Diabetes as a Risk Factor for Cardiovascular Events in Patients Receiving Permanent Pacemaker – A Propensity Score-Matched Cohort Study

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Abstract

Background:

Type 2 diabetes was associated with higher risk for permanent pacemaker (PPM) implantation. We aimed to compare the clinical outcomes between diabetic and non-diabetic patients receiving PPM treatment.

Methods:

Between January 2003 and December 2017, 1742 patients receiving naïve PPM treatment comprised this retrospective cohort study and were categorized into two groups by the presence or absence of diagnosis of diabetes: diabetic group (n=632, 36.3%) and non-diabetic group (n=1110, 63.7%). The primary outcome was cardiovascular events including heart failure (HF) hospitalization and acute myocardial infarction (AMI). Propensity score matching (PSM) was applied to reduce selection bias between the study groups.

Results:

During a mean follow-up of 7.8 ± 4.8 years, there were 264 cardiovascular events. A total of 746 patients with a 1:1 paired ratio between diabetic and non-diabetic groups were analyzed in the propensity score-matched series. After PSM, the incidence of cardiovascular events was higher in the diabetic group compared to the non-diabetic group (18.8% vs. 12.3%, $P=0.015$). Moreover, the incidence of HF hospitalization was higher in the diabetic patients compared to the non-diabetic patients (15.3% vs. 10.2%, $P=0.037$), whereas the incidence of AMI did not differ between the diabetic and non-diabetic groups (3.5% vs. 2.1%, $P=0.268$). After adjustments for covariates in multiple Cox regression analysis, diabetes remained as an independent predictor for cardiovascular events [hazard ratio, 1.54; 95% confidence interval, 1.04-2.29; $P=0.031$].

Conclusions:

In this cohort study of patients with naïve PPMs implantation, diabetes increased 1.54-fold risk of cardiovascular events in PPM recipients, especially for HF hospitalization.

Introduction

Diabetes mellitus is a serious chronic disease with an imperative influence on health of human being in the worldwide. Owing to ageing population, economic development and change of lifestyle, the growth in global and regional prevalence of type 2 diabetes markedly increased [1–4]. The number of patients with type 2 diabetes had doubled during the past two decades, and half of people with diabetes are not even aware that they have diabetes [1, 4]. Diabetes is a well-known risk factor for cardiovascular events, such as acute myocardial infarction (AMI) and heart failure (HF) [5, 6]. Previous studies demonstrated that lethal tachyarrhythmia occurs commonly in diabetic patients, possibly related to myocardial ischemia and sympathoadrenal activation in response to hypoglycemia [7–8]. On the other hand, an association between bradyarrhythmia and diabetes has also been reported, which is possibly caused by microangiopathy and increased cholinergic sensitivity [9–11]. From a national diabetes registry study, Rautio et al. reported that type 2 diabetes was associated with 1.6-fold higher risk for permanent pacemaker (PPM) treatment after adjustments for age, sex, and other factors [12]. However, the difference in cardiovascular outcomes between

type 2 diabetic patients and non-diabetic patients receiving PPM treatment remains unexplored. Moreover, type 2 diabetes as an independent risk factor for cardiovascular events in pacemaker recipients remains unexplored. Accordingly, we conducted this retrospective cohort study to investigate and compare the clinical outcomes between diabetic and non-diabetic patients receiving PPM treatment after propensity score matching (PSM). Moreover, this study also aimed to identify whether type 2 diabetes was a risk factor for cardiovascular events in PPM recipients.

Methods

Study population

This retrospective cohort study enrolled 2706 consecutive patients receiving cardiac implantable electronic devices implantation in our hospital between January, 2003 and December, 2017. A total of 964 patients, including 191 patients with implantable intracardiac defibrillators, 78 patients with cardiac resynchronization therapy and 695 patients with replacement of generator, were excluded (Figure 1). Finally, 1742 patients receiving single ventricular or dual chamber PPMs comprised this retrospective cohort study population and were categorized into two groups by the presence or absence of diagnosis of type 2 diabetes at the time of PPM implantation: diabetic group (n=632, 36.3%), and non-diabetic group (n=1110, 63.7%) (Figure 1). The standard protocol for PPM implantation in our center had been described in our previous study [15], mainly right ventricular lead placed at right ventricular outflow tract or high septum.

