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Scientific Update™

The Safety and Efficacy of Calcium Antagonists: Data from STEPHY II and Other Trials

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Unprecedented media and public attention have been focused on several reports that calcium antagonists, particularly short-acting nifedipine, can increase the risk of death and myocardial infarction (MI), cancer, and bleeding in persons with hypertension,[1-5] previous MI, unstable angina, or stable angina.[6]

However, all of these analyses (which are case-control or prospective cohort studies) have significant limitations, and the one meta-analysis based on prospective, randomized trials contains some errors. Furthermore, many subsequent reports have failed to support these findings. A few recently reported and several current large-scale randomized clinical trials should provide better guidance in the use of calcium antagonists.[6]

The recently reported prospective cohort study STEPHY II evaluated the relationship between the 3 year incidence of cancer and the use of calcium antagonists among hypertensive patients and found no increase in cardiovascular events or cancer.

Limitations of case-control studies

The first case-control study by Psaty et al.[1] was a retrospective analysis comparing those who had and had not suffered an MI with respect to their prior use of various antihypertensive drugs. The authors reported that the risk of MI was increased (risk ratio=1.6; 95% confidence interval (CI): 1.1-2.3; p=0.01) among hypertensive patients treated with a calcium-channel blocker compared with those treated with diuretics alone. In a similar analysis, the authors suggested that the risk of MI was also increased among those patients receiving low-, medium-, and high-dose calcium antagonists as compared to beta-blockers (risk ratios 1.13, 1.42, and 1.81, respectively).

Although these data appear striking, there are several important limitations that must be taken into account when considering a case-control study. In general, these studies have been a reliable strategy to generate hypotheses; however, they cannot test definitively whether there are small-to-moderate risks or benefits of a class of drugs when the factors associated with a prescription of a particular drug are difficult to control.[7] Even after employing state-of-the-art epidemiologic and statistical methods, the authors of this controversial study were able to control only those particular variables that they could identify. This limitation is inherent in the interpretation of the results of any case-control study.

Case-control studies are subject to two sources of bias that might invalidate their conclusions: selection (or indication) bias and confounding bias.[8] Selection bias occurs because of a systemic balance between cases and controls – for example, the MI patients in the study might have inadvertently included "sicker" patients who required more medicines, such as calcium antagonists. In the study by Psaty et al., diabetes and clinical cardiovascular disease were more frequent conditions in patients taking calcium antagonists than in those taking other antihypertensives. Indeed, the baseline rate of coronary heart disease was 32% in patients taking beta-blockers and 46-78% in patients taking calcium blockers. Thus, under these circumstances, it is likely that calcium-antagonist-treated patients were at higher risk to begin with, and these patients were probably given calcium antagonists because diuretics and beta-blockers (recommended as first-choice therapy) were not indicated or were ineffective.

Confounding bias occurs as a result of unknown or unmeasured confounders. For example, there might have been an occult confounding factor in the patients with acute

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MI (left ventricular dysfunction with congestive heart failure, for instance) that contributed to the observed association of worse outcome among patients receiving calcium antagonists.

Although the Psaty et al.[1] study sparked the recent controversy about the safety of calcium antagonists, an earlier case-control study that was almost identical in design suggested no difference in the risk of MI among patients treated with diuretics, beta-blockers, or calcium blockers.[9] Furthermore, another case-control study among hypertensives that was published one month after the Psaty et al. analysis suggested an increased risk for sudden death among those receiving *non-potassium-sparing diuretics and beta-blockers.*[10] Although there had been some previous controversy regarding non-potassium-sparing diuretics, there is overwhelming evidence, particularly among post-MI patients, that beta-blockers *significantly reduce* sudden cardiac death.

Unfortunately, the Hoes et al.[10] case-control study suffers from the same limitations as the Psaty et al.[1] analysis. It therefore highlights further the problem of using results from case-control studies in determining appropriate therapeutic practice.

The controversy continues…

Despite the recognized limitations of these studies, and despite a prospective cohort study[11] of 11,575 patients with coronary artery disease that showed no increased risk for mortality among patients taking calcium-channel blockers, Pahor and colleagues published additional prospective cohort studies finding an increased risk of gastrointestinal hemorrhage[4] and cancer[3,5] among elderly hypertensive patients taking calcium antagonists. The participants were different sub-groups of an on-going descriptive study of older persons living in three communities in the United States. However, close scrutiny of these analyses reveals extensive flaws that call into question many of the authors' conclusions:

Skewed sample[12-15]

Thousands of patients were excluded from the original prospective cohort, including those who were taking diuretics or combinations of antihypertensives. In addition, it is unclear why the authors defined older persons differently from publication to publication; for example, the original cohort included persons aged ≥65 years, but the authors chose to report only on gastrointestinal hemorrhage in patients >67 years and on cancer in those ≥71 years.

