Journal of Cardiology 62 (2013) 31–36

Contents lists available at SciVerse ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Supplemental benefit of an angiotensin receptor blocker in hypertensive patients with stable heart failure using olmesartan (SUPPORT) trial—Rationale and design☆

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ARTICLE INFO

Article history:
Received 18 December 2012
Received in revised form 6 February 2013
Accepted 18 February 2013
Available online 12 June 2013

Keywords:
Heart failure
Hypertension
Angiotensin receptor blocker
Olmesartan

ABSTRACT

Background: Although angiotensin receptor blockers (ARBs) are now one of the first-line drug classes for the management of hypertension, recommendations for the management of chronic heart failure (CHF) are limited. The supplemental benefit of angiotensin receptor blocker in hypertensive patients with stable heart failure using olmesartan (SUPPORT) trial investigates whether an additive treatment with an ARB, olmesartan, reduces the mortality and morbidity in hypertensive patients with stable chronic heart failure.

Methods and results: The SUPPORT trial is a prospective randomized open-label blinded endpoint study. Between October 2006 and March 2010, 1147 stable CHF patients treated with evidence-based medications were successfully randomized to either olmesartan or control group. In the olmesartan group, the ARB was initiated at the dose of 5.0–10 mg, and was then increased up to 40 mg/day, when possible. No ARBs were allowed in the control group. Primary outcome measure in the SUPPORT trial is the composite of all-cause death, non-fatal acute myocardial infarction, non-fatal stroke and hospital admission due to worsening heart failure. The participants will be followed for at least 3 years until March 2013.

Conclusions: The SUPPORT trial will elucidate the supplemental benefits of an ARB, olmesartan, in hypertensive patients with CHF.

Introduction

In patients with heart failure (HF), inhibition of the renin–angiotensin–aldosterone system (RAAS) is generally recommended to improve mortality and morbidity [1,2]. Although several RAAS inhibitors, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and aldosterone blockers, are currently available in the clinical setting, ACE inhibitors are recommended as the first choice for the inhibition of RAAS in patients with stable HF based on the large body of evidence for their beneficial prognostic effects in patients with HF [1,2]. ARBs could be considered as a reasonable alternative to ACE inhibitors since they have been shown to improve outcomes in patients with HF and reduced ejection fraction (HFrEF) who were intolerant of ACE inhibitors [3,4], as well as in those who have already been treated with ACE inhibitors [4–6]. However, it is still controversial whether the supplemental use of an ARB provides beneficial impacts in hypertensive patients with HF treated with conventional therapies, particularly in Japan.

Olmesartan is an ARB with strong blood pressure lowering effects [7] and unique properties to reduce plasma angiotensin II (Ang II) levels [8–11] and to act as a strong inverse agonist for angiotensin type I (AT1) receptors [12,13]. In the supplemental benefit of angiotensin receptor blocker in hypertensive patients with stable heart failure using olmesartan (SUPPORT) trial, we thus aimed to test our hypothesis that an additive treatment with olmesartan reduces the mortality and morbidity of hypertensive patients with stable HF who are treated with conventional therapies.

☆ *Trial registration*: This study is registered at ClinicalTrials.gov – NCT00417222.

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http://dx.doi.org/10.1016/j.jjcc.2013.02.011

Methods

Study design and objective

The SUPPORT trial is a prospective randomized open-label blinded endpoint (PROBE) study. The objective of the study is to investigate whether additive treatment with an ARB, olmesartan, reduces the mortality and morbidity of hypertensive patients with stable HF. The study has been conducted according to the ethical principles described in the Declaration of Helsinki.

