Rationale, Design, and Organization of the Diastolic Heart Failure Assessment Study in Tohoku District (DIAST)

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Background High mortality and a high readmission rate characterize diastolic heart failure (DHF), but evidence-based therapeutic strategies have not been established for DHF.

Methods The aim of a multicenter, randomized open trial (the Diastolic Heart Failure Assessment Study in Tohoku District, DIAST) is to evaluate the safety and prognostic efficacy of the multiple action non-selective β-blocker carvedilol in 160 patients with DHF (left-ventricular ejection fraction ≥50%). The target dose of carvedilol is 10 mg twice a day and the mean follow-up is estimated to be 2 years. The primary endpoints are to evaluate (1) all-cause mortality or hospitalization, (2) cardiovascular mortality or hospitalization and (3) worsening heart failure. The secondary endpoints are to assess (1) cardiovascular events, (2) the individual components of the above combined endpoints, (3) the duration of hospitalization, (4) the functional class and exercise capacity and (5) the safety and tolerability. All patients’ data are processed using an original registration system on an internet homepage. Several substudies to assess neurohumoral factors, heart rate variability, oxidative stress and sleep apnea will clarify the pathophysiology of DHF.

Conclusions The DIAST will contribute to establish therapeutic guidelines for DHF. (Circ J 2004; 68: 660–664)

Key Words: Beta-blocker; Carvedilol; Diastolic heart failure; Morbidity; Mortality

The prevalence of chronic heart failure (CHF) in developed countries is increasing with the aging of the population,1,2 representing an increasing burden on public health. A prospective observational study based on a large population in Japan (the Chronic Heart Failure Analysis Registry in Tohoku District, CHART) revealed the annual mortality of CHF to be 8% and 12% in total and ischemic origin-patients, respectively.3 CHF with preserved systolic function represents 40–50% of all cases and its annual mortality (10–20%) is comparable with that of CHF with systolic dysfunction (SHF).4 We have estimated the 2-year mortality and rate of overall death or hospitalization because of heart failure in CHF patients with preserved systolic function (left ventricular ejection fraction, LVEF >45%) as 19% and 30%, respectively5 which are comparable values to those reported in Western countries.6,7 In view of public health and medical economics, finding therapeutic strategies for managing CHF with preserved systolic function or diastolic heart failure (DHF)§ as well as SHF, is an important issue in developed countries.

Many studies of SHF have established pharmacological evidence for decreases in death and/or hospitalization, whereas medications for DHF have been empirically selected because of a lack of evidence for their therapeutic efficacy. Recently, the CHARM-preserved trial demonstrated that candesartan, an angiotensin receptor blocker, moderately decreased hospitalization because of heart failure in patients with preserved systolic function6 and a trial for perindopril, an angiotensin-converting enzyme inhibitor, is ongoing.10 The effectiveness of the highly β1-selective, vasodilatory β-blocker, nebivolol, for patients of SHF and CHF with preserved systolic function is being investigated (SENIORS).11 In contrast, there has not been a report showing the effectiveness of carvedilol for patients with DHF.

The concentration of norepinephrine is increased in both DHF and SHF12 and experimental studies have demonstrated that norepinephrine increases the amount of collagen13,14 and transforming growth factor (TGFB)-β15 in the myocardium. Carvedilol decreases the mRNA of TGFB-β and fibronectin16 connective tissue growth factor, profibrotic cytokines induced by TGFB-β17 and matrix metalloprotease-918 as well as reducing the formation of collagen in the myocardium.19,20 All these mechanisms may decrease myocardial stiffness. Norepinephrine increases protein kinase A (PKA), eliciting hyperphosphorylation and an increase in the open probability of the ryanodine receptor. Finally, [Ca2+]i leaks to the cytosol, thereby increasing diastolic [Ca2+]i and left ventricular end-diastolic pressure (LVEDP).21 Beta-blockers may decrease diastolic [Ca2+]i.
through restoration of the FKBP12.6-mediated stabilization of the ryanodine receptor.\(^3\)\(^2\) Alternatively, \(\beta\)-blockers inhibit the phosphorylation of PKA and decrease the cyclic AMP-mediated \(\text{Ca}^{2+}\) inward current, thereby decreasing diastolic \(\text{Ca}^{2+}\).\(^3\)\(^4\) Furthermore, in a heart failure model \(\beta\)-blockers restored \(\text{Ca}^{2+}\);\(^2\)\(^5\) cycling and normalized both the expression of \(\text{Ca}^{2+}\)-handling protein and the diastolic function.\(^3\)\(^3\) Lengthening of the diastolic filling time by \(\beta\)-blockers is crucial not only for an increase in left ventricular (LV) filling, but also for the reuptake of \(\text{Ca}^{2+}\); by the sarcoplasmic reticulum (SR) \(\text{Ca}^{2+}\) pump. The latter decreases activator \(\text{Ca}^{2+}\) in diastole, and thereby LVEDP. Norepinephrine increases oxidative stress,\(^2\)\(^4\) which induces hypertrophy and apoptosis.\(^2\)\(^6\) Antioxidants attenuate LV hypertrophy,\(^2\)\(^7\)\(^2\)\(^8\) and apoptosis.\(^2\)\(^9\) LV hypertrophy and myocardial fibrosis caused by apoptosis increase the stiffness leading to diastolic dysfunction. Therefore, the antioxidant effect of carvedilol\(^3\)\(^0\) may exert a beneficial effect in DHF and thus the results of numerous experiments suggest the potential benefit of \(\beta\)-blockers for impaired diastolic function.

