AM/BN to AM or BN monotherapy (Frishman et al, *J Clin Pharmacol* 1995;35:1060-6; Pool et al, *J Hum Hypertens* 2001;15:495-8; Kuschnir et al, *Clin Ther* 1996:18:1213-24). Efficacy outcomes were mean reduction in seated systolic BP (SBP) and diastolic BP (DBP) and response rate (proportion of patients achieving a DBP <90 mmHg or ≥10 mmHg decrease from baseline) after 8 weeks of therapy (Table).

<table>
<thead>
<tr>
<th>Combination therapy (mg)</th>
<th>No. of subjects</th>
<th>SBP/DBP reduction, mmHg (response rate %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLM/HCTZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20/12.5</td>
<td>502</td>
<td>20.1/16.4 (76.6)</td>
</tr>
<tr>
<td>40/25</td>
<td></td>
<td>26.8/21.9 (92.3)</td>
</tr>
<tr>
<td>AM/BN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5/10</td>
<td>332</td>
<td>13/11 (61.5)</td>
</tr>
<tr>
<td>5/10</td>
<td>530</td>
<td>11.7/8.6 (66)</td>
</tr>
<tr>
<td>5/20</td>
<td>308</td>
<td>24.7/13.2 (87)</td>
</tr>
<tr>
<td>AM/BN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/20a</td>
<td>364</td>
<td>25.5/14.3</td>
</tr>
</tbody>
</table>


OM/HCT 20/12.5 and 40/25mg reduced SBP/DBP by 20.1/16.4 and 26.8/21.9 mmHg respectively, compared with 13/11, 11.7/8.6, 24.7/13.2 mmHg for AM/BN 2.5/10, 5/10, and 5/20mg. All combinations were well tolerated. Although the highest marketed dose of AM/BN (10/20mg) was not tested in these factorial studies, data from a recent non-factorial study are listed in the Table for indirect comparison vs the highest marketed OM/HCT dose. In conclusion, data from these studies suggest that the lowest and highest marketed doses of OM/HCT produce greater decreases in BP vs the lowest and highest marketed doses of AM/BN. Additional head-to-head clinical trials should be done to confirm whether these observations reach statistical significance.

Key Words: Combination Therapy, Factorial Design Studies, Olmesartan

**P-186**

**COSTS OF MORE EFFECTIVE ANTIHYPERTENSIVE TREATMENT**

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The advantages of blood pressure (BP) reduction are well known and the controlled clinical trials have clearly demonstrated that with intensive therapy the BP targets set by the scientific guidelines may be reached in most of the patients; on the other end the degree of BP control in the community is still disappointing and the effectiveness and costs of more intensive treatment are largely unknown.

Purpose of our study was to evaluate the outcome of a regular attendance to an hypertension clinic on BP control and the extra costs associated with a more effective drug treatment. All outpatients attending the clinic in a two years period were retrospectively identified. BP values and data on drug treatment and on other cardiovascular risk factors were collected at baseline and at the last available visit; the level of global cardiovascular risk was classified according to the ESH guidelines. The daily cost of drug treatment was calculated assuming the reference price for each drug class, set by the Italian Health Agency for reimbursement.

579 patients with 3 or more visits (average follow-up 20 months) were included; patients excluded (with less than 3 visits) had BP better controlled and an overall lower risk, while for most of the patients included the level of risk was high (52.7%) or very high (31.4%); 87% were already on drug treatment at baseline but diastolic BP was controlled in about 20% of them. With judicious changes of initial drug therapy or, more often, the addition of new drugs (average n° of drugs/patient = 1.4 at baseline and 2.15 at follow-up) BP was reduced from 152/97 mmHg to 141/89 mmHg and a satisfactory dyastolic BP control was reached in about 50% of the patients; as expected patients at very high risk required more drugs (2.75 vs 1.9). At follow-up all classes of drugs were used more often than at baseline and 25% of the patients were treated with 3 or more drugs. This was associated with an increased cost of treatment; for the entire group the average daily cost of treatment increased from 0.647 Euro to 1.02 Euro, which means that the substantial improvement in BP control that we obtained, costs an extra 136 Euro/year.

**Conclusions:** More rational drug treatment, more drugs and an improved compliance allow a better BP control in the community and the extra costs involved seem reasonable.

Key Words: Cost of Drug Treatment, Drug Therapy, Hypertension

**P-187 MP-15**

**EVALUATION OF HEALTHCARE RESOURCE UTILIZATION ASSOCIATED WITH AMLODIPINE BESYLATE AND DIURETICS IN A LARGE MANAGED CARE POPULATION**

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JNC 7 guidelines prefer the use of diuretics (DIR) based in part on their low acquisition costs. When evaluating the economics of treatment strategies, however, use of healthcare resources, such as office visits, lab testing, and concomitant medications, should be included in the total direct medical cost of treating hypertension. This study examined healthcare resource utilization between patients treated with amlodipine besylate (AML) versus DIR in a large managed care population.

