



The gender difference of utilization of cardiac implantable electronic device in China: data from Arrhythmia Interventional Therapy Data Registry

Ruo-Han CHEN¹, Ke-Ping CHEN¹, Wei HUA¹, Jing XU², Lin CHEN³, Yang-Gang SU⁴, Xi SU⁵, Jian-Gang ZOU⁶, Ji YAN⁷, Jing-Feng WANG⁸, Bao-Peng TANG⁹, Mei-Xiang XIANG¹⁰, Shu ZHANG¹

¹Center of Arrhythmia, Fuwai Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China

²Department of Cardiology, Tian Jing Chest Hospital, Tianjing, China

³Department of Cardiology, Fujian Provincial Hospital, Fuzhou, China

⁴Department of Cardiology, ZhongShan Hospital, FuDang University, Shanghai, China

⁵Department of Cardiology, WuHan Asia Cardiology Hospital, Wuhan, China

⁶Department of Cardiology, the First Affiliated Hospital of Nanjing Medical University, NanJing, China

⁷Department of Cardiology, AnHui Provincial Hospital, Hefei, China

⁸Department of Cardiology, Sun-Yat-Sen Memorial Hospital, Guangzhou, China.

⁹Department of Cardiology, the First Affiliated Hospital of XinJiang Medical University, Urumichi, China

¹⁰Department of Cardiology, the Second Affiliated Hospital of ZheJiang University of School of Medical, Hangzhou, China

Abstract

Background Cardiac implantable electronic devices (CIEDs) greatly improve survival and life quality of patients. However, there are gender differences regarding both the utilization and benefit of these devices. In this prospective CIED registry, we aim to appraise the gender differences in CIED utilization in China. **Methods** Twenty centers from 14 provinces in China were included in our registry study. All patients who underwent a CIED implantation in these twenty centers between Jan 2015 and Dec 2016 were included. **Results** A total of 8570 patients were enrolled in the baseline cohort, including 7203 pacemaker, 664 implantable cardiac defibrillators (ICD) implants and 703 cardiac resynchronization therapy device (CRT/D). Totally, 4117 (48.0%) CIED patients were female, and more than 59% pacemaker patients were female, but women account only one third of ICD or CRT/D implantation in this registry. There were significant differences between genders at pacemaker and ICD indications. Female was more likely received a pacemaker due to sick sinus syndrome (SSS) (63.9% vs. 51.0%, $P < 0.001$). Female patients receiving an ICD were more likely due to cardiac ion channel disease (29.2% vs. 4.2%, $P < 0.001$). The percentage of utilization of dual-chamber pacemaker in female patients was significantly higher than male (85.3% vs. 81.1%, $P < 0.001$). But male patients were more likely received a cardiac resynchronization therapy devices with defibrillator than female (56.5% vs. 41.9%, $P = 0.001$). In pacemaker patient, male was more likely to have structure heart disease (31.3% vs. 28.0%, $P = 0.002$). In ICD patient, male patients were more likely to have ischemic heart disease (48.2% vs. 29.2%, $P < 0.001$). The mean age of women at the time of CRT/D implantation was older than men ($P = 0.014$). Nonischemic cardiomyopathy (70.9%) was the most common etiology in the patients who underwent the treatment of CRT/D, no matter male or female. **Conclusions** In real-world setting, female do have different epidemiology, pathophysiology and clinical presentation of many cardiac rhythm disorders when compared with male, and all these factors may affect the utilization of CIED implantation. But it also possibility that cultural and socioeconomic features may play a role in this apparent discrimination.

J Geriatr Cardiol 2018; 15: 310–314. doi:10.11909/j.issn.1671-5411.2018.04.010

Keywords: Cardiac implantable electronic devices; Gender; Registry

1 Background

The use of cardiac implantable electronic devices (CIEDs) has greatly increased in the past ten years in China, as tech-

niques advance and age of the population increased. The professional societies have issued several guidelines for CIED. However, these guidelines have often been derived from large clinic trials which enrolled predominantly males. Whether or not they are also suitable for the female patients is unknown as the gender differences in heart rhythm diseases and CIEDs usage have been increasingly recognized.

