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PROTOCOL PAPER

Rationale and Design of a Multicenter Trial on Exploratory Analysis of the Effects of Advance Care Planning Guided by the Prediction Program of Heart Failure Prognosis on Quality of Life in Patients With Heart Failure

— ACQUAINT-Trial —

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Background: Preplanning of care is necessary for patients with endstage heart failure (HF), but advance care planning (ACP) before the loss of a patient's comprehensive capacity is not yet routine for the public or the medical community. The challenge in accurately predicting a patient's prognosis is a strong barrier to implementing ACP. To address this problem, several models for risk stratification have been proposed and are available in clinical settings.

Methods and Results: We randomized the procedure to provide estimated patient survival information to attending physicians and then assessed whether there was a change in (1) the frequency of ACP initiation occurred (physician-side evaluation), and/or (2) the patients' quality of life, including mental state (patient-side evaluation).

Conclusions: This multicenter, open-label, single-blinded randomized clinical trial aims to assess the hypothesis that providing information on the estimated survival of a patient to the attending physicians will improve the frequency of ACP initiation and quality of life in patients with HF.

Key Words: Advanced care plans; Heart failure; Prognosis

Background of This Trial

Heart failure (HF) is a progressive disease resulting in repeated hospital admissions and leads to restriction of a patient's activity and decline in quality of life (QOL).[1] Because both physical and psychological support is necessary for patients with advanced HF, clinical practice guidelines recommend the initiation of palliative care to provide this support.[1,2] Thus, preplanning of patient care is necessary in endstage HF, but patients and their families are often poorly informed regarding the prognosis and poorly aware of disease's seriousness, leading to unnecessary inva-

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sive procedures sometimes being performed in the last days of life.[3,4] One solution to preventing poor decision making in the end stages of HF is advance care planning (ACP),[5,6] which is a process whereby a patient, in consultation with healthcare providers, family members, and significant others, makes decisions about future health care and creates a remaining-life plan before the loss of comprehensive capacity.[5–7] ACP informs and empowers patients to express their will about current and future treatment. One randomized clinical trial demonstrated that ACP improved end-of-life care and the satisfaction of patients and their families, reducing their levels of stress, anxiety, and depression.[8] However, ACP has not yet become popular among the public, and its implementation in clinical settings remains inconsistent.

Because HF is often progressive,[1] with large fluctuations in the patient's condition (**Figure 1**), it is generally recognized that predicting prognosis is challenging compared with other progressive diseases such as cancer.[9] The optimal timing for ACP initiation for HF has not been established, and several methods for risk stratification in clinical settings have already been proposed, such as the Seattle Heart Failure Model (SHFM).[10,11] The present randomized clinical trial aimed to assess the hypothesis that providing an estimated patient survival time to the attending physician improved both the frequency of ACP initiation and the patient's QOL in clinical settings.

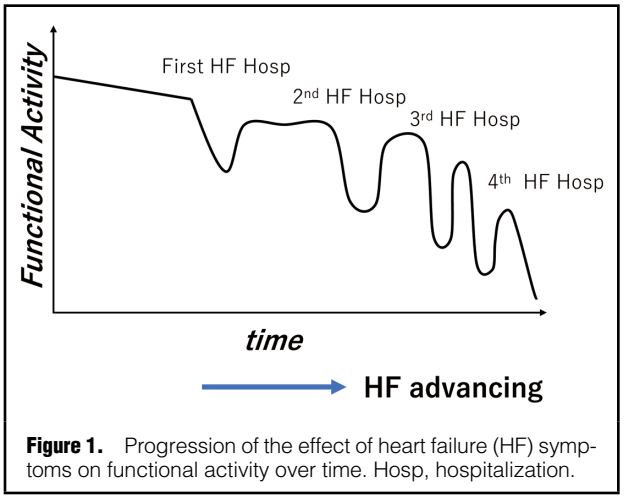

Figure 1. Progression of the effect of heart failure (HF) symptoms on functional activity over time. Hosp, hospitalization.

Methods

The Exploratory Analysis of the Effects of Advanced Care Planning guided by the Prediction Program of Heart Failure Prognosis on Quality of Life in Patients with Heart Failure Trial (ACQUAINT-trial, Clinical registry: jRCT1050200063) is a multicenter, open-label (for physicians), single-blinded, and randomized parallel-group comparison. It randomizes the provision of estimated patient survival rates from our research office to the attending physicians and then assesses whether there is a change in (1) the proportion of HF patients who have ACP initiated (physician-side evaluation), and (2) patients' QOL, including mental state (patient-side evaluation).