Definitions

Based on recommendations from the American Diabetes Association [16], diabetes was defined as prescription for oral antidiabetic drugs or insulin, or HbA1c $\geq 6.5\%$ (48 mmol/mol), or fasting plasma glucose level ≥ 126 mg/dl (7.0 mmol/L), or a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) with classic symptoms of hyperglycemia or hyperglycemic crisis during hospitalization for PPM implantation. According to the guidelines of Kidney Disease: Improving Global Outcomes [17], microalbuminuria was defined as at least two positive results obtained within 1 year and was defined as an albumin-to-creatinine ratio of 30-300 mg/g (3-30 mg/mmol); macroalbuminuria was defined as an albumin-to-creatinine ratio ≥ 300 mg/g (>30 mg/mmol). Estimated glomerular filtration rate (eGFR) was estimated from the creatinine value and calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [18]. Chronic kidney disease (CKD) was defined as eGFR lower than 60 mL/min/1.73m² without renal replacement therapy, and end-stage renal disease as the need for peritoneal dialysis, hemodialysis, or renal transplantation. Hyperlipidemia was defined as total cholesterol ≥ 240 mg/dL, low density lipoprotein ≥ 150 mg/dL, or triglyceride ≥ 200 mg/dL, or on lipid lowering medications [19]. Valvular heart disease was defined as moderate to severe regurgitation or stenosis of aortic, mitral or tricuspid valves. Cardiovascular surgery included coronary artery bypass graft and valvular surgery. Chronic lung disease was defined as a history of asthma, chronic obstructive pulmonary disease, or pulmonary fibrosis.

Clinical outcomes

The primary outcome of this study was cardiovascular events of patients after PPM implantation. Cardiovascular events included hospitalization related to HF event of New York Heart Association functional

class of III-IV, or AMI. The secondary outcomes of this study included pacing-induced cardiomyopathy, cerebrovascular accident, cardiovascular mortality and all-cause mortality. Pacing-induced cardiomyopathy was defined as a $\geq 10\%$ decrease of the baseline left ventricular ejection fraction (LVEF) with a resultant LVEF $< 50\%$. Cerebrovascular accident was defined as an episode of transient ischemic attack, ischemic stroke, intracranial hemorrhage, or any incident finding by images, including brain computed tomography or magnetic resonance imaging after PPM implantation. Cardiovascular mortality was defined as death from AMI, HF, refractory ventricular arrhythmias, or cardiac arrest. After PPM implantation, patients were followed up monthly for the first three months and then every three to six months until clinical outcomes of interest, death, loss to follow up, or the latest date in the dataset (31 December, 2020), whichever came first.

Study covariates

Baseline variables considered in the analyses included patient's age, sex, body mass index and comorbidities associated with clinical outcomes including hypertension, hyperlipidemia, coronary artery disease, HF, atrial fibrillation, valvular heart disease, chronic kidney disease, history of cardiovascular surgery, cancer, and chronic lung disease. The prescription for medication, such as beta-blocker, anti-hypertensive drugs, diuretic agents and lipid-lowering agents, laboratory data including hemoglobin and serum creatinine, the indication and lead number of PPM, baseline and pacing QRS duration were also obtained.

Statistical analysis

Continuous variables are expressed as a mean $\pm$ standard deviation or percentages. The clinical characteristics of the study groups were compared using the independent t-test for continuous variables and Chi-square test or Fisher's exact test for categorical variables. PSM was applied to reduce selection bias between the study groups. Using NCSS 10 Statistical Software (LLC, Kaysville, Utah, USA), the greedy method was used for matching at a 1:1 ratio between the study groups with a caliper width 0.2-fold the standard deviation of the propensity score between the study groups. The standardized mean difference was used to evaluate covariate balance after PSM, and a value of > 0.1 indicated meaningful imbalance after PSM [20]. The incidences of cardiovascular events during long-term follow-up were expressed with Kaplan-Meier survival curves and compared by log-rank test. The significance of each variable in predicting cardiovascular events was tested using the Cox proportional hazards model, analyzed with forward option. The multiple Cox regression analysis included parameters that had P values < 0.1 in univariate analysis. A two-sided P value < 0.05 was considered statistically significant. SPSS for Windows (version 22.0; SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis.

