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Role of heart rate lowering calcium antagonists in post MI secondary prevention:
hypertension, non-Q wave MI, adjunctive therapy post thrombolysis

Presented by: WILLIAM E. BODEN, MD

Reported and discussed by: Anatoly Langer, MD

Virtually unprecedented media and public attention has been focused over the past year on calcium antagonists. Allegations of potential harm and lack of safety beginning with reports of increased cardiac event rates in patients with hypertension[1] has created an atmosphere of fear and controversy among physicians and confusion among the millions of patients worldwide. The objective of Dr. Boden's presentation was to clarify pharmacologic and clinical outcome differences between dihydropyridine and non-dihydropyridine (heart rate lowering) subclasses of calcium antagonists, to provide evidence for the use of heart rate lowering calcium antagonists in selecting subsets of cardiac patients, and to highlight the rationale and role for heart rate lowering calcium antagonists as adjunctive anti-ischemic therapy post thrombolysis.

Safety and efficacy post MI

Boden's work presented in the previous meetings has demonstrated treatment effect of Verapamil or Diltiazem, based on full data from DAVIT II[2] and MDPIT[3] on longterm outcome in patients with non-Q wave MI. Of the 936 patients, there was an absolute 6% (relative 35%) cardiac event rate reduction which was statistically significant ($p = 0.0068$, 95% confidence interval = 0.42-0.89, odds ratio = 0.61). While this analysis is of a retrospective and post hoc nature, these data represent the only data available on the use of heart rate lowering calcium antagonists in patients with non-Q wave MI and suggest that these agents may reduce both cardiac deaths and non-fatal MI. A 6% absolute event rate reduction would result in 43,000 fewer cardiac deaths or non-fatal MI's in the United

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States on an annual basis, among the 750,000 acute non-Q wave MI's that occur each year.

Furthermore, a recent analysis of all 5,677 post MI survivors (Q and non-Q MI) from 3 randomized trials: DAVIT I,[4] DAVIT II,[2] MDPIT[3] demonstrated no increase in longterm cardiac events during 12-18 months of follow-up.[5] In particular, the use of Verapamil or Diltiazem was associated with an overall 12% event rate reduction by comparison to placebo ($p = 0.035$, 95% confidence interval = 0.77-0.99, Cox hazard ratio = 0.88).

Further analysis demonstrated similar findings in 1,325 post MI patients with hypertension. Longterm cardiac events were reduced from 27% in the placebo group to 21% in the heart rate lowering calcium antagonist group ($p = 0.004$), and after using the Cox proportional hazard model to adjust for relevant co-variates such as age, gender, diabetes, or prior MI, there was an overall 24% reduction in cumulative death or MI rate among hypertensive post MI patients randomized to Diltiazem or Verapamil by comparison to placebo (hazard ratio = 0.76, 95% confidence interval 0.61-0.95).

Meta analysis in non-Q MI

In a related but independent analysis our group[6] demonstrated in the pooled data, significant benefit of heart rate lowering calcium antagonists by comparison to beta blockers among non-Q wave MI patients (Figure 1).

