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Update on the calcium antagonist controversy:
the Furberg meta-analysis revisited

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Unprecedented media and public attention has been focused over the past year on a report of an increased risk of myocardial infarction in hypertensive patients treated with calcium antagonists.[1] This retrospective case-control study compared those who had suffered a myocardial infarction with those who had not, with respect to their prior use of various antihypertensive drug therapies. Psaty et al[1] concluded that the risk of myocardial infarction increased by 60% among hypertensive patients treated with a calcium channel blocker compared with those treated with either diuretic (risk ratio = 1.6; 95% confidence intervals (CI) 1.1 to 2.3; p = 0.01) or beta-blocker (risk ratio = 1.6; 95% CI 1.2 to 2.0; p < 0.001) alone.

The controversy was further intensified by publication of a meta-analysis suggesting that the risk of mortality in patients with coronary heart disease was strongly associated with the use of short acting nifedipine.[2] Furberg et al performed a dose-response analysis of nifedipine based on the results of 16 randomized clinical trials for which mortality data were available. The authors concluded that the use of short acting nifedipine was associated with a significant adverse effect on total mortality (risk ratio 1.16; 95% CI 1.01 to 1.33). Not surprisingly, this report has also sparked vigorous debate about the use and safety of calcium channel blockers. Dr. Franz Messerli has been particularly critical of several aspects of the Furberg et al meta-analysis;[3-5] Messerli discussed these issues further during a recent abstract presentation at the 45th Annual Scientific Session of the American College of Cardiology (March 27, 1996).[6]

Messerli first suggested that the major case Furberg et al[2] make against nifedipine in the meta-analysis hinges on the mortality seen in the INTACT study[7]. In contrast to the other studies in the meta-analysis which enrolled patients with

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either unstable angina or in the early phases of acute myocardial infarction, patients in the INTACT study were included on the basis of mild coronary artery disease. Indeed, two-thirds of these patients had mild exertional angina and only one-third had sustained a prior infarction. As patients in the INTACT had stable coronary disease, Messerli argued that it was inappropriate to include this group of patients in the Furberg overview since meta-analysis should be restricted to trials done in populations with similar risks.

Messerli also pointed to several misquotation errors (e.g. incorrect dose range, incorrect total number of events and patients) in the meta-analysis when compared to the original publications. This prompted a recalculation of the Furberg et al meta-analysis at two independent statistical centres, with the "adjusted" results seen in Table 1. After correction of the total number of events and patients as presented in the Furberg et al paper,[2] Messerli suggested that the apparent difference between nifedipine-treated and control patients moved to a range where the p value achieves only nominal significance ($p=0.046$ as compared to $p=0.01$). In addition, after reviewing the original publications and adjusting for apparent misquotation errors, Messerli found that the difference between nifedipine and controlled no longer achieved statistical significance ($p=0.19$). Finally, if one agrees with Messerli et al that a study dealing with stable, angiographically proven coronary artery disease (INTACT) should be excluded from a meta-analysis that otherwise focuses upon unstable angina and acute myocardial infarction patients, there does not appear to be any difference between the nifedipine-treated and control patients with respect to overall mortality ($p=0.36$). Regardless of which meta-analysis results are "accepted", Messerli also pointed out that an editorial in which Furberg was the senior author recommended that "results from overviews should only be accepted if the levels of statistical significance are extreme (e.g., $p<0.001$)".[8] Thus, Messerli et al suggested that the meta-analysis falls far short of Furberg's own ambitious goal by a factor of at least 10-fold, even if one accepts the original p value of 0.01.

Messerli also raised concerns about the conclusions by Furberg et al[2] suggesting a significance dose-response relationship between nifedipine and increased mortality. In particular, the risk for total mortality appears to be highest among patients who received a daily dose of ≥80 mg of short acting nifedipine as compared to control (risk ratio=2.83, 95% CI 1.35 to 5.93).[2] Although 6 month mortality data demonstrated similar outcomes among the nifedipine versus control subjects in two studies, [9,10] Furberg et al included only the 2 week mortality data in the meta-analysis. For example, in one study[9] there were 7 deaths in the nifedipine group (n=93), and 2 deaths in the control subjects (n=88) during the initial 14-day period. However, evaluating the same patient population over 6 months based on an intention-to-treat analysis revealed 10 deaths in the nifedipine group and 10 deaths in the placebo group, which are far less striking results. When Messerli et al utilized the 6 month data, the relative risk of mortality among those patients receiving short acting nifedipine as compared to control dropped to <2 and was no longer statistically significant.