Study population and sample size

The inclusion and exclusion criteria are listed in Table 1. The inclusion criteria were designed to enroll stable patients with HF signs and symptoms and treated with evidence-based conventional therapies. The exclusion criteria were designed to exclude patients with substantive confounding medical conditions or an inability to meaningfully participate in the SUPPORT trial. Based on the results from our preceding CHART-1 study [14,15], we assumed that the incidence of the primary composite endpoints employed in the SUPPORT trial would be ~12% per year and thus 480 patients on the condition of 3-year follow-up would be required for each arm to provide 80% power to detect 30% risk reduction by olmesartan, using a 2-sided significance level of 0.05 by the log-rank test. After considering a maximum 15% for the loss to follow-up or unsuitable for analysis, we calculated that more than 565 patients in each group (control and olmesartan) would be needed to complete the trial.

Study protocol

Patient randomization was performed according to a 1:1 ratio of olmesartan to control, through stratification by participating institute, sex, and age (Fig. 1). In the olmesartan group, the ARB was initiated at the dose of 5–10 mg, and then physicians were encouraged to increase the dose up to 40 mg/day, when possible. No ARBs were allowed in the control group. All the patients will be followed up for at least 3 years until March 2013. All physicians are encouraged to control blood pressure of the patients in each group according to the recommendations in the JNC7 [16].

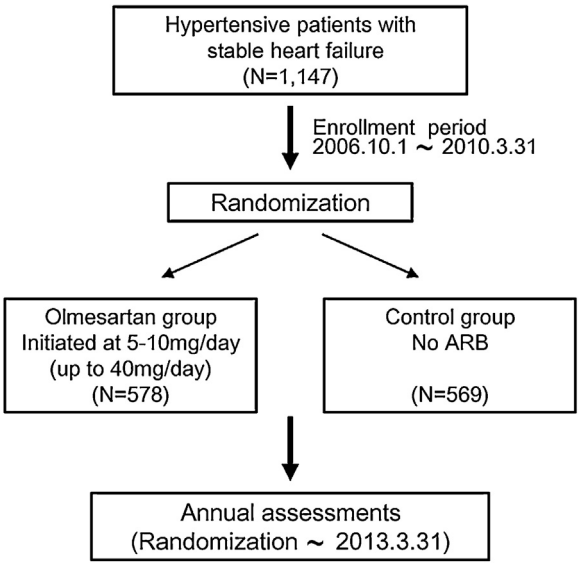

Fig. 1. Study protocol of the SUPPORT trial. A total of 1147 hypertensive patients with stable heart failure were successfully randomized into either the olmesartan or the control group. ARB, angiotensin receptor blocker.

In addition to the prognostic effects of olmesartan in patients with stable HF patients, the SUPPORT trial was designed to address its possible beneficial effects on metabolic markers, including serum levels of high sensitive C-reactive peptide, adiponectin [1–20], and several microRNAs [21,22], as well as each component of metabolic syndrome.

Study endpoints and data analysis

The primary and secondary outcome measures are listed in Table 2. Briefly, the primary endpoint is the composite endpoints of all-cause death, non-fatal acute myocardial infarction, non-fatal stroke, and hospital admission due to worsening heart failure. Secondary endpoints consist of the modes of death, worsening HF, surrogate markers for HF and development of cardiovascular disease, atrial fibrillation, diabetes, and renal failure. The primary

Table 1
Inclusion and exclusion criteria.

Inclusion criteria:
- Patients with New York Heart Association class II through IV chronic heart failure
- Patients who have a history of hypertension or those who are treated with antihypertensive medications
- Patients who are aged 20 years or older and less than 80 years at the entry
- Stable patients who have angiotensin-converting enzyme inhibitor and/or β-blocker
- Patients who are not treated with angiotensin II receptor blocker

Exclusion criteria:
- Patients who have renal dysfunction (serum creatinine ≥ 3.0 mg/dL) or those who are under chronic hemodialysis
- Drug hypersensitivity to olmesartan
- Severe liver dysfunction
- History of angioedema
- Malignant tumor or life-threatening illness of poor prognosis
- Pregnant or possibly pregnant patients
- Cardiovascular surgery within 6 months prior to the date of the entry
- Acute myocardial infarction within 6 months prior to the date of the entry
- Percutaneous coronary intervention with or without stent implantation within 6 months prior to the date of the entry

Other patients deemed unsuitable as subjects of the study by treating physician.

