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Benefits and safety of candesartan treatment in heart failure are independent of age: insights from the Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity programme

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Aims Ageing may affect drug efficacy and safety in patients with heart failure (HF). The Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) programme offered an opportunity to study the relationship between increasing age and the efficacy and safety of treatment in an uniquely broad spectrum of patients with symptomatic HF and either reduced or preserved left ventricular ejection fraction.

Methods and results A total of 7599 patients in NYHA Class II–IV HF were randomized to candesartan (target dose 32 mg once daily, mean dose 24 mg) or placebo, including 3169 patients age >70 years. Mean follow-up was 37.7 months. The proportional hazards model was used to estimate the treatment effect on efficacy and safety within five age groups: <50 years ($n = 605$) (8% of all study patients), 50–59 years ($n = 1474$) (19%), 60–69 years ($n = 2351$) (31%), 70–79 years ($n = 2474$) (33%), and ≥80 years ($n = 695$) (9%). The risk of cardiovascular (CV) death or HF hospitalization (primary outcome) increased from 24% in the lowest age group to 46% in the highest age group (and mortality from 13 to 42%). The relative reduction in risk of the primary outcome with candesartan (15% in the overall study population) was similar irrespective of age. Consequently, the absolute benefit was greater with advancing age (3.8 patients avoided a primary outcome per 100 patients treated in the lowest age group compared with 6.8 in the highest). Adverse events leading to drug discontinuation were more frequent in the candesartan group: placebo/candesartan risk (%), lowest compared with highest age category: hyperkalemia (0.0/1.6 vs. 0.6/2.7), increased serum creatinine (1.0/3.9 vs. 6.1/5.4) and hypotension (1.7/2.0 vs. 2.8/5.7).

Conclusion Older patients were at a greater absolute risk of adverse CV mortality and morbidity outcomes but derived a similar relative risk reduction and, therefore, a greater absolute benefit from treatment with candesartan, despite receiving a somewhat lower mean daily dose of candesartan. Adverse effects were more common with candesartan than with placebo, although the relative risk of adverse effects was similar across age groups. The benefit to risk ratio for candesartan was thus favourable across all age groups.

Keywords Heart failure • Candesartan • Age • Mortality • Hospitalization • Adverse events • Dose

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Introduction

Despite the fact that chronic heart failure (HF) predominantly afflicts the elderly,[1] there are few data on the response to the specific therapeutic interventions in older patients. Guidelines on the treatment of HF are derived from large therapeutic trials, carried out in patients mainly aged <70 years, most of which had a low left ventricular ejection fraction (LVEF).[2] Epidemiological studies and surveys have shown that, in clinical practice, patients with HF are much older than in trials and often have preserved LVEF. For example, in the improvement programme on evaluation and management of HF (IMPROVEMENT) Survey, the mean age was ~70 years and in the Euro HF Survey it was 71 years, i.e. an average of 5–10 years older than in the trials.[3,4] In addition, these surveys showed that as many as half of the older patients with HF had preserved LVEF.

Ageing may alter the response to treatment: lower body mass, reduced renal function, other co-morbidities, altered neurohumoral responses, increased susceptibility to orthostatic hypotension and polypharmacy may affect both drug tolerance and efficacy.[5–9]

As the CHARM programme enrolled a large number of elderly patients, including many with preserved LVEF, it offered an unique opportunity to study the relationship between age and the effect of an angiotensin-receptor blocker in HF.[10] The purpose of the present analysis was thus to examine the effect of age on clinical outcomes, including mortality, hospitalization, and adverse drug effects, and to determine whether the therapeutic response to candesartan was influenced by increasing age.

Methods

The Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity programme

The design, baseline findings, and results of the CHARM programme have been reported in detail.[10,11] Briefly, the CHARM programme consisted of three independent but related trials in which patients with NYHA Class II–IV HF were randomized to placebo or candesartan (target dose 32 mg once daily). Patients were enrolled, concurrently, into the individual CHARM trials according to LVEF and baseline treatment with an angiotensin converting-enzyme (ACE) inhibitor. Patients with a LVEF ≤0.40, intolerant of an ACE inhibitor, were enrolled in CHARM-alternative ($n = 2028$), whereas patients with a LVEF ≤ 0.40 and taking an ACE inhibitor were enrolled in CHARM-added ($n = 2548$). Patients with NYHA Class II required a cardiovascular (CV)

