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Angiotensin-receptor blockers in heart failure: Evidence from the CHARM trial

ABSTRACT

The large Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trial recently found that in patients with heart failure who were similar to those whom clinicians see in everyday practice, the angiotensin-receptor blocker candesartan was not only an acceptable alternative to angiotensin-converting enzyme (ACE) inhibitors, but also was beneficial when added to regimens that already included ACE inhibitors and beta-blockers. Candesartan was beneficial in heart failure patients with or without left ventricular systolic dysfunction.

IN TREATING heart failure, how should we use angiotensin-receptor blockers (ARBs)?

- As alternatives to angiotensin-converting enzyme (ACE) inhibitors for patients with a low left ventricular ejection fraction who cannot tolerate ACE inhibitors?
- In addition to ACE inhibitors in patients with a low left ventricular ejection fraction?
- In patients with heart failure but a normal left ventricular ejection fraction?
- All of the above?

The answer may be "all of the above," according to the findings of the recent Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trial.[1-4]

See related editorial, page 674

This review focuses on the importance of the renin-angiotensin-aldosterone system in the pathophysiology of heart failure, the important role of ACE inhibitors in the management of heart failure, and the controversy surrounding the use of ARBs as a substitute for or in addition to ACE inhibitors in heart failure management. We also summarize the background and study design, results, and implications of the CHARM trial.

CHARM found an ARB was beneficial, both as an alternative to an ACE inhibitor and in addition to one

EXCESS ANGIOTENSIN II HAS UNDESIRABLE EFFECTS

The renin-angiotensin-aldosterone system plays a key role in cardiovascular disease and heart failure.

In a cascade of reactions (FIGURE 1), angiotensinogen (synthesized by the liver) is cleaved by renin (released from the juxtaglomerular cells in the renal afferent arteriole) to form angiotensin I. ACE then cleaves two amino acids from angiotensin I to produce the octapeptide angiotensin II.

Angiotensin II has a number of undesirable effects on the cardiovascular system. It stimulates aldosterone synthesis in the zona glomerulosa of the adrenal gland, stimulates thirst, and leads to antidiuretic hormone release, resulting in sodium and water reten-

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This paper discusses therapy that is experimental or not approved by the US Food and Drug Administration for the use under discussion.

