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Scientific Update™

The Role of Calcium Channel Blockers in Congestive Heart Failure

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Despite apparent decreases in coronary heart disease mortality rates in western countries during the past 20 to 30 years, congestive heart failure remains an important and increasing public health problem. Treatments directed at improving prognosis include ACE inhibitors, beta-blockers, amiodarone, and more recently, calcium channel blockers. There appears to be differential effects of these agents with regard to treatment response, particularly among "ischemic" and "non-ischemic" heart failure patients. These differences are highlighted in the PRAISE study which evaluated the role of amlodipine in patients with moderate to severe chronic heart failure. An exploration of the potential mechanisms of cytoprotection of amlodipine in CHF serve as the basis for the ongoing PRAISE-II study.

Incidence and epidemiology of heart failure

Congestive heart failure (CHF) is a leading cause of disability and death world-wide. Chiefly the result of end stage hypertensive, coronary, and valvular cardiovascular disease, CHF is a growing problem in most affluent countries due to the increasing size of their aged populations and the prolongation of cardiac patients' lives by modern therapy. The Framingham Study[1] suggests that CHF incidence increases steadily with advancing age and that the difference in incidence between men and women diminishes with age (Figure 1).

Despite recent innovations in medical therapy, once it is clinically manifest, CHF is associated with an unacceptably high mortality rate. For example, in the Framingham Study, median survival was only 1.7 years for men and 3.2 years for women, with only 25% and 38%, respectively, surviving five years.[2] Not surprisingly, these figures correspond to a mortality rate that is four to eight times higher than that of the general population of the same age.[3] This poor outlook is the same for all etiolgies of CHF, with sudden death being a prominent feature of CHF-related mortality.

Based on population attributable risks, hypertension has the greatest impact on CHF and accounts for 39% of CHF events in men and 59% in women.[4] Despite its much lower prevalence in the population (3% to 10%), myocardial infarction (MI) also has a high attributable risk for CHF in men (34%) and women (13%). Valvular disease accounts for only 7% to 8% of CHF cases, while diabetes increases CHF risk two-to-fourfold, with a greater impact in women (12%), than in men (6%).[4]

Ischemic versus non-Ischemic CHF

In more recent clinical studies, a common approach to the classification of CHF is to divide patients into two categories: ischemic and non-ischemic. While the former relates to underlying coronary artery disease (CAD), the non-ischemic group is more heterogeneous and includes hypertensive, alcohol-induced and valvular CHF, and idiopathic dilated cardiomyopathy. However, there is some evidence that these two categories of CHF may also differ in terms of prognosis and response to treatment. Despite much conflicting evidence, a recent overview of the literature suggests that mortality is greater in ischemic than in non-ischemic CHF, and that the extent of CAD seems to contribute to the excess risk in ischemic CHF.[5] Differential effects with regard to response to treatment have been observed with angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, amiodarone, and calcium channel blockers (CCBs) in patients with heart failure of ischemic versus non-ischemic etiology.

ACE inhibitors

A meta-analysis of 11 ACE inhibitor trials (n=1,266) demonstrated a 65% reduction in mortality among patients with ischemic CHF (95% CI, 0.28-0.71, p=0.016) compared with a more modest, nonsignificant 30% reduction (95% CI, 0.39-1.50) in those with CHF of non-ischemic origin.[6] This

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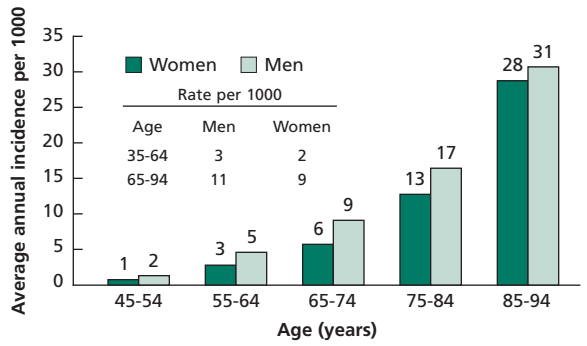
Figure 1: The Framingham Study: Incidence of cardiac failure by age and sex — 36-year follow-up[1]



beneficial effect of ACE inhibitors was not seen, however, in the Studies of Left Ventricular Dysfunction (SOLVD).[7] In SOLVD, there appeared to be a greater relative risk reduction with enalapril as compared to placebo in those with CHF of non-ischemic etiology (Relative Risk Reduction [RRR] 27%) as compared to those with ischemic CHF (RRR 12%).[7]

