Progressive Tricuspid Regurgitation and Elevated Tricuspid Regurgitation Pressure Gradient after Transvenous Permanent Pacemaker Implantation

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Abstract

Background The association of post-implant tricuspid regurgitation (TR) and heart failure (HF) hospitalization in patients without HF and preexisting abnormal TR and TR pressure gradient (PG) remain unclear. This study aimed to explore the clinical outcomes about progressive post-implant TR after permanent pacemaker (PPM) implantation.

Methods A total of 1,670 patients who underwent a single ventricular or dual-chamber transvenous PPM implantation at our hospital between January 2003 and December 2017 were included in the study. Patients with prior valvular surgery, heart failure (HF), and baseline abnormal TR and TRPG were excluded. Finally, a total of 1,075 patients were enrolled in this study. Progressive TR was defined as increased TR grade of ≥2 degrees and/or TRPG of >30 mmHg after implant.

Results 198 (18.4%) patients (group 1) experienced progressive post-implant TR and/or elevated TRPG, whereas 877 patients (group 2) did not have progressive post-implant TR. Group 1 had larger change in post-implant TRPG (group 1 vs. group 2; 12.8 ± 9.6 mmHg vs. 1.1 ± 7.6 mmHg; p < 0.001) than group 2. Group 1 had a higher incidence of HF hospitalization compared to group 2 (13.6% vs. 4.7%; p < 0.001). Pre-implant TRPG (HR: 1.075; 95% confidence interval (CI): 1.032-1.121; p = 0.001) was an independent predictor of progressive post-implant TR.

Conclusions After a transvenous ventricular-based PPM implantation, 18.4% of patients experienced progressive post-implant TR and/or elevated TRPG. Higher pre-implant TRPG was an independent predictor of progressive post-implant TR.

Background

In 1959, an endocardial transvenous lead was firstly introduced for permanent cardiac pacing, which has great benefits in reducing cardiac morbidity and mortality related to symptomatic bradycardia\(^1,\)\(^2\). However, the introduction of transvenous right ventricular pacing leads across the tricuspid valve can be associated with the development of tricuspid regurgitation (TR) and elevated tricuspid regurgitation pressure gradient (TRPG). Indeed, the prevalence of TR was increased in patients with transvenous permanent pacemaker (PPM) compared with the general population\(^3\). One previous report demonstrated that 21.2% of patients developed worsening TR degree after the transvenous lead implantation and a higher rate of worsening TR in patients with implantable cardioverter defibrillator (ICD) lead compared with PPM\(^4\). Another study showed that device type and number of leads placed did not affect the worsening degree of post-implant TR\(^5\).

The underlying mechanisms of transvenous cardiac pacing-related TR is not fully understood. Several mechanisms have been proposed that included a mechanical effect of the lead interfering the motion of the tricuspid leaflets, RV pacing-induced desynchronization\(^6,\)\(^7\) and leads related tricuspid leaflet injury or perforation, entanglement, impingement, or adherence to the tricuspid valve\(^6\). One study reported that
worsening TR occurred only in the chronic phase over 2 years, whereas another study reported a temporal trend toward increasing TR both acutely and chronically over 4 years after cardiac devices implantation\textsuperscript{5,8}. Therefore, the prevalence of increased degree of post-implant TR remains conflicting. Moreover, the association of post-implant TR and heart failure (HF) hospitalization in patients without HF and preexisting abnormal TR and abnormal TRPG remains unclear. Accordingly, we conducted this study to assess the prevalence of TR after cardiac device implantation and determine its clinical significance on HF hospitalization in a large retrospective cohort after transvenous ventricular-based PPM implantation.

**Methods**

**Patient population**

A total of 1,670 patients who underwent a single ventricular or dual-chamber transvenous PPM implantation at our hospital between January 2003 and December 2017 were included in this study. Patients with severe valvular heart disease and/or prior valvular surgery, HF and left ventricular ejection fraction (LVEF) <50%, dilated cardiomyopathy, hypertrophic cardiomyopathy, and preexisting abnormal (mild-moderate, moderate or severe) TR and abnormal (>30 mmHg) TRPG were excluded. Patients without follow-up records for PPM and without complete follow-up echocardiography were also excluded (Figure 1). Finally, a total of 1,075 patients were enrolled in this study and were divided into two groups: group 1 consisted of 198 patients with increased degree of post-implant TR ($\geq$2 degrees) and/or abnormal TRPG and group 2 consisted of 877 patients without increased degree of post-implant TR and abnormal TRPG.

