensin receptor blockers)*, and the following generic names of individual agents in current practice: *candesartan, eprosartan*, *irbesartan*, *losartan*, *tasosartan*, *telmisartan*, and *valsartan*.

TRIAL REVIEW

Studies were selected for inclusion when the following criteria were met: random allocation of 500 or more subjects to combination ARB plus ACE inhibitor or standard therapy for LV dysfunction that included ACE inhibitor; follow-up of 3 months or longer; and reports of adverse effects. We chose this sample size limitation to reduce uncertainty in the estimates of adverse effects and to reduce confounding due to publication bias and underpowered studies. We chose the minimum 3-month follow-up period to focus our analysis on the long-term effects of treatment in subjects for whom combination ACE inhibitor plus ARB therapy could be sustained. The search strategy is summarized in the **Figure**.

DATA EXTRACTION

Paired reviewers (C.O.P. and A.K.) independently reviewed each eligible report without the use of masking, tabulated important trial characteristics, and assessed methodological quality using the 5-point Jadad score, which assigns points (maximum of 5 points) for the following: randomization (1 point), method of randomization generation (1 point), double blinding (2 points), and loss to follow-up (1 point).[34] Extracted data also included patient demographics such as age, percentage of LV ejection fraction (LVEF), and comorbidity. Paired reviewers (C.O.P. and A.K.) also extracted adverse events according to treatment groups with the use of 2×2 tables. Adverse events were abstracted from trial reports and corroborated with publicly available data from the FDA Web site. Results reflect adverse event counts reported in the primary studies and are subject to rounding error because some studies reported event counts as a percentage. Discrepancies in data abstraction were resolved by consensus.

STATISTICAL ANALYSIS

Outcomes measures were medication discontinuations because of adverse effects (including hypotension, cough, and angioedema; worsening renal function [defined as elevations in serum creatinine level >0.5 mg/dL; to convert to micromoles per liter, multiply by 88.4], hyperkalemia [serum potassium level >5.5 mEq/L; to convert to millimoles per liter, multiply by 1], and symptomatic hypotension). The definitions for medication discontinuation because of adverse effects were specific for each trial. However, there was more consistency across studies in the definition of renal dysfunction, hyperkalemia, and symptomatic hypotension.

Using the intention-to-treat principle, we calculated the relative risk (RR) and 95% confidence interval (CI) for clinical efficacy and reported adverse effects in each study according to randomized assignments and pooled the results across studies using a fixed-effects model, which assumes that interstudy variability is due to random error. We rejected the assumption of homogeneity in study effects when χ^2 test results suggested the presence of significant heterogeneity ($P<.05$). In our exploration of potential factors that may have contributed to the presence of heterogeneity, we stratified our analyses by clinical setting (chronic HF or AMI with symptomatic LV dysfunction). To estimate and control for this type of quantitative heterogeneity, we also applied a random effects statistical model, which uses weighting based on inverse variance calculated according to DerSimonian and Laird.[35] This model gives a meta-estimate of the RR, which represents the mean effects of treatment under study conditions rather than the true effects in the population. A weighted log RR of the individual studies was calculated and then pooled to arrive at the combined RR. We derived final CIs by calculating the exponential of the upper and lower confidence limits for the log RR. We report random effects estimates when χ^2 tests suggested significant heterogeneity. From the pooled study population, we calculated separate estimates for adverse effects for subgroups of patients with chronic HF or patients with AMI and symptomatic LV dysfunction. For medication discontinuation because of adverse events and worsening, we conducted sensitivity analysis to test the

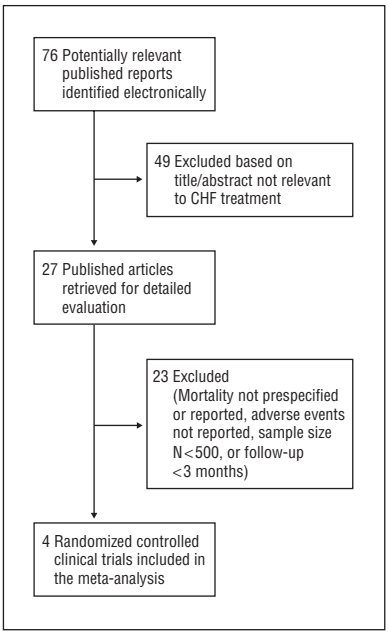

Figure. Published reports evaluated for inclusion in the meta-analysis. CHF indicates congestive heart failure.

