The Effect of Renin-Angiotensin System Inhibitors on Mortality and Heart Failure Hospitalization in Patients With Heart Failure and Preserved Ejection Fraction: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Although renin-angiotensin system (RAS) inhibitors have little demonstrable effect on mortality in patients with heart failure and preserved ejection fraction (HF-PEF), some trials have suggested a benefit with regard to reduction in HF hospitalization.

Methods and Results: Here, we systematically review and evaluate prospective clinical studies of RAS inhibitors enrolling patients with HF-PEF, including the 3 major trials of RAS inhibition (Candesartan in Patients with Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction [CHARM-Preserved], Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction [I-PRESERVE], and Perindopril in Elderly People with Chronic Heart Failure [PEP-CHF]). We also conducted a pooled analysis of 8021 patients in the 3 major randomized trials of RAS inhibition in HF-PEF (CHARM-Preserved, I-PRESERVE, and PEP-CHF) in fixed-effect models, finding no clear benefit with regard to all-cause mortality (odds ratio [OR] 1.03, 95% confidence interval [CI], 0.92-1.15; $P = .62$), or HF hospitalization (OR 0.90, 95% CI 0.80-1.02; $P = .09$).

Conclusions: Although RAS inhibition may be valuable in the management of comorbidities related to HF-PEF, RAS inhibition in HF-PEF is not associated with consistent reduction in HF hospitalization or mortality in this emerging cohort. (*J Cardiac Fail 2010;16:260–267*)

Key Words: Heart failure, meta-analysis, drugs, renin-angiotensin system.

With more than 5 million prevalent cases and nearly 1 million hospital discharges yearly, heart failure (HF) represents a rapidly growing therapeutic challenge for health care providers.[1] Although approximately 50% of patients with chronic HF have preserved left ventricular systolic function (so-called ''diastolic HF'' or heart failure with preserved ejection fraction, HF-PEF),[2,3] there have until recently been few randomized controlled trials to guide therapy in this expanding patient cohort.

Three large-scale, randomized, placebo-controlled studies of renin-angiotensin system (RAS) inhibitors in HF-PEF have now been published, including 2 trials of angiotensin-receptor blockade (ARB; Candesartan in Patients with Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction, CHARM-Preserved, and Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction, I-PRESERVE)[4,5] and 1 of angiotensin-converting enzyme (ACE) inhibition (Perindopril in Elderly People with Chronic Heart Failure, PEP-CHF).[6] Although all 3 studies highlight a lack of benefit of RAS inhibition with regard to overall and cardiovascular mortality in HF-PEF, the trials have reported variable outcomes with respect to HF hospitalization. In this review, we describe the major studies of RAS inhibition in HF-PEF. Because hospitalization for worsening HF portends a significantly worse short- and long-term prognosis in this patient population,[7] we also searched the medical literature (MEDLINE and EMBASE) and pooled data on all-cause mortality and HF hospitalization from well-known, large randomized controlled trials of RAS inhibition in HF-PEF.

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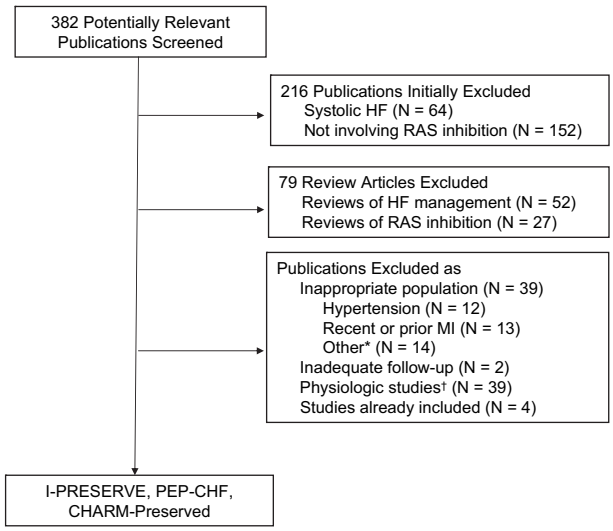

Fig. 1. Study selection algorithm.
*Other includes articles testing renin-angiotensin system (RAS) inhibition in conditions other than heart failure and preserved ejection fraction (HF-PEF) (eg, right ventricular dysfunction, diabetes mellitus, mitral stenosis) or epidemiologic studies.
†Physiologic studies could include patients with systolic HF not excluded in initial screen, or studies with physiologic end points such as exercise testing, neurohormone levels or echocardiographic indices.

