Worsening Renal Function and Outcome in Heart Failure patients with Reduced and Preserved Ejection Fraction and the Impact of Angiotensin Receptor Blocker Treatment

Data from the CHARM-study program

Brief title: WRF in HFREF and HFPEF

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Abstract

Aims. We investigated the association between worsening renal function (WRF) that occurs during renin angiotensin aldosterone system inhibition initation and outcome in heart failure (HF) patients with preserved ejection fraction (HFPEF) and compared this with HF patients with reduced ejection fraction (HFREF).

Methods and Results. We examined changes in estimated glomerular filtration rate (GFR) and the relationship between WRF (defined as e26.5 µmol/L and e25% increase in serum creatinine from baseline to 6 weeks) and outcome, according to randomized treatment, in patients with HFREF (EF <45%; n=1569) and HFPEF (EF e45%; n=836) in the CHARM program. The primary outcome was cardiovascular death or HF hospitalization. Estimated GFR decreased 9.0±21 versus 4.0±21 mL/min/1.73m^2 with candesartan and placebo, respectively, and this was similar in HFREF and HFPEF. WRF developed more frequently with candesartan 16 vs. 7%, *P*<0.001, with similar findings in patients with HFREF and HFPEF. WRF was associated with a higher risk of the primary outcome: multivariable hazard ratio (HR) 1.26, 1.03-1.54, *P*=0.022, in both treatment groups, and in HFREF and HFPEF (*P* for interaction 0.98). In HFREF, WRF was mostly related to HF hospitalization, while in HFPEF, WRF seemed more associated with mortality.

Conclusions. GFR decreased more and WRF was more common with candesartan compared with placebo, and this was similar in HFREF and HFPEF. WRF was associated with worse outcomes in HFREF and HFPEF. Although no formal interaction was present, the association between candesartan treatment, WRF and type of clinical outcome was slightly different between HFREF and HFPEF.

Key Words. Worsening Renal Function, HFPEF, HFREF, Prognosis, Angiotensin Receptor Blocker

Introduction

Chronic kidney disease (CKD) and worsening renal function (WRF) are important prognostic factors both in patients with heart failure (HF) and reduced fraction and in those with preserved ejection fraction (HFREF and HFPEF, respectively).[1,2]

However, evidence-based therapies that can worsen renal function, such as renin angiotensin aldosterone system (RAAS) inhibitors, improve outcome in HFREF, even in patients with *pre-existing* CKD.[3-5] Importantly, new evidence suggests that *worsening* of renal function during the initiation of a RAAS inhibitor, may not have the same adverse prognostic implications as WRF in other circumstances.[3-6]

For patients with HFPEF, data on WRF and outcome are scarce and data on the effect of treatment on the association between WRF and outcome are limited to one retrospective analysis of the I-Preserve trial with irbesartan.[7] In that analysis, WRF during initiation of irbesartan treatment was associated with an increased risk of cardiovascular death or HF hospitalization. This finding contrasts strikingly with those reported previously in studies in HFREF. The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity trials (CHARM) offer another opportunity to investigate the relationship between WRF and outcome in patients with HFPEF, and the effect of treatment with an angiotensin receptor blocker (ARB) on that relationship. Moreover, the same analyses are possible in patients with HFREF who were also enrolled in CHARM, allowing a direct comparison between patients with these two types of chronic HF.

Methods

In the CHARM program patients with symptomatic HF were randomly assigned to either candesartan or placebo.[8,9] Patients with a left ventricular ejection fraction (LVEF) d 40% were randomized into CHARM-Alternative (N=2028) if they were intolerant of an angiotensin converting enzyme inhibitor (ACEi) or CHARM-Added (N=2548) if taking an ACEi. Patients with a LVEF > 40% were enrolled in CHARM-Preserved (N=3023). A key exclusion criterion was a serum creatinine e 265 µmol/L (3 mg/dL). The present analyses were carried out in the 2500 patients with a central laboratory measurement of creatinine at baseline and follow-up (6 weeks, 14 months and 26 months), all of whom were enrolled in North America (See supplementary Table 1 for the number of patients in each of the component trials in the CHARM Programme).[10]

For the present analyses, HFPEF was defined as LVEF e 45% (with HFREF defined as LVEF <45%) to reflect more recent definitions of this syndrome and to be consistent with I-Preserve. Only patients with a serum creatinine at baseline and at least at the 6 week post-randomization visit were included. All patients gave written informed consent before being enrolled. All participating sites received approval from local ethics committees for the conduct of the study program.

Glomerular Filtration Rate and Worsening Renal Function

Estimated glomerular filtration rate (eGFR, mL/min/1.73m^2) was calculated using the simplified Modification of Diet in Renal Disease formula and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). There is no universal definition on WRF, and international guidelines do not agree on the best method in establishing WRF.[11-13] In this study, WRF was defined as both an absolute increase in serum creatinine of e 26.5 µmol/L (e 0.3 mg/dL) and together with a relative increase in serum creatinine of e 25% between baseline and 6 weeks during the uptitration phase of the CHARM-studies in the chronic

outpatient setting. In addition, as sensitivity analyses, we also examined WRF defined as an absolute increase in serum creatinine of e 26.5 µmol/L ora reduction in eGFR of either e 20% or e 30%.