A retrospective cohort study was conducted using a US-based managed care administrative claims dataset. Adults (≥18 years) who were hypertensive (by ICD-9 codes) and newly treated with either AML or any DIR (as a single-agent formulation) were identified. Patients were continuously enrolled in the same health plan for at least 1 year during the period of 2000-2002. Patients who were on AML/benazepril HCl combinations were excluded. A propensity scoring statistical methodology was used to adjust for differences in demographics, risk factors, and concomitant diseases to reduce confounding between the cohorts. Study measures included physician visits, lab testing, concomitant medications (cardiovascular [CV] and non-CV) among all hypertensive patients and those with diabetes.

A total of 111,027 patients were included in the study (17,541 on AML; 93,486 on DIR). The propensity scoring analysis was successful with only one variable (CD score) exhibiting lack of balance after adjustment (P < 0.05). Among hypertensive patients overall, per year there were 0.336 lab tests, 0.464 physician visits, 2.88 CV medications, and 3.81 non-CV medications more per DIR patient than per AML patient. Among patients with diabetes, there were 0.371 lab tests, 0.698 physician visits, 2.82 CV medications, and 5.55 non-CV medications more per DIR patient than per AML patient per year.

In this hypertensive population, the use of DIR was associated with higher healthcare resource utilization compared with the use of AML. As multiple medications are frequently needed to achieve treatment goals, it is important to consider total direct medical costs for all drugs and related resources when comparing costs among alternative antihypertensive therapies.

Key Words: Amlodipine, Diuretics, Healthcare Resource Utilization

**P-188**

**LONG-TERM ANTIPROTEINURIC EFFECT OF AN LN TYPE CALCIUM CHANNEL ANTAGONIST, CILINDIPINE**

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We investigated the long-term antiproteinuric effect of an LN-type calcium channel (Ca) antagonist, cilindipine in the patients with essential hypertension (EHT).
Subjects are 37 EHT patients (61 ± 2(SE) years, 22 females and 15 males). All patients underwent 24-h home urine collection and proved to have proteinuria greater than 0.1 g/day. Cilnidipine at a mean dose of 8 mg was administered to the patients. In 30 patients, cilnidipine was switched from other Ca antagonists including manidipine and amlodipine, while cilnidipine was newly added in the other 7 patients. Seventeen patients have been received either ACE inhibitors (ACEI) or ARBs at least 6 months before the administration of cilnidipine. Blood pressure (BP), blood chemistry and 24-h home urine collection were determined at 6, 12 and 24 months after the administration of cilnidipine.

Baseline BP was 142 ± 2/85 ± 1 mmHg. Systolic BP did not change significantly throughout the study, while diastolic BP was significantly lower at 6 months (82 ± 1 mmHg, p < 0.01), 12 months (84 ± 1 mmHg, p < 0.05) and 24 months (82 ± 2 mmHg, p < 0.05). Urinary protein excretion decreased significantly from 0.36 ± 0.23 g/day to 0.16 ± 0.12 g/day (-45.7 ± 6.7 %, p < 0.01) at 6 months and to 0.14 ± 0.16 g/day (-57.8 ± 12.0, p < 0.01) at 12 months. The reduction of proteinuria occurred independently of the changes in BP. Urinary salt excretion, estimated protein intake, and serum creatinine concentration did not change significantly during the observation period. The reduction of proteinuria at 6 months after cilnidipine was similar between the patients with the baseline administration of ACEI/ARB (-47.6 ± 11.2 %, p < 0.01) and those without ACEI/ARB (-44.4 ± 8.7 %, p < 0.01). On the other hand, the reduction of proteinuria continued until 24 months in the patients with ACEI/ARB (-41.1 ± 16.3 %, p < 0.05) but not in those without ACEI/ARB (-9.3 ± 49.1 %, ns). Results suggest that cilnidipine exerts antiproteinuric effect irrespectively of the co-administration of ACEI/ARB. However, the effect of cilnidipine may last longer in the presence of ACEI/ARB.

Key Words: 24-Hour Home Urine Collection, Cilnidipine, Proteinuria

P.189
LOSARTAN PREVENTS THE DIURETICS-INDUCED HYPOKALEMIA AND HYPERURICEMIA IN THE PATIENTS WITH ESSENTIAL HYPERTENSION
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Angiotensin II receptor blocker (ARB) losartan has a property to increase urinary excretion of uric acid. We compared the diuretics-induced changes in serum uric acid and potassium between losartan and other ARBs or ACE inhibitors in the patients with essential hypertension (EHT).