Search Strategy and Findings

We systematically searched the medical literature to identify all prospective, randomized clinical trials of RAS inhibition in patients with chronic, symptomatic HF with preserved left ventricular ejection fraction (LVEF) ≥0.40 followed for at least 1 year with data available on all-cause mortality or HF hospitalization. MEDLINE was searched between 1984 and 2008, with MeSH terms "heart failure," "randomized controlled trials," and "clinical trials," and with text words "angiotensin" and "diastolic." The EMBASE database was searched between 1990 and 2008 using OVID, with keywords "heart failure," "angiotensin" and "diastolic," and limited to human, controlled or randomized clinical trials.

Based on our systematic review (Fig. 1), a total of 382 potential unique articles (including CHARM-Preserved, PEP-CHF, and I-PRESERVE included a priori) were collected. Of the 382 articles, 379 were excluded on the basis of text, title, or abstract (Fig. 1). One of the excluded studies, the Hong Kong Diastolic Heart Failure Study, randomly assigned 150 patients with HF and LVEF ≥0.45 to diuretic therapy alone, diuretic plus irbesartan, or diuretic plus ramipril, and followed them for 1 year for echocardiographic and functional indices.[8] Though the Hong Kong study reported outcomes on mortality and HF hospitalization at 1 year, it was excluded from the pooled analysis given its small size in comparison to the other major trials and its primary focus on functional outcomes. We therefore focused on the three randomized clinical trials of RAS inhibition in HF-PEF: PEP-CHF, I-PRESERVE, and CHARM-Preserved. Data on all-cause mortality and HF hospitalization were abstracted and reviewed by all authors.

Study Overviews

Study design was similar in all three trials, with a placebo arm and a treatment arm with either an ACE inhibitor (perindopril in PEP-CHF) or ARB (irbesartan in I-PRESERVE, candesartan in CHARM-Preserved). Mean follow-up in the trials varied from 26 months in PEP-CHF to 50 months in I-PRESERVE. As there were no significant differences between drug and placebo arm in the studies, demographics for the placebo arm of each trial are reported in Table 1.

PEP-CHF

Before the publication of I-PRESERVE, PEP-CHF and CHARM-Preserved were the only 2 large trials examining the role of RAS inhibition in patients with HF-PEF. PEP-CHF was a randomized, blinded clinical trial comparing placebo with perindopril (4 mg/day) in patients older than 70 years with HF-PEF (as assessed via a study-specific wall motion index equivalent to LVEF >0.40) and documented diastolic dysfunction by echocardiography. Subjects enrolled in PEP-CHF were predominantly nonischemic, hypertensive patients with relatively normal renal function (Table 1). Overall, there was no benefit in death or unplanned HF hospitalization at a follow-up of 3 years. There was no interaction between gender, age, systolic blood pressure, history of myocardial infarction, serum creatinine, or N-terminal pro-BNP level and effect of RAS inhibition. An interval analysis at 1 year demonstrated a trend for reduced mortality or HF hospitalization (30% relative risk reduction, RRR; $P = 0.06$) and a statistically significant reduction in HF hospitalization (37% RRR, $P = .03$). In addition, patients receiving perindopril enjoyed improvements in functional capacity with small reductions in systolic blood pressure. Nine drug-related adverse events occurred in the perindopril group in PEP-CHF, which included angioedema, renal failure, and hypotension. The discrepancy between outcomes noted at 1 year and at the end of follow-up has been attributed to limited power related to the high rate of crossover to open-label ACE inhibitor use after the first year and a relatively low overall event rate. In summary, given the high crossover rate at 1 year and a significantly lower number of events, PEP-CHF did not definitively show a benefit to RAS inhibition in patients with HF-PEF.

