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ORIGINAL ARTICLE

Achieved dose and treatment discontinuation of candesartan in men and women with chronic heart failure: data from CHARM

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Abstract

Aims Angiotensin receptor blockers have been shown to reduce heart failure hospitalization and cardiovascular mortality in men and women with heart failure with reduced ejection fraction (HFrEF). It is unknown whether there are differences between men and women in achieved dose and treatment discontinuation due to adverse events of candesartan.

Methods and results We conducted a post hoc analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. A total of 3172 men and 1106 women with HFrEF [left ventricular ejection fraction (LVEF) $\leq$ 40%] in New York Heart Association class II–IV were randomized to candesartan or placebo. Every 2 weeks, patients were up-titrated from 4 or 8, to16, to 32 mg once daily, unless a higher dose was contraindicated or not tolerated. Women were older (66 vs. 64 years), had a higher LVEF (29.9% vs. 28.6%), and had more hypertension (54% vs. 47%) than men. The mean achieved dose of candesartan was 21.5 ± 12.6 mg in men and 20.7 ± 12.9 mg in women (P = 0.19). In both the candesartan and placebo groups, cardiovascular death and heart failure hospitalizations were higher in men and women who achieved lower dose levels. Event rates for achieved dose levels of 0, 4 or 8, 16, and 32 mg candesartan were 20.8, 17.2, 14.0, and 10.1 per 100 person-years in men, respectively, and 23.6, 13.7, 14.0, and 9.1 per 100 person-years in women, respectively. In each of the achieved dose levels, there was no sex difference in the proportion of patients with an event, neither in the candesartan group nor in the placebo group (P-value for all $>$ 0.05). There was no significant interaction between sex and treatment-related discontinuation for hypotension (P = 0.520), an increase in creatinine (P = 0.102), and hyperkalaemia (P = 0.905).

Conclusions In a randomized clinical trial in patients with HFrEF, men and women achieved similar doses of candesartan. Primary event rates and treatment-related discontinuation due to adverse events were also similar between men and women.

Keywords Heart failure; Candesartan; Sex; Women; Drug dose

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Introduction

Guidelines recommend similar pharmacological treatment of heart failure with reduced ejection fraction (HFrEF) in men and women.[1–3] However, several differences in anatomy, body composition, and physiology between men and women might influence the response to heart failure drugs.[4,5] For example, slower intestinal transit times and a higher gastric pH in women might affect drug absorption, while lower body mass index and total body water, greater body fat percentages, and a smaller organ size in women might affect drug distribution. Moreover, sex differences in enzymes of hepatic metabolism, lower creatinine clearance, and glomerular filtration rate in women may impact drug excretion.

Studies comparing responses to heart failure drugs between men and women show different results. However,

some studies show similar responses to sacubitril/valsartan,[6] irbesartan,[7] captopril,[8] and lisinopril[9] between men and women. In the elderly, the reduction of blood pressure with different angiotensin-converting enzyme (ACE) inhibitors was comparable between men and women.[10] Other studies, however, showed marked sex differences in response to heart failure drugs. Higher serum concentrations and greater toxic effects of digoxin in women than in men contributed to the increased risk of mortality in women.[11] Bioequivalence studies of beta-blockers have found almost two times higher plasma concentrations of propranolol and metoprolol in women than in men, as well as a greater reduction in systolic blood pressure and heart rate in women, even though women and men received similar doses.[12–15] Moreover, women had lower ACE activity and lower systolic blood pressure than men after administering enalapril.[16] Losartan concentrations were found to be two-fold greater in hypertensive women than in men, which is likely due to decreased systemic clearance in women.[17]

The majority of these data are retrieved from bioequivalence and observational studies, and data comparing stepwise dose up-titration and discontinuation due to adverse effects between men and women with HFrEF from randomized, placebo-controlled trials are largely lacking. We, therefore, performed a post hoc analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme to investigate the achieved dose and discontinuation between men and women with HFrEF.

