Rationale and design of the NAGOYA HEART Study: Comparison between valsartan and amlodipine regarding morbidity and mortality in patients with hypertension and glucose intolerance

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Summary

Background: Inhibitors of the renin angiotensin system are recommended as the first-line medications for diabetic hypertensive patients. However, there is less evidence supporting this recommendation especially among East Asians, a population with a unique distribution of cardiovascular disease compared to the Western population.

Methods and results: The NAGOYA HEART Study is a prospective randomized open-label blinded-endpoint study to compare an angiotensin II receptor blocker, valsartan, and a calcium channel blocker, amlodipine, regarding their efficacies on cardiovascular morbidity and mortality in Japanese hypertensive patients with glucose intolerance. Of 1168 eligible patients, we enrolled 1150 patients from October 2004 to January 2009. The participants will be followed for more than a median follow-up period of 3 years. The primary composite endpoint includes myocardial infarction, stroke, coronary revascularization, and admission due to congestive heart failure or sudden cardiac death. Any of these events are adjudicated by an independent committee under blinded information regarding the treatment arm. Secondary endpoints include all-cause mortality, changes in glucose tolerance status, kidney function, left ventricular structure measured by echocardiogram, and incident atrial fibrillation/flutter. The study was registered at ClinicalTrials.gov NCT00129233.

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Introduction

Hypertensive patients with type 2 diabetes mellitus (T2DM) have almost 2-fold higher risk for suffering from ischemic cardiovascular diseases compared to non-diabetic hypertensive patients [1]. Inhibitors of the renin angiotensin system [i.e. angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor-1 blockers (ARBs)] are widely recommended as the first-line medications for diabetic hypertensive patients in clinical guidelines issued by most developed countries [1—4]. This is because many clinical trials [5—8], but not all [9—11], have suggested that ACEIs and/or ARBs protect more effectively against the development of macrovascular and microvascular diseases compared to other types of antihypertensive drugs in this particular patient population.

Angiotensin II plays pivotal roles in the development of hypertension and vascular complications by inducing vasoconstriction, sodium and water retention, smooth muscle cell proliferation, myocardial fibrosis, superoxide formation, plasminogen activator inhibitor-1 production, and activation of the sympathetic nervous system [12—14]. Importantly, angiotensin II also reduces insulin sensitivity possibly through the inhibition of intracellular insulin signaling [12]. In fact, ACEIs and/or ARBs have been shown to prevent new onset of T2DM in many clinical trials [6,15]. Therefore, there is a concrete background supporting particular benefits of ACEIs and/or ARBs for the treatment of hypertensive patients with glucose intolerance [i.e. impaired glucose tolerance (IGT) or T2DM].

The epidemiology of cardiovascular diseases in Japan is different from that typically observed in Western countries. In particular, the age-adjusted incidence rate of ischemic heart disease in Japan is almost 80% lower than that in the USA [16]. In contrast, mortality rate due to stroke is 3—4-fold higher in Japan compared to the USA [16,17]. Given the fact that calcium channel blockers (CCBs) are useful for the prevention of stroke [18], one may assume that CCBs are more beneficial for Japanese hypertensive patients with T2DM or IGT. Regarding the incidence of heart failure, Japanese have a higher mortality rate due to heart failure compared to the Western population [17]. Since inhibitors of the renin angiotensin system can effectively prevent the development of heart failure compared to other antihypertensive drugs [19], ACEIs and/or ARBs may be beneficial to Japanese patients in this context.

Taken together, it is still unclear whether inhibitors of the renin angiotensin system can prevent adverse composite cardiovascular events more effectively than CCBs in Japanese hypertensive patients with T2DM or IGT. Accordingly, we designed a clinical trial comparing an ARB, valsartan, and a CCB, amlodipine, with respect to their efficacies on cardiovascular morbidity and mortality in Japanese hypertensive patients with glucose intolerance (T2DM or IGT).

Methods

Study design

The NAGOYA HEART Study is a multicenter study applying a prospective randomized open-label, blinded-endpoint (PROBE) design [20]. The study consists of two parallel arms of antihypertensive treatments, i.e. valsartan-based vs. amlodipine-based. The study was registered at ClinicalTrials.gov (http://www.clinicaltrials.gov/) with the identifier NCT00129233.

