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Calcium Channel Blockers in Heart Failure

Key Words

Amlodipine
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Dihydropyridines
Heart failure
Mibefradil

Abstract

A considerable effort has been made in the last 15 years to evaluate the safety and efficacy of calcium channel blockers (CCBs) in the treatment of patients with chronic congestive heart failure (CHF). Available studies have provided strong evidence for a potential detrimental effect of the first-generation calcium antagonists in patients with CHF, indicating the need for great caution when these drugs are used in patients with significant depression of left ventricular systolic function. A number of second-generation CCB have demonstrated a strong vasodilatory effect and favorable hemodynamic action but failed to show a similar improvement in exercise capacity, morbidity and mortality. Moreover, drugs such as nicardipine and nisoldipine have resulted in a detrimental effect in some patients and, therefore, cannot be considered safe when used in patients with moderate-to-severe heart failure. Available information from the V-HeFT III study demonstrate a lack of an unfavorable effect of felodipine on exercise tolerance in patients with chronic heart failure. Although mortality rate was similar in both the felodipine and the placebo group, because of the relatively small number of patients in this study, no clear conclusion can be drawn regarding the effect of felodipine on mortality in patients with CHF. An encouraging signal regarding a potential role of CCB in the treatment of chronic heart failure has been provided by the recently completed PRAISE study. This prospective large-scale study demonstrated the safety of amlodipine, a long-acting dihydropyridine derivative, when used in patients with heart failure due to coronary artery disease. Furthermore, this study demonstrated a substantial reduction in mortality in patients with CHF due to nonischemic cardiomyopathy and provided a strong indication for a potential therapeutic benefit of amlodipine when added to standard CHF therapy in this patient population. No clear explanation is available at the present time regarding the reason for the deleterious effect demonstrated with some of the dihydropyridines and the contrasting benefit seen with amlodipine. Finally, more information regarding the safety and efficacy of dihydropyridines should become available in the next year. The PRAISE II study is ongoing and will provide further information regarding the therapeutic role of amlodipine in patients with nonischemic dilated cardiomyopathy. The MACH-1 study is evaluating the effect of mibefradil, a predominant T-type channel blocker with an ideal activity profile, on morbidity and mortality in patients with chronic CHF.

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The calcium channel blockers (CCB) are a heterogeneous group of drugs with widely variable effects on heart muscle, sinus node function, atrioventricular conduction, peripheral blood vessels, and coronary circulation [1]. Ten of these drugs – nifedipine, nicardipine, nimodipine, felodipine, isradipine, amlodipine, verapamil, diltiazem, bepridil, and mibefradil – are approved in the United States for clinical use [2]. Although these drugs are mainly used for the treatment of hypertension and stable angina pectoris, there has been a strong interest and increasing experience in the use of CCB in patients with congestive heart failure (CHF).

Rationale for the Use of CCB in Heart Failure

The rationale for the use of CCB in the treatment of heart failure is multifactorial. These drugs have a strong arteriolar dilator effect leading to a reduction in systemic vascular resistance (SVR) and thus left ventricular (LV) afterload. Drugs with similar hemodynamic effects such as hydralazine when used in combination with isosorbide dinitrate were shown to improve exercise tolerance and ejection fraction and also survival in patients with mild-to-moderate heart failure [3, 4]. The majority of available CCB have a substantial anti-ischemic effect and many of them are used effectively in the treatment of myocardial ischemia [2]. Because coronary artery disease is the underlying cause of chronic CHF in 60–70% of patients with CHF [3–6], it is not surprising that CCB are considered by many clinicians a viable therapeutic option. The favorable effect of CCB on LV relaxation may lead to an improvement in diastolic dysfunction [7], an important cause of heart failure symptoms, even in patients with documented LV systolic dysfunction [8]. In addition, the prevention of calcium ion entry into myocardial cells was reported to prevent the development of alcohol-mediated cardiac dysfunction in hamster myocardium and could have a similar protective effect in humans [9].

Clinical Experience with Calcium Antagonists in Heart Failure

First-Generation CCB

Nifedipine. Initial evaluation by several investigators [10–16] reported hemodynamic improvement after single-dose administration of nifedipine given either orally or sublingually in patients with acute or chronic CHF. The majority of these data were reported as a mean group

response and demonstrated a reduction in SVR and mean blood pressure, with augmentation of cardiac output and stroke volume. Lack of change in both right and left ventricular filling pressures in most studies [8] verified the predominant arteriolar and negligible venous effects of the drug.

Although the initial experience with the use of nifedipine in CHF led some investigators to conclude [10–17] that the negative inotropic effect of nifedipine could be offset by its vasodilatory effect, further evaluation in larger groups of patients demonstrated the clinical relevance of the cardiodepressant effect of the drug [18–21]. Comparison of nifedipine with nitroprusside [22] demonstrated a smaller augmentation in cardiac output and a larger decrease in systemic blood pressure with nifedipine despite a similar reduction in SVR. These hemodynamic changes were associated with a decrease in the first derivative of LV pressure (dP/dt) [23]. Similarly, a comparison of change in hemodynamic indices of LV systolic function in the same patients with heart failure following a similar reduction in SVR with hydralazine and nifedipine [24] resulted in a significantly smaller augmentation of stroke volume, cardiac output and LV stroke work index with nifedipine, demonstrating the clinical relevance of its negative inotropic effect. Further evaluation of the hemodynamic profile of nifedipine in two large series of patients [18, 25] showed acute hemodynamic and clinical deterioration after a single dose of 20–50 mg in 19 and 29% of the patients, respectively. Hemodynamic response could not be predicted from baseline hemodynamic data and LV ejection fraction in one study [18]. In the second study [25], hemodynamic deterioration was associated with higher baseline levels of plasma renin activity and mean right atrial pressure and lower serum sodium concentration. In addition, a strong relationship was found between an unfavorable acute hemodynamic response to nifedipine and long-term mortality, supporting a hypothesis that hemodynamic deterioration after nifedipine administration was more likely to occur in patients with more severe heart failure.

