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# Calcium Channel Blockers in Heart Failure

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**The rationale for the use of calcium channel blockers in patients with chronic heart failure lies in their vasodilator action, anti-ischemic effect, ability to lessen left ventricular diastolic dysfunction and data showing their effect in preventing progression of myocardial dysfunction in animals with cardiomyopathy. Despite initial studies reporting improvement of the hemodynamic profile with nifedipine, further evaluation showed variable results, with hemodynamic worsening seen in up to 29% of patients. Longer-term controlled studies evaluating symptoms and clinical status demonstrated worsening chronic heart failure in ~25% of patients within 8 weeks of nifedipine therapy. Although diltiazem has a lesser myocardial depressant effect and its short-term use was associated with less frequent hemodynamic and clinical worsening, long-term exposure to the drug in a large group of patients with chronic heart failure due to left ventricular systolic dysfunction after myocardial infarction resulted in an increased incidence of cardiac events, with worsening heart failure and death. The use of verapamil in a similar patient cohort showed the loss of its demonstrated protective effect in patients with clinical evidence of heart failure.**

***In an attempt to improve the safety of calcium channel blockers, the following approaches were suggested: 1) use of second-generation drugs with less myocardial depressant effect; 2) concomitant use of angiotensin-converting enzyme inhibitors to prevent reported neurohormonal activation; and 3) development of drugs with favorable neurohormonal effects. These approaches led to mixed results. The use of some second-generation calcium channel blockers such as nisoldipine, felodipine and nicardipine resulted in no change or worsening of clinical status, which did not seem to be prevented by concomitant use of angiotensin-converting enzyme inhibitors. A recent study using amlodipine demonstrated improvement of both the clinical and neurohormonal profiles. Two large ongoing studies are evaluating the effects of felodipine and amlodipine on morbidity and mortality of patients with chronic heart failure and are likely to provide further information regarding the role of calcium blockers in the treatment of this cond'tion.***

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Although the incidence of the use of calcium channel blockers in the treatment of chronic congestive heart failure is not entirely known, recent published trials have indicated that such use is a common practice in both the United States and Canada. Over 30% of patients enrolled in the Studies of Left Ventricular Dysfunction (SOLVD) (1) were treated with calcium blockers at the time of their enrollment. These patients, although only mildly symptomatic, had severe depression of their left ventricular systolic function, with a mean left ventricular ejection fraction of 31%. Possibly more striking was the fact that patients enrolled in a recent study (2) evaluating the effect of milrinone on mortality were not infrequently on calcium channel blockers at the time of their enrollment (Packer M, personal communication). All these patients had to have severe symptoms of heart failure (class III and IV) to meet the inclusion criteria of the study and their mean left ventricular ejection fraction was 21%.

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## Rationale for the Use of Calcium Channel Blockers in Heart Failure

A theoretic rationale for the use of calcium channel blockers in the treatment of heart failure is multifactorial. These drugs and, in particular, the dihydropyridine derivatives have a strong arteriolar dilator effect and may result in reduction of systemic vascular resistance and thus left ventricular 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 reduce the incidence of death in patients with mild to moderate heart failure (3,4). The majority of available calcium antagonists have demonstrated to have a substantial anti-ischemic effect and many of them are used effectively in the treatment of the acute as well as the chronic ischemic syndrome (5–7). Because coronary artery disease is the underlying cause of chronic heart failure in 60% to 70% of patients (1–4), it is not surprising that many clinicians consider the use of calcium channel blockers in such patients a viable therapeutic option. The favorable effect of calcium antagonists on left ventricular relaxation may lead to improvement of diastolic dysfunction (8), which is an important cause of heart failure symptoms, even in patients with documented left ventricular systolic dysfunc-



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tion (9). In addition, the prevention of calcium ion entry into myocardial cells has been shown to prevent the development of alcohol-mediated cardiac dysfunction in hamster myocardium and could have a similar protective effect in humans (10).