Methods

Study population

For the current study, we utilized the CHARM-Added and CHARM-Alternative trials, whose design and primary findings had been previously published.[18–20] Briefly, 4576 patients with New York Heart Association (NYHA) class II–IV symptomatic HFrEF were randomized to candesartan vs. placebo in the two separate trials, CHARM-Added [left ventricular ejection fraction (LVEF) $\leq$ 40% who were treated with an ACE inhibitor, with 2548 patients, 32% women] and CHARM-Alternative (LVEF $\leq$ 40% who were unable to tolerate an ACE inhibitor, with 2028 patients, 21% women). Patients started their treatment dose at 4 or 8 mg once daily and doubled every 2 weeks until they achieved the target dose of 32 mg, unless a higher dose was contraindicated or could not be tolerated. After randomization, patients had a trial follow-up visit at 2, 4, and 6 weeks, at 6 months, and every 4 months thereafter until the end of the trials. Patients were also treated with other chronic heart failure therapies including loop diuretics, digitalis, beta-blockers, and/or mineralocorticoid receptor antagonists (MRAs). The studies were approved by national and local ethics committees at all involved centres. Signed informed consent has been provided by all participants.

For the present study, doses of candesartan or placebo achieved at the end of the up-titration period (6 months) and the average dose over the trial were observed in men and women. To explore long-term survival, patients who died within 6 months (up-titration period, n = 242), had LVEF $>$ 40%, or were missing LVEF (n = 5), as well as those who had their last visit within 6 months or did not attend the visit at 6 months (n = 51), were excluded from the analysis. As a result, 4278 patients with HFrEF (LVEF $\leq$ 40%) who were still participating in the trial at 6 months were analysed. The primary endpoint was defined as the composite of cardiovascular death or unplanned hospital admission for the management of worsening heart failure.

Statistical analyses

Baseline characteristics between men and women in candesartan and placebo were presented as mean and standard deviation for normally distributed continuous variables or number and percentage for categorical variables, respectively. Student's t-tests or χ^2 tests were used for group comparisons. The mean of candesartan and placebo dose levels at each of the up-titration and follow-up time points were plotted in both men and women. Repeated measures mixed effects models with Wald's tests were used to compare overall dose levels between men and women in the candesartan and placebo groups. Student's t-tests were used to compare the maximum achieved dose level of candesartan and placebo. We combined 4 and 8 mg dose levels as one category because the number of patients and events in these two groups were small. Follow-up time started at baseline, and event rates were expressed per 1000 patient-years with a 95% confidence interval. Adverse events leading to the cessation of therapy were shown in percentages by men and women, and the interaction between the effect of treatment and sex was tested. A two-tailed P-value of $<$0.05 was considered statistically significant. All statistical analyses were conducted in the software STATA Version 16 (STATA Corp., College Station, TX, USA).

Results

Baseline characteristics

Baseline clinical characteristics, medical history, and background treatment stratified by sex are shown in *Table 1*. The two treatment arms were well balanced at baseline in both men and women. Generally, women were older and had a lower prevalence of coronary artery disease, and

Table 1 Baseline characteristics by treatment allocation in patients with heart failure with reduced ejection fraction

