Circulation Reports
Circ Rep 2022; 4: 405–411
doi:10.1253/circrep.CR-22-0074

ORIGINAL ARTICLE
Heart Failure

Stratification of Destination Therapy Candidates by J-HeartMate Risk Score Among Elderly Non-Responders to Cardiac Resynchronization Therapy

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Background: For elderly patients with refractory heart failure (HF), destination therapy (DT) with a continuous-flow left ventricular assist device (LVAD) is a possible treatment. The aim of DT is for long-term, satisfying quality of life on LVAD support. Previously, elderly non-responders to cardiac resynchronization therapy (CRT) were primarily destined for palliative care, but DT has been available in Japan since April 30, 2021. This study investigated the prognosis of elderly CRT non-responders and assessed the feasibility of DT in these patients based on the J-HeartMate Risk Score (J-HMRS).

Methods and Results: Of the 559 patients who underwent CRT at Tokyo Women's Medical University between 2000 and 2018, 198 were aged 65–75 years. Among these, 76 were identified as non-responders based on echocardiographic data, and were included in this study. We calculated patients' J-HMRS and investigated associations between the J-HMRS and cardiac events after CRT. Patients were divided into 3 groups according to the J-HMRS: low (n=23), medium (n=29), and high (n=24) risk. Patients in the low-risk group experienced as many HF rehospitalizations and ventricular arrhythmia events as those in the other groups. However, survival analysis revealed that, after CRT, survival was higher for patients in the low- compared with high-risk group (P=0.04).

Conclusions: The J-HMRS classified 30% of elderly CRT non-responders as low risk and as suitable candidates for DT in Japan.

Key Words: Cardiac resynchronization therapy; Destination therapy; Elderly; J-HeartMate Risk Score; Left ventricular assist device

The number of patients with heart failure (HF) is increasing rapidly worldwide, leading to the description of a global "HF pandemic".[1] Although the outcomes for ambulatory patients with HF with reduced left ventricular ejection fraction (LVEF) have improved following the introduction of multiple evidence-based drugs and device therapies, hospitalized patients with HF still have a high post-discharge mortality and readmission rate.[2] Heart transplantation (HT) may be considered for patients with severe refractory HF despite appropriate treatment.[3,4] HT in Japan is limited due to a severe donor shortage; nevertheless, the results are excellent, despite most recipients waiting a long time for transplantation, necessitating the use of a left ventricular assist device (LVAD) as a bridge to transplantation (BTT).[4,5] Some patients with severe HF are not indicated for HT because of liver or kidney dysfunction, obesity, cancer, or systemic diseases. In addition, HT is not recommended for patients aged >65 years in Japan. In Japan, destination therapy (DT) using an implantable LVAD is an option for patients with severe HF who are not approved as HT candidates, and has been covered by health insurance since April 30, 2021.[6,7] The REMATCH trial showed that using an LVAD for patients with advanced HF who were ineligible for HT resulted in a 48% reduction in the risk of death from any cause in the LVAD compared with medical therapy group.[8] Since the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial,[8] the use of LVAD as a DT has progressed rapidly in Europe and the US. DT is used to treat approximately 1,000 patients with severe HF per year in the US, and LVAD is used more frequently for DT

Received July 29, 2022; accepted August 1, 2022; J-STAGE Advance Publication released online August 26, 2022 Time for primary review: 3 days
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ISSN-2434-0790

