Original Article

The Short Treatment with the Angiotensin Receptor Blocker Candesartan Surveyed by Telemedicine (STAR CAST) Study: Rationale and Study Design

Hiroyuki SASAMURA[1)], Hideaki NAKAYA[1),2)], Stevo JULIUS[3)], Toru TAKEBAYASHI[2),4)], Yuji SATO[2)], Hajime UNO[5)], Masahiro TAKEUCHI[5)], Kimiko ISHIGURO[1)], Marohito MURAKAMI[6)], Munekazu RYUZAKI[7)], and Hiroshi ITOH[1)], for the STAR CAST Investigators

Previous studies have shown that transient treatment of animal models of hypertension with an angiotensin receptor blocker (ARB) causes a sustained decrease in blood pressure values that persists even after the drug treatment is discontinued (*J Am Soc Nephrol* 12: 659–666, 2001; *Nephron* 91: 710–718, 2002; *Hypertens Res* 30: 63–75, 2007). These results have been shown to be clinically relevant by the recent TROPHY study (*N Engl J Med* 354: 1685–1697, 2006). We have recently found that transient treatment with an ARB may also cause regression of established hypertension in hypertensive rats (*J Am Soc Nephrol* 18: 157A, 2007). The Short Treatment with the Angiotensin Receptor Blocker Candesartan Surveyed by Telemedicine (STAR CAST) study is a prospective, randomized, open, blinded end-point study in patients aged 30–59 with a positive family history of hypertension that will be conducted in several centers in Japan. The aim of the study is to evaluate the antihypertensive drug withdrawal success rate, the median duration of drug withdrawal, and the changes in home and office blood pressure values in patients with mild hypertension after tapering and withdrawal of antihypertensive treatment following treatment for 1 year with the ARB candesartan or the calcium channel blocker (CCB) nifedipine slow-release. A unique feature of this study is the use of a home blood pressure monitoring telemedicine system (i-TECHO) to allow frequent evaluation of the changes in blood pressure in the trial patients. This study will be the first clinical study to examine if regression from stage 1 (mild) hypertension to prehypertension (high-normal blood pressure) is possible using an ARB or CCB. (*Hypertens Res* 2008; 31: 1843–1849)

***Key Words*: mild hypertension, angiotensin receptor blocker, calcium channel blocker, transient treatment, regression**

From the [1)]Department of Internal Medicine, [2)]Center for Clinical Research, and [4)]Department of Preventive Medicine and Public Health, School of Medicine, Keio University, Tokyo, Japan; [3)]Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, USA; [5)]Division of Biostatistics, School of Pharmaceutical Sciences, Kitasato University, Tokyo, Japan; [6)]Hino Municipal Hospital, Hino, Japan; and [7)]Kawasaki Municipal Ida Hospital, Kawasaki, Japan.

Address for Reprints: Hiroshi Itoh, M.D., Ph.D., Division of Endocrinology, Nephrology, and Metabolism, Department of Internal Medicine, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160–8582, Japan. E-mail: hrith@sc.itc.keio.ac.jp

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Introduction

Essential hypertension is a disease that affects an estimated 972 million persons worldwide, equivalent to 26.4% of the entire adult world population, and this figure is estimated to increase to 29.2% by the year 2025 (*1*). Patients with hypertension are at an increased risk for cardiovascular diseases including stroke, coronary heart disease, heart failure, and renal dysfunction. These cardiovascular diseases account for approximately 30% of death causes worldwide, which is a higher rate than that of cancer or infectious diseases. Across WHO regions, about 62% of strokes and 49% of heart attacks are caused by high blood pressure (*2*).

All national and international guidelines stress the importance of non-pharmacological therapies such as salt restriction, exercise, and the control of obesity as the first step in the treatment of hypertension (*3–6*). However, in spite of these lifestyle changes, the blood pressure in a large number of patients remains above target levels, and the patients therefore require pharmacological therapy with blood pressure–lowering drugs. It has generally been assumed that this drug treatment needs to be lifelong, which reflects the fact that treatment with antihypertensive agents causes a measurable reduction in blood pressure, without altering the pathophysiological processes involved in the development and maintenance of hypertension.

