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Calcium Channel Blockers in the Management of Myocardial Infarction Patients*

Mihai Gheorghiade, MD

Increased cardiovascular mortality during the post myocardial infarction (MI) period is related to left ventricular dysfunction, recurrent infarction, and arrhythmias. Several trials have demonstrated conclusively the effectiveness and safety of beta-blocker therapy for patients recovering from acute MI (1,2). Although structurally heterogeneous, calcium channel blockers are a group of drugs that have in common the pharmacological property of blocking or reducing the entrance of calcium into cardiac and smooth vascular muscle (3). The following agents are approved for use in the United States: diltiazem, verapamil, nifedipine, nicardipine, bepridil, isradipine, and nimodipine. For several years these agents have been used successfully in the treatment of vasospastic angina, exertional angina, unstable angina, supraventricular arrhythmias (verapamil, diltiazem), hypertension, and symptomatic hypertrophic cardiomyopathy (verapamil). Several experimental studies examined the effects of calcium channel blockers in experimental MI. In general, they have shown favorable results affecting infarct size in animal models (4-13). Because, unlike beta-blockers, the structure and cardiovascular pharmacology of calcium channel blockers are heterogeneous (14), this report will evaluate separately the effects of different calcium channel blockers in patients with suspected or confirmed MI.

Calcium Channel Blockers in Undifferentiated Acute MI

Nifedipine
The Nifedipine Angina Myocardial Infarction Study (NAMIS) (15) randomized patients with suspected MI within 6 hours after onset of symptoms to nifedipine or placebo; the therapy was continued for 14 days. The progression to MI was identical (75%) in the placebo and nifedipine groups. Although the two-week mortality rate was higher in the nifedipine group when compared with the placebo group at six months of follow-up, the mortality rate was approximately 10% in both groups (Table 1).

The Norwegian Nifedipine Multicenter Trial (16) examined patients with suspected MI enrolled within 12 hours of the onset of symptoms and randomized to nifedipine or placebo; therapy continued for 4 weeks. There was a trend toward a larger infarct size in the nifedipine group. This was particularly evident in patients with hypotension or an increased heart rate at the time of the randomization. At six months of follow-up, no differences in mortality were observed between the nifedipine and placebo groups (Fig 1).

The Trial of Early Nifedipine in Acute Myocardial Infarction (TRENT) (17) studied a large number of patients with suspected MI within 24 hours after the onset of symptoms. Those patients were randomized between two groups to receive initially two doses of sublingual nifedipine followed by oral nifedipine or placebo that was continued for the next 30 days. At one month of follow-up, the mortality rate in patients with confirmed MI was 10.2% in the nifedipine group and 9.3% in the placebo group. These differences were not statistically significant. Compared with the placebo group, the nifedipine-treated group was found to have a significant decrease in both systolic and diastolic blood pressure and an increase in heart rate. Ventricular arrhythmias, including ventricular fibrillation, were similar in the two groups. No benefit in the nifedipine-treated patients was observed in those randomized within 4 hours, as well as within 4 to 24 hours, after onset of symptoms. Since the cardiac events were similar in the two groups, this study was terminated prematurely.

The Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT-I) (18) randomized a large number of patients with confirmed MI 7 to 21 days after the event to nifedipine or placebo; therapy continued for one year. No significant differences in infarct size were detected between the two groups. The reinfarction rate was low and not different between the nifedipine or placebo groups. Similarly, the mortality rate was identical in the two groups. No differences were found between placebo and nifedipine-treated patients when patients were stratified in three groups (male-first MI, male-second MI, and female).

The SPRINT-II (19) enrolled high-risk acute MI patients (prior MI, anterior location, angina) to nifedipine or placebo.
The study was terminated early due to an excess mortality noted in the nifedipine group. This excessive mortality rate was particularly apparent during the first six days of the study.

Müller et al (20) studied patients with unstable angina who were randomized to nifedipine or placebo for 14 days. In a subset of patients not receiving prior propranolol, initiation of conventional therapy produced more rapid pain relief than initiation of nifedipine therapy, which tended to increase the heart rate. For the study population as a whole, nifedipine alone was equivalent to conventional therapy for unstable angina (Fig 2). This study suggests that combination nifedipine and beta-blocker therapy is safe and beneficial in patients with unstable angina.

The Holland Interuniversity Nifedipine/Metoprolol Trial (21) studied the effects of nifedipine, metoprolol, and their combination in patients with unstable angina. The endpoints were recurrent ischemia and infarction at 48 hours of follow-up. This study was terminated early because the interim analysis showed that the risk of developing acute MI was higher in the group receiving nifedipine alone. In the group that received prior beta-blocker therapy, the addition of nifedipine was beneficial in reducing ischemia. In patients not receiving a beta-blocker, nifedipine caused an increase in MI and ischemia. The combination of metoprolol and nifedipine had no advantage over metoprolol alone.

