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Clinical Outcomes According to Baseline Blood Pressure in Patients With a Low Ejection Fraction in the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) Program

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Objectives This study sought to investigate the efficacy and tolerability of candesartan, according to baseline blood pressure (BP), in the 4,576 patients with a low ejection fraction (EF) (≤0.40) in the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) program.

Background Hypotension is a predictor of poor prognosis in heart failure, yet many treatments shown to reduce morbidity and mortality lower blood pressure. This paradox creates a dilemma for physicians and may explain why low BP is reported as a reason for under-use of these agents.

Methods The interaction between treatment and baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP) was examined with patients divided into 6 SBP categories (≤100, 101 to 110, 111 to 120, 121 to 130, 131 to 140 and ≥141 mm Hg) and 4 DBP categories (≤60, 61 to 70, 71 to 80 and ≥81 mm Hg).

Results Low SBP and DBP were associated with worse clinical outcomes. Baseline BP did not modify the effects of candesartan on clinical outcomes: the interaction p value between SBP category and treatment was 0.38 (0.22 for DBP category). For both placebo and candesartan, study drug discontinuation for adverse effects (especially hypotension) was highest in patients in the lowest baseline BP categories. However, the relative risk of discontinuation for hypotension, renal dysfunction, and hyperkalemia in the candesartan compared with placebo group was not increased in patients with a low baseline BP.

Conclusions In patients with low EF heart failure, the relative risks and benefits of candesartan treatment were similar in patients with a low BP compared to those with a higher BP. (J Am Coll Cardiol 2008;52:2000–7) © 2008 by the American College of Cardiology Foundation

Hypotension is a recognized predictor of poor prognosis in patients with heart failure (HF), yet many of the treatments shown to reduce morbidity and mortality also lower blood pressure (BP) (1–4). This paradox presents a dilemma to physicians when treating patients (5). Indeed, this dilemma may explain why, in surveys of physician practice, low BP is often reported as a contraindication to the use of agents known to improve outcome in HF (or a reason for withdrawal of these treatments) (6,7). This is true for both angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, the combination of which is now the cornerstone of treatment of patients with HF and a low left ventricular ejection fraction (EF) (8–10).

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The issue of hypotension has been highlighted further by the recent recommendation of angiotensin receptor blockers as a third add-on treatment in patients with a low EF who remain symptomatic despite therapy with an ACE inhibitor and beta-blocker (8–10).

To investigate the efficacy and tolerability of candesartan, according to baseline BP, we analyzed the 2 low EF (≤0.40) trials in the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) program (11–14).

Methods

The CHARM program. The design, baseline findings, and primary results of the CHARM program have been reported in detail (11–15). Briefly, it consisted of 3 independent but related trials in which patients with New York Heart Association (NYHA) functional class II to IV HF were randomized to candesartan (force titrated over 6 to 8 weeks to a target dose of 32 mg once daily, as tolerated) or matching placebo. Patients were enrolled into the individual CHARM trials according to EF and treatment with an ACE inhibitor.

Patients with an EF ≤0.40 who were intolerant of an ACE inhibitor were enrolled in the CHARM-Alternative trial, whereas patients with an EF ≤0.40 and taking an ACE inhibitor were enrolled in the CHARM-Added trial. In this component trial, patients in NYHA functional class II must have had a hospital admission for a cardiac reason in the previous 6 months (this had the effect of increasing the proportion of NYHA functional class III/IV patients in the CHARM-Added trial). Investigators were also encouraged to use evidence-based doses of ACE inhibitors in patients randomized to the CHARM-Added trial.

Patients with an EF >0.40 were randomized into CHARM-Preserved trial, which was not considered further in this analysis because candesartan did not improve the primary outcome in this component trial and candesartan is not approved for the treatment of HF with a preserved EF.

There was no specific lower BP exclusion criterion, although patients with current symptomatic hypotension could not be randomized. Patients with a serum creatinine ≥3 mg/dl (265 μmol/l) were excluded. Patients with a serum potassium ≥5.5 mmol/l (or a history of marked ACE inhibitor–induced hyperkalemia resulting in a serum potassium ≥6.0 mmol/l or a life-threatening adverse event) also were excluded.