Post-hoc meta-analysis indicated that women with mild heart failure (HF), left bundle branch block (LBBB), and a QRS duration of 130–149 ms benefited more from cardiac

Correspondence to: Ke-Ping CHEN, MD, PhD, Center of Arrhythmia Diagnosis and Treatment, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China. E-mail: chenkeping@263.net

Received: June 13, 2017

Revised: September 7, 2017

Accepted: December 6, 2017

Published online: April 28, 2018

resynchronization therapy (CRT) than men with similar ECG and clinical findings.^[1] On the other hand, it has become evident that female is associated with an increased risk of acute complications during primary cardiac device implantation, irrespective of age or type of device implanted. However, very little is known about the gender effects on CIED used in China. The purpose of the current registry study was to systematically evaluate the effects of gender variations on CIED implantation.

2 Methods

2.1 Data sources

Data was from National Arrhythmic Intervention Therapy Registry, which is based on a unified database developed by the national cardiovascular disease center. Information consists of implantation and follow-up data of CIED. Collected data are regularly checked for internal consistency by the Registry administrator, and online statistics are updated on a daily basis.

This registry is sponsored by Key Projects in the National Science & Technology Pillar Program during the Twelfth Five-year Plan Period (2011BAII 1802). The registry is intended to identify the gender difference in CIED usage in nowadays China.

2.2 Study population

Twenty centers from 14 provinces whose CIED implantation amount were among the top 20 in 2014 in China have contributed to this registry study. All patients implanted with a CIED including pacemaker, implantable cardiac defibrillators (ICD) and cardiac resynchronization therapy device (CRT/D) in above centers between Jan 2015 and Dec 2016 were included. Informed consent for data entry was required by the ethics committee of each participating hospital.

2.3 Baseline data collection

Individual patient data are collected and the following variables are monitored in the registry: number of CIEDs, including pacemakers, ICDs and CRT/D, implanted or replaced per center, patient demographics (i.e., age and gender), clinical indications, underlying structure heart disease, etiology of cardiomyopathy, New York Heart Association (NYHA) classification, prophylactic therapy of sudden cardiac death (SCD), ultrasound data, perioperative and post-operative complications (including infection, pneumothorax, perforation, hematoma and dislodgment), and technical information on generators and leads (manufacturer, model,

lead parameters). Information regarding insurance type was also reported.

2.4 Data analysis

Categorical variables are reported as number and percentages, the continuous variables as mean values and standard deviations. Groups were compared with the chi-square test for discrete variables and the Mann-Whitney *U* for continuous variables with non-normal distributions. All statistical tests were 2-sided, and a *P* value less than 0.05 were considered as statistically significant.

3 Results

A total of 8570 patients were enrolled in the baseline cohort, including 7203 pacemaker, 664 ICD implants and 703 CRT/D. 4117 (49.0%) patients were female.

3.1 Pacemaker

The mean age of the pacemaker patients was 68.0 ± 13.0 years, 3695 were female (51.3%), and 3508 were male (48.7%). The mean age of female patients at the time of implantation was 67.5 ± 12.8 years, and male was 68.3 ± 13.6 years ($P = 0.021$). There were significant differences between genders at pacing indications: atrioventricular block (AVB) and permanent atrial fibrillation were less prevalent (40.3% vs. 30.1%, 13.5% vs. 9.1%, $P < 0.001$) and sick sinus syndrome was more prevalent (63.9% vs. 51.0%, $P < 0.001$) in female than male. Likewise, underlying structural heart disease was less frequent among female (28.0% vs. 31.3%, $P = 0.002$). Females received significantly more dual-chamber pacemaker than male (85.3% vs. 81.1%, $P < 0.001$), while male received more remote monitoring devices (5.5% vs. 3.0%, $P < 0.001$). The percentage of rate adaptive pacemaker usage was high in whole population, 78.8% and 77.6% in male and female patients, respectively ($P = 0.231$) (Table 1).