## Nifedipine

Because of nifedipine's powerful vasodilator effect, a strong interest has been shown over the last decade in using this drug as an unloading agent in the treatment of heart failure. Several investigators (11–15) reported hemodynamic improvement after single-dose administration of nifedipine given either orally or sublingually in relatively small groups of patients with acute or chronic heart failure. The majority of these data were reported as a mean group response and demonstrated a reduction in systemic vascular resistance 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 (16) verified the predominant arteriolar and negligible venous effects of the drug.

Although the initial experience with the use of nifedipine in heart failure led to the conclusion by some investigators (11–15) that the negative inotropic effect of nifedipine may be offset by its vasodilator effect, further evaluation in larger groups of patients demonstrated the clinical relevance of the negative inotropic effect of the drug (17–19). Comparison of nifedipine with nitroprusside (20) demonstrated a smaller augmentation in cardiac output and a larger decrease in systemic blood pressure with nifedipine despite a similar reduction in systemic vascular resistance. These hemodynamic changes were associated with a decrease in the first derivative of left ventricular pressure (dP/dt) with nifedipine (21). Similarly, a comparison of changes in hemodynamic indexes of left ventricular systolic function after a similar reduction in systemic vascular resistance with hydralazine and nifedipine in the same patients with heart failure (18) resulted in a significantly smaller augmentation of stroke volume, cardiac output and left ventricular 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 (19–22) showed acute hemodynamic and clinical deterioration after a single dose of 20 to 50 mg of the drug in 19% and 29% of the patients, respectively. Hemodynamic response could not be predicted from baseline hemodynamic data and left ventricular ejection fraction (19). However, a strong relation was found between an unfavorable acute hemodynamic response to nifedipine, and long-term mortality data (22) supported the hypothesis that hemodynamic deterioration after nifedipine administration is more likely to occur in patients with more severe heart failure.

The long-term effect of nifedipine in patients with heart failure due to left ventricular systolic dysfunction was recently evaluated in two randomized trials. In the first study,

**Table 1. Episodes of Hospitalizations and Increase in Diuretic Drugs for Worsening Congestive Heart Failure**

| Treatment | Patients (no.) | | | CHF Episodes (no.) |
|---|---|---|---|---|
| | Hospitalizations | Increase in Diuretic Dose | Total | |
| NIF ($n$ = 21) | 5* | 3 | 8 | 9† |
| ISDN ($n$ = 20) | 0 | 3 | 3 | 3 |
| NIF+ISDN ($n$ = 23) | 6* | 2 | 8 | 21‡§ |

*$p < 0.05$ versus isosorbide dinitrate (ISDN). †$p < 0.09$ versus isosorbide dinitrate; ‡$p < 0.0001$ versus isosorbide dinitrate; §$p < 0.001$ versus nifedipine (NIF). CHF = congestive heart failure. Reproduced, with permission of the American Heart Association, Inc., from Elkayam et al. (24).

Agostoni et al. (23) compared in a double-blind crossover design, the effect of captopril (50 mg three times daily) and nifedipine (20 mg three times daily) 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. Although in the short-term, nifedipine resulted in a reduction in systemic vascular resistance that led to augmentation of cardiac output and a small reduction in left ventricular filling pressure, after prolonged treatment, cardiac output returned to baseline values and pulmonary artery wedge pressure increased substantially. These changes were accompanied by worsening heart failure symptoms in some patients. In a second study, Elkayam et al. (24) 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 enhanced diuretic therapy or hospitalization, or both, in patients treated with nifedipine either alone or in combination with isosorbide dinitrate (Table 1). Hospitalization was required by 24% of patients during nifedipine therapy, by 26% during nifedipine–isosorbide dinitrate combination therapy in comparison with 0% during isosorbide dinitrate therapy alone. The total number of episodes of worsening chronic heart failure was 9 during nifedipine therapy, 3 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.

