

# Evaluation of Safety and Efficacy of Qinming8631 DR Implantable Cardiac Pacemaker in Chinese Patients: A Prospective, Multicenter, Randomized Controlled Trial of the First Domestically Developed Pacemaker of China

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## Abstract

**Background:** High cost of imported pacemakers is a main obstacle for Chinese patients suffering from bradyarrhythmia, and a domestically developed pacemaker will help lower the burden. This study aimed to evaluate the safety and efficacy of Qinming8631 DR (Qinming Medical, Baoji, China), the first domestically developed dual-chamber pacemaker of China, compared with a commercially available pacemaker Talos DR (Biotronik, Berlin, Germany) in Chinese patients.

**Methods:** A prospective randomized trial was conducted at 14 centers in China. Participants were randomized into trial (Qinming8631 DR) and control (Talos DR) groups. Parameters of the pacing systems were collected immediately after device implantation and during follow-ups. The effective pacing rate at 6-month follow-up was recorded as the primary end point. Electrical properties, magnet response, single- and double-pole polarity conversion, rate response function, and adverse events of the pacing system were analyzed. The Cochran-Mantel-Haenszel Chi-square test, paired *t*-test, and Wilcoxon signed-rank test were used for measuring primary qualitative outcomes and comparing normally and abnormally distributed measurement data.

**Results:** A total of 225 patients with a diagnosis of bradyarrhythmia and eligible for this study were randomly enrolled into the trial ( $n = 113$ ) and control ( $n = 112$ ) groups. They underwent successful pacemaker implantation with acceptable postoperative pacing threshold and sensitivity. Effective pacing rates of trial and control groups were comparable both in the full analysis set and the per protocol set (81.4% vs. 79.5%,  $P = 0.712$  and 95.4% vs. 89.5%,  $P = 0.143$ , respectively). In both data sets, noninferiority of the trial group was above the predefined noninferiority limit ( $-9.5\%$ ).

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**Conclusions:** This study established the noninferiority of Qinming8631 DR to Talos DR. The safety and efficacy of Qinming8631 DR pacemaker were comparable to those of Talos DR in treating patients with cardiac bradyarrhythmia.

**Key words:** Bradyarrhythmia; Cardiac Pacemaker; Qinming8631; Safety and Efficacy

## INTRODUCTION

Cardiac arrhythmia is a major clinical issue leading to considerable morbidity and mortality.<sup>[1]</sup> According to the statistics of American Heart Association, the incidence of bradyarrhythmia was reported to be 4%. It is estimated to affect 5.6–12.0 million people in 2050 and will lead to more than 400,000 annual sudden cardiac deaths in the United States.<sup>[2]</sup> Implanting a cardiac pacemaker is the most effective way for treating patients with bradyarrhythmia.<sup>[3-6]</sup> In the past decades, cardiac pacemakers has saved millions of patients suffering from cardiac bradyarrhythmia and has improved the quality of life of patients.<sup>[7]</sup>

An estimated 750,000 patients with cardiac bradyarrhythmia undergo cardiac pacemaker implantation every year all over the world.<sup>[8]</sup> Although the clinical application of pacemakers grew rapidly in China, the implantation cases was 35/1 million in 2012, which was significantly lower than the numbers in Europe (951/1 million in 2010).<sup>[9]</sup> Although great progression has been made in China at the field of cardiac device implantation,<sup>[10-13]</sup> we have to recognize that only 3% patients with symptomatic cardiac bradyarrhythmia undergo pacemaker implantation. The high cost of imported pacemakers was found to be the major reason holding Chinese people from pacemaker implantation. A domestically manufactured pacemaker with much lower cost would help more Chinese patients benefit from cardiac pacing.<sup>[14]</sup>

The Qinming8631 DR implantable cardiac pacemaker (Qinming Medical, Baoji, China) is the first domestically developed dual-chamber rate-responsive pacemaker in China. It has been qualified by the General Administration of Quality Supervision, Inspection and Quarantine of the People's Republic of China.

This study aimed to evaluate the safety and efficacy of the Qinming8631 DR implantable cardiac pacemaker. The commercially available Talos DR (Biotronik, Berlin, Germany) pacemaker was used as control, and noninferiority of the Qinming8631 DR to Talos DR pacemaker in Chinese patients was tested.