Clinical Outcomes

The primary outcome of each of the CHARM trials was the first occurrence of cardiovascular death or HF hospitalization. Secondary outcomes included all-cause mortality, HF hospitalization, combined endpoint of all-cause mortality or HF hospitalization and a composite of major adverse cardiac events (cardiovascular death, admission to hospital for HF, non-fatal myocardial infarction, non-fatal stroke, or coronary revascularisation).

Statistical Analysis

Data are reported as mean ± standard deviation when normally distributed, as median and interquartile ranges when the distribution was skewed and as frequencies and percentages for categorical variables. Student's t test or Mann-Whitney U tests were used to determine significant differences of variables between patients with and without WRF in both treatment groups, and in patients with HFREF and HFPEF. All patients that received the study treatment were included in this analysis and analysed according their treatment group. Logistic regression was used to determine odds ratios (OR) for the occurrence of WRF at 6 weeks for candesartan treatment compared with placebo. Change in renal function over time was assessed by repeated analysis mixed effect modelling using unstructured covariance. The variables already reported to be of prognostic value in this CHARM were used in multivariable modelling (age, gender, race, NYHA functional class, smoking status, LVEF, systolic and diastolic blood pressure, heart rate, history of angina, stroke, hypertension, diabetes, myocardial infarction and HF hospitalization, as well as certain medical therapies: diuretic, ACE-inhibitor, spironolactone, calcium channel blocker, other vasodilators and

aspirin)[10] We included a random intercept accounting for possible differences on patient level. To evaluate possible association between candesartan use or early discontinuation, change in blood pressure and WRF we used exploratory analysis evaluating the change in mean arterial pressure and disconuation rates among patients with and without WRF. We used a Cox proportional hazards model to estimate hazard ratios (HR) with 95% CI for the occurrence of the primary and all secondary endpoints. WRF was added to the model as a categorical variable. Interaction terms with treatment (WRF x treatment) were analysed separately. The Cox proportional hazard assumption was checked by visual inspection of the log-log plots and statistical testing of Schoenfeld residuals no violations were observed. Kaplan-Meier survival curves were plotted showing outcomes in patients who did or did not experience WRF in both treatment groups and in patients with HFREF and HFPEF. A 2-tailed *P*-value < 0.05 was considered significant, except for interactions where *P*-value < 0.10 was considered significant. Statistical analyses were performed using STATA, College Station, Texas, version 12.0.

Results

A total of 2405 out of 2500 (96%) patients had both a baseline and 6 week creatinine available. Of these 589 (24%), 836 (35%) and 980 (41%) were from the CHARM-Alternative, -Added and –Preserved trials, respectively. Differences between patients from North-America and elsewhere in CHARM have been described previously.[9]

Baseline characteristics and Worsening Renal Function

Baseline characteristics, stratified by treatment allocation and development of WRF are presented in Table 1 and stratified for HFREF and HFPEF in Table 2. There were few differences in baseline characteristics for patients with and without WRF. Examining WRF according to treatment assignment, patients developing WRF in the candesartan group more often received diuretics and beta-blockers, and had lower average hemoglobin levels than those who did not develop WRF.

In the overall CHARM population, WRF developed in 282 (12%) of patients at week 6, and was more common with candesartan than with placebo: odds ratio (OR) 2.44 (1.88-3.19), $P < 0.001$ (Table 3). Similar findings were observed using different definitions of WRF, and across the component trials of the CHARM Program (Supplementary Table 1).

WRF occurred in 12% of patients with HFREF. The most notable differences between patients with and without WRF in HFREF were more frequent use of loop diuretics and ACE-inhibitors in the WRF group. Similarly to HFREF, WRF occurred in 12% of patients with HFPEF. Among differences, patients who experienced WRF in HFPEF more frequently had a history of coronary artery disease or ischemic HF.

WRF and Clinical Outcome

CHARM-Overall

Table 4 shows the association between WRF and clinical outcome. WRF was related to the primary outcome of CV death or HF hospitalization in the entire CHARM population and this association remained after multivariable adjustment, although it was attenuated to some extent (HR 1.26, 1.03-1.54, $P = 0.022$) (Table 4). WRF was most consistently associated with HF hospitalisation, rather than CV death or all-cause mortality. The relationship between WRF and outcome was not influenced by study-drug discontinuation in the entire population and HFREF or HFPEF patients. Also, baseline eGFR did not modify the association between WRF, candesartan treatment and associated outcome (P for interaction 0.35). Supplementary table 2 shows the association between WRF, treatment and outcome in different CHARM studies. We found no evidence of a significant interaction between study arm allocation and the association between candesartan treatment, WRF and outcome. Additionally, there was no interaction between candesartan treatment, WRF, baseline LVEF (as a continuous measure) and relationship with outcome (P=0.771). Supplementary table 3 shows the association between the effect of candesartan treatment on outcome, and baseline WRF in different phenotypes of HF, showing no evidence of interaction and similar effects of candesarta in patients with and without WRF.

