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ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO

Scientific Update™

Comprehensive Management of Patients with Low and Preserved Ejection Fraction The Candesartan in Heart failure – Assessment of Reduction in Mortality and morbidity (CHARM) Study

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The prognosis of patients with congestive heart failure (CHF) has improved over the last decade due, in part, to the application of results from several landmark clinical trials in CHF. However, almost all of these clinical trials have focused on patients with reduced left ventricular ejection fraction (LVEF). In clinical practice, a substantial number of patients with CHF have preserved LVEF, for which there is no known effective evidence-based therapy. Moreover, a considerable number of patients do not tolerate angiotensin-converting enzyme (ACE) inhibitors, the cornerstone of treatment for CHF with reduced LVEF. The angiotensin II receptor blockers (ARBs) provide a pharmacologically distinct mechanism to inhibit the renin-angiotensin-aldosterone system (RAAS) and there is a strong theoretical basis for combining ARBs and ACE inhibitors in patients with CHF due to reduced LVEF. The Candesartan in Heart failure – Assessment of Reduction in Mortality and morbidity (CHARM) program is the largest study ever designed to assess the use of an ARB – candesartan – in a broad spectrum of patients with CHF, including those with reduced and preserved LVEF and those intolerant of ACE inhibitors. In this *Cardiology Scientific Update* the late-breaking results of CHARM and their clinical implications will be discussed.

With the aging of the population, both the prevalence and incidence of CHF are increasing in Canada and abroad, and further increases are predicted in the next decade.[1-4] As a result, the high mortality and significant morbidity of CHF have become major public health issues,[1,2,4,5] with the management of patients with CHF accounting for a substantial portion of healthcare expenditures.[6-8] Fortunately, for the first time, there are increasing data suggesting that the mortality of patients with CHF has improved over the last few decades.[9,10] This improvement is due, to a large extent, to the application of results from several landmark trials, most involving the use of ACE inhibitors and ß-blockers.[11-16] However, despite these advances, the mortality and morbidity of patients with CHF remain high.

The robust clinical trial experience currently places ACE inhibitors as the cornerstone of management of patients with CHF and reduced LVEF. However, many patients do not tolerate ACE inhibitors because of side effects, mainly cough.[17] Furthermore, it is now recognized that a large number of patients with CHF have preserved LV systolic function.[18-20] Patients with CHF and preserved EF tend to be older and, like patients with systolic CHF, have a high mortality and morbidity. However, unlike patients with impaired LV systolic function, no effective outcome-modifying therapy has been identified in these patients.

The search for a more efficacious and better-tolerated treatment for patients with CHF has followed several approaches. One approach involves the use of ARBs.[21] Inhibition of the type-1 angiotensin II (AT_1) receptor provides a pharmacologically distinct mechanism to inhibit the RAAS, and indeed, confers the theoretical advantage of more complete blockade of the action of angiotensin II. The existence of non-ACE-dependent pathways implies that angiotensin II can be generated from angiotensin I, even in the presence of ACE inhibitors.[22,23] Additional theoretical advantages that may be conferred by ARBs include the benefits of "unopposed" stimulation of type-2 angiotensin II (AT_2) receptors that are believed to produce effects opposite to those from AT_1 receptor stimulation.[24] On the other hand, ARBs do not enhance bradykinin to the same extent as ACE inhibitors, an effect that is

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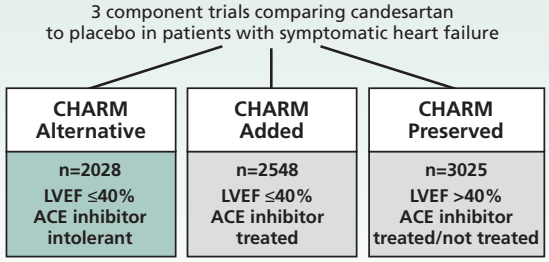
Figure 1: CHARM Programme Design



Primary outcome for each component trial:
Cardiovascular death or heart failure hospitalization

believed to contribute to the beneficial effects of ACE inhibitors,[25,26] but may also mediate some of their side effects.

