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Original article

Impact of candesartan on cardiovascular events after drug-eluting stent implantation in patients with coronary artery disease: The 4C trial

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ABSTRACT

Objective: The purpose of this study was to examine the cardiovascular protective effects of candesartan in patients undergoing percutaneous coronary intervention (PCI) with drug-eluting stents (DESs).
Background: Candesartan has been reported to reduce cardiovascular events when therapy was started 6 months after PCI with bare-metal stents in patients who survived restenosis. Candesartan started immediately after PCI with DESs was also effective in preventing cardiovascular events.
Methods: The 4C trial was a multicenter, prospective, randomized, open-label study. A total of 1145 patients at 39 centers in Japan were randomly assigned to receive candesartan plus standard medical treatment or standard medical treatment alone. The primary endpoints were all-cause death, and a composite of non-fatal myocardial infarction (MI), unstable angina pectoris (uAP), congestive heart failure (CHF), and non-fatal cerebrovascular events. The follow-up period was up to 3 years after the index PCI (ClinicalTrials.gov NCT00139386).
Results: The incidence of total death, one of the primary endpoints, was comparable between the two treatment groups (3.8% each, $p = 0.9702$). Another primary endpoint, non-fatal major cardiovascular events, tended to occur more often in the control group than in the candesartan group (9.2% vs. 12.5%, $p = 0.0985$). In contrast, candesartan significantly reduced one of the pre-specified secondary endpoints: cardiovascular events that included non-fatal MI, uAP, and CHF (4.4% vs. 6.7%, $p = 0.0136$). Furthermore, candesartan significantly reduced another secondary endpoint that included cardiovascular events and cardiovascular death (5.0% vs. 7.7%, $p = 0.0493$).

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Conclusions: The 4C trial showed that candesartan administered immediately after PCI with DESs did not improve the prognosis after the index procedure, but did reduce some cardiac-related events for 3 years.

Introduction

In patients with coronary artery disease (CAD) before the era of percutaneous coronary intervention (PCI), it was found that hypertension, congestive heart failure, abnormal hemodynamics, or left ventricular asynergy was associated with a diminished 5-year survival rate [1]. After the introduction of PCI by Andreas Grüntzig in Zurich, Switzerland in September 1977 [2], this technique has seen several developments, such as coronary stenting [3], rotational atherectomy [4], and the implantation of drug-eluting stents (DESs) [5]. It is well known that patients with critical risk factors such as dyslipidemia and complicated diabetes have worse prognosis in coronary artery diseases [6,7]. Therefore, intensive medical treatment to control significant coronary risk factors is widely recommended. Despite the above-mentioned advances in PCI, the COURAGE trial showed that PCI itself did not improve the prognosis of CAD as compared with optimal medical treatment (OMT) that included a combination of antiplatelet agents, statins, β-blockers, and angiotensin-converting enzyme inhibitors (ACEIs) [8]. In that trial, angiotensin II receptor blockers (ARBs), which have been shown to be effective in lowering cardiovascular morbidity and mortality in patients with high-risk hypertension [9] and heart failure [10], were used in less than 20% of the study population, raising the possibility that the prognosis of CAD patients undergoing PCI might be further improved by the addition of ARBs to OMT.

Before the era of DESs, Kondo et al. investigated patients who survived restenosis after PCI with bare metal stents (BMSs), and showed that a low dose of candesartan that did not decrease blood pressure reduced the cardiovascular event risk by more than 50% when therapy was started about 6 months after the index procedure [11]. Because DESs have been proven to decrease the restenosis rate [5], we hypothesized that in patients undergoing PCI with DESs, candesartan started immediately after the procedure may be effective in preventing cardiovascular events in a manner similar to that observed in patients who survived restenosis after the implantation of BMSs [11]. Therefore, the **C**andesartan for prevention of **C**ardiovascular events after **C**YPHER™ or TAXUS™ **C**oronary stenting (4C) trial was designed to evaluate the long-term effects of candesartan on the incidence of cardiovascular events in patients who had DES implantation.

Methods

The methodology and protocol of the 4C trial have already been published [12] and registered (ClinicalTrials.gov NCT00139386). In summary, the trial was an open-label, multicenter, randomized, prospective study to evaluate the effects of candesartan on cardiovascular events in patients with ischemic heart disease after implantation of sirolimus- and/or paclitaxel-eluting stents (SESs and/or PESs). Between October 2006 and April 2009, 1145 patients were enrolled at 39 medical centers in Japan and randomized to treatment with or without the ARB candesartan (C or NC groups, respectively, Fig. 1).

Eligibility criteria

Inclusion and exclusion criteria are listed elsewhere [12]. Basically, patients with acute or chronic myocardial ischemia who were treated with DES (SESs and/or PESs) and had hypertension or heart failure were eligible for participation. Study patients were ≥20 years old with no upper age limit.

Study drug

Patients in the C group were treated with candesartan orally at a dose of 4–8 mg daily starting within 48 h after PCI. If the therapy was tolerated at the initial dose, investigators were requested to increase the dose of candesartan up to 12 mg daily, if possible. Blood pressure of all the study patients was controlled in accordance with the guidelines of the Japanese Society of Hypertension (JSH) 2004 in the first half of the study period and JSH2009 in the latter half. Precise blood pressure control protocol in both groups is described elsewhere [12].

Endpoint assessment

Table 1 shows the primary and secondary endpoints of the trial. There were two primary endpoints: all-cause death and a composite of cardiovascular events. All-cause death included cardiovascular death, sudden death, and successful resuscitation from cardiopulmonary arrest. The composite primary endpoint of cardiovascular events included non-fatal myocardial infarction (MI), unstable angina requiring emergency hospitalization (uAP), congestive heart failure requiring emergency hospitalization (CHF), and cerebrovascular events. Judgments of emergency hospitalization due to CHF and uAP were made by each attending physician. A diagnosis of MI was made if the following conditions

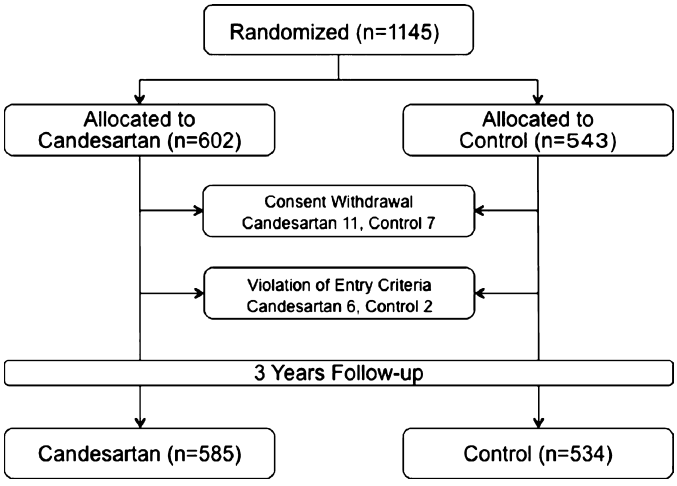

Fig. 1. Flow diagram of patients in the 4C trial. A total of 1145 patients were registered and randomized initially. After exclusion of patients who did not consent or who did not meet the inclusion criteria, 585 patients were assigned to the candesartan group and 534 to the control group.