Table 2
Primary and secondary outcome measures.

Primary outcome measures:
A composite of the following outcomes
- All-cause death
- Non-fatal acute myocardial infarction
- Non-fatal stroke
- Hospital admission due to worsening heart failure

Secondary outcome measures:
- Cardiovascular death
- Death due to heart failure
- Sudden death
- Acute myocardial infarction
- Stroke
- Hospital admission from any cardiovascular reasons
- Fatal arrhythmia or appropriate ICD discharge
- Newly diagnosed diabetes
- Development of renal failure
- New-onset atrial fibrillation
- A need to modify treatment procedures for heart failure
- A decrease in left ventricular ejection fraction
- An increase in B-type natriuretic peptide levels (≥2-fold increase if the baseline level was ≥50 pg/ml and an increase to 100 pg/ml if the baseline level was <50 pg/ml)
- Changes in serum markers for metabolic syndrome (high sensitivity C-reactive peptide, adiponectin, microRNAs)

and secondary endpoints will be analyzed based on the time to the first occurrence. Survival curves will be estimated using the Kaplan–Meier procedure and compared with a 2-sided log-rank test. The effects of olmesartan will be examined using Cox proportional hazards models. In addition, subgroup analysis will be performed according to gender, EF, and other parameters, if needed.

Study organization

The Executive Committee consists of a principal investigator and core members from the participating institutions and is responsible for the development of the study protocol and oversees the progress comprehensively. The Executive Committee also functions as the Publication Committee for this trial. A Steering Committee provides guidance on the logistics of the study. The Endpoint Evaluation Committee consists of 2 cardiologists and a neurologist, reviews clinical events, and adjudicates primary endpoints. The Data Safety Monitoring Board is independent of the study committees and provides the Steering Committee with advice when there exists any concern about participants' safety. The Statistical Analysis Board will perform statistical analyses independently from all of the committees.

Status of the study

The SUPPORT trial was registered at ClinicalTrials.gov (http://www.clinicaltrials.gov/) with the identifier NCT00417222, and received Ethics Committee approval before initiation in each institution. Written informed consent was obtained from every subject before trial participation. Between October 2006 and March 2010, a total of 1147 patients were successfully enrolled from the 24 participating hospitals of the Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) Study (NCT00418041) [23,24] (Table 3), and were successfully allocated randomly to either the olmesartan group ($N = 578$) or the control group ($N = 569$) (Fig. 1).

Table 3
Patient characteristics.

Male	858 (75%)
Age (years)	65.7 ± 10.2
BMI (kg/m^2)	24.5 ± 3.9
Systolic BP (mmHg)	127.9 ± 18
Diastolic BP (mmHg)	74.3 ± 11.7
Heart rate (bpm)	71.4 ± 14.2
LVEF (%)	54.1 ± 14.7
LVEF ≥ 50%	711 (62%)
Comorbidities	
Diabetes	446 (39%)
Dyslipidemia	883 (77%)
Cerebrovascular disease	168 (15%)
Cancer	89 (8%)
Ischemic heart disease	535 (47%)
Dilated cardiomyopathy	243 (21%)
Hypertrophic cardiomyopathy	37 (3%)
Valvular heart disease	215 (19%)
Hypertensive heart disease	139 (12%)
Medication	
Beta blockers	813 (71%)
ACE inhibitors	923 (80%)
Diuretics	648 (56%)
Calcium channel blockers	440 (38%)
Statins	548 (48%)

Numerical data are expressed as mean ± SD. BMI, body mass index; BP, blood pressure; LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme.