Patients with dual-chamber PPM implantation underwent pacing in the dual chamber rate-adaptive mode, whereas patients with single ventricular PPM implantation underwent pacing in the ventricular-inhibited rate-adaptive mode. General demographics, comorbidities, lead positions, pacing QRS durations, pacing percentages, echocardiographic parameters, HF hospitalization, and cardiovascular and all-cause mortality were compared between the groups.

Baseline electrocardiographic (ECG) and echocardiographic parameters were obtained at nearest to the implant date. After implantation, pacing-lead locations were determined using anteroposterior, right-oblique, and left-oblique views under fluoroscopy. The pacing QRS duration was measured from the surface 12-lead ECG within 3 days after PPM implantation. Patients visited the outpatient department at regular intervals (3-6 months). PPM records were obtained at regular intervals, and the ventricular pacing percentage was obtained by telemetry.

**Ethical statement**

This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved for human research by the institutional review committee of Kaohsiung Chang Gung Memorial Hospital. All
patients were informed to be enrolled in our PPM registry when PPM implantation and did not need informed consent due to the retrospective study.

**Echocardiography**

Echocardiographic parameters, including left atrial (LA) dimension, LVEF, LV end-diastolic volume (LVEDV), and TR grade/TRPG, were measured using GE Vivid 9 or Philips IE33. LVEF and LVEDV were quantified by the M-mode and corrected by the two-dimensional guided biplane Simpson's method of disc measurements. Baseline echocardiography was performed before implantation. Follow-up echocardiography was performed at 2-year intervals thereafter in the absence of clinical events or at the onset of HF.

**Definition**

Progressive TR was defined as increased TR grade of ≥2 degrees and/or TRPG of >30 mmHg after implant, and TRPG of >30 mmHg was suggestive of possible pulmonary hypertension. Moderate TR (grade III) was defined as a regurgitant jet extending to less than half of the right atrium, whereas severe TR (grade IV) as a jet extending to more than half of the length of the right atrium. HF hospitalization was defined as the occurrence of HF events according to a New York Heart Association functional class of III or IV in the absence of other alternative diagnoses. HF symptoms were classified as the New York Heart Association functional class II-IV required medical treatment. Cardiovascular mortality was defined as sudden death related to arrhythmias, HF, and myocardial infarction. All-cause mortality was defined as death related to any cause, such as sudden death with undefined reasons, natural course, sepsis, malignancy, and cardiovascular disease.

**Study end-points**

The primary study endpoint was TR progression (TR grade ≥3) and/or abnormal TRPG levels (PG >30 mmHg). The secondary study end-points were late-onset atrial fibrillation, HF hospitalization, sudden death or ventricular tachyarrhythmias, cardiovascular mortality, and all-cause mortality.

**Statistical analysis**

Data are presented as mean ± standard deviation or numbers (percentages). Clinical characteristics of the study groups were compared using the t-test for continuous variables and Chi-square test for categorical variables. Kaplan-Meier curve analysis was performed with the log-rank test for HF
hospitalization and progressive TR in both groups during the follow-up period. Univariable and multivariable Cox regression analyses for HF hospitalization and progressive TR were performed to determine significant determinants. Multivariable Cox regression analysis included a hazard ratio (HR) < 0.100 for HF hospitalization and progressive TR in univariable Cox regression analyses. Statistical analysis was performed using statistical software (SPSS for Windows, Version 22), and a two-sided $p$-value of $<0.05$ indicated statistical significance.