The acute neurohormonal effect of nifedipine in patients with CHF was evaluated in two different studies. Prida et al. [26] demonstrated a significant activation of the renin system following administration of 10 mg oral nifedipine. This change in plasma renin activity was, however, not associated with an increase in aldosterone level. Similar findings were reported by Elkayam et al. [27] and were most likely due to inhibition of calcium-mediated secretion of aldosterone in the renal macula densa.

The long-term effect of nifedipine in patients with heart failure due to LV systolic dysfunction was evaluated several years ago in two randomized trials. In the first study, Agostoni et al. [28] compared in a double-blind, crossover design the effect of captopril (50 mg t.i.d.) and nifedipine (20 mg t.i.d.) given for 8 weeks each in 18 patients with dilated cardiomyopathy who were optimally treated with digitalis and diuretic drugs. This study demonstrated symptomatic and functional improvement and enhancement of exercise tolerance with captopril but not with nifedipine. In this study, nifedipine initially resulted in a reduction in SVR that led to augmentation of cardiac output and a small reduction in LV filling pressure. After prolonged treatment, however, cardiac output returned to baseline values and pulmonary artery wedge pressure increased substantially accompanied by worsening heart failure symptoms in some patients. In a second study, Elkayam et al. [29] compared the effect of long-term administration (8 weeks) of isosorbide dinitrate (40 mg four times daily), nifedipine (20 mg four times daily) and their combination in patients with mild-to-moderate chronic heart failure. This study demonstrated a significantly higher incidence of heart failure worsening, necessitating an increase in diuretic dose or hospitalization, or both, in patients treated with nifedipine either alone or in combination with isosorbide dinitrate. Hospitalization was required in 24% of patients during nifedipine therapy and in 26% during nifedipine-isosorbide dinitrate combination therapy compared to 0% during isosorbide dinitrate therapy alone. The total number of CHF worsening episodes was nine during nifedipine therapy, three during isosorbide dinitrate therapy and 21 during nifedipine-isosorbide dinitrate combination therapy. Premature discontinuation of drug administration because of clinical deterioration or other side effects occurred in 29% of patients during nifedipine therapy, in 5% during isosorbide dinitrate therapy ($p = 0.05$ vs. nifedipine) and in 19% during combination therapy.

In summary, in spite of a strong vasodilatory effect, numerous studies have demonstrated an unfavorable effect of nifedipine on hemodynamic as well as clinical status in patients with CHF due to LV systolic dysfunction.

Diltiazem. The unfavorable results reported with the use of nifedipine in patients with chronic heart failure led to the attempts to use diltiazem, a first-generation calcium antagonist with a lesser myocardial depressant effect [30]. Hemodynamic evaluation of this agent in patients with severe chronic heart failure demonstrated either no change or improvement in hemodynamic profile [31–33] and no change in plasma renin activity and catechol-

amines [34]. In comparison with nifedipine, use of diltiazem was associated with a significantly smaller incidence of hemodynamic and symptomatic deterioration [33, 34]. In addition, a recent report also demonstrated a safe and effective use of intravenous diltiazem for heart rate control in patients with atrial fibrillation and LV systolic dysfunction [35]. However, occasional hemodynamic deterioration reported in some patients receiving oral diltiazem [33, 34, 36] presented the first indication of a potential hazard of this drug as well.

The chronic use of diltiazem in patients with CHF resulted in conflicting findings. Figulla et al. [37] have recently reported improvement in cardiac function, exercise capacity and subjective status without deleterious effects on transplant listing-free survival with diltiazem in patients with dilated cardiomyopathy. In contrast to this study, the Multicenter Diltiazem Postinfarction Trial [38] was conducted in a large number of patients and in a prospective, randomized, placebo-controlled fashion. This study evaluated the effect of chronic diltiazem therapy (240 mg/day) initiated 3–15 days after the onset of myocardial infarction, on mortality and reinfarction in 1,237 patients and compared it to the effect of placebo in 1,232 similar patients. In 490 patients with evidence of pulmonary congestion on the chest roentgenogram, diltiazem was associated with an increased incidence of cardiac events. A similar pattern was observed with respect to depressed radionuclide ejection fraction and anterolateral Q wave infarction. In contrast, in 1,909 patients without pulmonary congestion, diltiazem therapy resulted in a lower incidence of cardiac events. In a further evaluation of the development of congestive heart failure in this study, Goldstein et al. [39] showed that patients with pulmonary congestion, anterolateral Q wave infarction or reduced ejection fraction ($<40\%$) at baseline were more likely to develop chronic heart failure during follow-up when compared to patients without these markers of LV dysfunction. Furthermore, the likelihood of developing CHF with diltiazem was inversely related to the degree of LV systolic dysfunction. This trial conclusively demonstrated the hazard involved in the use of diltiazem in patients with LV systolic dysfunction due to coronary artery disease and myocardial infarction.