Table 1 Baseline characteristics of patients according to age

Age (years)	<50 ($n = 605$)	50–59 ($n = 1474$)	60–69 ($n = 2351$)	70–79 ($n = 2474$)	>80 ($n = 695$)	*P*-value
Patients' characteristics						
Male/female (%)	75.5/24.5	76.4/23.6	71.3/28.7	64.0/36.0	51.4/48.6	<0.001
SBP (mmHg)	125 (18)	128 (18)	130 (19)	134 (19)	135 (20)	<0.001
DBP (mmHg)	79 (11)	78 (10)	77 (11)	76 (11)	74 (11)	<0.001
NYHA Class						
II	49.3	49.4	45.3	43.2	36.8	<0.001
III	48.9	48.7	52.1	54.2	58.1	
IV	1.8	1.9	2.6	2.5	5.0	
Ejection fraction (%)	36 (14)	38 (14)	38 (15)	40 (15)	43 (16)	<0.001
Kalaemia (mmol/L)	4.3 (0.5)	4.3 (0.4)	4.4 (0.5)	4.4 (0.5)	4.4 (0.5)	0.0004
Haemoglobin (mmol/L)	14.2 (1.5)	13.9 (1.5)	13.6 (1.6)	13.3 (1.6)	13.2 (1.7)	<0.0001
Creatinininemia (mg/dL)	1.1 (1.5)	1.1 (0.4)	1.2 (0.4)	1.3 (0.7)	1.3 (0.5)	<0.0001
Medical history (%)						
Diabetes	22.1	29.8	31.5	28.6	20.4	<0.001
Hypertension	43.3	51.9	55.8	58.0	59.1	<0.001
Atrial fibrillation	12.4	19.2	24.6	34.2	43.3	<0.001
Medical treatment (%)						
Beta-blockers	63.5	63.0	57.7	50.3	41.6	<0.001
Diuretics	77.4	77.5	82.0	85.2	91.8	<0.001
ACE-I	49.1	46.0	44.1	37.4	27.2	<0.001
Spironolactone	19.3	14.7	16.9	16.9	17.8	0.084
Anticoagulant	27.8	29.3	30.2	33.2	29.9	0.022
Antiplatelet	50.9	62.4	64.2	59.8	55.7	<0.001
Lipid lowering agents	37.7	46.5	45.4	40.9	23.3	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE-I, angiotensin converting-enzyme inhibitors.
Values are given as mean (standard deviation) or as percentage (%).
Laboratory variables available only in a subset of North American patients.

Table 2 Proportion of patients receiving the dose 0, 4, 8, 16 and 32 mg, respectively, at the end of titration, by treatment group and age category

Age group (years)	Number of patients in treatment group		Dose level reached (%)									
			0 mg		4 mg		8 mg		16 mg		32 mg	
	Candesartan	Placebo	Candesartan	Placebo	Candesartan	Placebo	Candesartan	Placebo	Candesartan	Placebo	Candesartan	Placebo
<50	304	301	10.2	5.0	6.3	5.0	8.6	3.0	12.2	9.3	59.5	73.4
50–59	734	740	11.3	4.9	8.5	2.7	7.8	5.0	14.2	12.8	54.4	71.0
60–69	1196	1155	8.8	6.7	9.2	3.9	8.6	5.4	15.2	12.4	54.5	66.6
70–79	1235	1239	10.8	8.0	7.0	4.0	9.6	5.6	15.2	12.6	52.5	62.2
≥80	334	361	15.6	10.5	8.4	4.4	12.3	5.5	14.1	13.3	43.4	56.5

Table 3 Adverse effects leading to permanent discontinuation of study drug

AE leading to permanent treatment cessation	Age group (years)										Interaction *P*-value
	<50		50–59		60–69		70–79		≥80		
	C	P	C	P	C	P	C	P	C	P	
Hypotension	6 (2.0%)	5 (1.7%)	23 (3.1%)	13(1.8%)	39 (3.3%)	16 (1.4%)	45 (3.6%)	22 (1.8%)	19 (5.7%)	10 (2.8%)	0.8957
HR (95% CI)	1.21 (0.37, 3.97)		1.79 (0.91, 3.53)		2.29 (1.28, 4.09)		2.06 (1.24, 3.43)		2.03 (0.94, 4.36)		
Increased serum creatinine	12 (3.9%)	3 (1.0%)	40 (5.4%)	8 (1.1%)	70 (5.9%)	34 (2.9%)	94 (7.6%)	48 (3.9%)	18 (5.4%)	22 (6.1%)	0.0034
HR (95% CI)	4.25 (1.20, 15.09)		4.94 (2.31, 10.56)		1.96 (1.30, 2.96)		1.99 (1.40, 2.82)		0.84 (0.45, 1.56)		
Hyperkalemia	5 (1.6%)	0 (0.0%)	7 (1.0%)	2 (0.3%)	25 (2.1%)	8 (0.7%)	39 (3.2%)	9 (0.7%)	9 (2.7%)	2 (0.6%)	0.5870
HR (95% CI)	—		3.39 (0.70, 16.34)		2.95 (1.33, 6.55)		4.43 (2.14, 9.14)		4.71 (1.02, 21.79)		