Walker et al (22) examined patients with suspected MI enrolled within the first 6 hours after onset of symptoms. Patients were randomized to nifedipine sublingually, then orally for the next 24 hours, or placebo. At two weeks of follow-up, the mortality and reinfarction rates were similar in the two groups. The incidence of ventricular arrhythmias in-hospital was similar.

### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Entry After Symptoms</th>
<th>Oral Daily Dose</th>
<th>Duration of Therapy</th>
<th>Reinfarction</th>
<th>Mortality</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAMIS (1984) (15)</td>
<td>171</td>
<td>&lt; 6 hrs</td>
<td>120 mg</td>
<td>14 days</td>
<td>?</td>
<td>?</td>
<td>10.1% 8.5% None</td>
</tr>
<tr>
<td>Norwegian Trial (1984) (16)</td>
<td>227</td>
<td>&lt; 12 hrs</td>
<td>40 mg</td>
<td>6 weeks</td>
<td>?</td>
<td>?</td>
<td>8.9% 8.7% None</td>
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<tr>
<td>TREAT (1986) (17)</td>
<td>4,491</td>
<td>&lt; 24 hrs</td>
<td>40 mg</td>
<td>30 days</td>
<td>2.2% 1.5%</td>
<td>10.2% 9.3% None</td>
<td></td>
</tr>
<tr>
<td>SPRINT (1988) (18)</td>
<td>2,276</td>
<td>7-21 days</td>
<td>30 mg</td>
<td>12 months</td>
<td>4.4% 4.8%</td>
<td>5.8% 5.7% None</td>
<td></td>
</tr>
<tr>
<td>Gottlieb et al (1988) (23)</td>
<td>132</td>
<td>&lt; 12 hrs</td>
<td>120 mg</td>
<td>6 weeks</td>
<td>9.3% 10.2%</td>
<td>6.2% 5.8% None</td>
<td></td>
</tr>
<tr>
<td>Walker et al (1988) (22)</td>
<td>434</td>
<td>&lt; 6 hrs</td>
<td>60 mg</td>
<td>14 days</td>
<td>4.7% 2.5%</td>
<td>6.6% 5.8% None</td>
<td></td>
</tr>
<tr>
<td>SPRINT II (1988) (19)</td>
<td>1,373</td>
<td>&lt; 48 hrs</td>
<td>60 mg</td>
<td>6 months</td>
<td>?</td>
<td>?</td>
<td>15.4% 13.2% Excess</td>
</tr>
<tr>
<td>Erbel et al (1988) (25)</td>
<td>149</td>
<td>6 hrs</td>
<td>60 mg</td>
<td>28 days</td>
<td>16.0% 11.0%</td>
<td>13.0% 8.0% None</td>
<td></td>
</tr>
</tbody>
</table>

I = intervention with nifedipine, P = placebo.
Fig 3—Cumulative death rate for all patients included in study. (From The Danish Study Group on Verapamil in Myocardial Infarction. Eur Heart J 1984;5:516-28. Reprinted with permission.)

Gottlieb et al (23) randomized low-risk acute MI patients enrolled within the first 12 hours after onset of symptoms to nifedipine or placebo. At six weeks of follow-up, no significant differences between the two groups were noted in left ventricular function and dimensions and infarct size. The mortality and reinfarction rates were similar in the two groups.

Branagan et al (24) studied patients with suspected MI, randomized to nifedipine sublingually and followed by oral nifedipine for two days, or placebo. There were no differences between the two groups with regard to a one-month mortality rate or the progression to acute MI.

Erbel et al (25) examined patients with suspected MI who received intravenous and intracoronary streptokinase within the first 6 hours after onset of symptoms. These patients were randomized into two groups: nifedipine, 20 mg sublingually and intracoronary, followed by nifedipine, 20 mg orally three times a day for the duration of the hospital stay, or placebo. In both groups the mean time between onset of symptoms and the beginning of treatment was 2.5 hours. Creatine kinase (CK) MB isoenzyme release was higher in the nifedipine group. All patients underwent cardiac catheterization. Patients who continued to have an occlusion in the infarct-related artery underwent coronary angioplasty. In-hospital mortality was 13% in the nifedipine group and 8% in the placebo group. The incidence of reinfarction was 16% in the nifedipine group compared with 11% in the placebo group. The reocclusion rate was 20% in the nifedipine group compared with 13% in the placebo group. Ventricular function was similar in the two groups. The incidence of ventricular arrhythmias seemed to be reduced by the administration of nifedipine.