The CHARM program was completed, as planned, 2 years after the last patient was randomized. Because the rate of recruitment varied between the component CHARM trials, the median follow-up time was 41 months in the CHARM-Added trial and 34 months in the CHARM-Alternative trial (40 months in the 2 low-EF CHARM trials combined).

The primary outcome for each of the component trials was the composite of death from a cardiovascular (CV) cause or unplanned admission to the hospital for the management of worsening HF, and in the overall CHARM program, death from any cause (which was also a pre-specified outcome in the planned analysis of the 2 low-EF trials combined). At each follow-up visit, investigators were asked whether the study drug had been discontinued because of: symptomatic or severe hypotension, abnormal renal function, or hyperkalemia (or other reasons).

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
BP = blood pressure
CV = cardiovascular
DBP = diastolic blood pressure
EF = ejection fraction (left ventricular)
HF = heart failure
NYHA = New York Heart Association
SBP = systolic blood pressure

Baseline BP categories. The CHARM pre-specified analysis plan stated that outcomes according to randomized treatment allocation would be analyzed according to the following systolic blood pressure (SBP) categories: <100 and ≥100 mm Hg and <140 and ≥140 mm Hg; and the following diastolic blood pressure (DBP) categories: <70 and ≥70 mm Hg and <90 and ≥90 mm Hg. Subsequently, however, we decided that a more extensive analysis would be more valuable. Consequently, for this retrospective analysis, patients were divided into 6 clinically relevant SBP categories: ≤100, 101 to 110, 111 to 120, 121 to 130, 131 to 140 and ≥141 mm Hg. The following 4 DBP categories were analyzed: ≤60, 61 to 70, 71 to 80, and ≥81 mm Hg.

Statistical analysis. Summary statistics of an extensive list of baseline characteristics including demographics, history and etiology of HF, comorbidity, body mass index, vital signs, clinical signs and symptoms of HF, electrocardiographic findings, and HF medications were analyzed according to baseline SBP and DBP at randomization. The Cox proportional-hazards model was used to estimate the hazard ratio for the effect of treatment in each BP group as well as to calculate the p value for the interaction between treatment effect and BP group on each end point (CV death or HF hospitalization and all-cause death).

The same model was used to analyze the time to discontinuation of study drug (because of hypotension, renal dysfunction, or hyperkalemia).

Results

Baseline characteristics. There were 4,576 patients with an EF ≤0.40 randomized in the CHARM program. The baseline characteristics according to SBP are shown in Table 1. Patients with a lower SBP were younger and had a worse NYHA functional class status, a lower median EF, and a greater prevalence of coronary heart disease and history of atrial fibrillation, but less hypertension. Patients with a lower SBP were more likely to be treated with a diuretic, digoxin, and spironolactone but less likely to be

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Patient Characteristics According to Baseline Blood Pressure

