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# Tricuspid Regurgitation and Mortality in Patients with Transvenous Permanent Pacemaker Leads

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## Abstract

Estimates of the prevalence and importance of significant tricuspid regurgitation (STR) related to implantable device leads are based mainly on case reports, small observational studies or mixed samples that include defibrillators. We sought to assess whether patients with permanent pacemaker (PPM) leads have an increased risk of STR and to determine mortality associated with PPM-related TR in a large longitudinal single-center cohort. We examined the prevalence of STR (defined as moderate-severe or ≥ 3+) among all echocardiograms performed between 2005 and 2011 excluding those with defibrillators. We then examined mortality risk according to the prevalence of PPM and STR after adjusting for cardiac co-morbidities, left ventricular (LV) systolic/diastolic function, and pulmonary artery hypertension. We screened 93592 echocardiograms (1245 with PPM) among 58556 individual patients (634 with PPM). The prevalence of STR was higher in patients following PPM placement (mean age 79 ± 3 years; 54%

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males) compared to patients without a PPM (adjusted odds ratio 2.32, 95% confidence interval [CI], 1.54–3.49; p<0.0001). Among patients with a PPM lead, the presence of STR was associated with increased mortality (adjusted hazard ratios [HR] 1.40, 95% CI 1.04–2.11, p=0.027 versus no STR). Compared to having neither a PPM lead nor STR, adjusted HR for death were 2.13 (95% CI, 1.93–2.34) for STR but no PPM, 1.04 (0.89–1.22) for PPM without STR, and 1.55 (1.13–2.14) for PPM with STR. In conclusion, in a sample comprising over 58,000 individual patients, PPM leads are associated with higher risk of STR after adjustment for LV systolic/diastolic function and pulmonary artery hypertension; similarly to STR from other cardiac pathologies, PPM-related STR is associated with increased mortality.

**Keywords**

Pacemakers; tricuspid regurgitation; echocardiography; mortality

## INTRODUCTION

Tricuspid regurgitation (TR) is a common valvular lesion with 1.6 million people in the US affected by at least moderate to severe TR.[1] It can be functional (secondary to right or left heart disease) or structural (from primary leaflet pathology).[1] Significant TR (STR) from unselected causes can be associated with worsening congestive heart failure and decreased survival.[2] Device-related STR usually results from either damage of the tricuspid valve (perforation/laceration of leaflets or lead entrapment resulting in scar tissue), or interference with valve coaptation.[3] Another proposed mechanism is asynchrony, resulting from abnormal right ventricular activation from a permanent pacemaker (PPM).[3, 4] Specifically, in patients paced in the ventricular demand mode, pseudo-TR can occur as a result of contraction of the atrium against a closed tricuspid valve, which can be corrected by restoring atrioventricular synchrony. When clinically significant, management typically involves percutaneous extraction of the offending leads[3] or surgical treatment in some patients with advanced valvular disease. Prior literature regarding lead-related STR following implantation of a PPM or other cardiac devices such as an implanted cardioverter defibrillator (ICD) and/or cardiac resynchronization therapy (CRT) device has important limitations. It is largely based on case reports or observational studies, often shows discordant results,[5] lacks data on outcomes,[5–9] or fails to include a control group without an implantable device.[10, 11] Similarly, some studies include patients with ICDs and/or CRT devices,[10, 11] who usually have depressed left ventricular (LV) systolic function and advanced heart failure, leading to strong confounding by indication. We sought to establish whether patients with transvenous PPM leads have an increased risk of STR and to determine all-cause mortality associated with lead-related TR in a large longitudinal single-center cohort.

## METHODS

A longitudinal single-center cohort was selected from 121040 consecutive echocardiograms (69412 individual patients) performed at the Beth Israel Deaconess Medical Center between January 2005 and December 2011. Echocardiographic reports were created and stored using

an in-house software system (ENCOR) that allowed targeted queries. Among patients with diagnosis of a “right atrial/ventricular wire” on echocardiography report, we excluded those with temporary leads, ICDs, and CRT devices using a combination of electrophysiology reports, ICD9 codes, and review of medical records. We also excluded patients who underwent PPM implantation but did not undergo post-implantation echocardiogram at our institution. Our final sample size was 93592 echocardiograms (85997 transthoracic and 7595 transesophageal studies) (1245 with PPM) among 58556 individual patients (634 with PPM). This study was approved by the Beth Israel Deaconess Medical Center Institutional Review Board which waived informed consent.

