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Trends of sex differences in outcomes of cardiac electronic device implantations in the United States

Short Title: Trends of sex differences in CIED implantation outcomes.

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Abstract

Background: The disparity in outcomes of CIED implantations between sexes has been previously demonstrated in device-specific cohorts (e.g. implantable cardioverter defibrillators (ICD)). However, it is unclear whether sex differences are present with all types of CIED and, if so, what the trends of such differences were in recent years.

Methods: Using the National Inpatient Sample, all hospitalizations between 2004 and 2014 for de novo implantation of permanent pacemakers (PPM), cardiac resynchronization therapy with or without a defibrillator (CRT-D and CRT-P, respectively) and ICD were analyzed to examine the association between sex and in-hospital acute complications of CIED implantation.

Results: Out of 2,815,613 hospitalizations for de novo CIED implantation, 41.9% were performed on women. Women were associated with increased adjusted odds of adverse procedural complications (major adverse cardiovascular complications: 1.17 [1.16, 1.19], bleeding: 1.13 [1.12, 1.15], thoracic: 1.42 [1.40, 1.44], cardiac: 1.44 [1.38, 1.50]), while the adjusted odds of in-hospital all-cause mortality compared to men was 0.96 [0.94, 1.00]. The odds of adverse complications in the overall CIED cohort were persistently raised in women throughout the study period, whereas similar odds of all-cause mortality across the sexes were observed throughout the study period.

Conclusion: In a national cohort of CIED implantations we demonstrate that women are at an overall higher risk of procedure-related adverse events compared to men, but no increased risk of all-cause mortality. Further studies are required to identify procedural techniques that would improve outcomes amongst women undergoing such procedures.

Brief summary

Little is known about sex differences in procedural outcomes of CIED implantations. The present study examined trends of sex differences in outcomes over an eleven-year period in a national cohort of CIED implantations. Women were shown to be at a higher risk of adverse procedural outcomes over

Introduction

The rates of utilization of cardiac implantable electronic devices (CIED), including permanent pacemakers (PPM), cardiac resynchronization therapy with pacemakers (CRT-P) or defibrillators (CRT-D) and implantable cardioverter defibrillators (ICD) continue to grow. [1] Despite advances in implantation techniques, CIED systems (leads and devices) and proficiency of operators, the rate of major complications remains significant. [2, 3]

Previous studies have either examined the overall trends of CIED implant-related complications without differentiation between sexes, or the overall effect of sex on outcomes without analysis of historical trends. [2, 4-7] However, to the best of our knowledge no study has compared the trends in outcomes of CIED implantations between sexes. Women are more prone to major complications following CIED implantation due to anatomical differences such as smaller and thinner vessels, smaller chest cavities and lower body weight. [8, 9] Although these factors are less likely to change over the years, increasing awareness of complication risk and advancements in procedural techniques and skills to deal with these anatomical challenges could influence the trends of outcomes. Furthermore, little is known about sex differences in procedural outcomes of different device groups. Complex device

implantation is often associated with longer procedural time and more prolonged lead manipulation, which is known to predispose to more venous damage, secondary inflammation and infection.[10, 11] It is possible that sex differences in the susceptibility to these processes exist.[12]

The present study examined the temporal trends of de novo CIED implantation outcomes and according to sex and CIED type (PPM, CRT and ICD) in a nationwide cohort of procedures performed between 2004 and 2014.

Methods

Data Source

The National Inpatient Sample (NIS) is the largest publicly available all-payer database of hospitalized patients in the United States and is sponsored by the Agency for Healthcare Research and Quality as a part of the Healthcare Cost and Utilization Project (HCUP).[13] Further information about the structure and validation of NIS is available in Appendix A of the Supplemental Material.

Study Design and Population

All adults (aged ≥18 years) undergoing de novo CIED implantation (PPM, CRT-P, CRT-D, and ICD) during hospitalization were included in this study. We excluded any records with missing data (<3% of full dataset) on the following variables: age, sex, elective admission, primary expected payer, median household income and hospital bed size and location. A flow diagram illustrating the inclusion and exclusion process in the present study is presented in Figure S1 (Supplemental Material). Cases excluded due to missing variables represented less than 3% (n=18,321) of the original dataset. The final study cohort was stratified by sex into males and females.