CHARM HFREF

In patients with HFREF, there was a clear association between the occurrence of WRF and the primary outcome of CV death or HF hospitalization in univariate analysis (HR 1.46, 1.17-1.83, $P = 0.001$), which persisted after adjustment for other prognostic variables and concomitant therapy (Figure 1A and Table 4). WRF was an independent predictor of this composite outcome in both the placebo and candesartan group, without evidence of interaction. After adjustment for other prognostic variables and concomitant therapy, there was a persisting association between WRF and HF hospitalization in both treatment groups, but not for other outcomes.

CHARM HFPEF

Development of WRF showed the same trend with occurrence of the primary outcome (adjusted HR 1.30, 0.89–1.90), compared with patients with HFREF (*P* for interaction 0.98). However, this association did not reach statistical significance in either treatment group, after adjustment for the prespecified prognostic variables and concomitant therapy (Figure 1B, Table 4). Similar results were found secondary outcomes, with the exception of CV death. For this particular outcome, there was trend towards an interaction (*P*=0.10) between WRF and treatment; WRF was associated with a higher risk of CV death in patients allocated to candesartan in contrast to WRF that occurred with placebo. There was no significant interaction between treatment, WRF and outcomes on multivariable analysis.

Change in eGFR

For all patients, the mean baseline eGFR at baseline was 71 ± 27 mL/min/1.73m^2. Overall, estimated GFR decreased by 2.8 mL/min/1.73m^2/year, to 66 ± 27 mL/min/1.73m^2 at 26 months in surviving patients. Candesartan treatment was associated with a significantly greater decrease in eGFR at 6 weeks than placebo: -4.7 ± 19 versus -0.1 ± 19 mL/min/1.73m^2 (*P*< 0.001), respectively (Figure 2A). The difference between candesartan and placebo in change in was similar in patients with or without a history of diabetes at baseline (in both HF phenotypes).

Similar results were found for HFREF and HFPEF. Figures 2B and C show the time courses of eGFR in patients with HFREF and HFPEF, respectively. In patients with HFREF, mean eGFR decreased by -6.4 ± 21 mL/min/1.73m^2 overall. The change in eGFR was more pronounced in the candesartan group -8.9 ± 22 versus -3.9 ± 21 mL/min/1.73m^2 for placebo at 26 months follow up (*P* < 0.001).). In patients with HFPEF, eGFR decreased by -6.7 ± 21 mL/min/1.73m^2 at 26 months, a decline similar to that observed in the HFREF group (*P* = 0.91). Patients in the candesartan group showed a greater decrease in eGFR at 26 months: -

9.2 ± 21 mL/min/1.73m^2 versus -3.8 ± 20 mL/min/1.73m^2 in the placebo group (P = 0.042). In both HFREF and HFPEF, using the CKD-EPI instead of sMDRD formula showed similar results. Supplementary table 4 summarizes the change in eGFR across HF phenotypes, randomized candesartan treatment and study periods.

Change in mean arterial pressure and discontinuation rates

The reduction in mean arterial pressure (MAP) at 6 weeks was greater in patients with WRF than in those without (-7.9 ± 12 vs. -2.8 ± 11 mmHg , P < 0.001) and patients in the candesartan group with WRF had greater reductions in MAP than patients with WRF in the placebo group (-9.5 ± 11 vs. -4.4 ± 14 mmHg, P = 0.001). These results were similar in HFREF and HFPEF, although the difference of change in MAP between patients with WRF on either placebo or candesartan in HFPEF was numerically, but not statistically, different. Permanent discontinuation rates within 6 weeks after the second creatinine measurement were significantly higher in patients with WRF, compared to those without WRF (7 vs 2%, P < 0.001). Similar discontinuation rates were observed before WRF occurred (1 vs 2%, P = 0.36). The findings were similar in HFREF and HFPEF.

Discussion

In the present study, eGFR decreased more with candesartan compared with placebo, and this was similar in HFREF and HFPEF. We found that the incidence of WRF was similar in patients with HFREF and HFPEF, overall and separately within the placebo group and candesartan group. Candesartan was associated with a higher incidence of WRF in both types of HF. Overall WRF was associated with worse clinical outcomes. There was no significant interaction between type of HF (or LVEF on a continuous scale), candesartan treatment, occurrence of WRF and the relationship with outcome.

Change in eGFR and ARB treatment

CKD as defined by a reduced eGFR is frequently present in chronic HFREF and HFPEF patients.[1] While there are plentiful data on baseline CKD in HF (mostly HFREF), there are fewer data on change in eGFR over time. In HF patients that were followed after hospitalization, eGFR decreased 7.0 mL/min/1.73m^2 in the next 18 months.[14]

In Val-HeFT, patients in the placebo group had a mean decrease of 2.9 mL/min/1.73m^2 after 36 months.[4] In I-Preserve, the mean change in eGFR over 30 months was 5.0 mL/min/1.73m^2, which was more pronounced in the irbesartan group.[7] Our results are in alignment with these findings. We found a decrease in 4.0 mL/min/1.73m^2 over 26 months. In keeping with the results of Val-HeFT and I-Preserve, candesartan treatment led to an early (although small) decline in eGFR.[4,7] This initial decline in GFR is thought to be due to inhibition of the effect of angiotensin on glomerular efferent arterial tone leading to decreased filtration pressure and decreased GFR. This effect was similar in patients with HFREF and HFPEF. After the initial steep fall in eGFR, there was a subsequent slower decrease in eGFR and this was similar in the placebo and candesartan group. Thus, it seems clear from Val-HeFT, I-Preserve and CHARM that ARBs do not preserve renal function in patients with HFREF or HFPEF in contradistinction to patients with diabetic nephropathy.[15,16]