Results

Baseline characteristics of the study participants

Baseline characteristics of the study participants are listed in Table 1. During a median 4.9 (interquartile range: 4.7-5.1) years follow-up, 198 (18.4 %) patients (group 1, mean age 72.1 ± 9 years; 59.6% female) experienced progressive post-implant TR, whereas 877 patients (group 2, mean age 71.9 ± 12 years; 49.8% female) did not have progressive post-implant TR. The percentage of female individuals was higher in group 1 than group 2. Additionally, the prevalence of atrial fibrillation (paroxysmal or non-paroxysmal) was also higher in group 1. A higher percentage of sick sinus syndrome for PPM was noted in group 1 (group 1 vs. group 2; 63.1% vs. 53.9%; $p=0.022$). There was no difference in the distribution of ventricular lead position, pacing QRS duration, ventricular pacing percentage, serum creatinine level and medication used between the 2 groups.

Pre-implant and post-implant echocardiographic parameters of study patients

At pre-implant, group 1 had significantly larger LA dimension (group 1 vs. group 2; 37.8 ± 6.6 mm vs. 36.7 ± 6.3 mm; $p = 0.063$) and significantly higher average TRPG (group 1 vs. group 2; 23.1 ± 4.9 mmHg vs. 20.7 ± 6.1 mmHg; $p < 0.001$) than group 1 (Table 2). The two groups did not differ in LVEDV and LVEF.

The median follow-up period was similar between the two groups (group 1 vs. group 2; 4.7 (4.4-5.4) years vs. 4.5 (4.2-4.8) years; $p = 0.610$). At post-implant, group 1 had significantly larger LA dimension, lower LVEF and more severe TR grade than group 2. Additionally, group 1 had significantly higher post-implant TRPG (group 1 vs. group 2; 35.9 ± 9.1 mmHg vs. 21.8 ± 5.4 mmHg; $p < 0.001$) and larger changes in post-implant TRPG (group 1 vs. group 2; 12.8 ± 9.6 mmHg vs. 1.1 ± 7.6 mmHg; $p < 0.001$) than group 2. Figure 2 showed the changes in pre-implant and post-implant TRPG in group 1 ($p < 0.001$).

Figure 3 shows the cumulative incident rate of progressive TR grade and/or abnormal TRPG from 1.3% in the first year to 18.4% in the sixth year in the study cohort.

Univariable and multivariable Cox regression analyses of predictors of progressive post-implant TR
Female gender, end stage renal disease, atrial fibrillation, larger pre-implant LA dimension, and higher pre-implant TRPG, were included for multivariable Cox regression analyses of progressive post-implant TR (Table 3). However, only pre-implant TRPG (HR: 1.075; 95% confidence interval (CI): 1.035-1.117; p = 0.001) was independent predictor of progressive post-implant TR (Table 3).

Compared to patients with pre-implant TRPG ≤25 mmHg, patients with pre-implant TRPG between >25 and ≤30 mmHg had 1.825 times (CI: 1.202-2.770; p=0.006) of relative risk of developing progressive post-implant TR during follow-up period.

Clinical outcomes of the study patients

During the follow-up period, group 1 had a significantly higher incidence of HF hospitalization compared to group 2 (13.6% vs. 4.7%; p < 0.001) (Table 4 and Figure 4). However, the incidence of late-onset atrial fibrillation, sudden death or ventricular tachyarrhythmias, cardiovascular mortality (group 1 vs. group 2; 5.7% vs. 4.1%; p=0.413), and all-cause mortality (group 1 vs. group 2; 16.2% vs. 14.1%; p=0.503) did not differ between the two groups during follow-up period (Table 4).

Univariable and multivariable Cox regression analyses of predictors of HF hospitalization

By univariable Cox regression analyses, older age, high body mass index, diabetes mellitus (DM), coronary artery disease (CAD), longer pacing QRS length, ventricular lead position at the lower septum and apex, larger pre-implant LA dimension and larger pre-implant LVEDV, larger post-implant LVEDV, lower post-implant LVEF, and progressive post-implant TR were significant predictors of HF hospitalization (Table 5). However, by multivariable Cox regression analyses, only older age (HR: 1.073; 95% CI: 1.037-1.110; p < 0.001) and CKD stage of >3 (moderate to severe CKD) (HR: 1.865; 95% CI: 1.008-3.450; p = 0.047) were independent predictors of HF hospitalization. Post-implant LVEF (HR: 0.957; 95% CI: 0.934-0.980; p < 0.001) was independently inversely associated with HF hospitalization in multivariable analysis. Progressive post-implant TR was significantly associated with HF hospitalization in univariable analysis (HR: 2.459; 95% CI: 1.511-4.000; p < 0.001) and had a non-significant trend toward HF hospitalization in multivariable analysis (HR: 1.694; 95% CI: 0.959-2.994; p = 0.070).