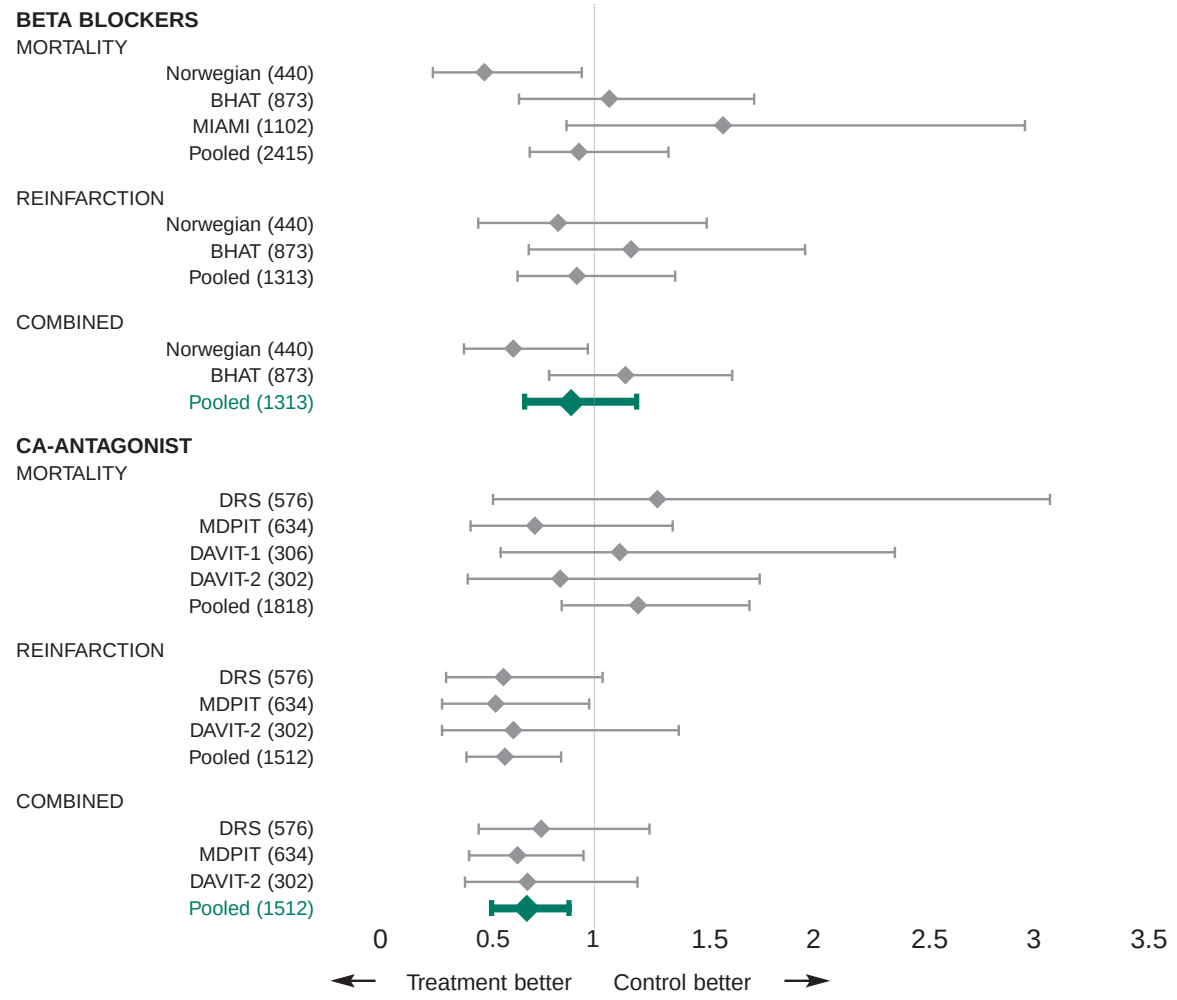
These data, together with other analyses and trials[7-10] provide convincing evidence regarding safety of heart rate lowering calcium antagonists and underscore the importance of dichotomising calcium antagonists into those that are associated with neurohormonal activation and increase in heart rate, for example short acting dihydropyridines, which should be avoided in patients with coronary artery disease and those that actually lower heart rate and, therefore, are associated with cardioprotection in selected post MI patients.

Boden went on to hypothesize that since both non-Q wave MI and MI treated with thrombolytic therapy share common pathophysiology, such as early reperfusion and clinical manifestations of "incomplete infarction," and are characterized by a similarly high incidence of recurrent ischemic complications, that prophylactic calcium antagonists administered post thrombolytic therapy might decrease the cumulative occurrence of reinfarction and refractory ischemia during longterm follow-up. This hypothesis is being tested in the Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis Post Thrombolysis (INTERCEPT) Trial.[11]

Safety and efficacy post thrombolysis

INTERCEPT is a multicenter, randomized, placebo controlled, double blind, parallel group comparison of long acting Diltiazem 300 mg a day and Aspirin 160 mg a day vs Aspirin alone administered in patients without heart failure or significant left ventricular dysfunction within 36-96 hours of receiving early thrombolytic therapy. Active enrollment has been underway since September, 1994 at 61 centers in the United Kingdom, Belgium, Netherlands, and Denmark and to date over 500 patients of an expected 920 have been randomized. The INTERCEPT trial represents the first longterm large scale prospective study of calcium antagonists administered as

Figure 1: Odds Ratio (95% Confidence Intervals)



adjunctive therapy to ST elevation acute MI patients post thrombolysis, where the primary trial objective is to assess the effect of blinded therapy on a 6 month cumulative occurrence of a combined clinical end point of cardiac death, recurrent non-fatal infarction, and medically refractory ischemia.

Conclusion

In conclusion, the currently available data suggests a significant benefit from administration of heart rate lowering calcium antagonists in selected patients surviving myocardial infarction, for example those with non-Q wave MI. Beyond this demonstrable efficacy of heart rate lowering calcium antagonists, there is convincing evidence of longterm safety in the use of heart rate lowering calcium antagonists in patients with hypertension or stable coronary artery disease, including those with or without hypertension. Additional data are underway from on-going large, prospective clinical trials.

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