Subjects are 49 EHT patients (65 ± 10(SD) years, 29 males and 20 females) who have been treated with either ACE inhibitors or ARBs. Either indapamide (mean dose 0.92 mg/day, n = 42) or trichlormethiazide (mean dose 1.86 mg/day, n = 7) was added to the patients. Blood pressure (BP) and blood chemistry were determined before and after the administration of diuretics. Comparison was made between the patients with losartan (Losartan group, mean dose 45.8 mg, n = 24) and those with other ARBs or ACE inhibitors (Control group, n = 25).

BP fell from 163 ± 17/90 ± 11 mmHg at baseline to 150 ± 15/85 ± 9 mmHg at 1 month (p < 0.01) and to 145 ± 14/83 ± 9 mmHg at 3 months (p < 0.01). Significant reductions of BP continued until the 12 months observation period. There was no significant difference in the reduction of BP between Losartan and Control groups. Blood chemistry determined at an average of 138 days of the diuretics administration showed the small but significant increase in serum creatinine (from 0.71 ± 0.18 to 0.75 ± 0.24 mg/dl, p < 0.01). Similarly, serum uric acid significantly (p < 0.01) increased from 5.76 ± 1.22 to 6.36 ± 1.30 mg/dl. The increase in serum uric acid in Control group was remarkable (from 5.79 ± 1.42 to 6.71 ± 1.41 mg/dl, p < 0.01), while that in Losartan group was insignificant (from 5.74 ± 0.97 to 5.99 ± 1.09 mg/dl, ns). Interestingly, serum potassium concentration decreased in Control group (from 4.24 ± 0.37 to 4.11 ± 0.35 mEq/L, p < 0.05) but not in Losartan group (from 4.05 ± 0.25 to 4.13 ± 0.26 mEq/L, ns).

Results suggest that diuretics-induced hypokalemia and hyperuricemia may be attenuated in the patients treated with losartan.

Key Words: Hypokalemia, Losartan, Uric Acid

P.190
INHIBITION OF THE MEK1 AND ERK PATHWAY BY AMLODIPINE INDUCES VASCULAR SMOOTH MUSCLE CELL DIFFERENTIATION IN HYPERTENSION
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Phenotypic modulation of smooth muscle cells (SMCs) is critical in the progression of atherosclerosis. Recent clinical trials have shown that the long-acting calcium antagonist amlodipine has an antiatherogenic property. The molecular mechanisms of this antiatherogenic property of amlodipine, however, remain unknown. We examined the molecular mechanisms behind the phenotypic modulation of aortic SMCs by amlodipine in stroke-prone spontaneously hypertensive rats (SHRSP). Male Wister-Kyoto rats (WKY) and SHRSPs were randomized and treated with a vehicle, amlodipine (5 mg/kg/day), or enalapril (10 mg/kg/day). Both drugs were significantly and equally effective at reducing systolic blood pressure, aortic morphology and collagen deposition in comparison to vehicle-treated SHRSP aortas. In the vehicle SHRSP aortas, contractile-type SM myosin heavy chain (MHC) SM2 was significantly lower, whereas synthetic-type MHC NMHC-B was significantly higher compared with those in the vehicle WKY aorta. Compared to the vehicle SHRSP group, significantly and to the same extent, both drugs reduced NMHC-B and increased SM2, indicating that both drugs induce the phenotype of SMCs in SHRSP aortas toward the differentiated state. In the vehicle SHRSP group, MKK6, p38MAPK, MEK1 and p-42/44 ERK were significantly increased compared with the vehicle WKY group. Both drugs significantly reduced these values in the SHRSP aorta. Furthermore, amlodipine significantly lowered MEK1 (23%) and p-42/44 ERK (20%) compared with enalapril, reducing MEK1 and p-42/44 ERK to the same levels as in the vehicle WKY group. In contrast, p-Akt and eNOS were significantly lower in the vehicle SHRSP group than in the vehicle WKY group. The two drugs significantly increased p-Akt and eNOS compared with the vehicle SHRSP group. Furthermore, enalapril was more effective than amlodipine at increasing p-Akt and eNOS in SHRSP aortas. Thus, amlodipine inhibited SMC dedifferentiation through the inhibition of the MEK1 and ERK pathway more effectively than did enalapril in SHRSP aortas, suggesting that the MEK1 and ERK pathways might be crucial determinants for the antiatherogenic property of amlodipine in hypertension.

Key Words: Calcium Antagonist, Signal Transduction, Smooth Muscle Cell

P.191 MP-14
ALISKIREN, A NOVEL ORALLY EFFECTIVE RENIN INHIBITOR, EXHIBITS SIMILAR PHARMACOKINETICS AND PHARMACODYNAMICS IN JAPANESE AND CAUCASIAN SUBJECTS
Sujata Vaidyanathan, Jo Jermany, Ching-Ming Yeh, Marie-Noelle Bizot, Riccardo P Camisasca. Exploratory Clinical Development, Novartis, East Hanover, NJ.

Aliskiren is the first in a new class of orally effective renin inhibitors. This study compared the single and multiple dose pharmacokinetics and...