combination therapy with aliskiren, a direct renin inhibitor, plus amlodipine, a calcium channel blocker, versus amlodipine alone. Deborah Keefe, MD, MPH, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA, presented the results.

The study enrolled 485 patients with stage 2 hypertension, defined as a mean sitting systolic blood pressure (msSBP) level between 160 mm Hg and <200 mm Hg. After a washout period ranging from 0 to 4 weeks, patients were randomly assigned to receive treatment with once-daily aliskiren/amlodipine 150/5 mg or amlodipine 5 mg for 1 week. After the first week of treatment, patients received increased doses of aliskiren/amlodipine (300/10 mg) or amlodipine (10 mg) for 7 additional weeks of therapy.

The primary outcome measures were changes in msSBP and mean sitting diastolic blood pressure (msDBP) after 8 weeks of therapy and the proportion of patients achieving BP control (<140/80 mm Hg) by Week 8. Patients were classified according to baseline msSBP as having moderate (<180 mm Hg) or severe (≥ 180 mm Hg) hypertension for a pre-specified subgroup analysis.

After 8 weeks, treatment with aliskiren/amlodipine resulted in a significantly greater reduction in msSBP compared with amlodipine monotherapy in both the moderate hypertension (-35.3 vs -28.8 mm Hg; p<0.0001) and severe hypertension (-47.5 vs -37.4 mm Hg; p=0.0005) groups. Reductions in msDBP were also greater with aliskiren/amlodipine versus amlodipine alone in the moderate hypertension (-15.7 vs -12.0 mm Hg; p<0.0001) and severe hypertension (-18.6 vs -14.0 mm Hg; p=0.0095) groups.

Combination therapy was also associated with greater BP control. Significantly more patients with moderate hypertension achieved BP control with aliskiren/amlodipine than with amlodipine monotherapy (69.7% vs 53.0%; p<0.01). Patients with severe hypertension were also significantly more likely to achieve BP control with combination aliskiren/amlodipine compared with amlodipine alone (55.6% vs 34.0%; p<0.05).

Combination therapy with aliskiren and amlodipine was well tolerated, with adverse event rates similar to those in the amlodipine monotherapy group. The major exception was peripheral edema, which occurred less frequently in the combination aliskiren/amlodipine group than in the amlodipine monotherapy group in patients with moderate (16.2% vs 18.1%) and severe (6.7% vs 18.8%) hypertension.

Current hypertension guidelines recommend first-line use of dual-combination therapy in patients with moderate or severe hypertension. Combination therapy with aliskiren/amlodipine may prove to be a valuable first-line treatment option for patients with moderate to severe hypertension, Dr. Keefe concluded.

Olmesartan Medoxomil versus Ramipril for the Treatment of Hypertension in the Elderly

Elderly hypertensive patients treated with olmesartan medoxomil demonstrated more favorable office blood pressure (BP) normalization rates and sustained 24-hour BP control compared with ramipril. Giuliano Tocci, MD, Sant'Andrea Hospital, Rome, Italy, presented findings from the Efficacy and Safety in Elderly Patients with Olmesartan versus Ramipril Treatment (ESPORT) trial.

ESPORT was an international, multi-center, randomized, double-blind study that consisted of a 2-week wash-out period followed by 12 weeks of active treatment with either olmesartan 10-40 mg daily (n=170) or ramipril 2.5-10 mg daily (n=175) administered with a glass of water after breakfast between 9:00 AM and 11:00 AM. Dosage was determined based on office BP reading at 2 weeks and 6 weeks on medication with a target BP normalization of <140 mm Hg systolic BP (SBP) and <90 mm Hg diastolic BP (DBP) for nondiabetic patients and <130 mm Hg SBP and <80 mm Hg DBP for diabetic patients. All patients had mild to moderate essential arterial hypertension (defined as sitting DBP 90-109 mm Hg and SBP 140-179 mm Hg after 2-week hypertensive medication wash-out period with placebo) and were between the ages of 65 and 89 years. The two groups were well-matched at baseline.

The primary efficacy endpoint was the rate of between-treatment BP normalization achievement at 12 weeks. The primary safety endpoint was the between-treatment incidence of adverse events and changes in laboratory or ECG data at 12 weeks. Secondary endpoints included between-treatment comparison of: percentage of DBP normalized patients after 2, 6, and 12 weeks, percentage of normalized plus responder patients after 2, 6, and 12 weeks, changes in sitting office pulse pressure after 12 weeks, changes in 24-hour daytime (6 AM – 10 PM) and night-time (10 PM – 6 AM) average SBP, DBP, and pulse pressure after 12 weeks, hourly averages of BP changes with treatment, BP changes in the last 4 hours of the dosing interval after 12 weeks, changes in office and ambulatory heart rate, and smoothness index of BP after 12 weeks.