## Diltiazem

These unfavorable results associated with the use of nifedipine in patients with chronic heart failure led to at-

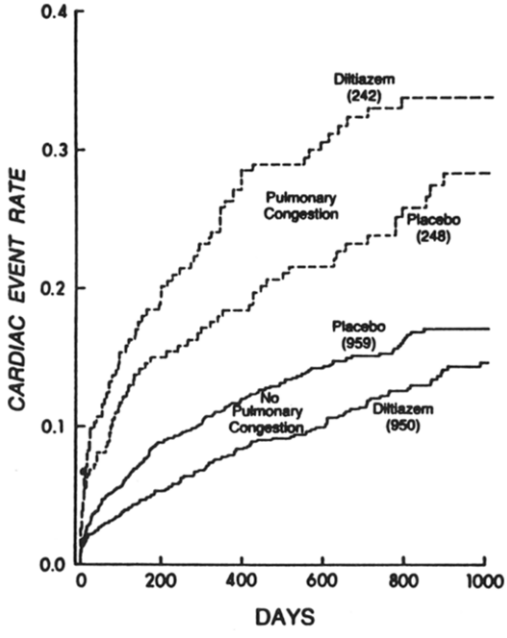


**Figure 1.** Cumulative rate of first recurrent cardiac events on diltiazem and placebo in patients with and without chest X-ray evidence of pulmonary congestion. Reproduced, with permission, from The Multicenter Diltiazem Postinfarction Trial Research Group (29).

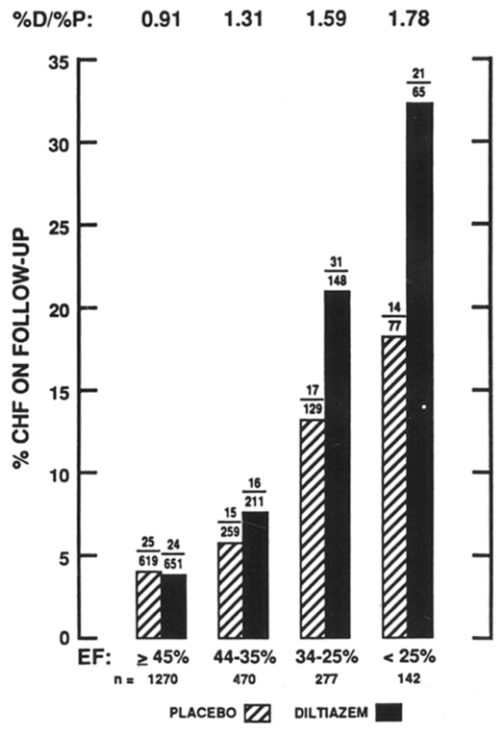


**Figure 2.** Relation between the percent of patients receiving diltiazem (D, **black bars**) or placebo (P, **hatched bars**) developing new or worsened congestive heart failure (CHF) during long-term follow-up. The number of patients with congestive heart failure is shown as the numerator and the total number in each ejection fraction (EF) group is shown as the denominator above each bar. Reproduced, with permission, of the American Heart Association, Inc., from Goldstein et al. (30).

tempts to use diltiazem, a first-generation calcium antagonist with a smaller myocardial depressant effect (25,26). Hemodynamic evaluation of this agent in patients with severe chronic heart failure demonstrated only little hemodynamic effect and a significantly lesser incidence of hemodynamic and symptomatic deterioration compared with results with nifedipine. However, occasional deterioration observed in these studies (25–27) was the first indication of the potential hazard of this drug as well. In 1989, Figulla et al. (28) reported on a prospective study using diltiazem (60 to 90 mg three times daily) in 22 patients with dilated cardiomyopathy in addition to conventional therapy with digitalis, diuretic drugs and vasodilators and compared their outcome with historical control data from 25 patients with chronic heart failure receiving conventional therapy alone. The mean survival of the control group was 29 months, whereas no patient treated with diltiazem died over a mean follow-up period of 15.4 months. In addition, a significant improvement in clinical status and left ventricular function was reported in the diltiazem group but not in the control group. Although the investigators suggested a beneficial effect of adjunctive diltiazem treatment in dilated cardiomyopathy, the uncontrolled design of the trial and the small number of patients in both arms severely limited both the scientific and the clinical value of the study.