Study population

Patients who were between 30 and 75 years old and had both hypertension and glucose intolerance (IGT or T2DM) were eligible to be enrolled in the NAGOYA HEART Study. Patients were considered as hypertensive when they were already taking antihypertensive drugs or when they had systolic or diastolic blood pressure equal to or more than 140 or 90 mmHg, respectively, on at least two different occasions despite education about appropriate lifestyle modification. Glucose intolerance consists of T2DM or IGT, which were defined according to the statement from the American Diabetes Association [21]. In brief, T2DM was defined when subjects had already been taking drugs for T2DM, fasting glucose equal to 126 mg/dL or more, or non-fasting glucose or glucose 2 hr after 75 g oral glucose tolerance test (OGTT) equal to 200 mg/dL or more. IGT was defined by glucose between 140 and 199 mg/dL at 2 h after the OGTT. We included patients with IGT but not those with impaired fasting glucose (IFG), since individuals with IGT have a similar risk of cardiovascular disease as diabetic patients, but the risk of subjects with IFG is approximately that of individuals with normal glucose tolerance [22].

Patients with the following conditions at enrollment were excluded: (1) history of heart failure, myocardial infarction, coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery), or stroke in the last 6 months; (2) patients who were taking CCBs for the purpose of the suppression of angina pectoris including coronary spastic angina; (3) impaired left ventricular ejection fraction less than 40%; (4) second- or third-degree atrio-ventricular block; (5) severe hypertension (systolic or diastolic blood pressure greater than 200 or 110 mmHg, respectively) or secondary hypertension; (6) serum creatinine equal to 2.5 mg/dL or more; (7) estimated prognosis less than 3 years due to other conditions; (8) pregnant women or women with a potential of childbearing; (9) other
Figure 1  Titration schedule of the assigned drugs for the NAGOYA HEART Study. Asterisk (*) indicates other antihypertensive drugs excluding ACEIs, ARBs, and CCBs.

Informed consent

Participating centers included 46 affiliated hospitals led by cardiology specialists in Nagoya City and its vicinity. All participants provided their written informed consent after receiving explanations by a physician in charge about study objectives, study protocol, possible adverse effects of the study drugs, measures for privacy protection, and study withdrawal. The Ethics Review Committee of Nagoya University School of Medicine and the Committee at each participating center approved the study protocol.

Study procedures

Randomization was automatically performed by a host computer system using the minimization method. The treatment protocol of the NAGOYA HEART Study is shown in Fig. 1. The initial doses are 80 mg/day for valsartan and 5 mg/day for amlodipine, respectively. Physicians increased doses until 160 mg or 10 mg per day, respectively, as needed. Also, diuretics, β-blockers, or α-blockers can be added to achieve target blood pressure for hypertensive patients with diabetes (i.e., 130/80 mmHg). For participants already taking antihypertensive drugs at the enrollment, ACEIs, ARBs, and CCBs were discontinued, and the allocated drug was prescribed without a run-in period. Diuretics, β-blockers or α-blockers could be continued when physicians considered appropriate. Clinical care for T2DM/IGT was conducted according to the guidelines of the Japanese Diabetes Society [23].

Measurements of interest

Demographic variables such as sex, age, smoking status, co-morbidities including dyslipidemia, T2DM/IGT, and a past history of cardiovascular disease were obtained at baseline. Also, physiological findings including blood pressure, anthropometry, blood examination, electrocardiogram (ECG), and echocardiogram were evaluated at baseline. The above measurements were repeated every 6 months except for echocardiogram, which was carried out once a year. The blood examination included the following items: fasting glucose, hemoglobin A1c, low-density and high-density lipoprotein cholesterol, triglyceride, uric acid, blood urea nitrogen, serum creatinine, sodium, and potassium. The follow-up OGTT was conducted every year only for subjects with IGT. During an echocardiogram, the following variables were measured: dimension of the left ventricle at both end-diastole and end-systole, thickness of the interventricular septum and left ventricular posterior wall at end-diastole, left ventricular ejection fraction, the ratio of early ventricular filling to atrial contraction velocity (E/A ratio).

Evaluation of outcomes

The primary endpoint is a composite of cardiovascular morbidity and mortality. Components of the primary endpoint include the following: (1) myocardial infarction (ECG change, elevation of cardiac enzymes, and culprit lesion detected by coronary angiogram); (2) stroke (neurological deficit persisting for more than 24 h and relevant findings in computed tomography or magnetic resonance imaging); (3) admission due to congestive heart failure (clinical symptoms including dyspnea, shortness of breath, and peripheral edema, together with pulmonary congestion in chest roentgenogram); (4) coronary revascularization (percutaneous coronary intervention or coronary bypass graft surgery unplanned at randomization); or (5) sudden cardiac death (unexpected death within 24 h after the onset of symptoms). Any of these events must be strictly adjudicated by an independent Endpoint Evaluation Committee under the blinded circumstance regarding assigned treatment.
The followings are classified as the secondary endpoints: (1) all-cause mortality; (2) glucose control and incident T2DM; (3) incident atrial fibrillation or flutter detected by ECG; (4) change in kidney function (doubling of plasma creatinine levels and transition to dialysis); and (5) change in cardiac function evaluated by echocardiogram.

