Mortality rates in congestive heart failure (CHF) are still increasing, but leading cardiologists believe there is cause for optimism in the light of recent trial results. For a while, it seemed that triple therapy with digoxin, diuretics and an ACE inhibitor could not be improved upon. But now, studies of β-blockers, calcium antagonists and an aldosterone inhibitor have shown that these agents may provide additional benefit to certain patients. These studies were discussed at the 44th Annual Scientific Sessions of the American College of Cardiology [New Orleans, US; March 1995]. No definitive conclusions have yet been drawn, but the groundwork has been laid for a new era of heart failure research.

The positive findings from 2 studies of the β-blocker carvedilol in patients with CHF could have considerable implications for cardiovascular medicine. Carvedilol's favourable effect on mortality in 2 placebo-controlled trials was so strong that the US Data and Safety Monitoring Board told SmithKline Beecham to terminate the trials prematurely. In the Board's opinion, it was no longer ethical to continue administering placebo in view of the interim mortality data.

About 400 patients with CHF were included in each trial. The patients received either carvedilol or placebo, in addition to standard CHF therapy (ACE inhibitor, digoxin and diuretics). Following trial termination, all patients were offered carvedilol.

First evidence
This is the first trial to provide definitive evidence regarding the ability of β-blockers to reduce mortality in patients with CHF. However, Dr Barry Massie from the University of California, San Francisco, US, warned that this does not mean that every patient [with heart failure] should run out to get a β-blocker'.

A clearer picture of the situation will emerge following presentation of the trial results, which are expected at the American Heart Association conference in November. Meanwhile, carvedilol will be available on a compassionate-use basis for this indication.

New concept
Using β-blockers to treat CHF is a relatively new idea. These agents have been used for many years to treat angina, hypertension and MI, but were considered unsuitable for CHF due to their suppressive negative inotropic effects.

However, certain β-blockers that exhibit vasodilatory properties, e.g. carvedilol, have shown beneficial effects in a number of small, randomised studies. The results of 2 such studies were presented at the ACC conference.

Cardiac Insufficiency Bisoprolol Study (CIBIS) – In this study, bisoprolol significantly improved left-ventricular function compared with placebo (p = 0.001 for fractional shortening) in patients with CHF. The results came from 164 patients randomised to bisoprolol or placebo who were assessed 5 months after study initiation. All patients were receiving a diuretic and vasodilator therapy.

The improvement in left ventricular function was seen regardless of the origin of CHF (i.e. whether ischaemic or nonischaemic) and was not correlated with any baseline patient parameters. However, it was significantly associated with survival beyond the 5-month period (p = 0.01).

The ANZ Research Collaborative Group study – This study showed that treating patients with very mild ischaemic CHF with carvedilol improved ejection fraction and reduced left ventricular chamber dimensions compared with placebo. However, the drug did not affect exercise performance, NYHA class, or mortality. The 415 patients had a baseline ejection fraction < 45% and were randomised to 6 months' treatment with carvedilol 12.5–50 mg/day or placebo.

Carvedilol is under joint development by SmithKline Beecham and Boehringer Mannheim. It is already marketed in several countries (excluding the US) for hypertension and angina.

An application for its use in CHF is expected to be filed by SmithKline Beecham later this year. This is considerably sooner than originally anticipated.
According to a recent, controlled study, amlodipine is a well-tolerated treatment for patients with severe CHF. Previous trials have indicated that calcium antagonists may be poorly tolerated in this indication. This concerned physicians who wished to use these agents to treat concomitant angina or hypertension.

**PRAISE for amlodipine**

But now, results from the Prospective Randomised Amlodipine Survival Evaluation (PRAISE) study can put those concerns to rest, at least for amlodipine. The trial clearly indicated that amlodipine is well tolerated in both ischaemic and nonischaemic heart disease.

In addition, it may provide a survival advantage in patients with nonischaemic CHF. This suggests that the drug's effects depend on the cause of disease.

Surprisingly, in patients with underlying coronary disease, i.e. ischaemic CHF, amlodipine had no effect on mortality or morbidity, compared with placebo. But in patients with nonischaemic dilated cardiomyopathy, amlodipine reduced the risk of death or hospitalisation for a cardiovascular event by 31% (p = 0.034) and mortality risk alone by 45% (p = 0.001), compared with placebo.

