

Renin–Angiotensin System Inhibition, Worsening Renal Function, and Outcome in Heart Failure Patients With Reduced and Preserved Ejection Fraction

A Meta-Analysis of Published Study Data

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Background—Renin–angiotensin aldosterone system (RAAS) inhibitors significantly improve outcome in heart failure (HF) patients with reduced ejection fraction (HFREF), irrespective of the occurrence of worsening renal function (WRF). However, in HF patients with preserved ejection fraction (HFPEF), RAAS inhibitors have not been shown to improve outcome but are still frequently prescribed.

Methods and Results—Random effect meta-analysis was performed to investigate the relationship between RAAS inhibitor therapy, WRF in both HF phenotypes, and mortality. Studies were selected based on literature search in MEDLINE and included randomized, placebo controlled trials of RAAS inhibitors in chronic HF. The primary outcome consisted of the interaction analysis for the association between RAAS inhibition–induced WRF, HF phenotype and outcome. A total of 8 studies (6 HFREF and 2 HFPEF, including 28 961 patients) were included in our analysis. WRF was more frequent in the RAAS inhibitor group, compared with the placebo group, in both HFREF and HFPEF. In HFREF, WRF induced by RAAS inhibitor therapy was associated with a less increased relative risk of mortality (relative risk, 1.19 (1.08–1.31); $P < 0.001$), compared with WRF induced by placebo (relative risk, 1.48 (1.35–1.62); $P < 0.001$; P for interaction 0.005). In contrast, WRF induced by RAAS inhibitor therapy was strongly associated with worse outcomes in HFPEF (relative risk, 1.78 (1.43–2.21); $P < 0.001$), whereas placebo-induced WRF was not (relative risk, 1.25 (0.88–1.77); $P = 0.21$; P for interaction 0.002).

Conclusions—RAAS inhibitors induce renal dysfunction in both HFREF and HFPEF. However, in contrast to patients with HFREF where mortality increase with WRF is small, HFPEF patients with RAAS inhibitor–induced WRF have an increased mortality risk, without experiencing improved outcome with RAAS inhibition.

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Key Words: heart failure ■ MEDLINE ■ phenotype ■ prognosis ■ renin–angiotensin system

In the past 3 decades, the introduction of renin–angiotensin aldosterone system (RAAS) inhibitors has significantly improved morbidity and mortality in chronic heart failure (HF) patients with reduced ejection fraction (HFREF).¹ Although RAAS inhibitors have beneficial effects on the heart and vasculature, they also induce a small decrease in renal function as estimated by glomerular filtration rate (eGFR). This effect is caused by the effect of RAAS inhibitors on renal autoregulation, primarily preventing efferent (post) glomerular arteriolar vasoconstriction. This action is often considered to be harmful because data from large epidemiological studies and meta-analyses suggest that even a slight decrease in eGFR is associated with an increased risk of poor clinical outcomes.² However,

this assumption based on associations is too simplistic. In fact, a recent meta-analysis showed that even if worsening renal function (WRF) occurs during the initiation of RAAS inhibition in patients with HFREF, the mortality benefit is maintained, although the net benefit of RAAS blockade may be less in patients with WRF because the favorable effects of RAAS blockade are partially offset by the risk associated with WRF.³ However, it is clear that the cause of WRF, rather than its occurrence per se, is what seems to be most important, and WRF caused by RAAS blockade has been dubbed “pseudo-WRF”.⁴

See Editorial by Testani and Brisco-Bacik
See Clinical Perspective

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Although evidence is lacking for a definite benefit of RAAS inhibitors in patients with HF with preserved ejection fraction (HFPEF), these therapies are frequently prescribed, mostly to control blood pressure for other comorbidities such as diabetic nephropathy, which are common in HFPEF, and for the primary and secondary prevention of cardiovascular events. For example, 84% of patients in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) study were treated with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker.⁵ A recent analysis of the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-Preserve) suggested that even WRF caused by RAAS blockade is associated with worse outcome in patients with HFPEF.⁶ However, in a retrospective analysis from the CHARM (Candesartan in Heart Failure–Assessment of Reduction in Mortality and Morbidity) study, differences in HFREF versus HFPEF patients with respect to RAAS inhibitor–induced WRF were less clear.⁷

Therefore, we aimed to investigate the interaction between the phenotype of chronic HF, treatment with RAAS inhibitors, the occurrence of WRF and association with clinical outcome in a meta-analysis of published studies.

Methods

Literature Search

MEDLINE was searched to identify eligible studies that were published from inception to December 1, 2015. We used keywords including (but not limited to) heart failure, ACE inhibition, angiotensin receptor blocker, mineralocorticoid receptor antagonist, aldosterone receptor blockers, renal function, WRF, and outcome. We included articles limited to the English language. Furthermore, we searched our own files, reviewed reference lists from eligible studies and consulted the Cochrane Library for publications that cited key publications. The corresponding author was contacted as needed to obtain data not included in the published report. As such, we obtained additional data from the Val-HeFT (Valsartan Heart Failure Trial), the RALES (Randomized Aldactone Evaluation Study), the EPHEUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study), and the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure).^{8–11} However, we could not obtain data from 3 important trials because access was declined by either sponsor or corresponding author.^{5,12,13} Data extraction and assessment of studies were done by 2 independent authors (IB and KD), and any disagreements were resolved by consensus.

Study Selection

Our primary analysis consisted of the following studies: studies investigating the relationship between randomized, placebo controlled RAAS inhibitor therapy, the occurrence of WRF, and subsequent mortality. Articles were excluded for the primary analysis if (1) no crude mortality data for the study groups (RAAS or placebo and WRF or no WRF) were available even after contact with the authors, (2) data were only published in abstract form, and (3) no clear definition for HF or specific HF phenotype was given. Any definition for WRF was included for this analysis. Data extracted from the study included first author name, year of publication, baseline characteristics, including medical history, therapy, and most importantly number of patients with and without WRF in patients allocated to placebo or RAAS inhibition, as well as the outcome (all-cause mortality and HF hospitalization crude numbers) in each of these groups. We performed multiple secondary analyses. In parallel to the primary analysis, we also evaluated the association with the outcome of HF hospitalization,

with similar inclusion criteria of studies. Furthermore, we also compared the incidence of “renal dysfunction” between patients allocated to RAAS inhibitors or placebo, specified as adverse events, as safety end point, or specific trial end point. Also, we evaluated the change in eGFR between the 2 treatment groups. For these 2 last analyses, the inclusion criteria for studies were different from the primary analysis: any study with patients with chronic HF of any phenotype that randomly received an RAAS inhibitor or placebo and had information on occurrence of renal dysfunction or change in eGFR available were included in the analyses, even if these studies were not included in the primary analysis.

Study Quality

The quality of the included studies was assessed using the Cochrane Risk of Bias tool, available via <http://cochrane.org/>.¹⁴ This tool is developed for meta-analyses of randomized clinical trials, and uses qualitative assessment of different domains to assess risk of bias.