The following baseline clinical variables were extracted from the electronic echocardiographic reports: age, gender, body mass index, heart rate and systolic blood pressure. The following additional variables were obtained from ICD9 codes: number of hospitalizations in the previous year, history of coronary artery disease, myocardial infarction, hypertension and diabetes. Among the post-implantation characteristics of patients with PPM and STR, we assessed number of ventricular leads as demonstrated by chest X-ray and/or implantation reports.

All study participants underwent standard two-dimensional echocardiography with a commercially available system (Vivid 7 or Vivid i, General Electric Ultrasound, Fairfield, CT) that used a 2.5-MHz transducer. Images included parasternal, apical, and subcostal views for transthoracic studies. Pertinent cardiac structures were assessed by advancing the imaging plane from 0 to 150 degrees with the probe in the mid-esophagus for transesophageal studies. Valvular regurgitation was estimated visually for both transthoraric and transesophageal echocardiograms using color flow Doppler. In addition to TR (mild 1+, mild-moderate 1–2+, moderate 2+, moderate-severe 3+, severe 4+), echocardiographic characteristics included: right ventricular dilatation (basal diameter ≥ 4.2 cm) and visual systolic dysfunction, pulmonary artery systolic pressure (PASP) (assessed both as a continuous and categorical variable - moderate or more pulmonary hypertension defined as ≥ 37 mmHg), LV ejection fraction by visual estimation, mitral regurgitation (similar gradation to TR), mitral stenosis (mild, moderate, severe based on mitral valve area and/or mean transvalvular gradient), and presence of a mitral annular ring or prosthesis. In transthoracic studies, LV diastolic function was assessed by using transmitral flow Doppler velocities and tissue Doppler imaging-derived mitral annular velocities. Transmitral early (E) and late (A) diastolic velocities were obtained using pulsed-wave Doppler in the apical four-chamber view at the tips of the mitral leaflets. Peak early diastolic septal and lateral myocardial velocities were measured by tissue Doppler imaging and averaged to calculate the mean early diastolic myocardial velocity (E'). The E/E' ratio was then obtained as a measure of LV filling pressures. Significant diastolic dysfunction was defined as E/E' ratio ≥ 13. STR was defined as ≥ 3+ (moderate-severe or more). Previous literature has shown good interobserver variability[9, 12] in qualitative assessment of TR. PASP was calculated as the sum of the tricuspid jet gradient (assessed by Doppler) and right atrial pressure. Right atrial pressure was estimated by visualizing the inferior vena cava and its response to respiration. Patients with other causes of primary TR (tricuspid valve vegetation, ring, rheumatic deformity, Epstein anomaly or prolapse) were excluded.

We first assessed the prevalence of STR and the degree of TR change over time using the comparison between echocardiograms following PPM implantation and echocardiograms prior to PPM implantation or without PPM during the January 2005 and December 2011 time-frame. We then examined the risk of all-cause mortality among study patients from the time of their last echocardiogram through October 2014 according to prevalence of PPM and STR. Mortality assessment was based on internal medical records, with periodic links of our patient registries to the Social Security Death Index.

Clinical and echocardiographic characteristics were compared between the two groups (PPM and no PPM). We used t-tests to compare continuous variables and Fisher's exact tests to compare binary variables.

We first performed logistic regression to estimate the association of having a PPM with prevalence of significant TR. We accounted for repeated echocardiograms within-subject using generalized estimating equations (GEE). Multivariable models were estimated adjusting for age, sex, body mass index, systolic blood pressure, history of coronary heart disease, diabetes, hypertension, number of hospitalizations in the previous year, and echo parameters (LV ejection fraction, mitral regurgitation ≥ 3+, any degree of mitral stenosis, history of mitral valve repair or replacement, E/E' ratio ≥ 13, and PASP ≥ 37 mmHg). As a sensitivity analysis, we repeated our analysis of PPM and STR using a propensity score approach, greedy-matching subjects with a PPM on a 1:5 basis with those without one, and repeating GEE analyses with adjustment for remaining imbalances.