Discussion

In the present study, the cumulative rate of progressive TR ranged from 1.3% in the first year to 18.4% in the sixth year. Higher pre-implant TRPG (per 1 mmHg) was positively associated with progressive post-implant TR, which was associated with a trend toward HF hospitalization. Compared to patients with pre-implant TRPG ≤25 mmHg, patients with pre-implant TRPG between >25 and ≤30 mmHg had 1.825 times of relative risk of developing progressive post-implant TR during follow-up period.
TR occurs mainly due to annular dilation and right ventricular enlargement, often secondary to LV dysfunction from myocardial or valvular causes, right ventricular volume and pressure overload, and cardiac chamber dilations. Lead-related TR is an underdetermined problem and may be caused by lead-related tricuspid leaflet injury or perforation or lead entanglement, impingement, or adherence to the tricuspid valve. However, lead-related tricuspid valve injury could not be fully detected and was only observed in 12% of patients with PPM-related severe TR by transthoracic echocardiography. Kim et al. reported that abnormal TR developed in 21.2%, worsened TR by ≥1 grade in 24.2%, and progressed to severe TR in 3.9% of patients with initially normal TR. However, Al-Bawardy et al. reported a small but significant increase in the prevalence of moderate and severe TR, both acutely and chronically after a cardiac device implantation. Arabi et al. reported that TR was worsened by 1 grade in 70.8% and 2 grades in 17.1% of patients, and 19.5% of patients without baseline TR developed new-onset TR after the lead implantation in the follow-up period. In this study, the cumulative rate of progressive post-implant TR (increased TR grade of ≥2 degrees and/or TRPG of >30 mmHg) was from 1.3% in the first year to 18.4% in the sixth year. Moreover, higher pre-implant TRPG was an independent predictor of progressive post-implant TR. Pacing-induced electrical and mechanical dyssynchrony of LV can also result in TR and MR. However, in this study, pacing percentage and pacing QRS length was not associated with the development of progressive post-implant TR. Our previous study showed that right and left atrial sizes were larger in patients with atrioventricular dyssynchrony after pacing. Atrial enlargement is a well-known predictor of atrial fibrillation. Utsunomiya et al reported that functional TR with a structurally normal tricuspid valve may occur secondary to chronic atrial fibrillation and is associated with advanced age and right atrial enlargement. However, atrial fibrillation and LA size were not associated with the development of progressive post-implant TR in our study.

In one retrospective cohort study, significant lead-induced TR was associated with a significantly increased incidence of all-cause mortality and HF events in patients after PPM implantation. Other studies also reported post-implant TR to be an independent risk factor for late death. However, a significant proportion of patients in previous studies included patients with HF and receiving ICD and cardiac resynchronization therapy (CRT). Patients with ICDs and/or CRT devices usually have poor LVEF and advanced HF and consequently, higher incident HF hospitalization and mortality. In our study, we only enrolled patients receiving PPM implantation and excluded patients receiving ICD or CRT and those with prior history of HF, valvular heart disease and preexisting abnormal (mild-moderate, moderate or severe) TR and abnormal (>30 mmHg) TRPG. In this large cohort study, progressive post-implant TR was significantly associated with HF hospitalization in univariable analysis (HR: 2.459; 95% CI: 1.511-4.000; P < 0.001) and was associated with a non-significant trend toward HF hospitalization (p = 0.070) in multivariable analysis, and progressive post-implant TR was not associated with cardiovascular and all-cause mortality. Therefore, patients with preserved LV function and without valve disease underwent transvenous ventricular-based pacemaker implantation should have baseline echocardiography evaluation before implant and those with higher pre-implant TRPG should have more vigorously echocardiographic follow-up for the development of progressive post-implant TR.
Study limitations

One limitation of this study is its retrospective nature, including data from only one medical center. Because of older age, the all-cause mortality rate was relatively high in this study. Another limitation was the absence of baseline and follow-up right heart size and function by echocardiography. However, we still provided important information about lead-related post-implant TR progression and its associated outcomes in patients with transvenous ventricular-based PPM.