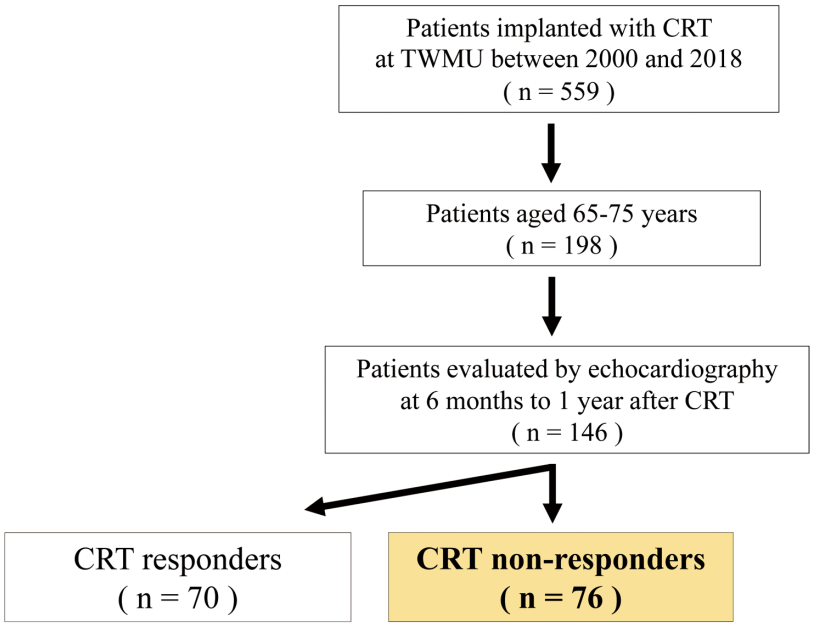

Figure 1. Flowchart showing patient selection in this study. CRT, cardiac resynchronization therapy; TWMU, Tokyo Women's Medical University.

than as a BTT.[9]

Cardiac resynchronization therapy (CRT) has been established as one of the treatments for drug-resistant patients with HF, regardless of eligibility for transplant.[10] In CRT responders, CRT significantly improves cardiac size and function; reverse remodeling of the left ventricle after CRT implantation has significantly reduced the risk of recurrent HF and death.[11,12] However, approximately 30% of patients are CRT non-responders, with poor prognoses;[13] thus, a new strategy needs to be established for these patients.

One selection criterion for DT in Japan involves risk assessment using the J-HeartMate Risk Score (J-HMRS). Particularly among the elderly (age ≥65 years), those determined to be at low risk using the J-HMRS are recommended as a reference group to carefully determine indications considering end-organ function and nutritional status.[7] The J-HMRS is based on the HeartMate II Risk Score (HMRS), which is a preoperative prognostic score calculated after HeartMate II (HM-II) implantation that is classified as low, medium, or high, with high scores indicating a poor prognosis after implantation.[14]

Considering the situation of patients with end-stage HF in Japan, the aim of this study was to investigate the prognosis of elderly CRT non-responders and assess the feasibility of DT in these patients according to the J-HMRS.

Methods

Patients

We retrospectively reviewed 76 elderly (age 65–75 years) non-responders to CRT (**Figure 1**). Among the 559 patients who underwent CRT implantation between 2000 and 2018, 198 were aged 65–75 years. CRT non-response is defined as echocardiography performed 6 months to 1 year after CRT implantation with no decrease of 15% or more in left ventricular end-systolic volume (LVESV).[15,16] Echocardiography was performed by experienced sonographers; left ventricular end-diastolic volume and LVESV were derived, and LVEF was calculated from the conventional apical 2- and 4-chamber images using the biplane Simpson's technique.[17] Patients without available echocardiography data at 6 months to 1 year after CRT implantation were excluded from the study (n=52). Among the remaining 146 patients, 76 were identified as non-responders based on the echocardiographic data described above. Patients were followed-up after CRT implantation until March 2020.

This study was approved by the Institutional Review Board of Tokyo Women's Medical University and was performed in accordance with the Declaration of Helsinki regarding investigations in humans.

J-HeartMate Risk Score

We calculated each patient's J-HMRS at the time of CRT implantation. The J-HMRS,[7] created as an adaptation of the HMRS,[14] was calculated as follows:

J-HMRS = 0.0274×age (years)−0.723×serum albumin (g/dL)+0.74×serum creatinine (mg/dL)+1.136×PT-INR+0.807×(0 or 1; 1 if LVAD center volume is <3 implants per 2 years)

where PT-INR is the prothrombin time-International Normalized Ratio and should be calculated in the absence of all anticoagulants under heparinization; however, the PT-INR in this retrospective study was calculated using actual measurements, with or without anticoagulants. Because our center performs ≥3 implants per 2 years, the J-HMRS was calculated using "0" for the "center LVAD volume" item. The J-HMRS cut-off values for the 3 risk groups were set as follows: low risk, J-HRMS <1.58; medium risk, 1.58<J-HMRS<2.48; and high risk, HMRS >2.48.[7]