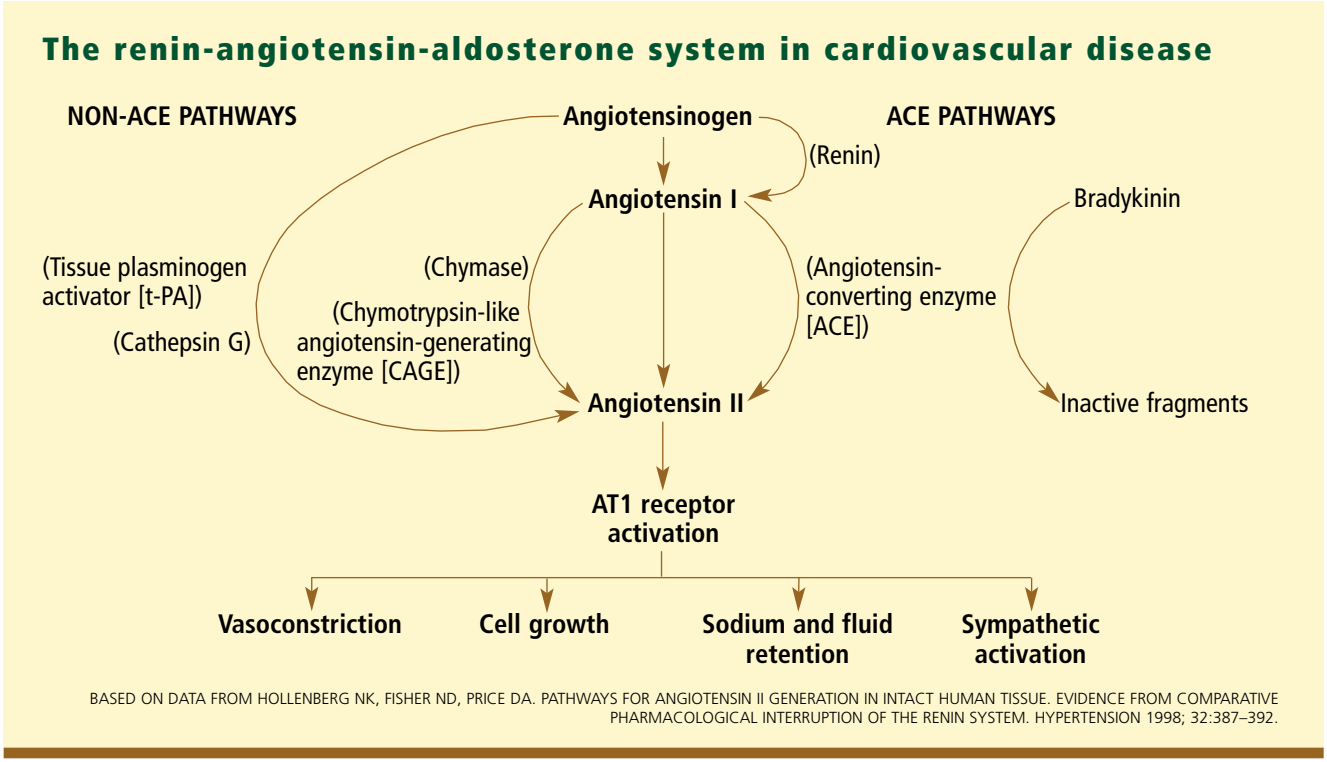

FIGURE 1

Side effects of ACE inhibitors: cough, hypotension, hyperkalemia, renal insufficiency, angioedema

tion. A potent vasoconstrictor, it raises peripheral vascular resistance, and it decreases cardiac output. It also stimulates synthesis of inflammatory cytokines, adhesion and chemotaxis of inflammatory cells such as macrophages, fibrosis (through the actions of activated fibroblasts), and collagen synthesis.[5]

ACE INHIBITORS: CORNERSTONE OF HEART FAILURE TREATMENT

The prognosis of heart failure has improved considerably, thanks to several new treatments.

ACE inhibitors have been the cornerstone of heart failure treatment for more than a decade. In addition, beta-blockers[6] such as metoprolol CR/XL, bisoprolol,[7] and carvedilol,[8,9] once contraindicated in heart failure, now constitute the standard of care. Mineralocorticoid receptor antagonists such as spironolactone[10] and eplerenone[11] also have been shown to be beneficial. And in selected patients, nesiritide[12] and cardiac resynchronization therapy[13] may improve symptoms and hemodynamics.

Antikininase activity is beneficial...

In addition to reducing levels of angiotensin II, the cardioprotective effects of ACE inhibitors are probably due to the ability of these drugs also to counter the actions of kininases and to prevent the breakdown of bradykinin.

The kinin family—bradykinin, kallidin, and methionyl-lysyl-bradykinin—has beneficial effects on the cardiovascular system. In particular, bradykinin lowers blood pressure via vasodilatation, decreasing peripheral vascular resistance, and causes diuresis and natriuresis. In the coronary arteries, it increases blood flow. It also has been shown to prevent left ventricular hypertrophy.[14]

Kinins are inactivated by enzymes called kininases in the plasma, the endothelium, and other tissues. The kininases include kininase 1, kininase 2 (also known as ACE), and enkephalinase. Both kininase 1 and kininase 2 break down bradykinin, but by different mechanisms.

