Calcium antagonists are frequently used for the treatment of patients with angina or hypertension. Their use post-MI continues to be a discussion point. On the one hand, heart rate-lowering calcium antagonists were shown to be beneficial in non-Q wave myocardial infarction (non-Q MI) based on the results of the Diltiazem Reinfarction, DAVIT II, and MDPIT studies. On the other hand, the latter two studies also indicated detrimental effects in patients with significant LV dysfunction. Short-acting dihydropyridines are detrimental and long-acting have not been studied. Interestingly, the results of the PRAISE and DiDi studies, and more recently, the large randomized SYST-EUR study, suggested safety even in patients with severe idiopathic cardiomyopathy or in elderly patients with hypertension. These conflicting results have been made even more confusing by recent controversy with respect to the safety of calcium antagonists. This issue has been adequately dealt with in our previous reports. The most recent analysis of the CAMI database adds to the safety experience.

The use of calcium channel blockers (CCBs) following myocardial infarction remains controversial. Recent studies have raised concerns regarding the safety of CCBs post-MI which would be best resolved in a properly designed randomized perspective study. However, it is possible that a post hoc analysis of a large, nonselected, postmyocardial infarction database may help better define the potential risk of using of CCBs in this patient population. The objective of this study was to assess the influence of CCB treatment on mortality and reinfarction following myocardial infarction.

The Canadian Assessment of Myocardial Infarction (CAMI) study entered patients from ten Canadian centres. All patients with documented myocardial infarctions presenting to participating centres were identified by reviewing all daily hospital admissions to coronary care units or intensive care units. As well, patients with myocardial infarction in other areas of the hospital, including the medical and cardiac wards and the emergency room, were identified by an ongoing screening process. In all, 4,133 consecutive patients were enrolled and followed for a minimum of 48 months. The definition of an acute myocardial infarction included at least two of the following criteria:

- chest pain lasting at least 20 minutes
- new Q-waves of at least 0.04 seconds in at least two contiguous leads
- creatine kinase \( \geq \) 1.5 times the upper limit of normal
- CK-MB fraction \( \geq \) 5% when simultaneous reference CK exceeded the upper limit of normal.

Selecting the patients and collecting the data

Patients were recruited from July 1, 1990 to October 31, 1991; the only exclusion criteria being age greater than 75 years. During that time period, 2,477 patients were recruited. Thereafter, 1,656 patients of all ages were included and there were no exclusion criteria. All patients had their demographic variables and cardiac history assessed. In addition, therapeutic interventions used to treat their acute myocardial infarctions were documented. Data were collected by specialized research nurses and verified by the participating physicians. Information was obtained by chart review, by direct interview.
with the patient and his/her family and by interviewing the treating physician. For endpoints, all data pertinent to the event were verified. Of the consecutive patients with acute myocardial infarction, 3,178 had presented directly to, or had their myocardial infarction in, the participating hospitals and 955 had been transferred from another institution.

**The results**

For the purpose of this report, the primary endpoint was death or recurrent myocardial infarction as defined above. Analyses were performed comparing patients treated with CCB with those not receiving CCB treatment. As well, patients receiving CCB treatment were compared with those receiving beta-blocker treatment (BB). Analyses were performed on the basis of the treatment received at discharge (i.e. “intention to treatment”) by Chi square analysis. As well, analyses were performed attributing events to the actual treatment received (i.e. “exposure analysis”) using a Wilcoxon rank-sum test.

As shown in figure 1, 4,133 patients were identified. Of these, 423 died in hospital. The remaining 3,714 patients who survived to discharge formed the study group. Of these, 921 received a CCB at discharge and 2,789 were not given a CCB. Of the CCB-treated group, 156 were on nifedipine and 765 were on a heart rate-lowering (HRL) CCB, the majority receiving diltiazem. Mortality or reinfarction based on treatment assignment at discharge is shown in figure 2. There were no significant differences between patients treated with CCB and those who were not. Similarly, there were no significant differences in events in patients receiving a HRL CCB compared to the non-calcium channel blocker treated group. A further analysis was performed examining the influence of BB therapy on event rate, either alone or in combination, with CCB therapy.
event rate that was not statistically different from those receiving CCB alone.