Statistical Analysis

Meta-analysis was performed using a random-effects model (Mantel–Haenszel) to determine risk associated with the presence of randomized RAAS inhibitor therapy, incident WRF, and all-cause mortality, as measured by combined crude mortality rates. The primary outcome consisted of the interaction analysis between the association of WRF with mortality in the RAAS inhibitor group in the HFREF versus the HFPEF population according to Bland and Altman.¹⁵ Also, the interaction analysis for the association between WRF and mortality in the placebo group in both HF phenotypes was assessed. For the secondary analysis of HF rehospitalization, similar approaches were used. For the incidence of renal dysfunction, another random-effects model was constructed and interaction analysis for the difference between HFREF and HFPEF was determined. Change in eGFR was evaluated by continuous measures random effects meta-analysis.

For all analyses among study heterogeneity of risk estimates was examined using a standard χ^2 test and I^2 statistic for heterogeneity. I^2 is the percentage of variance that is due to between-study variance. A funnel plot was constructed to visually investigate possible confounding of published studies. We performed meta-regression to assess possible confounding of the established associations, which included all available baseline characteristics of the studies in the primary analysis, and the definition (and timing) of WRF used in the individual studies. Results are presented as relative risks (RRs) with their 95% confidence intervals and P values. Odds ratios are presented for the risk of WRF in subgroup stratified by RAAS inhibition, placebo and HF phenotype. All reported probability values are 2-tailed, and a P value of <0.05 was considered statistically significant. Statistical analyses were performed using Stata 12.0, College Station, TX, and Revman 5.1.¹⁶

Results

Our search identified a total of 8 studies investigating the association between RAAS-inhibitor or placebo-associated WRF and mortality. Figure 1 shows the Quality of Report of Meta-analysis (QUOROM) diagram of the selection of studies. Of the 8 included studies, 6 investigated solely HFREF patients,^{8–11,17,18} 1 investigated only patients with HFPEF,⁶ and 1 published information about both HFREF and HFPEF patients.⁷ All studies were graded as sufficient quality. Risk of bias was highest for the blinding of outcome assessment, as in most studies it was unclear whether investigators were blinded to the development of WRF as (intermediate) outcome. (Figure I in the [Data Supplement](#)) For the primary analysis, 28 961 patients were included in the individual studies (24 520 in HFREF and 4 441 in HFPEF). Table 1 shows the baseline characteristics of these studies. Mean baseline eGFR was 70 ± 4.1 mL/min per 1.73 m^2 ,

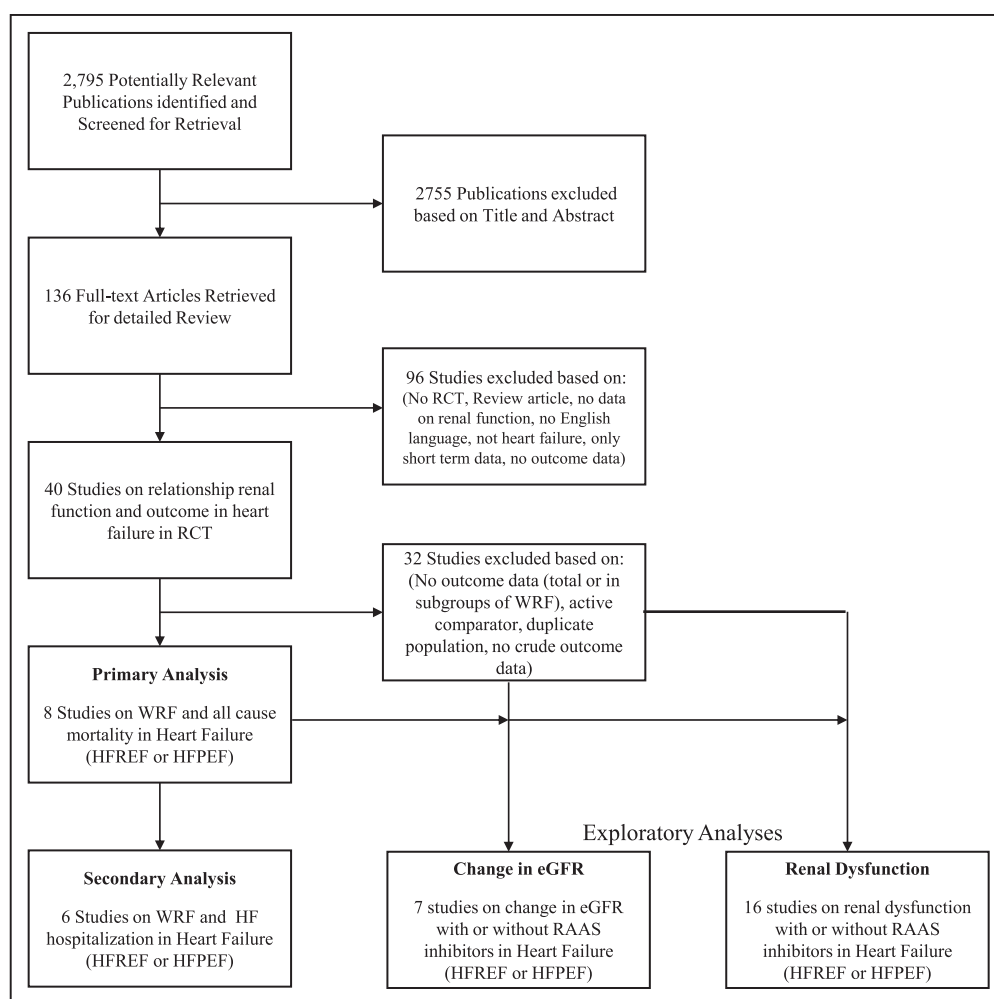


Figure 1. Quality of Reporting of Meta-analysis diagram of included studies. eGFR indicates estimated glomerular filtration rate; HFPEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; RAAS, renin–angiotensin aldosterone system; RCT, randomized clinical trial; and WRF, worsening renal function.

with an accompanying serum creatinine of 1.12 ± 0.07 mg/dL (99 ± 6.0 μ mol/L [7 studies]). Table I in the [Data Supplement](#) shows the definition of WRF used in each study.

In the overall study population, WRF developed in 3268 patients (11%) and was more frequent with RAAS inhibition, compared with placebo (13 versus 9%). WRF was overall more frequent with HFREF (12%) compared with HFPEF (7%). However, the excess risk of WRF associated with RAAS-inhibitor was similar in HFREF (odds ratio, 1.68 [1.25–2.25] and HFPEF [odds ratio, 2.03 [1.60–2.57]; $P=0.33$).

RAAS Inhibitor–Induced WRF and Mortality in HFREF and HFPEF

Table 2 shows the crude mortality rates stratified for treatment and WRF in each individual study. In HFREF, in patients randomized to RAAS inhibitors, WRF was associated with worse outcomes, compared with patients who experienced no WRF (RR, 1.19 [1.08–1.31]; $P<0.001$) (Figure 2). However, the risk associated with WRF in patients allocated to placebo was larger (RR, 1.48 [1.35–1.62]; $P<0.001$), and significantly different from patients randomized to RAAS inhibitors with WRF (P for interaction=0.005).