	SBP, mm Hg					
	≤100 (n = 385)	101 to 110 (n = 698)	111 to 120 (n = 910)	121 to 130 (n = 908)	131 to 140 (n = 751)	≥140 (n = 924)
Patient characteristics						
Mean (SD) age (yrs)	63 (11)	63 (12)	64 (11)	65 (10)	66 (11)	68 (10)
Age ≥75 yrs (%)	15	17	18	18	25	27
Male (%)	80	76	77	74	74	68
NYHA functional class (%)						
II	28	34	31	35	37	39
III	64	61	66	63	61	59
IV	8	5	3	2	3	2
Median LV ejection fraction	0.25	0.29	0.29	0.3	0.31	0.31
Mean (SD) heart rate (beats/min)	74 (5)	74 (14)	74 (13)	73 (12)	74 (14)	74 (13)
Mean (SD) blood pressure (mm Hg)						
Systolic	96 (5)	108 (3)	118 (3)	128 (3)	138 (3)	155 (9)
Diastolic	63 (7)	69 (8)	74 (8)	77 (9)	80 (9)	85 (10)
HF cause (%)						
Ischemia	69	66	68	64	65	61
Hypertension	3	2	4	7	8	13
Idiopathic	24	27	23	24	21	21
Medical history (%)						
Hospital admission for HF	79	75	71	74	72	72
Myocardial infarction	61	62	62	58	58	52
Current angina	18	21	22	21	23	22
Stroke	8	7	8	9	9	10
Diabetes mellitus	28	24	29	32	27	30
Hypertension	26	36	41	52	52	71
Atrial fibrillation	30	28	26	27	23	26
Pacemaker	14	10	10	10	6	7
Percutaneous coronary intervention	16	18	16	16	15	13
Coronary artery bypass grafting	24	26	26	24	23	25
Implantable cardioverter-defibrillator	9	6	3	3	2	2
Medical treatment (%)						
ACE inhibitor	69	62	60	56	50	47
Beta-blocker	57	59	56	54	53	52
Spironolactone	34	27	22	19	16	13
Diuretic	95	91	87	87	87	86
Digoxin	61	57	55	51	49	49
Aspirin	48	49	55	53	57	59
Oral anticoagulant	49	42	36	34	29	27
Antiarrhythmic agent (including amiodarone)	1	2	2	2	2	2
Lipid-lowering drug	43	43	42	41	40	40
Long-acting nitrate	32	33	35	35	37	34
Calcium-channel blocker	6	9	12	13	14	21
Other vasodilators (including hydralazine)	7	5	6	34	7	6

ACE = angiotensin-converting enzyme; HF = heart failure; IQR = interquartile range; LV = left ventricular; NYHA = New York Heart Association; SBP = systolic blood pressure.

treated with a calcium-channel blocker. Similar trends were noted when the DBP categories were analyzed and when the CHARM-Alternative and the CHARM-Added trials were analyzed separately.

Dose of candesartan and placebo achieved. The median (range) dose of both candesartan and placebo taken by patients still receiving treatment at the end of titration period was 8 mg (range 4 to 16 mg) in subjects with a baseline SBP ≤100 mm Hg and 16 mg (range 8 to 16 mg) for both treatments in patients with an SBP 101 to 110 mm Hg. For all other SBP groups, the dose of placebo was 16 mg (range 16 to 16 mg). For candesartan it was 16 mg (range 8 to 16 mg) in those with an SBP 111 to 140 mm Hg and 16 mg (range 16 to 16 mg) in those with an SBP >140 mm Hg. Similar trends were noted when the DBP categories were analyzed and when the CHARM-Alternative and CHARM-Added trials were analyzed separately (data not shown).

Change in BP. The change in SBP from baseline to the end of the titration period, for each SBP group, is shown in

Table 2. BP increased in the patients with the lowest starting value and decreased the most in those with a higher baseline pressure. BP increased less in the candesartan-treated patients (compared with placebo-treated patients) in the lower BP groups and decreased more with candesartan in the higher BP groups. There was, however, no evidence of a systematic difference in the placebo-corrected response to candesartan in the different BP groups.

Clinical outcomes CV death or HF hospitalization. Patients with a low SBP (or DBP, data not shown) at baseline had a greater risk of CV death or HF hospitalization than those with a higher BP (Fig. 1 and Table 3). This risk increased sharply at an SBP below 110 mm Hg, and especially below 100 mm Hg. Baseline SBP and DBP did not modify the effect of candesartan on this composite outcome (Fig. 2 and Table 3). The interaction p value between SBP (categories) and treatment was 0.38 (Fig. 2A). The interaction p value between DBP (categories) and treatment was 0.22 (Fig. 2B). These findings were similar when the CHARM-Alternative and -Added trials were analyzed individually (data not shown).

