Preliminary Update Report
on
Calcium Channel Blockers

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**Introduction**

The purpose of the Preliminary Update Report is to give the organizations advanced notice of the 6-month update search results and our preliminary assessment based only on the title and abstracts (where an abstract is available). This report is prepared 20 weeks after the submission of the most recent draft Report. We will classify our assessment into one of the following categories:

1. No new evidence available
   - This means that there are no new studies in the search results that meet the initial inclusion criteria

2. New evidence is available, but doesn’t substantially change the outcome of the previous Final Report
   - This means that there are studies that meet the initial inclusion criteria screen, but the results reported in the abstracts are consistent with the findings of studies included in the previous Final Report

3. New evidence is available which could substantially change the outcome of the previous Final Report
   - This means that there are studies that meet the initial inclusion criteria screen, and the results reported in the abstracts indicate findings that are different to those of studies included in the previous Final Report.

The assessments are based solely on the title and abstracts of the articles and are intended to assist the participating organizations in planning for handling the Updated Final Report within each organization’s unique process and timelines. The draft Updated Final Report will contain the complete details (abstraction, quality assessment and synthesis) of all new studies that meet inclusion criteria). This report is due six weeks after the receipt of the Preliminary Update Report.

There are a number of considerations to be made regarding the Preliminary Update Report. When full-text articles are obtained: these studies may not meet inclusion criteria; the results in the paper may differ from those in the abstract; the quality assessment may reveal a poor quality study; and the overall assessment of the body of literature may in fact not change after full assessment of the new studies in context with the previous Final Report. The Preliminary Update Report is distributed only to the participating organizations and is not posted on the public web site. The Updated Final Report is made public and posted to the public web site after review by the participating organizations.

**New FDA Information**

- *Amlodipine maleate* (Amvaz) was approved in October 2003 for hypertension, chronic stable angina and vasospastic angina. FDA announced a stay of this approval in February 2004 pending reevaluation of its review. Subsequently, a US Appeals Court has now ruled to restrain introduction of amlodipine maleate into the US market due to amlodipine besylate patent restrictions.
• *Amlodipine besylate* (Norvasc): FDA required a change in labeling to add a paragraph reporting results from the PRAISE-2 study which indicate that amlodipine had a neutral effect on all-cause mortality but caused more pulmonary edema than placebo.

• *Verapamil hydrochloride* (Covera HS): FDA required labeling changes including adding (a) clinical pharmacology data from a study of healthy elderly subjects; (b) cytochrome inducers, cytochrome inhibitors, aspirin, and grapefruit juice subsections to the Drug Interactions section; and (c) extrapyramidal symptoms to the Nervous System subsection of the Adverse Reactions section.

**Methods**

We searched Premedline, Medline (1996 to February Week 1 2004), Embase (1991 to 1st Quarter 2004), Cochrane Central Register of Controlled Trials (CCTR) (4th quarter 2003) and Cochrane Database of Systematic Reviews (CDSR) (4th quarter 2003). Previous search strategies were repeated. Medline and Embase were limited to publication dates from 2002-2004. Pharmaceutical manufacturers were invited to submit update dossiers. All citations were imported into an electronic database (EndNote 6.0). The key questions and inclusion criteria remained the same.

**Results**

The update search identified 492 citations. We received dossiers from the makers of Isradipine and Nisoldipine by the deadline of 3/5/04. Eight citations potentially met inclusion criteria based on screening of titles and abstracts (Appendix A). No new studies were identified through the dossier submission process.

**Head-to-head trials**

No citations of head-to-head trials were included.

**Active-controlled trials**

Six citations appear to be active-controlled trials. Four of these relate to previously reported study results (AASK, ALLHAT, INSIGHT). Another only describes methods of an ongoing trial of amlodipine and candesartan in Japanese high-risk hypertensive patients (CASE-J). The last is a 24-month open study of verapamil sustained release and atenolol in hypertensive patients with coronary artery disease (CAD) that measured the combined primary endpoint of first occurrence of all-cause death, nonfatal myocardial infarction or nonfatal stroke.

**Placebo-controlled trials**

Two placebo-controlled studies were identified. An abstract of the first full publication from the PRAISE-2 study of amlodipine in patients with severe nonischemic heart failure reported only results related to echocardiographic predictors of survival. If the full paper does not report included outcome measures, it would be excluded. No abstract was available for another placebo-controlled trial of chronotherapeutic graded-release diltiazem in patients with chronic stable angina.
Conclusion

One abstract of an open study of verapamil and atenolol in hypertensive CAD patients indicates no significant differences in 24-month primary outcome event rates. Description of safety and/or adverse effect measurement was not provided. All other studies identified appear to support previously reported data.