3.2 ICD

A total of 664 patients were included in the baseline cohort, of whom 180 (27.1%) was female. The mean age was 56.8 ± 14.2 years and 55.6 ± 16.6 years for male and female ($P = 0.43$). Totally, 65.5% patients implanted ICD due to secondary prevention of SCD, 64.1% and 69.1% for male and female patients, respectively ($P = 0.285$). As far as the type of ICD is concerned, 70.5% male and 67.2% female implanted a single-chamber ICD, there was no significant difference between genders ($P = 0.448$). Compared with male patients, female patients suffered ventricular tachycardia (VT) or ventricular fibrillation (VF) more likely due to car-

diac ion channel disease (29.2% vs. 4.2%, $P < 0.001$), less likely to have ischemic heart disease (29.2% vs. 48.2%, $P < 0.001$). Female patients do had better heart function, including smaller left ventricular end diastolic dimension (LVEDD), better left ventricular ejection fraction (LVEF) and higher percentage of NYHA I grade (Table 2).

Table 1. The characteristics of pacemaker patient.

	Male, <i>n</i> = 3508	Female, <i>n</i> = 3695	<i>P</i> value
Mean age, yrs	68.3 ± 13	67.6 ± 12	0.021
Pacing indication			
SSS	1790 (51.0%)	2360 (63.9%)	0.000
AVB	1414 (40.3%)	1111 (30.1%)	0.000
Chronic AF	475 (13.5%)	337 (9.1%)	0.000
Other	48 (1.4%)	58 (1.6%)	0.495
Structural heart disease	1098 (31.3%)	1034 (28.0%)	0.002
Type of PM			0.000
Single-chamber	663 (18.9%)	544 (14.7%)	
Dual-chamber	2845 (81.1%)	3151 (85.3%)	
Rate adaptive PM	2764 (78.8%)	2868 (77.6%)	0.231
Remote monitor PM	193	110	0.000

Data are presented as mean ± SD or *n* (%). AF: atrial fibrillation; AVB: atrial ventricular block; PM: pacemaker; SSS: sick sinus syndrome.

Table 2. The characteristics of ICD patient.

	Male, <i>n</i> = 484	Female, <i>n</i> = 180	<i>P</i> value
Mean age, yrs	56.8 ± 14.2	55.6 ± 16.6	0.430
Etiology	356 (73.6%)	89 (49.4%)	0.000
Ischemia cardiomyopathy	172 (48.2%)	26 (29.2%)	0.000
Non-ischemia cardiomyopathy	158 (44.4%)	48 (53.9%)	0.157
Ion channel disease	15 (4.2%)	26 (29.2%)	0.000
Other	66 (18.5%)	23 (25.8%)	0.898
SCD prevention			0.285
Primary prevention	166 (35.9%)	54 (30.9%)	
Secondary prevention	296 (64.1%)	121 (69.1%)	
NYHA class			0.169
I	163 (35.6%)	78 (45.1%)	0.034
II	167 (36.5%)	52 (30.0%)	0.135
III	105 (22.9%)	38 (22.0%)	0.832
IV	23 (5.0%)	5 (2.9%)	0.286
LVEDD, mm	59.19 ± 11.00	54.11 ± 09.86	0.000
LVEF	44.25% ± 15.38%	48.38% ± 15.96%	0.009
ICD type			0.448
Single chamber	341 (70.5%)	121 (67.2%)	
Dual chamber	143 (29.5%)	59 (32.8%)	

Data are presented as mean ± SD or *n* (%). ICD: implantable cardiac defibrillation; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; SCD: sudden cardiac death.

