Dilated cardiomyopathy (DCM) is a heterogeneous disease and, depending on the diagnostic approach used, 2–65% of cases are hereditable. Since the development of next-generation sequencing, tremendous advances have been made in understanding the genetic basis of DCM and the heritability of DCM has been attracting attention. However, it remains unclear whether the progression of the underlying disease differs among patients with and without heritability. Although several studies have assessed the prognostic effect of heritability, the results are inconsistent, which might be related to the retrospective nature of the studies or their small sample sizes. Furthermore, previous studies used different approaches to identify heritability of DCM, such as pedigree analysis, echocardiographic and electrocardiographic investigation of relatives, and systematic family screening including blood tests, chest X-ray, electrocardiogram (ECG), 24-h Holter monitoring, exercise stress test, or echocardiographic examination. Among these approaches, pedigree analysis is the simplest and easiest to apply in daily practice. However, no studies have assessed the prognostic effect of a family history (FHx) identified through pedigree analysis.

Therefore, we performed a prospective study to assess the prognostic outcomes of FHx based on pedigree analysis in an established cohort of patients with DCM. We also performed further analysis of myocardial fibrosis in patients with FHx vs. no-FHx using late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR).

Methods
Study Population
We conducted a prospective observational study of 514 consecutive Japanese patients with DCM. FHx was defined as the presence of DCM in ≥1 family member within 2-degrees relative based on pedigree analysis. The primary endpoint was a composite of major cardiac events (sudden cardiac death and pump failure death). The prevalence of FHx was 7.4% (n=38). During a median follow-up of 3.6 years, 77 (15%) patients experienced a major cardiac event. Multivariable Cox regression analysis identified FHx as independently associated with major cardiac events (hazard ratio [HR] 4.32; 95% confidence interval [CI], 2.04–9.19; P<0.001) compared with conventional risk factors such as age, QRS duration, and left ventricular volume. In the propensity score-matched cohort (n=38 each), the FHx group had a significantly higher incidence of major cardiac events (HR, 4.48; 95% CI, 1.25–16.13; P=0.022). In addition, the FHx group had a higher prevalence of a diffuse late gadolinium enhancement (LGE) pattern than the no-FHx group (32% vs. 17%, P=0.022).

Conclusions: DCM patients with FHx had a worse prognosis, which was associated with a higher prevalence of a diffuse LGE pattern, than patients without FHx.

Key Words: Cardiac events; Dilated cardiomyopathy; Familial history; Late gadolinium enhancement; Magnetic resonance
consecutive Japanese patients with DCM at the National Cerebral and Cardiovascular Center, Suita, Japan, between April 2007 and December 2015. The diagnosis of DCM was based on World Health Organization criteria and left ventricular ejection fraction (LVEF) <50%.11 All patients underwent invasive coronary angiography or computed tomography angiography (CTA) to rule out significant coronary artery stenosis (>50% diameter stenosis).12 Patients with a history of myocardial infarction or coronary revascularization, myocarditis, hypertrophic cardiomyopathy, secondary cardiomyopathy, valvular heart disease, or hypertensive heart disease were excluded. One patient with myocarditis diagnosed by endomyocardial biopsy, 2 patients with peripartum cardiomyopathy and 1 patient with Adriamycin-related cardiomyopathy were classified as secondary cardiomyopathy and excluded. Patients younger than 18 years of age were also excluded. CMR was performed while the patient was in a clinically stable, non-congested condition (New York Heart Association [NYHA] class ≤II). None of the patients had a typical subendocardial or transmural LGE pattern in the territory supplied by a coronary artery that might have resulted from myocardial damage secondary to coronary artery disease or coronary embolism. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board and ethics committee of the National Cerebral and Cardiovascular Center (M24-081).

**Diagnostic Approach for FHx**
Based on pedigree analysis of 3 generations,9 FHx was defined based on data from medical records obtained in 2 family members: the index patient and at least 1 1st- or 2nd-degree family member with DCM.9 We did not perform family screening in this study. We enrolled index patients with DCM who visited the Center, but not relatives with DCM who were identified by pedigree analysis in the present study.

