

Candesartan for cardiovascular prevention in Japanese hypertensive patients with coronary heart disease

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This editorial refers to ‘Angiotensin II receptor blocker-based vs. non-angiotensin II receptor blocker-based therapy in patients with angiographically documented coronary heart disease and hypertension: the Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease (HIJ-CREATE)[†], by H. Kasanuki et al., on page 1203

In the Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Heart Disease (HIJ-CREATE),¹ Kasanuki and colleagues randomized hypertensive patients with angiographically proven coronary heart disease either to candesartan or to blood pressure-lowering treatment not based on an angiotensin II type-1 receptor blocker (ARB), but possibly including an angiotensin-converting enzyme inhibitor (ACEI). The primary endpoint was the incidence of major cardiovascular events, a composite of cardiovascular death, non-fatal myocardial infarction, heart failure, stroke, and other cardiovascular events requiring hospitalization. During a median follow-up of 4.2 years, 264 patients of the candesartan group (25.8%) and 288 of the non-ARB group (28.1%) experienced an event. Neither for the composite primary endpoint [hazard ratio 0.89, 95% confidence interval (CI) 0.76–1.06] nor for any of its components did the hazard ratios comparing candesartan with non-ARB treatment approach statistical significance ($P > 0.19$).

Setting up a clinical trial in Japan is not an easy enterprise. The Japanese Pharmaceutical Affairs Law restricts the use of placebo in investigator-initiated studies.¹ A double-blind design goes against local perceptions of clinical experimentation. The HIJ-CREATE investigators have therefore to be congratulated for having randomized >2000 patients into an open-label actively controlled trial. Nonetheless, several features¹ make the interpretation of the HIJ-CREATE results difficult and weaken their external

validity. The HIJ-CREATE investigators recruited among selected hospitalized patients undergoing coronary angiography. Patients without stenotic coronary lesions were eligible for randomization in the presence of a history of coronary revascularization or coronary spasm. Of those screened, only 40.9% were enrolled. The trial was powered to detect a 20% reduction in the primary endpoint at a rate in the control group of 100 events per 1000 patient-years. The observed rate was only 67 events per 1000 patient-years and explains why the trial was underpowered. The primary endpoint included weak events, such as a clinically defined diagnosis of heart failure or growing aortic aneurysm without dissection. The daily dose of candesartan used in the HIJ-CREATE trial (range 4–12 mg) was lower than in most other countries (8–16 mg in hypertensive patients, and up to 32 mg in patients with heart failure). By the end of the trial, 23.0% of patients of the non-ARB group had crossed over to treatment with ARBs. Furthermore, the HIJ-CREATE trial had a prospective randomized open blinded endpoint (PROBE) design.² An independent and blinded endpoint committee adjudicated the endpoints. However, such a PROBE design does not protect against observer bias in the assessment and reporting of endpoints or side effects. Only reported endpoints and symptoms qualify for blinded validation.

HIJ-CREATE was not a trial of differential cardiovascular outcomes on ARB vs. non-ARB treatment, but a comparison of candesartan with a number of unspecified ACEIs.¹ In the non-ARB group, the use of ACEIs increased from 38.0% at randomization to 70.5%. About half of the patients in both treatment groups were on treatment with calcium channel blockers or β -blockers. Only 10% of patients were on treatment with diuretics. The investigators reported that the incidence of side effects leading to discontinuation of medications was 5.7% on candesartan and 12.2% on non-ARB treatment. Not unexpectedly, cough

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drove the difference ($P < 0.001$). The open design of the trial, the widespread belief in a placebo-like incidence of side effects on ARBs,³ and the well-known susceptibility of Asian patients to cough on ACEIs⁴ minimize the clinical significance of the differential incidence of adverse effects on candesartan vs. non-ARB treatment.

The baseline-corrected difference in the achieved blood pressure between the treatment groups was 1.5 mmHg systolic and 1.8 mmHg diastolic in favour of the ARB group. At 65 years of age, systolic blood pressure is the main predictor of cardiovascular outcome. In keeping with large-scale prospective observational studies,^{5,6} meta-regression analyses published by us^{7,8} and other research consortia⁹ demonstrated that small gradients in the achieved systolic blood pressure explained most of the differences in the cardiovascular outcomes as observed in randomized clinical trials. Although non-significant, the reported hazard ratio for the primary endpoint was similar to the hazard ratio which can be expected for a 1.5 mmHg difference in the achieved systolic blood pressure (hazard ratio 0.90, CI 0.78–1.04; Figure 1).⁸ The P -value for the comparison between the observed and predicted hazard ratios was 0.92. This strongly suggests that the small difference in the achieved systolic blood pressure explained the 11% trend in favour of the ARB group in the composite primary outcome in the HIJ-CREATE trial.¹