## METHODS

### Study design

This prospective, multicenter, randomized controlled, single-blind, noninferiority study was conducted at 14 clinical sites in China between September 2013 and December 2014. Through a central stratified random sampling, enrolled patients were assigned into trial (Qinming8631 DR)

or control (Talos DR) groups. Clinical follow-up visits were conducted at 1, 3, and 6 months after pacemaker implantation in all patients. The protocol was conducted in accordance with the *Declaration of Helsinki* (2013 No. 007) and approved by the Institutional Review Board at the Second Affiliated Hospital of Zhejiang University School of Medicine (Hangzhou, China) and the institutes that participated in the clinical trial. Every patient signed written informed consent. Data were collected at each clinical site by a third-party analyzer who was responsible for data processing and statistical analysis.

Bipolar passive and active fixation pacing leads were used in this study. In the trial group, QM7222 (Qinming Medical, Baoji, China) was used as the atrial electrode lead and QM7211 (Qinming Medical, Baoji, China) active lead as the ventricular electrode lead. In the control group, Selox JT (Biotronik, Berlin, Germany) was used as the atrial electrode lead and Setrox S (Biotronik, Berlin, Germany) as the ventricular electrode lead. The effective pacing rate, defined as acceptable pacing capture threshold and sensing amplitude, at the 6-month follow-up was recorded as the primary end point. Electrical properties, magnet response, single- and double-pole polarity conversion, rate response function, and adverse events of the pacing system after implantation were collected and analyzed at the end of the study. All-cause mortality, cardiovascular death, and pacemaker-related adverse events were reported by each center and analyzed at the end of the study.

### Study population

#### Inclusion criteria

Patients were deemed eligible for the enrollment in the trial if they (1) suffered from bradyarrhythmia due to sick sinus syndrome (SSS) or atrioventricular (AV) block and indicated for dual-chamber pacemaker implantation; (2) were 18–85 years old; (3) signed the informed written consent; and (4) were capable of finishing 6 months of follow-up.

#### Exclusion criteria

Patients were excluded from the study if (1) they had tricuspid atresia; (2) the tricuspid valve was replaced with a mechanical valve; (3) auricular appendix was absent; (4) they had persistent atrial fibrillation; (5) they had indications for implantable cardioverter defibrillator; (6) they were contraindicated to 1.0 mg dexamethasone; (7) they were pregnant or lactating; (8) they had a life expectancy of <1 year; (9) they had coagulation dysfunction; (10) they had high-sensitivity carotid sinus syndrome and neurocardiogenic syncope; (11) they had intracardiac mural thrombus or suffered from ventriculotomy or atriotomy in the last 4 weeks; (12) they had heart transplantation,

neuromuscular diseases, sleep apnea syndrome, and cardiac sarcoidosis; (13) they had acute or severe infection, malignant tumor, or end-stage diseases; (14) they used other medical devices that might interfere with the pacemaker; or (15) they had any other conditions unsuitable for the trial as considered by researchers.

## Efficacy assessments

### Primary end points

The effective pacing rate at the 6-month follow-up was used to be the primary end point. It mainly comprised the following parameters:

1. Acceptable pacing threshold (acute): With 0.5 ms of the pulse width, the pacing threshold of the right atrium was  $\leq 1.5$  V and the threshold of the right ventricle was  $\leq 1.0$  V. When the voltage outputs were set to two times the pulse amplitude of the measured pacing threshold, the target atrium or ventricle was continuously captured and observed on a surface electrocardiogram (ECG)
2. Acceptable long-term threshold: When the pulse width was 0.5 ms, the pacing threshold of the right atrium was  $\leq 1.5$  V (fluctuated upward  $\leq 20\%$ ) and the threshold of the right ventricle was  $\leq 1.0$  V (fluctuated upward  $\leq 20\%$ ). When the voltage outputs were set to two times the pulse amplitude of the measured pacing threshold, the target atrium or the ventricle was continuously captured and observed on a surface ECG at 1, 3, and 6 months after the procedure
3. Postoperative sensing: The sensitivity threshold of right atrium was  $\geq 2.0$  mV and the threshold of the right ventricle was  $\geq 4.0$  mV. When the sensitivity was set at 1/3–1/4 of the sensitivity threshold (should not exceed the setting range advised by the manufacturer), an electrocardio signal could be effectively perceived
4. Magnet response: Magnet response of the pacemaker at 3 months after the procedure was evaluated
5. Polarity conversion (unipolar and bipolar): Unipolar and Bipolar conversion of the pacemaker at 3 months after the procedure was evaluated
6. Rate response: Rate response of the pacemaker at 6 months after the procedure was evaluated.