**CMR Protocol**
CMR examinations were performed using a 1.5-T magnetic resonance (MR) imaging system (Magnetom Sonata, Siemens, Erlangen, Germany) with a 4-channel surface coil. The procedures used to acquire MR images in this study have been previously described.10,13,14 Briefly, we identified LGE using segmented inversion recovery prepared true fast imaging with steady-state precession sequence with ECG triggering 10 min after the administration of 0.15 mmol/kg body weight of gadolinium diethylenetriamine pentaacetic acid. LGE was only considered present if it was visible in 2 orthogonal views.15,16 Mid-wall LGE was only considered present if the area of LGE was confined to the intermural and/or subepicardial layers.17 In cases other than mid-wall LGE, LGE in multiple territories was defined as diffuse LGE, and isolated LGE was defined as focal LGE.13 Experienced radiologists (Y.M. and H.M.), who were blinded to clinical data and outcomes, independently assessed LGE presence and location. A third blinded reader adjudicated cases in disagreement (4.9%). There was acceptable interobserver concordance for diffuse LGE ($\kappa=0.88$), mid-wall LGE ($\kappa=0.89$), and focal LGE ($\kappa=0.83$). There was also acceptable intraobserver concordance for diffuse LGE ($\kappa=0.90$), mid-wall LGE ($\kappa=0.92$), and focal LGE ($\kappa=0.89$).
Table 1. Baseline Characteristics of the Study Patients With Dilated Cardiomyopathy

|                              | All patients (n=514) | No-FHx (n=476) | FHx (n=38) | P value |
|------------------------------|----------------------|----------------|------------|---------|
| Age, years                   | 53±16                | 53±16          | 45±12      | 0.002   |
| Male, n (%)                  | 387 (75)             | 359 (75)       | 28 (74)    | 0.811   |
| BMI, kg/m²                   | 22.9±4.0             | 22.9±4.0       | 23.2±4.1   | 0.632   |
| Current smoker, n (%)        | 117 (23)             | 111 (23)       | 6 (16)     | 0.266   |
| NYHA functional class, n (%) |                      |                |            | 0.813   |
| I                            | 148 (29)             | 137 (29)       | 11 (29)    |         |
| II                           | 226 (44)             | 211 (44)       | 15 (39)    |         |
| III                          | 81 (16)              | 73 (15)        | 8 (21)     |         |
| IV                           | 59 (11)              | 55 (12)        | 4 (11)     |         |
| Medical history, n (%)       |                      |                |            |         |
| Diabetes mellitus, n (%)     | 100 (19)             | 97 (20)        | 3 (8)      | 0.061   |
| Atrial fibrillation          | 157 (31)             | 145 (30)       | 12 (32)    | 0.886   |
| Sustained VT                 | 11 (2.1)             | 11 (2.3)       | 0          | 0.344   |
| Nonfatal VF                  | 4 (0.8)              | 4 (0.8)        | 0          | 0.571   |
| BNP, pg/mL                   | 200 [55–561]         | 196 [54–556]   | 155 [79–593] | 0.640 |
| Creatinine, mg/dL            | 0.87±0.24            | 0.88±0.24      | 0.85±0.22  | 0.479   |
| eGFR, mL/min/1.73 m²         | 73±22                | 73±22          | 78±20      | 0.201   |
| Serum sodium, mEq/L          | 140.1±2.9            | 140.1±2.9      | 140.1±2.0  | 0.955   |
| Hemoglobin, g/dL             | 14.0±1.6             | 14.0±1.6       | 14.4±1.5   | 0.131   |
| ECG parameters               |                      |                |            |         |
| Heart rate, beats/min        | 69±12                | 69±13          | 67±11      | 0.360   |
| PR duration, ms (n=415)      | 181±31               | 181±31         | 181±33     | 0.912   |
| Prolonged PR interval, n (%) | 79 (19)              | 73 (19)        | 6 (19)     | 0.963   |
| QRS duration, ms             | 118±29               | 118±29         | 121±27     | 0.572   |
| Wide QRS duration, n (%)     | 169 (33)             | 155 (33)       | 14 (33)    | 0.589   |
| CLBBB, n (%)                 | 87 (17)              | 81 (17)        | 6 (16)     | 0.846   |
| CRBBB, n (%)                 | 30 (5.8)             | 26 (5.5)       | 4 (11)     | 0.200   |
| IVCD, n (%)                  | 49 (9.5)             | 45 (9.5)       | 4 (10.5)   | 0.829   |
| QTC interval, ms             | 446±42               | 446±42         | 447±39     | 0.780   |
| Medications at baseline, n (%)|                      |                |            |         |
| β-blocker                    | 460 (89)             | 426 (89)       | 34 (89)    | 0.997   |
| ACEI or ARB                  | 417 (81)             | 387 (81)       | 30 (79)    | 0.721   |
| Aldosterone antagonist       | 244 (47)             | 219 (46)       | 25 (66)    | 0.019   |
| Diuretic                     | 286 (56)             | 266 (56)       | 20 (53)    | 0.698   |
| Digoxin                      | 98 (19)              | 93 (19)        | 5 (13)     | 0.335   |
| CMR measurements             |                      |                |            |         |
| LVEDVI, mL/m²                | 145±54               | 145±55         | 154±51     | 0.310   |
| LVESVI, mL/m²                | 111±54               | 110±54         | 120±52     | 0.275   |
| LVSVI, mL/m²                 | 35±12                | 35±12          | 34±10      | 0.761   |
| LV mass, g                   | 141±51               | 142±51         | 131±48     | 0.236   |
| LVEF, %                      | 26±11                | 27±11          | 24±10      | 0.185   |
| RVEF, %                      | 35±11                | 35±11          | 35±10      | 0.868   |
| LGE, n (%)                   | 303 (59)             | 276 (58)       | 27 (71)    | 0.115   |
| Mid-wall pattern             | 163 (32)             | 151 (32)       | 12 (32)    | 0.985   |
| Focal pattern                | 48 (9.3)             | 45 (9.5)       | 3 (7.9)    | 0.751   |
| Diffuse pattern              | 92 (18)              | 80 (17)        | 12 (32)    | 0.022   |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CLBBB, complete left bundle branch block; CMR, cardiac magnetic resonance; CRBBB, complete right bundle branch block; DCM, dilated cardiomyopathy; ECG, electrocardiogram; EDVI, end-diastolic volume index; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESVI, end-systolic volume index; FHx, family history; IVCD, interventricular conduction delay; LGE, late gadolinium enhancement; LV, left ventricular; NYHA, New York Heart Association; RV, right ventricular; SVI, stroke volume index; VF, ventricular fibrillation; VT, ventricular tachycardia.
Determination of B-Type Natriuretic Peptide (BNP) Levels
Blood samples were collected in tubes containing ethylenediaminetetraacetic acid. Plasma BNP levels were measured using a validated commercially available immunoassay kit (Tosoh, Tokyo, Japan).