After 12 weeks of treatment, more patients in the olmesartan group achieved SBP and DBP normalization than in the ramipril group (p<0.05). This was also true at Weeks 2 and 6. Additionally, patients taking olmesartan demonstrated larger reductions in average 24-hour SBP and DBP compared with ramipril (p<0.001 for both).

The number of patients reporting adverse events was comparable between the two groups. Fifteen patients withdrew from study participation due to adverse events (8 in the olmesartan group and 7 in the ramipril group). The majority (89%) of reported adverse events were categorized as mild or moderate. While three events met the serious adverse event criteria, they were not deemed drug-related.

Overall, olmesartan medoxomil was found to be effective and well-tolerated in elderly hypertensive patients. Patients taking olmesartan had more favorable rates of office BP normalization and sustained 24-hour BP control compared with ramipril. Adverse events associated with olmesartan were mainly mild or moderate in severity.

Results from the ACCORD BP Trial

Intensive blood pressure (BP) control did not reduce the rate of a composite outcome of major cardiovascular (CV) events in high-risk patients with type 2 diabetes mellitus (T2DM), according to the Action to Control Cardiovascular Risk in Diabetes (ACCORD; NCT00000620) BP Trial. However, intensive BP control correlated with reductions in the rate of total stroke and nonfatal stroke. Richard H. Grimm, MD, PhD, Berman Center for Clinical Research, Minneapolis, MN, presented new findings from the ACCORD BP Trial.

The ACCORD BP Trial included 4733 patients with stable T2DM >3 months (average duration 10 years) who were considered to be at high risk for CVD (defined as clinical or subclinical disease or ≥2 CV risk factors, in addition to DM). Patients were randomized to receive either intensive therapy (n=2362; initial 2-drug therapy of thiazide-type diuretic plus an angiotensin-converting enzyme inhibitor [ACEI], an angiotensin receptor blocker [ARB], or a β-blocker was recommended with drugs added or titrated at each visit in order to achieve a systolic BP of <120 mm Hg) or standard therapy (n=2371; where therapy was modified based on BP readings in an effort to acheive target BP). The target systolic BP for the intensive therapy group was <120 mm Hg versus <140 mm Hg for the standard therapy group.

The primary outcome was the first occurrence of a major CV event (defined as nonfatal myocardial infarction [MI], nonfatal stroke, or CV death). Secondary outcomes included an expanded macrovascular outcome (defined as a combination of the primary outcome plus revascularization or hospitalization for congestive heart failure), major coronary disease events (defined as a combination of a fatal coronary event, a nonfatal MI, or unstable angina), hospitalization or death due to heart failure, all stroke, death from any cause, or death from CV causes.

The rate of serious adverse events, although infrequent, was significantly higher in those who were treated with intensive therapy compared with those who received standard therapy (3.3% vs 1.3%, respectively; p<0.0001; Table 1). One year from study end, the mean systolic BP averaged 119.3 mm Hg versus 133.5 mm Hg for intensive and standard therapy groups, respectively, amounting to a difference of 14.2 mm Hg.

The annual rate of the composite of fatal and nonfatal CV events was similar in both groups (1.87% vs 2.09% per year for standard therapy; p=0.20). There was no difference in death from any cause between the two groups.

Table 1. Adverse Events.

	Intensive n (%)	Standard n (%)	p value
Serious AE	77 (3.3)	30 (1.3)	<0.0001
Hypotension	17 (0.7)	1 (0.04)	<0.0001
Syncope	12 (0.5)	5 (0.2)	0.10
Bradycardia or Arrhythmia	12 (0.5)	3 (0.1)	0.02
Hyperkalemia	9 (0.4)	1 (0.04)	0.01
Renal Failure	5 (0.2)	1 (0.04)	0.12
eGFR ever <30 mL/min/1.73m2	99 (4.2)	52 (2.2)	<0.001
Any Dialysis or ESRD	59 (2.5)	58 (2.4)	0.93
Dizziness on Standing†	217 (44)	188 (40)	0.36

†Symptom experienced over past 30 days from HRQL sample of 969 participants assessed at 12, 36, and 48 months post-randomization

Interestingly, the prespecified secondary outcomes of total stroke (p=0.01) and nonfatal stroke (p=0.03) were lower in the intensive therapy group. Based on these findings, the number needed to treat to lower systolic BP in order to prevent one stroke over 5 years would be 88. Interactions were also observed related to stroke rates and age (interaction p=0.13), CVD history (interaction p=0.94), baseline hemoglobin A1C (interaction p=0.008), and baseline diastolic BP (interaction p=0.10).

These results failed to demonstrate that lower target systolic BP (<120 mm Hg), through the use of intensive therapy, reduces the rate of fatal and nonfatal CV events (composite primary endpoint) in high-risk patients with T2DM. However, interesting data emerged regarding the secondary endpoints of total stroke and nonfatal stroke. These stroke related interactions merit further evaluation.

Further Reading: The ACCORD Study Group. *N Engl J Med* 2010; published online ahead of print March 14, 2010.