The follow-up will be conducted every month in the first 3 months and every 1–3 months after then according to physicians’ decisions and will be terminated when the first event among the primary outcomes occurs. Participating physicians will obtain information about clinical outcomes from patients or their families and report those to the Data Management Group of the NAGOYA HEART Study.

**Study organization**

The study organization is shown in Fig. 2. The Executive Committee created the protocol of the NAGOYA HEART Study and observes the progress comprehensively. The Steering Committee approved the study protocol and makes a decision about the management of the study. The Data and Safety Monitoring Board consists of a physician, an epidemiologist, an endocrinologist, and a cardiologist and provides the Steering Committee with advice when there are any concerns about participants’ safety. The Endpoint Evaluation Committee comprised a cardiologist, a vascular surgeon, and a neurologist, and they adjudicated primary endpoints reported from physicians. The data are collected through the Internet into a secure server and are centrally managed by the independent Data Management Group. The Statistical Analysis Board will perform all statistical analyses independently from any of the above committees.

**Sample size and statistical analysis**

In the Hisayama study, incidence rate of coronary heart disease (myocardial infarction and sudden cardiac death) and stroke among Japanese patients with T2DM was 5.0 and 6.5 per 1000 person-years [24]. In the Japan Diabetes Complications Study (JDCS), incidence rate of coronary heart disease consisting of angina pectoris and myocardial infarction, and brain infarction were 6.7 and 6.5 per 1000 person-years, respectively [25]. Since myocardial infarction, unstable/stable angina pectoris requiring revascularization, congestive heart failure, sudden cardiac death, and stroke were all included as a primary composite endpoint in the present study and all participants had hypertension, we estimated at least 5—8% of participants would have cardiovascular events each year. Under the assumption that valsartan can reduce cardiovascular events by 20% and the median follow-up time would be 3 years, sample size for each group was estimated to be 1500 with a two-sided \( \alpha \) level of 0.05 and statistical power of 80%.

Patients’ enrollment began in October 2004 and was anticipated to be finished by the end of 2006. Of 1168 patients eligible for the recruitment of the present study, we had recruited 1150 patients by the end of January 2009, when the Data and Safety Monitoring Board suggested stopping patient recruitment due to relatively longer recruitment period than anticipated. Consequently, the Steering Committee decided not to recruit patients after February 2009 and to follow-up participants until median of follow-up period reaches more than 3 years.

Analyses will be performed by an independent Statistical Analysis Board based on the intention-to-treat approach. All randomized patients \( (n=1150) \) were included in the analysis. Cox proportional hazard model will be used for comparing the difference in risk between the two treatment groups.
Discussion

The NAGOYA HEART Study (the NHS) is the first large-scale clinical trial comparing an ARB, valsartan, and a CCB, amlodipine, specifically among Japanese hypertensive patients with glucose intolerance (IGT or T2DM). The benefit of ACEIs/ARBs compared to CCBs with respect to prevention of major cardiovascular events among diabetic hypertensive patients was mainly demonstrated in relatively small studies with participants <500 such as the ABCD or the FACET Trials [5,8]. However, no superiority of ACEIs/ARBs with respect to the prevention of macrovascular disease has been shown in larger clinical studies (e.g. the ALLHAT or the IDNT) [9,26]. More importantly, the Blood Pressure Lowering Treatment Trialists’ Collaboration (BPLTTC) investigators conducted a meta-analysis to elucidate this issue, and they found that ACEIs were equivalent to CCBs regarding protection against composite cardiovascular events in hypertensive patients with T2DM [19]. Only few studies had compared ARBs and CCBs directly at this moment.

This meta-analysis included only one clinical study from Asia, that was the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) trial [19]. This JMIC-B trial compared ACEIs and a CCB, long-acting nifedipine, among 1650 Japanese hypertensive patients and could not show any significant difference in cardiovascular events in the two treatment arms during 3-year follow-up period [27]. Since the JMIC-B included only 372 patients with T2DM, Asian population with both hypertension and T2DM has been understudied. Therefore, although we could not enroll a priori planned number of patients, we anticipate that the NAGOYA HEART Study will provide us with clinically relevant information regarding appropriate treatment of hypertension with glucose intolerance among an East Asian population.