Following the work of Harrap, Berecek, and others (*7–9*), several studies from our laboratory that used a variety of animal models have suggested that brief intervention with a renin-angiotensin system (RAS) inhibitor, *i.e.,* an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) can cause a sustained reduction in blood pressure, through a mechanism that may involve early disruption of a "reno-vascular amplifier" mechanism, resulting in a fundamental change in the processes underlying the maintenance of hypertension (*10–12*). These results have been supported by the results of the Trial of Preventing Hypertension (TROPHY) study recently reported by Julius *et al*. (*13*).

An important feature of the TROPHY study was that the study subjects were patients with prehypertension. As defined by the guidelines of the seventh Joint National Council for Blood Pressure Treatment (JNC 7), these patients had a systolic blood pressure (SBP) of 130–139 mmHg, and a diastolic blood pressure (DBP) of 85–89 mmHg. These patients were randomized to either placebo or active treatment with the ARB candesartan for 2 years, and then taken off active treatment for a further 2 years. Interestingly, the patients who had been treated with an ARB had a significantly lower incidence of hypertension, not only during the treatment period, but also after the active treatment had been discontinued for 2 years (*13*).

These results raise the question of whether treatment with an ARB can cause changes in patients already diagnosed with mild hypertension, to the extent that hypertension drug treatment can be discontinued, an effect referred to as regression. Preliminary experimental studies from our laboratory have suggested that regression of hypertension may be possible using an ARB but not a calcium channel blocker (CCB) in the spontaneously hypertensive rat (SHR) animal model (*14*). At present, there is no clinical data available that provides information about whether ARB treatment can cause regression of the changes involved in the onset of hypertension. Also, it is unclear whether the effect would be different with antihypertensive agents other than ARBs.

The aim of this study is therefore to examine the effects of a 1-year treatment with the ARB candesartan or the CCB nifedipine slow-release, followed by tapering and discontinuation of the drug for a further year. The possibility for hypertension regression after therapy with these two agents will be compared, by evaluating the drug withdrawal success rates and median duration of drug withdrawal after discontinuation of these medications.

Methods

Subjects

The Short Treatment with the Angiotensin Receptor Blocker Candesartan Surveyed by Telemedicine (STAR CAST) study is a multi-center study conducted in Japan (Fig. 1). The inclusion criteria include the presence of mild hypertension (SBP 140–159 and/or DBP 90–99 mmHg, as defined by the Japanese Society of Hypertension Guidelines (JSH 2004), which corresponds to Stage 1 Hypertension according to JNC 7, in patients with a family history of hypertension, and no pharmacological treatment for at least 3 months before the start of the study. Exclusion criteria include the presence of secondary hypertension, diabetes, renal dysfunction, and a history of cardiovascular disease (Table 1). The initial estimate of the number of patients to be enrolled was 220, based on an α value of 0.10 and β value of 0.25, but this number may need to be modified. The study is being conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, and Declaration of Tokyo, 1975, as revised in 1983), and has been approved by the respective Institutional Review Boards. The study will be conducted with the written informed consent of the study participants.

Study Design and Registration

The clinical study is a prospective, randomized, open, blinded-endpoint (PROBE) study. The expected enrollment period is 3 years, starting in April 2008. The study has been registered at the UMIN-ICFJE clinical trials registry (Registration ID No. 000000941).

