ORALS: Theme III: Does the FDA Approval Process for Antihypertensive Agents Assure Efficacy, Safety, and Timeliness?

PREVENTION OF DEMENTIA IN THE SYSTOLIC HYPERTENSION IN EUROPE (SYST-EUR) TRIAL. P.Forget, JA. Strauss, ML. Sterk, L. Thus, ON BEHALF OF THE SYST-EUR INVESTIGATORS. HORTAL, BROCA, UNIVERSITE PANS V, 54596 PARIS, FRANCE.

Systolic hypertension increases the risk of dementia in the elderly. This vascular dementia project, set up in the framework of the double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial, examined whether antihypertensive drug treatment could reduce the incidence of dementia in older patients with isolated systolic hypertension.

Eligible patients were non-demented at least 60 years old and had a sitting blood pressure ranging from 160 to 219 mm Hg systolic and below 95 mm Hg diastolic. Active treatment consisted of nitrindipine (10-40 mg/day) with the possible addition of enalapril (5-20 mg/day), hydrochlorothiazide (12.5-25 mg/day), or both drugs titrated or combined to reduce the systolic blood pressure by at least 20 mm Hg to below 150 mm Hg. Cognitive function was assessed by the Mini Mental State Examination (MMSE). If the MMSE score was 23 or less, the diagnosis of dementia was made.

The MMSE score at randomisation was 29 in both treatment groups and the median systolic/diastolic blood pressure was 173/106 mm Hg. The incidence of dementia was reduced by 50% from 7.7 cases per 1000 patient-years in the placebo group (n=1180) to 3.8 cases in the active treatment group (n=1238) (21±11 patients, p=0.05). In conclusion, antihypertensive treatment initiated with the dihydroxypridine calcium-channel blocker, nitrindipine, halved the incidence of dementia. Treating 1000 hypertensive patients for 5 years could prevent 10 cases.

Key Words: Elderly, systolic hypertension, calcium-channel blockers, vascular dementia and Alzheimer's disease.


We conducted a prospective cohort study in 164 consecutive patients with essential hypertension, non-insulin-dependent diabetes and no cardiovascular risk factors. The patients were studied before therapy and followed for up to 12 years (mean, 9). The use of calcium antagonists that preceded the event was considered for classification. At entry, the patients who were subsequently given calcium antagonists had a higher clinic (172/88 vs 161/85 mm Hg, both p<0.01) and 24-hour ambulatory blood pressure (150/90 vs 141/84 mm Hg, both p<0.01) than those who were not. During follow-up, the rate of total CV events was 53 major CV morbidity events (6.46/100 person-years).

The rate of total CV events (5.6 vs 6.8 events per 100 person-years, relative risk 0.88 [95% CI: 0.47-1.61]) and that of ischemic heart disease (2.6 vs 4.3 events per 100 person-years, relative risk 0.62 [95% CI: 0.28-1.38]) did not differ between users of calcium antagonists (n=50) and non-users. In our study, the use of angiotensin converting enzyme inhibitors (n=66) was unrelated to the rate of CV events (relative risk 1.24, 95% CI: 0.71-2.12). The CV event rate was slightly lower (p=0.040, log-rank test) among users of calcium antagonists or ACE-inhibitors, alone or combined (5.80 events per 100 person-years) than among the subjects receiving different classes of drugs, mostly diabetics and beta-blockers (10.0 events per 100 person-years). In a Cox multivariate analysis, only age (p=0.002) and 24-hour ambulatory pressure (p=0.04) were independent predictors of CV morbidity events.

These findings are not consistent with an association between use of calcium antagonists and increased CV morbidity in subjects with essential hypertension and type II diabetes.

Key Words: Hypertension, Diabetes, Calcium antagonists, Therapy, Prognosis.

EVIDENCE OF CONFOUNGING BY INDICATION: PRESCRIBING OF CALCIUM ANTAGONISTS. S. LEADER*, L. Roht*, Paecon, Reston, VA.

The observed increased risk of adverse outcomes associated with calcium antagonist (CA) use for hypertension reported by some epidemiological studies may be due, in part, to underlying confounding by indication. To test this hypothesis, we conducted a retrospective cohort analysis of 11,141 Pennsylvania Medicaid enrollees who received antihypertensive monotherapy between 1989 and 1992. The data source was paid Medicaid claims which record ICD-9 codes for diagnoses and NDC codes for dispensed prescriptions. Diagnoses of 12 known cardiovascular risk factors recorded 7 days or less prior to initiation of antihypertensive drug therapy were examined. We used logistic regression analyses to evaluate the association between each pre-existing condition and CA use, controlling for age, race, gender, and the other conditions. The adjusted odds ratios (OR) and 95% confidence intervals (CI) were as follows: for arteriosclerotic cardiovascular disease OR=7.78, CI=2.72-22.28, for angina OR=2.92, CI=1.77-4.83, for COPD OR=2.26, CI=1.19-4.28, for diabetes OR=1.49, CI=1.07-2.06; and for ischemic heart disease OR=1.56, CI=1.04-2.35. Among monotherapy users, CA was prescribed significantly more often for subjects with several pre-existing diseases.

The data provide strong evidence of the occurrence of confounding by indication in this population.

Key Words: Calcium antagonists, confounding by indication.


NHNES III data suggested that less than half of hypertensive patients treated pharmacologically reach the JNC-VI goal of SBP <140/90 mm Hg. Omapatrilat (Oma), a novel vasopeptidase inhibitor, is a single molecule that inhibits both neutral endopeptidase (NEP) and angiotensin converting enzyme. Inhibition of NEP prevents the degradation of endogenous vasodilators, including natriuretic peptide, Bradykinin, and adrenomedullin. The safety and efficacy of Oma (2.5-80 mg once daily) were evaluated in three placebo (Pbo)-controlled, 8–12 week, dose-ranging studies in more than 1800 patients with DBP 95–110 mm Hg and SBP 117–201 mm Hg. Amlodipine (Aml) 10 mg and lisinopril (Lis) 20 mg were also included as controls. Treatment with Oma was well tolerated and resulted in excellent dose-dependent reduction in SBP/DBP (p<0.001 for all doses ≥5 mg vs Pbo). Oma 80 mg produced SBP/DBP changes of −15.5±14.2 mm Hg at trough, with DBP normalized (<90 mm Hg) in 83% of stage 1 patients (baseline DBP <140 mm Hg) and 53% of stage 2 patients (baseline DBP 100–110 mm Hg). The percentage of patients who reached JNC-VI treatment goal of <140/<90 mm Hg—with Oma (20–80 mg, doses being studied in phase III), Aml, and Lis—were shown by baseline severity.

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<thead>
<tr>
<th>Oma</th>
<th>Lis</th>
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<td>20 mg</td>
<td>40 mg</td>
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<td>Stage 1 (%)</td>
<td>50</td>
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<td>Stage 2 (%)</td>
<td>31</td>
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Monotherapy with Oma produced excellent BP reduction and treatment success rate, compared with current therapy. Development of Oma represents an important advance toward optimal antihypertensive therapy and BP control.

Key Words: omapatrilat, vasopeptidase inhibitor, dose ranging, optimal antihypertensive therapy, safety.