Until recently, only 2 large, prospective, randomized, controlled outcome trials of ARBs in CHF had been reported, namely the Evaluation of Losartan In the Elderly (ELITE II)[27] and the Valsartan in Heart Failure (Val-HeFT) trial.[28] Although both provided very important information regarding the use of ARBs in CHF, many questions remained unanswered. For example, in ELITE II, the ARB, losartan, was found to be no better than the ACE inhibitor, captopril.[27] In Val-HeFT, the addition of the ARB, valsartan, to background therapy, including ACE inhibitors, reduced combined mortality and CHF hospitalizations. The reduction of this combined primary endpoint was accounted for mostly by a reduction in heart failure hospitalization. However, *post hoc* subgroup analysis suggested a possible adverse interaction between ACE inhibitors, ß-blockers, and ARBs.[28]

The Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) study was therefore conceived as a program to provide definite and quantitative clinical information regarding the role of the ARB, candesartan cilexitil, in the management of a broad spectrum of patients with CHF. Candesartan is a long-acting ARB with sustained receptor binding.[29-31] The rationale and design of CHARM has been published previously[32] and was based on finding answers to 3 important questions in CHF:

- Does the addition of an ARB to ACE inhibitor therapy confer more effective protection than ACE inhibitor alone in patients with CHF and systolic dysfunction?
- Do ARBs have a greater protective effect than placebo in patients with systolic CHF who are intolerant to ACE inhibitors?
- Does an ARB protect CHF patients with preserved LV systolic function?

Study design

To test whether candesartan would reduce cardiovascular (CV) death or hospitalization for CHF, the CHARM program prospectively identified 3 distinct groups: CHARM Alternative; CHARM-Added, and CHARM-Preserved (Figure 1). Importantly, each of the 3 studies had adequate power to detect an impact of candesartan on the primary outcome of CV death and CHF hospitalization. The common inclusion criteria for the CHARM program were: age ≥18 years and New York Heart Association (NYHA) class II to IV CHF for ≥4 weeks. In all 3 studies, the initial dose was 4 or 8 mg of candesartan once daily or matching placebo. Study drug dose was doubled every 2 weeks to the target dose of 32 mg once daily (average dose was 24 mg). Randomization to each of the studies was dependent on LVEF and tolerance to ACE inhibitors. These study-specific inclusion criteria were:

CHARM-Alternative

- LVEF ≤40% within 6 months
- not on ACE inhibitors because of prior intolerance defined as the decision to discontinue therapy based on an ACE inhibitor-related adverse event with the specific cause classified
- symptomatic HF (NYHA class II-IV)

CHARM-Added

- LVEF ≤40% within 6 months
- NYHA class III or IV symptoms or, if in NYHA class II, must have been hospitalized for a cardiac reason within 6 months
- on a constant dose of an ACE inhibitor for ≥30 days

CHARM-Preserved

- LVEF >40%
- history of prior hospitalization for a cardiac reason
- statement by investigators that patient's signs and symptoms were primarily due to CHF
- NYHA class II-IV of at least 4 weeks duration

Initially, in CHARM-Preserved, the use of ACE inhibitors was one of the exclusion criteria. After the results of the Heart Outcome Prevention of Events (HOPE) study,[33] however, the protocol was amended to allow concurrent treatment with an ACE inhibitor if the patient fulfilled the HOPE criteria. The overall CHARM program was also designed with adequate power to detect whether candesartan would reduce the primary endpoint of total mortality in the overall population of patients with symptomatic CHF using pooled analysis of the 3 trials. The key secondary endpoints were:[32]

- CV mortality, CHF hospitalization, or nonfatal myocardial infarction (MI)
- CV mortality, CHF hospitalization, nonfatal MI, or stroke
- CV mortality, CHF hospitalization, nonfatal MI, stroke, or coronary revascularization procedures
- all-cause mortality and all-cause hospitalization
- each of the individual components of the above composite endpoints.