Results

Baseline characteristics of the study patients with and without type 2 diabetes

Table 1 lists the clinical characteristics of the study patients before and after PSM. Before PSM, the mean age of the patient population was 73 ± 11 years and 48.6% of the study patients were male. There were 632 (36.3%) diabetic patients, which were under diet control alone (12.8%), oral antidiabetic drugs (74.7%) or insulin-based therapy (12.5%), and 1110 (63.7%) non-diabetic patients (Figure 1). The diabetic group had more patients with overweight and higher prevalence of hypertension, hyperlipidemia, coronary artery disease, CKD

and end-stage renal disease (all $P<0.001$) compared to the non-diabetic group. The diabetic group also had a higher prevalence of history of HF ($P=0.033$), atrial fibrillation ($P=0.007$), and cerebrovascular accident ($P=0.028$) compared to the non-diabetic group. The diabetic group had more prescription for beta-blocker ($P=0.001$), angiotensin converting enzyme inhibitors/angiotensin receptor blocker (ACEi/ARB), diuretic agents, and statin (all $P<0.001$). The diabetic group had higher serum creatinine, hemoglobin A1c and triglyceride, and higher prevalence of albuminuria including microalbuminuria and macroalbuminuria (all $P<0.001$) compared to the non-diabetic group. The diabetic group had lower levels of hemoglobin, eGFR, low-density lipoprotein and high-density lipoprotein (all $P<0.001$) compared to the non-diabetic group. The diabetic group had higher prevalence of atrioventricular block ($P=0.001$), larger number of PPM leads ($P=0.025$) and wider baseline and pacing QRS durations ($P=0.037$ and $P=0.019$, respectively) compared to the non-diabetic group. The diabetic group had larger pre-procedural left atrial size ($P=0.010$) and LV end-diastolic volume ($P=0.049$), and lower pre-procedural LVEF ($P=0.042$) compared to the non-diabetic group (Table 1).

In the cohort after 1:1 PSM, 373 diabetic and non-diabetic pairs were analyzed. The baseline characteristics were balanced in the matched groups (Table 1). After PSM, the matched diabetic group still had lower low-density lipoprotein ($P=0.001$) and high-density lipoprotein ($P=0.005$) and higher triglyceride ($P=0.049$) levels as well as higher prevalence of albuminuria ($P<0.001$) compared to the matched non-diabetic group (Table 1).

Clinical outcomes of the study patients before and after PSM

During a mean follow-up period of 7.8 ± 4.8 years, before PSM, the incidence of cardiovascular events was higher in the diabetic group compared to the non-diabetic group (19.8% vs. 12.5%, $P<0.001$) (Table 2), and the incidences of pacing-induced cardiomyopathy, cardiovascular mortality, and all-cause mortality were all higher in the diabetic group compared to the non-diabetic group (Table 2). After PSM, the incidence of cardiovascular events was still higher in the diabetic group compared to the non-diabetic group (18.8% vs. 12.3%, $P=0.015$) (Table 2). The diabetic patients had a higher incidence of HF hospitalization compared to the non-diabetic patients (15.3% vs. 10.2%, $P=0.037$), whereas the incidence of AMI did not differ between the two groups (Table 2). After PSM, the incidences of secondary outcomes, including pacing-induced cardiomyopathy, cerebrovascular accident, cardiovascular mortality and all-cause mortality, did not differ between the two groups (Table 2). The Kaplan–Meier curve analysis for cardiovascular events showed that diabetic patients had a higher cumulative incidence of cardiovascular events compared to non-diabetic patients before and after PSM (log-rank test, $P<0.001$ and $P=0.001$, respectively) (Figure 2a and Figure 2d). Moreover, the diabetic group had a higher cumulative incidence of HF hospitalization compared to the non-diabetic group before and after PSM (log-rank test, $P<0.001$ and $P=0.005$, respectively) (Figure 2b and Figure 2e). However, the cumulative incidence of AMI did not differ between the two groups before and after PSM (Figure 2c and 2f).