C, candesartan; P, placebo; HR, hazard ratio; CI, confidence intervals.

hospitalization in the previous 6 months which had the effect of increasing the proportion of NYHA Class III/IV patients in CHARM-added. Patients with a LVEF > 0.40 were randomized into CHARM-preserved ($n = 3023$). There were few exclusion criteria and the main ones were a serum creatinine ≥ 265 μmol/L (3 mg/dL), known bilateral renal artery stenosis, a serum potassium ≥ 5.5 mmol/L and current symptomatic hypotension; there was no specific blood pressure exclusion. At randomization, study drug was initiated at 4 or 8 mg once daily; the lower dose was advised in patients treated with >40 mg furosemide (or equivalent) daily or with suspected hypovolemia, patients in NYHA Class III or IV, with a systolic BP ≤ 110 mmHg, serum creatinine >150 μmol/L (1.7 mg/dL), in patients considered frail or at the investigator's discretion.

The dose was then doubled every 2 weeks, as tolerated, up to a maximum target dose of 32 mg candesartan (or matching placebo) once daily. Visits were scheduled at 2, 4, and 6 weeks (with an additional 8 week visit, if needed); 6 months; and then every 4 months until study end. At each visit, the investigator was asked to complete a check box question about adverse events that had led to a reduction in the dose or discontinuation of study drug since the previous visit. The question asked specifically about symptomatic or severe hypotension, increase in serum creatinine and hyperkalemia (and other reasons). There was no predefined absolute or relative cutoff value to determine serious risk in relation with change in kalemia or plasma creatinine and the decision of treatment reduction or discontinuation was left at the investigator discretion.

The CHARM programme was terminated, as planned, 2 years after the last patient was randomized. Because the rate of recruitment varied between the CHARM trials, overall follow-up varied from a median of 41 months in CHARM-added, from 37 months in CHARM-preserved to 34 months in CHARM-alternative (38 months in the CHARM programme). In the present analysis, 7599 patients were retrospectively grouped into five age categories: <50 ($n = 605$) (8%), 50–59 ($n = 1474$) (19%), 60–69 ($n = 2351$) (31%), 70–79 ($n = 2474$) (33%), and ≥80 years ($n = 695$) (9%).

Statistical methods

Total mortality (the primary endpoint of the overall programme), and the combined endpoint of CV death or hospitalization related to worsening HF (the primary endpoint of each individual trial), as well as the individual components of the composite outcome, was analysed by age group. The proportional hazards model was used to estimate the treatment effect within age group. Data are presented as the estimated hazard ratio for treatment (candesartan vs. placebo) together with a corresponding 95% confidence interval for the hazard ratio. Kaplan–Meier curves were plotted by age category and treatment. Similarly, the proportional hazards model was used to estimate the safety of treatment within age group. Events leading to cessation of therapy were considered from baseline to the end of the titration phase and the study (defined as last dose carried forward). In addition, interaction analyses were carried out to determine whether age influenced the effect of treatment on outcomes and adverse effects; to adjust for differences between the three CHARM studies, the analyses were stratified by study.

All baseline data are reported as means (± standard deviation) or as percentage (laboratory variables were available only in a subset of 2743 North American patients). The significance level is 5% except for tests of interaction for which it was 10%. All tests were two-sided.