...but also causes cough

Unfortunately, ACE inhibitors frequently cause side effects, posing an obstacle to the use

TABLE 1

Previous clinical trials of angiotensin-receptor blockers in heart failure

TRIAL	NUMBER OF PATIENTS	FINDINGS
ELITE-I[18]	722	**Primary end point:** No difference in incidence of increase in serum creatinine with losartan vs captopril (10.5% vs 10.5%) **Secondary end points:** Trend toward fewer deaths or hospitalizations for heart failure with losartan (9.4% vs 13.2%, $P = .075$) All-cause mortality 4.8% with losartan vs 8.7% with captopril ($P = .035$)
ELITE-II[19]	3,152	**Primary end point:** No difference in all-cause mortality with losartan vs captopril (11.7% vs 10.4%) **Secondary end points:** No difference in sudden death or resuscitated arrest with losartan vs captopril (9.0% vs 7.3%)
RESOLVD[20]	768	No difference in 6-minute walking distance or quality of life with candesartan, enalapril, or combination Combined therapy group had significantly less increase in end-diastolic and end-systolic volumes and decreases in blood pressure, aldosterone, and brain natriuretic peptide
Val-HeFT[21]	5,010	No difference in mortality with valsartan vs ACE inhibitor (19.7% vs 19.4%) Lower incidence of composite end point (mortality, cardiac arrest and resuscitation, heart failure hospitalization, need for intravenous vasodilators or inotropes) with valsartan (28.8% vs 32.1%, $P = .009$)

of these drugs in patients with heart failure.

Cough develops in 5% to 10% of Caucasian patients and up to 50% of Chinese patients taking ACE inhibitors.[15] The cough is probably mediated by bradykinin, which is increased owing to the inhibition of kininases by ACE inhibitors.

Woo et al[16] examined the difference between Chinese and Caucasian patients in the incidence of cough with ACE inhibitors in a case-control study. The investigators prospectively followed 111 Chinese patients in Hong Kong and 49 Caucasian patients in Auckland, New Zealand, randomly selecting and pairing patients in each population who were already receiving an ACE inhibitor (either captopril or enalapril) with control patients not taking ACE inhibitors. Dr. Woo interviewed all the patients.

Of the Chinese patients, 53% of those taking an ACE inhibitor reported having a cough, vs only 10% of control patients, a difference that was statistically significant. Among Caucasian patients, 18% of those taking ACE an inhibitor and 5% of control patients reported cough, a difference that also was statistically significant but not as pronounced as the difference in the Chinese population.

These findings suggest that Chinese patients are at higher risk for cough due to ACE inhibitors than are non-Chinese patients. (This brief report did not determine if a specific Chinese ethnic group is more susceptible than another, and the investigators did not elaborate upon this possibility.)

Up to half of Chinese patients on ACE inhibitors may develop cough

Other disadvantages of ACE inhibitors

Other adverse effects of ACE inhibitors that may necessitate stopping them include hypotension, hyperkalemia, and renal insufficiency.[17] Angioedema is rare but potentially lethal.

Another disadvantage of ACE inhibitors is that they incompletely block the formation of angiotensin II, which can be produced by ACE-independent pathways (FIGURE 1). Continued synthesis of angiotensin II, especially in the presence of chronic ACE inhibition, can lead to deleterious effects on the heart and vasculature and further heart failure progression.[17]

THEORETICAL ADVANTAGES OF ARBs

ARBs were developed to block the renin-angiotensin-aldosterone system more completely at the level of the receptor without inhibiting kininases. These drugs were expected to provide the benefits of ACE inhibition with less frequent cough and angioedema.

Through their specific effects on the angiotensin II type 1 receptor, ARBs also were thought to provide more specific inhibition of deleterious effects of the activated renin-angiotensin-aldosterone system, at the same time leaving the angiotensin II type 2 receptor available to mediate antiproliferative effects.[17]

However, up to now there has been considerably less clinical experience with ARBs than with ACE inhibitors, so the safety and efficacy of ARBs in heart failure needed to be tested.