Conclusions

After a transvenous ventricular-based PPM implantation, 18.4% of patients experienced progressive post-implant TR and/or elevated TRPG. Patients with progressive post-implant TR had a higher incidence of HF hospitalization. Higher pre-implant TRPG was an independent predictor of progressive post-implant TR.

Abbreviations

TR: tricuspid regurgitation; TRPG: tricuspid regurgitation pressure gradient; PPM: permanent pacemaker; ICD: implantable cardioverter defibrillator; HF: heart failure; LVEF: left ventricular ejection fraction; ECG: electrocardiographic; LA: left atrial; LVEDV: LV end-diastolic volume; DM: diabetes mellitus; CAD: coronary artery disease; CRT: cardiac resynchronization therapy.

Declarations

Ethics approval and consent to participate

All procedures were following the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revisions. This study was already approved for human research by the institutional review committee of Kaohsiung Chang Gung Memorial Hospital and did not need informed consent due to the retrospective study.

Consent for publication

All authors agree with this publication.

Availability of data and material

The data was available when request to corresponding author.
Competing interests

None

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None

Authors' contributions

Data curation, HC Chen and HY Fang; formal analysis, WC Lee; investigation, WC Lee; methodology, WC Lee; project administration, WC Lee; resources, YL Chen, TH Tsai, KL Pan, YS Lin, WH Liu, MC Chen; supervision, MC Chen; validation, WC Lee; visualization, WC Lee; writing original draft, WC Lee; writing, reviewing and editing, MC Chen. All authors have read and approved the manuscript.

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Tables
Table 1
Baseline characteristics of the study patients

|                         | Group 1       | Group 2       | P value |
|-------------------------|---------------|---------------|---------|
|                         | (N = 198)     | (N = 877)     |         |
| **General demographics**|               |               |         |
| Age (years)             | 72.1 ± 9.4    | 71.9 ± 11.9   | 0.830   |
| Female sex (%)          | 118 (59.6)    | 437 (49.8)    | 0.015   |
| BMI (kg/m$^2$)          | 24.8 ± 3.9    | 25.0 ± 3.7    | 0.606   |
| **Risk factors**        |               |               |         |
| Hypertension (%)        | 150 (75.8)    | 623 (71.0)    | 0.190   |
| Diabetes mellitus (%)   | 68 (34.3)     | 299 (34.1)    | 0.934   |
| Hyperlipidemia (%)      | 41 (20.7)     | 176 (20.1)    | 0.845   |
| Prior stroke (%)        | 27 (13.6)     | 142 (16.2)    | 0.449   |
| Atrial fibrillation (%) | 74 (37.4)     | 249 (28.4)    | 0.016   |
| ESRD (%)                | 15 (7.6)      | 41 (4.7)      | 0.110   |
| PAOD (%)                | 5 (2.5)       | 18 (2.1)      | 0.595   |
| CAD (%)                 | 41 (20.7)     | 154 (17.6)    | 0.308   |
| CKD stage > 3 (%)       | 45 (22.7)     | 189 (21.6)    | 0.704   |
| **Indication of PPM**   |               |               | 0.022   |
| Sick sinus syndrome     | 125 (63.1)    | 473 (53.9)    |         |
| AV block                | 73 (36.9)     | 404 (46.1)    |         |
| **Lead position**       |               |               | 0.474   |
| Lower septum or apex (%)| 56 (28.3)     | 225 (25.7)    |         |
| High septum or near RVOT region (%) | 142 (71.7) | 652 (74.3)    |         |