### Secondary end points

1. Failure to pace as detected by the 24-h ambulatory ECG at 6 months
2. Failure to sense as detected by the 24-h ambulatory ECG at 6 months.

## Safety assessments

Safety assessments were conducted by recording all-cause death, cardiovascular death, and pacemaker-related adverse events within 6 months after the procedure. Moreover, the clinical symptoms, vital signs (blood pressure and heart rate), and laboratory parameters were monitored. If abnormal changes were noted, their correlation with the pacemaker was analyzed. Laboratory parameters included complete blood count, liver function, renal function, and blood clotting tests.

## Statistical analysis

### Sample size estimation

On the basis of clinical experience, this study hypothesized that the effective pacing rate in the control group was 95% (taking into account the incidence of lead-related complications), and the noninferiority margin was 9.5%. The sample size in each group would have a power of 0.80 with a level of significance of 0.05; if the expected dropout rate was 10%, the final sample size was 100 in each group.

### Analysis of population

The full analysis set (FAS) comprised cases in accordance to the principle of “intention to treat,” including all the enrolled patients. For patients without the primary effect assessment, the last observation carried forward (LOCF) was conducted to carry forward the missing data. The per protocol set (PPS) was a subgroup of enrolled patients completing the trial. The safety analysis set (SAS) included cases with at least one result of safety evaluation during the follow-up.

### Statistical analysis method

All continuous values were presented as mean  $\pm$  standard deviation (SD), and all categorical variables were presented as number of patients (percentages). Group comparisons of categorical data were conducted by Cochran-Mantel-Haenszel Chi-square test or Fisher’s exact test (when 25% of the cells have expected frequencies of  $<5$ ); group comparisons of normally distributed measurement data were analyzed by student *t*-test; and group comparisons of abnormally distributed measurement data were analyzed by Wilcoxon signed-rank test. Data management was conducted by the EpiData 3.0 software (The EpiData Association, Odense, Denmark). Data analysis was done using the SAS 9.13 software (SAS Institute Inc., Cary, USA). A two-sided  $P \leq 0.05$  was considered statistically significant.

### Analysis of efficacy

For primary quantitative outcome measurements, group comparisons were conducted by analysis of covariance. After testing the homogeneity of variance of each center, the least mean square (LMS), LMS error between groups, and 95% confidence interval (CI) of dependent variable were calculated. For primary qualitative outcome measurements, the Cochran-Mantel-Haenszel Chi-square test, adjusting the influence of center, was conducted and differences in the event rate between groups and the 95% CI were calculated. To evaluate the proposed noninferiority of the trial instrument, 95% CI of group variances of outcome measurements was compared with the critical value, which was clinically meaningful and specified preliminary in the trial. For other outcome measurements, comparison of the normally distributed measurement data in a group was conducted by the student *t*-test and that of abnormally distributed measurement data was conducted by the Wilcoxon signed-rank test.

### Analysis of safety

Normal cases and proportions before the treatment and abnormal cases and proportions after the treatment were

calculated in the two groups, respectively. Cases and proportions of adverse events were calculated and analyzed by continuous correction *U*-test or Fisher's exact test. The specific appearance, degree, and relationship with the instrument in each group were recorded.

## RESULTS

### Study population

A total of 225 patients from 14 centers all over China were enrolled in this study and randomized into two groups based on a third-party random assignment: Qinming8631 DR pacemaker was implanted in 113 patients (trial group) and Talos DR pacemaker was implanted in 112 patients (control group). Comparisons of baseline characteristics, such as demographics and comorbidities, are shown in Table 1. No significant difference was found between the two groups, except for the history of syncope, which was higher in the trial group than in the control group. Patients with a diagnosis of SSS, second-degree AV block, and complete AV block were 62 versus 58 ( $\chi^2 = 0.215$ ,  $P = 0.643$ ), 10 versus 11 ( $\chi^2 = 0.063$ ,  $P = 0.802$ ), and 41 versus 43 ( $\chi^2 = 0.107$ ,  $P = 0.744$ ) in the trial versus control group, respectively. No statistical significance of diagnosis was found in these two groups [Table 1]. Study population of FAS and PPS are shown in Table 2. Finally, 87 (77.0%) patients in the trial group and 86 (76.8%) patients in the control group completed the 6-month follow-up (PPS). Reasons for discontinuation are provided in Supplementary Table 1.