	Men		Women	
	Candesartan (n = 1607)	Placebo (n = 1565)	Candesartan (n = 561)	Placebo (n = 545)
Clinical				
Age at randomization	63.7 ± 10.8	64.0 ± 10.9	66.4 ± 10.9	65.9 ± 11.3
Baseline BMI (kg/m^2)	27.7 ± 4.9	27.9 ± 4.8	27.7 ± 6.1	27.5 ± 5.6
NYHA class				
II	581 (36.2)	537 (34.3)	181 (32.3)	199 (36.5)
III	984 (61.2)	989 (63.2)	359 (64.0)	325 (59.6)
IV	42 (2.6)	39 (2.5)	21 (3.7)	21 (3.9)
Baseline heart rate (b.p.m.)	73.6 ± 14.1	72.9 ± 12.8	75.2 ± 12.3	75.1 ± 13.2
Systolic blood pressure (mmHg)	126.4 ± 18.4	127.0 ± 18.5	129.3 ± 19.6	130.2 ± 18.5
Diastolic blood pressure (mmHg)	76.2 ± 10.7	76.3 ± 10.6	74.6 ± 11.2	75.9 ± 10.2
LVEF (%)	28.6 ± 7.5	28.6 ± 7.4	29.7 ± 7.4	30.1 ± 7.2
Baseline creatinine	1.2 ± 0.4	1.3 ± 1.3	1.0 ± 0.4	1.0 ± 0.4
Smoking habit	270 (16.8)	273 (17.4)	55 (9.8)	59 (10.8)
Medical history				
Previous hospitalization for CHF	1164 (72.4)	1113 (71.1)	419 (74.7)	409 (75.0)
Previous myocardial infarction	988 (61.5)	957 (61.2)	284 (50.6)	260 (47.7)
Angina pectoris	327 (20.3)	341 (21.8)	126 (22.5)	125 (22.9)
Stroke	136 (8.5)	135 (8.6)	36 (6.4)	49 (9.0)
Diabetes mellitus	449 (27.9)	426 (27.2)	159 (28.3)	162 (29.7)
Hypertension	742 (46.2)	746 (47.7)	307 (54.7)	292 (53.6)
Atrial fibrillation	440 (27.4)	412 (26.3)	126 (22.5)	129 (23.7)
Pacemaker implanted	139 (8.6)	137 (8.8)	50 (8.9)	44 (8.1)
Percutaneous coronary revascularization	250 (15.6)	267 (17.1)	73 (13.0)	78 (14.3)
Coronary artery bypass grafting	466 (29.0)	419 (26.8)	98 (17.5)	84 (15.4)
Implanted cardioverter defibrillator	70 (4.4)	66 (4.2)	14 (2.5)	8 (1.5)
Cancer	88 (5.5)	93 (5.9)	42 (7.5)	43 (7.9)
Medication				
ACE inhibitor	957 (59.6)	939 (60.0)	255 (45.5)	252 (46.2)
Beta-blocker	905 (56.3)	907 (58.0)	293 (52.2)	280 (51.4)
Diuretics	1385 (86.1)	1359 (86.8)	515 (91.8)	487 (89.4)
Spironolactone	325 (20.2)	288 (18.4)	115 (20.5)	107 (19.6)
Digitalis glycoside	837 (52.1)	823 (52.6)	294 (52.4)	283 (51.9)
Calcium channel blocker	189 (11.8)	202 (12.9)	92 (16.4)	76 (13.9)
Other vasodilators	583 (36.2)	620 (39.6)	242 (43.1)	236 (43.3)
Oral anticoagulant	590 (36.7)	580 (37.1)	172 (30.7)	144 (26.4)
Antiarrhythmic agent	215 (13.4)	216 (13.8)	60 (10.7)	54 (9.9)
Acetylsalicylic acid	884 (55.0)	861 (55.0)	282 (50.3)	304 (55.8)
Other anti-platelet agents	73 (4.5)	82 (5.2)	19 (3.4)	14 (2.6)
Lipid-lowering drug	708 (44.0)	652 (41.7)	203 (36.2)	211 (38.7)

ACE, angiotensin-converting enzyme; BMI, body mass index; CHF, chronic heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
Results expressed as mean ± standard deviation or no. (%).

they were less often treated with ACE inhibitors and beta-blockers but more often with diuretics than men. Baseline characteristics of patients who died before 6 months compared with those who survived and baseline characteristics of included and excluded patients in the present study are shown in Supporting Information, *Tables S1* and *S2*, respectively.