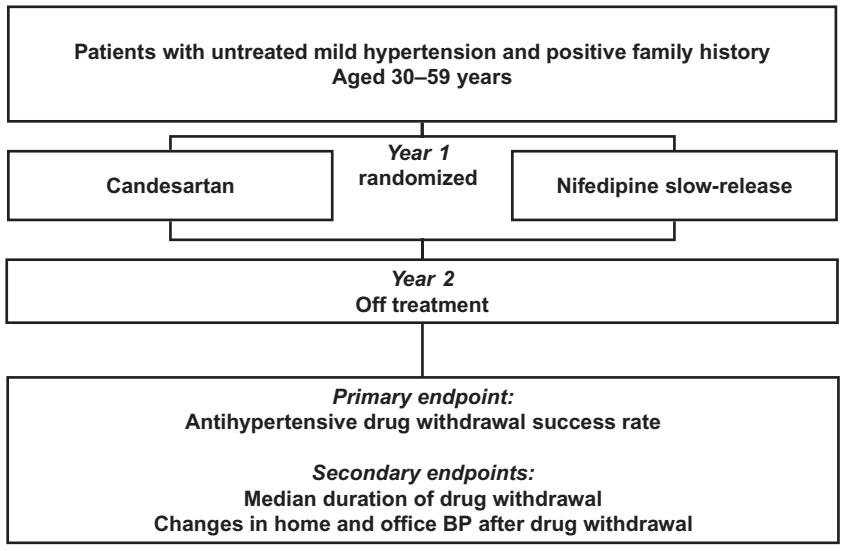

Fig. 1. *Outline of the protocol of the STAR CAST study.*

Table 1. Inclusion and Exclusion Criteria in the STAR CAST Study

Inclusion criteria
Patients satisfying all the following criteria will be included in the study
1. Age 30 to 59
2. Family history of hypertension (within 2 degrees)
3. Diagnosed with mild hypertension according to JSH 2004 and JNC 7 guidelines (SBP of 140–159 mmHg and/or DBP of 90–99 mmHg on two successive occasions), taking no hypertensive medications for the previous 3 months
4. Agrees to the study with informed consent
Exclusion criteria
Patients satisfying any one of the following criteria will be excluded from the study
1. Secondary hypertension
2. Diabetes mellitus (HbA1c values of 6.5% or greater)
3. Renal dysfunction (serum creatinine values of 2 mg/dL or greater)
4. Patients with a history of cardiovascular disease (stroke, transient ischemic attack, coronary heart disease, heart failure)
5. Patients with severe liver dysfunction
6. Patients with malignancies
7. Pregnant patients, or patients intending to be pregnant
8. Other patients judged to be inappropriate by the attending physician

SBP, systolic blood pressure; DBP, diastolic blood pressure.

Screening Period

During the screening period (2–4 weeks), the patients will be assessed for eligibility for entry to the study, using the inclusion and exclusion criteria set out in Table 1. Patients with written consent for inclusion in this study will be registered and randomized to one of two treatment groups, the C (candesartan) group, or the N (nifedipine-slow release) group. The patients will also be provided with a home blood pressure monitoring system (Omron HEM-705IT; Omron, Tokyo, Japan) linked to an internet-based data transfer system (i-TECHO telemedicine system; Clinography, Tokyo, Japan) for transfer of blood pressure measurement data to a central server. Standard non-pharmacological treatment (diet and exercise therapy) will be prescribed to all patients from the first visit according to JSH 2004.

Active Treatment Period

For the active treatment period, patients in the C group will commence treatment with candesartan cilexetil (4 mg/d) while patients in the N group will commence treatment with

Table 2. Primary and Secondary Endpoints in the STAR CAST Study

Primary endpoint
Antihypertensive drug withdrawal success rate
Secondary endpoints
1. Median duration of drug withdrawal
2. Changes in home and office blood pressure after drug withdrawal
Definition of End BP
Patients satisfying any of the following criteria will be assessed to have reached End BP
1. Office SBP of at least 140 mmHg and/or DBP of at least 90 mmHg at two separate visits
2. Office SBP of at least 160 mmHg and/or DBP of at least 100 mmHg at any visit
3. Mean weekly home SBP of at least 140 mmHg and/or DBP of at least 90 mmHg for 2 consecutive weeks
4. Mean weekly SBP of at least 160 mmHg and/or DBP of at least 100 mmHg at any week
Prespecified analyses
1. Changes in markers of end-organ damage: BNP, high sensitivity CRP, lipid peroxides, urine albumin/creatinine ratios, urine 8-hydroxyguanosine/creatinine ratios, blood/urine metabolome profiles
2. Changes in markers of glucose metabolism: blood glucose, immunoreactive insulin, hemoglobin A1c, HOMA-IR, adiponectin, leptin, angiopoietin
3. Changes in markers of extracellular matrix metabolism: type III procollagen propeptide, stromelysin-1, PAI-1