Clinical Outcomes

The primary endpoint was all-cause mortality, whereas the

secondary endpoint was readmission for worsening HF, or ventricular arrhythmia events such as ventricular tachycardia (VT) or ventricular fibrillation (VF), including appropriate therapy by CRT with a defibrillator. Detailed causes of death were based on the clinical history obtained from the medical charts or information from affiliated hospitals. Death due to HF was defined as death in the context of clinically worsening signs or symptoms of HF with no other apparent cause. Sudden cardiac death was defined as unexpected endogenous death within 24 h after the last observation of being alive, unrelated to a specific cause of circulatory failure. Worsening HF was defined as new or progressive symptoms and signs of HF, such as dyspnea on exertion, orthopnea, fatigue, leg edema, rales, third heart sound gallops, and jugular venous distention, as well as the need for treatment with diuretics, vasodilators, positive inotropic drugs, or an intra-aortic balloon pump. Sustained VT was defined as a heart rate of >100 beats/min, a >30-s duration (or less if treated by electrocardioversion within 30 s) of VT on the electrocardiogram, or VT that required external defibrillation or intravenous antiarrhythmics, such as amiodarone and implantable cardioverter defibrillator (ICD) therapy, for termination. A review of the medical records validated the occurrence of these events after CRT implantation. Patients without available echocardiographic data from 6 months to 1 year after CRT implantation were excluded from the study; thus, patients who died within 6 months after CRT implantation were also excluded.

Statistical Analysis

Continuous data are presented as numbers, and categorical data are presented as the median and interquartile range (IQR). Patients in the study were divided into 3 groups based on the J-HMRS. One-way analysis of variance was used to compare continuous variables between groups, and the Kruskal-Wallis test was used for other variables among 3 groups. Categorical variables were analyzed using Chi-squared analysis, which was also used to analyze the event rate of all-cause death, HF hospitalization, and VT/VF between the 3 J-HMRS risk groups. Cumulative event-free rates were calculated using the Kaplan-Meier method, and differences in event-free rates were compared using the log-rank test. One-sided $P<0.05$ was considered significant. Data analyses were performed using SPSS version 22.0 (SPSS, Chicago, IL, USA).

Results

Distribution of J-HMRS

The distribution of J-HMRS among patients is shown in **Figure 2**. The mean J-HMRS was 2.2 points. There were 23 (30%), 29 (38%), and 24 (32%) patients in the low-, medium-, and high-risk groups, respectively.

Patient Characteristics at CRT Implantation

Patients' baseline characteristics are presented in **Table 1**. The mean age was 68 years, 68% of patients were male, and 25% of patients had dilated cardiomyopathy. The mean albumin concentration was 3.8 g/dL, the mean serum creatinine concentration was 1.1 mg/dL, and the median PT-INR was 1.8. The median B-type natriuretic peptide (BNP) concentration was 369 pg/mL; 57% and 33% of patients were classified as NYHA (New York Heart Association) functional class II and III, respectively. The mean LVEF

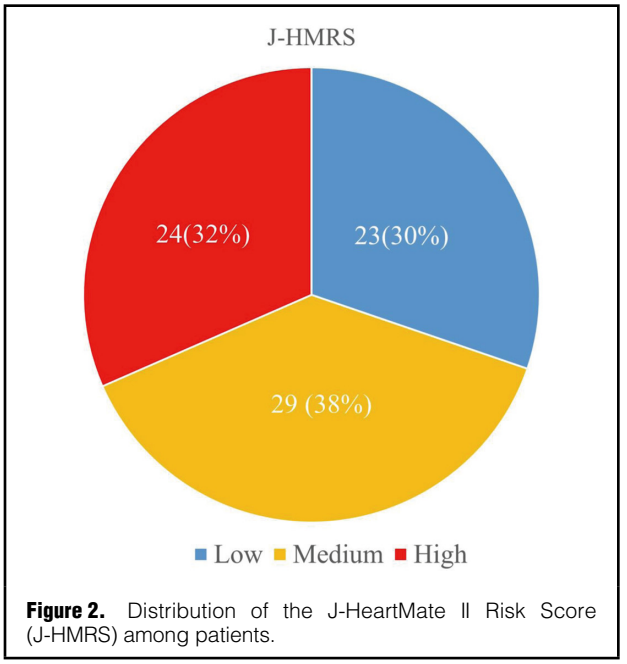

Figure 2. Distribution of the J-HeartMate II Risk Score (J-HMRS) among patients.