CHARM-PRESERVED

CHARM-Preserved enrolled patients older than 18 years with symptomatic HF for at least 4 weeks, a cardiovascular hospital admission, and an LVEF >0.40. As compared with those enrolled in PEP-CHF, patients in CHARM-Preserved had more ischemic heart disease; baseline medical therapy and other comorbidities were comparable between the 2 studies. At a median follow-up of 37 months,

Table 1. Baseline Characteristics across Randomized Controlled Trials of RAS Inhibition in HF-PEF (Placebo Arm)

Characteristic	I-PRESERVE	CHARM-Preserved	PEP-CHF
Patients, n	4128	3023	850
Age, y	72 ± 7	67 ± 11	75 (72-79)
Female, %	61	41	57
White or European, %	93	92	NR
Body mass index (kg/m^2)	30 ± 5	29 ± 6	28 (25-31)
NYHA Class III or IV, %	79	40	26
LVEF, %	60 ± 9	54 ± 9	64 (56-66)
Etiology of HF			
Ischemic	24	57	NR
Hypertensive	63	23	NR
Medical history, %			
Hypertension	88	64	79
Diabetes	27	28	20
Atrial fibrillation	29	29	22
PCI or CABG	13	19-22*	3-8*
Angina	40	29	NR
Medical therapy, %			
Diuretic	52	74	44
β-blocker	58	56	54
ACE inhibitor	25	19	0
Spironolactone	15	12	11
Digoxin	13	27	13
Nitrate	27	NR	49
Calcium blocker	39	32	33
Creatinine, mg/dL	1.0 ± 0.3	NR	1.1 (0.9-1.2)‡
Blood pressure, mm Hg			
Systolic	136 ± 15	136 ± 18	140 (129-150)
Diastolic	79 ± 9	78 ± 11	80 (73-88)

ACE, angiotensin-converting enzyme; BP, blood pressure; CABG, coronary artery bypass grafting; CHARM-Preserved, Candesartan in Patients with Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction; HF, heart failure; I-PRESERVE, Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction; LVEF, left ventricular ejection fraction; NR, not reported; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PEF, preserved ejection fraction; PEP-CHF, Perindopril in Elderly People with Chronic Heart Failure.

Results are reported as mean ± standard deviation for placebo group for all studies except for PEP-CHF, where results are reported as median with interquartile range. Where specified, ''diuretic'' includes loop diuretic therapy.

†Includes angina and myocardial infarction.

*Range includes PCI or CABG in trials where these procedures were specified.

‡Creatinine converted from μmol/L to mg/dL.

there was no benefit to RAS inhibition with respect to death or HF hospitalization. However, similar to PEP-CHF, there was a trend for reduction in HF hospitalization (15% RRR, $P = .07$). Although nearly 70% of patients reached the target dose of candesartan by 6 months, the modest reduction in HF events was counterbalanced by an increased risk of serious adverse events (hypotension, renal failure, or hyperkalemia) in patients receiving candesartan.

I-PRESERVE

The most recent study of RAS inhibition in HF-PEF, I-PRESERVE, studied the angiotensin receptor blocker irbesartan. I-PRESERVE enrolled patients older than 60 years with symptomatic HF and LVEF >0.45. These patients were more similar to the PEP-CHF cohort (more hypertension, less ischemic heart disease), with a similar profile of medical therapy. At a mean of 50 months, there was no difference between irbesartan and placebo in a composite of all-cause mortality or cardiovascular hospitalization, and there was no effect of irbesartan therapy on hospitalization for worsening HF. Irbesartan did not demonstrate any benefit in the composite outcome in any specific subgroup (age, gender, left ventricular ejection fraction <0.60, concomitant ACE inhibition or β-blockade, diabetes, or recent HF hospitalization). Similar to perindopril, irbesartan had an excellent safety profile in I-PRESERVE.