The blood pressure-lowering effect caused not only by \(\beta\)-blockade but also by vasodilatory \(\beta\)-blockade advantageously reduces ventricular afterload in failing heart. The vasodilatory effect attenuates the negative inotropism of \(\beta\)-blockers as well as the potential negative effect of coronary vascular resistance. Because \(\beta\)-stimulation elicits LV hypertrophy through subcellular processes that enhance protein synthesis, carvedilol may inhibit LV remodeling. The \(\beta\)-blocking action advantageously decreases oxygen consumption in ischemic heart disease, which is one of the major predisposing factors of DHF.\(^3\)\(^1\)

The \(\beta\)-blocking effect has been associated with an improved survival rate for DHF in a population-based-observational study.\(^3\)\(^1\) Carvedilol increased the ratio of the early filling velocity to the late filling velocity of the transmitral inflow in patients with DHF (SWEDIC study).\(^3\)\(^2\) Also in SHF, carvedilol improved the diastolic function before the advent of systolic modifications.\(^3\)\(^3\) A preliminary study has demonstrated that carvedilol decreased the functional class and BNP in DHF.\(^3\)\(^4\) These promising clinical data have led to the development of the current DIAST trial to investigate the effectiveness of carvedilol for patients with DHF.

**Aims of the DIAST Trial**

The aim of this trial is to assess the safety and efficacy of medical therapy with carvedilol in patients with DHF.

**Patient Population and Study Design**

This study is a multicenter, randomized, open trial involving patients with all types of DHF defined by the Framingham study group.\(^8\) Briefly, DHF is defined as LVEF \(\geq50\%\) and either present or previous definitive evidence of congestive heart failure including clinical symptoms and signs.\(^3\)\(^5\) DHF can be classified into 3 types (definite, probable and possible) according to the following 2 criteria: (a) LVEF \(\geq50\%\) measured within 72 h of a congestive heart failure event and (b) objective evidence of LV diastolic dysfunction. Definite DHF fulfils (a) and (b), probable DHF is (a) but not (b) and possible DHF is neither (a) nor (b).

Patients fulfilling the inclusion criteria are randomized to optimal medical therapy with and without carvedilol. Fifteen regional hospitals participating in this trial are responsible for the recruitment of appropriate patients. All participants are monitored by cardiologists. This trial will be terminated when the expected numbers of all-cause mortality or hospitalization are achieved in accordance with the advice of the Steering Committee. The planned number of patients for enrollment is 160 and the trial started from July 2003. The end of the trial is anticipated to be August 2005.

**Eligibility**

The inclusion criteria are as follows: (1) written informed consent; (2) age older than 19 years and younger than 80 years; (3) optimal medical therapies have been performed for at least 1 month before entry to this trial; and (4) LVEF \(\geq50\%\) using echocardiography routinely with the Teichholz method; for the patients with abnormalities in regional wall motion, the modified Simpson method is required; and (5) present symptoms of CHF or previous hospitalization related to CHF.

