"Lots of CHARM"

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This *Heartbeat* will review results of the two largest and most important current clinical trials. First will be the CHARM trial, which shows benefit with an angiotensin receptor blocker (ARB)—candesartan (Atacand, AstraZeneca)—in a broad range of heart failure (HF) patients. As the large amount of data is reviewed, the overall response from the experts has been generally positive, but there is some disagreement.

Second, lest the allure of CHARM makes us forget about the wonderful benefits of ACE inhibitors, we will review the results of EUROPA.

CHARM—**C**andesartan in
Heart failure—
Assessment of
Reduction in
Mortality & morbidity

The mission of the trial was to cover the entire spectrum of HF patients—those intolerant to ACE inhibitors or on ACE inhibitors with left ventricular (LV) systolic dysfunction and those with symptomatic HF and normal (preserved) LV function. The CHARM program consisted of 4 subsets—3 component trials, each comparing candesartan with placebo in a distinct population of patients with symptomatic HF and the overall program (total):

1. CHARM-Alternative: patients with left ventricular ejection fraction (LVEF) </= 40% and intolerant of ACE inhibitors; [1]

2. CHARM-Added: patients with LVEF </= 40% who tolerated and were treated with whichever ACE inhibitor the patient's physician chose; [2]

3. CHARM-Preserved: patients with LVEF > 40%, who may or may not have received an ACE inhibitor.[3]

4. CHARM-Total: the results assessed over the entire trial enrollment.[4]

Patients were randomized in a double-blind manner to receive either candesartan or placebo. The initial dose of candesartan was 4 mg or 8 mg once daily, doubled up to a maximum dose of 32 mg daily, based on tolerability. A very important part of the trial design was that patients were being treated with current state-of-the art heart failure therapy, including beta-blockers, diuretics, digitalis, spironolactone, and/or ACE inhibitors, at dosages close to current recommended levels.

The overall (total) results show that the long-acting angiotensin II type-1 receptor blocker (ARB) candesartan reduces both cardiovascular (CV) mortality and hospital admissions for HF in a broad spectrum of patients. Most notably, these benefits were achieved on top of "best treatment" with other effective concomitant therapies as noted above. New-onset diabetes mellitus (DM) was reduced by 28% in the candesartan-treated patients.

Table 1. CHARM Program Results

End point	Alternative trial (n=2028)	Added trial (n=2548)	Preserved trial (n=3025)
All-cause mortality	**Trend to benefit**	**Trend to benefit**	**No effect**
CV death/HF hospitalization	**Significant benefit (P < 0.004**	**Significant benefit P = 0.011**	**Trend to Benefit P = 0.118**
CV death benefit	**Significant benefit P = 0.072**	**Significant benefit P = 0.029**	**No effect**
HF hospitalization	**Significant benefit P < 0.001**	**Significant benefit P = 0.014**	**Trend to benefit P < 0.072**

CHARM-Alternative: Candesartan reduced CV mortality and hospitalization by 23% and was well tolerated. There was only one case of angioedema associated with treatment in the 39 patients who were intolerant to ACE inhibitors because of angioedema. All the experts agree that this trial firmly establishes that patients intolerant to ACE inhibitors should be

given an ARB. This was the probably the most important part of the trial. Using ARBs in ACE intolerant patients results in benefits equivalent to those achieved for those on ACE inhibitors. Of all parts of the trial, it showed the biggest benefit, lowest dose needed to treat and the most difference between placebo and candesartan.

CHARM-Added: The results suggest that adding candesartan at the relatively high mean dose of 24 mg on top of good background therapy with a beta-blocker and an ACE inhibitor in NYHA heart failure class II-III patients with reduced LV ejection fraction (EF) will reduce both cardiovascular mortality and HF by 17%. This data suggests that adding an ARB to our stair-step incremental treatment approach to HF can be done safely—with some benefit. Contrary to a signal of harm seen in the Val-HeFT[5], this study confirms the safety of using an ACE inhibitor, beta-blocker, and an ARB together. However, only a little over 15% of these patients were on an aldosterone blocker.

CHARM- Preserved: There was a trend toward a reduction in CV death and hospitalization of 9% which was not statistically significant. Most of this reduction was in hospitalizations. There was also a 40% reduction in new-onset DM.

This study also provides some evidence for treatment of HF with normal or near normal LV function (LVEF > 45%) — a population for which we essentially have no evidence based treatment recommendations. Most experts agreed that these results represent a positive step showing a substantial reduction in hospitalizations when candesartan is used. In patients with a non-dilated ventricle and relatively preserved LV function candesartan should be considered for treatment. There is nothing to lose and there is no alternative.

CHARMED again….Is it the RAAS?

The results of CHARM further emphasize the importance of blocking the deleterious effects of the rennin-angiotensin aldosterone system (RAAS) on the CV system. It is no coincidence that the use of *beta-blockers*, which are rennin inhibitors and block the conversion of angiotensinogen to angiotensin I; *ACE inhibitors*, which block the conversion of angiotensin I to angiotensin II; *ARBs* which block the effects of angiotensin II at the receptor sites; and *aldosterone blockers*, have all been associated with improved outcomes in large CV clinical trials. Three of these four medications, excluding aldosterone blockers, have also been shown to slow renal disease progression and/or prevent diabetes.

What do these results mean for the practicing physician?