*These results do not substantially change the main findings of the previous Final Report*

Citations and Abstracts of New Studies

Active-controlled trials:


   An interim analysis of the AASK trial at three years demonstrates a renoprotective effect [slower decline in glomerular filtration rate (GFR), delayed onset of significant decrease in GFR, end-stage renal disease (ESRD) or death, and a decrease in urinary protein excretion] of the angiotensin converting enzyme (ACE) inhibitor, ramipril, as compared to the dihydropyridine calcium channel blocker (DHP-CCB), amlodipine, in patients with mild-to-moderate renal insufficiency. The beneficial effect occurred in the presence of similar levels of blood pressure control and was apparent in patients with proteinuric (beyond the threshold of "dipstick positive" proteinuria, 300 mg/day) and non-proteinuric hypertensive nephrosclerosis. At the time of the interim analysis, the effectiveness of the beta-blocker metoprolol was not significantly different from that of the ACE inhibitor. The data suggest that DHP-CCBs should be used with caution in the presence of mild-to-moderate renal insufficiency.


   The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) compared four antihypertensive agents in patients 55 years and older: chlorthalidone, doxazosin, amlodipine, and lisinopril. The doxazosin arm was terminated early because of an excess of congestive heart failure. Chlorthalidone was at least equivalent to amlodipine and lisinopril in all of the outcomes measured, and was better in some, notably heart failure.

To investigate the impact of treatment on cardiovascular mortality and morbidity, we assessed outcomes in patients with hypertension and diabetes who received co-amilozide or nifedipine in the International Nifedipine GITS Study: Intervention as a Goal in Hypertension. Participants had to be 55 to 80 years of age, with hypertension (≥150/95 or ≥160 mm Hg) and at least one additional cardiovascular risk factor. Patients received 30 mg nifedipine once daily or co-amilozide (25 mg hydrochlorothiazide and 2.5 mg amiloride) daily. Doses were doubled if target blood pressures (<140/90 mm Hg) were not achieved. Primary (composite of cardiovascular death, myocardial infarction, heart failure, and stroke) and secondary outcomes (composite of primary outcomes, including all-cause mortality and death from vascular and nonvascular causes) were assessed by means of intent-to-treat analyses. There was no significant difference in the incidence of primary outcomes between nifedipine-treated and co-amilozide-treated patients with diabetes at baseline (n=1302) (8.3% versus 8.4%; relative risk, 0.99, 95% CI, 0.69 to 1.42; P=1.00). A significant benefit for nifedipine-treated patients was seen for the composite secondary outcome (14.2% versus 18.7%; relative risk, 0.76, 95% CI, 0.59 to 0.97; P=0.03). Among patients without diabetes at baseline (n=5019), there was a significant difference in the incidence of new diabetes (nifedipine 4.3% versus co-amilozide 5.6%, P=0.023). Nifedipine GITS once daily is as effective as diuretic therapy in reducing cardiovascular complications in hypertensive diabetics. Nifedipine-treated patients were also less likely to have diabetes or have secondary events (a composite of all-cause mortality, death from a vascular cause, and death from a nonvascular cause) than co-amilozide recipients. Our results suggest that nifedipine could be considered as first-line therapy for hypertensive diabetics.

Hypertension continues to be a major public health issue in the world. To combat this problem, many anti-hypertensive drugs have been developed and proven effective at controlling blood pressure in the last half century. In recent decades, antihypertensive drugs have been shown to have cardiovascular benefits beyond the reduction of blood pressure, and the focus has shifted to clarification of these effects. Angiotensin II receptor antagonists and calcium channel blockers are the most widely used antihypertensive drugs in Japan. However, these two classes of drugs have not yet been compared with respect to their efficacy for treating cardiovascular events. The Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial described herein is a prospective, multicenter, randomized, open-label, active-controlled, 2-arm parallel group comparison with a response-dependent dose titration and blinded assessment of endpoints in high-risk hypertensive patients treated with either an angiotensin II receptor antagonist (candesartan cilexetil) or a third-generation calcium channel blocker (amlodipine besilate). The eligibility criteria in this study were 1) age between 20 and 85 years; 2) systolic blood pressure (SBP) ≥140 mmHg in those below 70 years of age or ≥160 mmHg in those above 70 years of age or diastolic blood pressure (DBP) ≥90 mmHg on two consecutive measurements at clinic; and 3) at least one of the following high risk factors for
cardiovascular events: a) SBP ≥ 2180 mmHg or DBP ≥ 110 mmHg on two consecutive visits, b) type 2 diabetes mellitus (fasting blood glucose ≥ 126 mg/dl, casual blood glucose ≥ 200 mg/dl, HbA1c ≥ 6.5%, 2 h blood glucose on 75 g oral glucose tolerance test (OGTT) ≥ 200 mg/dl, or current treatment with hypoglycemic therapy), c) history of cerebral hemorrhage, cerebral infarction, or transient ischemic attack until 6 months prior to the screening, d) left ventricular hypertrophy on either echocardiography or ECG, angina pectoris, or history of myocardial infarction until 6 months prior to screening, e) proteinuria or serum creatinine ≥ 1.3 mg/dl, and f) symptoms of arteriosclerotic artery obstruction. The therapeutic goals of blood pressure control were set as follows: SBP < 130 mmHg and DBP < 85 mmHg for patients below 60 years of age, SBP < 140 mmHg and DBP < 90 mmHg for those in their 60s, SBP < 150 mmHg and DBP < 90 mmHg for those in their 70s, and SBP < 160 mmHg and DBP < 90 mmHg for those in their 80s. A total of 3,200 patients, equally allocated to each of the two treatment arms, were required based on a two-sided alpha level 0.05 and 90% power. The CASE-J is also the first study to employ the newly developed Automatic Bar Code Data-Capturing/Allocation, Booking & Trial Coding, Data Management (ABCD) system for data collection and management. Enrollment of patients started in September 2001 and ended in December 2002. Follow-up data will be collected every 6 months until December 2005. The CASE-J trial will provide important evidence on the comparative effectiveness of candesartan cilexetil and amlodipine besilate on cardiovascular morbidity and mortality among Japanese. In addition, the use of the ABCD system is expected to contribute to the development of more efficient data management systems for large-scale clinical trials.