Worsening Renal Function, Outcome and candesartan treatment in *HFREF*

WRF, however defined, is associated with poor clinical outcomes in chronic HF although the data supporting this conclusion come predominantly from studies in patients with HFREF.[2]

In SOLVD the incidence of WRF with enalapril was similar to what we found in CHARM. WRF on enalapril was not associated with worse clinical outcome, in contrast to the placebo group.[3] Similarly, in Val-HeFT, valsartan treatment was associated with an increased

frequency of WRF compared with placebo (12.3 vs. 5%, respectively), but the beneficial effect of valsartan over placebo was maintained, even in patients experiencing WRF.[4]

Some increase in serum creatinine is frequently observed after initiation of an ACE inhibitor, and the European Society of Cardiology HF guidelines suggest only reducing the dose of ACE/ARB therapy (or stopping treatment) when such increases are large i.e. >50% or when the absolute creatinine concentration exceeds 266 µmol/L (3 mg/dL), while the 2013 ACC/AHA HF guidelines mainly suggest monitoring renal function closely. This relatively relaxed approach reflects the belief that an initial decrease in renal function as a result of RAAS inhibition is not thought to be detrimental with respect to clinical outcome unless extreme. This is supported by a meta-analysis of RAAS inhibitor trials examining the relationship between WRF and outcome which showed that the beneficial effects of these drugs over placebo were maintained, even in the presence of WRF.[6]

In CHARM, WRF in patients with HFREF was independently associated with a higher risk of the composite endpoint of CV death or HF hospitalization, and this was primarily attributable to an association with HF Hospitaliations. In SOLVD the increased risk related to WRF (versus no WRF) was greater in the placebo than in the enalapril group for the endpoint of all-cause mortality and HF hospitalization was not assessed.[3]

In RALES, EMPHASIS-HF and EPHESUS, WRF seemed to be more strongly associated with HF hospitalization than with all-cause mortality.[5][17][18]

A similar association was seen in HF-REF patients in CHARM, although in the candesartan group the risk of HF hospitalization related to WRF was not increased as much in the candesartan group as in the placebo group. It has been difficult to predict beforehand which patients will experience WRF (and have poor outcome).[2] Also from our present analysis, no specific factors, other than severity of heart failure were significantly associated with the occurrence of WRF, irrespective of outcome and treatment.

Worsening Renal Function, Outcome and candesartan treatment in *HFPEF*

Only two studies to date have examined the prognostic importance of WRF in patients with HFPEF, and in the largest, an analysis from I-Preserve, the picture was different than in HFREF.[7,19] In I-Preserve, the risk of WRF was twice as high in patients allocated to irbesartan (8 vs. 4%) consistent with what is seen with an ACEi or ARB in HFREF. WRF in the entire study population, irrespective of study drug allocation, was associated with a greater risk of cardiovascular death or HF hospitalization. In contrast to HFREF, WRF in I-Preserve patients allocated to irbesartan was associated with poor clinical outcome, which was even worse compared with WRF that occurred in patients allocated to placebo. In patients with HFPEF in CHARM, WRF also appeared to be associated with worse outcomes although this finding was not statistically significant, possibly due to the relatively small number of patients an events studied. WRF occurring during candesartan treatment in HFPEF patients was associated with a higher risk of CV death, while this relationship was less clear in patients receiving placebo or for other endpoint such as HF hospitalization, which was the predominant association with WRF for HFREF patients. Although this apparent difference could reflect the play of chance, it might also indicate that the consequences of ARB-related WRF are different in patients with HFPEF compared with HFREF. We believe that this hypothesis is possible as WRF in the irbesartan group in I-Preserve was also mainly associated with a higher risk of all-cause death, in contrast to that in the placebo group (multivariable P-value for interaction 0.078).[7] However, in our current analysis when LVEF was examined as a continuous variable, there was no interaction between WRF, treatment and outcome. Therefore, we cannot be sure that patients with HRPEF definitely do differ from those with HFREF, although patients with HFPEF and HFREF are dissimilar not only in relation to ejection fraction, but also in relation to demographics, the pathophysiology of heart failure,and therefore possible also in the relationship between WRF and outcome. Finally, we know that ACE inhibitors and ARBs do not improve outcomes in HFPEF in

contrast to HFREF.[20,21] Therefore, whereas any detrimental effect of RAAS inhibition may be entirely outweighed by benefit in HFREF, this will not be the case in HFPEF.

Clinical Perspective on difference between WRF in HFREF and HFPEF

In HFREF, if WRF develops during RAAS-inhibition, treatment should be continued as RAAS inhibition remains advantageous overall, although the benefit may be attenuated (compared with patients not developing WRF), especially with respect to HF hospitalization. The picture is different in HFPEF patients. Despite the fact that RAAS-inhibitors have not been shown to reduce mortality or morbidity in these individuals, RAAS blockers are frequently used, presumably, in the majority of cases, to treat hypertension. RAAS blockade leads to a drop in eGFR and induces WRF at a similar rate to that observed in HFREF. The findings of the present analysis from CHARM, together with those from I-PRESERVE, suggest that clinicians should monitor for development of WRF when a RAAS blocker is used in these patients because its occurrence is associated with worse clinical outcomes than in patients without WRF. If WRF does develop, an alternative treatment, if available, should be considered.