Data are expressed as mean ± standard deviation or as number (percentage).
Abbreviation: BMI: body mass index; ESRD: end stage renal disease; CAD: coronary artery disease; PAOD: peripheral arterial occlusive disease; AV block: atrioventricular block; RVOT: right ventricular outflow tract; ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blocker.
|                                | Group 1   | Group 2   | P value |
|--------------------------------|-----------|-----------|---------|
|                                | (N = 198) | (N = 877) |         |
| **Pacing QRS duration (msec)** | 152.7 ± 30.1 | 150.2 ± 28.1 | 0.305  |
| > 150 mesc (%)                 | 109 (55.1) | 451 (51.4) | 0.387  |
| **Pacing percentage (%)**      | 48.5 ± 43.4 | 53.9 ± 44.4 | 0.243  |
| > 50%                          | 51 (25.8)  | 214 (24.4) | 0.715  |
| **Laboratory examination**     |           |           |         |
| Creatinine (exclude ESRD) (mg/dL) | 1.65 ± 1.12 | 1.50 ± 0.63 | 0.340  |
| **Medication**                 |           |           |         |
| ACEI/ARB use (%)               | 101 (51.3) | 439 (50.9) | 0.937  |
| β-blocker use (%)              | 44 (22.3)  | 197 (22.8) | 0.925  |

Data are expressed as mean ± standard deviation or as number (percentage).

Abbreviation: BMI: body mass index; ESRD: end stage renal disease; CAD: coronary artery disease; PAOD: peripheral arterial occlusive disease; AV block: atrioventricular block; RVOT: right ventricular outflow tract; ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blocker.
Table 2
Pre-implant and post-implant echocardiographic parameters of study patients

|                        | Group 1 (N = 198) | Group 2 (N = 877) | P value |
|------------------------|-------------------|-------------------|---------|
| **Pre-implant**        |                   |                   |         |
| LA dimension (mm)      | 37.8 ± 6.6        | 36.7 ± 6.3        | 0.063   |
| LVEDV (ml)             | 107.0 ± 31.9      | 106.9 ± 29.4      | 0.963   |
| LVEF (%)               | 69.1 ± 9.0        | 69.7 ± 8.3        | 0.437   |
| Average TRPG (mmHg)    | 23.1 ± 4.9        | 20.7 ± 6.1        | < 0.001 |
| The duration of follow-up (years) | 4.7 (4.4–5.4) | 4.5 (4.2–4.8) | 0.610   |
| **Post-implant**       |                   |                   |         |
| LA dimension (mm)      | 40.0 ± 6.4        | 37.2 ± 6.0        | < 0.001 |
| LVEDV (ml)             | 112.3 ± 41.8      | 111.0 ± 38.3      | 0.690   |
| LVEF (%)               | 61.2 ± 13.2       | 64.2 ± 12.2       | 0.006   |
| < 40%                  | 13 (6.6)          | 26 (3.0)          | 0.020   |
| TR grade               |                   |                   | < 0.001 |
| Severe (%)             | 21 (10.6)         | 0 (0)             |         |
| Moderate (%)           | 97 (49.0)         | 0 (0)             |         |
| Mild (%)               | 80 (40.4)         | 375 (42.8)        |         |
| Trivial or absence (%) | 0 (0)             | 502 (57.2)        |         |
| Average TRPG (mmHg)    | 35.9 ± 9.1        | 21.8 ± 5.4        | < 0.001 |
| Categories of TRPG (%) |                   |                   | < 0.001 |
| >55 mmHg               | 8 (4.0)           | 0 (0)             |         |
| 55 – 40 mmHg           | 35 (17.7)         | 0 (0)             |         |
| 40 – 30 mmHg           | 114 (57.6)        | 0 (0)             |         |

Data are expressed as mean ± standard deviation or as number (percentage).
Abbreviation: LA: left atrium; LVEDV: left ventricular end diastolic volume; LVEF: left ventricular ejection fraction; TRPG: tricuspid regurgitation pressure gradient.
|                                | Group 1 (N = 198) | Group 2 (N = 877) | P value |
|--------------------------------|-------------------|-------------------|---------|
| <30 mmHg                       | 41 (20.7)         | 0 (0)             |         |
| Changes in post-implant TRPG (mmHg) | 12.8 ± 9.6       | 1.1 ± 7.6         | < 0.001 |

Data are expressed as mean ± standard deviation or as number (percentage).
Abbreviation: LA: left atrium; LVEDV: left ventricular end diastolic volume; LVEF: left ventricular ejection fraction; TRPG: tricuspid regurgitation pressure gradient.