End BP, endpoint blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; BNP, brain natriuretic peptide; CRP, C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; PAI-1, plasminogen activator inhibitor 1.

nifedipine slow-release (10 mg/d). The doses of these agents will be titrated at the discretion of the physician to a maximum dose of 12 mg/d for candesartan cilexetil and a maximum dose of 40 mg/d for nifedipine slow-release to obtain the target blood pressure level. For the purposes of this study, the target blood pressure level has been set to a value of less than 140 mmHg for the SBP and less than 90 mmHg for the DBP, in accordance with international guidelines (*3*–*5*) in order to enable international comparisons. Every reasonable attempt will be made to up-titrate the test drug to the maximum dose, even if the target blood pressure levels are achieved. However, if the target blood pressure levels are not achieved in a patient with the maximal dosage the test drug, the addition of trichlormethiazide (2 mg/d) will be permitted. The use of other antihypertensive agents will not be allowed. If patients do not achieve the target blood pressure level, they will be removed from the study and provided with standard care.

The patients will be scheduled to visit the clinic every 4 weeks for the duration of the study. At each visit, blood pressure, body weight, and waist circumference will be measured, and any adverse events noted. Blood and urine tests will be performed during the screening period and then at 6-month intervals throughout the study.

At the same time, the home blood pressures of the patients will be monitored using the i-TECHO telemedicine system described above. Patients will be instructed to measure home blood pressures twice a day (with two or more measurements on each occasion), in the morning after wakening, and at night prior to sleeping. Patients will be required to measure the home blood pressures in this manner at least 3 d a week for retrieval to the central server by the data management team.

Drug Tapering and Withdrawal Period

After drug treatment for 1 year, the antihypertensive medication will be tapered and withdrawn according to the following protocol: weeks 1 and 2, reduce to half the current dose; weeks 3 and 4, half-dose to be taken once every 2 d; week 5, discontinue medication. During this time, the effects on blood pressure will be closely monitored using the i-TECHO telemedicine system. If either the office blood pressure value or the home blood pressure value is assessed to reach preset criteria refered to as the endpoint blood pressure (End BP) (Table 2) by an observer blinded to the treatment group, then the patient will be instructed to restart their medication at a dose to be determined by the attending physician. All patients will be followed-up for 1 year and 1 month after the start of drug tapering, irrespective of the status of their antihypertensive medications.

Study Endpoints

The study endpoints are set out in Table 2. The primary endpoint is the antihypertensive drug withdrawal success rate, defined as the proportion of patients who have discontinued antihypertensive medication, but have not reached End BP

and have not been represcribed any antihypertensive medication. The secondary endpoints are the median durations of drug withdrawal, and the changes in home and office blood pressure values after withdrawal of antihypertensive medications.

Statistical Analysis

Sample-Size Estimation

The expected incidences of the endpoint in the two groups are unclear. Based on the assumption of a drug withdrawal success rate of 0.25 in the C group and 0.1 in the N group, using data from studies of older antihypertensive agents and animal studies, approximately 101 patients are needed in each treatment group to detect a statistically significant difference between treatment groups using a log-rank test with $a=0.05$ (two-sided) and $1-b=0.80$. Assuming that fewer than 10% of patients will be lost to follow-up, the number of patients is estimated to be 110 per group.

Analysis Sets

Statistical analysis will be performed on all patients who completed the 1-year active treatment period, patients who completed the active treatment period without major protocol violations, and all patients enrolled in the study (intention-to-treat).

Analysis of Endpoints

Survival time analysis of the duration of drug withdrawal will be performed on patients entering the drug tapering and withdrawal period. An event will be defined as the recommencement of the antihypertensive drug treatment. If drug recommencement does not occur during the study period, the final blood pressure will be utilized. A survival function for drug withdrawal success will be estimated for both groups, together with inter-group comparisons using log-rank analysis. In addition, the median value for the duration of drug withdrawal will be computed. Following the results of the primary and secondary endpoints, other values will be analyzed to provide additional insights into differences between the two test agents.

Committees

Central Study Committee

The Central Study Committee is responsible for the design, funding, and execution of the study.