Table 1. Baseline Characteristics of Patients and Trials of Combination ARB Plus ACE Inhibitor Therapy Included in Meta-analysis

Source	Patients Randomized[a]	Entry Criteria	Age, Mean, y	Men, %	Combination ARB + ACE Inhibitor Evaluated		Follow-up, mo
					Intervention	Control	
VALIANT,[20] 2003[b]	9794	AMI	65.0	69.1	Valsartan + captopril	Captopril	24.7
CHARM-added,[36] 2003	2458	Chronic HF	64.0	78.7	Candesartan + enalapril	Placebo	41.4
ValHeFT,[37,38] 2002[c]	4644	Chronic HF	62.7	80.0	Valsartan + ACE inhibitor[d]	Placebo	23.0
RESOLVD,[39] 1999	441	Chronic HF	63.0	87.5	Candesartan + enalapril	Enalapril	10.8[e]
Pooled cohort	17 337	NA	64 (range, 63-65)	79 (range, 69-88)	NA	NA	25 (range, 11-41)

Abbreviations: ACE, angiotensin-converting enzyme; ARB angiotensin II type I receptor blocker; HF, heart failure; NA, not applicable.
[a] Only patients exposed to combination ARB plus ACE inhibitor vs standard HF therapy that included an ACE inhibitor were included for analysis.
[b] Acute myocardial infarction with symptomatic left ventricular dysfunction.
[c] Patients not receiving an ACE inhibitor at baseline (n=366) were excluded from the analysis (5010−366=4644).
[d] Multiple ACE inhibitors were used for treatment.
[e] Reported as 43 weeks of follow-up.

Table 2. Baseline Use of Recommended Pharmacotherapy in Studies of Combination ARB Plus ACE Inhibitor Therapy vs Background Treatment That Includes ACE Inhibitors

Variable	Source			
	VALIANT,[20] 2003	CHARM-Added,[36] 2003	ValHeFT,[37,38] 2002	RESOLVD,[39] 1999
Study cohorts	AMI	Chronic HF	Chronic HF	Chronic HF
Intervention, daily dose				
Combination ARB + ACE inhibitor	Valsartan, 320 mg	Candesartan, 8 mg	Valsartan, 320 mg	Candesartan, 4 mg or 8 mg
Control agent or placebo	Captopril, 150 mg	Placebo[a]	Placebo[a]	Enalapril, 20 mg
Proportion of patients at target dose, %				
ARB plus ACE inhibitor	47	61	84	. . .
Control or placebo	56	73	93	. . .
Background therapy, % of patients				
β-Blockers	70.4 vs 70.1	55.0 vs 55.9	35.4 vs 35.3	13.0 vs 23.0[b]
Diuretics	50.3 vs 49.4	90.0 vs 90.1	85.8 vs 85.2	84.0 vs 87.0
Digoxin	. . .	57.6 vs 59.2	67.1 vs 67.6	64.0 vs 79.0
Potassium-sparing agents[c]	9.0 vs 9.1	17.4 vs 16.9	5	. . .

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blocker; AMI, acute myocardial infarction; HF, heart failure; ellipses, data not reported in primary report.
[a] Control subjects receiving a variety of ACE inhibitors including captopril, enalapril, lisinopril, quinapril, and ramipril.
[b] $P<.05$.
[c] Includes aldosterone antagonists. Potassium-sparing diuretics were only reported in VALIANT.[20]

effects of plausible changes in assumptions with respect to different statistical models and type of ARB (candesartan or valsartan), the control agent (placebo or ACE inhibitor), and duration of follow-up. We did not perform a formal assessment of publication bias given our limitation to a sample size of 500 or more and analysis of adverse events. Statistical analyses were performed with STATA 8.0 (StataCorp, College Station, Texas).

RESULTS

OVERVIEW OF THE TRIALS

The search strategy and results are described in the Figure. We screened 76 studies for eligibility and retrieved 27 for in-depth review. Five reports for 4 studies met our inclusion criteria and were selected for analysis.[20,36-39] Individual study quality was high (Jadad score, 4; interquartile range, 3-5).