Table 3
Univariable and multivariable Cox regression analyses of predictors of progressive post-implant TR
|                      | Univariable analyses |                      |                      |                      | Multivariable analysis |
|----------------------|----------------------|----------------------|----------------------|----------------------|------------------------|
|                      | HR       | 95% CI  | p value | HR       | 95% CI  | p value |
| 1.485                | 1.086-   | 2.031   | 0.013   | 1.264    | 0.840-   | 0.262   |
| 1.001                | 0.988-   | 1.015   | 0.830   |                      |                        |                      |
| 0.988                | 0.946-   | 1.032   | 0.593   |                      |                        |                      |
| mellitus             | 1.011    | 0.731-   | 0.947   |                      |                        |                      |
|                      | 1.399    |                      |                      |                      |                        |                      |
| 1.274                | 0.892-   | 1.819   | 0.183   |                      |                        |                      |
| 1.071                | 0.740-   | 1.549   | 0.717   |                      |                        |                      |
| 1.671                | 0.906-   | 3.084   | 0.100   | 1.964    | 0.893-   | 0.093   |
| 1.505                | 1.092-   | 2.709   | 0.013   | 1.280    | 0.833-   | 0.260   |
| 1.071                | 0.533-   | 2.606   | 0.685   |                      |                        |                      |
| set                  | 1.119    | 0.533-   | 0.300   |                      |                        |                      |
| 2.606                |                      |                      |                      |                      |                        |                      |
| 1.226                | 0.834-   | 1.802   | 0.248   |                      |                        |                      |
| 0.997                | 0.992-   | 1.002   | 0.105   |                      |                        |                      |
| 0.715                | 0.477-   | 1.072   | 0.054   | 1.022    | 0.990-   | 0.188   |
| 1.003                | 0.997-   | 1.009   | 0.054   | 1.022    | 1.055   | 0.054   |
| 1.172                | 0.845-   | 1.626   | 0.342   |                      |                        |                      |
| 1.172                | 0.845-   | 1.626   | 0.342   |                      |                        |                      |
| 1.143                | 0.810-   | 1.613   | 0.448   |                      |                        |                      |
| 1.143                | 0.810-   | 1.613   | 0.448   |                      |                        |                      |
| nt LA                | 1.026    | 1.000-   | 0.961   |                      |                        |                      |
| 1.054                |                      |                      |                      |                      |                        |                      |
| nt LVEDV             | 1.000    | 0.995-   | 1.006   |                      |                        |                      |
| nt LVEF              | 0.992    | 0.972-   | 0.413   |                      |                        |                      |
|                      | 1.012    |                      |                      |                      |                        |                      |
| TRPG (per 1 mmHg) | 1.078 | 1.039-1.120 | < 0.001 | 1.075 | 1.035-1.117 | 0.001 |
|------------------|-------|--------------|---------|-------|--------------|-------|
|                   |       |              |         |       |              |       |
|                   |       |              |         |       |              |       |
|                   |       |              |         |       |              |       |
|                   | 1.016 | 0.746-1.385 | 0.919   | 0.972 | 0.671-1.409 | 0.882 |

Abbreviation: TR: tricuspid regurgitation; OR: odds ratio; CI: confidence interval; BMI: body mass index; CKD: chronic kidney disease; ESRD: end-stage renal disease; V: ventricular; LA: left atrium; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; TRPG: tricuspid regurgitation pressure gradient; ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin II receptor blocker.