Data Monitoring Committee

The Data Monitoring Committee is responsible for data management, evaluation of blinded endpoints, and statistical analyses.

Independent Safety Monitoring Committee

The Independent Safety Monitoring Committee is responsible for assessment of adverse events, and has the right to terminate the study for safety reasons.

Participating Hospitals

Hospitals participating in this study are Keio University Hospital, Hino Municipal Hospital, and Kawasaki Municipal Ida Hospital.

Discussion

Hypertension is a disease caused by a complex interplay of genetic and environmental factors. Since patients with hypertension are known to be at an increased risk for complications such as stroke, coronary heart disease, heart failure, and renal dysfunction, the optimal treatment of patients with hypertension is important for lifelong maintenance of health. Moreover, since the prevalence of hypertension is remarkably high (26.7% of the adult population worldwide) and is increasing year by year, the scientific treatment of hypertension is one of the major issues health care has faced in this century.

Many major advances in pharmacological treatment of hypertension have been made over the past 50 years, and the newer drugs such as ARBs and CCBs have a very low side-effect profile, and are therefore easier to take than previous medications which had multiple side effects that could lower a patient's quality of life. Despite this, the percentage of patients who are compliant with medication, and whose blood pressure is optimally controlled to target levels is only a fraction of the total number of patients who need to be treated.

One of the major psychological barriers to starting antihypertensive medication is the fact that pharmacological therapy is assumed to be a "life-long sentence"; in other words, once the medication is started, the expectation is that the patient will continue the medication every day for the rest of his or her life. Since many patients who start antihypertensive medication are in their 40s or 50s, and since the average life expectancy in Japan is increasing and is currently around 80 years, this means that once the patient agrees to pharmacological therapy, the patient is in essence committing himself or herself to 30 or 40 years of daily medication. As well as the burden on the individual patient, the economic burden on society is already immense (*15*) and is likely to increase as the population ages.

One reason that the medication is life-long lies in the fact that the older antihypertensive agents were effective in decreasing blood pressure, but did not alter the pathophysiological mechanisms underlying the development and maintenance of hypertension. Consequently, continued administration of the antihypertensive agent was required to maintain the decreased blood pressure.

However, initial reports by Harrap and Berecek's groups suggested that RAS inhibitors could alter these pathophysiological mechanisms, since treatment of SHRs with an ACE inhibitor at an early age was found to cause a permanent attenuation of the development of hypertension (*7–9*). Studies

from our laboratory have shown that a permanent suppressive effect is also seen with the ARB candesartan, and that the results are similar in Dahl salt-sensitive rats (*10–12*). Moreover, our studies suggested that transient ARB treatment could cause not only a permanent attenuation of hypertension, but also a sustained suppression of hypertensive end-organ damage. A possible mechanistic rationale for these results was suggested by the ability of ARBs to block the "reno-vascular amplifier" involved in the development and maintenance of hypertension (*12*). Recently we have found that transient treatment with an ARB can also cause a regression of hypertension at an age when hypertension has been fully established in SHRs (*14*).

The purpose of this study is to compare the effects of treatment with the ARB candesartan or the CCB nifedipine slow-release for 1 year, followed by tapering and withdrawal of the drug. The preset primary endpoint is the antihypertensive drug withdrawal success rate, defined as the proportion of patients who have not reached End BP and have not been represcribed the antihypertensive medication. The secondary endpoints are the median duration of drug withdrawal, and the changes in home and office blood pressure values after drug withdrawal. Pre-specified analyses include changes in the markers of end-organ damage, changes in glucose metabolism, and changes in the markers of extracellular matrix metabolism. These data will be monitored by an independent Data Monitoring Committee. At the time of writing (April 2008), the first 5 patients are expected to be enrolled and randomized.

An important feature of this study is the use of a specialized home blood pressure monitoring telemedicine system (i-TECHO) to allow safe, accurate, and frequent evaluation of the changes in home blood pressure in the study patients. This system was successfully used in a previous clinical study (*16*). The reason for using this telemedicine system is to enable the changes in blood pressure after discontinuing therapy to be closely monitored in real time by a qualified medical professional, in order to minimize any risks associated with treatment tapering and withdrawal. It should be noted that all measurements made will be recorded and transferred to the central server so that the patient will not be able to select or edit the data in any way. Moreover, the data will be transmitted anonymously and analyzed by a member of the Data Monitoring Committee who is blinded to the treatment group.