Exclusion criteria are: (1) CHF caused primarily to valvular disease or LV outflow tract obstruction; (2) serious renal or pulmonary disease; (3) serious liver disease: if the aspartate aminotransferase or alanine aminotransferase is greater than 3-fold the normal value, further investigation of the liver disease must be performed before inclusion; (4) hypertension that has not been controlled to the satisfaction of the investigators; (5) hemodynamically unstable ischemic heart disease occurred in the 1 month prior to the start of the trial; (6) systolic blood pressure \(<90\text{mmHg}\); (7) stroke or serious neural disease occurred in the 1 month prior to this trial; (8) malignant disease with predicted survival less than 2 years; (9) cardiac surgery or angioplasty in the 2 months prior to this trial; (10) pregnant women and females with childbearing potential unless using adequate contraception; (11) current use of \(\beta\)-blocker; (12) an important contraindication to \(\beta\)-blocker use including bronchial asthma, bradycardia, atrioventricular block, hypotension or allergy to \(\beta\)-blocker; (13) unable to tolerate the initial dose of 1.25 mg of carvedilol once daily; (14) unable to clearly state their intention to participate in this trial.

**Endpoints**

Primary endpoints were: (1) all-cause mortality or hospitalization; (2) cardiovascular mortality or hospitalization; (3) worsening CHF defined as worsening symptoms or signs of CHF requiring an intravenous injection of diuretics, an increase of furosemide of more than 40 mg/day compared with baseline (or equivalent eg, 8 mg torasemide), new administration of diuretics, vasodilators and inotropic agents for the management of CHF.

Secondary endpoints were: (1) cardiovascular events, including worsening CHF, cardiac death, life-threatening arrhythmia, myocardial infarction, coronary artery disease, stroke and transient ischemic attack; (2) individual components of the above combined endpoints; (3) duration of hospitalization; (4) functional class (New York Heart Association (NYHA) heart failure score) and exercise capacity (specific activity scale, SAS); and (5) safety and tolerability.

**Safety Parameters**

Safety will be discussed in terms of the following parameters to be observed throughout the trial: (1) vital signs, (2) hematological and biochemical laboratory tests, (3) ECG parameters and (4) adverse events.
Baseline Assessment

After patients fulfilling the inclusion criteria are screened, written informed consent will be obtained. The baseline assessment will include: history, demographic data, current medications, physical examination, NYHA functional class, specific activity scale (SAS) as a semi-quantitative index of exercise capacity estimated by a specific scale based on questionnaires for ordinary physical scale36 routine laboratory tests, brain natriuretic peptide (BNP), high-sensitive C-reactive protein (CRP), inter-leukin-6 (IL-6) and urine 8-epi-prostaglandin F2α (8-epi-PGF2α), chest X-ray, 12-lead ECG and 24-h ambulatory ECG, echocardiogram, and overnight home recording of SpO2 (Puls ox8-M24, Teijin, Tokyo, Japan).

High-sensitive CRP, IL-6 and urine 8-epi-PGF2α will be measured at a central laboratory and the overnight home recording of SpO2 will be analyzed in an independent analysis center. Other source data verification will be performed in all centers by a professional clinical research organization.

Titration and Follow-up

Patients are randomized to carvedilol and control groups at a ratio of 1:1. Randomization with an optimal allocation method and registration of data are performed on an internet home page provided by the Independent Statistics and Database Center. In the carvedilol group, the carvedilol titration schedules are as follows: 1.25 mg once daily (if necessary), 1.25 mg, 2.5 mg, 5 mg and 10 mg twice daily every 1–2 weeks at the outpatient clinics. At each visit during the titration, the clinical status and tolerability of carvedilol are documented. The patients are kept under observation at the clinic for 2 h after the first dose at each dosage step. If patients are not tolerating the new dose, the carvedilol is down titrated until the symptoms or signs disappear.

After dose of the carvedilol reaches the target or the maximal tolerable dose, clinical assessment is performed at every visit at intervals of 2–4 weeks. After a 1-year follow-up in both groups, baseline investigations will be repeated and the patients will be continuously observed until the end of the trial.

At any time throughout this trial, if the investigators become aware of any clinical symptom or signs that might have been caused by carvedilol, the dose of the drug is reduced or its administration is stopped. During the study, patients can receive any additional medication for CHF, which is documented and evaluated later by the Independent Endpoint Committee. Even if patients withdraw from this trial, they will continue to be observed according to the intention-to-treat principal.

Several substudies are planned based on heart rate variability, neurohumoral factors, oxidative stress and sleep apnea with assessments at baseline and 1 year in order to elucidate the pathophysiology of DHF.