Results

Baseline characteristics

The baseline characteristics of patients in each of the five age groups are summarized in *Table 1*. With increasing age, patients were more likely to be women, hypertensive, and have atrial fibrillation. Mean systolic blood pressure and LVEF also increased with age, whereas diastolic blood pressure decreased. Plasma creatinine tended to increase with age, whereas haemoglobin tended to decrease (these data are, however, available only in a limited subset of patients and thus to be analyzed with more caution). The use of beta-blockers

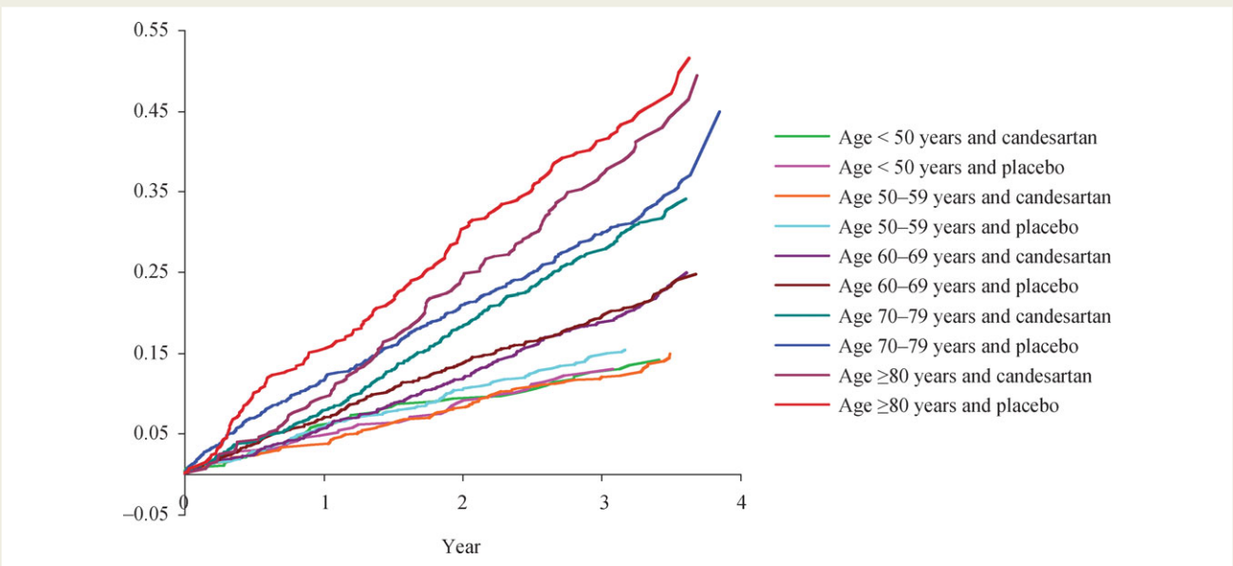

Figure 1 Kaplan–Meier survival curves in the 5 age categories for all-cause mortality.

and ACE-inhibitors decreased with age. The rate of prescription of spironolactone was identical across age groups.

The proportion of patients reaching different study—drug dose levels by the end of the titration period—is shown in *Table 2*. Mean (SD) candesartan dose (mg/day) at the end of the titration period, for those still receiving study drug, was 25.4 (10.3), 24.3 (10.7), 23.9 (10.9), 24.1 (10.7), and 22.3 (11.3) in the <50, 50–59, 60–69, 70–79, and ≥80 years groups, respectively (*P* for trend = 0.0268). The figures for placebo were the following: 28.0 (8.5), 27.6 (8.4), 27.0 (9.0), 26.7 (9.2), and 26.1 (9.5) (*P* = 0.0319).

Safety and tolerability

The frequency of the selected pre-specified adverse effects (hypotension, increased serum creatinine, and hyperkalemia) is shown as a function of age and treatment assignment in *Table 3*. The relative increment in incidence with candesartan over placebo, leading to treatment withdrawal, did not vary by age category with the exception of increase in serum creatinine, which was relatively less common with candesartan in the most elderly.

Clinical outcomes

The primary composite outcome and its components, CV mortality and HF hospitalization, as well as death from any cause increased with age (*Figure 1* and *Table 4*; *P*-values for log rank test <0.0001 for all). Hazard ratios and 95% CI for candesartan vs. placebo, by age group, are shown in *Table 4* and *Figure 2*. There was no interaction between drug assignment and age category for any of the four endpoints. Candesartan improved outcome irrespective of age, and therefore, the absolute benefit was greater with advancing age. The number of patients per 100 treated who avoided a primary outcome event because of treatment with candesartan was 3.8 in <50, 3.6 in 50–59, 4.8 in 60–69, 6.1 in 70–79, and 6.8 in those ≥80 years. The results were homogeneous across the three CHARM studies (alternative, added, and preserved) (*Table 5*).