3.3 CRT/D

Among 703 CRT/D patients, 242 were female (34.4%), and 461 were male (65.6%). The mean age of female patients at the time of implantation was 63.3 ± 9.2 years, male was 61.2 ± 11.3 years ($P = 0.014$). Non-ischemic cardiomyopathy (70.9%) was the most common etiology that underlying the treatment of CRT/D, no matter male or female (69.1% vs. 74.3%, $P = 0.328$). There was no significant difference between male and female patients in QRS duration [166.2 ± 36.1 vs. 162.6 ± 30.0 ms, $P = 0.198$], NYHA heart function grade ($P = 0.645$) and LVEF (34.7% ± 11.3% vs. 36.5% ± 11.7%, $P = 0.083$), but LVEDD was small in female than in male (63.7 ± 11.1 vs. 69.0 ± 11.2 mm, $P < 0.001$). More male patients received CRTD therapy than female (56.5% vs. 41.9%, $P = 0.001$). The usage of beta-blockers, ACEI/ARB and Aldactone in CRT/D patients were 53.6%, 69% and 88.1%, there was no significant different between genders. Male were more likely prescribed Statins (Table 3).

Table 3. The characteristics of CRT/D patient.

	Male, <i>n</i> = 461	Female, <i>n</i> = 242	<i>P</i> value
Mean age, yrs	61.2 ± 11.3	63.3 ± 9.2	0.014
Etiology			0.326
Ischemia cardiomyopathy	142 (30.9%)	62 (25.7%)	
Non-ischemia cardiomyopathy	318 (69.1%)	179 (74.3%)	
QRS duration, ms	166.2 ± 36.1	162.6 ± 30.0	0.198
LVEDD, mm	69.0 ± 11.2	63.8 ± 11.1	0.000
LVEF	34.7% ± 11.3%	36.5% ± 11.7%	0.083
NYHA class			0.645
I	22 (4.8%)	10 (4.1%)	0.849
II	103 (22.3%)	55 (22.8%)	0.924
III	295 (64.0%)	158 (65.6%)	0.740
IV	41 (8.9%)	18 (7.5%)	0.569
CRT type			0.001
CRT/P	199 (43.5%)	140 (58.1%)	
CRT/D	258 (56.5%)	101 (41.9%)	
Medications			0.144
Beta-blockers	164 (55.0%)	89 (51.1%)	0.188
ACEI/ARB	213 (71.5%)	113 (64.9%)	0.105
Aldactone	259 (86.9%)	157 (90.2%)	0.084
Diuretics	254 (85.2%)	151 (86.8%)	0.162
Digoxin	174 (58.4%)	94 (54.0%)	0.252
Statin	56 (18.8%)	18 (10.3%)	0.038

Data are presented as mean ± SD or *n* (%). ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker; CRT: cardiac resynchronization therapy; CRT/D: cardiac resynchronization therapy-defibrillator; CRT/P: cardiac resynchronization therapy-pacemaker; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

4 Discussion

Our data showed there was large difference between genders in CIEDs utilization, including underlying heart disease, implantation indication and device choices. These phenomena, some could be explained by the gender difference of electrophysiological properties, some is more complicated, cultural and socioeconomic features may also play a role in this apparent discrimination.

4.1 Pacemaker

Our data showed significant differences for pacemaker indication and device selection between both genders. Concerning pacing indications, females have a lower incidence of atrioventricular block and higher incidence of sinus node dysfunction as primary pacing indication, compared with males. This distribution can be found in previous studies as well.^[2-4] The underlying mechanism is unclear. This gender disparity could be explained to some extent by the effects of sex hormones on autonomic tone modification and on the electrophysiological properties of the myocardial cell.

Many clinic trials have shown that the DDD (dual-chamber pacing) is better than VVI (single-chamber ventricular pacing) in reducing the HF and atrial fibrillation events. Rate adaptive pacing could increase the pacing rate according to metabolism, it is more physiological. Nowadays, more than 80% patients underwent a dual-chamber pacemaker implantation, more than 75% devices has rate adaptive function in China. In our study, more women were implanted a dual-chamber pacemakers, this may be because the lower percentage of persistent AF in women in this registry. But no sex difference in the selection of rate adaptive pacemaker was demonstrated in this study.