### Table 4
Clinical outcomes of the study patients

|                               | Group 1 | Group 2 | P value |
|-------------------------------|---------|---------|---------|
|                               | (N = 198) | (N = 877) |
| Incidence of late-onset atrial fibrillation (%) | 8 (6.5) | 35 (5.6) | 0.672 |
| Incidence of HF hospitalization (%) | 27 (13.6) | 41 (4.7) | < 0.001 |
| Incidence of sudden death or VTAs (%) | 4 (2.1) | 23 (2.6) | 0.803 |
| Incidence of cardiovascular mortality (%) | 10 (5.7) | 32 (4.1) | 0.413 |
| Incidence of all-cause mortality (%) | 32 (16.2) | 124 (14.1) | 0.503 |

Data are expressed as number (percentage).

Abbreviation: HF: heart failure; VTAs: ventricular tachyarrhythmias.

### Table 5
Univariable and multivariable Cox regression analyses of predictors of HF hospitalization
|                      | Univariable analyses |                      |                      | Multivariable analysis |                      |                      |
|----------------------|----------------------|----------------------|----------------------|------------------------|----------------------|----------------------|
|                      | HR 95% CI p value    | HR 95% CI p value    |                      |                        |                      |                      |
| 0.951 0.591-1.530    | 0.836                |                      |                      |                        |                      |                      |
| 1.061 1.032-1.091    | < 0.001              | 1.073 1.037-1.110    | 0.001                |                        |                      |                      |
| 1.145 1.082-1.211    | < 0.001              |                      |                      |                        |                      |                      |
| Ellitius             | 2.729 1.692-4.402    | < 0.001              |                      |                        |                      |                      |
| n                   | 1.588 0.882-2.859    | 0.123                |                      |                        |                      |                      |
| Of 3                 | 1.634 0.970-2.755    | 0.065 1.865 1.008-3.450 | 0.047                |                        |                      |                      |
| 1.292 0.405-4.119    | 0.665                |                      |                      |                        |                      |                      |
| Atration             | 0.841 0.490-1.441    | 0.528                |                      |                        |                      |                      |
| -                    | -                    | -                    |                      |                        |                      |                      |
| Atery disease        | 2.773 1.685-4.562    | < 0.001              | 1.790 0.986-3.251    | 0.056                  |                      |                      |
| Entage               | 1.003 0.994-1.012    | 0.476                |                      |                        |                      |                      |
| -                    | -                    | -                    |                      |                        |                      |                      |
| Length               | 1.013 1.004-1.013    | 0.008                |                      |                        |                      |                      |
| -                    | -                    | -                    |                      |                        |                      |                      |
| Ion at the lower septum | 1.812 1.107-2.968 | 0.018 1.713 0.952-3.082 | 0.072                |                        |                      |                      |
| LA                   | 1.063 1.024-1.102    | 0.001                |                      |                        |                      |                      |
| LVEDV                | 1.010 1.002-1.017    | 0.014                |                      |                        |                      |                      |
| LVEF                 | 0.971 0.945-0.999    | 0.042                |                      |                        |                      |                      |
| TRPG                 | 1.020 0.968-1.075    | 0.448                |                      |                        |                      |                      |
|             | t LVEDV |       |       |       |       |
|-------------|---------|-------|-------|-------|-------|
|             | 1.017   | 1.013-| <     | 1.010 | 1.004-|
|             |         | 1.021 |       |       | 1.017 |
| t LVEF      | 0.923   | 0.907-| <     | 0.957 | 0.934-|
|             |         | 0.940 |       |       | 0.980 |
|             |         |       |       |       |       |
| post-implant TR | 2.459   | 1.511-| <     | 1.694 | 0.959-|
|             |         | 4.000 |       |       | 2.994 |
|             | 1.600   | 0.975-| 0.063 |       |       |
|             |         | 2.625 |       |       |       |
|             | 1.329   | 0.781-| 0.294 |       |       |
|             |         | 2.260 |       |       |       |

Abbreviation: HF: heart failure; HR: hazard ratio; CI: confidence interval; BMI: body mass index; CKD: chronic kidney disease; ESRD: end-stage renal disease; V: ventricular; LA: left atrium; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; TRPG: tricuspid regurgitation pressure gradient; ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin II receptor blocker.