CLINICAL TRIALS OF ARBs IN HEART FAILURE

ELITE I: An ARB appears equivalent to an ACE inhibitor

The Evaluation of Losartan in the Elderly (ELITE I) trial[18] was the first long-term clinical trial to compare an ARB (losartan) with an ACE inhibitor (captopril) in patients with heart failure and decreased left ventricular ejection fraction. The study's objective was to determine if losartan was safer than captopril.

Clinical experience is greater with ACE inhibitors than with ARBs

The investigators randomized 722 patients (age 65 years or older, who had never received an ACE inhibitor, and whose left ventricular ejection fraction was ≤ 40%) to receive either losartan (target dose 50 mg daily) or captopril (target dose 50 mg three times daily).

Among the exclusion criteria were serum concentrations of creatinine greater than 2.5 mg/dL and potassium lower than 3.5 mEq/L or greater than 5.5 mEq/L.

The primary end point was a rise in creatinine. Secondary end points included death and hospitalization for heart failure.

The study found no difference between losartan and captopril in the primary end point of a rise in creatinine. However, fewer patients in the losartan group than in the captopril group had to stop therapy due to intolerance. Of note, the all-cause mortality rate was significantly lower (4.8% vs 8.7%, P = .035) in the losartan group than in the captopril group, even though the study was not designed to have the statistical power to detect a difference in mortality (TABLE 1).[18-19]

ELITE II: No mortality advantage with an ARB vs an ACE inhibitor

The objective of ELITE II[19] was to confirm whether losartan conferred a survival advantage over captopril. A total of 3,152 patients (60 years or older; in New York Heart Association [NYHA] functional class II, III, or IV; and with a left ventricular ejection fraction ≤ 40%) were randomized to receive losartan or captopril in the same dosages used in the ELITE I trial.

There was no statistically significant difference in the primary end point (all-cause mortality), sudden death, or resuscitated cardiac arrest. As in the ELITE I trial, fewer patients had to stop taking losartan compared with captopril.

The investigators concluded that ACE inhibitors should be preferred over ARBs, given the greater amount of clinical evidence and experience with ACE inhibitors. However, since losartan was better tolerated in both ELITE trials, the investigators recommended that it could be used as an alternative in patients unable to tolerate ACE inhibitors.

RESOLVD: Combination therapy may be beneficial

The Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) trial[20] compared three treatments: an ARB (candesartan), an ACE inhibitor (enalapril), and the combination of candesartan and enalapril.

Outcomes assessed included the distance patients could walk in 6 minutes, ventricular function as assessed by ejection fraction and end-diastolic and end-systolic volumes, blood pressure, quality of life, and levels of aldosterone and brain natriuretic peptide (BNP)—neurohormones known to be elevated in heart failure.

The study found no significant differences among the treatment groups in 6-minute walking distance, NYHA functional class, or quality of life. In the group that received both can-

desartan and enalapril, end-diastolic and end-systolic volumes increased significantly less than in the groups that received either drug alone, suggesting that heart failure progressed more slowly with combination therapy. In addition, blood pressure, aldosterone, and brain natriuretic peptide levels decreased significantly more in the combination therapy group.

The authors concluded that candesartan and enalapril were equally effective with respect to the study's end points and in terms of safety and tolerability. The benefits of combination therapy on ventricular volumes suggested that this approach attenuated left ventricular remodeling more powerfully than therapy with either agent alone.

Val-HeFT: Combination therapy may be harmful

In the Valsartan Heart Failure Trial (Val-HeFT),[21] 5,010 patients with heart failure and a low left ventricular ejection fraction were randomized to receive placebo or the ARB valsartan titrated to a goal dose of 160 mg twice daily.

The two primary end points were mortality and a composite end point consisting of cardiac arrest with resuscitation, heart failure hospitalization, or use of intravenous vasodilators or inotropes.