The present analysis included only patients randomized to combination ARB plus ACE inhibitor therapy vs standard therapy for HF or AMI that included ACE inhibitors. **Table 1** summarizes the distribution of individual trial characteristics and study patients. Across the 4 studies selected for inclusion, there were 2 distinct study populations: chronic stable HF (n=7543; pooled mean age, 63 years; 82% men [range 80%-88%]; mean LVEF, 27% [range 27%-28%]; and mean duration of follow-up, 25 months [range, 11-41 months]), and AMI complicated by LV dysfunction (n=9794; mean age, 65 years; 69% men; mean LVEF, 35%; and median duration of follow-up, 24.7 months). End points for efficacy and adverse effects were reported as having been assessed at the end of the follow-up period in all studies.

The combination of valsartan and an ACE inhibitor was evaluated in 2 studies.[20,37,38] The combination of candesartan plus enalapril was evaluated in another 2.[36,39] Two studies were listed as placebo-controlled trials; however, control groups were receiving a variety of ACE inhibitors as background therapy.[36-38] **Table 2** summarizes the individual agents used for combination therapy, the target dose, the percentage of patients achieving the tar-

Table 3. Results for Medication Discontinuations Because of Adverse Events and Symptomatic Hypotension With Combination ARB Plus ACE Inhibitor Therapy

Source	Discontinuation Because of Adverse Effects, No. of Events/No. of Patients Randomized (%)[a]		*P* Value for Heterogeneity	Symptomatic Hypotension, No. of Events/No. of Patients Randomized (%)[b]		*P* Value for Heterogeneity
	Intervention	Control		Intervention	Control	
VALIANT,[20] 2003	438/4885 (9.0)	375/4909 (7.6)		884/4885 (18.1)	582/4909 (11.9)	
CHARM-Added,[36] 2003	309/1276 (24.2)	233/1272 (18.3)		58/1276 (4.5)	40/1272 (3.1)	
ValHeFT,[37,38] 2002[c]	231/2326 (9.9)	158/2318 (7.2)		32/2326 (1.3)	19/2318 (0.8)	
RESOLVD,[39] 1999	. . .	. . .		4/332 (1.2)	1/109 (0.9)	
Subtotals						
Chronic HF[36-39]	540/3602 (15.0)	391/3590 (11.0)		94/3934 (2.4)	60/3699 (1.5)	
RR (95% CI)	1.38 (1.22-1.55)		.43[a]	1.50 (1.09-2.07)		.94[b]
AMI with LV dysfunction[20]	438/4885 (9.0)	375/4909 (7.6)		884/4885 (18.1)	582/4909 (11.9)	
RR (95% CI)	1.17 (1.03-1.34)			1.48 (1.33-3.18)		. . .
Pooled cohort	978/8487 (11.5)	766/8499 (9.0)		978/8819 (11.1)	642/8608 (7.5)	
RR (95% CI)	1.28 (1.17-1.40)		.17[a]	1.48 (1.34-1.62)		.99[b]

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blocker; AMI, acute myocardial infarction; CI, confidence interval; HF, heart failure; LV, left ventricular; RR, relative risk; ellipses, data not reported or could not be evaluated.
[a] Included symptoms of dizziness, fainting, and syncope.
[b] Events for patients not receiving ACE inhibitors at baseline were excluded from the analysis.

Table 4. Results for Severe Renal Toxic Effects and Severe Hyperkalemia With Combination ARB Plus ACE Inhibitor Therapy

Source	Worsening Renal Function, No. of Events/No. of Patients Randomized (%)[a]		*P* Value for Heterogeneity	Hyperkalemia (Serum Potassium Level >5.5 mEq/L), No. of Events/ No. of Patients Randomized (%)[b]		*P* Value for Heterogeneity
	Intervention	Control		Intervention	Control	
VALIANT,[20] 2003	232/4885 (4.8)	148/4909 (3.0)		57/4885 (1.2)	43/4909 (0.9)	
CHARM-Added,[36] 2003	100/1276 (7.8)	52/1272 (4.1)		44/1276 (3.5)	9/1272 (0.7)	
ValHeFT,[37,38] 2002[c]	27/2326 (1.1)	4/2318 (0.4)		. . .	. . .	
RESOLVD,[39] 1999	2/332 (0.6)	0/109 (0.0)		. . .	. . .	
Subtotals						
Chronic HF[36-39]	128/3934 (3.3)	55/3699 (1.5)		44/1276 (3.5)	9/1272 (0.7)	
RR (95% CI)	2.17 (1.59-2.97)		.18[a]	4.87 (2.39-9.94)		. . .
AMI with LV dysfunction[20]	232/4885 (4.8)	148/4909 (3.0)		57/4885 (1.2)	43/4909 (0.9)	
RR (95% CI)	1.61 (1.31-1.98)		. . .	1.33 (0.90-1.98)		. . .
Pooled cohort	360/8819 (4.1)	203/8608 (2.4)		101/6161 (1.6)	52/6181 (0.8)	
RR (95% CI)	1.76 (1.49-2.09)		<.01[a]	2.46 (0.68-8.87)		<.01[b]