Beta-blockers

Early studies with beta-blockers in CHF suggest a greater benefit in non-ischemic than in ischemic CHF, and in the Cardiac Insufficiency Bisoprolol Study (CIBIS-I),[8] this mortality difference was statistically significant (bisoprolol 9% vs. placebo 20%, p=0.01). In contrast, the CIBIS-II study[9] reported at the XXth Congress showed a relatively greater survival benefit with bisoprolol compared to placebo in patients with ischemic CHF (mortality in ischemic CHF 20% vs. 9%, p=0.001, in non-ischemic 19% vs. 12%, p=0.06). Finally, the recent U.S. Carvedilol Heart Failure Study demonstrated reductions in morbidity and mortality in patients with ischemic (hazard ratio [HR] 0.35; 95% CI, 0.16-0.73), as well as in non-ischemic CHF (HR 0.35; 95% CI, 0.15-0.83).[10]

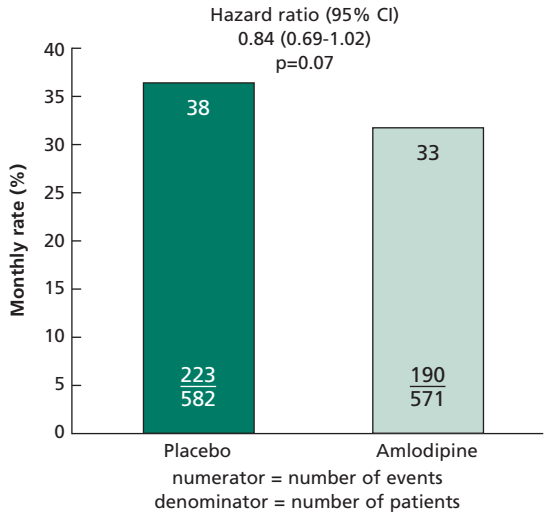
Amiodarone

While the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (CHF-STAT) trial showed no overall mortality reduction with active therapy, subgroup analysis revealed a trend towards a reduction in death with amiodarone in patients with non-ischemic CHF (p=0.07).[11] The GESICA Study, which included a substantial number of patients with non-ischemic CHF, demonstrated a significant mortality reduction with amiodarone (p=0.024).[12]

Calcium channel blockers in CHF

In general, the results with CCBs in patients with CHF have been disappointing. The short-term administration of these drugs has produced immediate adverse hemodynamic and clinical effects, and long-term therapy has been associated

Figure 2: All-cause mortality in all patients in PRAISE-I[18]



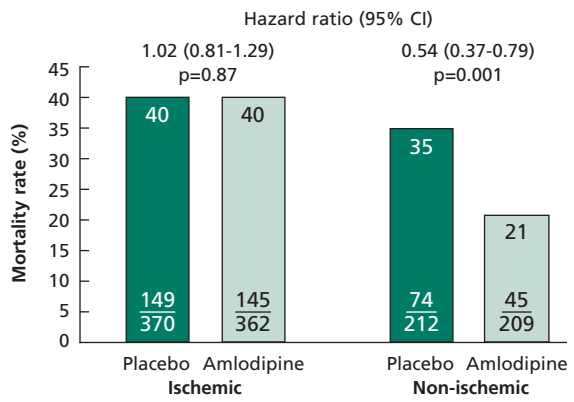
with an increased risk of worsening heart failure and cardiovascular mortality.[13-16] However, it is not clear whether all CCBs produce deleterious effects in patients with left ventricular systolic dysfunction. In the Vasodilator-Heart Failure Trial (V-HeFT),[17] there were similar 39-month (average 18) mortality rates in the placebo and felodipine treatment arms. However, due to the small size of the study (n=450), this trial was not powered to test for a mortality difference with felodipine. In addition, there was an early trend toward worsening CHF in felodipine-treated patients, although this difference did not persist after three months. This occurred despite an early, significant reduction in blood pressure and an increase in ejection fraction (2.1% vs -0.1% units in the placebo group, p=0.001). Finally, there was no significant improvement in exercise tolerance, quality of life, or the need for hospitalization.

PRAISE

In contrast, in a large multicenter study of patients (n=1,153) with severe heart failure, amlodipine did not appear to increase the risk of death or cardiovascular hospitalization over a period of six to 33 months. The Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial[18] involved double-blind treatment with either placebo or amlodipine among patients with New York Heart Association class IIIB-IV chronic CHF and left ventricular ejection fractions of <33% in addition to usual therapy (ACE inhibitor, digitalis, and diuretics). The primary end point was the combined risk of all-cause mortality and cardiovascular morbidity, and this was similar in the placebo and amlodipine groups (42% vs 39%, p=0.31).