ACEIs and ARBs are considered particularly effective to protect renal function [1,4]. Indeed, a number of studies have reported that these two types of drugs can prevent deterioration of glomerular filtration rate and deterioration of proteinuria [28]. However, a meta-analysis conducted by Casas and colleagues demonstrated that the effectiveness of ACEIs and ARBs is clearly shown in small studies with participants <500 but is less evident in larger clinical studies [28]. Typically, the ALLHAT including ≈13,000 patients with T2DM of more than 30,000 hypertensive patients did not show a superior benefit of an ACEI, lisinopril, compared to amlodipine or a thiazide-type diuretic with respect to renal protection [26,28]. Typically, the ALLHAT including ≈13,000 patients with T2DM of more than 30,000 hypertensive patients did not show a superior benefit of an ACEI, lisinopril, compared to amlodipine or a thiazide-type diuretic with respect to renal protection [26,28]. Interestingly, when four clinical studies comprising only diabetic patients were combined, the occurrence of end-stage renal disease was not statistically different between ACEIs/ARBs and other antihypertensive drugs [28]. Thus, renal protective effects of ACEIs/ARBs beyond lowering blood pressure remain to be proved [28].

This is particularly the case for Japanese. The Japan Multicenter Investigation of Antihypertensive Treatment for Nephropathy in Diabetics (J-MIND) Study reported that a CCB, nifedipine, was similarly protective against deterioration of albuminuria compared to an ACEI, enalapril, among 438 Japanese diabetic hypertensive patients. Thus, the NAGOYA HEART study will provide us relevant information regarding renal protection by antihypertensive drugs among Japanese.

After the NAGOYA HEART Study was initiated, a few studies investigated whether an ARB is superior to a CCB regarding risk reduction of cardiovascular diseases. The VALUE trial compared the effects of valsartan- and amloidipine-based regimens among 15,245 hypertensive patients aged 50 years or older and reported that there was no statistical difference in the two treatment groups for the prevention of cardiovascular events [29]. The risk of myocardial infarction and stroke tended to be lower in the amloidipine-based treatment group compared to the valsartan group. The authors raised a possibility that significantly lower blood pressure levels achieved in the amloidipine group might contribute to the lower cardiovascular incidences. Similarly, Ogihara and colleagues have recently reported that there was no statistical difference in the risk of cardiovascular morbidity and mortality between ARB candesartan-based and amloidipine-based regimens among 4728 Japanese hypertensive patients enrolled in the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) Trial [30,31]. Although the CASE-J trial has not shown that an ARB-based regimen may be beneficial particularly in obese patients, results specific to T2DM participants, 43% of the entire study population, have not been reported [30,31].

In contrast, Mochizuki and colleagues reported 40% reduction of the risk for their primary composite endpoint (i.e. composite of cardiovascular mortality and morbidity) with valsartan compared to non-ARB treatment group in the JIKEI HEART Study including 3081 Japanese patients with hypertension, coronary heart disease, or heart failure [32]. Similarly, the KYOTO HEART Study reported 45% reduction of incident cardiovascular disease by valsartan as compared with non-ARB treatment in Japanese patients with hypertension [33]. The precise reasons of the inconsistent results observed among these studies are under debate [34,35]. The fact that there was no evident control drug in the JIKEI HEART Study might explain the results. In fact, participants in the non-ARB group in the JIKEI HEART Study tended to take less antihypertensive drugs than those in the valsartan group in the first 2-year follow-up [32]. Furthermore, since the JIKEI HEART Study recruited not only patients with hypertension but also those with heart failure and coronary heart disease, a part of patients with certain characteristics (e.g. prevalent heart failure) might receive specific benefits of an ARB-based regimen.

Taken together, since it is still unclear whether an ARB is superior to a CCB with respect to the prevention of cardiovascular events among Japanese diabetic hypertensive patients, the results of the NAGOYA HEART Study will be quite valuable.

Funding and conflict of interest

The study is funded by Nagoya University Graduate School of Medicine. The Department of Cardiology, Nagoya University Graduate School of Medicine has received donation grants from various pharmaceutical companies. However, the research topics of these donation grants are not restricted. The Executive Committee has full access to all the data at the end of the study, and has final responsibility for the decision to submit for publication.
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Appendix A.

Toyoaki Murohara supervises the NAGOYA HEART Study as the principal investigator.

Organization (Indicates Chairman of the Committee)

The Executive Committee

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References