We next used the Bhapkar test to assess the change in the proportion of patients with 0–1+, 1–2+, 2+, 3+, and 4+, respectively, between pre- and post-implantation echocardiograms among the subset of patients with echocardiograms in both time periods. We also performed longitudinal analyses using GEE with an autoregressive correlation structure to assess the association between having a PPM and TR change over time (i.e., the TR × time slope). Patients with STR at entry were excluded from this analysis.

We performed multivariable logistic regression analysis to assess determinants of STR within the PPM group among clinical and echocardiographic characteristics. In these analyses we again used generalized estimating equations to account for multiple echocardiograms within-individual.

Finally, we used Cox proportional hazards models to examine associations of STR with death after adjusting for all the variables above except for PASP ≥ 37 mmHg (given the potential position of pulmonary hypertension as an intermediate between TR and death). All analyses were conducted using SAS version V9.3 (Cary, NC). A two-sided p value < 0.05 was the criterion for statistical significance.

## RESULTS

Baseline clinical characteristics of the study sample are summarized in Table 1. The PPM group (n=1245) was older, and had a higher prevalence of coronary artery disease, diabetes and hypertension compared to the group without PPM (n= 92347) (all p < 0.05). The number of all hospitalizations in the previous year was similar between the two groups.

Among the patients with PPM and STR, the majority (197/204 or 96%) had 1 ventricular lead and only 7 (3%) had 2 ventricular leads.

Echocardiographic characteristics are compared in Table 1 based on the presence of a PPM. The group with PPM had slightly lower average LV ejection fraction (but still above 40%), higher prevalence of mitral valve disease (treated or untreated), larger number of patients with a dilated or hypokinetic right ventricle, and higher PASP (all $p < 0.05$).

The prevalence of STR was over 2-fold higher in patients following PPM implantation compared to patients without PPM, even in highly-adjusted models (adjusted odds ratio [OR] 2.32, 95% confidence interval [CI], 1.54–3.49; $p<0.0001$). The association between STR and PPM remained highly significant (OR 2.48, CI 1.87–3.29; $p<0.0001$) even after potential over-adjustment for right ventricular dilatation and systolic dysfunction, which may be consequences of STR. In propensity score analyses comparing 1245 observations with a PPM to a matched group of 5471 without one, groups were similar except for modest significant differences in age, prevalence of coronary artery disease, mitral valve surgery, right ventricular dilation, and LV ejection fraction (Supplementary Table 1). The adjusted OR for STR in this matched group was 2.60 (2.05–3.30).

When we examined the predictors of STR within the PPM group, BMI, heart rate, history of mitral valve repair or replacement, ≥ 3+ MR, PASP ≥ 37 mmHg, and right ventricular dilatation remained significant in the multivariate regression analysis (Table 2).

Among the 169 patients with available pre- and post-implantation echocardiograms at our institution within the study timeframe, we observed a clear shift toward greater severity in TR in the first follow-up echocardiogram (Bhapkar $p < 0.0001$) (Figure 1). The mean number of years of post PPM implantation follow-up was 1.3 years (median 0.7 years). In addition, we observed a 2-fold greater change in TR over time among patients following PPM implantation (mean change of TR grade $0.06 \pm 0.03$ per year) compared to patients without a PPM ($0.03 \pm 0.002$), although this comparison was not statistically significant among the smaller sample of patients with repeated echocardiography ($p = 0.16$). The median number of years of post PPM implantation follow-up was 1.6 years with a maximum number of 7.8 years.

During 281102 person-years of follow-up, 8353 individuals (14%) died. Among patients with a PPM lead, the presence of STR was associated with an increased risk of death (adjusted hazard ratio [HR] 1.40, 95% CI 1.04–2.11, $p = 0.027$ versus no STR) (Figure 2). Compared to patients with neither a PPM lead nor STR, adjusted HRs for death were 2.13 (95% CI, 1.93–2.34) for those with STR but no PPM, 1.04 (0.89–1.22) for patients with PPM but no STR, and 1.55 (1.13–2.14) for those with both PPM and STR (Table 3). The HR for STR without a PPM compared with a PPM was numerically higher (i.e. 2.13 versus 1.55) but not statistically significant ($p = 0.06$).