The Multicenter Diltiazem Postinfarction Trial (29) provided useful information regarding the long-term use of this drug in patients with clinical heart failure (Fig. 1). This study evaluated the effect of diltiazem (240 mg/day) on mortality and reinfarction in 1,237 patients 3 to 15 days after the date of onset of myocardial infarction and compared it with 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 number of cardiac events. A similar pattern was observed with respect to depressed radionuclide ejection fraction and anterolateral Q wave infarction. In 1,909 patients without pulmonary congestion, diltiazem was associated with a smaller number of cardiac events. In a further evaluation of the development of congestive heart failure in this study, Goldstein et al. (30) 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 than were patients without these markers of left ventricular dysfunction. In addition, the diltiazem-associated increased likelihood of developing chronic heart failure was inversely related to the degree of left ventricular dysfunction (Fig. 2). This trial conclusively demonstrated the hazard involved in the use of diltiazem in patients with chronic heart failure due to left ventricular systolic dysfunction.

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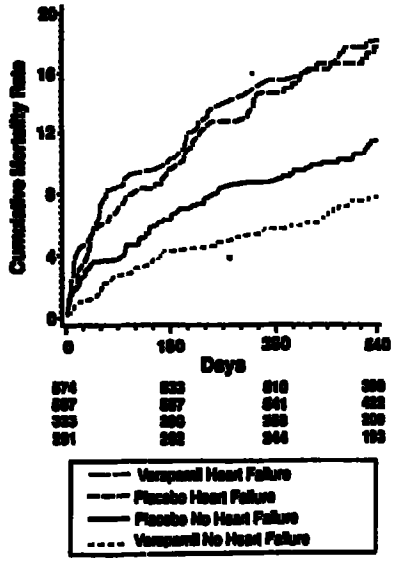


**Figure 3.** Cumulative cardiac event rate on verapamil and placebo in patients with and without heart failure. Reproduced, with permission, from The Danish Study Group on Verapamil in Myocardial Infarction (33).

## 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 (31). In a small study, Ferlinz and Gallo (32) followed up 10 patients with heart failure who initially demonstrated acute hemodynamic improvement after verapamil administration. However, during the follow-up period, four patients demonstrated symptomatic deterioration on long-term verapamil therapy. The Danish study on the effect of verapamil on death or reinfarction (33) 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 three times daily) versus placebo in patients 7 to 15 days after their myocardial infarction. At a mean follow-up time of 16 months verapamil had caused a significant reduction of mortality and cardiac events in patients without but not in patients with chronic heart failure (Fig. 3). The exclusion criteria to this study included 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.

## Causes of Unfavorable Effects of Calcium Channel Blockers

In summary, available information demonstrates a risk associated with the use of first-generation calcium antagonists in patients with heart failure due to left ventricular systolic dysfunction. These drugs have been shown to cause hemodynamic as well as clinical deterioration in a considerable number of patients and to increase the incidence of cardiac events in survival after myocardial infarction with clinically documented heart failure.

Is the etiology of chronic heart failure important in the response of patients to a calcium channel blocker? Controlled studies demonstrating the efficacy of calcium channel blockers as antianginal agents have usually excluded patients with chronic heart failure. However, unfavorable effects of these drugs in patients with chronic heart failure after myocardial infarction (24,30,33) and in patients with chronic heart failure due to coronary artery disease (22,24) suggest that calcium antagonists may not be safe, even in patients with chronic heart failure and ischemic heart disease.

The mechanism responsible for the clinical deterioration associated with calcium antagonists in heart failure is probably multifactorial. Immediate hemodynamic deterioration reported by some investigators (19–22,24,25) is most likely due to the negative inotropic effect of these drugs. Reported clinical deterioration despite hemodynamic improvement (32,34,35) may suggest activation of unfavorable neurohormonal mechanisms as a cause of the deterioration (36). Activation of the sympathetic nervous system, the renin-angiotensin system and vasopressin have been documented with nifedipine (21,37) and nisoldipine (35), a second-generation dihydropyridine. Because there is no evidence for reduction in renal blood flow with calcium antagonists in chronic heart failure (25,38), an increase in renin level is probably the result of blockade of the inhibitory effect of calcium on renin production (39). A third potential mechanism for clinical deterioration with calcium antagonists in chronic heart failure may be an increase in blood volume as shown by an increase in body weight (34) and decrease in hematocrit (27,34). An increase in blood volume may be due to decreased water excretion (35) and may be the cause of a substantial increase in pulmonary artery wedge pressure described by Agostoni et al. (23) during long-term treatment with nifedipine.