### Procedure characteristics

All the patients underwent successful pacemaker implantation. More than 75% patients underwent electrode lead implantation through the subclavian vein (around 20%

was through the axillary vein) and very few through the cephalic vein, in both groups. About 70% pacemakers were implanted into the left side of the chest, and no difference was found between the two groups (69.9% vs. 70.5%,  $\chi^2 = 0.011$ ,  $P = 0.919$ ). The atrial lead was fixed in the right atrial (RA) appendage in all patients. In 39.8% of the trial group and 40.2% of the control group, the ventricular lead was fixed in the right ventricular (RV) apex, while in others, it was fixed in the ventricular septum. The RA pacing threshold was  $0.63 \pm 0.28$  V vs.  $0.65 \pm 0.27$  V ( $t = -0.643$ ,  $P = 0.521$ ) in trial and control groups while RV pacing threshold was  $0.67 \pm 0.27$  V vs.  $0.58 \pm 0.22$  V ( $t = 2.628$ ,  $P = 0.009$ ). RA and RV sensing threshold were similar between the two groups ( $6.09 \pm 5.30$  mV vs.  $5.18 \pm 4.36$  mV,  $t = 1.377$ ,  $P = 0.170$ ;  $11.03 \pm 5.76$  mV vs.  $11.62 \pm 6.00$  mV,  $t = -0.751$ ,  $P = 0.453$ , respectively).

### Efficacy assessment

#### Primary end points

On the basis of comparability of the two groups, the primary end points in FAS and PPS were evaluated [Table 3]. The results showed that in FAS, the effective pacing rate was 81.4% in the trial group and 79.5% in the control group. The difference was 1.3% (95% CI: -7.0%-10.6%), and thus noninferiority of the trial group compared with the control group with respect to the effective pacing rate was shown with a margin of -7.0%, which was well above the predefined noninferiority limit (-9.5%). In PPS, the effective pacing rate was 95.4% in the trial group and 89.5% in the control group. The difference was 11.8% (95% CI: 0.3%-24.9%), and thus noninferiority of the trial group compared with the control group with respect to the effective pacing rate was shown with a margin of 0.3%, which was also well above the predefined noninferiority limit (-9.5%). The effective pacing rate

**Table 1: Baseline characteristics of patients with bradyarrhythmia implanted cardiac pacemakers**

Variables	Qinming8631 DR group (n = 113)	Talos DR group (n = 112)	Statistical values	P
Age (years)	65.6 ± 11.0	65.3 ± 11.6	0.207	0.837
Female	57 (50.4)	50 (44.6)	0.759	0.384
SBP (mmHg)	137.3 ± 22.5	139.1 ± 21.8	-0.613	0.541
DBP (mmHg)	73.9 ± 12.1	74.8 ± 12.2	-0.562	0.575
Heart rate (beats/min)	50 ± 14	53 ± 17	-1.659	0.099
Coronary heart disease	6 (5.3)	7 (6.3)	0.091	0.762
Hypertension	47 (41.6)	53 (47.3)	0.748	0.387
Diabetes	9 (8.0)	13 (11.6)	0.850	0.357
Stroke	3 (2.7)	6 (5.4)	Fisher	0.333
Dilated cardiomyopathy	1 (0.9)	0 (0)	Fisher	1.000
Valvular disease	1 (0.9)	2 (1.8)	Fisher	0.622
MI	0 (0)	2 (1.8)	Fisher	0.247
Paroxysmal atrial fibrillation	3 (2.7)	8 (7.1)	2.522	0.112
History of syncope	10 (8.9)	3 (2.7)	4.209	0.040
Diagnosis				
Sick sinus syndrome	62 (54.9)	58 (51.8)	0.215	0.643
Second degree AV block	10 (8.8)	11 (9.8)	0.063	0.802
Complete AV block	41 (36.3)	43 (38.4)	0.107	0.744

