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.

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. However, current guidelines for recommended pharmacotherapy in patients with HF have not endorsed this approach. 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. 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, 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 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. 12,13 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). 14 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 χ² tests 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. 15 This model gives a metaestimate 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 χ² 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
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.30,36-39 Individual study quality was high (Jadad score, 4; interquartile range, 3-5).

The present analysis included only trials randomized to combination ARB plus ACE inhibitor 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).

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

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients Randomized</th>
<th>Entry Criteria</th>
<th>Age, Mean, y</th>
<th>Men, %</th>
<th>Combination ARB + ACE Inhibitor Evaluated</th>
<th>Follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>VALIANT,20 2003b</td>
<td>9794</td>
<td>AMI</td>
<td>65.0</td>
<td>69.1</td>
<td>Valsartan + captopril</td>
<td>24.7</td>
</tr>
<tr>
<td>CHARM-added,36 2003</td>
<td>2458</td>
<td>Chronic HF</td>
<td>64.0</td>
<td>78.7</td>
<td>Candesartan + enalapril</td>
<td>41.4</td>
</tr>
<tr>
<td>ValHeFT,37,38 2002c</td>
<td>4644</td>
<td>Chronic HF</td>
<td>62.7</td>
<td>80.0</td>
<td>Valsartan + ACE inhibitord</td>
<td>23.0</td>
</tr>
<tr>
<td>RESOLVD,39 1999</td>
<td>441</td>
<td>Chronic HF</td>
<td>63.0</td>
<td>87.5</td>
<td>Candesartan + enalapril</td>
<td>10.8e</td>
</tr>
<tr>
<td>Pooled cohort</td>
<td>17337</td>
<td>NA</td>
<td>64 (range, 63-65)</td>
<td>79 (range, 69-88)</td>
<td>NA</td>
<td>25 (range, 11-41)</td>
</tr>
</tbody>
</table>

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.
bAcute myocardial infarction with symptomatic left ventricular dysfunction.
cPatients not receiving an ACE inhibitor at baseline (n=366) were excluded from the analysis (5010−366=4644).
dMultiple ACE inhibitors were used for treatment.
eReported 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

<table>
<thead>
<tr>
<th>Source</th>
<th>VALIANT,20 2003</th>
<th>CHARM-Added,36 2003</th>
<th>ValHeFT,37,38 2002</th>
<th>RESOLVD,39 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study cohorts</td>
<td>AMI</td>
<td>Chronic HF</td>
<td>Chronic HF</td>
<td>Chronic HF</td>
</tr>
<tr>
<td>Intervention, daily dose</td>
<td>Valsartan, 320 mg Captopril, 150 mg</td>
<td>Candesartan, 8 mg Placeboa</td>
<td>Valsartan, 320 mg Placeboa</td>
<td>Candesartan, 4 mg or 8 mg Enalapril, 20 mg</td>
</tr>
<tr>
<td>Proportion of patients at target dose, %</td>
<td>ARB plus ACE inhibitor</td>
<td>47</td>
<td>61</td>
<td>84</td>
</tr>
<tr>
<td>Control or placebo</td>
<td>56</td>
<td>73</td>
<td>93</td>
<td>. . .</td>
</tr>
<tr>
<td>Background therapy, % of patients</td>
<td>Proportions vary across studies.</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
</tbody>
</table>

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.
bP<.05.
cIncludes aldosterone antagonists. Potassium-sparing diuretics were only reported in VALIANT.20

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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.

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 Table 3.