was 28%. Overall, 78% of patients underwent CRT with a defibrillator, whereas 22% received a CRT pacemaker (CRT-P) without defibrillation. Cardioprotective drugs, namely β-blockers and angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers, were prescribed in 72% and 78% of patients, respectively.

Patients' characteristics according to J-HMRS are also presented in **Table 1**. There was no significant difference in age, NYHA functional class, or LVEF among the 3 groups. The percentage of male patients and those on hemodialysis were significantly higher in the high- than low-risk group. PT-INR, serum creatinine, and BNP concentrations were significantly higher in the high- than low-risk group. Moreover, serum albumin and hematocrit levels were significantly lower in the high- than low-risk group. Regarding the medium-risk group, serum creatinine, albumin, hematocrit, and BNP concentrations did not differ significantly from values in the low-risk group. Regarding medications, the rate of warfarin use, which is strongly associated with PT-INR, was significantly higher in the high- and medium-risk groups than in the low-risk group.

Regarding the HMRS formula items, age did not differ significantly among the 3 groups. However, serum albumin, creatinine and PT-INR were higher in the high-risk group.

Clinical Outcomes After CRT Implantation

Patients' clinical outcomes after CRT implantation are presented in **Table 2**. During the median follow-up period of 1,125 days (IQR 629–1,719 days), 25 (33%) patients died, 45 (59%) were readmitted for worsening HF, 32 (54%) received appropriate ICD therapy for VT/VF, and 5 (29%) with CRT-P experienced VT/VF events. The median observation period from CRT implantation to death was 729 days (IQR 468–1,178 days). Of the 21 cardiovascular deaths, 18 were due to HF and 3 were due to sudden cardiac death.

Patients' clinical outcomes after CRT implantation according to J-HMRS are also presented in **Table 2**. The

Table 1. Baseline Characteristics of Participants (n=76)

	All (n=76)	J-HMRS			P value
		Low (n=23)	Medium (n=29)	High (n=24)	
Age (years)	68±3	67±3	69±3	68±3	0.441
Sex (male)	52 (68)	11 (48)	21 (72)	20 (83)*	0.027
Clinical diagnosis					0.574
Dilated cardiomyopathy	19 (25)	6 (26)	8 (28)	5 (21)	
Ischemic cardiomyopathy	20 (26)	4 (17)	7 (24)	9 (37)	
Valvular cardiomyopathy	16 (21)	4 (17)	8 (28)	4 (17)	
Others	21 (28)	9 (40)	6 (20)	6 (25)	
Sodium (mEq/L)	139±4	139±4	139±4	138±5	0.567
Creatinine (mg/dL)	1.1±1.7	0.8±0.3	1.1±0.3	1.6±2.7**	<0.001
Hematocrit (%)	37±5	40±5	37±4	34±6*	0.032
Albumin (g/dL)	3.8±0.5	4.0±0.4	3.8±0.4	3.5±0.5**	<0.001
PT-INR	1.8 [1.6–1.8]	1.1 [1.0–1.3]	1.9 [1.7–2.0]**	2.1 [1.8–2.3]**	<0.001
BNP (pg/mL)	369 [456–896]	222 [212–581]	337 [356–688]	518 [491–1,769]*	0.016
HD (%)	6 (8)	0 (0)	1 (3)	5 (21)*	0.016
NYHA functional class					0.394
II	43 (57)	14 (61)	16 (55)	13 (54)	
III	25 (33)	9 (39)	9 (31)	7 (29)	
IV	8 (10)	0 (0)	4 (14)	4 (17)	
LVEF (%)	28±10	28±10	30±10	26±11	0.600
CRT-D	59 (78)	16 (70)	24 (83)	19 (79)	0.513
Medications					
Warfarin	57 (75)	10 (43)	25 (86)**	22 (92)**	<0.001
Direct oral anticoagulants	1 (1)	1 (4)	0 (0)	0 (0)	0.311
ACE inhibitors/ARBs	59 (78)	15 (65)	23 (79)	21 (88)	0.180
β-blockers	55 (72)	19 (83)	16 (55)*	20 (83)	0.031
Mineralocorticoid receptor antagonist	48 (63)	19 (83)	18 (62)	11 (46)*	0.033
Loop diuretic	62 (82)	17 (74)	27 (93)	18 (75)	0.125
Amiodarone	28 (37)	8 (35)	10 (34)	10 (42)	0.839
Intravenous catecholamine	5 (7)	2 (9)	0 (0)	3 (13)	0.167