Prior to the enrollment of patients, the study protocol was approved by the institutional review boards of all participating centers (R20036, the National Cerebral and Cardiovascular Center). This study is being conducted in accordance with the Declaration of Helsinki. Written informed consent is given by each patient before enrollment. Personal information about potential and enrolled participants remains confidential, and the data are de-identified using participant numbers.

Key Objectives

This trial aims to assess the hypothesis that providing information on the estimated patient survival rate to attending physicians improves both the frequency of ACP initiation and QOL in patients with HF.

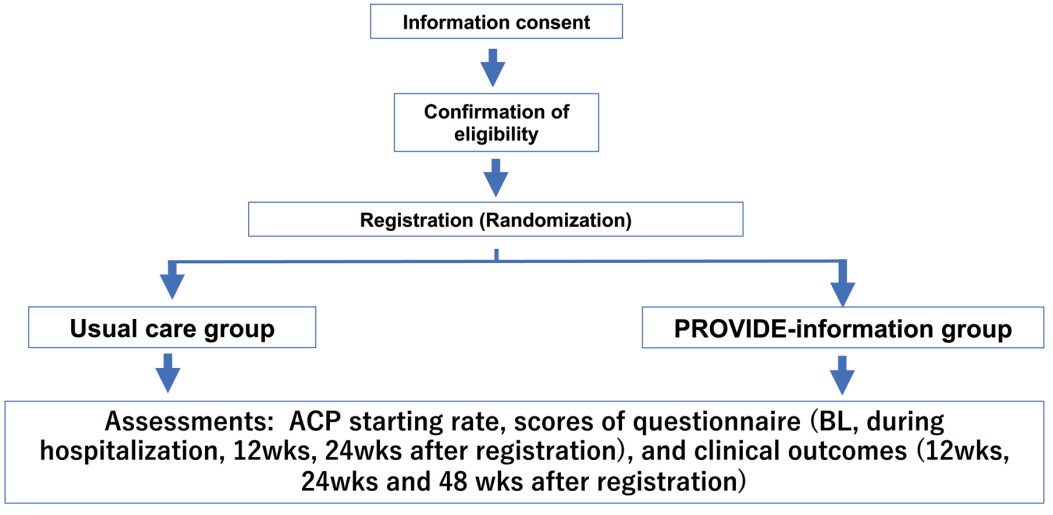

Figure 2. Study protocol. ACP, advance care planning; BL, baseline; wks, weeks.

Table. Inclusion Criteria and Primary Endpoints of the ACQUAINT-Trial
Inclusion criteria
1. Age >20 years at enrollment
2. Hospitalized patients diagnosed as HF
3. Patients with HF symptoms (NYHA functional class III–IV)
4. Patients who are able to provide written consent
5a. Patients with a history of HF hospitalization >2 times before study enrollment
5b. Patients presenting with BNP ≥500 pg/mL or NT-proBNP ≥2,000 pg/mL within 6 months of the corresponding hospital admission
Primary endpoints
The proportion of ACP initiation during the period from registration to discharge
Differences in questionnaire score (SDM-Q-9) during the period from registration to discharge

ACP, advanced care plan; BNP, B-type natriuretic peptide; HF, heart failure.