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

<table>
<thead>
<tr>
<th>Source</th>
<th>Discontinuation Because of Adverse Effects, No. of Events/No. of Patients Randomized (%)b</th>
<th>P Value for Heterogeneity</th>
<th>Symptomatic Hypotension, No. of Events/No. of Patients Randomized (%)b</th>
<th>P Value for Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>VALIANT,20 2003</td>
<td>438/4885 (9.0)</td>
<td></td>
<td>884/4885 (18.1)</td>
<td></td>
</tr>
<tr>
<td>CHARM-Added,26 2003</td>
<td>309/1276 (24.2)</td>
<td></td>
<td>58/1276 (4.5)</td>
<td></td>
</tr>
<tr>
<td>ValHeFT,27,28 2002</td>
<td>231/2326 (9.9)</td>
<td></td>
<td>32/2326 (1.3)</td>
<td></td>
</tr>
<tr>
<td>RESOLVO,29 1999</td>
<td>. . .</td>
<td></td>
<td>4/332 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Subtotals</td>
<td>. . .</td>
<td></td>
<td>. . .</td>
<td></td>
</tr>
<tr>
<td>Chronic HF36-39</td>
<td>. . .</td>
<td></td>
<td>. . .</td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.38 (1.22-1.55)</td>
<td>.43a</td>
<td>1.50 (1.09-2.07)</td>
<td>.94b</td>
</tr>
<tr>
<td>AMI with LV dysfunction20</td>
<td>438/4885 (9.0)</td>
<td></td>
<td>884/4885 (18.1)</td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.17 (1.03-1.34)</td>
<td></td>
<td>1.48 (1.33-1.8)</td>
<td></td>
</tr>
<tr>
<td>Pooled cohort</td>
<td>978/8487 (11.5)</td>
<td>.17a</td>
<td>1.48 (1.34-1.62)</td>
<td>.99b</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.28 (1.17-1.40)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

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

<table>
<thead>
<tr>
<th>Source</th>
<th>Worsening Renal Function, No. of Events/No. of Patients Randomized (%)b</th>
<th>P Value for Heterogeneity</th>
<th>Hyperkalemia (Serum Potassium Level &gt;5.5 mEq/L), No. of Events/No. of Patients Randomized (%)b</th>
<th>P Value for Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>VALIANT,20 2003</td>
<td>232/4885 (4.8)</td>
<td></td>
<td>57/4885 (1.2)</td>
<td></td>
</tr>
<tr>
<td>CHARM-Added,26 2003</td>
<td>100/1276 (7.8)</td>
<td></td>
<td>44/1276 (3.5)</td>
<td></td>
</tr>
<tr>
<td>ValHeFT,27,28 2002</td>
<td>27/2326 (1.1)</td>
<td></td>
<td>. . .</td>
<td></td>
</tr>
<tr>
<td>RESOLVO,29 1999</td>
<td>2/332 (0.6)</td>
<td></td>
<td>. . .</td>
<td></td>
</tr>
<tr>
<td>Subtotals</td>
<td>. . .</td>
<td></td>
<td>. . .</td>
<td></td>
</tr>
<tr>
<td>Chronic HF36-39</td>
<td>128/3934 (3.3)</td>
<td></td>
<td>44/1276 (3.5)</td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>2.17 (1.59-2.97)</td>
<td>.18a</td>
<td>4.87 (2.39-9.94)</td>
<td></td>
</tr>
<tr>
<td>AMI with LV dysfunction20</td>
<td>232/4885 (4.8)</td>
<td></td>
<td>57/4885 (1.2)</td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.61 (1.31-1.98)</td>
<td></td>
<td>1.33 (0.90-1.98)</td>
<td></td>
</tr>
<tr>
<td>Pooled cohort</td>
<td>360/8487 (4.1)</td>
<td>.10a</td>
<td>101/6161 (1.6)</td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.76 (1.49-2.09)</td>
<td>.10a</td>
<td>2.46 (0.88-8.7)</td>
<td>.01b</td>
</tr>
</tbody>
</table>

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.

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 COMBINATIONARB 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, 1.31-1.98]; NNH = 56) (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).

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 reviews16-19 including a recent meta-analysis by Lee et al10 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 morbidity16-19,23 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 al45 and others46,47 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 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 al53 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, 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.

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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.

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