Verapamil. The experience related to the use of verapamil in heart failure is limited because of the known negative inotropic effect of the drug and the warning by the manufacturer concerning the risk of developing heart failure [40]. In a small study, Ferlinz and Gallo [41] demonstrated symptomatic deterioration in 4 of 10 patients with CHF on long-term verapamil therapy in spite of acute

hemodynamic improvement. The Danish study on the effect of verapamil on death or reinfarction [42] in survivors of acute myocardial infarction may provide some indirect but useful information regarding the effect of this calcium antagonist in patients with chronic heart failure. This multicenter double-blind, placebo-controlled study evaluated verapamil (120 mg t.i.d.) versus placebo in patients 7–15 days after their myocardial infarction. At a mean follow-up time of 16 months, verapamil had caused a significant reduction in mortality and cardiac events in patients without but not in patients with chronic heart failure. This study excluded patients with heart failure not controlled with furosemide (≤ 160 mg/day), which resulted in exclusion of 13% of the patients. Although the investigators concluded that in contrast to diltiazem, verapamil had no detrimental effect in patients with heart failure, one cannot exclude the possibility that the favorable effect of verapamil reported in patients without heart failure was offset by the myocardial-depressant effect of the drug in patients with heart failure.

Second-Generation CCB

Nisoldipine. In a study of the hemodynamic and neurohumoral effects of nisoldipine [43] in 17 patients with NYHA functional class II–IV CHF, the drug decreased SVR and mean systemic arterial pressure and increased stroke volume and LV ejection fraction at rest and during exercise and reduced exercise values of LV filling pressure. Intravenous infusion of nisoldipine demonstrated coronary vasodilatory effect leading to increased resting coronary sinus blood flow and decreased resting and exercise coronary vascular resistance. The systemic hemodynamic benefits were maintained during oral administration of nisoldipine for 4 weeks. Baseline group mean values of plasma norepinephrine and renin were elevated and did not change during chronic therapy, however, a reduction in sympathetic activity was noted in individual patients who showed hemodynamic improvement. A similar hemodynamic effect of nisoldipine was demonstrated by other investigators [44, 45]. A further evaluation of chronic administration (2 months) of nisoldipine in patients with CHF [44], however, resulted in hospitalization of 70% of the patients because of worsening heart failure in spite of initial improvement in hemodynamic profile. This disappointing clinical effect was attributed to neurohumoral activation induced by the therapy [46].

Del Cas et al. [47] studied the acute and chronic effects of nisoldipine on resting and exercise hemodynamics, neurohumoral parameters and functional capacity in 14 patients with mild-to-moderate heart failure. Nisoldipine

therapy (20 mg orally) was associated with a reduction in blood pressure and SVR and an increase in cardiac index both at rest and during exercise. LV filling pressures were also improved by nisoldipine at peak exercise. Hemodynamic effects of the drug were preserved following chronic therapy. In spite of these hemodynamic improvements, there were no significant changes in exercise duration or peak oxygen consumption after both acute and chronic nisoldipine therapy. Evaluation of nisoldipine effect on neurohormones in this study showed a slight but significant increase in plasma norepinephrine levels at rest but not at peak exercise. No significant changes were observed in plasma renin activity and aldosterone levels.

Haitas et al. [48] compared the acute hemodynamic effects of intravenous nisoldipine and hydralazine in 9 patients with moderate-to-severe CHF due to coronary artery disease. Both agents reduced LV preload and afterload and increased cardiac output. The effect of hydralazine, however, was greater and longer-lasting and resulted in the development of hypotension in 2 patients and angina in the other 2.

Two recent studies have evaluated the effect of nisoldipine in patients with heart failure following myocardial infarction. In a double-blind study, Lewis et al. [49] compared the effect of nisoldipine and placebo given for 8 weeks, each on exercise performance in 19 patients with moderate-to-severe heart failure following myocardial infarction. At the end of the 8-week period, the peak estimated workload, the rate of perceived exertion and, to a lesser degree, the duration of treadmill exercise increased in patients receiving nisoldipine compared with those receiving placebo. There was no change in peak double product, suggesting that myocardial oxygen demand was not altered. Resting LV ejection fraction measured using radionuclide ventriculography was also unchanged in the two groups after 8 weeks. In a second study, Eichstaedt [50] compared the effect of nisoldipine (20 mg daily) and β -acetyldigoxin (0.3 mg daily) on LV ejection fraction in patients with LV dysfunction and heart failure due to multiple myocardial infarctions. Patients were studied at rest and during exercise. β -Acetyldigoxin was superior to nisoldipine in improving LV function in a subgroup of patients with moderately decreased ejection fraction (20–33%). However, in a subgroup of patients with an ejection fraction $<25\%$, nisoldipine was associated with a significant increase in ejection fraction (4% at rest and 5.4% during exercise), whereas β -acetyldigoxin did not improve LV function in this group of patients.

In summary, available information demonstrate a strong vasodilatory effect of nisoldipine in patients with

CHF resulting in decreased LV afterload and leads to augmentation of cardiac output and LV ejection fraction in some patients. These changes, however, result in either no or small changes in exercise capacity. In spite of initial hemodynamic improvement, clinical deterioration may occur, indicating a potential risk associated with the chronic use of nisoldipine in patients with chronic CHF.

Nicardipine. Evaluation of the effect of nicardipine in small groups of patients with CHF suggested favorable acute and short-term effects. Ryman et al. [51] evaluated the effect of 1-week therapy with oral nicardipine (30 mg t.i.d.) at rest and during exercise on hemodynamics, oxygen consumption and catecholamines in 10 patients with severe CHF. Therapy resulted in a decrease in SVR and pulmonary artery wedge pressure and an increase in cardiac index both at rest and during exercise. Plasma norepinephrine concentrations did not change.