It appears from the above studies that nifedipine does not reduce infarct size, reinfarction, or mortality in patients with suspected or confirmed MI when given early (less than 24 hours) or in the postinfarction period. This lack of benefit is noted in all patients: male or female, those at low risk or high risk, those with ST elevation or ST depression, or when used alone or in combination with a beta-blocker or a thrombolytic agent. Some of the studies suggest that nifedipine may have a detrimental effect, particularly in patients with a relatively decreased blood pressure and/or increased heart rate. This detrimental effect may be related to a sudden and marked decrease in blood pressure resulting in a decrease in coronary artery perfusion pressure (26), disproportional dilatation in the coronary artery adjacent to the ischemic area (coronary artery steal), or reflex activation of the sympathetic nervous system (27) with a resultant increase in myocardial oxygen consumption.

Verapamil

The Danish Verapamil Infarction Trial (DAVIT-I) (28) randomized 3,498 patients with confirmed MI into two groups: intravenous verapamil or placebo (Table 2). Of these, 1,436 had a confirmed MI and therapy with oral verapamil or placebo was continued. Enrollment occurred in the first 48 hours after onset of symptoms (58% of patients were enrolled within 6 hours, 26% between 6 and 24 hours, and 16% between 24 and 48 hours). Of these, 1,436 had a confirmed MI and therapy with oral verapamil or placebo was continued. Enrollment occurred in the first 48 hours after onset of symptoms (58% of patients were enrolled within 6 hours, 26% between 6 and 24 hours, and 16% between 24 and 48 hours).
hours). Patients over 75 years of age and those with cardiogenic shock, heart failure, sinoatrial or atrioventricular block, or concomitant therapy with a calcium channel blocker or beta-blocker were excluded. At six months of follow-up, the mortality and reinfarction rates were similar in the verapamil and the placebo groups (Fig 3). However, the in-hospital complication rate was significantly greater in patients who received verapamil therapy (heart failure, second- or third-degree atrioventricular block), resulting in early withdrawal. There was also an excess in-hospital mortality rate from cardiogenic shock in the verapamil group. However, verapamil-treated patients who survived for 14 days and 21 days had a lower mortality and reinfarction rate, respectively, at six months of follow-up. In 100 patients in the DAVIT-I (29), randomized within 4 hours after the onset of symptoms of acute MI to verapamil or placebo, infarct size was similar in the verapamil and placebo groups.

The DAVIT-II (30) examined 1,775 patients with confirmed MI; 878 were randomized to verapamil and 897 to placebo approximately 10 days after the index MI. After 18 months there was no significant reduction in mortality in the verapamil group compared to the placebo group. Cardiac events defined as mortality and reinfarction combined were lower in the verapamil group. Subgroup analyses demonstrated that heart failure was related to the event rate. In the group of patients without heart failure, verapamil therapy caused a significant reduction in 18-month mortality and/or reinfarction. The group with no heart failure constituted 65% of the total study population. No significant differences were found between the two treatment groups in the remaining 35% of patients with heart failure (Fig 4).

It appears that verapamil may be useful in reducing mortality and reinfarction rate when used in patients with preserved left ventricular function and no signs of heart failure and when started several days after the acute MI. Verapamil is relatively contraindicated in patients with heart failure or bradyarrhythmias or in the first 24 to 48 hours after the onset of symptoms of the acute MI.

Diltiazem

The Multicenter Diltiazem Postinfarction Trial (MDPIT) (31) evaluated the effect of diltiazem on cardiac event rate (mortality and/or reinfarction) in a large number of patients who had a recent MI (Table 3). The mean follow-up was 25 months. Although the incidence of cardiac events, mortality rate, and reinfarction was lower in the diltiazem group, this difference was not statistically significant. Patients receiving diltiazem had an increased incidence of atrioventricular block and hypotension. Patients without pulmonary congestion on chest x-ray or a left ventricular ejection fraction of greater than 40%, representing 80% of the patients enrolled, had a 30% reduction in cardiac events when compared with the placebo group. In contrast, in patients with pulmonary congestion on chest x-ray, diltiazem was associated with a significant 25% increase in cardiac events (Fig 5).

![Fig 4—Cumulative mortality rates in patients with and without heart failure (P = 0.02), according to treatment. The numbers of patients at risk are shown at the bottom (placebo, no heart failure, n = 574; verapamil, no heart failure, n = 587; placebo, heart failure, n = 323; verapamil, heart failure, n = 291). (From the Danish Study Group on Verapamil in Myocardial Infarction. Effect of verapamil on mortality and major events after acute myocardial infarction. Am J Cardiol 1990;66:779-85. Reprinted with permission).](image)