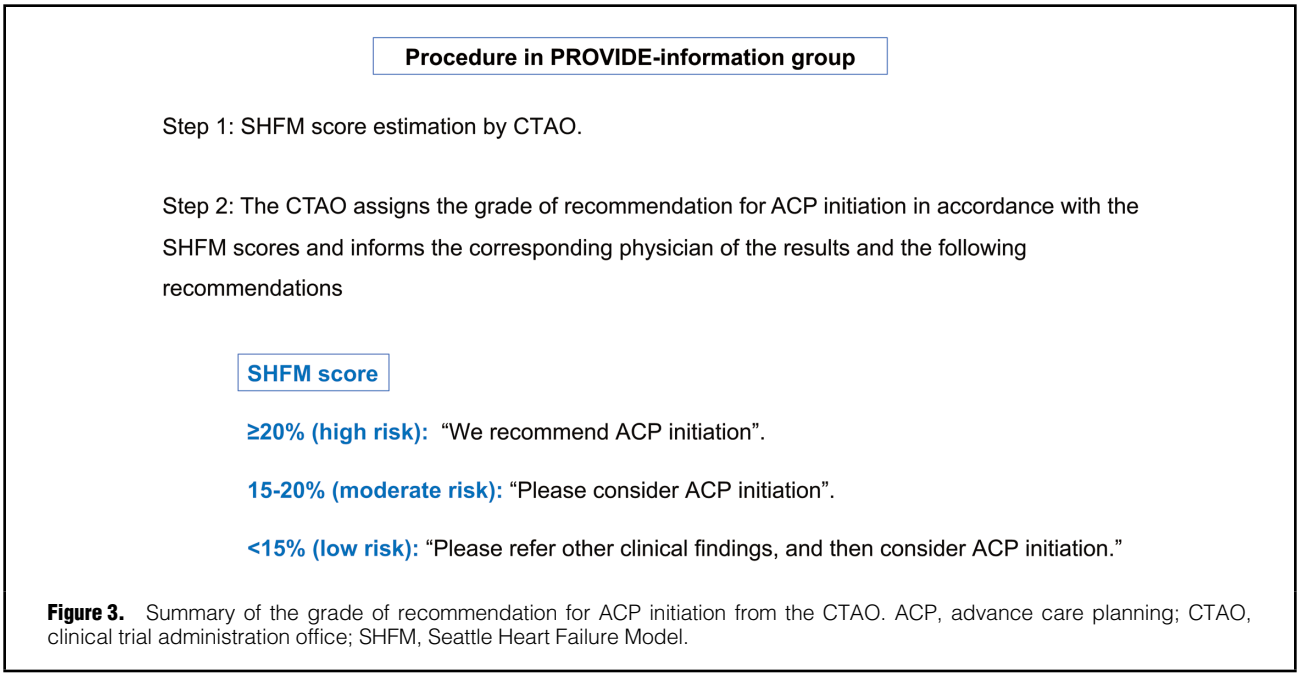

Figure 3. Summary of the grade of recommendation for ACP initiation from the CTAO. ACP, advance care planning; CTAO, clinical trial administration office; SHFM, Seattle Heart Failure Model.

Inclusion and Exclusion Criteria

Specific patient inclusion criteria are: (1) >20 years of age at enrollment, (2) hospitalized and diagnosed with HF, (3) presence of HF symptoms (NYHA functional class III–IV), (4) can provide written consent, and (5) history of HF hospitalization >2 times before enrollment, or B-type natriuretic peptide (BNP) level ≥500 pg/mL or NT-proBNP level ≥2,000 pg/mL within 6 months of enrollment (Table). Enrollment requires that patients meet all inclusion criteria. We set the BNP cutoff value for HF hospitalization patients in accordance with previous studies.[12–14] The exclusion criteria are listed in **Supplementary Table 1**.

Study Protocol

The ACQUAINT-trial is a randomized study (1:1) comparing the initiation rate of ACP in clinical settings and QOL in patients with HF between a usual-care group (USUAL-CARE group) and the PROVIDE-information group, in which information about estimated patient survival time is provided to an attending physician, as summarized in **Figure 2**.

After confirmation of enrollment, the allocation of patients to each group is conducted by Pocock and Simon's minimization method stratified by the presence of the following factors: (1) plasma BNP level >800 pg/mL or NT-proBNP >3,200 pg/mL, (2) estimated glomerular filtration rate <15 mL/min/1.73 m^2, (3) left ventricular ejection fraction <20% or >50%, (4) age >75 years, and (5) sex. After allocation, the following procedure is performed in each group.

USUAL-CARE Group The clinical trial administration office (CTAO) does not provide any information on the patient's survival rate. The investigators evaluate the endpoints, as described in the **Table** and **Supplementary Table 2**. Whether ACP is initiated is determined solely by the attending physician in the usual manner. There are no restrictions on the attending physician's independent prediction of the patient's prognosis from the CTAO in the USUAL-CARE group.