Limitations

This was a retrospective analysis of a randomized controlled trial, and therefore these results can only be extrapolated to the general HF population with caution. Not all patients had serum creatinines available, and as such selection bias could have arisen. However, serum creatinine determination was done by protocol, which minimizes the bias of having more creatinine values available for high risk patients. The definition of WRF used in this analysis accounts for the exponential relationship between serum creatinine and eGFR, but there is no universal definition of WRF and other definitions might have given different results. On the other hand, our sensitivity analyses with different estimates of WRF showed similar results.

We had no data on dose of diuretics, which could have been helpful in determining the association between diuretic use, WRF and clinical outcome. We cannot account for unmeasured confounding from known (such as natriuretic peptides) and unknown variables.

Conclusions

Initiation of candesartan led to an immediate but small reduction in eGFR which was similar in patients with HFREF and HFPEF. Approximately one in eight patients reached the threshold for WRF which also occurred with equal frequency in HFREF and HFPEF. WRF was associated with worse clinical outcomes, particularly HF hospitalization in HFREF, and mortality in HFPEF. This association was observed in both the placebo and candesartan groups although the magnitude of excess risk related to WRF was less in the candesartan group. Overall, observations were similar in patients with both HFREF and HFPEF, although subtle differences for different endpoints in multivariable analysis were observed, suggesting that at least some caution should be exercised in HFPEF patients who develop WRF on ARB therapy.

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Disclosures

None.

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Figure Legends

Figure 1. Candesartan treatment, Worsening Renal Function and CV death or HF Hospitalization

A) Patients with HFREF

B) Patients with HFPEF

Abbreviations: CV: Cardiovascular, HF: Heart Failure, WRF: Worsening Renal Function

Figure 2: Change in eGFR stratified for treatment

A) Entire CHARM population

B) Patients with HFREF

C) Patients with HFPEF

$ $P < 0.050$, # $P < 0.01$, * $P < 0.001$. P for overall interaction < 0.001. Abbreviations: eGFR: estimated Glomerular Filtration Rate. Presented are least square means ± standard error from adjusted mixed effects model. Random intercept on patient level, fixed effects: age, gender, race, NYHA functional class, smoking status, left ventricular ejection fraction, systolic and diastolic blood pressure, heart rate, history of angina, stroke, hypertension, diabetes, myocardial infarction or heart failure hospitalization and medical therapy: diuretics, angiotensin converting enzyme inhibitor, calcium channel blockers, aspirin, vasodilators and spironolactone use.

Table 1. Baseline Characteristics of the overall study population stratified by treatment and WRF

	Candesartan			Placebo		
Variables	**WRF**	**No WRF**	***P*-value**	**WRF**	**No WRF**	***P*-value**
N	193 (16)	998 (84)		89 (7)	1125 (93)	
Age (years)	64 ± 11	65 ± 12	0.67	67 ± 10	65 ± 12	0.10
Male gender (%)	134 (69)	669 (67)	0.52	61 (69)	752 (67)	0.74
Heart rate (bpm)	73 ± 12	72 ± 12	0.37	74 ± 13	71 ± 12	0.07
SBP (mmHg)	127 ± 19	128 ± 19	0.61	131 ± 21	129 ± 18	0.13
DBP (mmHg)	73 ± 11	74 ± 11	0.15	73 ± 11	74 ± 11	0.57
BMI (kg/m^2)	30 ± 7	30 ± 6	0.91	30 ± 5	29 ± 6	0.41
LVEF (%)	37 ± 16	39 ± 16	0.15	39 ± 17	39 ± 16	0.89
LVEF e 45% (%)	32	35	0.45	39	35	0.38
Ischemic HF (%)	62	59	0.37	61	58	0.56
Medical History (%)						
Hypertension	65	66	0.71	70	67	0.55
Diabetes	37	37	0.95	45	36	0.10
Atrial Fibrillation	31	28	0.34	24	30	0.21
Stroke	10	10	0.97	12	11	0.74
Myocardial Infarction	57	54	0.46	56	52	0.43
Laboratory						
Hemoglobin (g/dL)	13.3 ± 1.6	13.6 ± 1.6	0.01	13.5 ± 1.5	13.7 ± 1.5	0.32
Creatinine (µmol/L)	97 (80-124)	89 (80-115)	0.019	97 (71-115)	97 (80–115)	0.10
eGFR ($mL/min/1.73m^2$)						
sMDRD	69 ± 29	72 ± 26	0.15	77 ± 29	72 ± 27	0.09
CKD-EPI	64 ± 22	68 ± 23	0.04	70 ± 21	67 ± 23	0.28
Medical Therapy (%)						
ACE-inhibitors	47	46	0.75	57	44	0.01
MRA	17	15	0.36	13	15	0.69
Diuretics	94	85	0.002	92	85	0.06
Loop Diuretic	88	79		88	80	
Other	6	6		4	5	
Beta-blockers	51	58	0.05	55	55	0.95
NSAIDs	8	7	0.67	9	9	0.91
Digoxin	54	54	0.92	50	53	0.49

Abbreviations: ACE: angiotensin converting enzyme, BMI: body mass index, DBP; diastolic blood pressure, eGFR: estimated glomerular filtration rate, HF: heart failure, LVEF: left ventricular ejection fraction MRA: mineralocorticoid receptor antagonist, NSAIDs: non-steroidal anti-inflammatory drugs, SBP: systolic blood pressure, WRF: worsening renal function.