In another study, intravenous nicardipine (10 mg) resulted in acute and short-term improvement in LV performance in patients with mild-to-moderate CHF [52, 53]. The same investigators [54] reported significant improvements in ejection fraction, cardiac output and peak filling rate assessed by radionuclide ventriculography acutely after intravenous nicardipine administration and after 4 weeks of long-term oral therapy (20–40 mg t.i.d.) in patients with CHF due to ischemic heart disease, suggesting a beneficial effect of nicardipine on both LV systolic and diastolic function.

Gheorghiade et al. [55] evaluated the long-term effect of nicardipine (20–30 mg every 8 h) given over 4 months in patients with chronic CHF treated with standard CHF drug therapy including angiotensin-converting enzyme (ACE) inhibitors. In this study, adjunctive therapy with nicardipine resulted in clinical worsening in 60% of the patients compared to only 20% of patients receiving placebo ($p = 0.06$). Concomitant use of captopril did not prevent neurohormonal activation (renin increased from 7 ± 6 to 22 ± 28 ng/ml/h, $p < 0.05$).

In summary, in spite of reported favorable effects of nicardipine on hemodynamic profile and both systolic as well as diastolic LV function, long-term administration of this drug may result in a significant clinical deterioration in patients with chronic CHF.

Felodipine. Felodipine was reported to have negligible negative inotropic effects and high selectivity to smooth muscle [56]. The short-term administration of felodipine in patients with CHF during the resting state resulted in a reduction in SVR and blood pressure along with elevated LV filling pressure and an increase in cardiac output [57–60]. Studies examining the long-term effects of felodipine

in chronic CHF have demonstrated hemodynamic benefits similar to those seen during short-term administration [61–64]. Dunselman et al. [62] examined the long-term hemodynamic effects of felodipine in 23 patients with moderate-to-severe (NYHA class III) CHF who were already on a regimen of digoxin and diuretics. At the end of an 8-week treatment period, those receiving felodipine as opposed to placebo were found to have a modest increase in stroke volume and cardiac output and a reduction in SVR. Similar results were obtained by Kassis and Amtrop [63, 64] who reported a reduction in LV afterload, improvement in LV systolic function during felodipine therapy and normalization of abnormal baroreflex control of peripheral circulation.

Several studies analyzing the effect of long-term administration of felodipine on cardiovascular hemodynamics during exercise demonstrated felodipine-mediated decrease in vascular resistance and increase in cardiac output during moderate exercise with a variable effect on pulmonary artery wedge pressure [65, 66].

In a double-blind study, Dunselman et al. [62] compared the effects of enalapril and felodipine on cardiopulmonary exercise in patients with NYHA class III CHF secondary to coronary artery disease. These investigators found an improvement in aerobic capacity and exercise duration after 16 weeks of enalapril (10 mg twice daily) therapy in 11 patients but not in 9 patients receiving felodipine therapy (10 mg twice daily).

The largest experience with the use of felodipine in patients with heart failure has been provided by the recently completed [67] V-HeFT III study. This study enrolled 451 male patients with heart failure and exercise tolerance limited by dyspnea or fatigue who were treated with diuretics and enalapril. The mean age was 63 years, the etiology of CHF was coronary artery disease in 52% of the patients, the mean ejection fraction was 30% and the mean treadmill exercise time was 568 s. These patients were randomized to receive either felodipine 5 mg b.i.d. or placebo. The preliminary analysis of the outcome of the study demonstrated no difference between felodipine and placebo in mortality both in patients with and without coronary artery disease. Similarly, felodipine did not have an effect on peak exercise capacity 12 weeks after randomization. Plasma norepinephrine was elevated at baseline (515 ± 257 pg/ml) and demonstrated a similar rise in both the felodipine and the placebo groups (26 and 24 pg/ml, respectively). Plasma atrial natriuretic peptide (ANP) was 128 ± 107 pg/ml at baseline and was reduced by felodipine 4.0 pg/ml while it increased in the placebo group 27 pg/ml ($p = 0.014$). Based on these preliminary results,

the investigators of the V-HeFT III study concluded that felodipine, when used as adjunctive therapy to ACE inhibitors and diuretics in patients with CHF, may exert a sustained favorable effect on ANP which may be due to its hemodynamic effect but does not influence either mortality or exercise tolerance in this patient population. It should be noted, however, that any conclusion based on the V-HeFT III study regarding effect of felodipine on mortality in patients with CHF is limited by the small number of patients included in the trial.

In summary, therefore, overall available information suggests a beneficial hemodynamic effect of felodipine, another vasoselective CCB of the dihydropyridine group, in patients with chronic CHF. However, there is no evidence that these hemodynamic changes can lead to clinical improvement or reduced mortality.

Amlodipine. A recent multicenter study [68] randomized 142 patients with CHF to either placebo (n = 49), amlodipine 5 mg (n = 48) or 10 mg q.d. (n = 45) for 12 weeks while standard CHF therapy was kept constant. Amlodipine was found to produce a dose-dependent increase in cardiac index (p = 0.02) and decreases in systemic and pulmonary resistance (p = 0.06 and 0.01, respectively) without change in LV filling pressure. These hemodynamic changes were seen with 10 but not with 5 mg. In contrast, 5 mg of amlodipine but not 10 mg was reported to improve quality of life (p = 0.01) and health perception (p = 0.05) and reduced the number of days confined to bed (p = 0.03).