A multivariate analysis was performed to determine whether these differences were due to differences in baseline clinical characteristics. As shown in Table 1, there were highly significant differences in important clinical characteristics known to influence outcome following myocardial infarction between the four groups. Interestingly, patients treated with CCB at discharge belonged to a higher risk group than those treated with BB. Patients who received neither BB nor CCB appeared to be a heterogeneous group; many exhibited low risk characteristics. However, there was a substantial proportion of patients in Killip class IV (6%) which undoubtedly influenced the outcome. When corrected for these differences in baseline characteristics, the P values for differences in event rates following myocardial infarction were no longer significant between the groups. Therefore, based on an “intention to treat” analysis attributing events to treatment at discharge, no significant differences could be found between patients receiving or not receiving CCB therapy.

**Refining the analysis**

There are significant limitations to this analysis. First of all, patients may not have remained on the “assigned” treatment throughout the follow-up period, and secondly, patients may have been started on CCB treatment after hospital discharge. For this reason, an “exposure” analysis was performed and

<table>
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<tr>
<th>Table 1: Clinical characteristics</th>
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<tr>
<td><strong>CCB (511)</strong></td>
</tr>
<tr>
<td>Age(y)</td>
</tr>
<tr>
<td>Sex(m)</td>
</tr>
<tr>
<td>Diabetes</td>
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<tr>
<td>Angina</td>
</tr>
<tr>
<td>Prev. MI</td>
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<td>Hyperchol.</td>
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<td>Thrombolysis</td>
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<td>Killip Class: IV</td>
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Corrected p value 0.62 0.07
mortality was attributed at each follow-up visit based on the
treatment assignment at the prior visit. In this way, there could
be a high degree of confidence that the patient was actually
receiving the assigned treatment at the time when the events
occurred. The results of this analysis are shown in figure 4.

Interestingly at each follow-up visit, the mortality of
patients receiving CCBs tended to be lower than that of
patients not receiving CCBs, and for specific comparison
involving heart rate-lowering CCBs only, there was a signif-
cicant difference. In addition, there were strong trends
(0.05<p<0.1) favouring CCBs at 6- and 12-month follow-up
visits. It should be noted that there was a reasonably con-
stant number of patients receiving calcium channel blockers
throughout the follow-up period. As well, there was a large
number of patients that “crossed-over” between treatment
groups; that is, they either stopped CCB treatment or were
started on CCB treatment. This group of patients afforded
the opportunity to perform a paired analysis of event rates
based on exposure to CCB using each patient as his or her
own control.

Therefore, 1,082 patients were identified who at some
period during the course of their follow-up were receiving
CCBs, and at another period, did not. As shown in Figure 5,
the event rates were lower during periods when patients were
receiving CCB treatment compared to periods when they were
not, although this did not reach statistical significance.

A second analysis was performed in 354 patients who at
some time during the course of their follow-up were receiving
CCB (without BB) and at another time were receiving BB
(without CCB). Again, as shown in figure 5, there was no dif-
fERENCE in the event rates during periods of CCB versus BB use.

Summary

These data show that, based on the treatment assignment
at discharge, there were no significant differences in outcome
between patients receiving and not receiving CCB. Moreover,
an apparent excess of events in patients treated with CCB,
compared to BB, was not statistically significant when cor-
rected for differences in baseline characteristics between
these groups of patients. Finally, an “exposure analysis” did
not unmask differences in event rates attributable to CCB
therapy. The authors conclude that a detailed post hoc analy-
ysis of a large consecutive myocardial infarction database did
not reveal excess mortality or reinfarction in patients treated
with CCB. Therefore, the use of heart rate-lowering CCBs
and possibly long-acting dihydropyridines is safe when used
in appropriately selected patients. Further data with respect
to the efficacy of calcium antagonists is expected from large
randomized studies which are ongoing.

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