The trial involved 1153 patients randomised to amlodipine 5–10 mg/day or placebo. 732 of these patients had ischaemic heart disease, the remainder had nonischaemic dilated cardiomyopathy. CHF in all patients was severe, as indicated by the average ejection fraction value of 21%.

**VHEFT-III results soon**

The third Veterans Affairs Heart Failure Trial (VHEFT-III) is due to be completed this month. This is another trial testing the effects of a calcium antagonist in CHF. In this case, the calcium antagonist felodipine was chosen for:

* its selective vasodilatory effects on the peripheral circulation
* a lower level of negative inotropism compared with some other calcium antagonists.

500 male patients were included in the trial, all of whom had NYHA class II/III CHF. Throughout the trial, a number of physiological variables were closely monitored in all patients. Again, presentation of the results is expected to take place at the American Heart Association meeting in November.

Adding the aldosterone antagonist, spironolactone [Aldactone®] to a combination of ACE inhibitors, diuretics and digoxin is another potential method of further reducing mortality in patients with CHF. The rationale for adding an aldosterone antagonist comes from the CO-operative North Scandinavian ENalapril SUrrial Study (CONSENSUS).

CONSENSUS indicated that blood levels of aldosterone rise in patients with CHF, and are positively correlated with mortality risk. While ACE inhibitors initially reduce aldosterone levels, a number of studies have shown that the decline does not last.

Thus, researchers were keen to test an agent that had a greater antagonistic effect against aldosterone. Spironolactone, the only approved aldosterone antagonist, seemed to be the ideal candidate. Several small trials have shown that the agent has potential as therapy for CHF, when combined with standard drugs.

**RALES now on track**

A larger, controlled study of spironolactone has now been set in motion. Referred to as the Randomised Aldactone® Evaluation Study (RALES), the project was designed to determine whether spironolactone could provide any survival benefit in patients with CHF.

Phase I of the study was a dose-finding/tolerability trial, RALES-003. This has now been completed. In the study, 214 patients with NYHA class II, III or IV CHF were randomised to placebo or spironolactone 12.5, 25, 50 or 75 mg/day. All patients were already receiving an ACE inhibitor and diuretics.

There were no deaths during the drug administration period, and no significant changes in NYHA class in either study group. However, an increased incidence of hyperkalaemia was seen in patients receiving spironolactone ≥ 50 mg/day, compared with placebo recipients. Efficacy was also assessed in the study, by measuring BP and changes in plasma levels of atrial natriuretic factor. All doses were found to be effective compared with placebo, and a dose-response relationship was observed, said Dr Bertram Pitt from the University of Michigan, Ann Arbor, US. Consequently, spironolactone 25 mg/day was chosen

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**Agents to watch in R&D for CHF**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class</th>
<th>Stage of development</th>
<th>Company</th>
<th>Study results from ACC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF-1035</td>
<td>Dopamine receptor antagonist</td>
<td>Phase II</td>
<td>Chiesi</td>
<td>CHF-1035 5, 10 and 15 mg induced significant improvement in haemodynamic parameters in a placebo-controlled trial in 18 pts with CHF</td>
</tr>
<tr>
<td>SDZ-WAG-994</td>
<td>A. adenosine receptor agonist</td>
<td>Clinical</td>
<td>Sandoz</td>
<td>SDZ-WAG-994 1, 2 or 5 mg had significant neurohormonal effects in a placebo-controlled trial of 50 patients with NYHA class I CHF</td>
</tr>
<tr>
<td>Brain natriuretic peptide (BNP)</td>
<td></td>
<td>Phase II</td>
<td>Solis Nova</td>
<td>Short-term IV infusion of exogenous BNP in 10 patients with NYHA class III CHF improved several haemodynamic parameters compared with placebo. Exogenous atrial natriuretic peptide did not exert similar effects.</td>
</tr>
<tr>
<td>MCI-154</td>
<td>Phosphodiesterase inhibitor and calcium sensitizer</td>
<td>Phase II</td>
<td>Mitsubishi Kasei</td>
<td>MCI-154 exerted potent inotropic activity in a dog model of CHF</td>
</tr>
<tr>
<td>OPC-21268</td>
<td>Vasopressin V1 receptor antagonist</td>
<td>Phase II</td>
<td>Otsuka</td>
<td>OPC-21268 prevented chronic ventricular remodelling in a dog model of CHF</td>
</tr>
</tbody>
</table>

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