Abbreviations: ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin II type 1 receptor blocker; CI, confidence interval; HF, heart failure; LV, left ventricular; RR, relative risk; ellipses, data not reported or could not be evaluated.
SI conversion factor: To convert potassium to millimoles per liter, multiply by 1; to convert creatinine to micromoles per liter, multiply by 88.4.
[a] Worsening renal function with an increase in serum creatinine level of 0.5 mg/dL or greater over baseline values.
[b] Events for patients not receiving ACE inhibitors at baseline were excluded from the analysis.

get dose, and details of background therapy. The Valsartan in Myocardial Infarction Trial (VALIANT) did not report the use of aldosterone antagonists but did report overall use of potassium-sparing diuretics. For the Valsartan in Heart Failure Trial (ValHeFT), we excluded event counts for the subgroup of patients (n=366) who were not receiving concomitant ACE inhibitors at baseline and were randomized to valsartan vs placebo.[38]

Because of potential confounding due to clinical differences in the physiologic condition of patients with chronic HF and patients with AMI and symptomatic LV dysfunction, we performed separate analyses for these 2 distinct study populations. There was no evidence for statistical heterogeneity in the pooled results for the 3 studies with outcome measures for subgroup of patients with chronic HF. A summary of the results for individual studies, the pooled estimates for the combined study populations, and the *P* values for statistical heterogeneity are reported in **Tables** 1, 2, **3**, and **4**.

MEDICATION DISCONTINUATIONS BECAUSE OF ADVERSE EFFECTS OF COMBINATION ARB PLUS ACE INHIBITOR THERAPY

Combination ACE inhibitor plus ARB therapy vs control treatment that included ACE inhibitors was associated with a significant increase in medication discontinuation because of adverse effects in chronic HF (15.0% vs 11.0%: RR, 1.38 [95% CI, 1.22-1.55]; number needed to harm

[NNH] = 25) and also in patients with AMI and symptomatic LV dysfunction (9.0% vs 7.6%; RR, 1.17 [95% CI, 1.03-1.34]; NNH = 71) (Table 3).

SYMPTOMATIC HYPOTENSION WITH COMBINATION ARB PLUS ACE INHIBITOR THERAPY

Combination ARB plus ACE inhibitor therapy vs control treatment was also associated with significant increases in the risk of symptomatic hypotension in chronic HF (2.4% vs 1.5%: RR, 1.50 [95% CI, 1.09-2.07]; NNH = 111) and patients with AMI and symptomatic LV dysfunction (18.1% vs 11.9%: RR, 1.48 [95% CI, 1.33-3.18]; NNH = 16) (Table 3). Complete details for these end points in individual trials are listed in Table 3.

WORSENING RENAL FUNCTION AND HYPERKALEMIA WITH COMBINATION ARB PLUS ACE INHIBITOR THERAPY

Worsening renal function (defined as an increase in serum creatinine level > 0.5 mg/dL, up to a doubling over baseline values) was significantly increased with combination ARB plus ACE inhibitor therapy vs control treatment in patients with chronic HF (3.3% vs 1.5%: RR, 2.17 [95% CI, 1.59-2.97]; NNH = 56), and there was a significant increase in the risk of hyperkalemia with serum potassium level of 5.5 mEq/L or greater (3.5% vs 0.7%: RR, 4.87 [95% CI, 2.39-9.94]; NNH = 36). Combination ARB plus ACE inhibitor therapy vs control treatment was also associated with a significant increase in the risk of worsening renal function in AMI with symptomatic LV dysfunction (4.8% vs 3.0%; 1.61 [95% CI, 1.31-1.98]; NNH = 56) and a nonsignificant increase in the risk of hyperkalemia (1.2% vs 0.9%; 1.33 [95% CI, 0.90-1.98]; NNH = 333).