1. Results of the *alternative* trial were the point of most general agreement among HF specialists—providing evidence on which to base the use of an ARB among patients unable to tolerate an ACE inhibitor. Efficacy is comparable.
2. Most HF experts are going to use an ARB in a HF patient with *preserved* LV function because there is no alternative, and there appear to be some potential benefits—saving money (decreased hospitalizations) and preventing the development of DM. There is nothing to lose by trying candesartan. This is my intention too.
3. The most controversial part of this program of trials is CHARM-*added*. Interestingly, this is not because of the results. Most would agree they were reasonably convincing. Adding candesartan to other drugs for HF is probably beneficial. Physicians simply have difficulty agreeing on whether they must now consider adding yet another drug to the treatment of patients who are already taking–and sometimes paying full price for—up to 10 drugs for HF and/or other comorbidities. First it was adding ACE inhibitors to diuretics and digoxin. Then came adding beta-blockers, a good illustration of positive results met with resistance. Incremental benefits (decreased morbidity and mortality) have been shown with each addition and physicians are gradually using all of these agents. Now, the new CHARM data show that ARBs have an added further incremental benefit on top of ACE inhibitors and beta-blockers.

Is “triple therapy” the answer, and what should the third drug be?

The real controversy centers on whether the next step after ACE inhibitors and beta-blockers should be an ARB or an aldosterone blocker. Improving outcome in CHF patients with the addition of an aldosterone blocker on top of a beta-blocker and an ACE inhibitor has been proven by two major trials: the

Randomized Aldactone Evaluation Study (RALES)[6], in NYHA class III-IV CHF patients with reduced LVEF; and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)[7], in post-MI CHF patients with reduced LVEF. In both RALES (using the nonspecific aldosterone antagonist spironolactone) and EPHESUS (using the selective aldosterone antagonist eplerenone), all-cause mortality was highly statistically significantly reduced, which stands in contrast to the less significant results in the CHARM-*Added* trial subset. Retrospective analysis of EPHESUS showed a 33% reduction of sudden death in addition to the 21% reduction in total mortality.

Based on the more convincing results of the RALES and EPHESUS data with respect to mortality and sudden death and a similar safety profile, most expert HF clinicians will have more interest in adding aldosterone blockade as the next incremental step instead of an ARB.

What do these results mean for patients? The overall consistency of the results provides strong support for use of ARBs in the populations of patients enrolled in CHARM. Over 3 years, the treatment effect equates to one death prevented per 63 patients treated, one first hospitalization with HF prevented per 23 patients treated, and one new case of DM prevented per 71 patients treated. ARBs should be prescribed in addition to ACE inhibitors, beta-blockers and an aldosterone blocker on top of digoxin and diuretics in patients with EFs of 40% or less, and as an alternative to ACE inhibitors in patients with ACE intolerance. ***The clinical trials have shown us a stair-step incremental decrease in mortality with each additional drug and as clinicians –to get these improved outcomes—that is what we're going to have to do.*** Use of an ARB should be considered in patients with ejection fractions of more than 40% to reduce the risk of hospitalization with heart failure.

EUROPA - Class effect of ACE inhibitors?

ACE inhibitors have been shown to have the broadest impact of any drug in CVD, reducing the risk of death, MI, stroke, DM, and renal impairment. They benefit patients with HF or LV dysfunction post-MI, peripheral vascular disease, DM, stroke, or transient ischemic attack. The results of the **EUR**opean trial **O**n reduction of cardiac events with **P**erindopril in stable coronary **A**rtery disease (**EUROPA**)[8] were impressive and extend the findings of The **H**eart **O**utcomes **P**revention **E**valuation (**HOPE**)[9] trial to demonstrate the benefits of therapy with ACE inhibitors to nearly all patients with coronary artery disease. In contradistinction to HOPE, which used the ACE inhibitor ramipril (Altace) 5-10 mg, EUROPA used perindopril (Aceon) 8 mg once daily and demonstrated a statistically significantly improved cardiovascular outcome. In an important contrast to the HOPE population, however, the EUROPA population was at a much lower risk and received more optimal concomitant medications, including a lipid-lowering agent (mainly a statin, 69%), a beta-blocker (60%), and a platelet inhibitor (mainly aspirin, 91%).

Perindopril reduced the combined frequency of cardiovascular death, myocardial infarction, and cardiac arrest within 4·2 years by 20% (from 603 patients [9·9%] to 488 patients [8·0%], p=0·0003). There was a non-significant 14% reduction in cardiovascular mortality and a significant 22% reduction in non-fatal myocardial infarction (p=0·001).

Given the consistent results in these 2 important trials, the question arises, "Does it matter which ACE inhibitor we use?" My approach to deciding whether this is a class effect issue is very pragmatic. I feel safe to recommend the use of those drugs that have been subjected to trials, and to use the dose that was tested and proven effective. Both ramipril and perindopril are long-acting ACE inhibitors with high penetration into tissue. We don't know the equivalent dose of other ACE inhibitors (this same premise applies to ARBs). Pharmaceutical companies, which invest heavily in major clinical trials upon which we are increasingly basing our practice, should be rewarded for their efforts. However, when the cost of drugs is an obstacle, use the cheapest of the ACE inhibitors available, rather than none.

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Heartbeats can be found @ www.sjhg.salu.net
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[1] Granger CB, et al, for the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* Sept 6 2003; 362: 772-76.

[2] McMurray JJV, et al, for the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* Sept 6 2003; 362:767-71.

[3] Yusuf S, et al, for the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. *Lancet* Sept 6 2003; 362: 777-81.

[4] Pfeffer MA, et al, for the CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Overall programme. *Lancet* Sept 6 2003; 326:759-66.

[5] Cohn JN, Tognoni G, for the Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor inhibitor valsartan in chronic heart failure. N Engle J Med. 2001; 345:1667-1675.

[6] Pitt B et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* Sept 2 1999; 341: 709-17.

[7] Pitt B et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* April 3 2003; 348: 1309-21

[8] The EURopean Trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomized, double-blind, placebo-controlled, multi-center trial (the EUROPA study). *Lancet* Sept 6 2003; 326:782-788.

[9] Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*. 2000; 342:145-153.