Clinical predictors of cardiovascular events in the propensity score-matched patients receiving pacemakers

In this study, there were 264 cardiovascular events during follow-up (Table 2). Patients with cardiovascular events were older ($P=0.004$) and had higher prevalence of diabetes ($P=0.008$), coronary artery disease ($P<0.001$), history of HF ($P<0.001$), atrial fibrillation ($P=0.005$), CKD ($P<0.001$) and albuminuria ($P<0.001$), wider pacing QRS duration ($P=0.007$), larger pre-procedural left atrium ($P=0.035$) and LV end-diastolic volume ($P=0.037$), lower LVEF ($P=0.005$) and more prescription for ACEi/ARB ($P<0.001$) and diuretic agents ($P<0.001$) than patients without cardiovascular events (Table 3). After adjustments for age, sex, diabetes, coronary artery

disease, HF, atrial fibrillation, valvular heart disease, CKD, albuminuria, pacing QRS duration, pre-procedural left atrium and LV end-diastolic volume, LVEF, administration of ACEi/ARB and diuretic agents (all $P < 0.1$) in multiple Cox regression analysis, independent predictors of cardiovascular events were female [hazard ratio (HR), 1.72; 95% confidence interval (95% CI), 1.14-2.61; $P = 0.010$], diabetes [HR, 1.54; 95% CI, 1.04-2.29; $P = 0.031$], coronary artery disease [HR, 1.66; 95% CI, 1.09-2.52; $P = 0.017$], HF history [HR, 2.12; 95% CI, 1.38-3.53; $P = 0.004$], CKD [HR, 2.01; 95% CI, 1.32-3.07; $P = 0.001$], albuminuria [HR, 1.56; 95% CI, 1.00-2.43; $P = 0.049$], and prescription for ACEi/ARB [HR, 1.82; 95% CI, 1.19-2.78; $P = 0.006$] (Table 3).

Discussion

In this cohort study, the prevalence of diabetes was 36.3%, over one-third of naïve PPM recipients. During a mean follow-up of 7.8 ± 4.8 years, after PSM, the incidences of cardiovascular events and HF hospitalization were significantly higher in the diabetic group compared to the non-diabetic group. Moreover, the cumulative incidences of cardiovascular events and HF hospitalization were significantly higher in the diabetic matched group compared to the non-diabetic matched group. Furthermore, by multiple Cox regression analysis, diabetes remained as an independent predictor for cardiovascular events in patients after naïve PPM implantation.

The prevalence of diabetes in patients receiving pacemakers

The global prevalence of diabetes is rising from 8% in 1980 to 9.3% in 2019, and is estimated to be 10.9% by 2045, which may be attributable to population growth and ageing [1,2]. In the Taiwanese population, the annual prevalence of diabetes increased significantly from 5.8% in 2000 to 8.3% in 2007, especially in the subgroup of men, age ≥ 80 years, and individuals residing in aging society areas [3]. In the elderly ≥ 65 years, around 15%-20% of people live with diabetes [1,21]. In this study, PPM recipients were aged and the prevalence of diabetes was 36.3%, which was higher than general population [1-3,21] and was compatible with previous data of PPM recipients [13,14]. Moreover, similar to other reports [1-3,21], the trend in the prevalence of diabetes in this study, also increased from 28.8% (between 2003 and 2007) and 36.0% (between 2008 and 2012) to 41.4% (between 2013 and 2017).

Prior study reported that diabetes was possibly associated with sinus nodal dysfunction and cardiac conduction abnormalities [9-11,22]. Movahed et al. reported that the incidence of complete atrioventricular block in the diabetic patients was 1.1%, which was 3-fold increased risk compared to the non-diabetic patients [11]. Diabetic patients of this study had a higher prevalence of atrioventricular block compared to non-diabetic patients (44.0% vs. 35.8%, $P = 0.001$) (Table 1), similar to other reports [10-12]. From a national diabetes registry study, Rautio et al. reported that diabetes increased 1.6-fold risk for implantation of PPM after adjustments for age, sex, and other factors [12]. Therefore, type 2 diabetes is a risk factor for PPM implantation and vigilant follow-up for bradyarrhythmia in diabetic patients is necessary.