The study found no difference in mortality, but it did find a 13.2% lower incidence of the composite end point, due primarily to fewer hospitalizations for heart failure in the valsartan group than in the placebo group. The valsartan group also improved in functional class, symptoms, and quality of life. However, in a post hoc subgroup analysis of patients already receiving both a beta-blocker and an ACE inhibitor, those randomized to receive valsartan had a higher incidence of the combined end point of mortality and indicators of heart failure compared with patients already on double therapy in the placebo group.

These findings led to speculation that "triple therapy" with an ARB, an ACE inhibitor, and a beta-blocker may be harmful, possibly due to excessive neurohormonal blockade. However, since this study was not designed prospectively to test this interaction, the possibility of statistical chance could not be excluded.

Unanswered questions provide rationale for the CHARM trial

Even after the four trials summarized above (TABLE 1), ARBs, unlike ACE inhibitors, did not have the requisite clinical evidence to show they are effective, and so could not be considered equivalent to ACE inhibitors. Since they were so well tolerated, however, ARBs were considered an acceptable alternative to ACE inhibitors in patients who could not tolerate an ACE inhibitor. Indeed, the US Food and Drug Administration permitted this claim for valsartan in heart failure on the basis of the 7% of Val-HeFT patients not on ACE inhibitors who showed a marked benefit.

These data left three key questions unanswered:

- In patients who cannot tolerate ACE inhibitors, do ARBs as alternatives provide equivalent benefit?
- In patients who are already taking an ACE inhibitor and a beta-blocker, can ARBs be added safely and provide added benefit?
- Can ARBs provide benefit in patients with heart failure and preserved left ventricular ejection fraction, a group underrepresented in previous heart failure clinical trials?

These questions provided the background and rationale for the CHARM program.

THE CHARM PROGRAM: THREE STUDIES IN ONE

CHARM was one of the largest trials ever done in heart failure patients

The CHARM Program, one of the largest trials ever undertaken in heart failure patients, consisted of three simultaneous, parallel arms in which three different populations were studied prospectively with the same doses of candesartan or placebo. The three arms of the study were:

- **CHARM-Alternative:** Patients with a left ventricular ejection fraction of 40% or less who could not tolerate an ACE inhibitor[2]
- **CHARM-Added:** Patients with a left ventricular ejection fraction of 40% or less who were currently taking an ACE inhibitor, with or without a beta-blocker[1]
- **CHARM-Preserved:** Patients with a left ventricular ejection fraction greater than 40%.[3]