Other pre-specified outcomes included the development of diabetes and investigator-reported outcomes. The CHARM program screened 13,202 eligible patients and subsequently randomized 7601 patients from 618 centres in 26 countries.

Results

The results of each of the component studies, as well as the overall CHARM program, were published online on September 1, 2003.[34-37] Between March 1999 and March 2001, 7601 patients were randomized. The median follow-up interval for the entire program was 37.7 months. The baseline demographics of the CHARM program were published previously[38] and selected baseline characteristic are shown in Table 1. Compared to the other 2 components, patients in CHARM-Preserved were older, more often female, and more often had hypertension. Conversely, the frequency of prior MI was lower. Diuretics were the most commonly prescribed agents in all 3 trials. ß-blockers were used in over 50% of the patients, whereas aldosterone receptor antagonists were used in about 20% of the patients with systolic dysfunction. Lipid-lowering therapy and aspirin were also used in a substantial number of patients.

Table 1: Baseline characteristics of patients in the CHARM program

	Alternative (n=2028)	Added (n=2548)	Preserved (n=3023)	All (n=7599)
Mean age (yr)	67	64	67	66
Female (%)	32	21	40	32
SBP/DBP (mm Hg)	130/77	125/75	136/78	131/77
LVEF	0.30	0.28	0.54	0.39
NYHA class II (%)	48	24	61	45
III (%)	49	73	38	52
IV (%)	4	3	2	3
History of MI (%)	62	56	44	53
Hypertension (%)	50	48	64	55
Diabetes (%)	27	30	28	28
Atrial fibrillation (%)	25	26	29	27
Use of ACE inhibitors (%)	0	100	19	41
ß-blockers (%)	55	56	56	55
Spironolactone (%)	24	17	12	17
Digoxin (%)	46	58	22	43
Diuretics (%)	86	90	75	84
ASA (%)	58	52	58	56
Lipid-lowering (%)	41	41	42	41

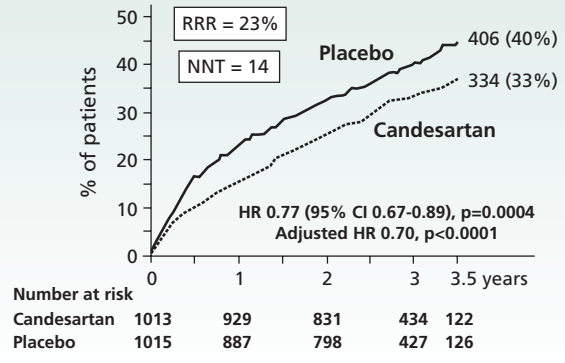
SBP/DBP = systolic/diastolic blood pressure; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association

CHARM-Alternative

In this study, 2028 patients with CHF and reduced LVEF who were intolerant to ACE inhibitors were randomly assigned to candesartan (n=1013) or placebo (n=1015). Two patients in the candesartan group and 1 patient in the placebo group were lost to follow-up. The stated reasons for ACE inhibitor intolerance were cough in 70% and 74%, renal dysfunction in 13% and 10%, and angioedema/anaphylaxis in 4% and 4% of the candesartan and placebo groups, respectively. The median follow-up was 33.7 months.