In HFPEF the pattern was different. In patients with HFPEF randomized to RAAS inhibitors WRF was associated with worse outcomes compared with those who experienced WRF (RR, 1.78 [1.43–2.21]; $P<0.001$). Patients with HFPEF who experienced WRF on placebo had a lower risk of mortality compared with patients who did not experience WRF on placebo (RR, 1.25 [0.88–1.77]; $P=0.29$), and showed a trend toward a difference with those with WRF on RAAS inhibitors (P for interaction=0.092).

The association between RAAS inhibitor–induced WRF and outcome was significantly different between HFREF and HFPEF patients (P for interaction=0.002). The risk associated with placebo-induced WRF was similar in HFREF and HFPEF (P for interaction=0.34). The funnel plot showed no evidence of publication bias (Figure 3). Meta-regression did not find any statistical significant study characteristics that influenced the study results, nor did the definition or timing of WRF affect our findings.

RAAS Inhibitor–Induced WRF and HF Hospitalization in HFREF and HFPEF

Similar studies contributed to the end point of HF hospitalization, with the exception of the SOLVD (Studies of Left Ventricular Dysfunction) and Val-HeFT. The total number of patients for

Table 1. Baseline Characteristics of Included Studies for the Primary Analysis

Study	Year	Randomized Treatment	Total No. in Original Study	Follow-Up Time, d	LVEF (%)	Creatinine, mg/dL	eGFR, mL/min per 1.73 m ²	Concomitant Therapy, %				Medical History, %				Baseline Vitals			
								ACEi	ARB	BBL	MRA	Loop Diuretic	Digoxin	AF	HT	DM	Ischemic	SBP, mmHg	DBP, mmHg
HFREF																			
Angiotensin-converting enzyme inhibitors (ACEi)																			
SOLVD ¹⁸	1991	Enalapril	6377	1230	27	1.20	65.6	50	18	6.1	32	33		38	19	75	119	74	76
SAVE ¹⁷	1992	Captopril	2231	1278	31	1.19	70	50	35		35	26		43	22	100	113	70	78
Angiotensin II receptor blockers (ARB)																			
Val-HeFT ³	2001	Valsartan	5010	1000	27		61.3	93	50	35	4.8	85			7	25	20	124	76
CHARM-HFREF ^{*7}	2003	Candesartan	1569	1000	28	1.10	71.5	57	50	56	18	88	64	28	61	36	59	125	73
Mineralocorticoid receptor antagonists (MRA)																			
RALES ⁹	1999	Spironolacton	1663	720	26	1.30	64	95	0	11	50	100	73				55	122	75
EPHESUS ¹⁰	2003	Eplerenone	5792	480	33		70		76	50	50	59		61	32	100	118	71	
EMPHASIS-HF ¹¹	2010	Eplerenone	2737	630	26	1.15	71	78	19	87	50	85	27	31	66	31	50	124	75
HFPEF																			
Angiotensin II receptor blockers (ARB)																			
CHARM-HFPEF ^{*7}	2003	Candesartan	836	1000	57	1.00	73.5	24	50	57	10	83	33	31	76	39	41	134	75
I-Preserve ⁶	2008	Irbesartan	3595	1380	60	1.00	73	26	50	59	15	83	14	29	89	28	24	137	79

*Total number of patients from renal substudy as the definition of HFREF/HFPEF was different in the main trial program. AF indicates atrial fibrillation; BBL, β -blocker; CHARM, Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; HT, hypertension; I-Preserve, Irbesartan in Heart Failure With Preserved Ejection Fraction Study; LVEF, left ventricular ejection fraction; RALES, Randomized Aldactone Evaluation Study; SAVE, Survival and Ventricular Enlargement; SOLVD, Studies of Left Ventricular Dysfunction; SBP, systolic blood pressure; and Val-HeFT, Valsartan Heart Failure Trial.

Table 2. Incidence of Worsening Renal Function and Clinical Outcome in the Individual Studies

Study	Total No. (Renal Substudy)	Overall		Mortality				HF Hospitalization			
				RAASI		Placebo		RAASI		Placebo	
		WRF	No WRF	Mortality, n (%)	WRF	Mortality, n (%)	No WRF	WRF	HF Hospitalization, n (%)	No WRF	HF Hospitalization, n (%)
HFREF											
SOLVD ¹⁸	6377	186 (31)	1241 (22)	84 (26)	599 (21)	102 (36)	642 (22)	NA	NA	NA	NA
SAVE ¹⁷	1813	59 (27)	308 (19)	26 (22)	137 (17)	33 (32)	171 (22)	16 (14)	98 (12)	22 (21)	130 (17)
Val-HeFT ⁸	4928	104 (24)	627 (43)	71 (24)	404 (19)	33 (27)	436 (19)	NA	NA	NA	NA
CHARM-HFREF ⁷	1569	49 (26)	31 (25)	31 (24)	152 (23)	18 (33)	189 (26)	47 (36)	151 (23)	27 (50)	204 (28)
RALES ⁹	1663	98 (49)	627 (43)	56 (40)	256 (37)	42 (70)	371 (48)	31 (22)	117 (17)	21 (35)	204 (26)
EPHESUS ¹⁰	5807	133 (15)	532 (11)	66 (13)	256 (11)	67 (16)	276 (11)	82 (17)	248 (10)	79 (19)	307 (12)
EMPHASIS-HF ¹¹	2763	48 (12)	224 (11)	24 (11)	98 (10)	24 (14)	126 (13)	23 (10)	116 (12)	35 (21)	172 (17)
HFPEF											
CHARM-HFPEF ⁷	836	21 (22)	104 (14)	14 (23)	47 (13)	7 (20)	57 (15)	15(24)	66 (19)	9 (26)	87 (22)
I-Preserve ⁶	3595	72 (31)	672 (20)	53 (35)	320 (19)	19 (25)	352 (21)	42 (27)	240 (14)	18 (24)	273 (16)

CHARM indicates Candesartan in Heart Failure–Assessment of Reduction in Mortality and Morbidity; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; HF heart failure; I-Preserve, Irbesartan in Heart Failure With Preserved Ejection Fraction Study; RAASI, renin–angiotensin aldosterone system inhibition; RALES, Randomized Aldactone Evaluation Study; SAVE, Survival and Ventricular Enlargement; SOLVD, Studies of Left Ventricular Dysfunction; Val-HeFT, Valsartan Heart Failure Trial; and WRF, worsening renal function.