CIED procedures, patient characteristics, comorbidities, and clinical outcomes were extracted using the International Classification of Diseases, ninth revision (ICD-9), procedure and diagnosis codes provided in the supplements (Table S1 in Supplemental Material); procedure-related bleeding, cardiac complications (composite of cardiac tamponade, hemopericardium, pericardial effusion and pericardiocentesis) and thoracic complications (composite of acute pneumothorax or hemothorax, with or without drainage, or thoracic vascular injury). Procedure-related bleeding was defined as any post-procedural hemorrhage or anemia after hemorrhage according to ICD-9 diagnosis codes (998.11 and 285.1). (Table S1)

Outcomes

The primary outcomes were in-hospital adverse events, including major acute cardiovascular events (MACE), all-cause mortality and procedural-related complications (bleeding, thoracic and cardiac) between sexes according to type of CIED implanted. In-hospital MACE was defined as a composite of all-cause mortality, cardiac complications, thoracic complications and device-related infection.

Statistical Analysis

Statistical analysis was performed using SPSS version 24 (IBM Corp, Armonk, NY). The use of sampling weights is required because the design of the study means that different observations may have different probabilities of selection. For calculation of national estimates and correct variances, sampling weights for each individual discharge that were provided by the AHRQ were used in SPSS. Continuous variables are presented as medians with interquartile range (IQR) and were compared using the Kruskal-Wallis test. Categorical variables are presented as percentages and were analyzed using the chi-squared (X^2) test.

Trend analysis was performed using linear regression modeling with the inclusion of time (years) as a covariate for assessing sex differences in type of device use over time, and by assessing the interaction between sex and time (years) in logistic regression analysis for clinical outcomes.

Multiple logistic regression models were constructed to identify the adjusted odds ratio (aOR [95% confidence interval]) of procedure-related adverse outcomes in women using men as the reference category, adjusting for differences in covariates that may directly influence in-hospital outcomes (Appendix B in Supplemental Material).

Results

A total of 569,061 records of de novo CIED implantations between 2004 and 2014 were identified, which corresponded to 2,815,613 hospitalizations. The percentage of women in the total cohort was 41.9%. The prevalence of women amongst those undergoing CIED implantation increased throughout the years in all device subgroups (CRT-P, CRT-D and ICD) except PPM where proportions were similar over the study period (PPM: 49.5% in 2004 to 50.7% in 2014) (Figure 1).

We observed several key differences in patient characteristics between sexes in the overall cohort (Table 1). Overall, women were older with fewer elective admissions and a significantly lower prevalence of cardiovascular risk factors such as dyslipidemia, smoking history, history of IHD, previous AMI and PCI, life-threatening arrhythmias such as ventricular fibrillation and tachycardia, renal failure, as well as shock. In contrast, women had a higher prevalence of atrial fibrillation, hypothyroidism, hypertension, previous CVA and deficiency anemias. The differences in characteristics between sexes were generally consistent across different device groups, however, some exceptions were observed. (Tables S2-4 in Supplemental Material) For example, the prevalence of atrial fibrillation was lower in

women undergoing CRT-D and ICD compared to men, and there was no difference in the prevalence of previous CVA between sexes in patients undergoing CRT-D implantation.

In-hospital adverse outcomes

The overall crude rate of MACE in the entire CIED cohort was 5.0%, primarily driven by thoracic complications (3.0%) followed by all-cause mortality (1.0%), device related infection (0.9%) and cardiac complications (0.4%), while the rate of procedure-related bleeding was 2.9%. (Table 2) The rates of all adverse events were generally higher amongst patients undergoing CRT-P implantation compared to all other device groups. (Table 3)