Follow-up and Endpoints
After the CMR data were obtained, study patients were followed at 3 months, 6 months, and 12 months and annually thereafter until the occurrence of any of the following events: sudden cardiac death (SCD), aborted SCD (nonfatal ventricular fibrillation [VF], sustained ventricular tachycardia [VT], or appropriate implantable cardioverter-defibrillator [ICD] discharge for VT or VF), pump failure death (heart failure [HF] death, cardiac transplantation, or left ventricular assist device [LVAD] implantation), or rehospitalization for HF. The duration of the follow-up period was calculated from baseline CMR until an endpoint occurred or the last patient contact. The primary endpoint was a composite of major cardiac events (SCD, aborted SCD, or pump failure death). The secondary endpoint was rehospitalization for HF. Independent attending cardiologists (E.T. and H.M.) blinded to the patient’s baseline characteristics reviewed the medical records to determine if hospitalizations and deaths qualified as cardiac events. SCD was defined as unexpected death either within
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using the log-rank test. Univariable Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for each endpoint. Multivariable Cox regression analysis was performed using covariates that significantly predicted each endpoint in the univariable analysis or are established prognostic risk factors for chronic HF (age, sex, diabetes mellitus, BNP, estimated glomerular filtration rate [eGFR], hemoglobin, β-blocker use, and angiotensin-converting enzyme inhibitor [ACEI] or angiotensin-receptor blocker [ARB] use). Stepwise selection with a P-value of 0.05 for forward selection was used to select the best predictive model.