Heart failure hospitalization in diabetic patients after pacemaker implantation

The prevalence of diabetes in HF patients is around 20%, and diabetes increased 1.74-fold risk and 1.95-fold risk of HF in men and women, respectively [6,23]. The reasons for increasing risk of HF in diabetic patients included combined comorbidities such as hypertension, acceleration of the development of coronary

atherosclerosis, and diabetic cardiomyopathy, which was related to microangiopathy, metabolic factors or myocardial fibrosis [23]. Moreover, a study using the National Readmission Database showed that the most common cause for readmission in PPM recipients was HF hospitalization [24]. In this study, we showed that the incidence of HF hospitalization was significantly higher in the diabetic group compared to the non-diabetic group before and after PSM. Diabetic cardiomyopathy is characterized by diastolic relaxation abnormalities in its early stage and later systolic dysfunction [25]. The pathophysiological mechanisms of diabetic cardiomyopathy include systemic metabolic disorders, inappropriate activation of the renin–angiotensin–aldosterone system, subcellular component abnormalities, oxidative stress, inflammation and dysfunctional immune modulation and finally, interstitial fibrosis of cardiac tissue, which contributed to substantial cardiac stiffness with diastolic dysfunction and later, systolic dysfunction [25]. Furthermore, diabetes is an important phenotype for HF with preserved LVEF, and is also an independent predictor for HF hospitalization, despite under treatments of ACEi/ARB [26]. Interestingly, the study population in this study had preserved LVEF and the administration of ACEi/ARB was higher in the diabetic group compared to the non-diabetic group before PSM (Table 1). In this study, prescription for ACEi/ARB was an independent risk for cardiovascular events (Table 3). Of note, patients prescribed with ACEi/ARB were older and had higher prevalence of hypertension, hyperlipidemia and CKD, and had larger LV end-systolic volume and lower LVEF (even within the normal range) compared to those without prescribed with ACEi/ARB (supplementary Table 1), consequently worse clinical outcome. These findings deserve further investigations regarding angiotensin receptor-neprilysin inhibitor or sodium-glucose cotransporter 2 inhibitor in diabetic patients with preserved LVEF for PPM implantation [27,28].

Right ventricular pacing is associated with HF hospitalization [29]. Recently, physiological pacing, such as His bundle pacing, has been reported to reduce HF hospitalization compared to right ventricular pacing [30]. Our study was the first to show that diabetes was an independent predictor for cardiovascular events, including HF hospitalization, in patients after right ventricular PPM implantation. Our findings provided the hypothesis for future studies of physiological pacing in diabetic patients who required PPM implantation.

Other predictors for cardiovascular events in patients after pacemaker implantation

Previous studies reported that type 2 diabetes was associated with higher risk of HF in women than men [6,23]. There are several potential explanations including poorer glycemic control in women, under-treatment for diabetic women contributing to the development of diabetic cardiomyopathy, prolonged exposure to hyperglycemia during the prediabetic state in women, diastolic dysfunction of LV more common in women and deteriorations in major cardiovascular risk factors in women than in men [6]. In this study, women, compared with men, had a 1.72-fold increased risk for cardiovascular events (Table 3), which was compatible with other studies [6,23]. In diabetic patients with diabetic nephropathy, the risk of cardiovascular events increased by the decline of eGFR and the presentation of macroalbuminuria [31]. This study showed that CKD and presentation of albuminuria were independent risk factors for cardiovascular events (Table 3). Therefore, regular follow-up of renal function and serial measurement for albuminuria for PPM recipients, especially in women, is necessary.

Limitation

In this study, some potential limitations existed. First, although this was a retrospective single-center study, the sample size was large. Still, the potential bias inherent to nonrandomized investigations cannot be excluded. However, we performed PSM to minimize the bias between diabetic and non-diabetic groups. Second, the compliance period and dosage of prescription for beta-blocker, ACEi/ARB, diuretic agents, and statin during follow-up period were not available in this study. Third, the duration of diagnosed diabetes before PPM implant was unknown. Finally, the pre-procedural echocardiographic parameters of diastolic function by tissue Doppler or speckle-tracking imaging were not performed.