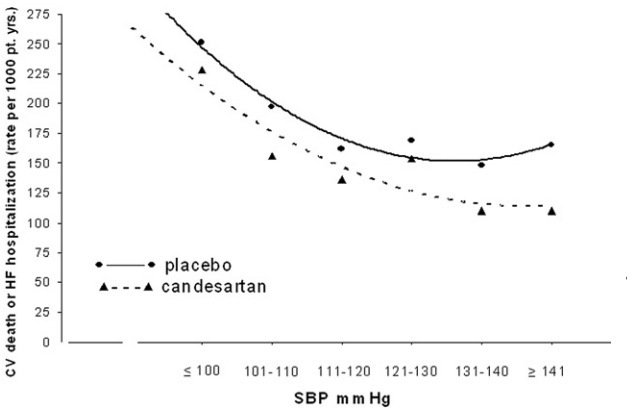
All-cause mortality. Similarly, patients with a low SBP (or DBP at baseline, data not shown) had a greater risk of death from any cause than those with a higher BP (Table 3). Baseline SBP and DBP did not modify the effect of candesartan on this outcome (Fig. 3 and Table 3). The interaction p value between SBP (categories) and treatment was 0.85 (Fig. 3A). The interaction p value between DBP (categories) and treatment was 0.76 (Fig. 3B). These findings were similar when the CHARM-Alternative and -Added trials were analyzed individually (data not shown).

Tolerability and safety. The proportion of patients that discontinued the study drug for hypotension, renal dysfunction, and hyperkalemia in each SBP category is shown in Table 4. Patients in the lowest SBP category had the highest placebo-group rate of discontinuation for each of these adverse effects. Generally, patients treated with candesartan had an increased rate of discontinuation for each of these adverse effects compared with patients treated with placebo, although the increased risk was most apparent for hyperkalemia. The risk of discontinuation because of hypotension in both the placebo and the candesartan groups increased markedly when the baseline SBP was <110 mm Hg. For patients in the lowest SBP category, the greatest relative increase in risk for discontinuation with candesartan was for hypotension, with no evidence of increased risk of hyperkalemia or renal dysfunction. Similar findings were noted when the DBP categories were examined and when the CHARM-Alternative and -Added trials were analyzed individually (data not shown).

Mean (SD) Change in SBP From Baseline to End of Forced Titration in Each SBP Category

Baseline SBP Category (mm Hg)	CHARM–Low EF	
	Placebo	Candesartan
<100	+8.3 (13.4)	+4.6 (14.6)
101 to 110	+4.0 (14.2)	−0.1 (14.0)
111 to 120	+0.8 (14.1)	−4.9 (14.9)
121 to 130	−1.8 (14.7)	−8.3 (16.0)
131 to 140	−6.6 (15.4)	−11.4 (17.3)
>140	−13.1 (17.7)	−16.6 (19.1)

CHARM = Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity trials; EF = ejection fraction; SBP = systolic blood pressure.



Risk of CV Death or HF Hospitalization According to Baseline SBP in the Randomized Placebo and Candesartan Treatment Groups

CV = cardiovascular; HF = heart failure; SBP = systolic blood pressure.

Discussion

The principal findings of this analysis of the CHARM low-EF trials were that a low SBP (and a low DBP) was associated with worse clinical outcomes and that baseline BP did not modify the effects of candesartan on clinical outcomes.

These findings are important because practicing physicians often are concerned about giving additional treatment with a hypotensive action to HF patients with a low BP (7). Our analyses show that this can be done with a low incidence of adverse effects and anticipation of as much clinical benefit as in patients with a higher BP. Furthermore, the incremental risk of adverse effects with candesartan, compared with placebo, was not greater in patients with a low baseline BP compared with those with a higher BP at trial entry.