Inadequate ascertainment of drug intake

Patients in the study were originally screened in 1982, and those still alive in 1988-89 were interviewed with regard to blood-pressure status and treatment. However, the type of drug used at one moment in 1988-89 might not have been taken over the ensuing 4 years of follow-up, since absolutely no ascertainment of subsequent drug use was made. For example, patients might have taken the original drug for as little as one day or as much as every day over the next 4 years, or they might have taken an entirely different type of drug for any interval.

Uneven ascertainment of risk

Not surprisingly, the patients given calcium antagonists were sicker (a higher number of co-morbid conditions such as heart disease) and were, therefore, almost certainly examined and hospitalized more frequently, thus increasing the chance that they would be diagnosed with gastrointestinal bleeding and cancer. It is puzzling that in the Pahor et al. study, the use of calcium antagonists conferred an even greater relative risk (1.86) than did the use of acetylsalicylic acid (ASA) (1.5) and other non-steroidal anti-inflammatory drugs (NSAIDs) (1.4). ASA and other NSAIDs are well known to be associated with a higher bleeding risk, especially in the elderly.[16]

Small numbers of events

In the article purporting to show an increase in cancer, there were 27 cases and 11 fatalities in the 202 patients taking calcium antagonists. While this rate was double that seen among those taking a beta-blocker or an angiotensin-converting enzyme (ACE) inhibitor, the 95% confidence interval was quite large and often crossed 1.0, indicating no statistically significant difference.

Biologic plausibility

The fact that patients developed a wide spectrum of carcinomas, each with very different pathogenesis and pathophysiology, makes a single trigger mechanism implausible. For reasons that remain unexplained but are based on several prospective studies, hypertension itself is a significant risk factor for cancer. Other antihypertensive agents (such as beta-blockers, diuretics, reserpine, and ACE inhibitors) have previously been implicated as harmful in retrospective cohort studies similar in design to those of Pahor and colleagues. Further, the increased relative risk of cancer and death among hypertensives has been observed in both treated and untreated patients.[17] With respect to GI bleeding, Pahor et al. raised the possibility that inhibition of vascular constriction could increase the severity of gastrointestinal hemorrhage. However, if this were a major factor, nifedipine would have been expected to cause at least as much trouble as verapamil or diltiazem, but this was not the case.[18]

Cancer and antihypertensive therapy: Further insights

A prospective cohort study evaluating the relationship between the 3-year incidence of cancer and the use of calcium-channel blockers was undertaken in the STEPHY (STanberg study on Epidemiology of Parkinsonism and Hypertension in the Elderly) population.[19] In 1992, STEPHY investigated (questionnaire and home examination) the total population ≥65 years (n=1,182) of two villages in Bavaria, Germany. The prevalence of hypertension (subjects with blood pressure ≥160/95 mm Hg or on antihypertensive

therapy) was 53%. Of all hypertensives, 54% were treated, with 26% (n=137) receiving calcium-channel blockers. Of those patients taking calcium-channel blockers, 41% were on nifedipine, 26% on verapamil, 16% on diltiazem, 8% on nitrendipine, 5% on felodipine, and 4% received some other type. Any participants with a history of cancer or manifest cancer at the time of the interview were excluded from further analysis. In 1995, STEPHY II, a 3-year follow-up, assessed fatal and non-fatal cancers, total mortality, and cardiovascular events based on a second interview or case records of hospitals and patients' general practitioners.

Total mortality was 12.1% (n=119). There were 22 deaths due to cancer and 75 cases of newly diagnosed non-fatal cancer. The incidence of fatal cancer was 2.2% (n=3) for those on calcium-channel blockers and 2.1% (n=19) for those not on calcium-channel blockers at the time of the original interview (odds ratio[OR] 0.98, 95% CI: 0.39, 2.21). The incidence of non-fatal cancer was 12% (n=12) for those on calcium blockers and 11% (n=63) for those not on calcium blockers (OR 1.13; 95% CI: 0.42, 1.97). Total mortality was also similar among the calcium-channel blocker group (14.6%; n=20) as compared to other antihypertensive-treated groups (11.7%, n=99; OR 1.29; 95% CI: 0.77, 2.16). When this result was adjusted not only for age and sex but also for other co-morbid factors such as coronary artery disease and diabetes mellitus, the odds ratio was even closer to 1 (0.92), suggesting no significant difference between the two groups. Cardiovascular events were also similar among the two groups (29.9%, n=29 vs 28.5%, n=156; OR 1.18, 95% CI: 0.74, 1.90; after adjustment for other factors, OR 1.1).