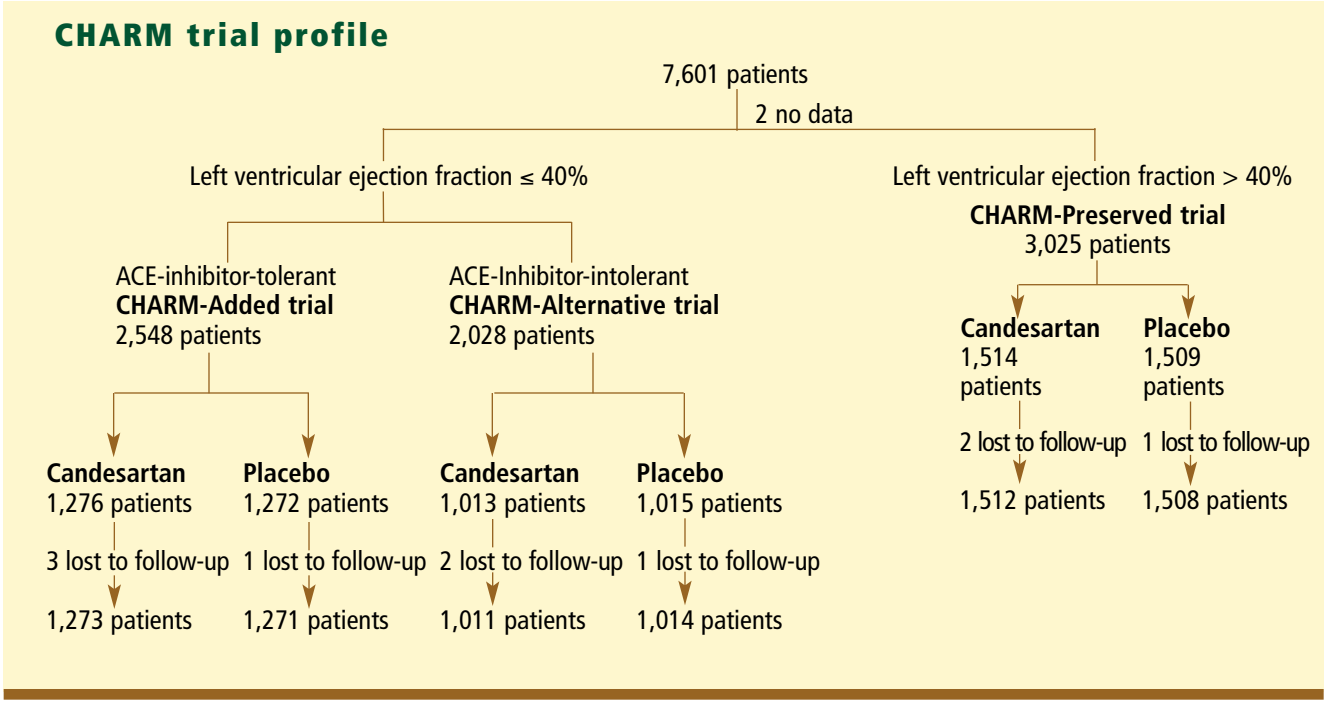

FIGURE 2

The findings from all three arms were also combined into one overall program.[4] This novel design allowed statistical analysis of each population without introducing the bias of post-hoc subgroup analysis.

At baseline, more than half the patients were on beta-blockers

Patients and methods

CHARM recruited patients older than 18 years with heart failure and in NYHA functional class II, III, or IV from 618 sites in 26 countries.

Key exclusion criteria were:

- Serum creatinine concentration > 3 mg/dL (265 µmol/L)
- Serum potassium > 5.5 mEq/L
- Bilateral renal artery stenosis
- Symptomatic hypotension
- Critical aortic stenosis or severe mitral stenosis
- Open-heart surgery within the previous 4 weeks
- Myocardial infarction or stroke within the preceding 4 weeks
- Poor anticipated 2-year survival as a result of a noncardiac condition.

Patient characteristics. The average age of the patients was 66 years, and approximately 23% were 75 years or older. More than 30% were women, with considerably fewer women in the CHARM-Added trial and considerably more in the CHARM-Preserved trial. Approximately 90% of patients were of European ethnic origin, and 4.3% were black. More than half of all patients had advanced heart failure (NYHA functional class III or IV). Over one quarter of the patients had diabetes.

At baseline, more than half the patients were on beta-blockers, approximately 60% were on aspirin or other antiplatelet therapy, and about 40% were on lipid-lowering therapy.

The number of patients in each arm is outlined in FIGURE 2.

Protocol. Patients were randomized to receive either placebo or candesartan, started at either 4 or 8 mg daily and titrated upward every 2 weeks to a target dose of 32 mg daily. Patients were seen every 4 months and were followed for at least 2 years. In the North American sites, patients underwent laboratory testing for safety monitoring at baseline, after 6 weeks, after 14 months, and then every year. All patients were allowed to be treated with standard therapy, ie, beta-blockers, diuretics, digoxin, spironolactone, and, in the CHARM-Added and CHARM-Preserved trials, ACE inhibitors.