Discussion

ARBs for the management of hypertensive patients with HF

Inhibition of the RAAS is widely recommended as one of the first-line treatments for chronic HF [1,2]. Besides lowering blood pressure, ARBs promote regression of left ventricular hypertrophy and improve morbidity and mortality in patients with hypertension and other cardiovascular diseases. However, few previous trials evaluated the effects of an ARB in hypertensive patients with HF, although ARBs generally appear to provide benefits in hypertensive patients without HF but at high risk for cardiovascular events (Table 3). In addition, it is still controversial whether the supplemental use of ARBs may provide beneficial impacts in HF patients treated with conventional therapies [4–6,25,26]. Thus, in the SUPPORT trial, we aimed to investigate the beneficial impacts of an ARB, olmesartan, in Japanese hypertensive patients with stable HF (Table 4).

ARBs for metabolic disorder in hypertensive patients with HF

Metabolic syndrome comprises a cluster of abdominal obesity, dyslipidemia, elevated blood pressure, and insulin resistance. Patients with metabolic syndrome have manifestations that occur in sequence, called the metabolic domino. Because activation of the renin–angiotensin system (RAS) is involved in this domino effect, RAS blockade by ARB will offer a therapeutic tool by improving metabolic disorder as well as by lowering blood pressure. Thus, in the SUPPORT trial, we sought to investigate the effect of olmesartan, an ARB, on improvement of metabolic parameters with special reference to changes in several serum markers (Table 2) [17–22].

ARBs for HF with preserved ejection fraction

Although it has been unclear which type of medications could improve mortality and morbidity in patients with preserved ejection fraction (HFpEF), a recent report from the Swedish Heart Failure Registry suggested a beneficial effect of RAS inhibitors on prognosis in patients with HFpEF [27]. In addition, a post hoc analysis of I-Preserve trial revealed that use of irbesartan was associated with improved outcomes in HFpEF patients with relatively low levels of N-terminal proB-type natriuretic peptide (NT-proBNP) (≤339 pg/mL), suggesting the effects of ARB on early, but not later, stages of HFpEF [28].

In the SUPPORT trial, we have enrolled a considerable number of HFpEF patients with various disease backgrounds (Table 3). Thus, we will examine the clinical impact of olmesartan in patients with HFpEF in relation to several clinical parameters including NT-proBNP.

ACE inhibitory action of olmesartan

In order to explore the clinical potential of ARBs in hypertensive patients with HF, we employed olmesartan in the SUPPORT trial since it has several unique properties compared with other ARBs. Firstly, olmesartan could reduce plasma Ang II levels in hypertensive patients [8–11]. In general, ARBs increase plasma levels of Ang II due to a lack of negative feedback on renin activity, which could be harmful in patients with cardiovascular disease. In contrast, olmesartan, unlike other ARBs, has been reported to reduce plasma Ang II levels [8–10]. Ichikawa et al. reported that long-term treatment with olmesartan reduced both blood pressure and plasma Ang II levels in hypertensive patients [8]. Furthermore, several studies demonstrated that change of an ARB from candesartan to olmesartan ameliorated left ventricular hypertrophy associated with a reduction in plasma Ang II levels [9,10].

Table 4
Trials of ARB in hypertensive Japanese patients.