Another study by Packer et al. [69] evaluated the effect of amlodipine (10 mg q.d.) on exercise tolerance, CHF score and plasma catecholamines in 186 patients with LV ejection fraction <40% and moderate to severe symptoms of heart failure. All patients received diuretics and digitalis, and 80% were also treated with ACE inhibitors. The results of the study demonstrated a significantly larger improvement in exercise time (62 ± 17 vs. 22 ± 13 s, p < 0.05) and a reduction in CHF symptoms and signs (55 vs. 29%, p < 0.05) with 4-month amlodipine treatment compared to placebo. These favorable changes were associated with a significant reduction in the serum norepinephrine level in the amlodipine group.

Based on these encouraging results, the PRAISE study (a prospective randomized amlodipine survival evaluation) was designed and conducted [70]. This study evaluated the effect of chronic treatment with amlodipine 10 mg/day in addition to background therapy with digitalis, diuretics and ACE inhibitors on morbidity and mortality in patients with chronic severe (NYHA class IIIb–IV) CHF. The study was prospectively designed to evaluate

separately the effect of therapy in patients with ischemic and nonischemic cardiomyopathy. 1,153 patients were randomized and were followed for 6–33 months, with a median follow-up time of 14.5 months. 732 patients were diagnosed of having ischemic and 421 patients nonischemic, dilated cardiomyopathy (NIDCM). The results of the study demonstrated an identical effect on the combined endpoint of mortality and morbidity in the subgroup of patients with ischemic cardiomyopathy (45.4% for placebo and 45.3% for amlodipine, p = 0.741). In contrast, there was a significant reduction in the combined endpoint in the group of patients with NIDCM (36.8 vs. 27.8%, p < 0.034). Similarly, all-cause mortality was lower 37% in the patients with NIDCM treated with amlodipine (35 vs. 22%, p < 0.001) but not in patients with ischemic cardiomyopathy (40 vs. 40%, p = 0.871). Based on the results of the PRAISE study it seems that overall, amlodipine had neutral effects on mortality and morbidity in patients with heart failure due to ischemic heart disease but offered a substantial favorable effect on survival of patients with CHF due to NIDCM.

New Class of Calcium Antagonists

Mibefradil (Ro 40-5967). Mibefradil is a chemically novel calcium antagonist substituted tetraline derivative and the only calcium antagonist which is able to block both L- and T-type voltage-operated calcium channels. Animal experimentations comparing equipotent doses of mibefradil, verapamil and diltiazem failed to show a negative inotropic effect with mibefradil [71, 72]. Recent studies have shown effectiveness and safety of mibefradil 25–150 mg given up to 28 days in patients with chronic stable angina and hypertension [73]. Two studies have recently evaluated the effect of mibefradil in patients with impaired LV function. In the first study, hemodynamic effect of a single intravenous mibefradil dose was evaluated in 24 patients with an LV ejection fraction of <40% and in 26 patients with LV an ejection fraction >40%. Mibefradil administration resulted in a fall in arterial pressure, heart rate, LV end-systolic pressure and end-diastolic volume, systolic and diastolic wall stress and peripheral vascular resistance. There was no change in LV end-diastolic pressure as well as cardiac output and LV ejection fraction. A decrease in cardiac contractility was found in 1 patient. There was no clinical deterioration noted, and plasma norepinephrine remained stable.

A second study examined the safety of mibefradil at doses of 6.25, 12.5, 25, 50 and 100 mg given orally for 8 days to patients with ischemic cardiomyopathy and NYHA class II–III CHF with an LV ejection fraction of

<40%. This study demonstrated that mibefradil was well tolerated [73].

A recent study [74] showed that mibefradil in a rat model subjected to coronary artery ligation improved survival to the same extent as an ACE inhibitor. Nine months of treatment with mibefradil resulted in reduction in LV weight and fibrosis without impairing LV function.

Based on the above preliminary findings suggesting a potent vasodilatory and anti-ischemic effect in addition to negative chronotropic effect and lack of effect on contractility and neurohormonal profile, it seems reasonable to assume that mibefradil could be a suitable addition to standard heart failure therapy. For these reasons, the largest CCB CHF trial was designed to evaluate the efficacy and safety of this drug in the treatment of chronic CHF (MACH-1 – Mortality Assessment of Congestive Heart Failure [75]). This study, which is presently ongoing, was designed as a multicenter, double-blind, placebo-controlled study randomizing patients with chronic CHF, at NYHA class II–IV, LV ejection fraction of <35% and

echocardiographic LV end-diastolic dimension ≥ 60 mm who are symptomatic on optimal dose of loop diuretics and ACE inhibitors. 2,591 patients were randomized; the objectives of the study were to assess the effect of mibefradil on: (1) cardiovascular mortality; (2) cardiovascular morbidity (dropout for CHF, hospitalizations for worsening of CHF or for angina, myocardial infarction, stroke, or other cardiovascular events); (3) combined cardiovascular mortality/morbidity; (4) NYHA functional class and physical examination; (5) exercise tolerance; (6) quality-of-life assessment (in selected centers); (7) neurohormonal and cytokine activity (in selected centers): plasma norepinephrine, atrial natriuretic factor, angiotensin II, endothelin, and cytokines; (8) LV systolic function (in selected centers): echo-ejection fraction and LV end-diastolic diameter, and (9) survival: stratified with respect to ischemic and nonischemic heart failure etiology. The results of this study are expected to be presented at the XXth congress of the European Society of Cardiology in August 1998.