Discussion

This study showed that, in chronic HF, increasing age was associated with different patient characteristics at baseline, and a worse prognosis. However, the relative benefit from candesartan in older patients was similar to that observed in younger patients. Tolerability of candesartan, relative to placebo, was similar across all age ranges at the doses achieved.

It is often anticipated that with increasing age (and associated comorbidities), tolerability to therapy with inhibitors of the renin–angiotensin system is lessened because of the decreased renal function, hyperkalemia, and hypotension. These arguments are also often used to not titrate HF drugs to the high doses recommended by guidelines. In CHARM, the mean drug dose at the end of the titration phase was only 10 and 15% lower in the candesartan than in the placebo group in the 70–79 and >80 age categories, respectively. Furthermore, the proportion of patients discontinuing candesartan compared with placebo for these three adverse effects was similar across all age groups, with no interaction between age and treatment, except for the risk of increased serum creatinine which was relatively lower in the

Table 4 Candesartan:placebo hazard ratio for cardiovascular outcomes and all cause mortality according to age (years)

	<50 (*n* = 605)		50–59 (*n* = 1474)		60–69 (*n* = 2351)		70–79 (*n* = 2474)		≥80 (*n* = 695)	
	Number (%) of patients with event	Candesartan: placebo HR (95% CI)	Number (%) of patients with event	Candesartan:placebo HR (95% CI)	Number (%) of patients with event	Candesartan:placebo HR (95% CI)	Number (%) of patients with event	Candesartan: placebo HR (95% CI)	Number (%) of patients with event	Candesartan: placebo HR (95% CI)
CV death or HF hospitalization	144 (23.8)	1.02 (0.74, 1.42)	335 (22.7)	0.87 (0.70, 1.08)	710 (30.2)	0.85 (0.73, 0.98)	949 (38.4)	0.81 (0.71, 0.92)	322 (46.3)	0.79 (0.63, 0.98)
CV death	74 (12.2)	1.13 (0.72, 1.79)	178 (12.1)	0.93 (0.69, 1.25)	406 (17.3)	0.84 (0.69, 1.02)	583 (23.6)	0.88 (0.75, 1.03)	219 (31.5)	0.87 (0.66, 1.13)
HF hospitalization	101 (16.7)	0.87 (0.59, 1.28)	224 (15.2)	0.78 (0.60. 1.02)	500 (21.3)	0.81 (0.68, 0.97)	634 (25.6)	0.79 (0.67, 0.92)	216 (31.1)	0.69 (0.53, 0.91)
All-cause death	78 (12.9)	1.07 (0.68, 1.67)	205 (13.9)	0.84 (0.64, 1.10)	495 (21.1)	0.95 (0.8, 1.14)	761 (30.8)	0.93 (0.81, 1.07)	292 (42.0)	0.86 (0.69, 1.09)