COMMENT

Our main findings reinforce why the decision to provide combination ARB plus ACE inhibitor therapy is not straightforward. The pooled analyses indicate that combination therapy was accompanied by marked increases in the risk of medication discontinuation because of adverse effects, symptomatic hypotension, worsening renal function, and hyperkalemia in subjects with chronic HF or AMI with symptomatic LV dysfunction.

In contrast to previous reviews[16-19] including a recent meta-analysis by Lee et al[19] that have focused on the potential benefit of combination ARB plus ACE inhibitor therapy in patients with chronic HF or high-risk AMI, we limited our analysis to an examination of the expected risks of adverse effects. Moreover, the assessment of multiple end points for adverse effects enhanced the robustness of our findings with respect to the overall safety profile of combination ARB plus ACE inhibitor therapy in these 2 distinct patient populations. Our overall findings place the known benefit of combination therapy in reducing morbidity[16-19] within the context of expected risks of adverse effects and may provide a more rational approach to clinical decision making. When applied to an analysis of benefit vs risks of adverse effects of combination ARB plus ACE inhibitor therapy, our findings suggest that per 1000 patients, 25 will discontinue this form of therapy because of adverse effects, 17 will experience renal dysfunction, 8 will develop hyperkalemia, and 36 will experience symptomatic hypotension. These types of adverse effects can negatively affect patients' quality of life and reduce overall benefit as a result of increased risk of medication nonadherence. It is rather remarkable that even in the context of these adverse effects there was a lower hospitalization rate with the combination strategy,[16-19] a finding that may lend support to this approach for selected patients.

To our knowledge, this is the first analysis to characterize and quantify the risk of adverse effects of combination ACE inhibitor plus ARB therapy in patients with chronic HF or AMI with symptomatic LV dysfunction, particularly the associated risk of worsening renal function. Worsening renal function in patients with chronic HF or AMI is associated with a poor prognosis.[40-52] Dries et al[45] and others[40-44,46,47] have previously reported an associated increase in the risk of death with worsening renal function in chronic HF. This finding has also been observed among patients with AMI[48-52] and recently confirmed by Anavekar et al[51] in a large cohort of patients with AMI and symptomatic LV dysfunction who were enrolled in VALIANT. Therefore, the observation of an incremental increase in the risk of worsening renal function with combination ARB plus ACE inhibitor therapy in comparison with background treatment that includes ACE inhibitors is a serious clinical concern.

Complex medication regimens may have adverse consequences because of the increased potential for adverse multidrug interactions. This issue is clinically relevant given the large number of medications that are commonly taken by patients with symptomatic LV dysfunction, particularly those with chronic HF. The addition of an ARB to recommended therapy with ACE inhibitors may be an appealing strategy for some patients with various causes of LV dysfunction given the continuing high morbidity associated with its progression or the development of symptomatic HF. However, optimal patient safety in drug prescribing should involve timely knowledge about the interplay between benefit and adverse effects in clinical decision making. A reanalysis of the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) studies by Young et al[53] focusing on patients with low LVEF showed modest increases in medication intolerance or discontinuations because of adverse multidrug interactions, worsening renal function, and hyperkalemia (serum potassium level ≥ 5.5 mEq/L) for subgroups of patients receiving background therapy with ACE inhibitors, spironolactone, and β-blockers who were randomized to candesartan vs placebo. Knowledge about the potential for adverse effects may facilitate better physician prescribing practices and improve the process of informed consent between clinicians and their patients with respect to selective use of combination ARB plus ACE inhibitor therapy as an alternative for

selected patients rather than routine application as a standard approach in the management of chronic HF or AMI with symptomatic LV dysfunction.

The present analysis is subject to the following limitations. First, although we cannot completely rule out selection bias due to the English language limitation,[54,55] we believe that our findings are not confounded because of type II errors associated with small sample size. This updated analysis incorporating the largest available published studies of combination ARB plus ACE inhibitor therapy for HF enhanced our ability to detect meaningful changes in a range of important clinical end points for adverse effects. Second, we accounted for the observed quantitative heterogeneity in the pooling of results for some outcome measures; however, residual confounding owing to unadjusted differences in baseline characteristics of the pooled study cohorts cannot be completely assessed or ruled out using study level data. As such, our overall findings reflect the mean estimates for adverse effects of combination ARBs plus ACE inhibitors as a therapeutic approach for selected patient populations but did not provide an identity of individual patient characteristics that are more likely to be associated with adverse outcomes. Third, we could not adequately characterize the incidence or magnitude of adverse multidrug interactions because event counts were not available. Finally, the adverse effect profile observed in the present analysis may be higher when combination ARB plus ACE inhibitor therapy is used for unselected patients in contemporary clinical practice. In the trials we reviewed, the study populations were highly selected and tended to include patients who were most likely to derive benefit from the combination and least likely to be affected by the adverse effects. Therefore, the ever-increasing complexity of pharmacotherapy subjects with symptomatic LV dysfunction suggests that clinicians exercise vigilance in monitoring patients for adverse multidrug interactions, particularly hyperkalemia, complications that are likely to be magnified as concurrent use of aldosterone antagonists increases.

