Use of Calcium Antagonists in Post-Myocardial Infarction Patients*

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What is known? It has been recognized for about a decade that short-acting formulations of dihydropyridine calcium antagonists may be deleterious in acute ischemic syndromes. This has been particularly clear with the immediate-release formulation of nifedipine, for which multiple randomized clinical trials have indicated trends for, or significant adverse effects on, ischemia-related outcomes. The Trial of Early Nifedipine in Acute Myocardial Infarction (TRENT) (1) included 4,091 patients treated within 48 h of onset of suspected myocardial infarction (MI) and showed a trend toward more deaths (~7% excess) at 28 days in patients assigned nifedipine. This trend was consistent in subgroup analysis. For example, in the 1,180 patients in whom treatment was initiated but not continued, mostly because MI was not confirmed, the mortality rate was 9.7% in those given nifedipine versus 9.1% in those given placebo. Presumably, these were mostly patients with unstable angina. Unfavorable trends were also noted in those already receiving beta-adrenergic blocking agents as well as those not receiving beta-blockers at randomization. Then, the Holland Ischaemia Nifedipine Trial (HINT) (2) of 668 patients with unstable angina was terminated early because of excess MI in nifedipine-assigned patients. At 48 h, 15% of placebo-assigned patients and 28% of nifedipine-assigned patients had developed MI. Even in the subgroup with ST segment elevation (presumably patients who had coronary spasm) there was no evidence for benefit.

After these trials, where rapid-release nifedipine had been given to patients presenting with an acute ischemic syndrome, several trials were done in patients after confirmed MI. The Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT) (3) initiated treatment 7 to 21 days after MI, whereas SPRINT II initiated treatment up to 2 days after MI and used a higher nifedipine dose than SPRINT (60 vs. 30 mg) (4). Again, both trials showed excess death and reinfarction in nifedipine-assigned patients. These poor results with immediate-release short-acting nifedipine in acute ischemic syndromes were rehighlighted in a recent meta-analysis of all secondary prevention trials (5). These findings were not unexpected because others had established that patients with acute MI given potent vasodilators intravenously do not do well (6).

What about nondihydropyridines? The situation appears to be different with the nondihydropyridine antagonists regardless of immediate- or slow-release dosing forms. Data from the first and second Danish Study Group on Verapamil in Myocardial Infarction (DAVIT-I and II) studies (7,8), the Calcium Antagonist Reinfarction Italian Studies (CRIS) of verapamil in post-MI patients and four smaller trials (9–13) that totaled over 4,000 patients overall suggested no harm and even some evidence for benefit. The benefit derived from reducing either reinfarction alone or, more appropriately, the aggregate outcome of death or reinfarction. Although, most of these trials used an oral immediate-release verapamil formulation, DAVIT-I initiated treatment intravenously, and CRIS used a slow-release preparation. More recent reports using verapamil in a slow-release formulation with an angiotensin-converting enzyme (ACE) inhibitor suggest improved left ventricular function (11,14). One recent randomized pilot trial suggested that verapamil added to an ACE inhibitor reduced cardiovascular adverse outcomes in high risk post-MI patients with systolic dysfunction compared with the ACE inhibitor alone (11). Less pronounced but similar directional trends have been observed in two studies comprising a total of ~3,000 patients randomized to short-acting diltiazem (15,16).

What about newer agents? These findings with different formulations and different types of calcium antagonists are not entirely unexpected because the heterogeneity of the class of calcium antagonists is well known. It perhaps needs to be reemphasized that there are significant pharmacologic differences between slow-release, long-acting formulations and rapid-release, short-acting formulations, even among those of the same chemical entity, that include different hemodynamic and neurohumoral effects (17,18). In addition, there is emerging evidence to suggest that some newer long-acting dihydropyridine formulations may be beneficial in post-MI patients. The recently reported Doppler Flow and Echocardiography in Functional Cardiac Insufficiency: Assessment of Nisoldipine Therapy (DEFIANT-II) study (19) assessed the effects of slow-release, long-acting nisoldipine (coat-core) versus placebo on exercise, exercise-induced ischemia, left ventricular function and clinical outcome in 542 patients with reduced ejection fraction (median 38%) 7 to 10 days after MI. In these high risk patients, approximately half of whom had an anterior MI, long-acting nisoldipine was associated with improved diastolic left ventricular function and strong trends toward reduced cardiovascular events. The absence of harmful effects in patients with coronary artery disease with impaired left ventricular function (most likely due to remote MI) has also been observed with the slow onset, long-acting dihydropyridine amlodipine in the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) study (20). In that study, patients were receiving ACE inhibitors, and amlodipine treatment was associated with an overall trend toward reduced cardiovascular events.
Abbreviations and Acronyms
ACE = angiotensin-converting enzyme
CRIS = Calcium Antagonist Reinfarction Italian Studies
DAVIT = Danish Study Group on Verapamil in Myocardial Infarction
Mannitol
MI = myocardial infarction
SPRINT = Secondary Prevention Reinfarction Israeli Nifedipine Trial

What about case-control studies in post-MI patients? This issue of the Journal contains a report by Leitch et al. (21) on community-based follow-up of post-MI patients treated with calcium antagonists, beta-blockers, both or neither. Neither drug release/duration formulation nor dose were recorded; however, very few patients received newer long-acting calcium antagonist formulations. The investigators found that, compared with those receiving a beta-blocker, calcium antagonist recipients had higher rates of MI or cardiac death, cardiac death and all-cause mortality (22). Calcium antagonist recipients were not at increased risk for these outcomes compared with patients receiving neither beta-blockers nor calcium antagonists, and compared with the latter group, there was no increased risk of MI or cardiac death among patients who received verapamil, diltiazem or nifedipine. The authors conclude that the findings support the benefit of beta-blocker therapy after MI (22,23) and the absence of effect, rather than a deleterious effect, of calcium antagonists on reinfarction and mortality. However, the study is open to some of the same methodologic objections leveled at previous retrospective analyses of calcium antagonists in this setting: 1) The nonrandom assignment of treatment allows for potential selection bias that cannot be excluded as an explanation for the difference in risk in the calcium antagonist patients; 2) the retrospective design omitted recording of drug formulation and dose, preventing evaluation of differences in effect between short-acting and long-acting agents; 3) the data captured had limited ability to assess the severity and control of hypertension and associated disorders, such as dyslipidemia, diabetes and other conditions, including treatment adherence/compliance, which are all likely to influence ischemia-related outcomes.

Questions raised by recent case-control studies about calcium antagonist use (5,24) have emphasized our lack of knowledge and, perhaps more important, the inherent weaknesses of case-control methodologies when applied to ischemic heart disease with or without hypertension. Questions regarding the risks and benefits of currently used and new slow-release, longer-acting calcium antagonist formulations will be answered only by large prospective, randomized, controlled trials, and a number of these trials are planned or ongoing. Finally, it may be important to note that the administrative-type data, currently used to mold national health care strategies, are also gathered by nonrandomized, case-control methodology and as such are likely to be limited in the area of ischemic heart disease. Perhaps we should use this opportunity to demand more controlled trial data for these important health policy-setting decisions before it is too late.

References