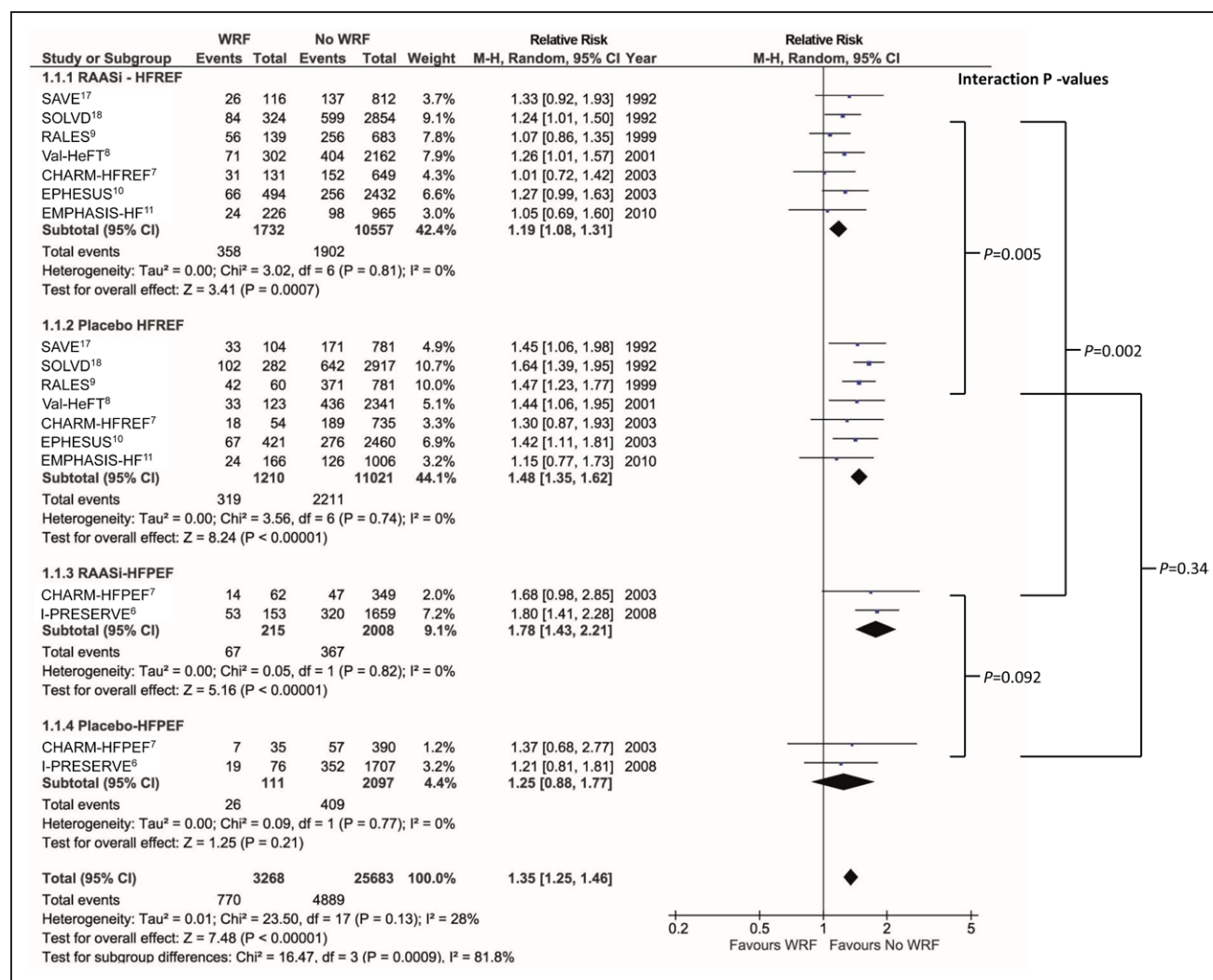


Figure 2. Forest plot of association between renin–angiotensin aldosterone system (RAAS) inhibition, worsening renal function (WRF), heart failure phenotype, and mortality. CHARM indicates Candesartan in Heart Failure–Assessment of Reduction in Mortality and Morbidity; CI, confidence interval; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; HFPEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; I-Preserve, Irbesartan in Heart Failure With Preserved Ejection Fraction Study; RALES, Randomized Aldactone Evaluation Study; RCT, randomized clinical trial; RR, relative risk; SAVE, Survival and Ventricular Enlargement; SOLVD, Studies of Left Ventricular Dysfunction; and Val-HeFT, Valsartan Heart Failure Trial.

this analysis was, therefore, 17656. Overall, WRF was associated with more frequent HF hospitalization (RR, 1.44 [1.30–1.59]; $P < 0.001$), and did not significantly differ between RAAS and placebo-induced WRF. Table 2 shows the crude HF hospitalization rates stratified for treatment and WRF for individual studies. Figure 4 shows the results of the meta-analysis for HF hospitalization. WRF was associated with increased risk of HF hospitalization in all groups, but most pronounced for RAAS inhibitor–induced WRF in HFPEF (RR, 1.64 [1.13–2.39]; $P < 0.001$). However, this was not significantly different from placebo-related WRF in HFPEF (P for interaction=0.47) or RAAS inhibitor–induced WRF in HFREF (P for interaction=0.29).

RAAS Inhibitor–Induced, Investigator Reported, Renal Dysfunction in HFREF and HFPEF

For this analysis, 12 HFREF and 5 HFPEF studies contributed data.^{5–8,11,12,19–27} Renal dysfunction as adverse event or safety

end point (and therefore defined by different definitions in each study) occurred overall in 3.2% of patients (3.9 versus 2.6% in RAAS-inhibitors versus placebo; RR, 1.52 [1.24–1.88]; $P < 0.001$). The incidence of renal dysfunction was similar in HFREF and HFPEF, and the risk associated with RAAS inhibition was similar in both HF phenotypes (P for interaction=0.63; Figure 5).

RAAS Inhibitor–Induced Changes in eGFR in HFREF and HFPEF

For change in eGFR, we evaluated change during the entire study period, but for each study this time period differed.^{6–11,26} Overall, RAAS inhibitor therapy resulted in a greater decline in eGFR compared with placebo (mean treatment difference -3.61 mL/min per 1.73 m² Figure 6). The mean treatment difference in HFREF versus HFPEF for RAAS inhibitors versus placebo was similar (P for heterogeneity 0.38).