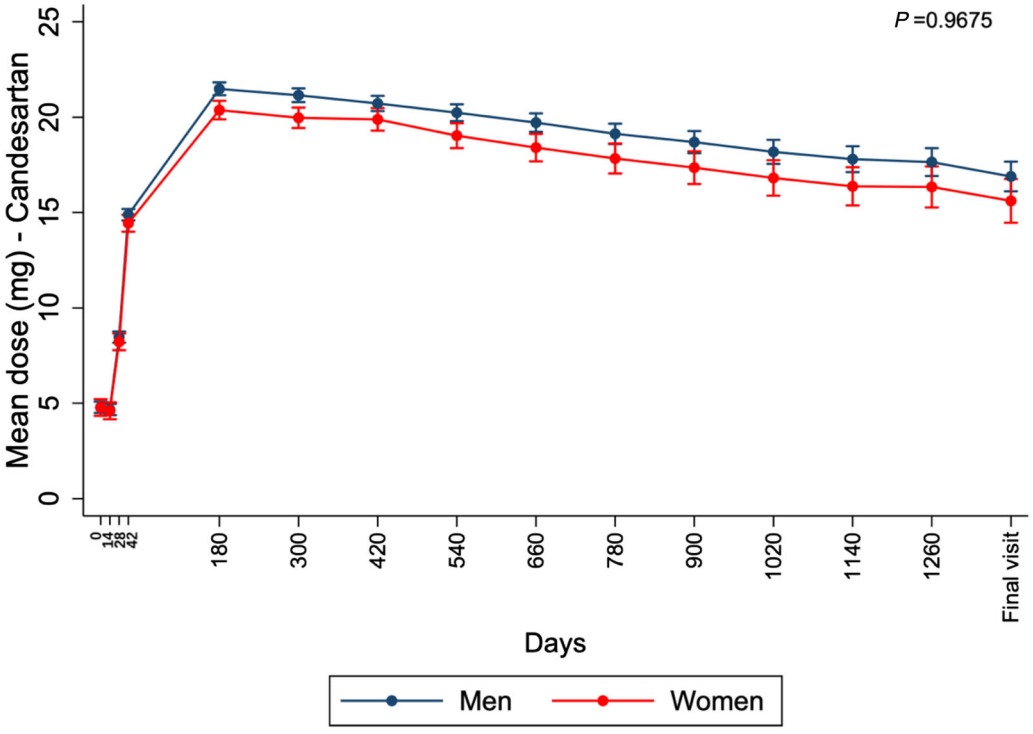
Achieved dose levels in men vs. women

Figure 1 presents the trajectory of the mean dose of candesartan (*Figure 1A*) and placebo (*Figure 1B*) at each follow-up time point in men and women. Over a median follow-up of 3.3 years, men and women received similar doses of candesartan (P = 0.97) and placebo (P = 0.82). At 6 months, the target dose of 32 mg was achieved in 903 (56.2%) men and 298 (53.4%) women.

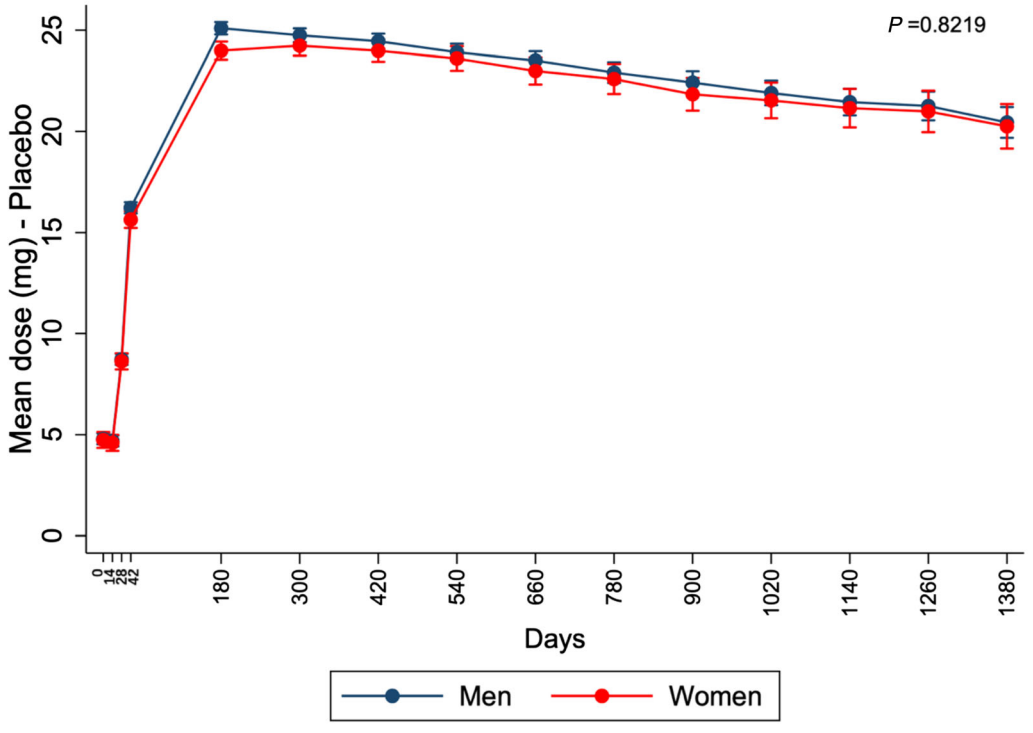
Event rates according to achieved dose levels of candesartan and placebo in men and women