## DISCUSSION

In our sample comprising over 58000 individual patients, PPM leads were associated with over 2-fold higher risk of STR after adjustment for age, cardiac co-morbidities, common

determinants of secondary TR, such as pulmonary hypertension, left sided systolic/diastolic dysfunction and mitral valve disease, and even right ventricular systolic function and cavity size, suggesting a strong and robust association.

Other studies have demonstrated an association of STR with an implantable device lead but have relied on smaller numbers or mixed samples including ICDs and CRT devices. Most of these studies have focused on change of TR following PPM implantation rather than on comparing TR in a group with and without a PPM lead.[8–11] Among the small studies with a referent group,[6,7] the prevalence of STR ranged between 25–29% in patients with a lead versus 12–13% without a lead ($p < 0.05$). Other investigators have not found evidence of worsening of TR with PPM implantation.[5,13] In our large, single-center longitudinal cohort, we focused our attention on patients with PPMs so as to tease out the mechanical or electrical effects of PPM leads from other determinants of STR (i.e. severe biventricular systolic dysfunction) characteristic of advanced heart failure patients in need for an ICD or CRT device.

Consistent with the 2-fold higher overall prevalence of STR among patients with PPM, the proportion of patients with STR increased from pre- to post-PPM lead implantation. In addition, when we examined the change of TR over time (TR slope), the steepness of the slope (or change of TR) was twice as high in patients with a PPM lead compared to patients without a PPM lead. The short available follow-up time following PPM implantation (median 1.6 years, with a maximal number of 7.8 years) may explain the lack of statistical significance of TR slope. Among the patients with STR and available information on the number of ventricular leads implanted (approximately 1/3 of PPM patients), only a minority (3%) had 2 ventricular leads. This small number likely did not affect the overall prevalence of PPM-related STR in our sample, as previously demonstrated.[10] As expected, left sided heart disease and consequent pulmonary hypertension with right ventricular dilatation contributed significantly to STR within the PPM group. Nevertheless, after adjustment for these common etiologies of secondary TR, the association between having a PPM and STR remained strong.

Our study demonstrates that PPM-related STR is not a benign epiphenomenon, but is associated with increased risk of death compared to having a PPM lead and no STR. Other studies have indicated that lead-related STR conveys adverse prognosis,[10, 11] but are limited by the lack of a control group and the use of mixed samples that include ICDs/CRTs. In our investigation, having a PPM lead alone does not pose any mortality risk compared to patients without a PPM or STR, but having a PPM *and* STR is associated with a risk of death almost as high as patients with STR unrelated to PPM. These findings suggest that excess mortality in PPM patients is due to STR per se, rather than the conditions presumed to be responsible for implantation of a PPM (i.e. conduction disease reflective of myocardial fibrosis from hypertension, coronary artery disease or diabetes). Finally, it is not surprising that patients with STR but no PPM have the highest risk of death, as having a PPM lead is arguably the most `benign' reason for STR in a patient population with prevalent cardiac co-morbidities.

The main strengths of our study are the large sample size and the longitudinal single cohort design which allowed for assessment of outcomes in a fairly homogeneous sample. The focus on patients with PPMs rather than ICDs and/or CRT devices enabled us to pursue a more accurate assessment of mortality in a population with predominantly normal biventricular systolic function and mild degrees of TR at entry. Finally, we carried out rigorous adjustment for confounders and repeated echocardiograms within-subject.

Knowledge of the high prevalence and negative outcomes of lead-related TR in a large study sample could improve patient care for several reasons. First, less traumatic implantation techniques[14] could be implemented based on a standardized protocol rather than operator preference. Second, PPM or ICD/CRT implantation is currently guided by fluoroscopy, not allowing targeted lead positioning relative to the tricuspid valve leaflets. Recent literature[15] demonstrates the role of 3-dimensional transthoracic echocardiography in identifying the location of lead-leaflet interference and its impact on TR severity. Routine 3-dimensional echocardiographic guidance of PPM lead implantation may reduce the incidence of lead-related STR. Third, patients with implanted leads could benefit from echocardiographic monitoring over the years, especially individuals with TR that predated PPM placement. No data regarding echocardiographic surveillance exist at this time. More aggressive medical therapy, specifically diuretics, could be used at earlier stages to prevent progression from moderate TR to STR. Lastly, novel approaches to cardiac pacing, specifically epicardial or leadless devices, may be preferred over conventional PPM therapy. Recent literature demonstrates that leadless pacemakers have very stable performance and reassuring safety results during intermediate-term follow-up.[16]