In conclusion, dual angiotensin inhibition with combination ARB plus ACE inhibitor therapy in symptomatic LV dysfunction is associated with significant increases in the overall risks of medication nonadherence, renal dysfunction, and symptomatic hypotension. The results of our systematic review are consistent with current HF guidelines that have expressed reservations about a routine strategy for dual angiotensin inhibition using ARBs plus ACE inhibitors.

Accepted for Publication: April 18, 2007.

Correspondence: Christopher O. Phillips, MD, MPH, Section of Hospital Medicine, Desk E13, Department of General Internal Medicine, The Cleveland Clinic Lerner College of Medicine, 9500 Euclid Ave, Cleveland, OH 44195 (Chr_phi@yahoo.com).

Author Contributions: Dr Phillips had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Phillips, Kashani, and Krumholz. *Acquisition of data:* Phillips and Kashani. *Analysis and interpretation of data:* Phillips, Kashani, Ko, and Krumholz. *Drafting of the manuscript:* Phillips. *Critical revision of the manuscript for important intellectual content:* Phillips, Kashani, Ko, Francis, and Krumholz. *Statistical analysis:* Phillips. *Obtained funding:* Krumholz. *Administrative, technical, and material support:* Phillips and Kashani. *Study supervision:* Francis and Krumholz.

Financial Disclosure: None reported.

Funding/Support: Dr Phillips is supported by supplement 3 R01 HL080228-01S1 from the National Heart, Lung, and Blood Institute of the National Institutes of Health, Bethesda, Maryland. Dr Ko is supported by a Heart and Stroke Foundation of Ontario Clinician Scientist Award, Toronto, Ontario, Canada.

REFERENCES

1. Baruch L, Anand I, Cohen I, Ziesche D, Judd D, Cohn JN; Vasodilator Heart Failure Trial (V-HeFT) Study Group. Augmented short- and long-term hemodynamic and hormonal effects of an angiotensin receptor blocker added to angiotensin converting enzyme inhibitor therapy in patients with heart failure. *Circulation.* 1999;99(20):2658-2664.
2. Krombach RS, Clair MJ, Hendrick JW, et al. Angiotensin converting enzyme inhibition, AT1 receptor inhibition, and combination therapy with pacing induced heart failure: effects on left ventricular performance and regional blood flow patterns. *Cardiovasc Res.* 1998;38(3):631-645.
3. Kasama S, Toyama T, Kumakura H, et al. Addition of valsartan to an angiotensin-converting enzyme inhibitor improves cardiac sympathetic nerve activity and left ventricular function in patients with congestive heart failure. *J Nucl Med.* 2003;44(6):884-890.
4. Pitt B, Chang P, Grossman W, Dunlay M, Timmermans PB. Rationale, background, and design of the randomized angiotensin receptor antagonist–angiotensin-converting enzyme inhibitor study (RAAS). *Am J Cardiol.* 1996;78(10):1129-1131.
5. Hara Y, Hamada M, Shigematsu Y, Ohtsuka T, Hiwada K. Beneficial effect of replacing of angiotensin-converting enzyme inhibitor with angiotensin II antagonist for heart failure patients. *J Clin Pharm Ther.* 2002;27(4):267-271.
6. Hamroff G, Katz SD, Mancini D, et al. Addition of angiotensin II receptor blockade to maximal angiotensin-converting enzyme inhibition improves exercise capacity in patients with severe congestive heart failure. *Circulation.* 1999;99(8):990-992.
7. Carson PE. Rationale for the use of combination angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker therapy in heart failure. *Am Heart J.* 2000;140(3):361-366.
8. Struckman DR, Rivey MP. Combined therapy with an angiotensin II receptor blocker and an angiotensin-converting enzyme inhibitor in heart failure. *Ann Pharmacother.* 2001;35(2):242-248.
9. Granger CB, Ertl G, Kuch J, et al. Randomized trial of candesartan cilexetil in the treatment of patients with congestive heart failure and a history of intolerance to angiotensin-converting enzyme inhibitors. *Am Heart J.* 2000;139(4):609-617.
10. Yasumura Y, Miyatake K, Okamoto H, et al. Rationale for the use of combination angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker therapy in heart failure. *Circ J.* 2004;68(4):361-366.
11. Ellis GR, Nightingale AK, Blackman DJ, et al. Addition of candesartan to angiotensin converting enzyme inhibitor therapy in patients with chronic heart failure does not reduce levels of oxidative stress. *Eur J Heart Fail.* 2002;4(2):193-199.
12. Blanchet M, Sheppard R, Racine N, et al. Effects of angiotensin-converting enzyme inhibitor plus irbesartan on maximal and submaximal exercise capacity and neurohumoral activation in patients with congestive heart failure. *Am Heart J.* 2005;149(5):938.e1-7.
13. Cruden NL, Newby DE. Angiotensin antagonism in patients with heart failure: ACE inhibitors, angiotensin receptor antagonists or both? *Am J Cardiovasc Drugs.* 2004;4(6):345-353.
14. Heart Failure Society of America. 2006 Comprehensive Heart Failure Practice Guideline. *J Card Fail.* 2006;12(1):e1-e2.
15. Hunt SA, Abraham WT, Chin MH, et al; American College of Cardiology. American Heart Association Task Force on Practice Guidelines; American College of Chest Physicians; International Society for Heart and Lung Transplantation; Heart