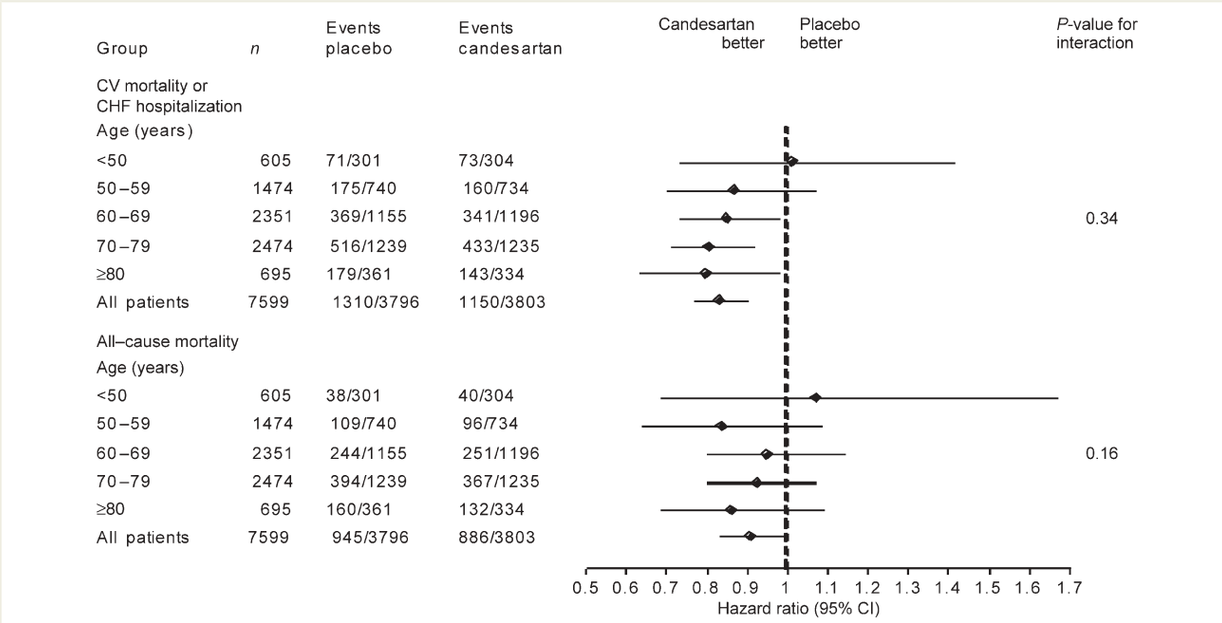

Figure 2 Absolute events according to age categories with the corresponding hazard ratio for the combined endpoint of CV death or HF hospitalization and for all-cause mortality.

Table 5 Analyses of the interactions between treatment, age and study (CHARM-added, - alternative, or -preserved)

Endpoint	Interaction	*P*-value for interaction
CV death or HF hospitalization	Treatment by age	0.177
	Treatment by study	0.276
	Age by study	0.032
	Treatment by age by study	0.357
CV death	Treatment by age	0.607
	Treatment by study	0.734
	Age by study	0.159
	Treatment by age by study	0.195
HF hospitalizations	Treatment by age	0.383
	Treatment by study	0.104
	Age by study	0.030
	Treatment by age by study	0.755
All cause death	Treatment by age	0.776
	Treatment by study	0.547
	Age by study	0.039
	Treatment by age by study	0.440
Hypotension	Treatment by age	0.787
	Treatment by study	0.458
	Age by study	0.577
	Treatment by age by study	0.413
Hyperkalaemia	Treatment by age	0.772
	Treatment by study	0.470
	Age by study	0.508
	Treatment by age by study	0.292
Increased serum creatinine	Treatment by age	0.001
	Treatment by study	0.518
	Age by study	0.065
	Treatment by age by study	0.061

Nominal *P*-values for the interaction in Cox regression model with treatment, age and study as factors.

most elderly. Moreover, even in the very elderly, the proportion and absolute number of patients having to discontinue treatment was small. The beneficial actions of candesartan were thus not diminished by advancing age.

Indeed, as an increased rate of all cause death, CV death and CV death or HF hospitalization, was observed with increasing age, the absolute benefits of candesartan were greatest in the elderly. We previously showed that in CHARM, increasing age was the more powerful predictor of mortality among 33 variables and that the increase in mortality was linear until age 60 years, with a number of deaths increasing nearly two-fold every 10 years above 60.[12] However, there was no interaction between age categories and candesartan use regarding any of the outcome endpoints.

Study limitations

Randomization in the CHARM study was not stratified by age. Although the absolute and relative numbers of older patients in CHARM were larger than most HF trials, the proportion of patients aged more than 80 was less than that found in HF epidemiological studies and registries. Moreover, patients enrolled in clinical trials are selected and even very elderly patients may not be fully representative of patients in the community. In trials, patients are closely monitored and recent studies have shown that when treatment is not given in accordance with recommended indications and doses, the rate of side effects may be greater than expected from clinical trial.[13]

Conclusions

This study showed that, in a broad population of symptomatic patients with chronic HF and reduced or preserved LVEF, increasing age is associated with different patient characteristics at baseline and a worse prognosis. Older patients were at a greater absolute risk of adverse CV mortality and morbidity outcomes but derived a similar relative risk reduction and, therefore, a greater absolute benefit from treatment with candesartan, despite receiving a somewhat lower mean daily dose of candesartan. Adverse effects were more common with candesartan than with placebo although the relative risk of adverse effects was similar across age groups. Vigilance and monitoring are warranted in clinical practice to provide optimal benefit and minimize risk with the use of candesartan in more vulnerable, older patients with symptomatic HF.

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Conflict of interest: M.A.P., K.S., J.J.V.M., S.Y., C.B.G., and A.C-S. have served as consultants to or received research grants and honoraria from AstraZeneca and/or other major pharmaceutical companies. E.L.M. and M.P. are employees of AstraZeneca.

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