Our findings are in keeping with those of the A-HeFT (African-American Heart Failure Trial) study, in which the effects of adding the combination of hydralazine and isosorbide dinitrate to conventional therapy were consistent above (n = 513) and below (n = 537) the median SBP of 126 mm Hg. Despite the findings of the A-HeFT study, however, there was still uncertainty about the use of drugs with a hypotensive action in patients with a very low SBP, because in that study only 229 patients had an SBP <112 mm Hg and only 79 had an SBP ≤100 mm Hg (4). By contrast, the

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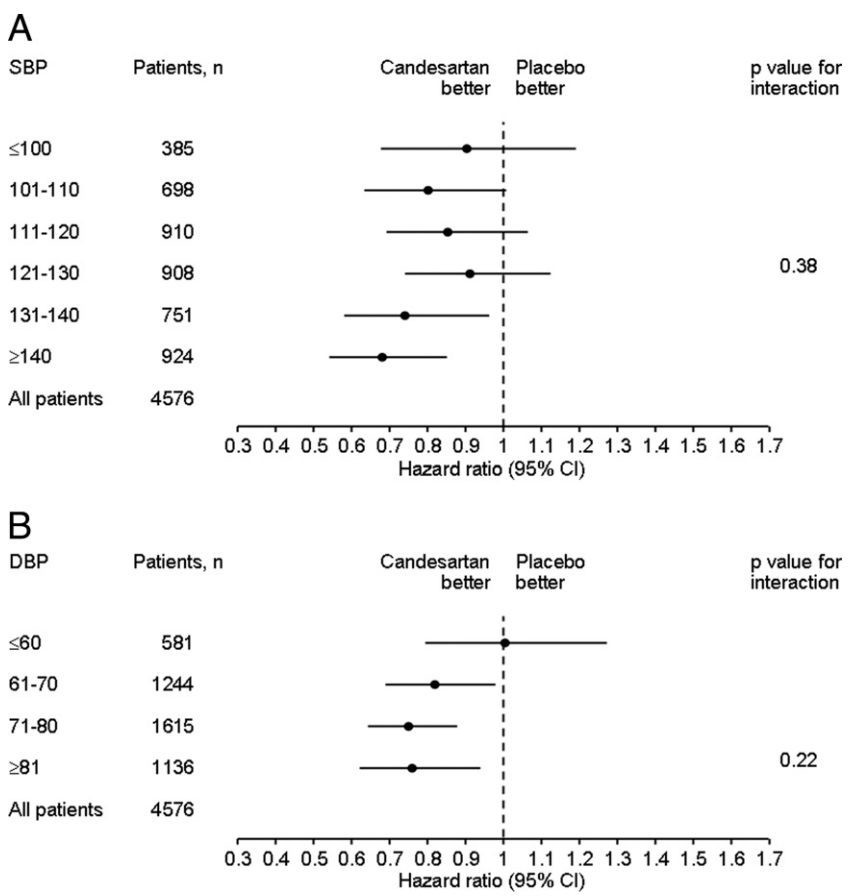
Pre-Specified Composite Mortality/Morbidity Outcome and All-Cause Death in the CHARM Low LVEF Trials According to Baseline SBP