Fisher: No available statistical value according to Fisher exact test. Data were expressed as n (%) or mean ± SD. SD: Standard deviation; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; AV: Atrioventricular; MI: Myocardial infarction; 1 mmHg = 0.133 kPa.

immediately after the procedure was no significant difference in the two groups (trial: 100% vs. control: 99.1%,  $P = 1.000$ ). The effective sensitivity rate immediately after the procedure was 94.8% and 93.6% in the trial and control groups, respectively, with no significant difference ( $P = 0.716$ ). The stability of pacing during follow-up was very high (99.0% in trial and 98.1% in control groups), and the difference was not significant ( $P = 0.621$ ). Magnet response, single- and double-pole polarity conversion at 3 months, and rate response at 6 months were 100% in both groups. Pacing threshold, sensing threshold, and lead impedance of RA and RV in both groups are shown in Figure 1.

### Secondary end points

At 6-month follow-up, the 24-h ambulatory ECG monitoring did not detect any failure of pacing or sensing in both groups.

### Safety assessment

Analysis of safety parameters was based on SAS. The rate of adverse event was 3.53% in the trial group and 2.67% in the control group, with no significant difference ( $P = 1.000$ ). The four cases of adverse events in the trial group (three noncardiovascular and one cardiovascular) and three cases of adverse events in the control group (zero noncardiovascular and three cardiovascular) were severe. However, the adverse events were not associated with the pacing system [Table 4 and Supplementary Table 2].

**Table 2: Study deviation of bradyarrhythmia patients underwent pacemaker implantation during 6 months of follow-up**

Population	Qinming8631 DR group ( $n = 113$ )	Talos DR group ( $n = 112$ )
Cancellation of informed consent, $n$	0	0
FAS, $n$	113	112
Deviation from the protocol, $n$ (%)		
Absence of primary end points	22 (19.5)	23 (20.5)
Loss of follow-up	4 (3.5)	3 (2.7)
PPS, $n$ (%)	87 (77.0)	86 (76.8)

FAS = Number of randomized patients – number of patients withdrawing informed consent; Deviation from the protocol = Patients absence of primary end points + patients loss of follow-up; PPS = FAS – deviation from the protocol. FAS: Full analysis set; PPS: Per protocol set.

**Table 3: Primary endpoint after 6 months of follow-up in the full analysis set and per protocol set**

Variables	Qinming8631 DR group ( $n = 113$ )	Talos DR group ( $n = 112$ )	Difference	95% CI	$P$
FAS*, $n$ (%)					
Valid	92 (81.4)	89 (79.5)	1.3	-7.0–10.6	0.712
Invalid	21 (18.6)	23 (20.5)			
PPS, $n$ (%)					
Valid	83 (95.4)	77 (89.5)	1.8	0.3–24.9	0.143
Invalid	4 (4.6)	9 (10.5)			