Unless indicated otherwise, data are given as the mean±SD, median [interquartile range], or n (%). *P<0.05, **P<0.01 compared with the low-risk group. ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; BNP, B-type natriuretic peptide; CRT-D, cardiac resynchronization therapy-defibrillator; HD, hemodialysis; J-HMRS, J-HeartMate II Risk Score; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PT-INR, prothrombin time-International Normalized Ratio.

Table 2. Clinical Outcomes After Cardiac Resynchronization Therapy Implantation

	All (n=76)	J-HMRS			P value
		Low (n=23)	Medium (n=29)	High (n=24)	
Mortality	25 (33)	4 (17)	10 (34)	11 (46)*	0.113
Heart failure	18 (72)	3 (75)	8 (80)	7 (64)	
Sudden death	3 (12)	0 (0)	1 (10)	2 (18)	
Non-cardiac death	4 (16)	1 (25)	1 (10)	2 (18)	
HF readmission	45 (59)	13 (57)	20 (69)	12 (50)	0.358
VT/VF	37 (49)	10 (43)	14 (48)	13 (54)	0.763

Unless indicated otherwise, values are shown as n (%). *P<0.05 compared with the low-risk group. HF, heart failure; J-HMRS, J-HeartMate II Risk Score; VF, ventricular fibrillation; VT, ventricular tachycardia.

mortality rate in the low-, medium-, and high-risk groups was 17%, 34%, and 46%, respectively. Although the mortality rate did not differ significantly between the 3 groups (P=0.113), the mortality rate was significantly higher in the high- than low-risk group (P<0.05). Kaplan-Meier curves for survival after CRT implantation in the 3 groups are shown in **Figure 3**. Patients in the high-risk group had increased mortality risk compared with those in the low-risk group (P=0.040). There was no significant difference in mortality rate between the low- and medium-risk groups, or between the medium- and high-risk groups. The HF readmission rate was 57%, 69%, and 50% in the low-, medium-, and high-risk groups, respectively, with no significant differences among the 3 groups. There were also no significant differences in VT/VF events, including ICD-appropriate therapy, among the 3 groups (**Table 2**).