Table 2. Baseline Characteristics of the overall study population stratified by HFREF/HFPEF and WRF

	HFREF			HFPEF		
Variables	**WRF**	**No WRF**	***P*-value**	**WRF**	**No WRF**	***P*-value**
N	185 (12)	1384 (88)		97 (12)	739 (88)	
Age (years)	64 ± 11	65 ± 12	0.77	67 ± 10	66 ± 11	0.19
Male gender (%)	140 (76)	1008 (73)	0.41	55 (57)	413 (56)	0.88
Heart rate (bpm)	74 ± 13	72 ± 12	0.013	70 ± 11	71 ± 11	0.67
SBP (mmHg)	123 ± 20	126 ± 18	0.20	137 ± 18	133 ± 17	0.022
DBP (mmHg)	72 ± 11	74 ± 11	0.047	75 ± 10	75 ± 11	0.99
BMI (kg/m^2)	29 ± 6	29 ± 6	0.45	31 ± 7	31 ± 7	0.94
LVEF (%)	27 ± 8	29 ± 9	0.006	57 ± 8	57 ± 8	0.60
Ischemic HF (%)	62	64	0.71	61	48	0.016
Medical History (%)						
Hypertension	61	61	0.98	76	76	0.97
Diabetes	38	35	0.50	42	38	0.45
Atrial Fibrillation	28	28	0.97	31	31	0.97
Stroke	12	11	0.64	8	10	0.53
Myocardial Infarction	59	59	0.999	51	40	0.046
Laboratory						
Hemoglobin (g/dL)	13.5 ± 1.5	13.7 ± 1.6	0.075	13.0 ± 1.7	13.5 ± 1.6	0.008
Creatinine (µmol/L)	97 (80-124)	97 (80-115)	0.083	89 (71-115)	89 (71-115)	0.53
eGFR ($mL/min/1.73m^2$)						
sMDRD	71 ± 30	72 ± 26	0.58	74 ± 25	73 ± 27	0.64
CKD-EPI	65 ± 23	68 ± 23	0.17	68 ± 24	68 ± 20	0.94
Medical Therapy (%)						
Candesartan	71	47	< 0.001	64	47	0.002
ACE-inhibitors	64	56	0.034	25	24	0.93
MRA	17	18	0.87	13	9	0.19
Diuretics	96	87	0.001	89	82	0.10
Loop Diuretics	92	82		80	75	
Other	4	5		9	7	
Beta-blockers	50	57	0.11	56	57	0.75
NSAIDs	9	7	0.34	7	10	0.45
Digoxin	62	65	0.53	34	32	0.76

Abbreviations: ACE: angiotensin converting enzyme, BMI: body mass index, DBP; diastolic blood pressure, eGFR: estimated glomerular filtration rate, HF: heart failure, HFREF: heart failure with reduced ejection fraction, HFPEF: heart failure with preserved ejection fraction, LVEF: left ventricular ejection fraction MRA: mineralocorticoid receptor antagonist, NSAIDs: non-steroidal anti-inflammatory drugs, SBP: systolic blood pressure, WRF: worsening renal function.

Table 3. Prevalence of WRF in different CHARM study arms and relationship to treatment allocation

	Overall CHARM (N=2405)		HFREF (N=1569)		HFPEF (N=836)	
WRF Definition	**Candesartan (N=1191)**	**Placebo (N=1214)**	**Candesartan (N=780)**	**Placebo (N=789)**	**Candesartan (N=411)**	**Placebo (N=425)**
e 26.5 µmol/L ánd e 25% increase in creatinine at 6 weeks	193 (16)	89 (7)	131 (17)	54 (7)	62 (15)	35 (8)
OR for WRF with Candesartan	2.44 (1.88 - 3.19), *P* < 0.001		2.75 (1.97 – 3.84), *P* < 0.001		1.98 (1.28 – 3.07), *P* = 0.002	
e 26.5 µmol/L increase in creatinine at 6 weeks	235 (20)	113 (9)	162 (21)	69 (9)	73 (18)	44 (10)
OR for WRF with Candesartan	2.39 (1.88 – 3.05), *P* < 0.001		2.74 (2.02 – 3.70), *P* < 0.001		1.87 (1.25 – 2.79), *P* = 0.002	
e 20% decrease in eGFR at 6 weeks	284 (24)	160 (13)	186 (24)	95 (12)	98 (24)	65 (15)
OR for WRF with Candesartan	2.06 (1.67 – 2.55), *P* < 0.001		2.29 (1.75 -3.00), *P* < 0.001		1.73 (1.22 – 2.46), *P* = 0.002	
e 30% decrease in eGFR at 6 weeks	124 (10)	69 (6)	82 (11)	38 (5)	42 (10)	31 (7)
OR for WRF with Candesartan	1.92 (1.42 – 2.62), *P* < 0.001		2.32 (1.56 -3.46), *P* < 0.001		1.45 (0.89 – 2.35), *P* = 0.136	