There were several differences in enrolled patient characteristics among the trials. Although age, race, and LVEF were similar across all 3 trials, there were fewer female patients in CHARM-Preserved (41%) relative to the other trials (57% to 61%). In addition, patients in I-PRESERVE were more symptomatic with HF (79% with New York Heart Association [NYHA] Class III or IV) than in the other trials (26% to 40%), and were more likely to have angina. Etiology of HF in I-PRESERVE was predominantly hypertensive, whereas patients in CHARM-Preserved had a higher proportion of patients with ischemia as a cause for HF. The prevalence of hypertension, diabetes mellitus, and atrial fibrillation, comorbidities typically associated with HF-PEF, was similar across all of the trials examined.

Beyond these clinical characteristics, there were minor differences in background medical therapy across the 3 trials. The use of loop diuretics (44% to 74%), β-blockers (54% to 58%), and calcium channel blockers (32% to 39%) was similar in each trial. Where reported, target doses of study drug specified in each study were reached in a majority of enrolled patients, and mean reduction in systolic and diastolic blood pressure was similar between studies (Table 2). Few patients were lost to follow-up in any of the studies.

Concomitant RAS Inhibition: Drop-ins and Drop-outs

In the CHARM-Preserved trial, study investigators allowed clinician-initiated ACE inhibitor therapy. By the conclusion of CHARM-Preserved, concomitant use of ACE inhibitors in the candesartan arm had not changed (20%), whereas use of ACE inhibitors in the placebo arm increased slightly from 19% to 23%. The frequency of concomitant spironolactone therapy (approximately 10%) remained stable throughout the study. Of the randomized patients in CHARM-Preserved, only 3 were lost to follow-up.

In PEP-CHF, there was significant attrition in the use of perindopril (the study ACE inhibitor) in the treatment arm, and crossover to ACE inhibitor in the placebo arm (Table 2). At 1 year, 90% of patients in the study drug arm were taking perindopril. However, 6 months later, only 60% of the perindopril arm was taking study drug, and by study end, this number fell further to 35%. As well, by trial end, nearly 37% of patients initially assigned to placebo were receiving open-label ACE inhibitor. Similar to CHARM-Preserved, 11% of patients in PEP-CHF were

Table 2. Study Drug Regimens, End Points, and Follow-up

	I-PRESERVE	CHARM-Preserved	PEP-CHF
Study drug	Irbesartan	Candesartan	Perindopril
Target dose, mg	300	32	4
Patients at target, %	84	67 (at 6 mo)	90 (at 1 y)
Mean dose, mg	275	25 (at 6 mo)	NR
Difference in BP between placebo and drug arms, mm Hg			
Systolic	−3.6 (at 6 months)	−6.9 (at 6 months)	−3 (at 1 y)
Diastolic	−1.9 (at 6 months)	−2.9 (at 6 months)	NR
Primary end point	All-cause mortality or CV hospitalization	CV death or HF hospitalization	All-cause mortality or HF hospitalization
Follow-up, months	50 (mean)	37 (median)	26 (mean)
Lost to follow-up, n	73	3	4
Crossovers, %*			
≤1 y	13	11 (at 6 months)	10
End of trial	34	22	40 (at 18 months)

BP, blood pressure; CHARM-Preserved, Candesartan in Patients with Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction; CV, cardiovascular; HF, heart failure; I-PRESERVE, Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction; NR, not reported; PEP-CHF, Perindopril in Elderly People with Chronic Heart Failure.

*Crossover rates are reported as percentage of patients in the treatment arm who were not taking study drug at the time specified.

treated with spironolactone at baseline. Of the randomized patients in PEP-CHF, only 4 were lost to follow-up.