Conclusions

In this cohort study of patients with naïve PPMs implantation, the incidences of cardiovascular events and HF hospitalization were significantly higher in the diabetic group compared to the non-diabetic group. Moreover, diabetes increased 1.54-fold risk of cardiovascular events in PPM recipients, especially for HF hospitalization.

Abbreviations

ACEi/ARB: Angiotensin converting enzyme inhibitors/angiotensin receptor blocker; AMI: Acute myocardial infarction; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; HF: Heart failure; LVEF: Left ventricular ejection fraction; PPM: Permanent pacemaker; PSM : Propensity score matching

Declarations

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Authors' contributions

HCC contributed to analysis and interpretation of data., and wrote the manuscript. WHL and CHT contributed to discussion, reviewed and edited the manuscript. YLC, WCL, YNF, and SZC contributed to collection of data. MCC contributed to study design, and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Chang Gung Medical Foundation (permit number: 202100907B0).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Baseline characteristics of the study patients before and after propensity score matching

	Before matching				After matching			
	Diabetes (n=632; 36.3%)	Non- Diabetes (n=1110; 63.7%)	P value	SMD	Diabetes (n=373)	Non- Diabetes (n=373)	P value	SMD
Baseline characteristics								
Age, (years)	73 ± 9	73 ± 12	0.080	0.080	74 ± 9	75 ± 11	0.232	0.088
Male	300 (47.5)	547 (49.3)	0.467	0.030	185 (49.6)	190 (50.9)	0.714	0.027
Body mass index, (kg/m ²)	26 ± 4	24 ± 4	<0.001	N/A	25 ± 4	25 ± 4	0.046	N/A
Overweight (>30 kg/m ²)	59 (9.3)	44 (4.0)	<0.001	0.187	22 (5.9)	26 (7.0)	0.551	0.044
Underweight (<20 kg/m ²)	21 (3.3)	116 (10.5)	<0.001	0.248	17 (4.6)	21 (5.6)	0.505	0.049
Hypertension	524 (82.9)	716 (64.5)	<0.001	0.433	296 (79.4)	295 (79.1)	0.928	0.007
Hyperlipidemia	319 (50.5)	293 (26.4)	<0.001	0.567	160 (42.9)	163 (43.7)	0.825	0.016
Coronary artery disease	187 (29.6)	162 (14.6)	<0.001	0.368	79 (21.2)	74 (19.8)	0.650	0.033
Heart failure history	130 (20.6)	183 (16.5)	0.033	0.092	63 (16.9)	63 (16.9)	1.000	<0.001
Valvular heart disease†	27 (4.3)	68 (6.1)	0.101	0.081	19 (5.1)	21 (5.6)	0.745	0.024
Atrial fibrillation	219 (34.7)	457 (41.2)	0.007	0.188	143 (38.3)	147 (39.4)	0.764	0.022
Cerebrovascular accident	142 (22.5)	201 (18.1)	0.028	0.077	75 (20.1)	75 (20.1)	1.000	<0.001
Chronic kidney disease‡	291 (46.0)	396 (35.7)	<0.001	0.210	170 (45.6)	169 (45.3)	0.941	0.005
End-stage renal disease§	68 (10.8)	46 (4.1)	<0.001	0.254	20 (5.4)	20 (5.4)	1.000	<0.001
Chronic lung disease¶	27 (4.3)	54 (4.9)	0.572	0.073	14 (3.8)	16 (4.3)	0.709	0.027
History of cardiovascular surgery	31 (4.9)	55 (5.0)	0.963	0.014	17 (4.6)	16 (4.3)	0.859	0.013
History of cancer	74	121	0.607	0.055	45	51	0.512	0.048