Rhythm Society. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation*. 2005;112(12):e154-e235.
16. Dimopoulos K, Salukhe TV, Coats AJ, Mayet J, Piepoli M, Fransis DP. Meta-analyses of mortality and morbidity effects of an angiotensin receptor blocker in patients with chronic heart failure already receiving an ACE inhibitor (alone or with a beta-blocker). *Int J Cardiol*. 2004;93(2-3):105-111.
17. Jong P, Demers C, McKelvie RS, Liu PP. Angiotensin receptor blockers in heart failure: meta-analysis of randomized controlled trials. *J Am Coll Cardiol*. 2002;39(3):463-470.
18. Garg R, Yusuf S; Collaborative Group on ACE Inhibitor Trials. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure [published correction appears in *JAMA*. 1995;274(6):462]. *JAMA*. 1995;273(18):1450-1456.
19. Lee VC, Rhew DC, Dylan M, Badamgarav E, Braunstein GD, Weingarten SR. Meta-analysis: angiotensin-receptor blockers in chronic heart failure and high-risk acute myocardial infarction [published correction appears in *Ann Intern Med*. 2005 Mar 1;42(5):391; dosage error in text]. *Ann Intern Med*. 2004;141(9):693-704.
20. Pfeffer MA, McMurray JJ, Velazquez EJ, et al; Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003;349(20):1893-1906.
21. Bakris GL, Siomos M, Richardson D, et al; VAL-K Study Group. ACE inhibition or angiotensin receptor blockade: impact on potassium in renal failure. *Kidney Int*. 2000;58(5):2084-2092.
22. Mangrum AJ, Bakris GL. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in chronic renal disease: safety issues. *Semin Nephrol*. 2004;24(2):168-175.
23. Ahmed A. Use of angiotensin-converting enzyme inhibitors in patients with heart failure and renal insufficiency: how concerned should we be by the rise in serum creatinine? *J Am Geriatr Soc*. 2002;50(7):1297-1300.
24. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med*. 2000;160(5):685-693.
25. Roig E, Perez-Villa F, Morales M, et al. Clinical implications of increased plasma angiotensin II despite ACE inhibitor therapy in patients with congestive heart failure. *Eur Heart J*. 2000;21(1):53-57.
26. Tang WH, Vagelos RH, Yee YG, et al. Neurohormonal and clinical responses to high- versus low-dose enalapril therapy in chronic heart failure. *J Am Coll Cardiol*. 2002;39(1):70-78.
27. MacFadyen RJ, Lee AFC, Morton JJ, Pringle SD, Struthers AD. How often are angiotensin II and aldosterone concentrations raised during chronic ACE inhibitor treatment in cardiac failure. *Heart*. 1999;82(1):57-61.
28. Tang WH, Francis GS. Polypharmacy of heart failure. Creating a rational pharmacotherapeutic protocol. *Cardiol Clin*. 2001;19(4):583-596.
29. Amabile CM, Spencer AP. Keeping your patient with heart failure safe: a review of potentially dangerous medications. *Arch Intern Med*. 2004;164(7):709-720.
30. Juurlink DN, Hansten PD. Drug safety in patients with heart failure [letter]. *Arch Intern Med*. 2005;165(1):118.
31. Hanlon JT, Schmader KE, Koronkowski MJ, et al. Adverse drug events in high risk older outpatients. *J Am Geriatr Soc*. 1997;45(8):945-948.
32. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement: Quality of Reporting of Meta-analyses. *Lancet*. 1999;354(9193):1896-1900.
33. Ioannidis JP, Evans SJ, Gotzsche PC, et al; CONSORT Group. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med*. 2004;141(10):781-788.
34. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12.
35. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.