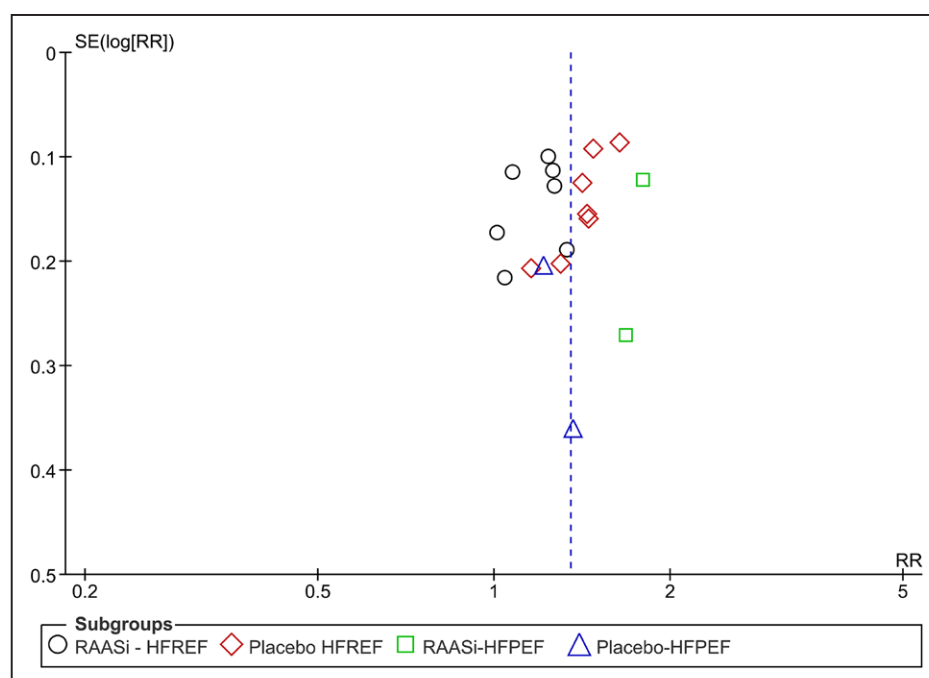


Figure 3. Funnel plot of included studies in primary analysis. HFPEF indicates heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; RAASi, renin–angiotensin aldosterone system inhibition; and RR, relative risk.

Discussion

There are three essential findings of this meta-analysis. First is that RAAS inhibitor treatment–induced WRF in both phenotypes of chronic HF compared with placebo. Second, WRF in patients with HFREF randomized to RAAS inhibitors was associated with slightly worse outcomes compared with patients without WRF. However, the incremental risk of mortality associated with WRF in patients with HFREF allocated to placebo was larger. Likewise, WRF in patients with HFPEF randomized to RAAS inhibitors was strongly associated with worse outcomes compared with patients without WRF.

However, in contrast to HFREF, patients with HFPEF who experienced WRF on placebo had a smaller incremental risk of mortality (versus placebo treated patients without WRF) compared with patients with HFPEF experiencing WRF on RAAS inhibition.

RAAS Inhibition and WRF in HFREF

Our findings are consistent with other studies, which demonstrated the deterioration of renal function after the use of RAAS inhibitors in patients with HFREF. The CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) demonstrated a reduction in mortality with ACE inhibition, despite an enalapril-induced increase in mean serum creatinine of 10% to 15% above baseline.¹⁹ In the SAVE (Survival and Ventricular Enlargement) study, mild to moderate chronic kidney disease was associated with a heightened risk of all major cardiovascular events, and also showed that increases in serum creatinine are frequently found in these patients.¹⁷ SOLVD observed the same survival benefit imparted by RAAS inhibitor treatment in

patients with HFREF, compared with placebo, despite the development of early WRF.¹⁸ Findings from HFREF studies on RAAS inhibitor–induced WRF were meta-analyzed by Clark et al.³ In that study, the authors found that patients with WRF had overall worse outcomes compared with patients without WRF. However, the reduction in all-cause mortality associated with the use of RAAS inhibitors was significantly greater in the presence of WRF compared with the no WRF group. Also, the risk associated with WRF was significantly smaller in patients allocated to RAAS inhibitors versus placebo.

Our findings further support and extend the findings by Clark et al. In our present analysis in patients with HFREF, which also included data from CHARM and EMPHASIS-HF,^{11,28} we found that RAAS inhibitors–induced WRF more frequently compared with placebo. Furthermore, WRF was associated with worse outcomes (mortality and HF hospitalization) in both the RAAS inhibitor and the placebo groups (compared with no WRF in the respective treatment groups), but the survival benefit with RAAS inhibitors was largely maintained. In other words, WRF induced by RAAS inhibitors was associated with a smaller increment in the risk of worse outcomes than WRF associated with placebo in patients with HFREF. These findings suggest that decreases in eGFR during the up-titration of RAAS inhibitors should not immediately lead to treatment discontinuation, as there is still likely to be a net benefit from treatment.

RAAS Inhibition and WRF in HFPEF

One major limitation of the aforementioned studies and meta-analysis is that they did not distinguish between the phenotypes of HF and only included patients with HFREF.