	(11.7)	(10.9)			(12.1)	(13.7)		
Prescription for drugs								
Beta-blocker	121 (19.1)	146 (13.2)	0.001	0.177	64 (17.2)	51 (13.7)	0.187	0.097
ACEi/ARB	370 (58.5)	506 (45.6)	<0.001	0.297	212 (56.8)	203 (54.4)	0.507	0.049
Diuretic agents	212 (33.5)	257 (23.2)	<0.001	0.265	113 (30.3)	114 (30.6)	0.937	0.006
Statin	193 (30.5)	152 (13.7)	<0.001	0.439	89 (23.9)	95 (25.5)	0.610	0.037
Diabetic therapy								
Diet control alone	81 (12.8)				59 (15.8)			
Oral antidiabetic drugs	472 (74.7)				282 (75.6)			
Insulin-based therapy	79 (12.5)				32 (8.6)			
Laboratory data								
Hemoglobin, (g/dL)	12.0 ± 1.9	12.8 ± 1.9	<0.001	0.409	12.3 ± 1.9	12.2 ± 1.9	0.754	0.023
Serum creatinine, (mg/dL)	2.0 ± 2.1	1.4 ± 1.7	<0.001	0.301	1.7 ± 1.8	1.6 ± 2.0	0.732	0.025
eGFR, (mL/min/1.73m ²)	54 ± 30	67 ± 29	<0.001	N/A	58 ± 28	61 ± 29	0.171	N/A
HbA1c, (%)	7.1 ± 1.3	5.7 ± 0.4	<0.001	N/A	6.9 ± 1.1	5.7 ± 0.4	<0.001	N/A
LDL, (mg/dL)	90 ± 34	101 ± 34	<0.001	N/A	89 ± 33	101 ± 39	0.001	N/A
HDL, (mg/dL)	47 ± 13	53 ± 16	<0.001	N/A	48 ± 13	52 ± 15	0.005	N/A
Triglyceride, (mg/dL)	128 ± 87	103 ± 55	<0.001	N/A	124 ± 99	109 ± 59	0.049	N/A
Albuminuria, (mg/g)	141 (22.3)	70 (6.3)	<0.001	N/A	89 (23.9)	36 (9.7)	<0.001	N/A
Microalbuminuria	91 (14.4)	53 (4.8)	<0.001	N/A	58 (15.5)	25 (6.7)	<0.001	N/A
Macroalbuminuria	50 (7.9)	17 (1.5)	<0.001	N/A	31 (8.3)	11 (2.9)	0.001	N/A
Electrocardiographic and pacemaker data								
Patients with	278	397	0.001	0.282	154	156	0.882	0.011

atrioventricular block	(44.0)	(35.8)			(41.4)	(41.8)		
Number of pacemaker lead	1.9 ± 3.8	1.8 ± 3.8	0.025	0.107	1.9 ± 0.3	1.9 ± 0.3	0.661	0.034
Baseline QRS duration (ms)	103 ± 25	101 ± 24	0.037	0.127	103 ± 24	103 ± 25	0.928	0.007
Pacing QRS duration (ms)	167 ± 19	164 ± 19	0.019	0.154	165 ± 17	164 ± 18	0.180	0.098
Pre-procedural echocardiographic data								
LA size, (mm)	39 ± 7	38 ± 8	0.010	N/A	39 ± 7	39 ± 8	0.895	N/A
LVEDV, (ml)	114 ± 35	110 ± 38	0.049	N/A	114 ± 33	113 ± 39	0.676	N/A
LVESV, (ml)	39 ± 23	37 ± 38	0.065	N/A	38 ± 21	38 ± 24	0.898	N/A
LVEF, (%)	67 ± 12	68 ± 11	0.042	N/A	68 ± 11	67 ± 12	0.876	N/A

* Data are presented as mean ± SD or number (%) of patients.

† Defined as moderate to severe regurgitation or stenosis of aortic, mitral or tricuspid valves.

‡ Defined as eGFR lower than 60 mL/min/1.73m² without renal replacement therapy.

§ Defined as the need for peritoneal dialysis, hemodialysis, or renal transplantation.

¶ Defined as the history of asthma, or chronic obstructive pulmonary disease, or pulmonary fibrosis.

ACEi/ARB = angiotensin converting enzyme inhibitors/angiotensin receptor blocker, eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LA = left atrium; LDL = low-density lipoprotein; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; N/A = not applicable; SMD = standardized mean difference.