4.2 ICDs

ICDs reduce mortality in patients resuscitated from malignant ventricular arrhythmias.^[5,6] There is also evidence that these devices are useful for the primary prevention of SCD in patients with reduced LVEF.^[7-9] In our study, more than two thirds patients implanted an ICD due to secondary prevention, no significant difference between male and female.

In our study, women were less prone to ventricular arrhythmias except ion channel disease including long-QT syndrome and Idiopathic ventricular fibrillation. Men were more likely implanted ICD due to ischemia cardiomyopathy. Women have better heart function than men, the percentage of NYHA I grade was higher and LVEDD and LVEF were better in women than in men. These were similar as the previous researches. In both congenital^[10] and acquired^[11] LQTS, a female predominance has been reported. Furthermore,

among patients with LQTS, female gender is well recognized as an independent risk factor for sudden cardiac death, irrespective of the presence of underlying CAD, electrolyte imbalance, level of QTc at baseline, or prescribed medications.^[12] In idiopathic VT, it has been reported that a higher prevalence of life-threatening arrhythmias in women, such as VF.^[13] But in patients of coronary artery disease, VT or VF is less inducible in women despite similar ejection fractions, number of diseased coronary arteries and history of myocardial infarction.^[14] These findings could not be merely explained by the gender differences in SCD substrates and mechanisms. The gender difference in susceptibility to ventricular arrhythmia under difference pathophysiological situation may also play a role.

4.3 CRT/D

Our study found that the only 34.4% patients implanted CRT/D were female. Meanwhile, the percentage of CRT/D was much less in female than in male. Clinical trials and observational studies also demonstrate a significant gender disparity in utilization of CRT: less than one-third of CRT device recipients are women.^[15-18] Data regarding gender-related differences in outcomes after CRT demonstrate women seem have a greater clinical benefit from CRT than men.^[19,20] Although nonischemic HF is more frequent in women, which is associated with a better prognosis.^[21] The mechanisms behind the more favorable response of women to CRT could not be merely explained by the influence HF etiology on prognosis, cause these gender differences persist even when comparing nonischemic female and male subgroup.^[20,21] In our study, nonischemic cardiomyopathy was the most common etiology among the patient underlying CRT/D treatment, no matter male or female. But the percentage of ischemic cardiomyopathy is higher in male than in female, this may be could explained why the Statin prescription is more common in male than in female in this study.

4.4 Gender difference in utilization

Despite expanding indications and a clear survival benefit in patients at risk, the gender disparities in the CIEDs' utilization remain. Our study showed the ratio between male and female in pacemaker patient is about 1: 1, but female is three times less likely to receive a CRT/D compared with men. Previously study showed female made up > 50% of patients with HF,^[22] and had a greater clinical benefit from CRT/D than men,^[23,24] but female patients account only one third of CRT/D implantation no matter in clinic trials but also in the real-world registry. Why are women less likely to receive a more sophisticated device? A longer time to diagnosis, later referral for invasive procedures, difficultly access to specialized implanting physicians also may be partly

responsible for these phenomena. A selection bias by implanting physicians due to somewhat the smaller body size with a more challenging implantation in female may also play a role. Additionally, women may be more reluctant to a device therapy at all, when compared with men.

This study lies in the source of the data that were obtained through the National Arrhythmic Interventional Therapy Data Registry, evaluating a large cohort of patients taken from the real world of clinical practice, and not from trials that collect patients who fulfill only selected criteria. Our study found out the gender difference in CIED clinic usage in China. Female share the same opportunity in routinely pacing for bradycardia, but there is great discrimination in sophisticated device for the treatment of SCD and HF. Gender exerts a profound influence on the epidemiology, pathophysiology and clinical presentation of many cardiac rhythm disorders, and all these factors may affect the outcome of invasive electrophysiological procedures. But it also possibility can't be ruled out that cultural and socioeconomic features may play a role in this apparent discrimination.