36. McMurray JJ, Ostergren J, Swedberg K, et al; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet*. 2003;362(9386):767-771.
37. Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345(23):1667-1675.
38. Maggioni AP, Anand I, Gottlieb SO, Latini R, Tognoni G, Cohn JN; Val-HeFT Investigators (Valsartan Heart Failure Trial). Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. *J Am Coll Cardiol*. 2002;40(8):1414-1421.
39. McKelvie RS, Yusuf S, Pericak D, et al; the RESOLVD Pilot Study Investigators. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. *Circulation*. 1999;100(10):1056-1064.
40. Shlipak MG, Smith GL, Rathore SS, Massie MB, Krumholz HM. Renal function, digoxin therapy, and heart failure outcomes: evidence from the digoxin intervention group trial. *J Am Soc Nephrol*. 2004;15(8):2195-2203.
41. Forman DE, Butler J, Wang Y, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol*. 2004;43(1):61-67.
42. Krumholz HM, Chen YT, Vaccarino V, et al. Correlates and impact on outcomes of worsening renal function in patients ≥65 years of age with heart failure. *Am J Cardiol*. 2000;85(9):1110-1113.
43. Gottlieb SS, Abraham W, Butler J, et al. The prognostic importance of different definitions of worsening renal function in congestive heart failure. *J Card Fail*. 2002;8(3):136-141.
44. Smith GL, Vaccarino V, Kosiborod M, et al. Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure? *J Card Fail*. 2003;9(1):13-25.
45. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. *J Am Coll Cardiol*. 2000;35(3):681-689.
46. Bibbins-Domingo K, Lin F, Vittinghoff E, Barrett-Connor E, Grady D, Shlipak MG. Renal insufficiency as an independent predictor of mortality among women with heart failure. *J Am Coll Cardiol*. 2004;44(8):1593-1600.
47. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation*. 2004;109(8):1004-1009.
48. Wright RS, Reeder GS, Herzog CA, et al. Acute myocardial infarction and renal dysfunction: a high-risk combination. *Ann Intern Med*. 2002;137(7):563-570.
49. Shlipak MG, Heidenreich PA, Noguchi H, Chertow GM, Browner WS, McClellan MB. Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. *Ann Intern Med*. 2002;137(7):555-562.
50. Goldberg A, Hammerman H, Petcherski S, et al. Inhospital and 1-year mortality of patients who develop worsening renal function following acute ST-elevation myocardial infarction. *Am Heart J*. 2005;150(2):330-337.
51. Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med*. 2004;351(13):1285-1295.
52. Gibson CM, Pinto DS, Murphy SA, et al; TIMI Study Group. Association of creatinine and creatinine clearance on presentation in acute myocardial infarction with subsequent mortality. *J Am Coll Cardiol*. 2003;42(9):1535-1543.
53. Young JB, Dunlap ME, Pfeffer MA, et al; Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) Investigators and Committees. Mortality and morbidity reduction with Candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. *Circulation*. 2004;110(17):2618-2626.
54. Moher D, Fortin P, Jadad AR, et al. Completeness of reporting of trials published in languages other than English: implications for conduct and reporting of systematic reviews. *Lancet*. 1996;347(8998):363-366.
55. Pham B, Klassen TP, Lawson ML, Moher D. Language of publication restrictions in systematic reviews gave different results depending on whether the intervention was conventional or complementary. *J Clin Epidemiol*. 2005;58(8):769-776.