

# Scientific Update™

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## The Safety and Efficacy of Heart Rate Lowering Calcium Channel Blockers Revisited

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Recent meta-analyses and case control studies purport to show harm associated with the use of short acting calcium channel blockers – particularly dihydropyridines – in both hypertensive and ischemic patients subsets. These concerns regarding safety and efficacy have created an atmosphere of uncertainty among practicing physicians, and confusion and fear among thousands of Canadians receiving these agents for hypertension and/or ischemic heart disease.

During an abstract presentation<sup>1</sup> at the 45th Annual Scientific Session of the American College of Cardiology (March 27, 1996), Dr. William Boden criticized the case control studies which impugn calcium channel blocker use based on their retrospective and non randomized nature. In addition, he emphasized that most of the meta-analyses have utilized pooled data of calcium channel blockers which have divergent pharmacologic effect based on an increase (dihydropyridines) or

decrease (diltiazem or verapamil) in heart rate.

Boden et al<sup>1</sup> performed a post hoc analysis of pooled data obtained from 5,677 post myocardial infarction patients from 3 randomized trials comparing a heart rate lowering calcium channel blocker versus placebo. The study population included all patients enrolled in the first<sup>2</sup> and second<sup>3</sup> Danish Verapamil Infarction Trials (DAVIT I: n=1436; DAVIT II: n=1775), and the Multicentre Diltiazem Post Infarction Trial (MDPIT: n=2466)<sup>4</sup>. The entry criteria in these 3 studies was similar, and included male or females < 75 years of age with cardiac enzyme confirmed myocardial infarction. In the DAVIT I study,<sup>2</sup> verapamil was initiated intravenously (0.1 mg/kg) followed by an oral dose (120 mg tid) initiated within 6 to 24 hours of infarct onset and continued for up to six months. In DAVIT II,<sup>3</sup> oral verapamil (120 mg tid) was initiated 8 to 14 days post infarction and continued for up to 18 (mean 16) months.

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In MDPIT,<sup>4</sup> oral diltiazem (60 mg qid) was initiated 3 to 15 days post infarction and continued for up to 52 (mean 25) months. The mean follow up for the pooled analysis was 550±376 days (approximately 18 months). Of note, concomitant beta blocker use was not allowed in either DAVIT I or DAVIT II; in contrast 52% of patients in MDPIT received oral beta blocker therapy.

The combined cardiac event (cardiac death or reinfarction) rate was 18% in the heart rate lowering calcium channel blocker group as compared to 20% in the placebo group. This 2% absolute (10% relative) difference was associated with a two-sided p value of 0.018 (see figure 1). Actuarial event-free survival is summarized in figure 2.

