Candesartan and Amlodipine: Effect on the Incidence of Cardiovascular Events and New-Onset Diabetes

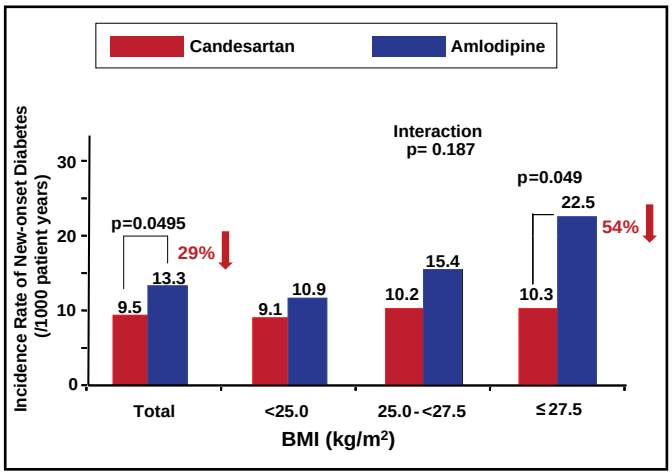
The 3-year extension of the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) Study demonstrated comparable efficacy of the angiotensin receptor blocker candesartan and the calcium channel blocker amlodipine on the incidence of cardiovascular (CV) events in high-risk hypertensive Japanese patients. As observed in the earlier phase of the study, cadesartan exhibited sustained superiority over amlodipine with regards to reduction in new-onset diabetes throughout the 3-year extended follow up. Kazuwa Nakao, MD, Kyoto University, Kyoto, Japan, presented findings from the CASE-J extended follow-up study.

The Case-J Extension included 2232 hypertensive patients from the original trial who were randomized to either candesartan (n=1140) or amlodipine (n=1092). The two groups were characteristically well-matched at baseline with a mean systolic blood pressure (SBP) of 163 mm Hg and a mean diastolic blood pressure (DBP) of 92 mm Hg. The mean age of study participants was 64 years and the mean body mass index (BMI) was ~24.5. The two groups also had similar comorbidities and risk factors at baseline. The primary composite endpoint was the incidence of CV mortality and morbidity, defined as sudden death and CV, cardiac, renal, and vascular events. The secondary endpoints included the incidence of all-cause death, CV death, and new-onset diabetes.

BP was well-controlled in both treatment groups throughout the duration of the early trial and this benefit was maintained over the extended course of follow-up. There was no significant difference in the incidence of CV events between the two groups. Analysis of the single primary endpoint components (sudden death, CV events, cardiac events, renal events, and vascular events) found no significant difference between cadesartan and amlodipine treatment. The incidence of all-cause death was also comparable for both treatment groups.

Treatment with candesartan significantly reduced the incidence of new-onset diabetes compared with amlodipine during the original study arm (p=0.031) and this benefit was demonstrated further in the extension arm of the study. A 29% relative risk reduction of new-onset diabetes was observed in the candesartan group compared with amlodipine (HR, 0.71; 95% CI, 0.51 to 1.00; p=0.0495; Figure 1). There also appeared to be an interaction between BMI and new-onset diabetes (interaction p=0.187). Increases in risk reduction correlated with increased BMI, particularly in patients with BMI ≥ 27.5 (p=0.049; Figure 1).

Figure 1. Relationship Between New-onset Diabetes and BMI.



Findings from the CASE-J Extension study provided valuable long-term data regarding the efficacy of candesartan and amlodipine on the incidence of CV events and new-onset diabetes in high-risk hypertensive patients. While results were comparable for both treatments concerning CV events, the incidence of new-onset diabetes was significantly reduced with candesartan compared with amlodipine and this benefit was sustained over time.

First-Line Treatment with Combination Aliskiren/Amlodipine Improves Blood Pressure Control Over Amlodipine Alone in Moderate and Severe Hypertension

First-line combination therapy with aliskiren and amlodipine provided greater reductions in blood pressure (BP) levels and higher rates of BP control compared with amlodipine monotherapy in patients with moderate or severe hypertension, according to new findings from a prospective trial. Combination therapy was also well tolerated, suggesting an important role for aliskiren/amlodipine in the management of patients with type 2 hypertension.

For many patients with moderate or severe hypertension, effective treatment requires combination antihypertensive therapy using agents with complementary mechanisms of action. This 8-week, double-blind, randomized trial was designed to compare the effectiveness of first-line

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).