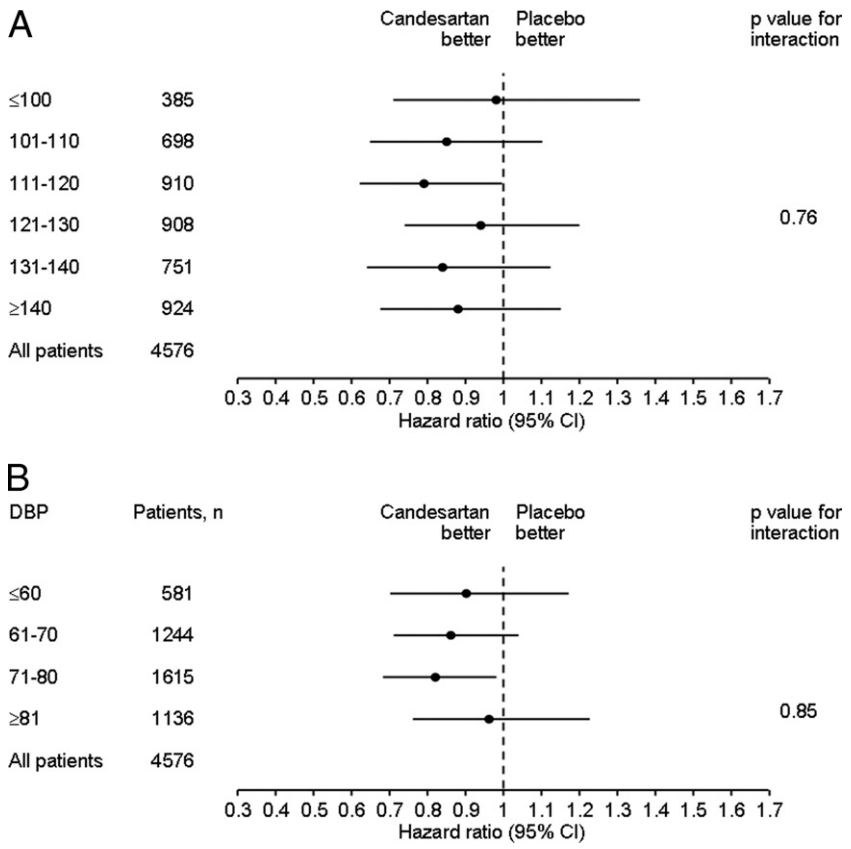
	Events Per 1,000 Years Follow-Up			
	Candesartan	Placebo	HR (95% CI)	p for Interaction
Cardiovascular death or heart failure hospitalization				
SBP ≤100 mm Hg (n = 385)	228	251	0.90 (0.68–1.19)	
SBP 101 to 110 mm Hg (n = 698)	156	197	0.80 (0.63–1.00)	
SBP 111 to 120 mm Hg (n = 910)	136	162	0.85 (0.69–1.06)	0.38
SBP 121 to 130 mm Hg (n = 908)	154	169	0.91 (0.74–1.12)	
SBP 131 to 140 mm Hg (n = 751)	110	148	0.58 (0.58–0.96)	
SBP ≥141 mm Hg (n = 924)	110	165	0.54 (0.54–0.85)	
All patients (n = 2,548)	140	173	0.82 (0.74–0.90)	
All-cause death				
SBP ≤100 mm Hg (n = 385)	154	153	0.98 (0.71–1.36)	
SBP 101 to 110 mm Hg (n = 698)	108	127	0.85 (0.65–1.10)	0.85
SBP 111 to 120 mm Hg (n = 910)	96	122	0.79 (0.62–1.00)	
SBP 121 to 130 mm Hg (n = 908)	101	107	0.94 (0.74–1.20)	
SBP 131 to 140 mm Hg (n = 751)	84	101	0.84 (0.64–1.12)	
SBP ≥141 mm Hg (n = 924)	82	93	0.88 (0.68–1.15)	
All patients (n = 2,548)	99	112	0.88 (0.79–0.98)	

CI = confidence interval; HR = hazard ratio; LVEF = left ventricular ejection fraction; other abbreviations as in Table 2.



Effect of Candesartan on Primary Composite Outcome According to Baseline Blood Pressure

(A) Effect of candesartan compared with placebo on the risk of cardiovascular death or heart failure hospitalization according to baseline systolic blood pressure (SBP). **(B)** Effect of candesartan compared with placebo on the risk of cardiovascular death or heart failure hospitalization according to baseline diastolic blood pressure (DBP). CI = confidence interval.



Effect of Candesartan on All-Cause Mortality According to Baseline Blood Pressure

(A) Effect of candesartan compared with placebo on the risk of all-cause mortality according to baseline SBP. **(B)** Effect of candesartan compared with placebo on the risk of all-cause mortality according to baseline DBP. Abbreviations as in Figure 2.

CHARM low-EF trials included almost 2,000 patients with an SBP ≤120 mm Hg and 385 with an SBP ≤100 mm Hg.

In the same way, our findings also support and extend those of an analysis of the COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) study, in which the benefits of the beta- and alpha-adrenergic receptor blocking agent used were consistent across the SBP categories examined (1). In that analysis, 264 patients had an SBP in the range of 105 to 96 mm Hg and 132 in the range of 95 to 85 mmHg.

