SMH ST. MICHAEL'S HOSPITAL Cardiology
UNIVERSITY OF TORONTO
A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO
Scientific Update™

Are Calcium Channel Blockers Safe Post-Myocardial Infarction? The CAMI Experience

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70th Scientific Sessions of the American Heart Association
Orlando, Florida, November 9-12, 1997

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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[1], DAVIT II[2,] and MDPIT[3] 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[4] and DiDi[5] studies, and more recently, the large randomized SYST-EUR study,[6] 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 ≥1.5 times the upper limit of normal
- CK-MB fraction ≥ 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

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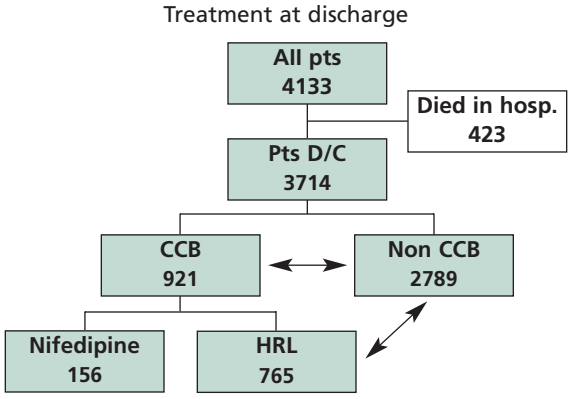
Figure 1: Selection of patients



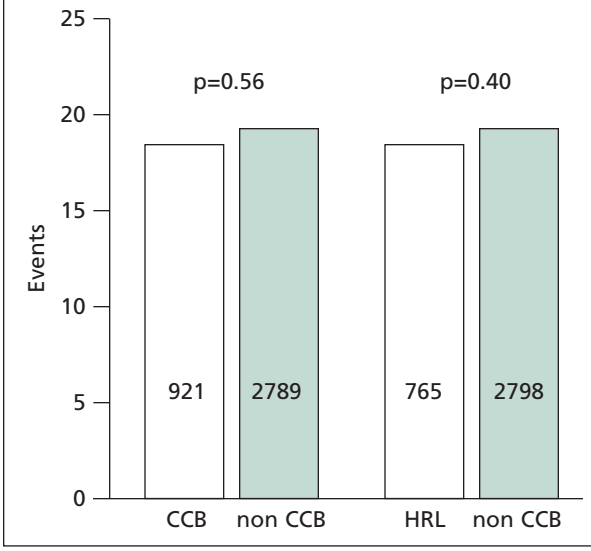
with the patient and his/her family and by interviewing the treating physician. For endpoints, all data pertinent to the event were verified. Of the consecutive patients with acute myocardial infarction, 3,178 had presented directly to, or had their myocardial infarction in, the participating hospitals 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 from hospital (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 Wiloxon 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 nifedepine 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.

Figure 2: Mortality or reinfarction based on treatment at discharge.



As a result, four groups of patients were identified as shown in figure 3. Compared to patients who received BB alone (i.e. without CCB), the group treated with a CCB alone (i.e. without BB) showed a significantly higher event rate over the follow up period. Those treated with both CCB and BB had similarly low event rates as did those receiving BB alone. Patients treated with neither CCB nor BB had a higher

Figure 3: Mortality or reinfarction based on treatment at discharge.