Other criticisms of the meta-analysis have been published by Kloner,[11] and include the concern that not all patients in the control groups received the same type of medications, with some receiving placebo and others beta blockers depending on the study. A further limitation involves the inclusion of studies that start treatment both early and late after myocardial infarction with different doses and drawing conclusions about dose rather than timing of drug

administration. This is demonstrated by the SPRINT I[12] and II[13] studies which are both included in the meta-analysis by Furberg et al. In the SPRINT I study,[12] lower doses of nifedipine given 7 to 22 days after myocardial infarction did not increase mortality. However, in SPRINT II,[13] higher doses given with the first few days of myocardial infarction did increase mortality. Although the Furberg et al meta-analysis ascribes the increased mortality to high dose, Kloner suggests that the observation of higher mortality with short acting nifedipine may be due to the timing of drug administration (too early after infarction) and have nothing to do with dose per se.

In conclusion, Messerli et al questioned the scientific validity of the Furberg et al meta-analysis and cautioned against overemphasizing and generalizing the risks associated with short acting nifedipine to all clinical situations. Nevertheless, Messerli stated that while the Furberg et al analysis may not stand up to close scrutiny, there may indeed be risks associated with the use of short acting nifedipine, particularly at higher doses, in unstable clinical situations.

Furberg et al have responded to Messerli and other critics of the meta-analysis in a recent series of Letters to the Editor in Circulation.[14] While recognizing several errors in dosage, patient events and numbers in the original meta-analysis, Furberg et al maintain that these errors had only small effects on several point estimates, and therefore do not affect either the overall results, the dose-response analysis, or the interpretation of the findings.

Diverging opinions regarding this controversy will continue to exist since neither case-control studies nor meta-analyses are capable of giving the final solution to the problem.[15] The strength of these types of studies is to create hypotheses to be tested in subsequent prospective, clinical trials. Accordingly, the debate regarding the risks and benefits of calcium antagonists will continue until the release of data from several such investigations. Importantly, 2 recently published studies (the Total Ischaemic Burden European Trial (TIBET)[16,17] and the Angina Prognosis Study In Stockholm (APSIS)[18] of patients with stable angina after 2-3 years of follow-up suggest no differences in fatal or non-fatal cardiovascular events among beta-blocker (atenolol and metoprolol, respectively) or calcium antagonist (sustained release nifedipine and verapamil, respectively) treated groups. Data from an earlier meta-analysis of patients with acute myocardial infarction had already suggested that early administration of short acting nifedipine or verapamil might be harmful; however, heart-rate lowering calcium antagonists such as diltiazem or verapamil appear to be effective in reducing the risk of reinfarction (risk ratio =0.79; 95% CI 0.67 to 0.94) without any adverse impact upon mortality.[19] The apparent safety of some calcium channel blockers in congestive heart failure patients due to ischemic heart disease or dilated cardiomyopathy (PRAISE with amlodipine, VHeFT III with felodipine, DiDi with diltiazem) has also been presented in preliminary reports.

A recent preliminary report of the STONE study on elderly hypertensive patients demonstrated a significant ($p<0.001$) decrease in the probability of all events by intention-to-treat analysis in the sustained release nifedipine group as compared with the placebo group. Additional studies, including ALLHAT (with amlodipine), INSIGHT (with nifedipine), HOT (with felodipine), SYST-EUR (with nisoldipine), CONVINCE (with verapamil), and PREDICT (with diltiazem), will hopefully provide morbidity and mortality data in patients who are treated with calcium antagonists for hypertension within the next several years.

Table 1

Reassessment of the Furberg Hypothesis*

Source	Nifedipine (deaths/ patients)	Control (deaths/ patients)	Relative Risk	95% Confidence Intervals	p Value**
Furberg et al[2]	335/4171	274/4183	1.16	1.01 to 1.33	0.01
Furberg et al recalculated	390/5301	339/5329	1.16	1.01 to 1.33	0.046
Originals*** (including INTACT)	320/5109	291/5160	1.11	0.94 to 1.32	0.19
Originals (excluding INTACT)	380/4895	289/4949	1.08	0.91 to 1.28	0.36

*adapted from Messerli[5] and Messerli et al[6]
**chi-squared test of listed proportions for comparison only
***originals refers to data extracted from the original publications by Messerli et al[5,6]
INTACT = International Nifedipine Trial on Antiatherosclerotic Therapy[7]

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