TABLE 2

CHARM trial data: Benefit of candesartan in heart failure

ARM	NUMBER OF PATIENTS	RELATIVE RISK IN CANDESARTAN GROUP*			
		UNADJUSTED	*P*	ADJUSTED	*P*
CHARM-Added[1]	2,548	0.85	.011	0.85	.010
CHARM-Alternative[2]	2,028	0.77	.0004	0.70	.0001
CHARM-Preserved[3]	3,023	0.89	.118	0.86	.051
CHARM-Overall[4]	7,599	0.91	.055	0.90	.032

*Relative risk of the primary outcome (composite of cardiovascular death and heart failure hospital admission for the component trials and all-cause mortality in the overall program)

Outcomes measured. In the overall CHARM program, the primary outcome was all-cause mortality. For each of the three component trials, the primary outcome was the composite of cardiovascular death or hospital admission for an exacerbation of heart failure. Secondary outcomes included a composite of cardiovascular death, heart failure hospitalization, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, all-cause mortality, and onset of diabetes mellitus.

Statistical analysis was performed separately for the overall program and each component trial, as the sample size and statistical power of each trial differed. Data from the CHARM-Alternative and CHARM-Added trials were combined by prespecified analysis, as these groups of patients represented those in a "typical" heart failure trial: ie, all had a left ventricular ejection fraction of 40% or less.

Overall findings: ARB is beneficial

Over a median follow-up of 37.7 months, 23% of patients in the three candesartan groups died, vs 25% in the placebo groups, for an unadjusted hazard ratio of 0.91 (P = .055) or an adjusted (for predetermined covariates) hazard ratio of 0.90 (P = .032) (TABLE 2).

The incidence of cardiovascular death in the candesartan groups was 18%, vs 20% in the placebo groups, for a hazard ratio of 0.88 (P = .012). Twenty percent of patients in the candesartan groups needed to be hospitalized for heart failure, vs 24% in the placebo group (P < .0001).

CHARM-Alternative results: ARB a good alternative to an ACE inhibitor

In the patients known to be intolerant of ACE inhibitors and who therefore were not receiving one concurrently, the primary outcome, cardiovascular death or hospitalization for heart failure, occurred in 33% of those in the candesartan group and in 40% of those in the placebo group, for an unadjusted hazard ratio of 0.77 (P = .0004). Differences in the primary end point were seen across all prespecified subgroups.

All of the secondary outcomes occurred less frequently in the candesartan group than in the placebo group. There also was a 20% relative risk reduction in all-cause mortality or heart failure hospital admission among the candesartan patients (P = .001).

No significant differences were noted for the percentages of patients in each treatment group who stopped taking the study drug. Although hypotension, hyperkalemia, and renal insufficiency occurred more often in the candesartan group than in the placebo group, cough—the most common adverse effect of ACE inhibitors—occurred in only two patients randomized to candesartan.

Angioedema, perhaps the most feared adverse effect of ACE inhibitors, was reported as the cause of ACE intolerance in 39 patients who were subsequently randomized to candesartan. One of these 39 patients had the study drug discontinued due to angioedema but was not hospitalized for it.

Only 2 patients on candesartan developed cough

The authors concluded that candesartan not only was well tolerated even in patients with the most worrisome adverse effects of ACE inhibitors, but also could significantly reduce cardiovascular mortality and morbidity in patients who previously tried an ACE inhibitor and could not tolerate it.

CHARM-Added results: Combination therapy is beneficial

The CHARM-Added trial studied the use of candesartan added to standard therapy with ACE inhibitors with or without baseline treatment with beta-blockers. The median follow-up was 41 months.

The primary outcome of cardiovascular death or heart failure hospitalization occurred in 38% of the candesartan group vs 42% of the placebo group (hazard ratio 0.85, $P = .011$). All secondary outcomes occurred less frequently in patients receiving candesartan than in those receiving placebo. Patients receiving candesartan also experienced a statistically significant decrease in blood pressure, and were at higher risk for increases in potassium and creatinine.

Patients with preserved ejection fraction had fewer hospitalizations with candesartan than placebo

The benefits seen in the primary and secondary end points were consistent with or without baseline treatment with beta-blockers, and with higher or lower doses of ACE inhibitors. Thus, the benefits were unlikely to be due to inadequate ACE inhibition.