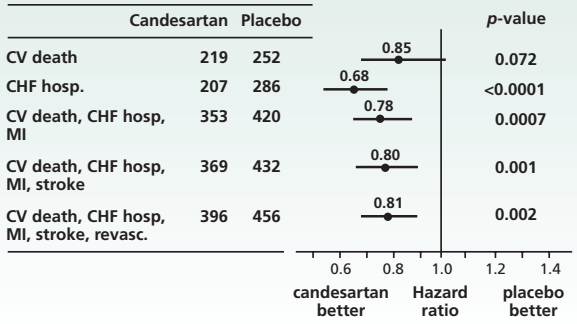
Data for the primary outcome – CV death and CHF hospitalization – are shown in Figure 2. Candesartan reduced this combined endpoint by 23%. This reduction was more significant after pre-planned covariate adjustment for prespecified baseline variables that are known to affect prognosis. The survival curves of the

Figure 2: CHARM-Alternative: Primary outcome – CV death or CHF hospitalization



RRR = relative risk reduction;
NNT = number needed to treat to prevent one event

Figure 3: CHARM-Alternative: Secondary outcomes



2 groups separated early (3-6 months) after randomization and remained virtually parallel during the entire follow-up. Data for the secondary endpoints are shown in Figure 3. Candesartan significantly reduced all of the composite endpoints, as well as CHF hospitalization. There were 265 deaths from any cause in the candesartan group, and 296 in the placebo group (unadjusted hazard ratio 0.87 [0.74–1.03], p=0.11; covariate adjusted 0.83 [0.70–0.99], p=0.033). The investigator-reported number of patients admitted to hospital for CHF and the total number of hospital admissions for CHF were significantly lower in the candesartan group. The effect of candesartan on CV death or CHF hospitalization was generally consistent across pre-specified subgroups.

Angioedema occurred in 3 candesartan patients and in none of the placebo patients. None of the 3 cases was deemed life-threatening and 2 cases continued on candesartan without recurrence. All 3 cases occurred in patients who had a history of ACE inhibitor intolerance because of angioedema. Thus, angioedema that required the discontinuation of candesartan occurred in only 1/39 patients with a history of angioedema on ACE inhibitors.

CHARM-Added

In this component, 2548 patients were randomized to candesartan (n=1276) or placebo (n=1272). Three patients in the candesartan group and 1 patient in the placebo group were lost to follow-up. The median duration of follow-up was 41 months. Investigators stated that 96% of patients were receiving an optimum dose of ACE inhibitors, eg, the mean daily dose for enalapril was 16.8 mg in the candesartan group and 17.2 mg in the placebo

Figure 4: CHARM Added: Primary outcome – CV death or CHF hospitalization

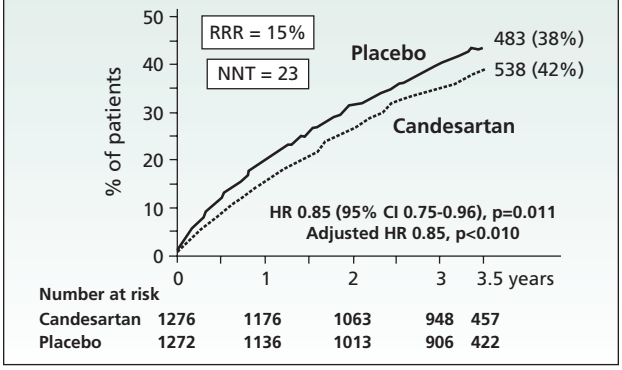
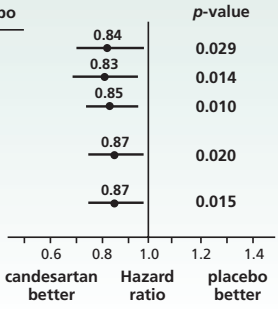


Figure 5: CHARM-Added: Secondary outcomes

	Candesartan	Placebo	*p*-value
CV death	302	347	0.029
CHF hosp.	309	356	0.014
CV death, CHF hosp, MI	495	550	0.010
CV death, CHF hosp, MI, stroke	512	559	0.020
CV death, CHF hosp, MI, stroke, revasc.	548	596	0.015



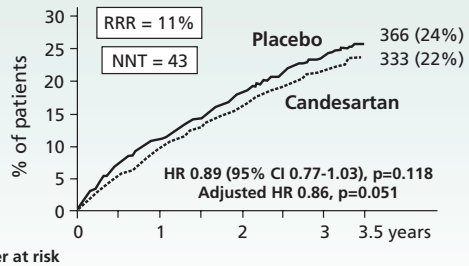
group. Importantly, 55% of patients were treated with ß-blockers at baseline and 17% with spironolactone. By the end of the study, 64% and 68% of patients in the candesartan and placebo group, respectively, were taking ß-blockers.