In the I-PRESERVE study, approximately 20% of patients in both the irbesartan and placebo arms not on an ACE inhibitor at the beginning of the study started ACE inhibitor therapy during follow-up. In addition, use of spironolactone increased from 15% to nearly 30% in both arms of the study during follow-up. An equivalent proportion of patients discontinued irbesartan or placebo over the course of the study, from 13% at 1 year to 34% at the end of the study. At study termination, mortality data was not available on 29 patients (1%) of the irbesartan arm and 44 patients (2%) in the placebo arm.

Pooled Morbidity and Mortality Data

We conducted a meta-analysis of all-cause mortality and HF hospitalization from the 3 individual trials included in this study, as individual patient-level data were not available for review. For each study, data regarding all-cause mortality or HF hospitalization in the placebo and study drug groups were used to generate odds ratios (OR) and 95% confidence intervals (CI). Pooled odds ratios were derived in fixed effects models. Between study heterogeneity was formally assessed via Cochran Q statistic, with $P < .05$ considered significant. Publication bias was not formally tested given the small number of studies and overall negative results in all studies found in our search. Summary data from included trials were pooled without regard to overall duration of follow-up, given limited data on yearly mortality or HF hospitalization. All analyses were conducted using StatsDirect version 2.7.2 (StatsDirect Ltd, Cheshire, UK).

Table 3. Pooled Outcomes Data from Randomized Controlled Trials of RAS Inhibition in HF-PEF

	All-cause Mortality		HF Hospitalization	
Trial	Placebo	RAS Inhibitor	Placebo	RAS Inhibitor
I-PRESERVE	436/2061	445/2067	336/2061	325/2067
CHARM-Preserved	237/1509	244/1514	276/1509	241/1514
PEP-CHF	53/426	56/424	73/426	64/424

CHARM-Preserved, Candesartan in Patients with Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction; HF, heart failure; I-PRESERVE, Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction; PEF, preserved ejection fraction; PEP-CHF, Perindopril in Elderly People with Chronic Heart Failure; RAS, renin-angiotensin system.

Pooled data for all-cause mortality and HF hospitalizations are detailed in Table 3, with results of fixed effects meta-analysis shown in Figs. 2 and 3. Overall pooled OR for the risk of all-cause mortality in patients with HF-PEF treated with RAS inhibition was 1.03 (95% CI, 0.92-1.15, $P = .62$). Overall pooled OR for the risk of HF hospitalization in patients with HF-PEF treated with RAS inhibition was 0.90 (95% CI 0.80-1.02, $P = .09$). There was no significant heterogeneity as assessed by the Q statistic in either analysis.

To assess the impact of heterogeneity of patient selection and characteristics on pooled effect estimates, we conducted several sensitivity analyses. First, given the higher symptom severity of patients in I-PRESERVE, we recalculated pooled effect estimates excluding the results of I-PRESERVE, with no effect on all-cause mortality (OR 1.04, 95% CI 0.87-1.24; $P = .69$) and a nonsignificant trend toward reduced HF hospitalization (OR 0.85, 95% CI 0.72-1.00; $P = .06$).

Given the marked rate of discontinuation of ACE inhibitor after the first year of follow-up in PEP-CHF, we recalculated pooled effect estimates limiting the results of PEP-CHF to 1 year (ie, before significant crossover). There was no change in the pooled effect estimate for all-cause mortality (OR 1.02, 95% CI 0.91-1.15; $P = .72$), but there was a modest significant benefit for RAS inhibition on HF hospitalization (OR 0.88, 95% CI 0.78-1.00; $P = .04$)