References

- 1 Frishman WH: Current status of calcium channel blockers. *Curr Probl Cardiol* 1994;14:637–688.
- 2 Veniant M, Clozel JP, Hess P, et al: Hemodynamic profile of Ro 40-5967 in conscious rats: Comparison with diltiazem, verapamil and amlodipine. *J Cardiovasc Pharmacol* 1991; 18(suppl 10):S55–S58.
- 3 Cohn JN, Archibald DG, Ziesche S, et al: Effect of vasodilator therapy on mortality in chronic congestive heart failure: Results of a Veterans Administration cooperative study (V-HeFT). *N Engl J Med* 1986;314:1547–1552.
- 4 Cohn JN, Johnson G, Ziesche S, et al: A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;325: 303–310.
- 5 The SOVLD 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.
- 6 Packer M, Carver JR, Rodeheffer RJ, et al, and the PROMISE Study Research Group: Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med* 1991;325:1468–1475.
- 7 Lahiri A, Rodrigues EA, Carboni GP, Raftery EB: Effects of long-term treatment with calcium antagonists on left ventricular diastolic function in stable angina and heart failure. *Circulation* 1990;81(suppl III):130–138.
- 8 Zile MR: Diastolic dysfunction: Detection, consequences and treatment. 2. Diagnosis and treatment of diastolic dysfunction. *Mod Concepts Cardiovasc Dis* 1990;59:1.
- 9 Garrett JS, Wikman-Coffelt J, Sievers R, Finkbliner WE, Parmley WW: Verapamil prevents the development of alcoholic dysfunction in hamster myocardium. *J Am Coll Cardiol* 1987; 9:1326–1331.
- 10 Low RI, Takeda P, Mason DT, DeMaria AN: The effects of calcium channel blocking agents on cardiovascular function. *Am J Cardiol* 1982;49:547–553.
- 11 Klugman S, Salvi A, Camerini F: Hemodynamic effects of nifedipine in heart failure. *Br Heart J* 1980;43:440–446.
- 12 Matsumoto S, Ito T, Sada T, et al: Hemodynamic effects of nifedipine in congestive heart failure. *Am J Cardiol* 1980;46:476–480.
- 13 Ludbrook PA, Tiefenbrun AJ, Sobel BE: Influence of nifedipine on left ventricular systolic and diastolic function: Relationship to manifestations of ischemia and congestive failure. *Am J Med* 1981;71:683–692.
- 14 Magorien Rd, Leier CV, Kolibash AJ, Barbush TJ, Unverferth DV: Beneficial effects of nifedipine on rest and exercise myocardial energetics in patients with congestive heart failure. *Circulation* 1984;70:884–890.
- 15 Hof RP: Comparison of cardiodepressant and vasodilator effects of PN 200-110 (isradipine), nifedipine and diltiazem in anesthetized rabbits. *Am J Cardiol* 1987;59(suppl):37B–42B.
- 16 Miller AB, Conetta DA, Bass TA: Sublingual nifedipine: Acute effects in severe chronic congestive heart failure secondary to idiopathic diseased cardiomyopathy. *Am J Cardiol* 1985; 55:1359–1362.
- 17 Millard RW, Lathrop DA, Grupp G, Ashraf M, Grupp IL, Schwartz A: Differential cardiovascular effects of calcium-channel blocking agents: Potential mechanisms. *Am J Cardiol* 1982;49:499–506.
- 18 Elkayam U, Weber L, McKay C, Rahimtoola SH: Spectrum of acute hemodynamic effects of nifedipine in severe congestive heart failure. *Am J Cardiol* 1985;56:560–568.
- 19 Elkayam U, Weber L, Torkan B, Berman D, Rahimtoola SH: Acute hemodynamic effect of oral nifedipine in severe chronic congestive heart failure. *Am J Cardiol* 1983;52:1041–1054.
- 20 Fleckenstein A: Specific pharmacology of calcium in myocardium, cardiac pacemakers and smooth muscle. *Annu Rev Pharmacol Toxicol* 1977;17:149–166.
- 21 Gillmer DJ, Kark P: Pulmonary edema precipitated by nifedipine. *Br Med J* 1980;280:1420–1421.
- 22 Elkayam U, Weber L, Torkan B, McKay CR, Rahimtoola SH: Comparison of hemodynamic response to nifedipine and nitroprusside in severe chronic congestive heart failure. *Am J Cardiol* 1984;53:1321–1325.