Our study has several limitations. First, given the retrospective nature of our investigation, exposure (PPM lead) could obviously not be randomized. Hence, residual confounding may be present, highlighting the need for prospective assessment of PPM-related STR and outcomes in future studies. Second, exclusion of subjects who did not undergo post-implantation echocardiography may have introduced bias toward inclusion of subjects with more cardiac pathology. Third, patients without a PPM are likely to receive less frequent echocardiograms, leading to missing information in the non-exposed group. Fourth, most of our clinical characteristics were identified by ICD9 codes, which are inevitably associated with human error.[17] Lastly, the etiology of PPM-related STR (leaflet impingement versus atrioventricular asynchrony) was not well characterized. As our study was based on echocardiographic data, information on the amount of atrial or ventricular pacing was not available.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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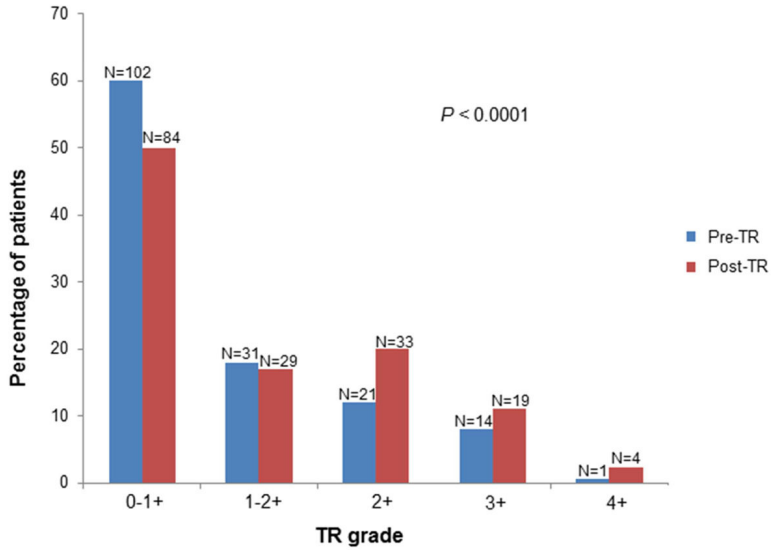


**Figure 1.**

Distribution of tricuspid regurgitation (TR) preceding (blue bars) and following (red bars) implantation of a permanent pacemaker lead.

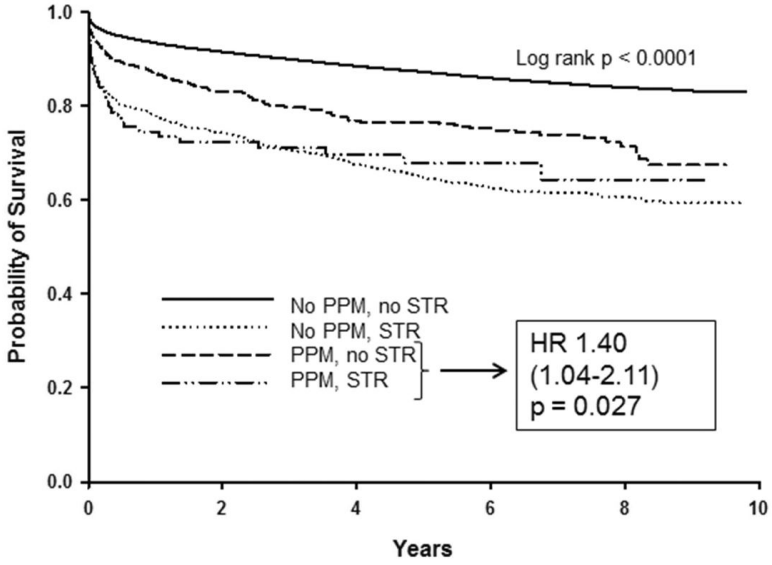


**Figure 2.**

Probability of survival according to prevalence of permanent pacemaker (PPM) lead and significant tricuspid regurgitation (STR). HR = hazard ratio.