A propensity score was used to adjust for baseline covariates that were significantly different between groups or could influence outcomes: age; sex; BNP; β-blocker, ACEI, ARB, or aldosterone antagonist use; and LVEF. Propensity score-matched cohorts were constructed by matching patients in the 2 groups on a 1:1 basis using the nearest-neighbor matching method within a caliper of 0.01 of the propensity score. Details on propensity score matching are described in Supplementary Table 1. All statistical tests were two-sided and P<0.05 was regarded as statistically significant. All statistical analyses were performed with SPSS.

1 h of cardiac symptoms in the absence of progressive cardiac deterioration, during sleep, or within 24 h of last being seen alive. HF death was defined as death associated with unstable, progressive deterioration of pump function despite active therapy. Aborted SCD was diagnosed in patients who received an appropriate ICD discharge for VT or VF, had nonfatal VF, or spontaneous sustained VT (>30 s) causing hemodynamic compromise requiring cardioversion. Rehospitalization for HF was defined as hospital admission for signs and symptoms of decompensated HF requiring treatment with an intravenous HF medication (diuretic, vasodilator, or inotropic agent). For composite endpoints, only the first event for each patient was included in the analysis.

Statistical Analysis

All continuous variables are presented as mean±SD. Unpaired t-tests were used to compare groups. Non-normally distributed variables are presented as median (interquartile range [IQR]). Noncontinuous and categorical variables are presented as frequencies or percentages, and were compared using the χ2 test. Cumulative event-free survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Univariable Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for each endpoint. Multivariable Cox regression analysis was performed using covariates that significantly predicted each endpoint in the univariable analysis or are established prognostic risk factors for chronic HF (age, sex, diabetes mellitus, BNP, estimated glomerular filtration rate [eGFR], hemoglobin, β-blocker use, and angiotensin-converting enzyme inhibitor [ACEI] or angiotensin-receptor blocker [ARB] use). Stepwise selection with a P-value of 0.05 for forward selection was used to select the best predictive model.

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software (version 24.0; IBM Corp, Armonk, NY, USA) and Stata 15 (StataCorp, College Station, TX, USA).

Results

Baseline Clinical Characteristics

At baseline, 530 Japanese patients met the inclusion criteria. The follow-up rate was 96.9%; 12 patients were lost to follow-up. Ultimately, 514 patients were included in the outcome analysis (Figure 1), of whom 127 (25%) were women. Of these 514 patients, 409 (80%) underwent endomyocardial biopsy either because of advanced age (>80 years) or because they declined the procedure, none had clinical features specific for secondary cardiomyopathy. Although the remaining 20% of patients did not undergo endomyocardial biopsy either because of advanced age (>80 years) or because they declined the procedure, none had clinical features specific for secondary cardiomyopathy. The mean LVEF was 26±11%. A total of 38 (7.4%) patients had FHx: 20 patients had FHx in a 1st-degree relative, 14 patients had FHx in a 2nd-degree relative, and 4 patients had FHx in both 1st- and 2nd-degree relatives.

We divided the study patients into 2 groups according to the presence or absence of FHx: FHx (n=38) or no-FHx (n=476). Baseline characteristics are summarized in Table 1. Patients in the FHx group were younger (P=0.002), but there were no significant differences in sex; NYHA functional class; β-blocker, ACEI or ARB use; BNP levels; and LVEF and LV volumes between the 2 groups. Although the proportion of patients with presence of LGE was similar between groups (P=0.115), the prevalence of a diffuse LGE pattern, which represents severe myocardial fibrosis, was significantly higher in the FHx group than in the no-FHx group (32% vs. 17%; P=0.022, Figure 2).

