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AMBULATORY BLOOD PRESSURE MONITORING (ABPM) IN THE VALUE TRIAL
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Background: The VALUE Trial evaluated the cardiac outcomes in a large group of high-risk, elderly hypertensive patients randomized to either a valsartan-based (VAL) or amlodipine-based (AML) antihypertensive regimen. During the entire 4.2 year study period office blood pressure (BP) at trough remained significantly lower in the AML group.

Methods: The present substudy aimed to demonstrate similar BP reductions in the two groups over 24 hours. ABPM was performed after one year of randomized treatment in 47 centres in Italy, USA and Denmark. Measurements were carried out with SpaceLab 90202 or 90207 monitors hooked up before the morning dose of medicine. 659 patients were available for ITT analysis.

Results: The two treatment groups were generally well balanced concerning BP and other demographic data at baseline. However, ECG-verified left ventricular hypertrophy was more prevalent in patients randomized to valsartan (15.7 vs. 8.0%, p=0.002). The mean doses of VAL and AML employed were 131±36 and 8±2 mg respectively. 34% were on monotherapy with VAL and 43% had AML alone. The average 24-SBP difference at one year was 1.1 mmHg in favour of AML (131.8 vs. 132.9 mmHg, ns), and the DBP difference was 0.4 mmHg in favour of VAL (75.0 vs. 75.4 mmHg, ns). Similar trends were seen both during day- and nighttime with a tendency for AML to be more effective during the late night hours. The number of combined cardiovascular endpoints (cardiac morbidity, mortality and stroke) were not different in the two groups, but correlated significantly with the level of 24-h SBP and DBP. Thus for the ITT-population a 10 mmHg increase in 24-h SBP translated into a 37% increase in combined risk (p<0.001). The difference between office DBP at trough and mean 24-h DBP tended to be less pronounced in the AML group than in the VAL treated patients (4.2 vs.5.4 mmHg). A tendency to more advanced BP-dipping during nighttime was observed in the VAL-treated patients.

Conclusion: After one year 24-h BP was similarly reduced by the valsartan and the amlodipine based regimen. Endpoints were strongly related to 24-h BP levels. Night BP during the last hours of the dosing interval tended to be lower on amlodipine.

Key Words: Ambulatory Blood Pressure Measurement, Amlodipine, Valsartan

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ANGIOEDEMA IN THE ANTIHYPERTENSIVE AND LIPID-LOWERING TREATMENT TO PREVENT HEART ATTACK TRIAL (ALLHAT)
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ALLHAT, the largest antihypertensive study conducted to date, randomized 42,418 participants to one of four antihypertensive drug classes/drugs (diuretic/chlorthalidone, calcium-channel blocker/amlodipine, angiotensin-converting enzyme (ACE) inhibitor/lisinopril, and alpha-blocker/doxazosin), with 9054 participants assigned to lisinopril. This large patient sample, combined with the double-blind design of ALLHAT, provides a large and diverse population in which to further examine the occurrence of angioedema, a rare but potentially life-threatening side effect of ACE-inhibitors. The purpose of this presentation is to describe the characteristics, both within and between treatment groups, of treated hypertensive patients with angioedema.

Patients who developed angioedema during ALLHAT were compared for baseline characteristics and for the temporal relationship of changes in antihypertensive drug administration to the onset of angioedema. Results were as follows: Fifty-three ALLHAT participants developed angioedema during active follow-up in ALLHAT. Of these, 55% were black, 60% male, 70% were assigned to the ACE-inhibitor lisinopril (0.83 events per 1000 person-years), 15% to chlorthalidone (0.11 events per 1000 person-years), 9% to doxazosin (0.17 events per 1000 person-years), and 6% to amlodipine (0.07 events per 1000 person-years). Three cases (6%) occurred within a day of randomization, 22% within the first week, 34% within the first month, and 68% within the first year. In addition, 3 patients (6%) had a dose increase of their assigned medication within a week prior to onset, but over half (51%) had no prior dose increase. One patient died following the angioedema onset. The occurrence of angioedema cases in the ACE-inhibitor arm of ALLHAT corresponds with the previously reported association of angioedema and ACE-inhibitor use.