CONTEXT: Despite evidence of efficacy of antihypertensive agents in treating hypertensive patients, safety and efficacy of antihypertensive agents for coronary artery disease (CAD) have been discerned only from subgroup analyses in large trials.

OBJECTIVE: To compare mortality and morbidity outcomes in patients with hypertension and CAD treated with a calcium antagonist strategy (CAS) or a non-calcium antagonist strategy (NCAS).

DESIGN, SETTING, AND PARTICIPANTS: Randomized, open label, blinded end point study of 22,576 hypertensive CAD patients aged 50 years or older, which was conducted September 1997 to February 2003 at 862 sites in 14 countries.

INTERVENTIONS: Patients were randomly assigned to either CAS (verapamil sustained release) or NCAS (atenolol). Strategies specified dose and additional drug regimens. Trandolapril and/or hydrochlorothiazide was administered to achieve blood pressure goals according to guidelines from the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) of less than 140 mm Hg (systolic) and less than 90 mm Hg (diastolic); and less than 130 mm Hg (systolic) and less than 85 mm Hg (diastolic) if diabetes or renal impairment was present. Trandolapril was also recommended for patients with heart failure, diabetes, or renal impairment. MAIN OUTCOME MEASURES: Primary: first occurrence of death (all cause), nonfatal myocardial infarction, or nonfatal stroke; other: cardiovascular death,
angina, adverse experiences, hospitalizations, and blood pressure control at 24 months.

RESULTS: At 24 months, in the CAS group, 6391 patients (81.5%) were taking verapamil sustained release; 4934 (62.9%) were taking trandolapril; and 3430 (43.7%) were taking hydrochlorothiazide. In the NCAS group, 6083 patients (77.5%) were taking atenolol; 4733 (60.3%) were taking hydrochlorothiazide; and 4113 (52.4%) were taking trandolapril. After a follow-up of 61 835 patient-years (mean, 2.7 years per patient), 2269 patients had a primary outcome event with no statistically significant difference between treatment strategies (9.93% in CAS and 10.17% in NCAS; relative risk [RR], 0.98; 95% confidence interval [CI], 0.90-1.06). Two-year blood pressure control was similar between groups. The JNC VI blood pressure goals were achieved by 65.0% (systolic) and 88.5% (diastolic) of CAS and 64.0% (systolic) and 88.1% (diastolic) of NCAS patients. A total of 71.7% of CAS and 70.7% of NCAS patients achieved a systolic blood pressure of less than 140 mm Hg and diastolic blood pressure of less than 90 mm Hg. CONCLUSION: The verapamil-trandolapril-based strategy was as clinically effective as the atenolol-hydrochlorothiazide-based strategy in hypertensive CAD patients.

Placebo-controlled trials:


BACKGROUND: Echocardiography is used commonly in clinical practice when caring for patients with heart failure. It is unknown whether the presence of certain findings provides an incremental ability to predict survival beyond the use of baseline clinical findings alone. The second PRAISE-2 echocardiographic study was prospectively designed to identify echocardiographic predictors of survival among patients with nonischemic cardiomyopathy and heart failure and to determine if components of the echocardiographic examination add prognostic information to baseline demographic and clinical information. METHODS: One hundred patients participated in the second Prospective Randomized Amlodipine Survival Evaluation Study (PRAISE-2) echocardiographic study; of these, 93 had full and interpretable echocardiographic examinations. Cox proportional hazards modeling was used to assess the relation between various characteristics and survival as well as to assess the incremental prognostic information gained by echocardiography beyond the clinical examination. RESULTS: Seven of 10 routine echocardiographic measures were significantly associated with death. These included mitral regurgitation (hazard ratio [HR], 2.31; 95% CI, 1.02, 5.27), left ventricular ejection fraction <20% (HR, 2.59; 95% CI, 1.14, 5.88), restrictive left ventricular filling pattern (HR, 2.37; 95% CI, 1.05, 5.32), and peak D velocity (HR, 1.62; 95% CI, 0.38, 0.87). The only statistically significant clinical predictor of survival was dyspnea at rest. The addition any of several echocardiographic parameters to baseline clinical information significantly improved the ability to predict survival. CONCLUSIONS: Several readily available echocardiographic parameters are predictive of death and when added to clinical examination findings significantly improve the ability to determine prognosis among patients with nonischemic cardiomyopathy and heart failure.