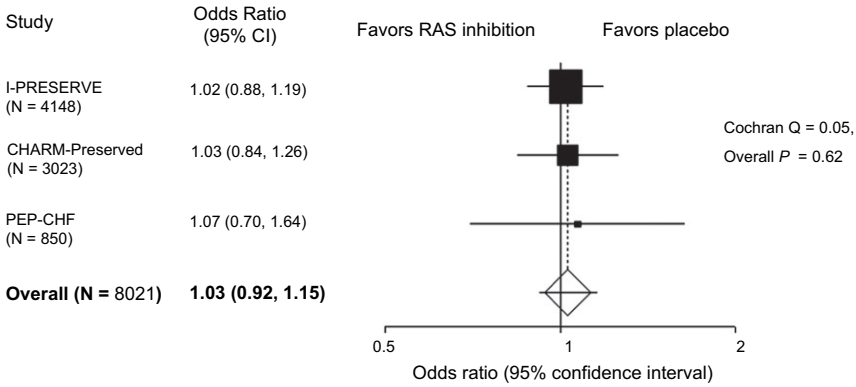

Fig. 2. All-cause mortality in randomized controlled trials of renin-angiotensin system (RAS) inhibition in heart failure and preserved ejection fraction (HF-PEF).

(Fig. 4). Finally, we performed a pooled analysis of CHARM-Preserved and I-PRESERVE, the largest trials of ARB therapy in HF-PEF. The results of the pooled analysis of these two trials were no different from the overall analysis, with respect to all-cause mortality (OR 1.03, 95% CI 0.91-1.15; $P = .69$) or HF hospitalization (OR 0.91, 95% CI 0.80-1.03; $P = .13$).

Commentary

Inhibition of the RAS is an integral component of the modern management of HF with LV systolic dysfunction. Recently released American College of Cardiology and American Heart Association guidelines for the management of chronic heart failure considers initiation and maintenance of ACE inhibition or angiotensin-receptor blockade a class I indication in patients with HF and reduced LV function.[9] However, given the lack of randomized trials investigating modes of therapy for HF-PEF, there are few recommendations for the management of HF-PEF beyond control of traditional cardiovascular risk factors.

In an effort to clarify further a potential benefit for RAS inhibition in HF-PEF, we performed a systematic review of the published medical literature, revealing only 3 large trials of RAS inhibitors enrolling patients with HF-PEF. Pooled analysis of these trials suggests no consistent benefit of RAS inhibition with regard to either overall mortality or HF hospitalization. Sensitivity analyses performed to account for observed heterogeneity in trial design and choice of study drugs did not alter our results. We conclude that the available evidence to date does not support routine prescription of RAS antagonists to reduce cardiovascular morbidity or mortality in this population.

Pathophysiologic Rationale for RAS Inhibition

Activation of the renin-angiotensin system plays a key role in the pathophysiology of disease progression in patients with chronic HF due to LV systolic dysfunction. Moreover, therapy targeted at RAS inhibition results in a significant reduction in neurohormone levels, attenuation of LV remodeling, and decreased HF morbidity and mortality.[10-12] Unfortunately, nearly all evidence supporting RAS inhibition in HF comes from patients with systolic dysfunction.[13] Nevertheless, sustained RAS activation has been implicated in progressive ventricular hypertrophy and myocardial fibrosis,[14-16] both of which may be important contributors to the pathogenesis of diastolic dysfunction,