Data for the primary outcome – CV death and CHF hospitalization – are shown in Figure 4. Candesartan reduced this combined endpoint by 15%. Secondary outcomes were all significantly reduced and are shown in Figure 5. Investigator-reported number of patients hospitalized for CHF and the number of CHF hospitalizations was significantly reduced. All-cause mortality was 30% in the candesartan group and 32% in the placebo group, with a trend for reduction by candesartan (unadjusted hazard ratio 0.89 [0.77-1.02], p = 0.086; adjusted p = 0.105). Candesartan reduced the risk of CV death or CHF admission in all pre-specified subgroups. In particular, candesartan reduced the risk of primary endpoint in patients, regardless of whether or not they were taking ß-blockers or the recommended dose of ACE inhibitor (defined as captopril 150 mg, enalapril 20 mg, lisinopril 20 mg or perindopril 4 mg, all daily). The study drugs were well-tolerated. Over 75% of patients were still taking the study medication at the end of study. Although adverse effects such as hyperkalemia and increased creatinine were more frequent in the candesartan group, the overall incidence for these adverse effects was still exceedingly low.

CHARM-Preserved

In this study, 3023 patients with NYHA class II-IV CHF and EF >40% were randomized to candesartan (n=1514) or

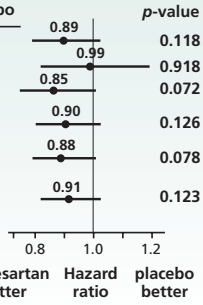
Figure 6: CHARM-Preserved: Primary outcome – CV death or CHF hospitalization



Number at risk					
Candesartan	1514	1458	1377	833	182
Placebo	1509	1441	1359	824	195

Figure 7: CHARM-Preserved: Primary and secondary outcomes

	Candesartan	Placebo	*p*-value	Covariate adjusted *p*-value
CV death, CHF hosp.	333	366	0.118	0.051
– CV death	170	170	0.918	0.635
– CHF hosp.	241	276	0.072	0.047
CV death, CHF hosp, MI	365	399	0.126	0.051
CV death, CHF hosp, MI, stroke	388	429	0.078	0.037
CV death, CHF hosp, MI, stroke, revasc.	460	497	0.123	0.13



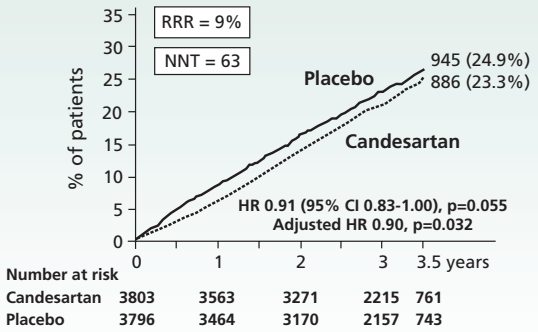
placebo (n=1509) (2 patients had no data post-randomization). Two patients in the candesartan group and 1 patient in the placebo group were lost to follow up. Median follow-up duration was 36.6 months. At baseline, 20% and 19% of patients in the candesartan and placebo group, respectively, were taking ACE inhibitors.