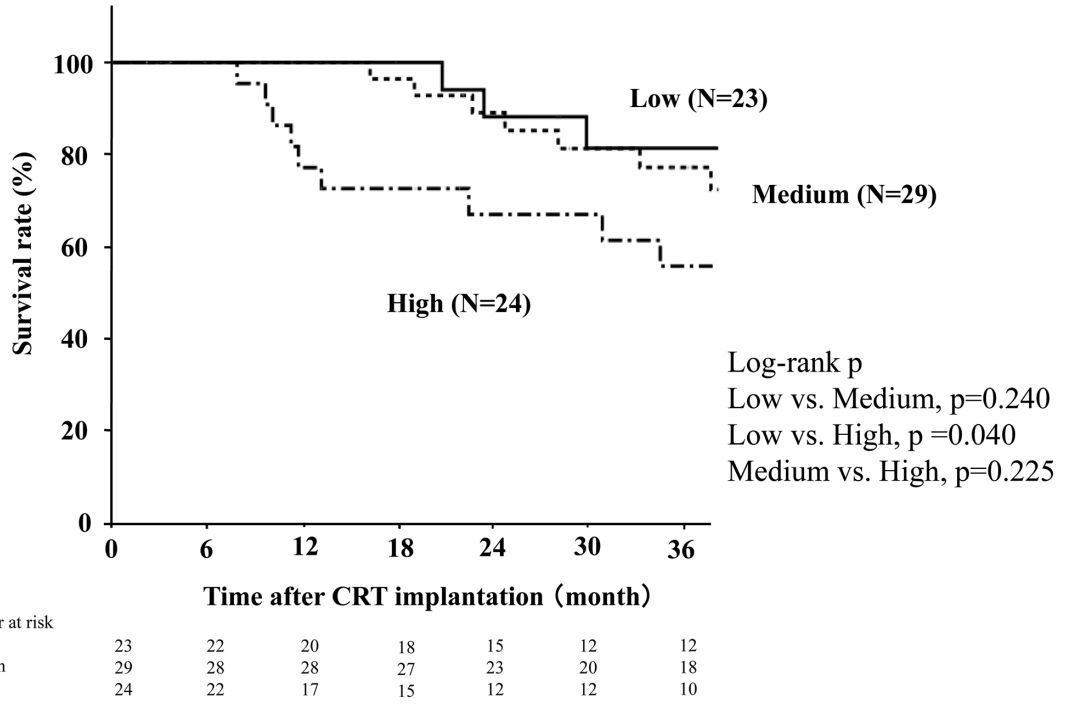

Figure 3. Kaplan-Meier analysis of survival after cardiac resynchronization therapy (CRT) implantation according to risk (low, medium, and high) based on the J-HeartMate II Risk Score.

Kaplan-Meier curves for the composite outcome of death, rehospitalization due to HF, and VT/VF after CRT implantation showed that there were no significant differences among the 3 groups (**Supplementary Figure**).

Discussion

In this study we clarified the clinical characteristics and prognosis of elderly CRT non-responders and the relationship between cardiac events and the J-HMRS, one of the criteria for DT indication in Japan. First, approximately one-third of patients were in the low-risk group based on the J-HMRS. Second, patients in the high-risk group had significantly higher PT-INR, creatinine, and BNP levels, and lower serum albumin and hematocrit, than patients in the low-risk group. In contrast, there were no significant differences in age, NYHA functional class, or LVEF at the time of CRT implantation among the 3 J-HMRS groups. Third, Kaplan-Meier analysis for survival after CRT implantation showed the survival rate was significantly higher among patients in the low-risk group than in the high-risk group. However, the incidence of rehospitalization due to HF and VT/VF was similar among the 3 J-HMRS groups.

As can be seen in the formula used to calculate the J-HMRS, this metric uses end-organ function, such as kidney and liver function, nutritional status, coagulopathy, and overall health to calculate a score. Original HMRS components (namely age, serum creatinine, PT-INR, and experience performing LVAD implants) have been used to predict the prognosis of HM-II implant patients (BTT and DT) in the US.[14] Because multivariable analysis in the previous study[14] showed that preoperative age, serum creatinine, albumin, PT-INR, and LVAD implanting center volume were correlated with overall survival during LVAD support, these parameters were used in the formula to predict outcome after LVAD implantation. Patients in the high-risk HMRS group also exhibited significantly worse outcomes than those in the low- and medium-risk groups.[14] These results suggested that the important predictors of successful LVAD outcomes are non-elderly age and preserved end-organ function. The J-HMRS, like the original HMRS, is useful for identifying patients who are too sick or too late for DT LVAD treatment. In addition, patients with severe right HF often exhibit renal, hepatic, and coagulation dysfunction; their J-HMRS is high, and they often need additional right ventricular assist devices after LVAD implantation.