Reasons for Permanent Discontinuation of Study Drug (Rate Per 1,000 Patient Years of Follow-Up) According to Baseline SBP

	Discontinuation of Study Drug								
	Hypotension			Renal Dysfunction			Hyperkalemia		
	Candesartan	Placebo	HR (95% CI)	Candesartan	Placebo	HR (95% CI)	Candesartan	Placebo	HR (95% CI)
SBP ≤100 mm Hg	43.4	13.7	3.16 (1.28–7.81)	23.1	22.9	1.01 (0.44–2.33)	3.7	4.5	0.82 (0.12–5.85)
SBP 101 to 110 mm Hg	26.4	16.0	1.68 (0.88–3.21)	32.1	15.9	2.03 (1.09–3.79)	9.6	1.0	9.37 (1.19–73.95)
SBP 111 to 120 mm Hg	12.7	9.5	1.35 (0.64–2.86)	24.1	13.5	1.79 (0.99–3.24)	7.1	0.8	9.15 (1.16–72.20)
SBP 121 to 130 mm Hg	11.6	6.5	1.81 (0.77–4.27)	26.7	8.1	3.28 (1.62–6.64)	12.4	2.4	5.08 (1.48–17.45)
SBP 131 to 140 mm Hg	10.3	3.8	2.75 (0.87–8.63)	24.8	11.4	2.17 (1.10–4.31)	13.2	1.9	6.91 (1.57–30.39)
SBP ≥141 mm Hg	5.3	3.1	1.84 (0.54–6.29)	24.4	11.5	2.11 (1.14–3.91)	10.1	2.3	4.44 (1.26–15.60)

Candesartan/placebo HRs with 95% CIs are also given.
Abbreviations as in Tables 2 and 3.

We found that BP decreased with both placebo and candesartan in the higher baseline BP categories. In contrast, the groups with a baseline SBP ≤100 mm Hg had an increase in BP after randomization, although the increase was smaller in the candesartan group. This finding is consistent with both the A-HeFT study and the COPERNICUS study, in which BP increased in those in the lowest baseline BP categories in both the placebo and active therapy groups (1,4). Although this pattern of BP change suggests regression to the mean, the considerably higher risk of clinical events in those with the lowest baseline BP indicates that the recorded baseline BP was of biologic importance.

Patients with the lowest baseline BP were less likely to be titrated to higher doses of study drug, but this was true of both placebo- and candesartan-treated patients. We also found that hypotension, reported as the cause of discontinuation of study drug, was more common in patients in the 2 lowest baseline BP categories, irrespective of treatment allocation. Overall, patients treated with candesartan were more likely to stop treatment because of hypotension than those treated with placebo. Although the highest absolute rate of treatment discontinuation for hypotension was in patients in the lowest SBP category at baseline treated with candesartan, the incremental risk with candesartan, compared with placebo, was not greater in these highest-risk patients in the lowest baseline BP category. Importantly, the majority of patients with a low BP at baseline remained on study drug and obtained similar benefits. These findings are also consistent with the results of the A-HeFT and COPERNICUS trials (1,4). Collectively, these studies show that HF patients with a low SBP are at greater risk of adverse clinical outcomes, are less likely to achieve target doses of evidence-based therapy, are no more likely in relative terms to discontinue such treatment, and in absolute terms, obtain as much or greater benefit from these treatments.

It was also noteworthy that there was no excess risk related to candesartan of renal dysfunction or hyperkalemia in patients with a low baseline BP, although study drug discontinuation for both of these adverse effects was more common overall in the candesartan group compared with the placebo group and more common in patients with a low baseline BP, irrespective of treatment group, than in those with a higher BP.

Our analyses have some limitations. They are retrospective, and although larger than in prior studies, the number of patients in the lowest SBP group at baseline is still relatively small.

Clinical implications. In summary, a low SBP should not deter physicians from prescribing evidence-based therapy with a hypotensive action, although such treatment should, of course, be used cautiously and with appropriate monitoring of patients for tissue underperfusion, for example, causing pre-syncope/syncope or worsening renal function.

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Key Words: heart failure ■ angiotensin receptor blockers ■ blood pressure.