New-onset diabetes mellitus, a pre-defined secondary endpoint, occurred in seven patients of the ARB group (2.7 per 1000 patient-years) and in 18 patients of the non-ARB group (7.2 per 1000 patient-years).¹ The hazard ratio of 0.37 (CI 0.16–0.89) in favour of candesartan was much smaller than could be expected on the basis of a recently published network meta-analysis, involving 48 randomized groups of 22 clinical trials with 143 153 participants, who did not have diabetes at randomization.¹⁰ In most of these trials, diabetes mellitus was not a pre-defined endpoint. With an initial diuretic as

the standard of comparator, the odds ratios were 0.57 (CI 0.46–0.72; $P < 0.0001$) for ARBs and 0.67 (CI 0.56–0.80; $P < 0.0001$) for ACEIs.¹⁰ The HIJ-CREATE results on new-onset diabetes mellitus are based on few events, which, along with the open design, probably explains the extreme estimate of benefit in the prevention of treatment-induced diabetes.¹ In the properly powered double-blind Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET),¹¹ new-onset diabetes occurred in 399 patients allocated to telmisartan (7.5%) and in 366 randomized to ramipril (6.7%), resulting in an hazard ratio disfavoring the ARB (hazard ratio 1.12, CI 0.97–1.29; $P = 0.12$). In two large simple trials with a double-blind placebo-controlled design,^{12,13} the ARB telmisartan did not significantly reduce the risk of new-onset diabetes mellitus, with hazard ratios of 0.82 (CI 0.65–1.04; $P = 0.10$)¹² and 0.85 (CI 0.71–1.02; $P = 0.08$).¹³

The prognostic significance of new-onset diabetes mellitus remains a matter of debate. In a prospective observational study of hypertensive patients (median follow-up 6 years), unconfounded by previous treatment, new-onset diabetes and having diabetes already at baseline carried similar cardiovascular risk.¹⁴ In contrast, in other trials with a median follow-up ranging from 4.2 to 5.5 years, reviewed elsewhere,¹⁵ new-onset diabetes mellitus was not associated with a significantly elevated risk. Nonetheless, avoiding diabetes mellitus over a patient's life span, although not yet formally proven, might represent benefit beyond blood pressure lowering, although in absolute terms the gain might be tiny. For instance, assuming an absolute risk of 10% over 5 years on older drugs (diuretics and β -blockers) and a relative benefit on the newer drugs of $\sim 30\%$, about 100 patients would have to be treated for 5 years with newer drugs (ARBs, ACEIs, or calcium channel blockers) to avoid about three iatrogenic cases of diabetes mellitus. An important caveat in the interpretation of the latter estimates is that the currently available trial evidence only shows a delay in the diagnosis of diabetes mellitus by 1–2 years, whereas antihypertensive treatment needs to be sustained for a patient's lifetime.

In conclusion, for the prevention of a composite cardiovascular endpoint in Japanese hypertensive patients with coronary heart disease candesartan behaved similarly to non-ARB-based treatment including an ACEI in 70.5% of patients. At first sight, the proposed conclusions of the HIJ-CREATE trial subscribe to commonly held beliefs about ARBs as drugs with placebo-like tolerance³ and a favourable metabolic profile.¹⁰ However, estimates of the prevention of new-onset diabetes mellitus in the HIJ-CREATE trial were based on no more than 25 incident cases and are at least one order of magnitude larger than in properly powered trials.¹¹ The open design of HIJ-CREATE minimizes the clinical significance of the differential incidence in side effects, in particular cough.

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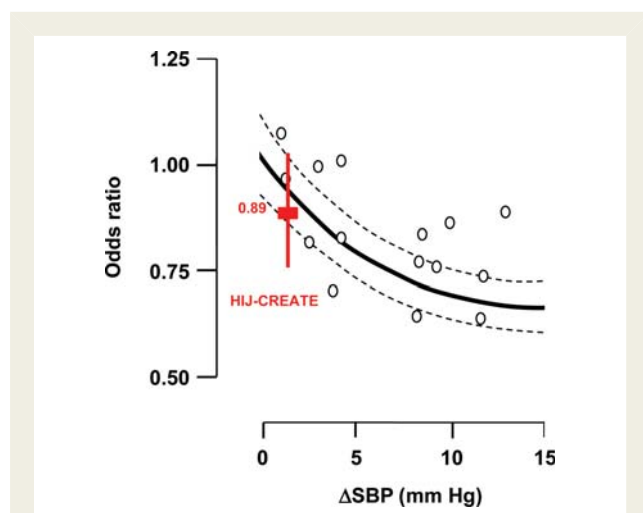


Figure 1 The odds ratio of the primary endpoint in the HIJ-CREATE trial fits the relationship between estimates of benefit and the reduction in systolic blood pressure (Δ SBP), as observed in randomized clinical trials published in 2000 or earlier. For more information on this relationship, see Staessen *et al.*⁷

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