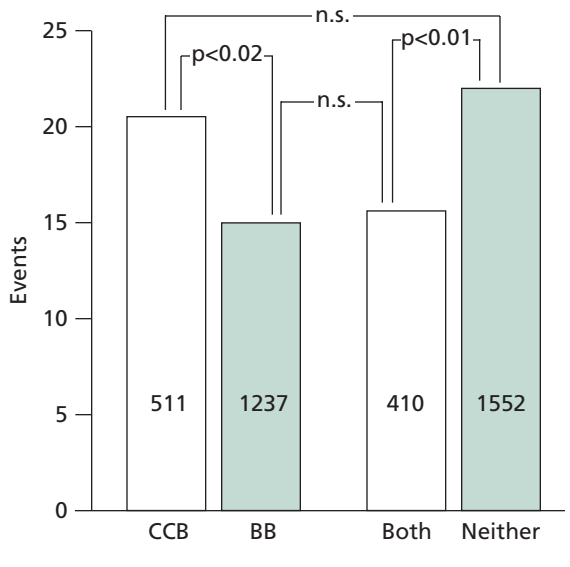


Table 1: Clinical characteristics

	CCB (511)		BB (1237)	Both (410)		Neither (1552)
Age(y)	61(11)	<0.0001	58(11)	61(11)	n.s.	62(12)
Sex(m)	69%	<0.001	80%	71%	n.s.	71%
Diabetes	22%	<0.001	15%	21%	n.s.	21%
Angina	58%	<0.001	47%	72%	<0.001	55%
Prev. MI	31%	<0.001	21%	39%	<0.001	31%
Hyperchol.	37%	<0.01	30%	34%	<0.01	27%
Thrombolysis	34%	<0.001	57%	34%	<0.01	41%
Killip Class: IV	0.6%	<0.05	1%	0.7%	<0.001	6%
Corrected p value		0.62			0.07	

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

Figure 4: Mortality at each follow-up visit based on treatment, p values shown by comparison to non-CCB group.

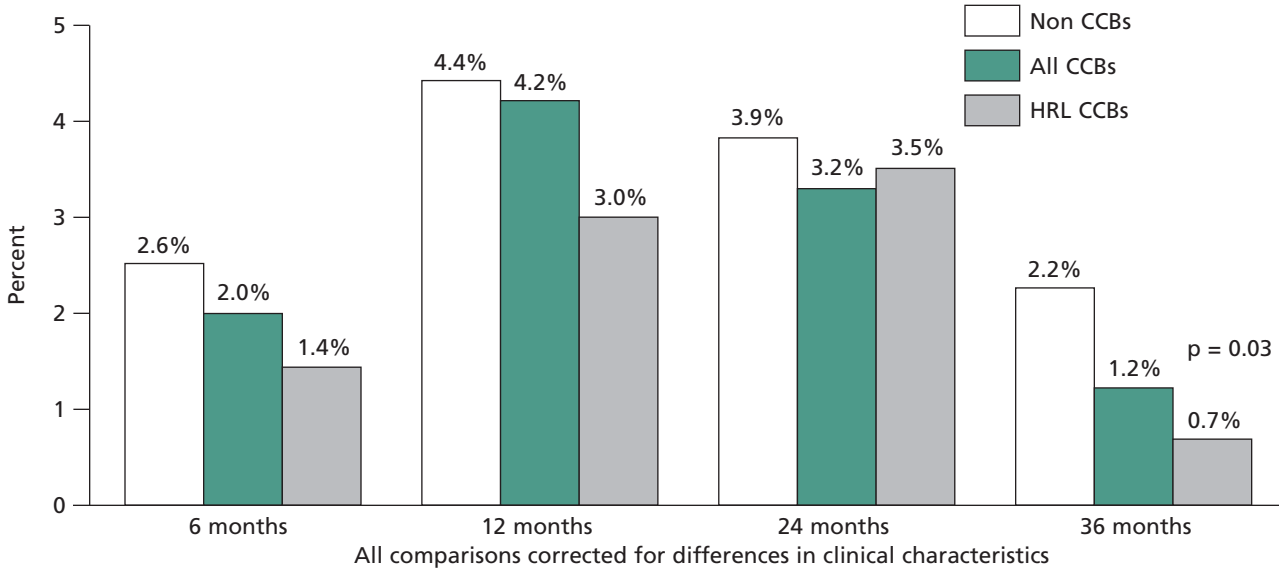
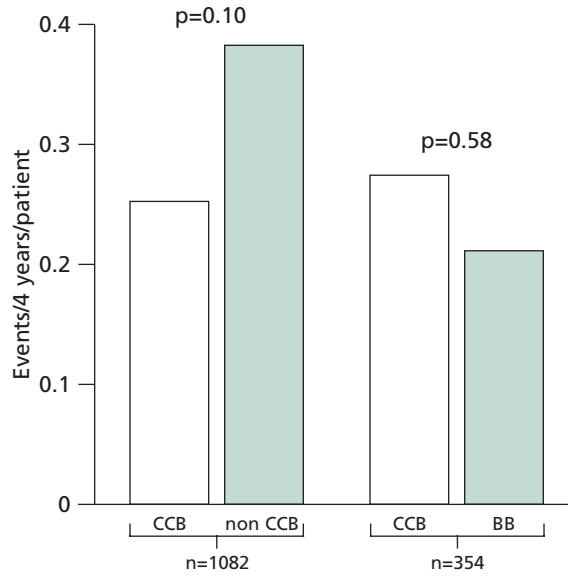


Figure 5: Paired analysis of event rates based on exposure



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 significant 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 constant 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 difference 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 corrected 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 analysis 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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