Concerning safety issues, the inclusion criteria were set to include only relatively young patients (aged 30–59) without significant comorbidities and to specifically exclude patients with a history of cardiovascular disease. The study will be conducted with the full informed consent of the patients, with ongoing communication and support by clinical coordinators and other qualified medical personnel throughout the study, and the patients will be free to restart medication and withdraw from the study at any time. An Independent Safety Monitoring Committee has the right to terminate the study at any time for safety reasons. Of note, the target blood pressure level was set at the outpatient blood pressure according to current international guidelines (*3–5*), however high values of home blood pressure were included in the End BP criteria in order to enhance the safety of the study, as specified by the Institutional Review Boards.

At present, the number of patients who will be able to withdraw successfully from these newer antihypertensive medications is unclear, since most studies on withdrawal of hypertensive medication were conducted over 30 years ago, before the use of newer antihypertensive agents. In a study by the Medical Research Council Working Party on Mild Hypertension, the investigators reported that a surprisingly large proportion (45–56%) of patients remained off antihypertensive medication (diuretic or β-blocker) 1 year after withdrawal of the drug (*17*). Similarly, Langford *et al*. (*18*) and Maland *et al*. (*19*) found withdrawal success rates of 50–74% at 1 year in their studies. In contrast, the Veterans Administration Cooperative Study Group on Antihypertensive Agents found a smaller withdrawal success rate of 15% at 18 months (*20*), but these values still appear higher than would be expected based on our clinical experience. It should be strongly emphasized that even if the withdrawal success rate is high in our study, this should not be falsely interpreted to mean that all hypertensive patients can withdraw from antihypertensive medication. In fact, it is anticipated that most patients with hypertension will, in general, still require lifelong medication.

Two recent studies have examined the effects of transient treatment with ARBs either on patients with prehypertension, or on normotensive patients with a strong family history of hypertension. In the TROPHY study conducted by Julius *et al*., prehypertensive patients were treated with either a placebo or candesartan for 2 years, and followed-up for an additional 2 years on placebo alone. Interestingly, 63% of patients treated throughout with a placebo had developed hypertension by year 4, whereas the numbers significantly decreased to 53.2% in the patients who had been transiently treated with ARB (*13*). In the DHyPP study conducted by Skov *et al*., normotensive patients whose parents both had essential hypertension were treated for 1 year with candesartan. In this study, the mean ambulatory blood pressure at 12 or 24 months was not significantly different compared to the placebo (*21*).

The STAR CAST study differs from these studies in both the methods used and its objectives. The main difference in design is that the subjects already have mild hypertension. Thus, the aim of this study is not to examine whether hypertension prevention is feasible, but to examine whether regression from stage 1 (mild) hypertension to prehypertension (high-normal blood pressure) is possible, with the result that patients can withdraw from previously started antihypertensive medication. Moreover, the STAR CAST study will compare the effects of the ARB with those of a CCB, since these two medications are the most commonly used antihypertensive medications in Japan. The duration of the treatment is

shorter than the TROPHY study duration, based on our observation that regression can occur with a short treatment time (2 weeks in rats (*14*)). One major difference from our animal studies is the fact that we are using standard doses of antihypertensive drugs in the STAR CAST study for ethical reasons, whereas high doses were used in the animal studies.

In summary, the STAR CAST study, a multi-center prospective study conducted in Japan, is expected to have several important impacts on our understanding of the treatment of hypertension. First, this is the first study in over 30 years to examine whether drug withdrawal is possible in treated hypertensive patients, and to provide a quantitative estimation of the feasibility of drug withdrawal. Second, this is the first head-to-head examination of the effects of transient treatment with an ARB *vs*. a CCB, to examine whether regression from stage 1 (mild) hypertension to prehypertension (high-normal blood pressure) is possible. Third, the novel use of our i-TECHO telemedicine system could provide further insights into new approaches to the treatment and monitoring of blood pressure in patients with essential hypertension.

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