Table 2 shows the percentage of women and men experiencing the primary composite endpoint of cardiovascular death or heart failure hospitalization according to the achieved dose of randomized treatment. In general, event rates were lower in both men and women with higher achieved doses, whether that was candesartan or placebo. In each of the achieved dose levels, there was no sex difference in the

Figure 1 Mean doses of (A) candesartan and (B) placebo over time in men and women with heart failure with reduced ejection fraction (HFrEF). X-axis for study time point, and Y-axis for mean dose of candesartan or placebo. The blue line describes men, and the red line describes women. The *P*-value was the overall interaction for men vs. women.



(A)



(B)

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Table 2 Event rates for candesartan and placebo in men vs. women

Dose level (6 months)	Candesartan					Placebo				
	Men		Women			Men		Women		
	Events, no. (%)	Event rate	Events, no. (%)	Event rate	*P*-value	Events, no. (%)	Event rate	Events, no. (%)	Event rate	*P*-value
0 mg	76/164 (46.3%)	20.8 (16.6–26.0)	34/69 (49.3%)	23.6 (16.9–33.1)	0.601	44/95 (46.3%)	21.7 (16.1–29.1)	26/50 (52.0%)	25.5 (17.4–37.4)	0.510
4 or 8 mg	127/298 (42.6%)	17.2 (14.5–20.5)	37/106 (34.9%)	13.7 (9.9–18.9)	0.215	81/170 (47.6%)	22.2 (17.8–27.6)	17/47 (36.2%)	14.3 (8.9–23.0)	0.091
16 mg	87/239 (36.4%)	14.0 (11.3–17.3)	31/85 (36.5%)	14.0 (9.9–19.9)	0.983	80/187 (42.8%)	17.7 (14.2–22.0)	30/69 (43.5%)	18.1 (12.6–25.8)	0.907
32 mg	254/903 (28.1%)	10.1 (8.9–11.4)	77/298 (25.8%)	9.1 (7.3–11.4)	0.433	397/1110 (35.8%)	13.5 (12.3–14.9)	115/378 (30.4%)	11.3 (9.4–13.6)	0.086

Events were a composite of death due to a cardiovascular cause or unplanned admission to the hospital for the management of worsening heart failure. Follow-up time for the event rate was started from baseline. The event rate was expressed in 100 person-years with a 95% confidence interval. *P*-value for comparing event rates in men and women.

proportion of patients with an event, either in the candesartan or placebo groups (all *P*-values for the event rate > 0.05).

Treatment discontinuation and adverse events

Table 3 summarizes treatment discontinuation in the candesartan and placebo groups due to hypotension, an increase in creatinine, and hyperkalaemia. Treatment discontinuation due to hypotension occurred in 71 (18.3%) men in the candesartan group compared with 33 (10.8%) men in the placebo group and in 19 (12.4%) women in the candesartan group compared with 11 (9.4%) women in the placebo group (*P*-value for sex interaction = 0.520). Similarly, no significant sex–treatment interaction was found for treatment discontinuation due to an increase in creatinine (*P*-value for sex interaction = 0.102) and hyperkalaemia (*P*-value for sex interaction = 0.905).