CHARM-Preserved results

The median follow-up in the CHARM-Preserved trial, which studied candesartan in patients with a left ventricular ejection fraction greater than 40%, was 36.6 months.

The primary end point occurred in 22% of the candesartan group vs 24% of the placebo group ($P = .118$). In particular, there was no difference in the cardiovascular death component of the primary end point, perhaps because cardiovascular mortality was low in this subgroup. (The annual cardiovascular mortality rate was 3.7%, compared with over 8% in patients with an ejection fraction of 40% or less.)

There were, however, significantly fewer hospital admissions for heart failure in the patients randomized to candesartan, and 40% fewer new cases of diabetes ($P = .005$). On the other hand, more patients in the candesartan group developed hypotension, hyperkalemia, or renal insufficiency.

IMPLICATIONS OF THE CHARM TRIAL

The CHARM trial was important for several reasons. The patient population was large, geographically diverse, and predominantly elderly—a group in whom heart failure is one of the most rapidly increasing diagnoses and one of the most common reasons for hospitalization. Also of note is that many women were included. Since the study population was very similar to patients whom clinicians see in everyday practice, the results are readily applicable to patients seen in the community.

- **An ARB can reduce morbidity and mortality in heart failure.** CHARM was the only clinical trial of ARBs to date to show a consistent benefit in terms of lower morbidity and mortality rates in patients with heart failure and decreased left ventricular systolic function. The findings also place candesartan among the ranks of ACE inhibitors, beta-blockers, and spironolactone—drugs shown previously to alter the natural history of heart failure progression and to decrease mortality in patients with heart failure and left ventricular systolic dysfunction.
- **An ARB can be used instead of an ACE inhibitor.** Before CHARM, although ARBs were considered appropriate alternatives in patients who could not tolerate ACE inhibitors, it was not clear whether they provided similar benefit. The 23% relative risk reduction in the primary end point with candesartan in the CHARM-Alternative trial compares favorably with the 26% relative risk reduction in cardiovascular death or heart failure hospitalization observed with enalapril in the Studies of Left Ventricular Dysfunction.[22]

  In addition, the low adverse effect profile with candesartan strongly reassures the clinician that patients who cannot tolerate ACE inhibitors will be likely to remain on an ARB.
- **Triple therapy appears beneficial.** In CHARM-Added, treatment with candesartan in patients already on ACE inhibitors and beta-blockers reduced the primary end point and all of the secondary end points. These

findings indicate that further blockade of the renin-angiotensin-aldosterone system provides added benefit in heart failure, and contrast with the findings from Val-HeFT, which suggested that the addition of an ARB to an ACE inhibitor and beta-blocker might be harmful.

This apparent discrepancy might have two explanations. First, the adverse outcome associated with so-called "triple therapy" in Val-HeFT was seen only upon subgroup analysis, while CHARM-Added was a separate clinical trial prospectively designed to answer this question. Second, candesartan may have pharmacologic properties different from those of valsartan that allow it to be added safely and with benefit to an ACE inhibitor and a beta-blocker in patients with heart failure.

- **An ARB might be beneficial even if the ejection fraction is normal.** CHARM-Preserved failed to show a mortality benefit with candesartan in patients with heart failure and a left ventricular ejection fraction greater than 40%, possibly due to the low mortality rate observed in these patients. However, the candesartan group had significantly fewer heart failure hospitalizations.

An ARB might therefore be cost-effective in this situation, considering the large number of hospitalizations for heart failure every year. Also, the remarkable decrease in the development of new cases of diabetes mellitus (a prospectively determined secondary end point) gives strong weight to the argument that candesartan is beneficial in patients with heart failure and preserved left ventricular ejection fraction.

- **A remaining question** is whether the findings from CHARM are applicable to black patients with heart failure. Only 4.6% of patients in CHARM were black. Heart failure is more prevalent and progresses more rapidly in blacks than in whites. Whether the findings of the CHARM trials can be extended to blacks with heart failure may require further studies with candesartan in this specific population.

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