4.5 Limitations

The study was conceived as a descriptive report of data collected by the Chinese National arrhythmia interventional therapy data registry system. A systematic analysis of factors potentially influencing global and regional implantation rates was out of the aim of this report and needs to be investigated further.

References

- Zusterzeel R, Selzman KA, Sanders WE, *et al.* Cardiac resynchronization therapy in women: US Food and Drug Administration meta-analysis of patient-level data. *JAMA Intern Med*; 174: 1340–1348.
- Nowak B, Misselwitz B; Expert committee 'Pacemaker', Institute of Quality Assurance Hessen. Do gender differences exist in pacemaker implantation?—results of an obligatory external quality control program. *Europace* 2010; 12: 210–215.
- Danish Pacemaker and ICD Register. <http://www.pacemaker.dk/stat2007.pdf> (accessed October 14, 2017).
- Swedish Pacemaker Register. Annual Statistical Report 2007. http://www.pacemakerregistret.se/icdpmr/annualReport/2007/annualReport_2007.pdf (accessed October 14, 2009).
- A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. *N Engl J Med* 1997; 337: 1576–1583.
- Connolly SJ, Gent M, Roberts RS, *et al.* Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000; 101: 1297–1302.
- Bardy GH, Lee KL, Mark DB, *et al.* Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; 352: 225–237.
- Kadish A, Dyer A, Daubert JP, *et al.* Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2004; 350: 2151–2158.
- Moss AJ, Zareba W, Hall WJ, *et al.* Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; 346: 877–883.
- Imboden M, Swan H, Denjoy I, *et al.* Female predominance and transmission distortion in the long-QT syndrome. *N Engl J Med* 2006; 355: 2744–2751.
- Drici MD. Influence of gender on drug-acquired long QT syndrome. *Eur Heart J* 2001; 3(Suppl K): K41–K47.
- Makkar RR, Fromm BS, Steinman RT, *et al.* Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. *J Am Med Assoc* 1993; 270: 2590–2597.
- Nogami A. Gender differences in idiopathic ventricular arrhythmias—understanding a woman's heart. *Circ J* 2011; 75: 1569–1570.
- Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008; 51: 2291–2300.
- Moss AJ, Hall WJ, Cannom DS, *et al.* Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009; 361: 1329–1338.
- Zabarovskaja S, Gadler F, Braunschweig F, *et al.* Women have better long-term prognosis than men after cardiac resynchronization therapy. *Europace* 2012; 14: 1148–1155.
- Dickstein K, Bogale N, Priori S, *et al.* The European cardiac resynchronization therapy survey. *Eur Heart J* 2009; 30: 2450–2460.
- Alaeddini J, Wood MA, Amin MS, Ellenbogen KA. Gender disparity in the use of cardiac resynchronization therapy in the United States. *Pacing Clin Electrophysiol* 2008; 31: 468–472.
- Arshad A, Moss AJ, Foster E, *et al.* MADIT-CRT Executive Committee. Cardiac resynchronization therapy is more effective in women than in men: The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial. *J Am Coll Cardiol* 2011; 57: 813–820.
- Mooyaart EA, Marsan NA, van Bommel RJ, *et al.* Comparison of long-term survival of men versus women with heart failure treated with cardiac resynchronization therapy. *Am J Cardiol* 2011; 108: 63–68.
- Durante A, Cianflone D, Camici PG. A critical reappraisal of differences in cardiac resynchronization therapy defibrillator effectiveness between men and women in the MADIT-CRT trial. *J Am Coll Cardiol* 2011; 58: 442–443.
- Go AS, Mozaffarian D, Roger VL, *et al.* Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation* 2013; 127: 143–152.
- Arshad A, Moss AJ, Foster E, *et al.* MADIT-CRT Executive Committee. Cardiac resynchronization therapy is more effective in women than in men: The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial. *J Am Coll Cardiol* 2011; 57: 813–820.
- Mooyaart EA, Marsan NA, van Bommel RJ, *et al.* Comparison of long-term survival of men versus women with heart failure treated with cardiac resynchronization therapy. *Am J Cardiol* 2011; 108: 63–68.