Abbreviations: OR: odds ratio, WRF: worsening renal function

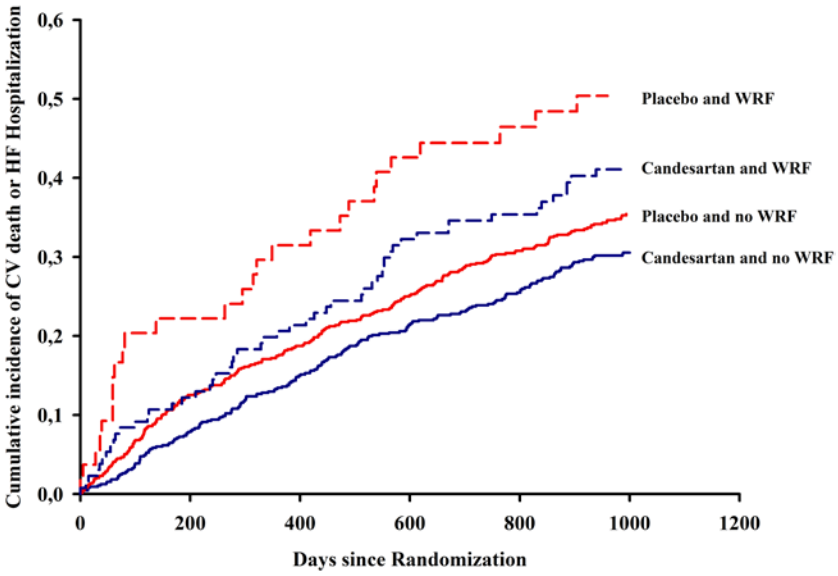
Table 4. Univariate and multivariable analysis of WRF in CHARM stratified for patients with HFREF and HFPEF

	CV death / HF Hosp		AC death		CV death		HF Hosp		AC death / HF Hosp		Combined Endpoint*	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
CHARM Overall												
WRF (univariate)	1.41 (1.17-1.72)	< 0.001	1.19 (0.92-1.53)	0.18	1.39 (1.05-1.83)	0.016	1.55 (1.25-1.93)	< 0.001	1.37 (1.14-1.65)	0.001	1.31 (1.09-1.57)	0.004
Multivariable												
WRF (entire population)	1.26 (1.03–1.54)	0.022	1.03 (0.79-1.33)	0.85	1.21 (0.91-1.59)	0.19	1.37 (1.09-1.71)	0.007	1.22 (1.01-1.48)	0.040	1.19 (0.99-1.44)	0.063
WRF with Candesartan	1.31 (1.02-1.68)	0.037	1.03 (0.75-1.44)	0.82	1.19 (0.83-1.72)	0.35	1.41 (1.06-1.88)	0.019	1.27 (1.01-1.63)	0.045	1.25 (0.99–1.58)	0.061
WRF with Placebo	1.24 (0.89-1.74)	0.19	1.09 (0.71-1.67)	0.69	1.31 (0.84-2.04)	0.24	1.38 (0.95-2.00)	0.087	1.20 (0.86-1.66)	0.29	1.13 (0.82-1.55)	0.47
P-value Interaction		0.95		0.76		0.58		0.89		0.93		0.91
HFREF												
WRF (univariate)	1.46 (1.17-1.83)	0.001	1.06 (0.79-1.44)	0.68	1.26 (0.92-1.72)	0.15	1.69 (1.32-2.17)	< 0.001	1.38 (1.11-1.72)	0.004	1.31 (1.05-1.62)	0.015
Multivariable												
WRF (entire population)	1.32 (1.05-1.67)	0.019	0.90 (0.66-1.23)	0.51	1.08 (0.78-1.49)	0.65	1.57 (1.21-2.03)	0.001	1.24 (0.99-1.56)	0.062	1.20 (0.96-1.50)	0.11
WRF with Candesartan	1.29 (0.96-1.73)	0.096	0.80 (0.54-1.20)	0.29	0.99 (0.65-1.52)	0.97	1.48 (1.01-2.08)	0.023	1.21 (0.91-1.61)	0.19	1.21 (0.92-1.60)	0.17
WRF with Placebo	1.51 (1.02-2.22)	0.039	1.13 (0.69-1.86)	0.63	1.23 (0.72-2.09)	0.45	1.87 (1.23-2.83)	0.003	1.40 (0.95-2.06)	0.085	1.24 (0.84-1.81)	0.29
P-value Interaction		0.51		0.40		0.32		0.33		0.56		0.29
HFPEF												
WRF (univariate)	1.30 (0.89–1.90)	0.17	1.60 (1.00-2.56)	0.049	1.93 (1.12-3.33)	0.018	1.24 (0.81-1.91)	0.32	1.36 (0.96-1.94)	0.087	1.31(0.94-1.84)	0.11
Multivariable												
WRF (entire population)	1.09 (0.72-1.65)	0.67	1.33 (0.80–2.19)	0.27	1.60 (0.89-2.90)	0.12	0.98 (0.61-1.57)	0.92	1.12 (0.77-1.65)	0.55	1.14 (0.80-1.63)	0.47
WRF with Candesartan	1.11 (0.65–1.90)	0.71	1.69 (0.87-3.28)	0.12	2.54 (1.10-5.86)	0.028	0.95 (0.52-1.75)	0.88	1.13 (0.69-1.86)	0.62	1.11 (0.70-1.78)	0.65
WRF with Placebo	0.84 (0.42-1.69)	0.63	0.77 (0.31-1.89)	0.57	0.72 (0.25-2.03)	0.53	0.82 (0.35-1.89)	0.64	0.89 (0.46-1.72)	0.73	0.99 (0.55-1.79)	0.98
P-value Interaction		0.50		0.20		0.10		0.72		0.48		0.17
***P*-value Overall Interaction[#]**		0.98		0.43		0.69		0.81		0.43		0.85