In a secondary analysis (Figure 2), there was a trend towards a reduction in the risk of death with amlodipine (38% vs 33%; 16% RRR, 95% CI, 31% reduction to 2%

Figure 3: All-cause mortality in patients with ischemic and non-ischemic cardiomyopathy in PRAISE-I[18]



increase; p=0.07). In another prespecified secondary analysis among patients with non-ischemic cardiomyopathy, amlodipine reduced the combined risk of fatal and nonfatal events by 31% (p=0.04) and decreased the risk of death by 46% (p=0.001). In contrast, among patients with ischemic heart disease, there was no difference between the amlodipine and placebo groups in the occurrence of either end point (Figure 3). The PRAISE study group investigators concluded that amlodipine did not increase cardiovascular morbidity or mortality in patients with severe CHF and suggested that the interesting apparent benefit seen among patients with non-ischemic cardiomyopathy required further study. Indeed, Dr. Milton Packer (PRAISE principal investigator) stated that, if anything, the Steering Committee had anticipated that amlodipine might reduce the risk of death in patients with *ischemic* cardiomyopathy, the opposite of what was actually observed in PRAISE. Appropriately, this hypothesis raised by PRAISE-I is currently under prospective evaluation in a second large-scale clinical trial in non-ischemic cardiomyopathy patients. It is anticipated that the results of PRAISE-II will become available in the next 12-18 months time.

Proposed mechanisms of cytoprotection for amlodipine in CHF

As seen in Table 1, the treatment of CHF has evolved over the past 20 to 30 years. The focus has extended beyond treating symptoms (eg, edema, dyspnea) secondary to pathophysiologic perturbations (eg, sodium retention, hemodynamic and neurohormonal abnormalities). More recently, there has been an emphasis on cellular mechanisms, including oxidative stress leading to necrosis apoptosis. The term "apoptosis" is derived from a classical Greek word that means "falling off," as in leaves falling from a tree. In medicine, apoptosis — an important type of programmed cell death — is a highly regulated process in which certain developmental or environmental factors trigger a genetic program. This activates a sequence of molecular events that ultimately result in the efficient disposal of the cell.

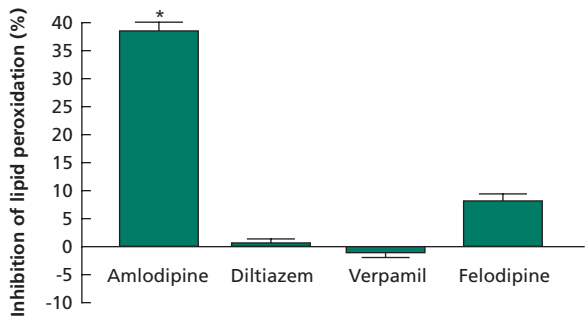
Sources of oxidative stress in CHF include increased catecholamine release, inflammatory cytokines, myocardial ischemia, an increased metabolic rate, and metabolic stunting. These processes lead to free radical-induced damage: imbalances in nitric oxide, inappropriate production of growth factors, and loss of calcium homeostasis. In some settings, apoptosis may, in fact, be a beneficial process. For example, if a precancerous cell is exposed to free radicals leading to DNA damage and the cell is not able to repair itself, its programmed death may be protective to the body. In contrast, in the setting of heart disease and concomitant oxidative stress, a cardiomyocyte may experience cellular damage and loss of normal calcium regulation leading to premature cell death.

Evidence from clinical trials demonstrates that an elevation in lipid peroxidation and oxidative stress (secondary to free radicals) is associated with heart failure. In cellular models of cytokines and free radical-induced apoptosis, CCBs appear to inhibit this process. However, it has been proposed that the cytoprotective activity of amlodipine may be related in part to antioxidant effects that are independent of calcium channel modulation. To test this concept, the antioxidant activities of representative CCBs were evaluated

Table 1: Evolution of treatment of CHF

Time frame	Clinical endpoint	Pathophysiology	Treatment
Pre-1970	Edema	Sodium retention	Diuretics
1970-85	Symptoms	Hemodynamic	Inotropes Vasodilators Digoxin
1985-95	Survival	Neurohormonal	ACE inhibitors Beta-blockers
1995-present and future	Cellular mechanisms	Apoptosis	Antioxidants Cytokine antagonists Nitric oxide regulators

Figure 4: Effect of calcium channel blockers on membrane lipid peroxidation.