## New Approaches

In an attempt to improve the safety of calcium channel blocking drugs in patients with chronic heart failure, the following approaches have been suggested (36): 1) use of second-generation calcium antagonists that have less direct myocardial effect; 2) combining calcium channel blockers with converting enzyme inhibition to prevent neurohormonal activation; and 3) developing calcium channel block-

ers that exert favorable neurohormonal effects. Some currently available information may help to assess the validity of these approaches. Barjon et al. (35) used nisoldipine, a second-generation calcium channel blocker with potent vasodilator effects and only mild negative inotropic effects (40), and reported the development of pulmonary edema in seven patients during a 2-month follow-up period. Felodipine, another calcium antagonist of dihydropyridine group, is reported to have negligible negative inotropic effects and high selectivity to smooth muscle (41). Its use was reported by Dunselman et al. (42), who found in a double-blind study, an improvement in aerobic capacity and exercise duration after 16 weeks of enalapril (10 mg twice daily) therapy in 11 patients with class III congestive heart failure but not in 9 patients receiving felodipine (10 mg twice daily). In a preliminary study, Gheorghiade et al. (43) evaluated the effect of nicardipine, another second-generation calcium antagonist, in patients with moderate to severe heart failure. To evaluate the hypothesis that calcium channel blockade may benefit patients with chronic heart failure when used concomitantly with angiotensin-converting enzyme inhibitors, which may prevent stimulation of neuroendocrine systems, all patients were concomitantly treated with captopril. Despite this adjunctive therapy, the use of nicardipine (20 to 30 mg every 8 h) over 4 months resulted in worsening of chronic heart failure in 60% of patients receiving nicardipine and 20% of patients receiving placebo ($p = 0.06$). Concomitant use of captopril also did not prevent neurohormonal activation mediated by nicardipine (renin increased from $7 \pm 6$ to $22 \pm 28$ ng/ml per h, $p < 0.05$). The studies just mentioned suggest that the use of second-generation calcium channel blockers with reported selectivity to smooth muscle and the concomitant use of angiotensin-converting enzyme inhibitors does not provide a simple solution to lack of efficacy or the deleterious effects of the calcium channel blockers in patients with chronic heart failure.

Will the use of calcium antagonists with favorable effects on neurohormonal systems be beneficial for the treatment of chronic heart failure? A positive answer to this question may be suggested by the results of a recently completed multicenter study (44) of amlodipine in chronic heart failure. In this study, 186 patients with class II and III chronic heart failure (left ventricular ejection fraction <40%) were randomized to treatment with amlodipine, a second-generation dihydropyridine calcium channel blocker, or to placebo and were followed up for 4 months. All patients received a diuretic drug and digitalis and 80% were also treated with angiotensin-converting enzyme inhibition. The results of this trial demonstrated a significantly larger improvement in exercise time ($62 \pm 17$ vs. $22 \pm 13$ s, $p < 0.05$) and reduction in chronic heart failure symptoms (55% vs. 29%, $p < 0.05$) with amlodipine than with placebo. These favorable changes were associated with a significant reduction in the serum norepinephrine level.

Although the results of this study are encouraging and may extend the therapeutic bridge of calcium antagonists (45) far enough to provide treatment benefit to patients with chronic heart failure, consistent evidence for deleterious effects of calcium channel blockade in such patients suggests the need for caution. Fortunately, more information is likely to become available regarding the safety and efficacy of calcium channel blocking agents in chronic heart failure. The ongoing Vasodilators in Heart Failure Trial (V-HeFT III) is evaluating the effect of felodipine compared with placebo on morbidity and mortality in patients with mild to moderate chronic heart failure treated with diuretic drugs and angiotensin-converting enzyme inhibitors with and without digoxin. In addition, the ongoing Prospective Randomized Amlodipine Survival Evaluation (PRAISE) is studying the effect of amlodipine versus placebo on survival in patients with class III and IV chronic heart failure who are concomitantly treated with angiotensin-converting enzyme inhibitors.

These studies are likely to provide the information needed to determine whether there is a role for calcium channel blockade in the treatment of chronic heart failure due to left ventricular systolic dysfunction.

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