Primary Endpoint: Composite of Major Cardiac Events

During a median follow-up period of 3.6 years (IQR, 1.7–5.5 years), 77 (15%) patients reached the primary endpoint. Table 2 summarizes the incidence of the primary endpoint. Patients with FHx had a higher incidence of major cardiac events (29% vs. 14%; P=0.012), aborted SCD (16% vs. 6.9%; P=0.047), and cardiac transplantation or LVAD implantation (13% vs. 2.7%; P=0.001) than patients without FHx. Patients with FHx had a higher incidence of ICD implantation than patients without FHx (34% vs. 18%, P=0.012). Among patients who underwent ICD implantation, appro-

### Table 3. Univariable and Multivariable Cox Regression Analyses of Risk Factors for Composite of Major Cardiac Events

|                         | Univariable analysis | Multivariable analysis |
|-------------------------|----------------------|------------------------|
|                         | HR 95% CI P value    | Model 1*  | Best predictive model| HR 95% CI P value |
| Age, per 10 year increment | 0.99 0.86–1.14 0.897 | 1.28 1.06–1.54 0.010 |
| Male sex                | 1.63 0.91–2.97 0.108 |           |                       |
| BMI, per kg/m² increment | 0.98 0.93–1.04 0.530 |           |                       |
| NYHA class ≥II          | 3.60 1.80–7.22 <0.001 | 2.01 0.94–4.33 0.073 |
| Current smoker          | 1.06 0.62–1.80 0.843 |           |                       |
| Diabetes mellitus       | 1.02 0.58–1.79 0.958 |           |                       |
| Atrial fibrillation     | 1.43 0.90–2.27 0.128 |           |                       |
| History of sustained VT or nonfatal VF | 3.38 1.55–7.35 0.002 | 3.17 1.30–7.72 0.011 |
| FHx of DCM              | 2.38 1.26–4.52 0.008 | 1.91 0.99–3.68 0.055 | 4.32 2.04–9.19 <0.001 |
| ECG parameters          |                     |           |                       |
| Heart rate, per 10 beats/min increment | 1.01 0.84–1.20 0.958 | 1.00 1.01–1.21 0.022 |
| QRS duration, per 10 ms increment | 1.18 1.10–1.26 <0.001 | 1.06 0.97–1.15 0.192 |
| QTc, per 10 ms increment | 1.09 1.04–1.14 <0.001 | 1.01 0.95–1.08 0.69 |
| Log (BNP), per 1 pg/mL increment | 2.14 1.48–3.09 <0.001 | 1.11 0.70–1.76 0.651 |
| eGFR, per 1 mL/m²/min increment | 1.00 0.99–1.01 0.407 | 0.96 0.91–1.05 0.580 |
| Serum sodium, per 1 mEq/L decrement | 0.98 0.82–1.07 0.328 | 0.82 1.05–1.54 0.530 |
| Medications             |                     |           |                       |
| β-blocker               | 0.91 0.42–1.98 0.807 |           |                       |
| ACEI or ARB             | 1.40 0.74–2.65 0.305 |           |                       |
| Diuretic                | 2.65 1.56–4.50 <0.001 | 1.40 0.77–2.53 0.272 | 2.55 1.29–6.05 0.007 |
| Amiodarone              | 4.04 2.46–6.64 <0.001 | 1.27 0.72–2.23 0.409 |
| Digoxin                 | 0.98 0.56–1.69 0.931 |           |                       |
| CMR parameters          |                     |           |                       |
| LVEDVI, per 10 mL/m²² increment | 1.14 1.10–1.18 <0.001 | 1.09 1.04–1.14 <0.001 | 1.09 1.05–1.14 <0.001 |
| LVSVI, per 10 mL/m²² increment | 0.96 0.79–1.16 0.647 | 1.03 1.00–1.07 0.163 |
| LV mass, per 1 g increment | 1.00 0.99–1.01 0.572 | 1.00 0.99–1.01 0.276 |
| Presence of LGE         | 6.09 3.13–11.85 <0.001 | 4.09 2.05–8.17 <0.001 |

*Multivariable Cox models were selected using a simultaneous forced entry method with factors that were significant in the univariable analysis. QRS duration, aldosterone antagonist, LVESVI, LVEF, and RVEF were dropped due to high collinearity, as suggested by variance inflation factors >10. †Best predictive model, adjusted for significant predictors selected by stepwise Cox regression analysis using factors that were significant in the univariable analysis and established risk factors for prognosis (age, sex, diabetes mellitus, BNP, eGFR, hemoglobin, β-blocker use, and ACEI or ARB use). CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.
Table 4. Univariable and Multivariable Cox Regression Analyses of Risk Factors for Rehospitalization for HF