*p<0.001 vs control and other agents

Values are mean ± standard deviation (N=3).
Drug concentration of 1.0 μM

in isolated membranes and cellular models of oxidative stress. Mason et al demonstrated that lipophilic calcium blockers, such as amlodipine, can inhibit lipid peroxidation as a result of their ability to intercalate into the cell membrane and interfere with the efficient intermolecular propagation of unstable free radicals (Figure 4).[19]

The distinct antioxidant activity of amlodipine is attributed, in part, to its very high affinity to the membrane lipid bi-layer. In addition, the anti-apoptotic activity of amlodipine in cell culture experiments was significantly greater than that seen with a shorter-acting CCB and was >1,000-fold more effective than the antioxidant vitamin E at pharmacologically relevant concentrations.[20]

Conclusion

The role of calcium channel blocker therapy in CHF remains unclear. However, the results of PRAISE suggest that amlodipine is safe in the setting of significant left ventricular systolic dysfunction — an effect that has not been established with any other CCB to-date — and may actually be beneficial among patients with non-ischemic cardiomyopathy. There are several potential mechanisms of benefit with amlodipine in CHF, including antioxidant activity that may inhibit the process of free-radical-induced apoptosis. Whether such properties translate into clinical benefit will be further addressed in the ongoing PRAISE-II study.

References

1. Kannel WB, Ho K, Thom T. Changing epidemiological features of cardiac failure. *Br Heart J* 1995;72:S3-S9.
2. Ho KKL, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation* 1993;88:107-115.
3. Kannel WB, Belanger AJ. Epidemiology of heart failure. *Am Heart J* 1991;121:951-957.
4. Levy D, Larson MG, Ramachandran SV, Kannel WB, Ho KKL. The progression from hypertension to congestive heart failure. *JAMA* 1996;275:1557-1562.
5. Bart BA, Shaw LK, McCants CB, et al. Clinical determinants of mortality in patients with angiographically diagnosed ischemic or non-ischemic cardiomyopathy. *J Am Coll Cardiol* 1997;30:1002-1008.
6. Nony P, Boissel JP, Girard P, Leizorovicz A, Lievre M, Chifflet R. Relative efficacy of angiotensin- converting enzyme inhibitors on mortality in patients with congestive heart failure: Implications of randomized trials and role of the aetiology (ischaemic or non-ischaemic) of heart failure. *Eur Heart J* 1992;13:1101-1108.
7. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-302.
8. CIBIS Investigators and Committees. A randomized trial of β-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). *Circulation* 1994;90:1765-1773.
9. Dargie HJ, for the CIBIS II Investigators. Presented at the XXth Congress of the European Society of Cardiology, August 23, 1998.
10. Packer M, Bristow MR, Cohn JN, et al for the US Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med* 1996; 334:1349-1355.
11. Singh SN, Fletcher RD, Fisher SG, et al for the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. *N Engl J Med* 1995;333:77-82.
12. Doval HC, Nul Dr, Grancelli HO, et al. Randomized trial of low-dose amiodarone in severe congestive heart failure. *Lancet* 1994; 344:493-498.
13. Goldstein RE, Boccuzzi SJ, Cruess D, Nattel S, Adverse Experience Committee, Multicenter Diltiazem Postinfarction Research Group. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. *Circulation* 1991;83:52-60.
14. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1988;319:385-92.
15. Elkayam U, Amin I, Mehra A, Vasquez J, Weber L, Rahimroola SH. A prospective, randomized, double-blind, crossover study to compare the efficacy and safety of chronic nifedipine therapy with that of isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. *Circulation* 1990;82:1954-61.
16. Barjon JN, Rouleau J-L, Bicher D, Juneau C, De Champlain J. Chronic renal and neurohumoral effects of the calcium entry blocker nisoldipine in patients with congestive heart failure. *J Am Coll Cardiol* 1987;9:622-30.
17. Cohn JN, Ziesche S, Smith R, et al for the Vasodilator-Heart Failure Trial (V-HeFT) Study Group. Effect of calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril. V-HeFT III *Circulation* 1997;96: 856-863.
18. Packer M, O'Connor CM, Ghali JK, et al for the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) Study Group. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *N Engl J Med* 1996;335:1107-1114.
19. Mason RP. Cytoprotective properties of a long-acting calcium channel blocker: New mechanisms of action. *Am J Hypertens* 1998; 11:254A.
20. Mason RP, Moisey DM, Shajenki L. Cholesterol alters the binding of Ca^{2+} channel blockers to the membrane lipid bilayer. *Mol Pharmacol* 1992;41:315-321.