Data on the primary outcome of CV death and CHF hospitalization are shown in Figure 6. The annualized event rate was 8.1% and 9.1% in the candesartan and placebo groups, respectively. The relative risk reduction of 11% was not significant. After adjustment for baseline variables, the relative risk reduction was 14% with borderline statistical significance. Data for the secondary outcomes are shown in Figure 7 and generally yielded results similar to those for the primary outcome. The number of patients admitted to hospital for CHF once, more than once, and the total number of CHF hospitalizations was significantly lower in the candesartan group. One additional pre-specified analysis was the development of diabetes. Forty percent (40%) fewer patients were diagnosed with new-onset diabetes in the candesartan group than in the placebo group (hazard ratio 0.60, [0.41, 0.86], p=0.005).

CHARM – Overall program

In the entire program, 7601 patients were randomized, 2 patients had no data, 3803 were assigned to candesartan (of which 7 were lost to follow-up), and 3796 were assigned to placebo (of which 3 were lost to follow-up). In the total CHARM program (including all 3 trials), there was only a total of 10 of 7601 patients lost to follow-up, which is exceedingly low. The pre-defined primary outcome of the overall program was all-cause mortality. Results are shown in Figure 8; 886 (23%) in the candesartan group and 945 (25%) in placebo group died, (hazard ratio 0.91 [0.83-1], p=0.055, adjusted hazard ratio 0.90 [0.82-0.99], p=0.032). The annual mortality rates were 8.1% and 8.8% in the candesartan and placebo groups, respectively. The reduction in mortality was driven almost exclusively by a reduction in CV deaths (hazard ratio 0.88 [0.79-0.97], p=0.012, adjusted 0.87 [0.78-0.96], p=0.006). Combined CV death and CHF hospitalization in the entire program was reduced by 16%, p<0.0001 (Figure 9). There were also significantly less investigator-reported hospital admissions for CHF. For the entire program, the cases for newly diagnosed diabetes were significantly reduced (hazard ratio 0.78 [0.64-0.96], p=0.02).

Figure 8: CHARM-Overall: Primary outcome – All-cause mortality



Discussion

CHARM-Alternative

Based on the Study of Patients Intolerant of Converting Enzyme Inhibitors (SPICE) Registry (total patients = 9580),[17] in patients with CHF deemed eligible to receive ACE inhibitor therapy, 20% do not receive therapy and this is due to intolerance to ACE inhibitors in 9% (862) of this total. The CHARM-Alternative program was designed specifically to address the needs of these patients and is, therefore, the only placebo-controlled trial of an ARB in patients with CHF with reported ACE inhibitor intolerance. Interestingly, the 23% relative risk reduction in CV mortality and CHF hospitalization was strikingly similar to the 26% reduction reported with the ACE inhibitor-placebo comparison in the Study of Left Ventricular Dysfunction (SOLVD) treatment trial.[16] The current findings are also consistent with the *post hoc* analysis of a subset of 366 patients who were not on ACE inhibitors in Val-HeFT that revealed a relatively large relative risk reduction with valsartan in the combined endpoint of mortality and morbidity.[39] However, the Val-HeFT data should be interpreted in light of the fact that it is unclear why these 366 patients were not on ACE inhibitors, and with the recognition of the limitations of *post hoc* subset analysis. Nevertheless, the totality of data now firmly supports the practice of substituting an ARB for an ACE inhibitor in patients with CHF and systolic dysfunction who are proven intolerant to ACE inhibitors. An ARB like candesartan appears to be very well tolerated in these patients.

Figure 9: CHARM-Overall: Secondary composite outcomes

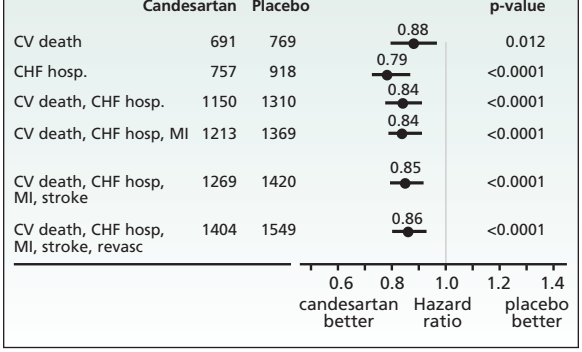


Table 2: Comparison of the patient characteristics and selected outcomes of CHARM-Added and Val-HeFT[28]