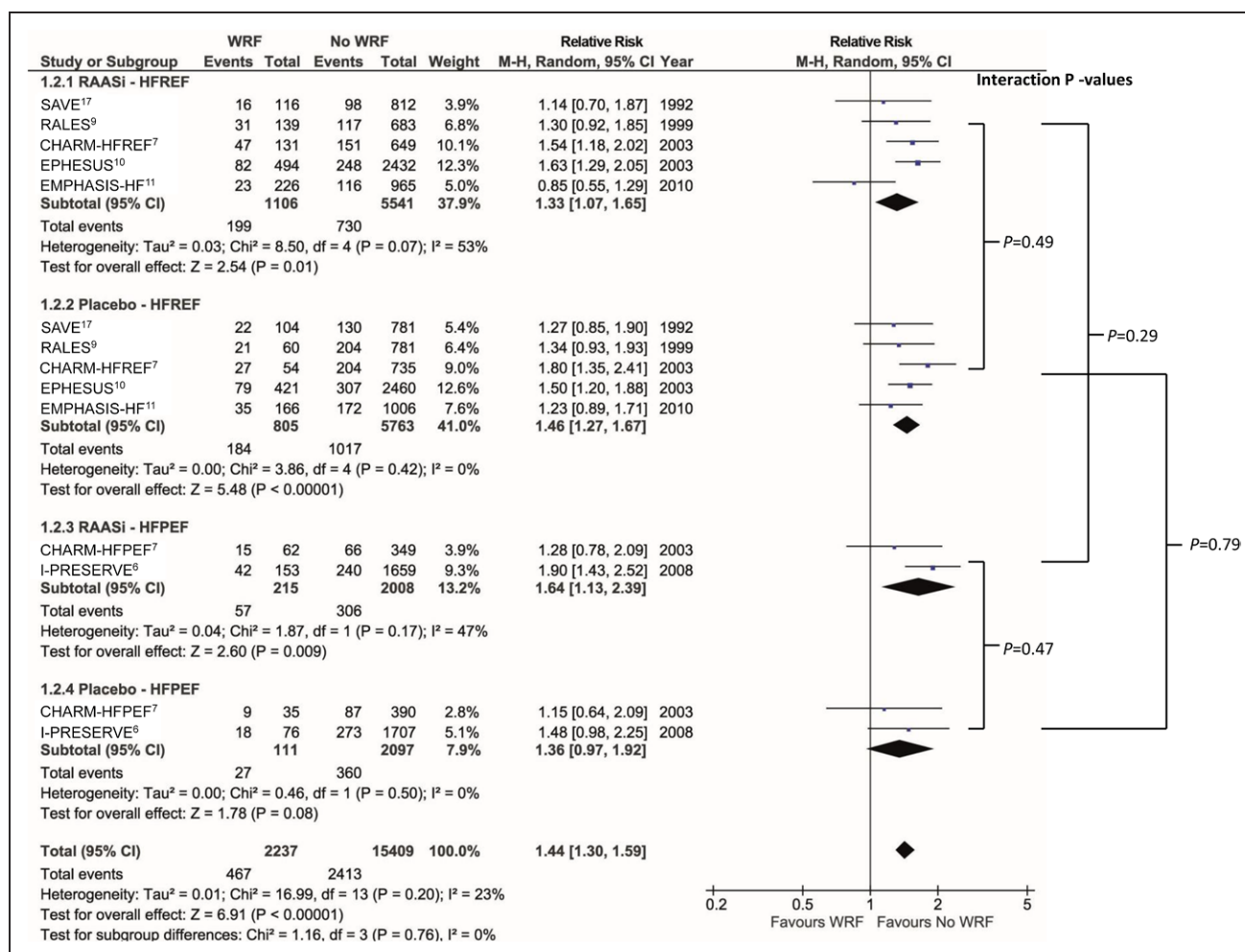


Figure 4. Forest plot of association between renin-angiotensin aldosterone system (RAAS) inhibition, worsening renal function (WRF), heart failure (HF) phenotype, and HF hospitalization. CHARM indicates Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity; CI, confidence interval; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; HFPEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; I-Preserve, Irbesartan in Heart Failure With Preserved Ejection Fraction Study; RALES, Randomized Aldactone Evaluation Study; RCT, randomized clinical trial; RR, relative risk; and SAVE, Survival and Ventricular Enlargement.

More recently, a retrospective analysis from the I-Preserve found that RAAS inhibitor-induced WRF was associated with worse outcomes, compared with placebo-induced WRF.⁶ Retrospective analysis of this question in patients with HFPEF in CHARM gave a less clear answer, as in that study no statistically significant differences were seen between the HF phenotypes, although qualitatively similar findings to those in I-Preserve were obtained.⁷ In our present meta-analysis, we were able to pool the data on I-Preserve and CHARM (HFPEF) and found that RAAS inhibitor-induced WRF was strongly associated with worse outcomes, and that this was significantly different from placebo-induced WRF. Importantly, this difference was significantly different from that observed in HFREF. The findings of this meta-analysis in patients with HFPEF and individual included studies, and the difference observed with findings in patients with HFREF may suggest that these different phenotypes of HF react differently to RAAS inhibition.

RAAS Inhibition, Change in eGFR, Incidence of Renal Dysfunction in HFREF Versus HFPEF

Although we found that the outcome related to RAAS-induced WRF was different between HFREF and HFPEF patients, the incidence of WRF was actually slightly lower in patients with HFPEF. However, WRF is not the only way to assess changes in kidney function, which was the reason to evaluate incidence of renal dysfunction as adverse events in the individual trials, and investigate change in eGFR. Early studies on the effect of, especially, ACE inhibitors in predominantly HFREF patients showed that RAAS inhibitors improve renal blood flow in patients with heart failure, but also lead to a significant reduction in GFR.^{29,30} For patients with HFPEF, data on renal hemodynamics are lacking. In the current meta-analysis we found that the incidence of renal dysfunction associated with RAAS inhibitor use, as reported in the original studies, was similar in HFREF and HFPEF studies. In both phenotypes, RAAS inhibitors increased the risk of renal dysfunction (using any definition) by 50%. For