- 23 Fifer MA, Colucci WS, Lorell BH, Jaski BE, Barry WH: Inotropic vascular and neuroendocrine effects of nifedipine and nitroprusside in severe chronic congestive heart failure. *Am J Cardiol* 1984;53:1321-1325.
- 24 Elkayam U, Weber L, McKay CR, Rahimtoola SH: Differences in hemodynamic response to vasodilation due to calcium antagonism with nifedipine and direct-acting agonism with hydralazine in chronic congestive heart failure. *Am J Cardiol* 1984;54:126-131.
- 25 Packer M, Lee WH, Medina N, Yushak M, Bernstein JL, Kessler PD: Prognostic importance of the immediate hemodynamic response to nifedipine in patients with severe left ventricular dysfunction. *J Am Coll Cardiol* 1987; 10:1303-1311.
- 26 Prida XE, Kubo SH, Largh JH, Cody RJ: Evaluation of calcium-mediated vasoconstriction in chronic congestive heart failure. *Am J Med* 1983;75:795-800.
- 27 Elkayam U, Roth A, Hsueh W, Weber L, Freidenberger L, Rahimtoola SH: Neurohumoral consequences of vasodilator therapy with hydralazine and nifedipine in severe congestive heart failure. *Am Heart J* 1986;111:1130-1138.
- 28 Agostoni PG, De Cesare N, Doria E, Polese A, Tamborini G, Guazzi MD: Afterload reduction: A comparison of captopril and nifedipine in dilated cardiomyopathy. *Br Heart J* 1986;55: 391-399.
- 29 Elkayam U, Amin J, Mehra A, Vasquez J, Weber L, Rahimtoola 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;82:1954-1961.
- 30 Henry PD: Comparative pharmacology of calcium antagonists: Nifedipine, verapamil and diltiazem. *Am J Cardiol* 1980;46:1047-1058.
- 31 Walsh RW, Porter CB, Starling MR, O'Rourke RA: Beneficial effects of intravenous and oral diltiazem in severe congestive heart failure. *J Am Coll Cardiol* 1984;3:1044-1050.
- 32 Charlap S, Frishman WH: Calcium antagonists and heart failure. *Med Clin North Am* 1989;73: 339-359.
- 33 Packer M, Lee WH, Medina Y, Yushak M: Comparative negative inotropic effects of nifedipine and diltiazem in patients with severe left ventricular dysfunction (abstract). *Circulation* 1985;72(suppl III):III-275.
- 34 Kulick DL, McIntosh N, Campese VM, et al: Central and renal hemodynamic effects and hormonal response to diltiazem in severe congestive heart failure. *Am J Cardiol* 1987;59: 1138-1143.
- 35 Heywood JT, Graham B, Marais GE, Zutzy KR: Effects of intravenous diltiazem on rapid atrial fibrillation accompanied by congestive heart failure. *Am J Cardiol* 1991;67:1150-1152.
- 36 Roth A, Harrison E, Mitani G, Cohen J, Rahimtoola SH, Elkayam U: Efficacy and safety of medium- and high-dose diltiazem alone and in combination with digoxin for heart rate control at rest and during exercise in patients with chronic atrial fibrillation. *Circulation* 1986;73: 316-324.
- 37 Figulla HR, Gietzen F, Zeymer U, Raiber M, Megselmann J, Soballa R, Hilgers R: Diltiazem improves cardiac function and exercise capacity in patients with idiopathic dilated cardiomyopathy: Results of the diltiazem in dilated cardiomyopathy trial. *Circulation* 1996;94: 346-352.
- 38 The Multicenter Diltiazem Postinfarction Trial Research Group: The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1988;319:385-392.
- 39 Goldstein RE, Bocuzzi SJ, Cruess D, Nattel S: Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. *Circulation* 1991; 83:52-60.
- 40 Montvale NJ: Physicians Desk Reference, ed 47. Medical Economics, 1993, p 2250.
- 41 Ferlinz J, Gallo CT: Responses of patients in heart failure to long-term oral verapamil administration (abstract). *Circulation* 1984; 70(suppl II):II-305.
- 42 The Danish Study Group on Verapamil in Myocardial Infarction: Secondary prevention with verapamil after myocardial infarction. *Am J Cardiol* 1990;66:331-401.
- 43 Kiowski W, Erne P, Pfisterer M, Beuhler FR, Burkart F: Arterial vasodilator, systemic and coronary hemodynamic effects of nisoldipine in congestive heart failure secondary to ischemic or dilated cardiomyopathy. *Am J Cardiol* 1987;59:1118.
- 44 Minderjahn KP, Hanrath P, Bleifeld W: The influence of nisoldipine on rest and exercise hemodynamics of the left ventricle in chronic left heart insufficiency. *Z Kardiol* 1983; 72(suppl 1):83.
- 45 Thier W, Rower N, Minderjahn KP, Hanrath P, Bleifeld W: Hemodynamic effect of nisoldipine in chronic congestive heart failure (abstract). *J Am Coll Cardiol* 1986;3:479.
- 46 Barjon JN, Rouleau JL, Bichet 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;9:622-630.
- 47 Del Cas L, Metra M, Ferrari R, Visioli O: Acute and chronic hemodynamic effects of the dihydropyridine calcium antagonist nisoldipine on resting and exercise hemodynamics, neurohumoral parameters and functional capacity of patients with chronic heart failure. *Cardiovasc Drugs Ther* 1993;7:103-110.
- 48 Haitas B, Meyer TE, Angel ME, Reef E: Comparative haemodynamic effects of intravenous nisoldipine and hydralazine in congestive heart failure. *Br J Clin Pharmacol* 1990;29:366-368.
- 49 Lewis BS, Makhoul N, Merdler A, Flugelman MY, Front A, Hardoff R, Halon DA: Effect of nisoldipine on exercise performance in heart failure following myocardial infarction. *Cardiology* 1991;79:39-45.
- 50 Eichstaedt H: Effects of calcium antagonists in patients with coronary disease and heart failure: Left ventricular function following nisoldipine measured by radionuclide ventriculography. *J Cardiovasc Pharmacol* 1992;29(suppl 5): 50-54.
- 51 Ryman KS, Kubo SH, Lystash J, Stone G, Cody RJ: Effects of nicardipine on rest and exercise hemodynamics in chronic congestive heart failure. *Am J Cardiol* 1986;58:583-588.
- 52 Lahiri A, Robinson CW, Kohli RS, Carvana MP, Raftery EB: Acute and chronic effects of nicardipine on systolic and diastolic left ventricular performance in patients with heart failure: A pilot study. *Clin Cardiol* 1986;9:257-261.
- 53 Lahiri A, Robinson CW, Tovey J, Carvana MP, Kohli RS, Harlow BJ, Raftery EB: Intravenous nicardipine in patients with chronic congestive heart failure: A nuclear stethoscope study. *Postgrad Med J* 1984;69(suppl 4):35-38.
- 54 Lahiri A, Rodrigues EA, Carboni GP, Raftery EB: Effects of long-term treatment with calcium antagonists on left ventricular diastolic function in stable angina and heart failure. *Circulation* 1990;81(suppl III):130-138.
- 55 Gheorghide M, Hall V, Goldberg D, Levine TB, Goldstein S: Long-term clinical and neurohormonal effects of nicardipine in patients with severe heart failure on maintenance therapy with angiotensin converting enzyme inhibitors (abstract). *J Am Coll Cardiol* 1991; 17(suppl A):274A.
- 56 Ljung B: Vascular selectivity of felodipine. *Drugs* 1985;29(suppl 2):46-58.
- 57 Timmis AD, Campbell S, Monaghan MJ, Walker L, Jewitt DE: Acute and metabolic effects of felodipine in congestive heart failure. *Br Heart J* 1984;51:445-451.
- 58 Emanuelsson H, Hjalmarsen A, Holmberg S, Waagstein F: Acute hemodynamic effects of felodipine in congestive heart failure. *Eur J Clin Pharmacol* 1985;28:489-493.
- 59 Tweddel AC, Hutton I: Felodipine in ventricular dysfunction. *Eur Heart J* 1986;7:54-60.
- 60 Binetti G, Pancaldi S, Giovanelli N, Negroni S, Ferretti RM, Branzi A, et al: Hemodynamic effects of felodipine in congestive heart failure. *Cardiovasc Drugs Ther* 1987;1:161-167.
- 61 Agostini P, Doria E, Riva S, Polese A: Acute and chronic efficacy of felodipine in congestive heart failure. *Int J Cardiol* 1991;30:89-95.
- 62 Dunselman PHJM, Kuntze CEE, Van Bruggen A, Hamer JPM, Scaf AHJ, Wesseling H, Lie KI: Efficacy of felodipine in congestive heart failure. *Eur Heart J* 1989;10:354-364.
- 63 Kassis E, Amtrop O: Cardiovascular and neurohumoral postural responses and baroreceptor abnormalities during a course of adjunctive vasodilatory therapy with felodipine for congestive heart failure. *Circulation* 1987;75: 1204-1213.
- 64 Kassis E, Amtrop O: Long-term clinical, hemodynamic, angiographic and neurohumoral responses to vasodilation with felodipine in patients with chronic congestive heart failure. *J Cardiovasc Pharmacol* 1990;15:347-352.