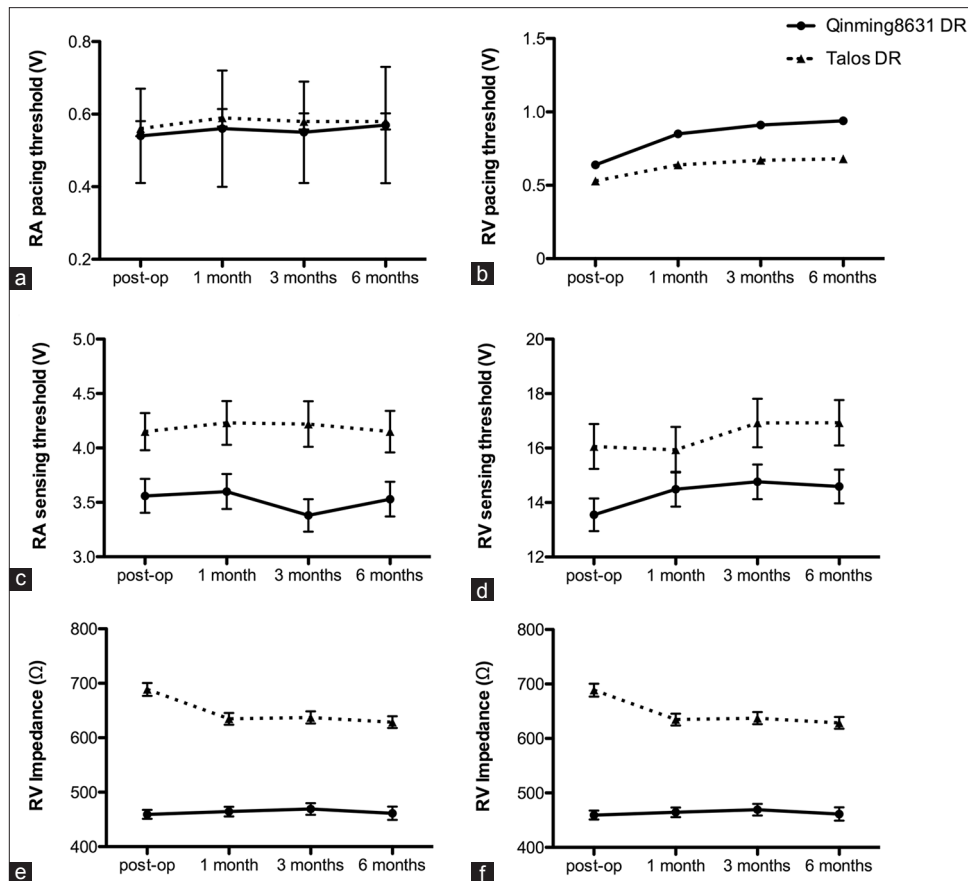
\*The first choice for dealing with missing value is LOCF. When there is still missing values after the data was added according to LOCF, the missing value would be regard as non-effective pacing. 95% CI was obtained through CMH Chi-square test adjusting center effect. FAS: Full analysis set; PPS: Per protocol set; CI: Confidence interval; LOCF: Last observation carried forward; CMH: Cochran-Mantel-Haenszel.

## DISCUSSION

This study demonstrated that the first domestically developed dual-chamber rate-responsive pacemaker of China was noninferior with respect to safety or efficacy compared with Talos DR at 6-month follow-up. Qinming8631 DR pacing system showed acceptable pacing and sensing threshold at both acute phase and long-term follow-up and good magnetic response, polarity conversion (unipolar and bipolar), and rate response function. No failure of pacing or sensing was found by 24-h ambulatory ECG. Most importantly, the prevalence of severe adverse events was low and similar in the two groups, and the adverse events were not associated with the pacing system.

In China, Qinming2312 implantable cardiac pacemaker, developed by Qinming Corporation in 2008, was the first domestic single-chamber cardiac pacemaker registered by the China Food and Drug Administration. In the past years, Qinming2312 implantable cardiac pacemaker was clinically used in 150 hospitals and spread over 26 provinces in China. The clinical effects obtained from different hospitals demonstrated that Qinming2312 implantable cardiac pacemaker was comparable with imported cardiac pacemaker and was, especially, inexpensive, which could be afforded by the majority of Chinese patients.<sup>[15,16]</sup> However, dual-chamber pacemaker accounted for 60% of all pacemakers in China,<sup>[9]</sup> which brought an urgent need of domestically developed dual-chamber pacemaker. On the basis of successful clinical application of Qinming2312 single-chamber cardiac pacemaker, Qinming Corporation developed Qinming8631 DR implantable cardiac pacemaker, which would be the first generation of domestically developed dual-chamber cardiac pacemaker of China.

This prospective, randomized, controlled, and single-blind study was conducted at 14 clinical centers in China. The Talos DR implantable cardiac pacemaker, which is widely distributed all over the world as the basic model of dual-chamber pacemaker, was selected as the control device. Rigorous inclusion and exclusion criteria were used while enrolling patients. The loss of follow-up rate was 2% at 1 month, 3% at 3 months, and 5% at 6 months. Good pacing performance and reliable safety shown in this study helped improve the confidence when using Qinming8631 DR implantable cardiac pacemaker in clinical practice.



**Figure 1:** Parameter of RA and RV leads at post-op and during follow-ups. (a and b) Pacing threshold at 0.4 ms pulse width; (c and d) sensing threshold; (e and f) impedance. Post-op: Postoperation; RA: Right atrium; RV: Right ventricle.