| Risk Factor                        | Univariable analysis | Multivariable analysis |
|------------------------------------|----------------------|------------------------|
|                                    | HR 95% CI P value    | HR 95% CI P value      | HR 95% CI P value |
| Age, per 10 year increment         |                      |                        |                |
| Male sex                           | 1.21 1.03–1.42 0.024 | 1.15 0.94–1.40 0.185   | 1.28 1.06–1.54 0.010 |
| BMI, per kg/m² increment            | 0.81 0.47–1.40 0.455 |                        |                |
| NYHA class ≥II                     | 0.98 0.93–1.05 0.615 | 2.24 1.17–4.29 0.015   | 0.85 0.40–1.78 0.663 |
| Current smoker                     | 0.48 0.24–0.98 0.044 | 0.49 0.40–1.78 0.066   |                |
| Diabetes mellitus                  | 1.46 0.83–2.57 0.193 |                        |                |
| Atrial fibrillation                | 5.67 0.68–47.14 0.109 |                        |                |
| History of sustained VT or nonfatal VF | 0.42 0.06–3.05 0.393 |                        |                |
| FHx of DCM                         | 3.50 1.83–6.72 <0.001 | 4.36 1.96–9.68 <0.001  | 4.32 2.04–9.19 <0.001 |
| ECG parameters                     |                      |                        |                |
| Heart rate, per 10 beats/min increment | 0.87 0.81–1.08 0.200 |                        |                |
| QRS duration, per 10 ms increment  | 1.20 1.17–1.28 <0.001 | 1.10 0.99–1.21 0.075   | 1.11 1.01–1.21 0.022 |
| QTc, per 10 ms increment           | 1.10 1.05–1.16 <0.001 | 1.01 0.95–1.08 0.687   |                |
| Log (BNP), per 1 pg/mL increment   | 2.31 1.54–3.26 <0.001 | 1.48 0.82–2.70 0.196   |                |
| eGFR, per 1 mL/min/1.73 m² increment | 1.00 0.98–1.01 0.433 |                        |                |
| Serum sodium, per 1 mEq/L decrement | 1.05 0.97–1.14 0.236 |                        |                |
| Hemoglobin, per 1 g/dL decrement   | 1.17 1.02–1.36 0.029 | 1.12 0.93–1.35 0.234   |                |
| Medications                        |                      |                        |                |
| β-blocker                          | 3.14 0.77–12.86 0.111 |                        |                |
| ACEI or ARB                        | 1.64 0.78–3.44 0.191 |                        |                |
| Diuretic                           | 3.72 1.99–6.98 <0.001 | 2.57 1.26–5.24 0.009   | 2.25 1.29–5.05 0.007 |
| Amiodarone                         | 2.09 1.12–3.91 0.022 | 0.70 0.33–1.46 0.342   |                |
| Digoxin                            | 1.09 0.60–1.98 0.768 |                        |                |
| CMR parameters                     |                      |                        |                |
| LVEDVI, per 10 mL/m² increment     | 1.12 1.08–1.16 <0.001 | 1.08 1.02–1.14 0.012   | 1.09 1.05–1.15 <0.001 |
| LVSVI, per 10 mL/m² increment      | 1.07 0.89–1.28 0.469 |                        |                |
| LV mass, per 1 g increment         | 1.01 1.00–1.01 0.036 | 1.00 1.00–1.01 0.757   |                |
| RVEF, per 5% decrement             | 1.12 0.99–1.26 0.052 |                        |                |
| Presence of LGE                    | 2.75 1.54–4.90 0.001 | 1.97 1.05–3.69 0.035   |                |

*Multivariable Cox models were selected using a simultaneous forced entry method with factors that were significant in the univariable analysis. QRS duration, Aldosterone antagonist, LVESVI, and LVEF were dropped due to high collinearity, as suggested by variance inflation factors >10. ‡Best predictive model, adjusted for significant predictors selected by stepwise Cox regression analysis based on factors that were significant in the univariable analysis and established risk factors for prognosis (age, sex, diabetes mellitus, BNP, eGFR, hemoglobin, β-blocker use, and ACEI or ARB use). Abbreviations as in Tables 1,3.