Table 2. Clinical outcomes of the patients with and without diabetes during a nearly 8-year follow-up period

	Before matching		After matching			
	Diabetes (n=632)	Non- Diabetes (n=1110)	P value	Diabetes (n=373)	Non- Diabetes (n=373)	P value
Primary outcome						
Cardiovascular events	125 (19.8)	139 (12.5)	<0.001	70 (18.8)	46 (12.3)	0.015
Heart failure hospitalization	94 (14.9)	112 (10.1)	0.003	57 (15.3)	38 (10.2)	0.037
Acute myocardial infarction	31 (4.9)	27 (2.4)	0.006	13 (3.5)	8 (2.1)	0.268
Secondary outcomes						
Pacing-induced cardiomyopathy	105 (16.6)	108 (9.7)	<0.001	64 (17.2)	46 (12.3)	0.063
Cerebrovascular accident	83 (13.1)	141 (12.7)	0.796	56 (15.0)	49 (13.1)	0.461
Cardiovascular mortality	56 (8.9)	69 (6.2)	0.040	25 (6.7)	21 (5.6)	0.543
All-cause mortality	186 (29.4)	238 (21.4)	<0.001	95 (25.5)	77 (20.6)	0.118

* Data are presented as number (%) of patients.

Table 3. Univariate and multivariate analyses of predictors of cardiovascular events in the propensity score-matched patients

Variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, (years)	1.03 (1.01-1.05)	0.004	1.02 (1.00-1.05)	0.056
Female	1.41 (0.97-2.04)	0.069	1.72 (1.14-2.61)	0.010
Body mass index, (kg/m ²)	0.98 (0.93-1.03)	0.393		
Hypertension	1.51 (0.92-2.50)	0.107		
Diabetes	1.65 (1.14-2.39)	0.008	1.54 (1.04-2.29)	0.031
Hyperlipidemia	1.33 (0.93-1.92)	0.123		
Coronary artery disease	2.11 (1.43-3.12)	<0.001	1.66 (1.09-2.52)	0.017
Heart failure history	2.93 (1.98-4.32)	<0.001	2.12 (1.38-3.53)	0.004
Atrial fibrillation	1.69 (1.18-2.44)	0.005	1.17 (0.78-1.75)	0.445
Valvular heart disease	1.92 (1.00-3.67)	0.050	0.65 (0.29-1.42)	0.275
History of cardiovascular surgery	1.38 (0.64-2.97)	0.406		
Cerebrovascular accident	0.86 (0.54-1.38)	0.530		
Chronic kidney disease	2.69 (1.83-3.97)	<0.001	2.01 (1.32-3.07)	0.001
Albuminuria	2.45 (1.62-3.70)	<0.001	1.56 (1.00-2.43)	0.049
Patients with atrioventricular block	1.27 (0.87-1.86)	0.213		
Pacing QRS duration (per 1 msec increment)	1.01 (1.00-1.02)	0.007	1.01 (1.00-1.02)	0.083
Pre-procedural left atrium, (mm)	1.02 (1.00-1.04)	0.035	1.01 (0.98-1.03)	0.629
Pre-procedural LVEDV, (mm ²)	1.01 (1.00-1.01)	0.037	1.00 (1.00-1.01)	0.212
LVEF (%)	0.98 (0.96-0.99)	0.005	1.00 (0.99-1.02)	0.645
Prescription for beta-blocker	1.33 (0.83-2.13)	0.243		
Prescription for ACEi/ARB	2.39 (1.58-3.62)	<0.001	1.82 (1.19-2.78)	0.006
Prescription for diuretic agents	2.07 (1.43-2.98)	<0.001	1.24 (0.82-1.87)	0.308
Prescription for statin	1.25 (0.83-1.88)	0.283		

*The definitions were the same as Table 1.

ACEi/ARB = angiotensin converting enzyme inhibitors/angiotensin receptor blocker. CI = confidence interval; HR: hazard ratio; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction.

Figures

Figure 1

Flow chart of enrollment of patients receiving cardiac implantable electronic devices. CIED, cardiac implantable electronic devices; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy

Figure 2

The Kaplan-Meier event-free survival curves of cardiovascular events (primary outcome) (Panel a, d), heart failure hospitalization (Panel b, e) and acute myocardial infarction (Panel c, f) between diabetic and non-diabetic groups before and after propensity score matching. PSM, propensity score matching

Supplementary Files

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- [SupplementaryTable1.docx](#)