

Long-term Candesartan Linked to Less New Diabetes vs Amlodipine

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SINGAPORE — While both the angiotensin blocker candesartan and the calcium-channel blocker amlodipine control blood pressure and reduce cardiovascular (CV) events equally over the long term in high-risk hypertensive patients, candesartan is associated with a significant reduction in incident diabetes, new observational findings indicate^[1]. In 10-year follow-up data presented at the 21st Asian Pacific Society of Cardiology (APSC) Congress, the researchers showed that there was no significant difference in blood-pressure reduction and a composite of CV events over 10 years with the two drugs, reinforcing the idea that blood-pressure lowering is key to controlling CV event rates. However, the findings, from an analysis of extension data on high-risk hypertensive participants in the [Candesartan Antihypertensive Survival Evaluation in Japan \(CASE-J\)](#) trial, showed those taking candesartan had a reduced risk of new-onset diabetes of 30%, although it remains to be determined why that did not translate into a reduction in adverse outcomes.

Jinliang Liu (Institute for Advancement of Clinical and Translational Science, Kyoto University Hospital, Kyoto, Japan) presented the results.

He told *theheart.org* | *Medscape Cardiology* that the findings "strongly support" the Japanese Society of Hypertension [Guidelines for the Management of Hypertension](#) statement that it is the degree of blood-pressure decrease, rather than antihypertensive drug class used, that determines the reduction in CV events.

Liu also believes that, should the results be confirmed in further studies, including in other populations, the potential impact of candesartan in terms of reducing the incidence of new-onset diabetes "will be worth recommending" in guidelines.

The researchers initially conducted the prospective, randomized CASE-J trial to compare the effect of candesartan and amlodipine on the incidence of CV events in 4728 high-risk hypertensive Japanese patients^[2].

After an average follow-up of 3.5 years, it was observed that the two drugs had a similar effect on preventing total CV events, although candesartan was associated with a significant reduction in the incidence of new-onset diabetes compared with amlodipine.

To try to clarify the comparative beneficial effects of the two drugs, the researchers next conducted the CASE-J extension (Ex) trial, in which the patients were followed up for a further 3 years, achieving similar results to the first trial^[3].

As several studies have suggested that new-onset diabetes is associated with an increased incidence of CV events in hypertensive patients, the team continued CASE-J Ex out to 10 years.

This current CASE-J 10 was, unlike the two previous prospective trials, a retrospective observational study of patients from the original CASE-J cohort, yielding a total of 1342 individuals with available data.

The analysis showed that blood pressure decreased markedly in the first 6 months after enrollment and then remained relatively stable throughout the 10-year follow-up.

Overall, systolic blood pressure decreased from 162.5 mm Hg to 133.5 mm Hg over the course of the study in the candesartan group and from 163.2 mm Hg to 134.5 mm Hg among amlodipine patients, while diastolic blood pressure decreased from 91.6 mm Hg to 71.0 mm Hg with candesartan and from 91.8 to 74.3 with amlodipine.

In terms of CV events, there were no significant differences between the two treatment groups during follow-up, at a 10-year Kaplan–Meier rate of composite CV events of 14.7% with candesartan and 14.8% for amlodipine, and a hazard ratio on multivariate analysis of 0.9 (95% CI 0.82–1.19; $P=0.703$).

However, there was a significant difference in rates of new-onset diabetes between the two groups, at a 10-year Kaplan–Meier rate of 4.7% among patients receiving candesartan and 6.4% in the amlodipine group, and a hazard ratio of 0.70 (95% CI 0.51–0.95; $P=0.029$).

Following on from their results, the researchers plan to conduct predefined subanalyses of their data, including identifying the optimal level of blood-pressure control for the maximum reduction of CV events, as well as an analysis restricted to obese patients.

Investigator-Led Study

Carolyn Lam (National Heart Centre, Singapore, and Duke-National University of Singapore), who commented on the research at the meeting, said that the researchers should be congratulated, as an investigator-led study of this kind is "not an easy thing to do" and that "we need more trials like that in Asia."

She noted that the two drugs had "the same effect" on CV events, but candesartan reduced the number of new diabetes cases. "If candesartan reduces the number of new diabetes cases, why did it not reduce the number of clinical events?" she asked.

"I think from the original CASE-J, you might say, 'Well, longer follow-up is needed to detect that,' but we're at 10 years and it's still the same results."

Lam pointed out that a subanalysis of the original study results suggested that there was a mortality reduction with candesartan among obese patients, which supports the theory that candesartan may be most effective in patients with lots of adipose tissue.

Another potential explanation is that there was "incredibly good blood-pressure control in both arms," underlining that "blood-pressure control per se is more important than any diabetes that you could avoid, and so on, in preventing events."

A third reason is that new diabetes cases were detected by either doctor report or the initiation of diabetes medications, which could, themselves, have affected the results, depending on their impact on CV events, she said.

The authors and Lam report no relevant financial relationships.

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