appropriate ICD discharge for VT or VF occurred in 6 of 13 (46%) patients in the FHx group and in 27 of 84 (32%) patients in the no-FHx group (P=0.321). Figure 3A shows the Kaplan-Meier curves for survival free from the primary endpoint. The FHx group had more patients who reached the primary endpoint than the no-FHx group (P=0.010). The estimated 5-year rate for the primary endpoint was higher in the FHx group than in the no-FHx group (44% vs. 15%; P=0.011) (Figure 3C). Table 3 shows the univariable and multivariable Cox regression analyses of risk factors for the primary endpoint. In model 1, a simultaneous forced entry multivariable Cox model that adjusted for factors that were significant in the univariable analysis, the following were identified as significant predictors for major cardiac events: history of sustained VT or nonfatal VF, LV end-diastolic volume index, and presence of LGE. To further investigate whether FHx was a better cardiac prognostic factor compared with conventional risk factors, we performed a multivariable Cox regression analysis that adjusted for factors that were significant in the univariable analysis as well as established risk factors for chronic HF (age, sex, diabetes mellitus, BNP, eGFR, hemoglobin level, β-blocker use, and ACEI or ARB use) (model 2). Because the number of events in this study was relatively low, we found that the best predictive model adjusted for significant predictors selected in a stepwise Cox regression analysis based on models 1 and 2. FHx (HR, 4.32; 95% CI, 2.04–9.19; P<0.001) remained a significant indicator of major cardiac events.

Secondary Endpoint: Rehospitalization for HF
Rehospitalization for HF occurred in 64 (13%) patients (Table 2). A higher proportion of patients in the FHx group reached this outcome (P<0.001) (Figure 3B). The FHx group had a higher estimated 5-year rate of rehospitalization for HF (42% vs. 16%; P<0.001) (Figure 3D) than the no-FHx group. In the multivariable model based on stepwise Cox regression analysis, FHx was a significant predictor of rehospitalization for HF (HR, 4.32; 95% CI, 2.04–9.19; P<0.001) (Table 4).
Propensity Score-Matched Analyses for Composite Endpoint of Major Cardiac Events and Rehospitalization for HF

In further analysis, a propensity score-matched cohort consisting of 38 patients with FHx and 38 patients without FHx was constructed (Supplementary Tables 1,2). In this model that matched for age, sex, BNP, β-blocker, ACEI, ARB, or aldosterone antagonist use, and LVEF, the composite endpoint of major cardiac events (HR, 4.48; 95% CI, 1.25–16.13; P=0.022) and rehospitalization for HF (HR, 3.38; 95% CI, 1.08–10.63; P=0.037) occurred more frequently in the FHx group than in the no-FHx group. A higher proportion of patients in the FHx group reached the composite endpoint of major cardiac events (P=0.004, Figure 4A), and rehospitalization for HF (P=0.027, Figure 4B). In addition, the FHx group had a higher 5-year event rate for the composite endpoint of major cardiac events (44%, P=0.011, Figure 4C) and rehospitalization for HF (42%, P=0.027, Figure 4D).

Discussion

This prospective cohort study of DCM from Japan is the first to assess the prognostic effect of FHx identified by pedigree analysis. We found that patients with FHx had a high risk for major cardiac events and rehospitalization for HF. In particular, the propensity score-matched model confirmed FHx as a significant prognostic factor for major cardiac events and rehospitalization for HF. We also showed that the FHx group had a higher prevalence of a diffuse LGE pattern than the no-FHx group.