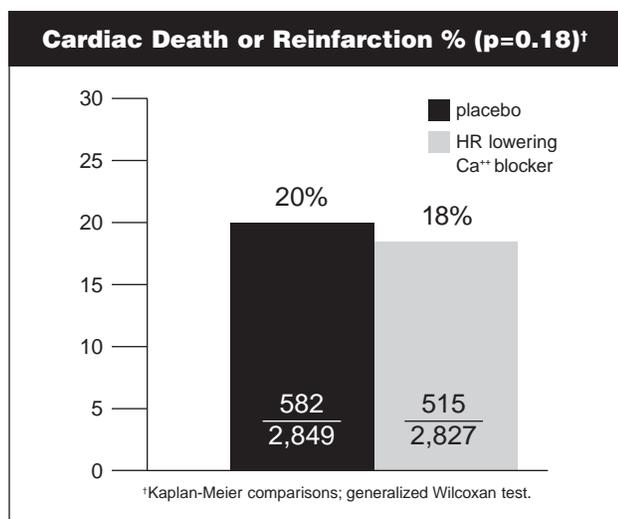


Figure 1

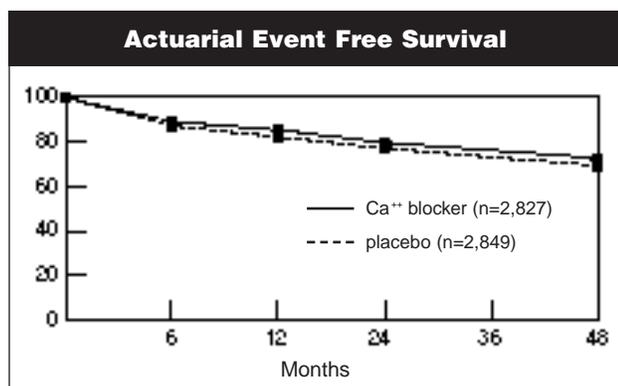


Figure 2

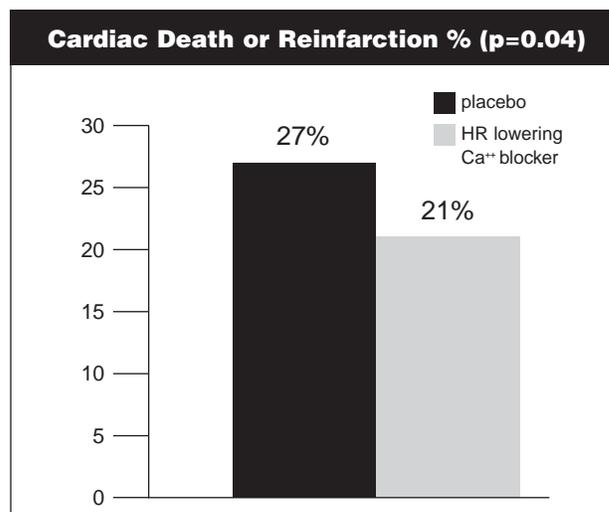


Figure 3 Patients with prior history of hypertension

In a secondary analysis, Boden et al compared those patients with (n=1325) and those without (n=4352) a prior history of hypertension. Post infarction patients with prior history of hypertension (figure 3) who received a heart rate lowering calcium channel blocker had a significantly lower cardiac event rate (21% vs 27% in the placebo group, p=0.004). In contrast, there was no difference in cardiac death or reinfarction rates among those post MI patients without prior hypertension.

Dr. Boden concluded that the use of heart rate lowering calcium channel blockers for the purposes of secondary prevention following myocardial infarction, was not associated with an increased cardiac event rate during long term follow up. In fact, compared to placebo, the administration of diltiazem or verapamil was associated with an overall 2% absolute (10% relative) reduction in the combined trial end points of cardiac death or non fatal reinfarction. However, Dr. Boden suggested that the statistically significant reduction in the overall cardiac event rate was nominal and should not be over interpreted based on the post hoc nature of the analysis.

This pooled analysis emphasizes the importance of differentiating calcium channel blockers which raise or lower heart rate<sup>5</sup> and is consistent with a previous meta-analysis demonstrating the effectiveness of diltiazem and verapamil in reducing the risk of non fatal reinfarction (risk ratio = 0.79, 95% confidence intervals 0.67 to 0.94) without any adverse impact upon mortality.<sup>6</sup> This benefit is particularly apparent among patients without congestive heart failure or severe left ventricular dysfunction (ejection fraction < 40%). Further, among patients with non Q wave infarction, diltiazem (and possibly verapamil) appears to reduce the risk of cardiac events by 25 to 35%.<sup>7-8</sup> Thus, it appears prudent to consider that not all calcium channel blockers are created equal.<sup>10</sup>

Another report describing a multicentre, double blind, randomized, placebo controlled trial evaluating the impact of verapamil post myocardial infarction was recently published in the American Journal of Cardiology.<sup>11</sup> 531 patients were randomized to a long acting preparation of verapamil (360 mg daily) and 542 patient to placebo 7 to 21 (mean 13.8) days post MI. The Calcium Antagonist Reinfarction Italian Study (CRIS) was undertaken between 1985 and 1987 in patients age 30 to 75 (mean 56) years and without history of severe heart failure. During a mean follow up of 23.5 months, 5.5% of patients died. There were no differences between the verapamil and placebo-treated groups in total mortality (5.6% vs 5.4%), cardiac death (4.0% vs 4.1%). The verapamil group had a non significant lower reinfarction rate (7.3% vs 9.0%) and were significantly less likely to develop angina during the follow up (18.8% vs 24.3%, p<0.05).

In an accompanying editorial,<sup>12</sup> Dr. Salim Yusuf combined the results of the CRIS with the data from DAVIT I and DAVIT II. Among the 4284 patients from these 3 trials, the combined mortality and non-fatal reinfarction rate was lower in the

verapamil as compared to the placebo-treated group (15.1% vs 17.2%; odds ratio 0.86; 95% confidence interval 0.73 to 1.01). Although these data approach statistical significance, Dr. Yusuf suggested that this type of cumulative meta-analysis (by which data are pooled each time a trial is published), should be viewed cautiously unless the evidence is extreme. He emphasized the established role of beta-blocker therapy for secondary prophylaxis and suggested a definitive study of a heart rate lowering calcium channel blocker of sufficient sample size would be required to convincingly demonstrate a clinically significant risk reduction in the combined end point of death and non fatal reinfarction.

Two prospective trials evaluating the safety and efficacy of long acting diltiazem will address this issue further. The Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis Post Thrombolysis (INTERCEPT)<sup>13</sup> is currently recruiting patients with an uncomplicated first acute myocardial infarction (without heart failure or left ventricular dysfunction) within 36 to 96 hours of receiving thrombolytic therapy. This multicentre, randomized, placebo controlled, double blind trial compares long acting diltiazem (300 mg daily) plus aspirin 160 mg daily versus aspirin alone in just under 1000 patients. The primary trial objective is to assess the effect of these two treatment strategies on the six months cumulative occurrence of a combined clinical end point of cardiac death, recurrent non fatal infarction, and medically refractory ischemia. A second study, the Prospective Reinfarction Outcomes in the Thrombolytic Era Cardizem CD Trial (PROTECT) will soon begin enrollment of uncomplicated non Q wave post infarction patients. This randomized, double blind trial will compare the safety and efficacy of long acting diltiazem vs atenolol initiated 24 to 96 hours post MI in just under 8000 patients in Canada with the primary endpoint of cardiovascular death and non fatal reinfarction.

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