Table 3

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Entry After Symptoms</th>
<th>Oral Daily Dose</th>
<th>Duration of Therapy</th>
<th>Reinfarction I</th>
<th>P</th>
<th>Mortality I</th>
<th>P</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRS (1986) (36)</td>
<td>576*</td>
<td>24-72 hrs</td>
<td>360 mg</td>
<td>2 weeks</td>
<td>5.2%</td>
<td>9.3%</td>
<td>3.8%</td>
<td>3.1%</td>
<td>Less reinfarction</td>
</tr>
<tr>
<td>MDPIT (1988) (31)</td>
<td>2,466</td>
<td>3-5 days</td>
<td>240 mg</td>
<td>25 months</td>
<td>8.0%</td>
<td>9.4%</td>
<td>10.3%</td>
<td>10.0%</td>
<td></td>
</tr>
</tbody>
</table>

*Confirmed non-Q wave myocardial infarction.
†Subgroup analysis suggests that in patients without heart failure in the coronary care unit, diltiazem when compared to placebo caused a significant reduction in major cardiac events (mortality and reinfarction).
I = intervention with a calcium channel blocker, P = placebo.
Non-Q Wave MI

Non-Q wave MI patients are different compared to Q wave MI patients (32). They have a smaller infarct size, more frequent patent infarct-related artery, and a larger residual mass of viable myocardium at risk within the perfusion zone of the infarct-related artery (33). Although the initial mortality is lower, the long-term prognosis is the same or even worse when residual ischemia is present, when compared to patients with Q wave MI (34). The pathophysiologic mechanism is probably related to transient coronary occlusion with spontaneous reperfusion (35).

The only study to be conducted prospectively in patients with non-Q wave MI was the multicenter Diltiazem Reinfarction Study (DRS) (36). In this trial, 576 patients were randomized into two groups: diltiazem, 90 mg four times a day, or placebo for 14 days. The treatment began 24 to 72 hours after onset of symptoms. In both placebo and diltiazem groups, approximately 60% of patients received beta-blocker therapy and 80% were taking nitrates. The combination of diltiazem and β-adrenergic blockers was well tolerated. During the 14-day follow-up, the reinfarction rate (Fig 6) and postinfarction angina were significantly lower in the diltiazem group when compared with placebo. The 14-day mortality rate was low and not different in the two groups. However, this study showed that despite maximal medical therapy with calcium channel blockers, beta-blockers, and nitrates, patients with non-Q wave MI developing postinfarction angina associated with electrocardiographic changes have a higher mortality (37) in the immediate postinfarction period. In addition, persistent ST depression (38,39) was an indicator of increased mortality and reinfarction at one year of follow-up.

In the MDPIT, Boden et al (40) found that patients with the first non-Q or the first inferior Q wave infarction who have a preserved left ventricular function appear to benefit from chronic diltiazem therapy (Fig 7). In this subgroup analysis, it was found that patients with their first non-Q wave MI, despite pulmonary congestion on chest x-ray at the time of admission, also had a lower mortality compared to the placebo group. This study concluded that long-term therapy with diltiazem may decrease the instance of recurring cardiac events in most patients after a non-Q or an inferior Q wave MI. However, such treatment is not indicated for patients with multiple infarctions or for those who exhibit pulmonary congestion or other objective evidence of left
ventricular dysfunction after the Q wave infarction, regardless of electrocardiographic location.

Recently Moss et al (41) found that diltiazem is of benefit in patients recovering from a Q and non-Q wave MI who have a history of hypertension and preserved left ventricular function. In contrast, patients with hypertension and a decrease in left ventricular ejection fraction had an increase in cardiac events in response to diltiazem therapy.

From these studies, it appears that patients who benefit most from long-term diltiazem are those with a non-Q wave MI or patients with a Q wave MI with preserved left ventricular function and no signs of heart failure, particularly if they have a history of hypertension.

**Therapeutic Implications**

Data indicating that beta-blockers reduce both mortality and reinfarction in the acute and long-term phases after MI are clear and overwhelmingly significant (1,2). However, evidence favoring the use of calcium channel antagonists early or postinfarction is significantly weaker (42-44). From available data, it can be concluded that dihydropyridine, like nicardipine and nifedipine, plays no role in the treatment of acute MI in either the acute or the recovery phase. In contrast, calcium channel blockers like verapamil and diltiazem can be used (45,46) in patients recovering from an acute MI who do not have signs and symptoms of congestive heart failure (47,48) (Fig 8) and have preserved left ventricular function, particularly if those patients have a contraindication to or cannot tolerate beta-blockers. Patients with non-Q wave MI are benefited by diltiazem therapy (49). It appears that verapamil and diltiazem are beneficial in patients with small MI (Q and non-Q wave MI) and no history of heart failure. In contrast, beta-blockers are particularly beneficial in patients with large MIs and/or a history of heart failure (50).

**References**

11. Foster E, Delong D, Connolly C, Apstein CS. Failure of nifedipine and reperfusion to reduce infarct size relative to region at risk as measured by NADH fluorophotography. Circulation 1984;70:506-12.