According to the INTERMACS database, which enrolled patients who underwent durable mechanical circulatory support implant between 2006 and 2017, the mean survival for continuous flow LVAD patients is now approaching 5 years, although adverse events such as neurologic events, gastrointestinal bleeding, and infection, among others, continue to have a detrimental impact on the success of LVAD support.[9] In the present study, the mortality rate of the high-risk J-HMRS group was as high as 46% during the observation period of 1,125 days (IQR 629–1,719 days) after implantation of CRT. Although LVAD may improve the prognosis of high-risk J-HMRS patients, complications from LVAD implantation are known to occur more frequently in older patients,[18] those with preoperative end-organ dysfunction,[19,20] and those with malnutrition.[21] Moreover, adverse events after implantation of LVAD and

postoperative end-organ dysfunction are strongly associated with worse long-term survival.[22] DT LVAD treatment is an expensive treatment option, and careful patient selection is paramount. In the present study, elderly CRT non-responders in the low-risk J-HMRS group had low mortality, even though rates of HF readmission and the occurrence of ventricular arrhythmia were high. Implantation of LVAD in these patients is likely to reduce the incidence of worsening HF and ventricular arrhythmia events. Considering the balance between benefits and risks, it is reasonable that DT in elderly patients is indicated for those with low J-HMRS risk to prevent HF rehospitalization and improve their quality of life.

Kaplan-Meier analysis of survival after CRT implantation indicated no difference in mortality between the low- and medium-risk groups or between the medium- and high-risk groups. The results of the comparison of baseline characteristics showed that compared with patients in the low-risk group, patients in the medium-risk group had a higher rate of warfarin use (43% vs. 86%; P<0.01) and significantly higher PT-INR; however, no significant differences in creatinine or albumin levels were observed. A prior consensus report on DT in Japan proposed that PT-INR should be measured in the absence of all anticoagulants under heparinization when calculating J-HMRS.[7] Unfortunately, due to the retrospective nature of this study, we could not do this; thus, the J-HMRS in the present study was overestimated. In the report on the original HMRS,[14] warfarin use was considered in the calculation because it was also considered a dense postoperative risk. However, the rate of preoperative warfarin use was very low in that study.

Despite its many strengths, the present study has some limitations. First, this was a single-center retrospective study with a small number of cases enrolled over a long period. Second, there was a relatively low introduction of drug therapy, such as β-blockers and ACE inhibitors. The treatments administered were not controlled during this long sampling period, and thus may have influenced the outcome for these patients; potential confounding factors associated with time and era could not be completely excluded. Third, some patients were excluded from the study due to a lack of echocardiographic data after CRT implantation. Fourth, we calculated J-HMRS from data at the time of CRT implantation. Essentially, J-HMRS is calculated from data before LVAD implantation. Although HF status may change after CRT implantation, this study included only elderly CRT non-responders determined by echocardiographic data obtained 6 months to 1 year after CRT implantation. Once a patient is determined to be a CRT non-responder, DT LVAD should be considered as a treatment option to manage HF. Fifth, 6 (8%) patients on dialysis were included in this study. Because the creatinine level was included in the J-HMRS formula, a significantly higher number of patients on dialysis were included in the high-risk group. An analysis of 70 patients, excluding patients on dialysis, showed no significant difference in mortality rate among the 3 groups as part of the present study. However, the mortality rate was lowest in the low-risk J-HMRS group. Finally, HMRS is a formula for predicting postoperative prognosis created in the HM-II era.[14] In the current HM-3 era, it is known to further improve prognosis and reduce complications by LVAD.[23] Therefore, in the future, it may be possible to consider expanding the application of DT in Japan.

Conclusions

Overall, 30% of elderly CRT non-responders in this study were categorized into the low-risk group according to the J-HMRS, and were consequently eligible for LVAD as DT in Japan. It is important to consider the introduction of LVAD as DT with reference to the J-HMRS, considering the contribution of end-organ function and general condition to survival.

Acknowledgments

The authors thank the "BIND team", a multidisciplinary advanced HF treatment team at Tokyo Women's Medical University, for their support and helpful suggestions.

Sources of Funding

This study did not receive any specific funding.

Disclosures

N.H. is a member of *Circulation Reports*' Editorial Team. There are no other conflicts of interest to declare regarding this study.

IRB Information

This study was approved by the Ethics Committee of Tokyo Women's Medical University (No. 4159-R2).

Data Availability

The deidentified participant data can be made available upon reasonable request to the corresponding author.

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Supplementary Files

Please find supplementary file(s);
http://dx.doi.org/10.1253/circrep.CR-22-0074