	Val-HeFT (n=5010)	CHARM Added (n=2548)
Recruitment period	4/97-3/99	3/99-11/99
Median follow-up	23 months	41 months
NYHA II (%)	62	25
NYHA III (%)	36	73
NYHA IV (%)	2	3
SBP/DBP (mm Hg)	124/76	130/77
LV ejection fraction	0.27	0.28
ACE inhibitors (%)	93	100
Diuretics (%)	86	90
ß-blockers (%)	35	55
Spironolactone (%)	2	17
Digoxin (%)	35	55
Mean dose of ACE inhibitors (mg/d)		
Enalapril	17	17
Captopril	80	83
All-cause mortality*	979 (20%)	789 (31%)
CV mortality*	846 (17%)	641 (25%)

*Data are from over the entire study period. CV, cardiovascular

CHARM-Added

Candesartan added to ACE inhibitors is effective and provides an additional reduction in CV mortality and CHF hospitalization of 15%. This beneficial effect was seen in all pre-specified subgroups, regardless of whether or not patients were on ß-blockade therapy. Val-HeFT, which also assessed the combined use of valsartan and ACE inhibitors in patients with reduced LVEF, reported a 13.2% reduction in combined morbidity and mortality, driven by a 27.5% reduction in CHF hospitalization.[28] The results of CHARM-Added and Val-HeFT were therefore similar in this regard. However, subgroup analysis in Val-HeFT has raised concerns regarding the use of this approach in patients on concomitant ß-blockade therapy.[28,40] It is, therefore, useful and appropriate to compare the characteristics and outcomes of patients in Val-HeFT and the CHARM-Added. As shown in Table 2, most of the baseline characteristics were comparable in both studies (although CHARM-Added had more patients with NYHA III symptoms). An important difference between the 2 studies was the use of concomitant medications at baseline. The percent of patients on ß-blockers and spironolactone was greater in CHARM-Added. Although the mortality of patients in CHARM-Added appeared to be higher than in Val-HeFT, the follow-up was also longer in CHARM.

In summary, the totality of data now suggests that adding an ARB such as candesartan to optimal background therapy of ACE inhibitors and ß-blockers confers additional benefit on CV death and CHF hospitalization in patients with CHF and reduced EF. There is no adverse interaction with ß-blockade therapy. Adverse effects such as hyperkalemia and renal dysfunction, although infrequent, will still occur more frequently in patients on combination therapy, mandating caution in monitoring these parameters.

CHARM-Preserved

While the primary endpoint of CHARM-Preserved was not statistically significant, this result does not exclude the possibility that clinically meaningful benefits might have been demonstrated if the trial had involved more patients and if the follow-up had been longer. Indeed, the point estimate favoured candesartan in almost all of the secondary endpoints, with the reduction in CHF hospitalization being significant after adjustment. CHARM-Preserved offers the first data in this patient population and provides supportive evidence that the ARB candesartan can prevent CHF hospitalizations and the development of diabetes mellitus. The ongoing I-PRESERVE study should provide additional data regarding the treatment of heart failure with preserved systolic function.

CHARM overall program

In terms of absolute reduction, the CHARM program demonstrated that in patients with systolic CHF, treating 23 patients with candesartan and ACE inhibitor for 3 years would prevent one CV death or admission for CHF. In patients with systolic CHF and intolerance to ACE inhibitors, this number to treat is 14. In a broad spectrum of patients with CHF, treating 63 patients will prevent 1 death and treating 71 patients will prevent 1 case of new diabetes. Given these data, there is now relatively strong evidence to support the use of an ARB such as candesartan in optimally-treated patients with CHF and reduced LV systolic function.

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