- 65 Tan LB, Murray RG, Little WA: Felodipine in patients with chronic heart failure: Discrepant haemodynamic and clinical effects. *Br Heart J* 1987;58:122-128.
- 66 Timmis AD, Smyth P, Kenny JF, Campbell S, Jewitt DE: Effects of vasodilator treatment with felodipine on hemodynamic responses to treadmill exercise in congestive heart failure. *Br Heart J* 1984;52:314-320.
- 67 Cohn JN, Ziesche SM, Loss LE, Anderson GF, and the V-HeFT Study Group: Effect of felodipine on short-term exercise and neurohormone and long-term mortality in heart failure: Results of V-HeFT III. *Circulation*, in press.
- 68 Smith WB, de Abate AC, Gollub SB, Tonkon MJ, Grossman WJ, Sharma SC, Goldenberg IF, Carley JE, Packer M: Beneficial long-term hemodynamic and clinical effects of amlodipine in chronic heart failure: Results of a multicenter randomized, double-blind, placebo-controlled, dose-ranging study. *Circulation* 1994;90(suppl):1-602.
- 69 Packer M, Nicod P, Khandheria BR, et al: Randomized, multicenter, double-blind, placebo-controlled evaluation of amlodipine in patients with mild-to-moderate heart failure (abstract). *J Am Coll Cardiol* 1991;17:274A.
- 70 O'Connor CM, Ghali JK, Pressler ML, Carson PE, Belkin RN, Miller AB, Neuberger GW, Frid D, Wertheimer JH, Cropp AB, DeMets DC: Effect of amlodipine on morbidity and mortality in severe chronic heart failure: Prospective randomized amlodipine survival evaluation study group. *N Engl J Med* 1996;335:1107-1114.
- 71 Clozel JP, Banken L, Osterrieder W: Effects of Ro 40-5967, a novel calcium antagonist, on myocardial function during ischemia induced by lowering coronary perfusion pressure in dogs: Comparison with verapamil. *J Cardiovasc Pharmacol* 1989;14:715-721.
- 72 Ezzaher A, Bouonani NEH, So JB, Hittinger L, Crozatier B: Increased negative inotropic effect of calcium channel blockers in the hypertrophied and failing rabbit heart. *J Pharmacol Exp Ther* 1991;257:466-471.
- 73 Investigational Drug Brochure Ro 40-5967 (calcium antagonist), January 1992, and addendum to the Investigational Drug Brochure (vers 4, January 1992) of Ro 40-5967 (calcium antagonist), January 1993.
- 74 Mulder P, Richard V, Compagnon P, Henry JP, Lallemand F, Clozel JP, Koen R, Mace B, Thuillez C: Increased survival after long-term treatment with mibefradil, a selective T-channel calcium antagonist, in heart failure. *J Am Coll Cardiol* 1997;29:416-421.
- 75 Levine BT for the MACH-1 Investigators: The design of the mortality assessment in congestive heart failure (MACH-1, mibefradil). *Clin Cardiol* 1997;20:320-326.