In the total CIED cohort, all in-hospital adverse events occurred at a higher crude rate in women compared to men (MACE: 5.6% vs. 4.5%; all-cause mortality: 1.0% vs. 0.9%; procedure-related bleeding: 3.2% vs. 2.7%; thoracic complications: 3.8% vs. 2.4%; and cardiac complications: 0.5% vs. 0.3%), except device-related infections that were higher in men (1.1% vs. 0.6%). (Table 2, Figure 2a) Although this pattern was generally consistent across all device subgroups, there were exceptions such as the lower rates of MACE (6.6% vs. 7.3%), all-cause mortality (1.0% vs. 1.6%) and procedure-related bleeding (3.3% vs. 3.6%) in women undergoing CRT-P implantation, and the lower rate of all-cause mortality (0.6% vs. 0.8%) in women undergoing CRT-D implantation. (Table 3, Figure 2b)

In multivariate analysis of the overall CIED cohort, women were at significantly increased odds of MACE (aOR 1.17 [1.16, 1.19]), procedure-related complications (aOR bleeding: 1.13 [1.12, 1.15], thoracic: 1.42 [1.40, 1.44] and cardiac: 1.44 [1.38, 1.50]). (Table 4, Figures 3a and 3b) There were statistically significant differences in odds of adverse events in women between device types. Although the odds of MACE and procedure-related complications were generally higher in women compared to men, women were associated with lower odds of MACE (aOR 0.91 [0.85, 0.97]) and no statistically significant difference

in odds of procedure-related complications (aOR bleeding: 1.01 [0.92, 1.11], thoracic: 1.04 [0.95, 1.12] and cardiac: 1.06 [0.84, 1.35]) in the CRT-P group.

No statistically significant difference in all-cause mortality was observed between sexes in the total CIED cohort (aOR 0.96 [0.94, 1.00]). (Table 4, Figure 3b) The strongest predictors of all-cause mortality in the total CIED cohort included a history of cardiac arrest (OR 4.99 [4.81, 5.17]), VT (OR 1.34 [1.29, 1.39]), VF (OR 1.44 [1.36, 1.52]), coagulopathy (OR 2.33 [2.2, 2.46]) or heart failure (OR 2.43 [2.36, 2.50]), and all-cause infection during admission (OR 5.87 [5.68, 6.07]) ($p<0.001$ for all). Within the device subgroups, women were associated with no statistically significant difference in odds of all-cause mortality in the PPM and ICD groups (aOR 1.01 [0.98, 1.05] and 1.05 [0.97, 1.13], respectively), and reduced odds of all-cause mortality in the CRT groups (aOR CRT-P: 0.70 [0.60, 0.82] and CRT-D: 0.72 [0.66, 0.80]) compared to men.

A trend analysis of the odds of adverse events over the study period shows persistently increased odds of MACE, bleeding thoracic and cardiac complications in women from 2004 to 2014, with a rising trend of these complications in women. (Figures 4a and 4b, $p<0.001$) In contrast, while the adjusted odds of all-cause mortality in women were generally non-significant compared to men throughout the study period, the trend analysis highlighted that there was a significant trend towards lower risk of mortality in women compared to men. (Figure 4b, $p<0.001$)

Discussion

The present study is the largest study to examine sex differences in procedural outcomes of CIED implantations, and the first to report the trends of these outcomes in a nationwide cohort of US hospitalizations. Over an 11-year horizon, we observe a rise in the prevalence of women amongst patients undergoing CIED implantations across all device types except PPM. Our findings demonstrate increased odds of in-hospital implant-related

complications (bleeding, thoracic and cardiac) in women, both in the overall CIED cohort as well as in individual CIED types other than CRT-P, and that this risk has persisted over the years. We also find that there was no difference in all-cause mortality between sexes in patients undergoing PPM and ICD implantations, while women undergoing CRT implant, with or without a defibrillator, were associated with reduced odds of all-cause mortality compared to men. The observed similarity in odds of all-cause mortality between sexes in the overall cohort was persistent over a decade.