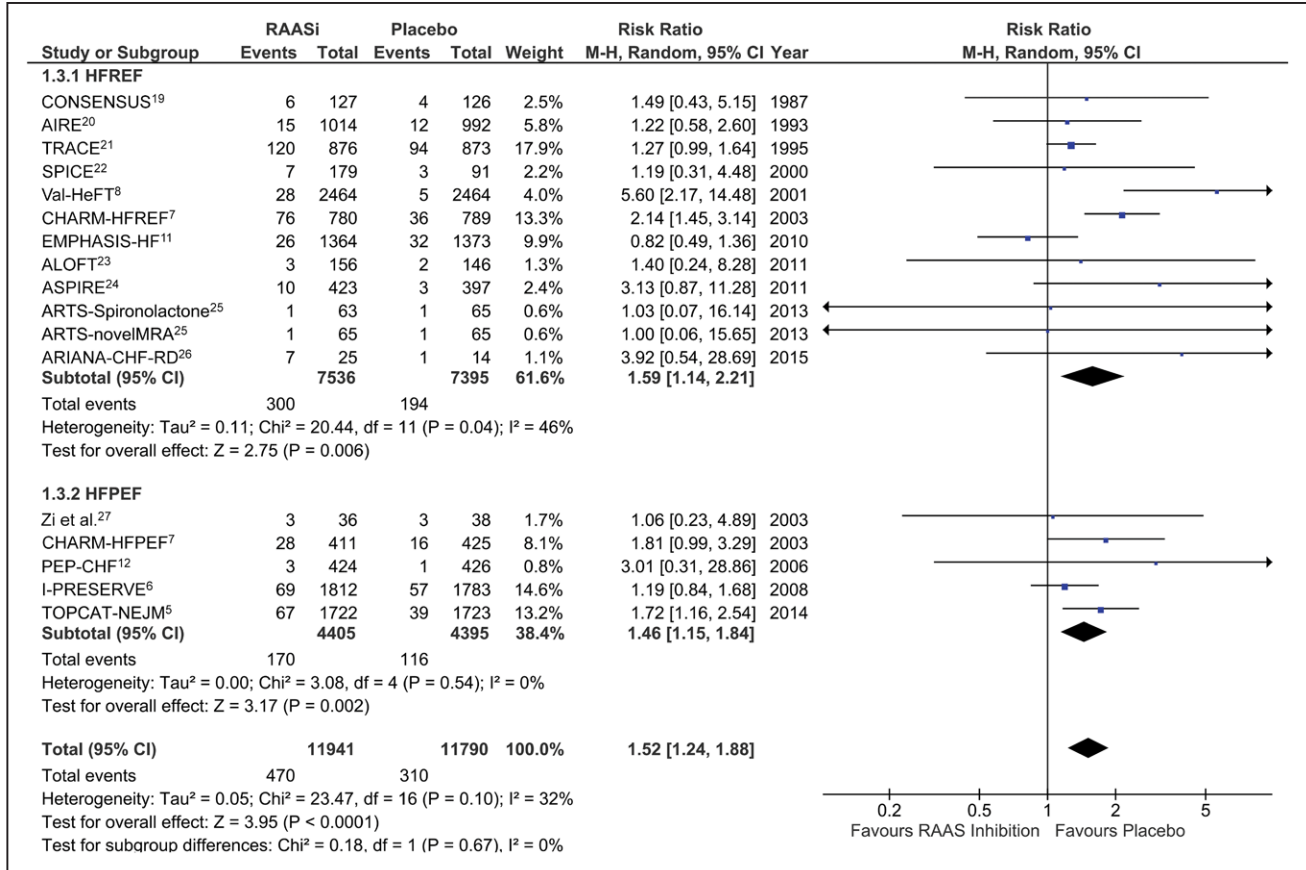


Figure 5. Association between renin–angiotensin aldosterone system inhibition (RAASi) and renal dysfunction in heart failure patients with reduced ejection fraction and heart failure patients with preserved ejection fraction. Renal dysfunction as defined in each individual study specified as either adverse event, as safety end point or specific trial end point. AIRE indicates Acute Infarction Ramipril Efficacy Study; ALOFT, Aliskiren Observation of Heart Failure Treatment; ARIANA-CHF-RD, Additive Renin Inhibition With Aliskiren on Renal Blood Flow and Neurohormonal Activation in Patients with Chronic Heart Failure; ARTS, The mineralocorticoid Receptor Antagonist Tolerability Study; ASPIRE, Aliskiren Study in Post-MI Patients to Reduce Remodeling; CHARM, Candesartan in Heart Failure–Assessment of Reduction in Mortality and Morbidity; CI, confidence interval; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; HFPEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; I-PRESERVE, Irbesartan in Heart Failure With Preserved Ejection Fraction Study; PEP-CHF, Perindopril in Elderly People With Chronic Heart Failure; RR, relative risk; SPICE, Study of Patients Intolerant of Converting Enzyme Inhibitors; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist; TRACE, Trandolapril Cardiac Evaluation Study; and Val-HeFT, Valsartan Heart Failure Trial.

the change in eGFR early during the treatment with RAAS inhibitors, we found that RAAS inhibitor therapy resulted in a significant decrease in eGFR compared with placebo. For both HFREF and HFPEF, the mean difference in change in eGFR between RAAS inhibitor and placebo was around 4 mL/min per 1.73 m²

Possible Explanations and Clinical Consequences

It is difficult to speculate on the specific underlying mechanisms that cause the apparent difference in outcomes associated with RAAS inhibitor–induced WRF in both phenotypes of HF. One obvious reason could be that the detrimental outcome related to WRF is not counteracted by the positive effects of RAAS inhibitors in HFPEF and that our findings are merely a reflection of the lack of benefit of these compounds in HFPEF. One other reason could be that the risk associated with RAAS-induced WRF in HFPEF is larger (and different) from that observed in HFREF. This is supported by the fact that the risk estimates for WRF were indeed

substantial for WRF in HFPEF. Our data on change in eGFR and renal dysfunction, which were similar in HFREF and HFPEF, also suggest that these differences cannot only be explained by the effect of RAAS inhibition on renal function and dysfunction. Hypothetically, the pathophysiology of renal dysfunction in HFPEF is different from that in HFREF; in the latter renal dysfunction has been associated with worse renal hemodynamics, whereas more recently, renal dysfunction in HFPEF has been attributed to inflammatory state and endothelial dysfunction.^{31,32} Also, a drop in blood pressure, induced by RAAS inhibitor therapy, may have differential effects on renal function (and subsequent outcome) in both phenotypes of heart failure. However, our current meta-analysis cannot give definite answers to these important questions. One other interesting observation from our analyses could be that placebo-associated WRF in HFPEF was not associated with increased mortality risk, something that goes against observational evidence showing a stronger association between WRF and clinical outcome with more

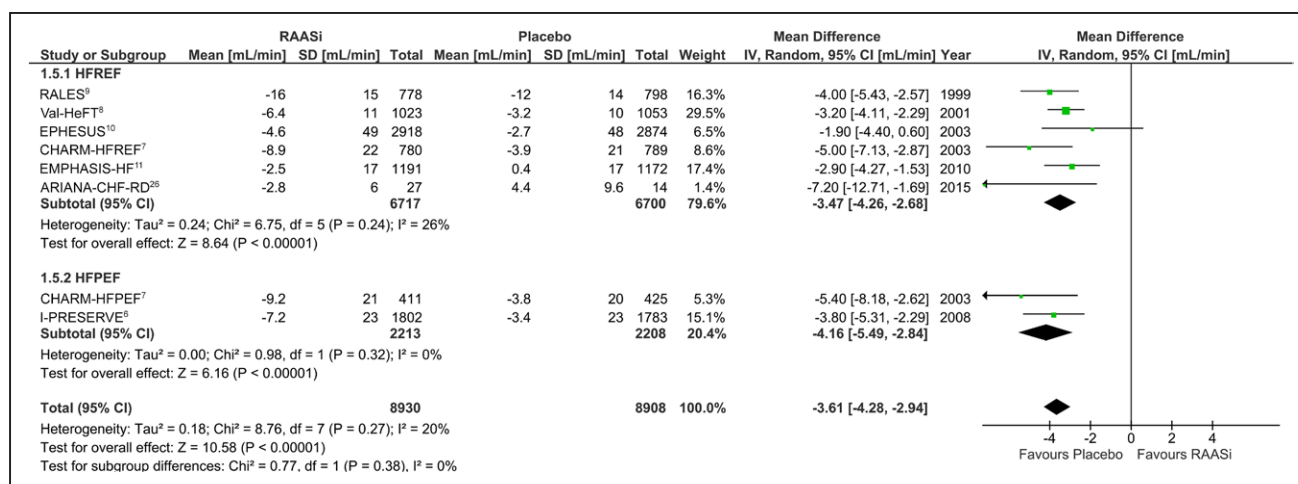


Figure 6. Association between renin–angiotensin aldosterone system inhibition (RAASI), heart failure phenotype, and change in estimated glomerular filtration rate (eGFR). ARIANA-CHF-RD indicates Additive Renin Inhibition With Aliskiren on Renal Blood Flow and Neurohormonal Activation in Patients With Chronic Heart Failure; CHARM, Candesartan in Heart Failure–Assessment of Reduction in Mortality and Morbidity; CI, confidence interval; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; HFPEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; I-PRESERVE, Irbesartan in Heart Failure With Preserved Ejection Fraction Study; RALES, Randomized Aldactone Evaluation Study; and Val-HeFT, Valsartan Heart Failure Trial.

preserved LVEF in HF.² For the clinician, the most important conclusion from our analysis should be that careful assessment of eGFR during uptitration of RAAS inhibitors is essential. This also holds for the situation in which these therapies are prescribed to patients with HFPEF for whatever reason. In those patients, the clinician should be even more careful in prescribing, uptitrating, and continuing RAAS inhibitor therapy when eGFR decreases, as our analysis suggests that these patients are at extremely increased risk for detrimental outcome.