PROVIDE-Information Group The CTAO estimates the patient's survival rate within 1 year using the SHFM and assigns the grade of recommendation for ACP initiation in

accordance with the SHFM score before informing the relevant physician of the results and the following recommendations: SHFM score: ≥20% (high risk): "We recommend ACP initiation"; 15–20% (moderate risk): "Please consider ACP initiation"; <15% (low risk): "Please refer other clinical findings, and then consider ACP initiation." (**Figure 3**). The investigators evaluate the endpoints, as described in the **Table** and **Supplementary Table 2**. ACP initiation is determined by the attending physician.

Definition of ACP

In this study, ACP initiation is defined as discussion between medical staff and the patient regarding (1) the location for provision of end-of-life care, (2) resuscitation at the end of life, and (3) whether an opportunity is provided to discuss points 1 and 2 with the patient's family. ACP is considered initiated if at least 1 of these is fulfilled. Whether the ACP initiation criteria are fulfilled in the enrolled patients is determined by an attending physician and confirmed by the CTAO committee.

Questionnaire

Patients' mental state is evaluated using the questionnaires, and the details are described in the **Supplementary Material**.

Endpoints

Two primary outcomes are set, because we believe it necessary to evaluate the impact for both medical staff and patients. For medical staff, the initiation frequency of ACP during the period from registration to the discharge date. For each patient, differences in SDM-Q-9 score during the period from registration to the discharge date, as summarized in the **Table**. The secondary outcomes are summarized in **Supplementary Table 2**.

Sample Size

The total sample size was set at 78 patients, with the assumption that 20% of the initial entries would drop out. The details are described in the **Supplementary Material**.

Statistical Analysis

The details are described in the **Supplementary Material**.

Current Status

The details are given in the **Supplementary Material**.

Discussion

Clinical Role of ACP in End-of-Life Care

Ideally, in patients with advanced HF, the prognosis is shared with the patient, his/her family, and medical staff, and ACP should be addressed through discussions among these parties. In reality, the role of ACP is still poorly understood, even among frontline medical staff. In Japan, the Health, Labour, and Welfare Ministry published questionnaire data from a 2017 investigation into decision processes at the end of life among the general population and healthcare professionals.[15] The investigation demonstrated that 75.5% of the general population and 41.6% of physicians answered that they "did not know about ACP", indicating a low awareness in society. Therefore, it is important to consider why ACP has not yet been routinely implemented in clinical practice. In addition to low awareness among the public, one reason for insufficient ACP implementation may be a perception among clinicians that it is difficult to perform because it relies on the difficult prediction of HF patient prognosis. Although several risk stratification tools to predict the prognosis of HF patients have been published, such as the SHFM, they have not been fully incorporated into routine clinical practice. We believe that if physicians have reliable prediction data for a patient's survival, it will help them to initiate ACP. Thus, we designed this study to utilize a risk model to estimate the optimal timing of ACP. Recent studies demonstrated that the prediction accuracy of the SHFM is limited,[16,17] but at that time of planning the study design, the SHFM had been validated in numerous settings,[18–21] including a Japanese patient cohort.[11] The SHFM provides risk strata, an estimation of 1-, 2- and 5-year survival rates,[10] which can be applied to this study regarding the prediction for 1-year survival. The SHFM is also cited in the International Society for Heart and Lung Transplantation guideline as a reference criterion for considering heart transplantation.[22] After considering several risk stratification models,[10,11,23,24] we chose to use the SHFM in this study. Based on these considerations, we designed the study to provide information on a patient's estimated 1-year survival and, based on the calculated risk level, to recommend ACP initiation to the attending physician, with particular encouragement to initiate ACP for high-risk patients.

Summary

Although the implementation of ACP is recommended with Class I recommendation level in the HF guidelines,[1] the optimal time to initiate it has not been formally established. Furthermore, the actual implementation rate of ACP in clinical settings remains inconsistent. In this study, we will evaluate the established risk score for HF patients and encourage the implementation of ACP by providing information to the attending physician on the estimated patient survival time within 1 year. Because the evidence of the optimal timing of ACP intervention is still limited in patients with HF, this study will play an important role in determining such timing, and the impact on society is likely to be high.

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Conflict of Interest/Competing Interests

All authors have nothing to declare conflict of interest/competing interests in connection with this article.

Disclosures

Dr. S. Yasuda and Dr. Y. Seo are members of *Circulation Reports*' Editorial Team.

IRB Information

National Cerebral and Cardiovascular Center Ethics Committee, reference number: R20036.

Availability of Data and Materials

Data sharing is not applicable.

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Supplementary Files

Please find supplementary file(s);
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