**Table 4: Adverse events in bradyarrhythmia patients underwent pacemaker implantation**

Adverse events	Qinming8631 DR group (n = 113)	Talos DR group (n = 112)	Statistical values	P
Noncardiac death, n (%)				
Nasopharyngeal carcinoma	1 (0.88)	0	Fisher	1.000
Hepatocellular carcinoma	1 (0.88)	0	Fisher	1.000
Intestinal obstruction (postcolectomy)	1 (0.88)	0	Fisher	1.000
Cardiac death, n (%)				
MI	0	2 (1.79)	Fisher	0.247
HF and acute renal insufficiency	1 (0.88)	0	Fisher	1.000
HF	0	1 (0.89)	Fisher	0.498
All-cause death	4 (3.53)	3 (2.67)	Fisher	1.000

Fisher: No available statistical value according to Fisher's exact test. MI: Myocardial infarction; HF: Heart failure.

### Clinical significance

As a result of the continuous development in economy and improvement in people's living standards, the aging trend has increased in China, leading to a dramatically increased number of patients relying on the treatment with pacemakers. So far, Qinming8631 DR implantable cardiac pacemaker is the first dual-chamber pacemaker developed in China with independent intellectual property, possessing efficacy and safety comparable to those of Talos DR pacemaker, is much cheaper than the imported pacemaker, and has huge potential for alleviating the financial burden of Chinese patients and providing more opportunities to those who are indicated for pacemaker implantation.

### Limitations

The follow-up period in this study was relatively short according to the battery expectancy of a dual-chamber pacemaker. A long-term outcome evaluation is warranted for both Qinming8631 DR and Talos DR pacemakers.

In conclusion, the present study demonstrated, through a 6-month follow-up trial, that Qinming8631 DR implantable cardiac pacemaker was feasible for treating patients with cardiac bradyarrhythmia with good safety and reliable pacing performance.

*Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.*

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## Conflicts of interest

There are no conflicts of interest.

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**Supplementary Table 1: Patients deviating from the protocol**

Center	Random number	Group	Gender	Age	Type	Detailed description
01	053	Trial	Male	77	Absence of primary end points	Death at the 70 <sup>th</sup> day
01	054	Trial	Female	71	Absence of primary end points	No assessment of frequency response at 6-month
01	068	Trial	Male	57	Absence of primary end points	No assessment of frequency response at 6-month
01	069	Control	Male	64	Absence of primary end points	No assessment of frequency response at 6-month
01	101	Trial	Female	64	Absence of primary end points	No assessment of perception threshold immediately after operation
01	122	Control	Male	55	Absence of primary end points	No assessment of perception threshold immediately after operation
01	129	Trial	Male	76	Absence of primary end points	Death at the 68 <sup>th</sup> day
02	179	Control	Female	74	Absence of primary end points	No assessment of perception threshold immediately after operation
02	191	Trial	Female	60	Absence of primary end points	No assessment of perception threshold immediately after operation
02	192	Control	Female	54	Absence of primary end points	No assessment of perception threshold immediately after operation
03	004	Control	Female	73	Absence of primary end points	No assessment of perception threshold immediately after operation
04	002	Trial	Male	60	Absence of primary end points	No assessment of perception threshold immediately after operation
04	015	Trial	Male	71	Absence of primary end points	No assessment of perception threshold immediately after operation
04	048	Trial	Male	79	Absence of primary end points	Death at the 162 <sup>nd</sup> day
04	049	Control	Male	77	Absence of primary end points	No assessment of perception threshold immediately after operation
04	056	Trial	Male	51	Absence of primary end points	No assessment of perception threshold immediately after operation
04	100	Trial	Male	75	Absence of primary end points	No assessment of perception threshold immediately after operation
04	107	Control	Male	66	Absence of primary end points	No assessment of perception threshold immediately after operation
04	138	Trial	Male	71	Absence of primary end points	No assessment of perception threshold immediately after operation
05	021	Trial	Male	78	Absence of primary end points	No assessment of perception threshold immediately after operation
05	025	Control	Male	70	Absence of primary end points	No assessment of perception threshold immediately after operation
05	043	Trial	Male	74	Absence of primary end points	No assessment of perception threshold immediately after operation
05	052	Control	Male	81	Absence of primary end points	Death at the 62 <sup>nd</sup> day
05	116	Trial	Male	76	Absence of primary end points	No assessment of perception threshold immediately after operation
06	203	Trial	Female	76	Loss of follow-up	6-month
06	223	Control	Female	82	Loss of follow-up	1-month
07	144	Control	Male	26	Absence of primary end points	No assessment of perception threshold immediately after operation
08	026	Trial	Male	26	Absence of primary end points	No assessment of perception threshold immediately after operation
08	040	Control	Male	81	Absence of primary end points	No perception threshold immediately after operation
08	135	Control	Male	33	Absence of primary end points	No assessment of perception threshold immediately after operation
08	178	Control	Male	56	Loss of follow-up	1-, 3-, and 6-month
08	189	Trial	Male	80	Loss of follow-up	6-month
09	038	Trial	Male	63	Absence of primary end points	Death at the 95 <sup>th</sup> day
09	074	Control	Male	78	Absence of primary end points	No assessment of perception threshold immediately after operation