Safety data from randomized trials

Unlike beta-blockers and ACE inhibitors, calcium antagonists are quite a heterogeneous class with very different pharmacologic characteristics. For example, while verapamil and diltiazem lower heart rate, short-acting nifedipine might actually cause reflex tachycardia; all three of these agents can cause a decrease in contractility and have been associated with precipitation of congestive heart failure (CHF) and with possibly worse prognosis post-MI. In contrast, newer second-generation calcium antagonists such as amlodipine and felodipine appear to be safe for patients with heart failure and severe left ventricular dysfunction based on carefully conducted, prospective, randomized, placebo-controlled (albeit relatively small) trials.[20,21] In fact, the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) study, in which amlodipine or placebo was administered to 1,153 patients with severe CHF, found that amlodipine benefited non-ischemic subjects by reducing the risk of sudden death and death from pump failure. The PRAISE-II study, now in progress, will attempt to confirm this apparent benefit in non-ischemic dilated cardiomyopathy.

Other randomized trials have failed to confirm the increased risk of MI, death, gastrointestinal bleeding, and cancer (see Table 1). In the post-MI setting, the small DEFIANT II study of nisoldipine showed a favourable trend towards decreased cardiovascular events as compared to placebo in patients with moderate left ventricular dysfunction treated over six months. The STONE study (single blind) also demonstrated a highly significant decrease in the risk of cardiovascular events compared with placebo. Most recently, and presented at this current meeting, the Systolic Hypertension in Europe (SYST-EUR) trial demonstrated a 42% reduction in the primary end point of fatal and non-fatal strokes (p=0.003) in nitrendipine – as compared to placebo-treated patients. In addition, fatal and non-fatal cardiac events were reduced by 26% (p=0.03) and cardiovascular mortality by 27% (p=0.07). Based on these results, treatment of 1,000 patients for five years with nitrendipine would prevent 29 strokes and 53 major cardiovascular events. This result is comparable to the effects of antihypertensive therapy in two large-scale trials of elderly hypertensive patients: STOP-Hypertension[24] (hydrochlorothiazide plus amiloride or one of three beta-blockers vs placebo) and

Table 1: Selected randomized calcium antagonist trials.

Trial	Clinical setting	Sample size (n=)	Calcium antagonist	Follow-up duration (months)	Results
Defiant II[22]	Post MI	542	Nisoldipine	6	Trend (p=0.07) towards ↓cardiovascular events
CRIS[23]	Post MI	531	Verapamil	23.5	Similar rates of MI, death Less recurrent angina (RR 0.8; 95%ct
STONE[24]	Hypertension	1632	Nifedipine	30	RR 0.43 (95% CIO) for stroke, 0.40 (0.25, 0.64) for cardiovascular events
SYST-EUR[25]	Hypertension	4695	Nitrendipine	24	42%↓ (p=0.003) in fatal and nonfatal strokes 26%↓ (p=0.03) in fatal and nonfatal cardiac events 27%↓ (p=0.07) in cardiovascular mortality

the Systolic Hypertension in the Elderly Program (SHEP) (chlorthalidone vs placebo).[25]

Several even larger-scale, prospective, randomized ongoing trials of other calcium-channel blockers should provide even more definitive information regarding the efficacy and safety of these agents. The largest and longest follow-up study is the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) initiated in February, 1994 and designed to examine the ability of 4 antihypertensive drugs (a thiazide diuretic, an ACE inhibitor, an alpha-blocker, and the calcium antagonist amlodipine) to reduce coronary heart disease in hypertensive patients.

Conclusion

A "Dear Doctor" letter was recently (June 25, 1997) sent to all Canadian physicians and surgeons from the Health Protection Branch of Health Canada. Unfortunately, this letter provided no new information; it simply highlighted the limitations of observational studies and recommended that short-acting, immediate-release nifedipine capsules not be prescribed for the management of hypertension or acute reduction of blood pressure. In light of Canadian and American guidelines that are supported by the greatest amount of randomized clinical trial evidence, I believe that uncomplicated hypertension should continue to be treated initially with diuretics and/or beta-blockers. Calcium antagonists and ACE inhibitors remain as second-line agents as recommended in the guidelines since there is less long-term information on these and other agents (e.g., alpha-blockers and angiotensin-II inhibitors). However, since some reports suggest that up to 50% of patients with hypertension do not have adequate blood-pressure control, it would be premature to accept the results of several relatively small, case-control or cohort studies and to deny patients effective antihypertensive therapy, particularly since the known risks of uncontrolled hypertension are far greater than the postulated, still unproven hazards of calcium antagonists. STEPHY II provides additional information on the safety of calcium antagonists and suggests no increased risk for cancer or cardiovascular events.

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