Discussion

In a randomized, placebo-controlled trial, 4278 patients with HFrEF underwent a stepwise up-titration of candesartan or placebo. Throughout the trial, men and women achieved similar dose levels. The incidence of cardiovascular death or heart failure hospitalization was higher in patients who achieved lower dose levels of both candesartan and placebo and was similar between men and women. Treatment discontinuation due to adverse events was similar between men and women.

Our finding that men and women achieved similar doses of candesartan and placebo is consistent with data from Dutch outpatient heart failure patients and from a European registry, both showing similar achieved dose levels of ACE inhibitors and angiotensin receptor blockers (ARBs) in men and women.[21,22] Throughout the STRONG-HF trial, the average percentages of the optimal dose across renin-angiotensin system (RAS) inhibitors, beta-blockers, and MRAs in the high-intensive care group were similar in men and women.[23] In the PARAGON-HF trial, a similar proportion of men and women achieved the target dose of sacubitril/valsartan.[24] Moreover, the achieved dose levels of sacubitril/valsartan or enalapril were also similar between men and women in the PIONEER-HF trial.[25] Also, no differences were found in the percentage of men and women who were unable to achieve the target dose of metoprolol in MERIT-HF.[26]

Due to pharmacokinetic differences between men and women, such as a smaller body size and a greater proportion of body fat, one might have expected the maximum tolerated dose to be lower and treatment discontinuation to be higher in women than in men.[4,27] For ARBs, however, a few studies reported higher maximum plasma concentrations of losartan,

Table 3 Treatment discontinuation during the trial for adverse events stratified by sex, no. (%)

Cause of discontinuation	Men			Women			*P* for interaction
	Candesartan	Placebo	*P*-value	Candesartan	Placebo	*P*-value	
Hypotension	71 (18.3%)	33 (10.8%)	0.006	19 (12.4%)	11 (9.4%)	0.420	0.520
Increase in creatinine	119 (29.8%)	60 (19.2%)	0.001	35 (23.0%)	9 (7.7%)	<0.001	0.102
Hyperkalaemia	51 (13.1%)	10 (3.3%)	<0.001	10 (6.6%)	2 (1.7%)	0.055	0.905

P for interaction between sex and the effect of treatment-related discontinuation.

telmisartan, and irbesartan in women than in men.[17,28–30] However, most studies with ARBs did not find sex differences in the pharmacokinetic parameters of candesartan, eprosartan, EXP3174, and valsartan.[6,31] Therefore, these potential pharmacokinetic differences in men and women do not appear to translate into clinically meaningful differences, at least not for candesartan.[32] An explanation for this difference might be that, in contrast to other ARBs, candesartan is not metabolized by the cytochrome P450 (CYP) system, and most of the medical activity of candesartan is due to the metabolites rather than being inherently active.[31,33,34] Pharmacokinetic differences between men and women were frequently related to the CYP system and the activity of CYP isoenzymes. However, these pharmacokinetic differences do not seem to translate into meaningful clinical differences in maximally tolerated doses of RAS inhibitors and beta-blockers.

We found that event rates were higher in patients who had achieved lower dose levels, irrespective of sex and irrespective of whether patients were treated with candesartan or placebo. These can be explained by men and women with lower achieved dose levels of candesartan and placebo having more severe heart failure than those with higher achieved dose levels. For instance, patients who achieved lower dose levels were older and had a higher average NYHA functional class, higher creatinine, and lower LVEF. Similarly, data from MERIT-HF showed that patients who were unable to achieve the target dose of metoprolol had a higher event rate.[26] During the double-blind phase of PARADIGM-HF, participants were started with the highest dose of sacubitril/valsartan or enalapril, and patients with any dose reduction showed an increased risk for the composite endpoint of initial hospitalization for heart failure or cardiovascular death.[35] Although a patient's condition and intolerance account for an important part of suboptimal guideline-directed medical therapy (GDMT), clinical inertia is still common. A recent study demonstrated that clinical inertia was a main contributor to the non-intensification of suboptimal GDMT prescribing.[36] Of these, 28.3% of ACE inhibitors/ARBs/angiotensin receptor-neprilysin inhibitors non-intensification was due to clinical inertia alone.