Limitations

The strength of this meta-analysis is that the data were derived from high-quality, randomized, controlled trials with over 25,000 patients, with extensive, high-quality assessments of patients and patients outcomes. However, the included data were all obtained from post hoc analyses and they should be considered hypothesis-generating only. In addition, this was a meta-analysis on aggregate data, rather than individual patient data, which clearly has its limitations on the generalizability. The definition of WRF and timing of the assessment of follow-up creatinine differed substantially between the included studies. Furthermore, aggregate data meta-analysis cannot account for possible selection bias in the individual studies. For instance, patients who had an event before a second creatinine was drawn will not have been included in this meta-analysis. These differences could have affected our main findings. Another limitation of this meta-analysis is that we pooled different types of RAAS inhibitors: ACE inhibitors, angiotensin II receptor blockers, and mineralocorticoid receptor antagonists, whereas the latter could not be considered for HFPEF. Because their pharmacological working mechanisms differ, a difference in outcome could be expected as well. Our study included only 2 HFPEF trials, and therefore the assessment of heterogeneity in this subset of the analyses should be interpreted with caution. Also, our findings need replication in

a larger (prospective) study to confirm our study results of a difference between HFREF and HFPEF patients on this subject. Finally, our analyses were carried out in a specific subset of patients, which included post myocardial left ventricular dysfunction, and specifically investigated WRF during initiation of (additional) RAAS-inhibition, not during long-term follow-up.

Conclusions

RAAS inhibitors cause a significant decline in eGFR and lead to more renal adverse events with similar magnitude in both HFREF and HFPEF patients. Despite this fact, although RAAS inhibitor–induced WRF in HFREF is associated with slightly increased event rates, the prognostic benefit over placebo-induced WRF is maintained. However, in HFPEF, especially WRF that occurs with RAAS inhibition seem detrimental, cautioning the clinician to carefully evaluate these HFPEF patients with increases in creatinine during RAAS inhibitor treatment.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Renin–angiotensin aldosterone system (RAAS) inhibitors are the cornerstone treatments of heart failure patients with reduced ejection fraction (HFREF), but have failed to live up to their expectations in heart failure with preserved ejection fraction (HFPEF). However, these therapies are still being used in patients with HFPEF, especially as secondary prevention. RAAS inhibitors frequently induce worsening renal function (WRF). This meta-analysis investigated a possible interaction between the phenotype of heart failure (HFREF versus HFPEF) and the association between RAAS inhibitor–induced WRF and clinical outcome. In both HFREF and HFPEF, RAAS inhibitor therapy was associated with a significant fall in estimated glomerular filtration rate and higher incidence of renal dysfunction. Despite these effects on renal function, RAAS inhibitor–induced WRF was not associated with worse outcomes in patients with HFREF. In contrast, in patients with HFPEF, especially, RAAS inhibitor–induced WRF related to higher event rates. These findings point toward an important differential effect of RAAS inhibitor–induced WRF in HFREF versus HFPEF patients. Because these therapies are widely prescribed in the entire cardiovascular population, including patients with HFPEF, clinicians should be aware of the clinically relevant WRF when treating these patients with RAAS inhibitors. In contrast to patients with HFREF where significant deteriorations in renal function can probably be accepted as long as the clinical course of the patient is favorable, any RAAS inhibitor–induced WRF in patients with HFPEF should be regarded as important. Patients with HFPEF receiving these drugs should be monitored closely with respect to their renal function, and dose adjustment or discontinuation should be considered when WRF develops.

Renin–Angiotensin System Inhibition, Worsening Renal Function, and Outcome in Heart Failure Patients With Reduced and Preserved Ejection Fraction: A Meta-Analysis of Published Study Data

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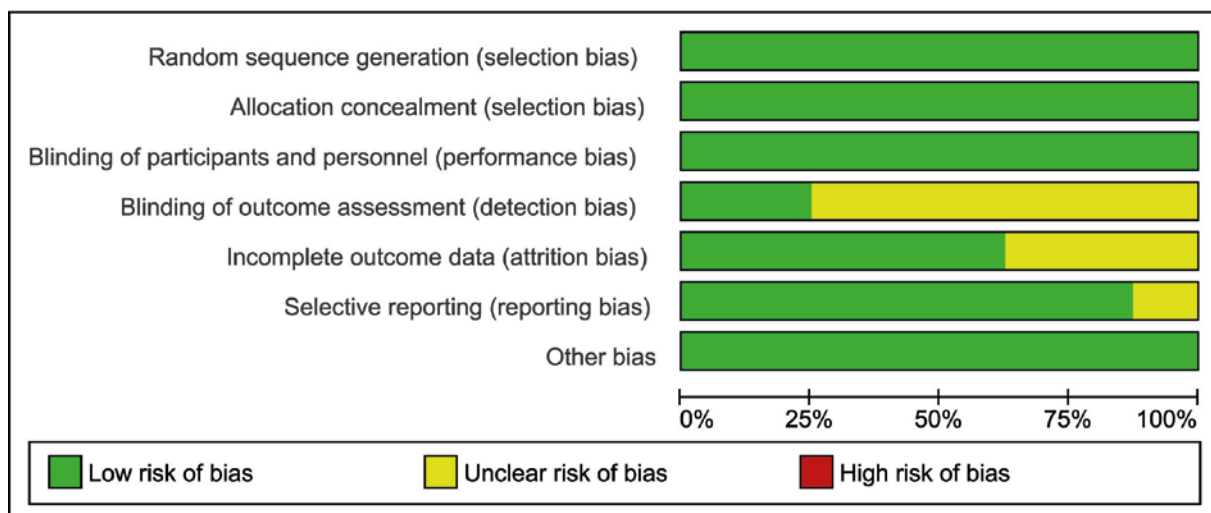
SUPPLEMENTAL MATERIAL

Supplementary Table 1. Definition of Worsening Renal Function in included studies

Study	Change in creatinine/eGFR	During Follow Period
SOLVD ¹	20% decrease in eGFR	2 weeks after randomization
SAVE ²	≥ 0.3 mg/dL increase	2 weeks after randomization
RALES ³	30% decrease in eGFR	12 weeks after randomization
Val-HeFT ⁴	20% decrease in eGFR	4 weeks after randomization
CHARM ⁵	≥ 0.3 mg/dL increase and ≥ 25% increase in serum creatinine	6 weeks after randomization
EPHESUS ⁶	20% decrease in eGFR	2 weeks after randomization
I-PRESERVE ⁷	≥ 0.3 mg/dL increase and ≥ 25% increase in serum creatinine	8 weeks after randomization
EMPHASIS-HF ⁸	20% decrease in eGFR	5 months after randomization

Abbreviations: eGFR: estimated Glomerular Filtration Rate. CHARM: Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity, EMPHASIS-HF: Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure, EPHESUS: Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study, I-PRESERVE: Irbesartan in Heart Failure with Preserved Ejection Fraction Study, RALES: Randomized Aldactone Evaluation Study, SAVE: Survival And Ventricular Enlargement Study, SOLVD: Studies Of Left Ventricular Dysfunction, Val-HeFT: Valsartan Heart Failure Trial

Supplementary Figure 1



1. Testani JM, Kimmel SE, Dries DL, Coca SG. Prognostic importance of early worsening renal function after initiation of angiotensin-converting enzyme inhibitor therapy in patients with cardiac dysfunction. *Circ Heart Fail*. 2011; 4: 685-691.
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