**Table 1**

Clinical and echocardiographic characteristics according to permanent pacemaker or no permanent pacemaker lead

| | Permanent Pacemaker | | |
|---|---|---|---|
| **Variable** | **YES (N = 1245)** | **NO (N = 92347)** | ***P* value** |
| Age (years) | 80 ± 10 | 62 ± 17 | < 0.0001 |
| Men | 675 (54%) | 46017 (50%) | 0.002 |
| BMI (kg/m$^2$) | 27 ± 6 | 28 ± 7 | < 0.0001 |
| Hypertension | 427 (34%) | 22788 (25%) | < 0.0001 |
| SBP (mmHg) | 129 ± 41 | 126 ± 26 | 0.049 |
| Heart rate (beats/min) | 72 ± 14 | 74 ± 20 | < 0.0001 |
| Diabetes mellitus | 344 (28%) | 14535 (16%) | < 0.0001 |
| Coronary artery disease | 514 (41%) | 19363 (21%) | < 0.0001 |
| All hospitalizations | 0.13 ± 0.5 | 0.13 ± 0.6 | 0.89 |
| Tricuspid regurgitation ≥ 3+ | 204 (16%) | 2277 (2%) | < 0.0001 |
| Right ventricular dilatation | 356 (29%) | 9415 (10%) | < 0.0001 |
| Right ventricular dysfunction | 209 (17%) | 7055 (8%) | < 0.0001 |
| PASP (mmHg) | 35 ± 11 | 29 ± 11 | 0.002 |
| PASP ≥ 37 mmHg | 367 (29%) | 10757 (12%) | < 0.0001 |
| LVEF (%) | 48 ± 5 | 53 ± 5 | < 0.0001 |
| MV repair or replacement | 105 (8%) | 1811 (2%) | < 0.0001 |
| Any mitral stenosis | 41 (3%) | 1206 (1%) | < 0.0001 |
| Mitral regurgitation ≥ 3+ | 86 (7%) | 2901 (3%) | < 0.0001 |
| E/E' > 13 | 116 (9%) | 4344 (5%) | < 0.0001 |

BMI = body mass index; SBP = systolic blood pressure; PASP = pulmonary artery systolic pressure; LVEF = left ventricular ejection fraction; MV = mitral valve ; values expressed as mean ± SD (%).

**Table 2**

Multivariable regression analysis to predict significant tricuspid regurgitation within the permanent pacemaker group

| Variable | OR | 95% CI | *P* value |
|---|---|---|---|
| Age (per 10 years) | 1.50 | 1.06–2.13 | 0.02 |
| BMI (per 5 kg/m$^2$) | 0.71 | 0.54–0.95 | 0.02 |
| Heart rate (per 10 beats/min) | 1.17 | 1.01–1.36 | 0.04 |
| Right ventricular dilatation | 5.32 | 2.86–9.81 | <.0001 |
| PASP ≥ 37 mmHg | 2.16 | 1.31–3.56 | 0.003 |
| MV repair or replacement | 3.71 | 1.61–8.55 | 0.002 |
| Mitral regurgitation ≥ 3+ | 1.70 | 1.01–2.35 | <.0001 |

OR = odds ratio; CI = confidence interval; BMI = body mass index; PASP = pulmonary artery systolic pressure; MV = mitral valve. Male gender, hypertension, diabetes, coronary artery disease, all hospitalizations, right ventricular dysfunction, any mitral stenosis, and E/E' ratio ≥ 13 were not retained in the model (all p > 0.05).

**Table 3**

Mortality risk according to presence of a permanent pacemaker lead and significant tricuspid regurgitation

| | N deaths/N total | Multivariable adjusted HR (95% CI) compared to no PPM, no STR | P Value |
|---|---|---|---|
| No PPM, STR | 477/1161 | 2.13(1.93–2.34) | < 0.0001 |
| PPM, STR | 38/110 | 1.55(1.13–2.14) | 0.007 |
| PPM, no STR | 165/618 | 1.04(0.89–1.22) | 0.59 |
| No PPM, no STR | 7673/56667 | 1.0 (reference) | |

HR = hazard ratio; CI = confidence interval; PPM = permanent pacemaker; STR = significant tricuspid regurgitation.