Trials	CASE-J trial	HIJ-CREATE study	NAGOYA HEART study	SUPPORT trial
Objective	To compare the long-term effects of candesartan and amlodipine on the incidence of cardiovascular events	To test whether ARBs can reduce the incidence of cardiovascular events compared with non-ARB-based standard pharmacotherapy in CAD patients with hypertension	To examine whether valsartan is superior to amlodipine to reduce cardiovascular events in hypertensive patients with glucose intolerance	To investigate whether an additive treatment with olmesartan will reduce the mortality and morbidity in hypertensive patients with stable chronic heart failure
Comparison	ARB vs. CCB	ARB vs. non-ARB	ARB vs. CCB	ARB vs. Control
Design	PROBE study	PROBE study	PROBE study	PROBE study
Patients	High-risk hypertensive patients (N = 4728)	CAD patients with hypertension (N = 2049)	Hypertensive patients with glucose intolerance (N = 1150)	Hypertensive patients with symptomatic heart failure (N = 1147)
Endpoints	Composite of sudden death and cerebrovascular, cardiac, renal, and vascular events	Composite of cardiovascular death, non-fatal MI, unstable angina, HF, stroke, and other cardiovascular events requiring hospitalization	Composite of MI, stroke, coronary revascularization, admission attributed to HF, or sudden cardiac death	Composite of all-cause death, non-fatal MI, non-fatal stroke and hospital admission due to worsening congestive HF
Follow-up	3.2 years (average)	4.2 years (median)	3.2 years (median)	At least 3 years
Results	No difference (ARB 5.7% vs. CCB 5.7%, HR: 1.01; 95% CI: 0.79–1.28; P = 0.969)	No difference (ARB 28.1% vs. non-ARB 25.8%, HR: 0.89; 95% CI: 0.76–1.06, P = 0.19).	No difference (ARB 9.4% vs. CCB 9.7%, HR 0.97, 95% CI: 0.66–1.40, P = 0.85).	–
Publication	Ref. [30]	Ref. [31]	Ref. [32]	–

CAD, coronary artery disease; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; PROBE study, a prospective randomized open-label study. MI, myocardial infarction; HF, heart failure; HR, hazard ratio; CI, confidence interval.

The effect of olmesartan to reduce circulating Ang II levels may be associated with up-regulation of ACE2, an ACE-related carboxypeptidase that hydrolyzes Ang II to angiotensin 1–7 [Ang-(1–7)] and angiotensin I to angiotensin-(1–9). Agata et al. reported that olmesartan increased ACE2 and prevented an increase in Ang II levels, suppressing cardiovascular remodeling through increased cardiac production of nitric oxide and endogenous Ang-(1–7) [11]. Since Ang-(1–7) potentiates the effect of bradykinin and acts as an endogenous ACE inhibitor, olmesartan may exert an ACE inhibitory action in addition to its blocking action on AT1 receptor.

Inverse agonist action of olmesartan

It has been reported that some ARBs act without blocking the AT1 receptor by its inverse agonist action [12,13,29]. In particular, olmesartan has a potent inverse agonist action through the hydroxyl group in the imidazole ring together with the carboxyl group [7,12,13]. Zou et al. reported that the AT1 receptor in cultured rat cardiomyocytes is activated by mechanical stretch without involvement of Ang II and that this effect was suppressed by an inverse agonist action of olmesartan [12]. Thus, olmesartan could be useful for the treatment of patients with HF, where RAAS in cardiomyocytes is activated in part in response to mechanical stretch.

Summary

The SUPPORT trial will elucidate whether additive treatment with an ARB, olmesartan, reduces the mortality and morbidity of hypertensive patients with stable HF and may provide new evidence for ARBs in the management of stable HF in the real world setting.

Disclosures

The Department of Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, is supported in part by the unrestricted research grants from Daiichi Sankyo Co., Ltd. (Tokyo, Japan), Bayer Yakuhin, Ltd. (Osaka, Japan), Kyowa Hakko Kirin Co., Ltd. (Tokyo, Japan), Kowa Pharmaceutical Co., Ltd. (Tokyo, Japan), Novartis Pharma K.K. (Tokyo, Japan), Dainippon Sumitomo Pharma, Co., Ltd. (Osaka, Japan), and Nippon Boehringer Ingelheim Co., Ltd. (Tokyo, Japan). H.S. has received lecture fees from Bayer Yakuhin, Ltd, (Osaka, Japan), Daiichi Sankyo Co., Ltd. (Tokyo, Japan) and Novartis Pharma K.K., (Tokyo, Japan).

Acknowledgments

We thank all the members of the Tohoku Heart Failure Society and staff of the Department of Evidence-based Cardiovascular Medicine for their kind contributions. This study was supported by grants-in-aid from the Ministry of Health, Labour, and Welfare and those from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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