Key Words: ALLHAT, Angioedema, angiotensin Converting Enzyme Inhibitor

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SAFETY AND TOLERABILITY OF COADMINISTERED AMLODIPINE AND ATORVASTATIN IN PATIENTS WITH CONCOMITANT HYPERTENSION AND DYSLIPIDEMIA IN THE RESPOND STUDY
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Amlodipine/atorvastatin combination therapy has been demonstrated to be an effective approach for the management of concomitant hypertension (HTN) and dyslipidemia (DYS). However, a potential barrier to the use of this treatment might be concerns regarding the occurrence of adverse events (AEs) when coadministering these 2 therapies.

This randomized, double-blind, multicenter, placebo-controlled, 3x5 factorial study assessed the safety of coadministered amlodipine plus atorvastatin therapy versus either drug alone or placebo. Patients aged 18–75 years with concomitant HTN/DYS were treated for 8 weeks with amlodipine (5 or 10 mg), atorvastatin (10, 20, 40, or 80 mg), 8 combinations of the aforementioned amlodipine plus atorvastatin doses, or placebo. Treatment-emergent (all-causality) AEs are reported.

A total of 1660 patients with concomitant HTN/DYS (n=110-111 per treatment group) were included in the safety analysis. Overall, 663 (40%) patients reported AEs. Rates of discontinuation due to AEs were similar in the combination (5.6%), amlodipine alone (5.4%), atorvastatin alone (4.1%), and placebo (4.5%) groups. Most AEs were mild or moderate in intensity. Overall, the most common AEs were peripheral edema (overall 7.4%: amlodipine alone 12.2%, atorvastatin alone 1.1%, amlodipine plus atorvastatin 9.9%, placebo 2.7%), headache (6.2%), and respiratory tract infection (4.3%). The incidence of myalgia in combination-treated patients was low (1.6%) and similar to the amlodipine or atorvastatin alone and placebo groups (1.4%, 1.8%, and 1.8%, respectively). No increase in the incidence of AEs was observed with coadministered amlodipine 10 mg plus atorvastatin 80 mg (41.4%) versus amlodipine 10 mg alone (47.7%), and only a small increase versus atorvastatin 80 mg alone (37.3%) (Table 1).
Coadministered amlodipine plus atorvastatin is well tolerated in patients with concomitant HTN/DYS. Furthermore, AEs observed with coadministered amlodipine plus atorvastatin are similar in nature, severity, and frequency to those seen with amlodipine or atorvastatin alone.

Key Words: Antihypertensive Agents, Lipid-Lowering Therapies, Safety and Tolerability

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AN 8-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER, AMBULATORY BLOOD PRESSURE MONITORING (ABPM) STUDY OF TEVETEN (EPROSARTAN MESYLATE) 600MG AND 1200MG QD IN PATIENTS WITH ESSENTIAL HYPERTENSION
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This was a double-blinded, placebo-controlled, parallel group, multicenter study in patients with essential hypertension (SDBP > 95 mmHg and ≤114 mmHg). The study was composed of a 2-4 week placebo run-in period, an 8-week double-blind treatment period, and a 5-7 day post-dose follow-up period. Eligible patients were randomized to receive placebo, Teveten 600mg QD, or Teveten 1200mg QD for 8 weeks and returned 2, 4 and 8 weeks after randomization for evaluation. 24 ABPM was performed on all patients.

The total number of randomized patients was 200, with 67 in the placebo group, 62 in the Teveten 600 mg group and 71 in the Teveten 1200 mg group. Following a single-blind placebo run-in period lasting 2-4 weeks, patients were randomized to double-blind treatment with placebo, Teveten 600 mg QD, or Teveten 1200 mg QD for 8 weeks. Study medication was taken once daily in the morning. Teveten was supplied as 300 mg tablets with corresponding placebo tablets. During the placebo run-in period, all patients took 4 placebo tablets corresponding to Teveten 300 mg tablets. During the double-blind period, placebo patients took 4 placebo tablets corresponding to Teveten 300 mg tablets. During the double-blind period, placebo patients took 4 placebo tablets corresponding to Teveten 300 mg tablets; patients randomized to Teveten 600 mg took 2 Teveten 300 mg tablets and 2 corresponding placebo tablets; patients randomized to Teveten 1200 mg took 4 Teveten 300 mg tablets.