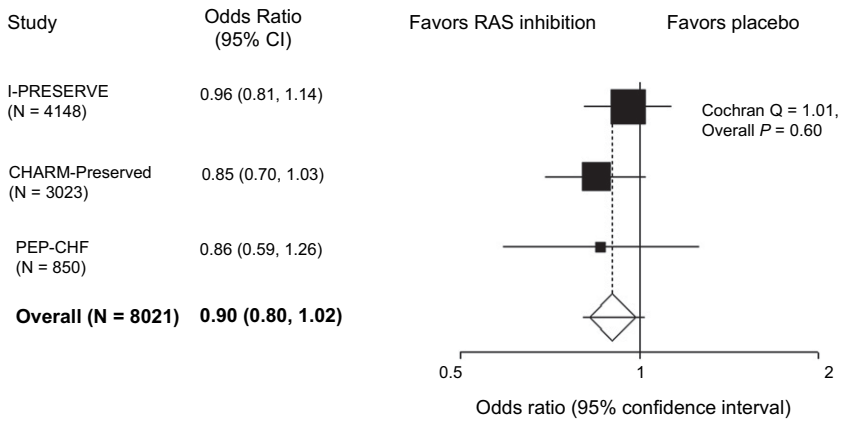

Fig. 3. Heart failure hospitalization in randomized controlled trials of renin-angiotensin system (RAS) inhibition in heart failure and preserved ejection fraction (HF-PEF).

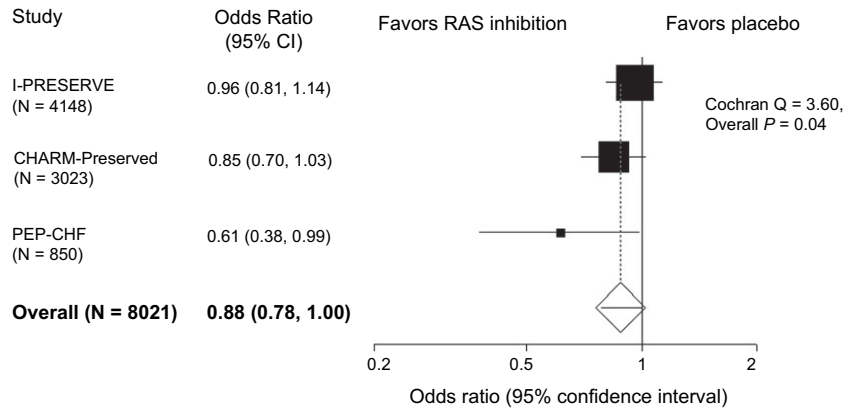

Fig. 4. Heart failure hospitalization in randomized controlled trials of renin-angiotensin system (RAS) inhibition in heart failure and preserved ejection fraction (HF-PEF), limiting Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) results to 1 year.

and RAS inhibition has been shown to be beneficial in a population of patients with vascular disease.[17]

The motivation for this pooled analysis was the apparent trend towards reduced HF hospitalization—a sentinel prognostic event in both systolic and diastolic HF—that was observed at 1 year in PEP-CHF and at the end of CHARM-Preserved. Unlike these 2 trials, the larger I-PRESERVE trial did not show a significant reduction in HF hospitalization with irbesartan in HF-PEF. There are several potential explanations for the lack of benefit to RAS inhibition seen in our analysis. First, the trial results are heavily driven by the results of I-PRESERVE, which enrolled more than 50% of the patients in the pooled analysis. Although CHARM-Preserved and PEP-CHF suggested some benefits with regard to HF hospitalization, no such benefit was seen in I-PRESERVE. The reasons for this variation may be related to heterogeneity in the populations studied or to key differences in trial design. Although there were no qualitative differences in age, gender, race, LVEF, concomitant therapies or blood pressure reduction between the 3 large studies, there was a difference in HF etiology, with more ischemic patients in CHARM-Preserved and more hypertensive patients in I-PRESERVE and PEP-CHF. Patients in I-PRESERVE also had more advanced heart failure at baseline, as evidenced by the higher event rates in the placebo group. Nonetheless, exclusion of I-PRESERVE results from the pooled analysis did not alter the statistical findings. Further, the high rate of crossover from placebo to open-label ACE inhibitor in the PEP-CHF trial may have attenuated the statistical power to observe a benefit from perindopril. Accordingly, by restricting our analysis to the 1-year results of PEP-CHF (confining outcomes to the time point before significant crossover occurred), we were able to identify a statistically significant impact (12% reduction) on HF hospitalization associated with RAS inhibition ($P = .04$). In addition, there was a greater degree of blood pressure reduction between drug- and placebo-treated arms of CHARM-Preserved, which may also account for some of the difference in HF hospitalization between this study and I-PRESERVE.