Statistical Considerations

Statistical Hypothesis and Sample Size

The estimation of mortality or hospitalization with DHF is based on the Chronic Heart Failure Analysis Registry in Tohoku District (CHART)5 The DIAST trial started from July 2003 and the average follow-up is expected to be 2 years. The event-free rate in the control group is expected to be 70% at 2 years. The risk reduction of all-cause mortality or all-cause hospitalization is assumed to be 76% for treatment with carvedilol compared with that without carvedilol based on the Multicenter Carvedilol Heart Failure Assessment Trial (MUCHA) performed in Japan.7 An over-all non-compliance rate of 15% is expected. With a power of 80% and a two-sided level of 5%, a risk reduction of 76% should be detected with 136 patients. A total of 160 patients (80 patients per group) will be enrolled to help preserve the power.

Analysis Plan

The baseline and 1-year follow up data of demographic and clinical characteristics in the 2 groups will be presented using appropriate statistics and a descriptive summary. All efficacy variables will be summarized as appropriate. A p<0.05 will be considered significant. The combined endpoints and individual components of the combined primary and secondary endpoints will be analyzed using the intention-to-treat principal and the Cox-proportional hazards model with Log-rank test. Kaplan-Meier curves will be given for the 2 groups. Patients who are lost to follow-up will be regarded as censored at the time of the last follow-up.

Interim analyses will be performed every 4 months unless otherwise decided by the Independent Data and Safety Committee, which may advise the Steering Committee to recommend early termination of the trial based on safety, scientific or ethical reasons. If the event rates are significantly lower than expected, the trial may be extended to achieve the expected numbers of all-cause mortality or hospitalization in accordance with the advice of the Steering Committee.

Ethical Issues

This study is being conducted in accordance with the principals stated in the Declaration of Helsinki, 1964, as revised in South Africa, 1996. The Ethics Committee in Tohoku University Graduate School of Medicine approved this study on November 12, 2002 (approval No. 2002-187) as did those of each of the participating hospitals. Written informed consent is required from each patient.

Study Organizations

Four committees control the operation of DIAST: (1) Steering Committee, (2) Independent Safety Committee, (3) Independent Endpoint Committee, and (4) Technical Committee. Each has specific roles and responsibilities throughout the DIAST study.

Steering Committee

The members include Kunio Shirato (Sendai, Chairman), Jun Watanabe (Sendai), Yutaka Kagaya (Sendai), Junichi Kikuchi (Towada), Kenji Tamaki ( Morioka), Nobuo Hoshi ( Miyako), Masato Hayashi ( Yokote), Yukio Onodera ( Yuzawa), Tetsuya Hiramoto ( Sendai), Jun Ikeda ( Sendai), Mitsumasa Fukuchi ( Sendai), Masafumi Sugi ( Iwaki), Tsuyoshi Shinozaki ( Sendai) and representatives of the Sponsor. The Committee is responsible for scientific policies, protocol design, data monitoring, substudies and all aspects of the operation of this trial, in cooperation with the Independent Data and Safety Committee.

Independent Data and Safety Committee

The members include Isao Ohno ( Sendai, Chairman), Atsushi Kato ( Sendai), and Yoshio Shimizu ( Sendai). The Independent Data and Safety Committee consists of one pharmacologist, and 2 cardiologists who are not trial inves-
tigators. The Independent Data and Safety Committee is responsible for protecting the patients’ safety and rights throughout this trial and may recommend early termination of the trial to the Steering Committee for safety, scientific or ethical reasons.

**Independent Endpoint Committee**

The members include Nobumasa Ishide (Sendai, Chairman), Masaharu Kanazawa (Sendai), and Satoshi Horiguchi (Katta). The Independent Endpoint Committee consists of 3 cardiologists who are not trial investigators. The Independent Endpoint Committee reviews and classifies all events involving death, hospitalization, worsening CHF and all cardiovascular events.

**Technical Committee**

The Technical Committee includes representatives of the Sponsor and the clinical trial data coordinator. The Technical Committee is responsible for protocol preparation, assessment of data and all other day-to-day operational issues that do not require review by the Steering Committee.

**Independent Statistic and Database Center**

The Independent Statistic and Database Center consists of Yoshio Kotto (Director) and technical staff members. This organization is located in the Division of Medical Informatics, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, which assumes responsibility for statistical analyses and maintenance of the database.

**Sponsor**

The sponsor is Dai-ichi Pharmaceutical Company.

**Conclusion**

There is no evidence of improved mortality and morbidity in DHF patients and so it is imperative to establish therapeutic strategies for such patients because the adverse prognosis and increasing medical cost for this disease are critical public health issues in developed countries. The DIAST study is the first to clarify the safety and prognostic efficacy of carvedilol for patients with DHF. In addition, the DIAST study and its various subanalyses will provide original insights concerning the pathophysiology of DHF.

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**References**