Teveten, when administered 600 mg, as well as, 1200 m once daily, statistically significantly lowered mean 24-hour Ambulatory DBP when compared with placebo (p<0.0001 for both comparisons). The placebo-corrected least squares mean change from baseline at study endpoint was 5.5 mmHg for Teveten 600 mg, and 5.1 for Teveten 1200 mg. The percentage of patients who achieved SitDBP response to Teveten 600 mg therapy at study endpoint (21.0% ;13/62) was not statistically different from the percentage achieving SitDBP response to placebo therapy (1.5%; 14/655; p=0.933). However, the percentage of patients who achieved SitDBP response to Teveten 1200 mg therapy at study endpoint (41.4%; 29/70) was statistically greater than the percentage achieving SitDBP response to placebo therapy (21.5%; 14/655; p=0.010).

Key Words: 24-Hour Ambulatory Blood Pressure Monitoring, Eprosartan Mesylate, Essential Hypertension

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EFFICACY AND SAFETY OF SILDENAFIL CITRATE IN PULMONARY ARTERIAL HYPERTENSION (PAH): RESULTS OF A MULTINATIONAL, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL
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The purpose of this study was to evaluate the efficacy and safety of sildenafil, a phosphodiesterase 5 inhibitor, in patients with PAH.

In this double-blind, placebo-controlled study, 278 patients with PAH were randomized to oral placebo or sildenafil (20, 40, or 80 mg) 3 times daily. The primary endpoint was change in 6-minute walk distance from baseline to Week 12. Secondary endpoints were change from baseline in mean pulmonary artery pressure (MPAP), time from randomization to clinical worsening, and change from baseline in Borg dyspnea score.

The 6-minute walk distance increased in all sildenafil groups compared with placebo; mean placebo-corrected treatment effects were 45 m (99% confidence interval [CI], 21–70; P<0.001), 46 m (99% CI, 20–72; P<0.001), and 50 m (99% CI, 23–77; P<0.001) for 20, 40, and 80 mg sildenafil 3 times daily, respectively. All sildenafil doses reduced MPAP at Week 12; mean placebo-corrected treatment effects were -2.7 mmHg (95% CI, -5.4 to -0.1; P=0.021) for 20 mg, -3.0 mmHg (95% CI, -5.3 to -0.7; P=0.006) for 40 mg, and -5.1 mmHg (95% CI, -7.5 to -2.6; P<0.001) for 80 mg sildenafil. Compared with placebo, there were trends towards reductions in the incidence of clinical worsening events (in particular, hospitalizations) and improvement in the level of dyspnea during exercise in the sildenafil-treated groups. Adverse events were of mild to moderate severity, consistent with the natural history of PAH and the established safety profile of sildenafil administered for erectile dysfunction.

This study confirms the efficacy and safety of sildenafil in the treatment of patients with PAH.

Key Words: Exercise Tolerance, Pulmonary Arterial Hypertension, Sildenafil

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HEMODYNAMIC EFFECTS OF SILDENAFIL CITRATE IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION (PAH)
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Sildenafil inhibits phosphodiesterase 5, enhancing cGMP-mediated relaxation of vascular smooth muscle. We report the hemodynamic effects of chronic oral sildenafil therapy in patients with PAH.

This 12-week, double-blind, placebo-controlled study randomized 278 PAH patients to placebo or sildenafil (20, 40, or 80 mg) 3 times daily. Hemodynamic measurements, performed at trough plasma concentrations of study medication, were made at baseline and Week 12.

Sildenafil significantly decreased mean pulmonary artery pressure (MPAP) and pulmonary vascular resistance (PVR), and increased cardiac output (CO) and mixed venous oxygen saturation (MVO2) (Table).