*Contd...*



**Supplementary Table 1: Contd...**

Center	Random number	Group	Gender	Age	Type	Detailed description
09	088	Trial	Male	50	Absence of primary end points	No assessment of perception threshold immediately after operation
09	098	Control	Male	56	Absence of primary end points	No assessment of perception threshold immediately after operation
09	175	Trial	Female	64	Absence of primary end points	No assessment of perception threshold immediately after operation
09	188	Trial	Male	84	Absence of primary end points	No assessment of perception threshold immediately after operation
09	195	Control	Male	69	Absence of primary end points	No assessment of perception threshold immediately after operation
09	089	Trial	Female	77	Loss of follow-up	3- and 6-month
09	168	Control	Female	82	Loss of follow-up	6-month
10	117	Trial	Male	43	Absence of primary end points	No assessment of perception threshold immediately after operation
10	133	Trial	Male	76	Absence of primary end points	Death at the 126 <sup>th</sup> day
10	153	Control	Male	76	Absence of primary end points	No assessment of perception threshold immediately after operation
13	029	Control	Male	53	Absence of primary end points	No assessment of perception threshold immediately after operation
13	046	Trial	Male	67	Absence of primary end points	No perception threshold immediately after operation
13	104	Control	Female	52	Absence of primary end points	No assessment of perception threshold immediately after operation
13	216	Trial	Female	59	Absence of primary end points	No assessment of perception threshold immediately after operation
14	091	Trial	Female	64	Loss of follow-up	1-month
14	090	Control	Male	56	Absence of primary end points	No assessment of perception threshold immediately after operation
14	115	Control	Male	76	Absence of primary end points	Death at the 75 <sup>th</sup> day
14	197	Control	Female	73	Absence of primary end points	No pace-making threshold at 6-month after operation; no assessment of frequency response at 6-month

Center - 01: The Second Affiliated Hospital of Zhejiang University School of Medicine; 02: The Affiliated Hospital of Qingdao University Medical College; 03: The First People's Hospital of Hangzhou; 04: The First Affiliated Hospital of Lanzhou University; 05: The First Affiliated Hospital of Xi'an Jiaotong University; 06: Northern Jiangsu People's Hospital; 07: The First Affiliated Hospital of Suzhou University; 08: The Second Affiliated Hospital of Nanchang University; 09: Bethune International Peace Hospital of the Chinese PLA; 10: The First Affiliated Hospital of Kunming Medical University; 13: Jilin Province People's Hospital; 14: Tianjin Chest Hospital.

**Supplementary Table 2: Description of patients with adverse events**

Center	Random number	Group	Age	Gender	Adverse event	Day after operation	Severity	Outcome	Instruments treatments	Quit the test
01	053	Control	77	Male	MI	70	Severe	Death	No	Yes
01	129	Trial	76	Male	Intestinal obstruction (postcolon cancer operation)	68	Severe	Death	No	Yes
04	048	Trial	79	Male	Hepatocellular carcinoma	162	Severe	Death	No	Yes
05	052	Control	81	Male	MI	60	Severe	Death	No	Yes
09	038	Trial	63	Male	HF and acute renal insufficiency	95	severe	Death	No	Yes
10	133	Trial	76	Male	Nasopharyngeal carcinoma	126	Severe	Death	No	Yes
14	115	Control	76	Male	HF	75	Severe	Death	No	Yes

Center - 01: The Second Affiliated Hospital of Zhejiang University School of Medicine; 04: The First Affiliated Hospital of Lanzhou University; 05: The First Affiliated Hospital of Xi'an Jiaotong University; 10: The First Affiliated hospital of Kunming Medical University; 14: Tianjin Chest Hospital. MI: Myocardial infarction; HF: Heart failure.