Several retrospective studies have assessed the prognostic effect of the heritability of DCM (Supplementary Table 3). In a study of 240 Hungarian patients with DCM, including 31 patients with hereditary DCM identified through population screening using chest X-rays, and 209 patients with idiopathic DCM, survival at 6 years was significantly lower in the hereditary DCM group than in the idiopathic DCM group (6% vs. 23%; P<0.05). Michels et al conducted a study of 30 patients who had hereditary DCM identified through familial screening of echocardiographic findings and 71 patients with idiopathic DCM. During the follow-up period of 6.0 years, there was no significant difference in the survival rate between the hereditary DCM (51.5%) and idiopathic DCM (57.5%) groups. Moretti et al conducted a matched cohort study of 48 patients with asymptomatic hereditary DCM identified through a systematic
clinical and echocardiographic screening program and 96 idiopathic DCM patients. They found that the rate of survival free from heart transplant at 5 years was lower in the hereditary DCM group than in the idiopathic DCM group (76% vs. 91%, P=0.04). However, after stratification by NYHA class, the difference disappeared.4 Thus, it remained unclear whether or not heritability of DCM affected disease progression. Therefore, we conducted a prospective observational study that included 514 patients with DCM. Indeed, the incidence of major cardiac events and rehospitalization for HF was higher in the FHx group than in the no-FHx group. Furthermore, a propensity score-matched model showed that major cardiac events (HR, 4.48; 95% CI, 1.25–16.13; P=0.022) and rehospitalization for HF (HR, 3.38; 95% CI, 1.08–10.63; P=0.037) occurred in a significantly higher proportion of patients in the FHx group than in the no-FHx group. In addition, we showed that the FHx group had a higher prevalence of a diffuse LGE pattern than the no-FHx group. Diffuse LGE represents severe myocardial fibrosis, which is associated with poor prognosis in patients with DCM.24,25 Therefore, our study showed that patients with FHx identified through pedigree analysis are at high risk of having diffuse myocardial fibrosis and future cardiac events.

DCM is associated with remarkable genetic heterogeneity. The cumulative effect of multiple genetic variants may affect DCM;23 to date, >40 genes have been shown to cause DCM in humans.23 For example, variants in LMNA or RBM20 are associated with high penetrance and poor prognosis.24 Variants in TTN are the most common cause of DCM, and are associated with incomplete penetrance and often milder phenotypes.26 A recent study of a Japanese cohort showed that LMNA variants were associated with a higher prevalence of hereditary DCM (92% vs. 25%; P<0.001) and worse outcomes, including life-threatening arrhythmic events, than TTN variants.27 Thus, the DCM patients with FHx in our study might have genetic variants with high penetrance and poor prognosis. Further study with genetic testing is warranted to assess the mechanisms responsible for poor prognosis in patients with FHx.

The worse outcomes observed in patients with FHx than in those without FHx could be explained by genetic anticipation. In order to assess for the presence of genetic anticipation, further study is needed to collect clinical data, including information on genetic variants, to compare age of onset and DCM severity by generation.

Although pedigree analysis does not have enough sensitivity for hereditary DCM detection, this simple approach is efficient for identifying patients with a high risk of future cardiac events.

Study Limitations

First, this study was performed in a single, high-volume center, which introduces the possibility of referral bias. Second, the prevalence of FHx in our study (7.4%) was lower than in previous studies based on pedigree analysis.4,7,9 although we used the same criteria to diagnose FHx as a previous study.9 Haas et al showed statistically significant difference of DCM mutation even among 8 European countries.28 Thus, the difference of prevalence between our study and the other studies may be related to the genetic heterogeneity of DCM between Japanese and Western individuals. Third, it is possible that late onset may have masked the disease phenotype in asymptomatic relatives. This problem is difficult to resolve until all genetic etiologies of DCM have been discovered and assessed. Fourth, we did not perform any genetic examinations. According to a recent study with next-generation sequencing of 639 patients with DCM, genetic mutations were identified in 203 of 265 patients with hereditary DCM.29 Unfortunately, however, it is difficult to routinely offer genetic testing to patients with DCM even in a referral center in Japan. Future studies should address the clinical importance of genetic mutations in patients with FHx. Fifth, although lower eGFR has been reported as a prognostic factor for cardiac events in patients with chronic HF, patients with chronic renal insufficiency (eGFR <30 mL/min/1.73 m²) were excluded because of the risk of nephrogenic systemic fibrosis associated with gadolinium exposure. Finally, we did not perform further evaluation of diffuse fibrosis using T1 mapping to quantify fibrosis.20 Punnett et al20 showed that native T1 is significantly associated with all-cause death and HF events in patients with DCM. Future studies with T1 mapping should investigate the relationship between diffuse fibrosis and FHx.

Conclusions

Patients with FHx of DCM had a higher prevalence of severe myocardial fibrosis detected through LGE and worse prognosis than patients without FHx.

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Data Availability

The deidentified participant data will not be shared.

Disclosures

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**Supplementary Files**

Please find supplementary file(s): http://dx.doi.org/10.1253/circj.CJ-19-1176