Discontinuation of candesartan due to adverse events was similar between men and women and confirms data from other randomized clinical trials with ARBs.[24,37] In the PARAGON-HF trial, the difference in adverse events between sacubitril/valsartan and valsartan was comparable in men and women.[24] In the HEAAL trial, no differences were found in the occurrence of hypotension, renal failure, and hyperkalaemia between men and women with losartan.[37] Renal impairment was the most common adverse event leading to treatment discontinuation in both sexes. Data from a pooled multinational observational study showed that the proportion of discontinued treatment of ARBs within 12 months was higher in men than in women (42% in men and 31% in women).[38]

Strengths and limitations

The findings of our study were based on a large, well-designed, randomized, placebo-controlled trial with a long-term follow-up. Several limitations should be acknowledged in our study. First, this was a post hoc analysis of the CHARM trial, which was not primarily designed to compare achieved dose levels and treatment discontinuation. Although the number of female patients in our study was not balanced with that of male patients, the proportion of women in the CHARM trials was larger than most of the HFrEF trials and similar to the proportions in HFrEF epidemiological registries.[39] Second, trial inclusion and exclusion criteria often exert a more substantial influence on participants presenting with more comorbid conditions. And trial participants are likely to be healthier than common heart failure patients, which may impact dose tolerance and achieve dose levels, underestimating the difference between dose levels and sex. Third, as ARBs are not routinely indicated in patients with LVEF $>$ 40%,[40] the current analysis was only focused on patients with LVEF $\leq$ 40% in the CHARM programme.

Conclusions

In a randomized, placebo-controlled trial using a gradual up-titration of candesartan or placebo in patients with chronic HFrEF, men and women achieved similar doses of both candesartan and placebo. Event rates were higher in patients with lower achieved dose levels of both candesartan and placebo and in both men and women, but in each dose level, event rates were similar between men and women. We observed no sex differences in treatment discontinuation due to adverse events.

Conflict of interest

J.J.V.M. reports payments through Glasgow University from work on clinical trials; consulting and other activities from Amgen, AstraZeneca, Bayer, Cardurion, Cytokinetics, GSK, KBP Biosciences, and Novartis; personal consultancy fees from Alnylam Pharmaceuticals, Bayer, BMS, George Clinical Pty Ltd., Ionis Pharmaceuticals, Novartis, Regeneron Pharmaceuticals, and River 2 Renal Corporation; and personal lecture fees from Abbott, Alkem Metabolics, AstraZeneca, Blue Ocean Scientific Solutions Ltd., Boehringer Ingelheim, Canadian Medical and Surgical Knowledge, Emcure Pharmaceuticals Ltd., Eris Lifesciences, European Academy of CME, Hikma Pharmaceuticals, Imagica Health, Intas Pharmaceuticals, J.B. Chemicals & Pharma Ltd., Luptin Pharma, Medscape/Heart.Org, ProAdWise Communications, Radcliffe Cardiology, Sun Pharmaceutical Industries Ltd., The Corpus, Translation Research Group, and Translational Medicine Academy. He is a director of Global Clinical Trial Partners Ltd. A.A.V. has received consultancy fees and research contracts from AnaCardio, AstraZeneca, BMS, Bayer, Boehringer Ingelheim, Corteria, Eli Lilly, Salubrio, Merck, Moderna, Novartis, Novo Nordisk, and Roche Diagnostics. The other authors declare no conflicts of interest.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics for patients who died before six months and included patients.
Table S2. Baseline characteristics for included and excluded patients.
Table S3. Baseline characteristics for candesartan achieved dose levels in men and women.
Table S4. Baseline characteristics for placebo achieved dose levels in men and women.
Table S5. Secondary outcomes for men and women according to candesartan dose (Visit 5-six months).
Table S6. Secondary outcomes for men and women according to placebo dose (Visit 5-six months).

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