* Cardiovascular death, admission to hospital for HF, non-fatal myocardial infarction, non-fatal stroke, or coronary revascularisation. # WRF x Treatment x HFREF/HFPEF. Abbreviations: AC: All-cause, CHARM: candesartan in heart failure assessment of reduction in mortality and morbidity study, CI: Confidence Interval, CV: cardiovascular, HF: heart failure, HFREF: heart failure with reduced ejection fraction, HFPEF: heart failure with preserved ejection fraction, HR: Hazard ratio, WRF: worsening renal function. Multivariable analyses included the following covariates: age, gender, race, NYHA functional class, smoking status, LVEF, systolic and diastolic blood pressure, heart rate, history of angina, stroke, hypertension, diabetes, myocardial infarction and HF hospitalization, as well as certain medical therapies: diuretic, ACE-inhibitor, spironolactone, calcium channel blocker, other vasodilators and aspirin.

Figure 1. Candesartan treatment, Worsening Renal Function and CV death or HF Hospitalization

A) Patients with HFREF



B) Patients with HFPEF

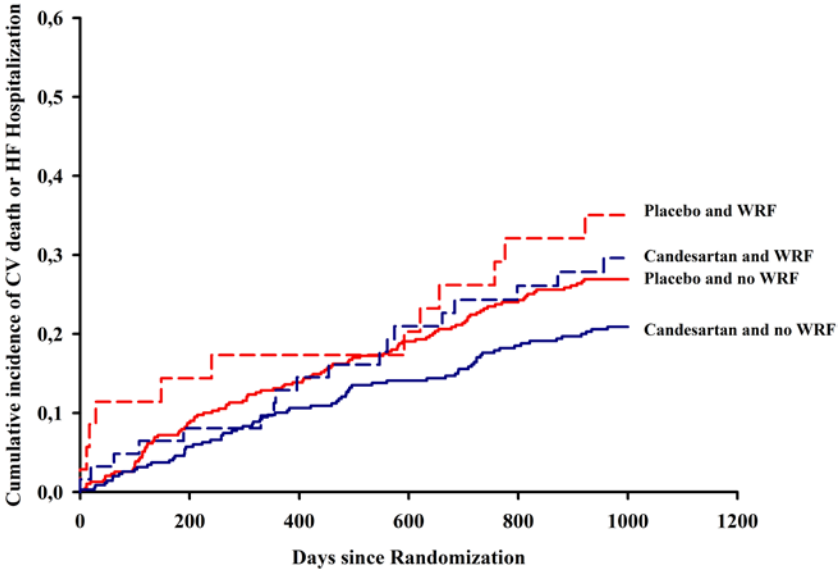
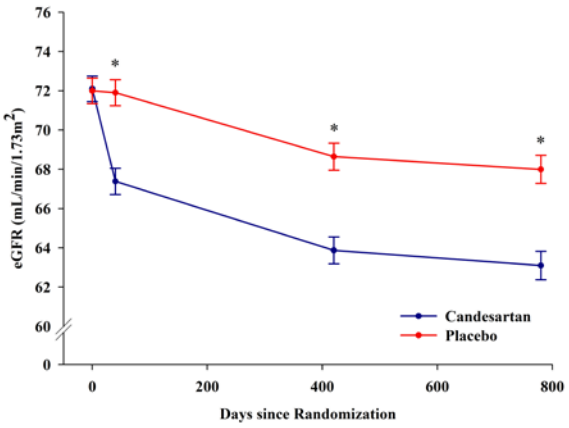
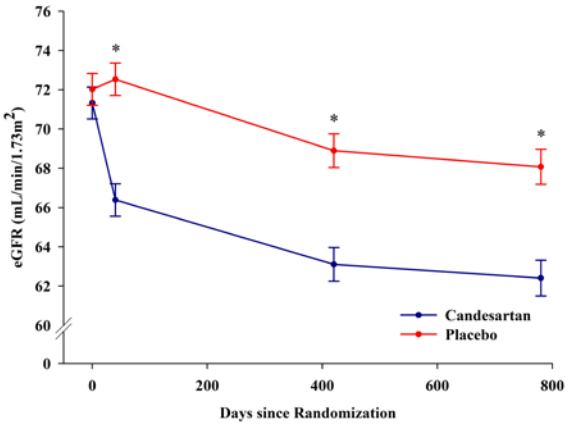


Figure 2: Change in eGFR stratified for treatment

A) Entire CHARM population



B) Patients with HFREF



C) Patients with HFPEF