Why Might RAS Inhibition not be Beneficial in HF-PEF?

It is possible that RAS inhibition may not be as effective in reducing HF hospitalization in patients with more advanced disease. This assertion is supported by a significant trend toward reduction in HF hospitalization in the pooled analysis excluding results from I-PRESERVE. A similar differential effect of β-blocker therapy on HF hospitalization in less advanced patients with systolic HF has been demonstrated.[18] The lower overall mortality rates in patients with mild HF may provide longer time for follow-up and decompensation leading to hospitalization.

The overall failure of RAS inhibition to affect morbidity and mortality in patients with HF-PEF may reflect a relatively smaller contribution of neurohormonal activation to HF progression in this population compared with patients with low EF. Recent evidence highlights that the pathophysiology of HF-PEF may depend importantly on nonmyocardial factors, including abnormal renal function and increased central aortic stiffening that may be less responsive to RAS antagonism, but may contribute to the HF syndrome of fluid retention and effort intolerance. Although regression of LV mass in hypertensive patients without HF receiving ARB therapy has been demonstrated,[19] RAS-based approaches for control of blood pressure appear to be no more effective than non-RAS approaches for improvement of diastolic function,[20] highlighting that control of blood pressure, rather than the choice of agent, may be the most important aspect of effective medical therapy.

HF-PEF as an Indistinct Clinical Entity

Rather than a distinct pathophysiologic entity, the syndrome of HF-PEF encompasses a heterogeneous group of patients with a wide array of factors that might contribute

to HF pathophysiology. A single approach to medical therapy of this diverse group may be inadequate to consistently improve clinical outcomes. Because the majority of trials included patients simply based on signs and symptoms of HF and a preserved EF by resting echocardiography, many patients with dynamic mitral regurgitation, intermittent ischemia, constrictive or restrictive cardiomyopathy, or exercise-induced pulmonary hypertension (none of which would be expected to respond to RAS inhibition) may have been included.[21] Improved taxonomy of patients with HF-PEF may be critical to defining a more homogeneous group of patients with a predictable response to drug therapy.

Limitations of the Analysis

An analysis such as ours should be viewed in the context of its limitations. All meta-analyses proceed from the assumption that limited between-trial heterogeneity permits synthesis of data across differently designed trials of different populations. Differences in study outcomes may reflect real differences in the efficacy of RAS antagonism in differing populations. For example, because patients in I-PRESERVE had less benefit in terms of HF hospitalization than patients in CHARM-Preserved and PEP-CHF who were less symptomatic, it is possible that the benefit of RAS inhibition on HF hospitalization may be limited to patients with less advanced disease. Further, although each study in our analysis was a randomized controlled trial of RAS inhibition in HF-PEF, different agents with different potencies were used. It is possible that the effects of ACE inhibition and angiotensin receptor blockade vary in HF-PEF, and that different approaches to RAS inhibition may therefore have different efficacy. However, this has not been true in the population of patients with HF and reduced EF.[22,23]

Beyond the agent under study, several important differences between trials, including study design, HF severity crossover rates, and duration of follow-up, may have neutralized our ability to distinguish a benefit to RAS antagonism in the pooled analysis. However, the relative consistency of our results across various sensitivity analyses argues against this. Finally, we did not have access to individual patient-level data, and therefore cannot exclude a potential benefit to RAS inhibition that might be detectable after accounting for the variable duration of follow-up and differences in background medical history and treatment amongst the patients enrolled in the various trials.

Conclusions

The consistent pattern of results across the major trials of RAS inhibition in HF-PEF argue against a clinically important benefit to routine prescription of RAS antagonists for reduction of mortality or HF hospitalization in this population. New therapeutic trials directed at alternative mechanisms or subgroup analyses of individual patient data from the trials that have been conducted are necessary to contribute substantively to improved clinical outcomes in this challenging patient population.

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