Previous studies have demonstrated an association between sex and adverse outcomes in patients undergoing cardiovascular procedures such as coronary artery bypass grafting 14, percutaneous coronary intervention 15-17 and catheter ablation 18. Although there is evidence to suggest worse outcomes in women after CIED implantations, it is derived from studies that have been subject to limitations such as the restriction of analysis to specific devices (e.g. ICD or PPM only), old registries (prior to 2010) or specific cohorts (e.g. heart failure) and, therefore, are not generalizable from a national or contemporary perspective. 5, 6, 19-23 Furthermore, the current evidence does not inform operators of the differences in trends of outcomes between sexes in recent years. For example, one recent study by Moore et al. examined sex differences in acute complications of CIED implants on a national level in over 80,000 CIED implantations in Australia and New Zealand.4 Their analysis looked at the effect of sex on procedural outcomes in the overall CIED cohort without comparison between CIED subtypes in multivariate analysis for in-hospital outcomes. Another study showed no difference in in-hospital mortality between sexes, in line with our findings, although this was also performed in the overall cohort without stratification of mortality by device type.4

Moore et al. reported increased odds of in-hospital complications (composite of death, reoperation including pleural/pericardial drainage, post-procedural shock and infective endocarditis) in women undergoing any CIED implant (OR: 1.20 [1.11, 1.30]), although

their analysis did not differentiate between CIED types except for pleural/pericardial drainage, despite the contrast in patient characteristics and operative risk between groups undergoing different devices. 4 Similarly, a national analysis of CIED implantations in Denmark between 2010 and 2011 demonstrated an increased risk of major complications in women (risk ratio: 1.4 [1.2-1.8]), although their analysis was not stratified according to type of CIED. 6 Our analysis confirms previous reports of increased odds of complications in women (bleeding, thoracic and cardiac) and also demonstrates this risk in all device types except CRT-P where the odds of complications were non-significant between sexes or lower in women. Furthermore, the present study is the first to report temporal trends of sex difference in procedure-related complications, and demonstrates a rising trend of in-hospital complications (bleeding, thoracic and cardiac) in women undergoing CIED implantations.

Our analysis shows no difference in all-cause mortality between sexes throughout the study period in the overall cohort, except in CRT groups, where all-cause mortality was lower in women. However, the interaction between sex and year indicated a trend towards lower risk of mortality in women compared to men. The reduced mortality in women undergoing CRT implantation could be explained by their more favorable CRT response, which has been previously shown to reduced their as lower risk of all-cause mortality compared to men in a meta-analysis (hazard ratio: 0.67 (0.61–0.74), p=0.03).24 The lack of difference in all-cause mortality between sexes despite increased odds of procedural complications in women may suggest that a significant proportion of deaths are not procedure-related. We were unable to explore this further since our dataset does not capture the cause of death. The majority of previous studies reporting outcomes of CIED implantation have also focused on all-cause mortality, but a Danish registry of 5942 patients undergoing CIED implantation only attributed 1 out of 327 deaths (0.3%) within 6 months to procedure-related causes.6 Previous studies that looked at sex differences demonstrated

similar findings to our study with respect to all-cause mortality, although they were derived from combined analyses of all CIED types, or from specific device cohorts (e.g. ICD only), without looking at sex differences in different device groups.[5, 25] Peterson et al. also reported no difference in all-cause mortality (in-hospital 0.42 vs. 0.41%, p=0.505) between sexes in a NCDR registry analysis of 161,470 patients undergoing ICD implantation in the United States between 2006 and 2007, as did MacFadden et al. in their provincial registry analysis of ICD implants between 2007 and 2010 (1 year mortality hazard ratio: 1.00 [0.64,1.55], p=0.99).[5, 25] The Australian/New Zealand cohort showed no difference in in-hospital mortality between sexes, in line with our findings. although this was also performed in the overall cohort without stratification of mortality by device type.[4]

The rising trend of in-hospital complications in women (bleeding, cardiac and thoracic) over our study period is particularly concerning in view of the advancements in implantation techniques, such as use of ultrasound, as well as more electrophysiologists performing this procedure that receive dedicated 1 to 2 years training (as opposed to cardiologists and surgeons), and suggests that sex is an independent predictor of outcomes. [26] The higher risk of thoracic and cardiac complications in women could be explained by anatomical differences such as smaller thoracic cavity size, smaller subclavian/axillary vein diameters increasing the risk of pneumothorax; and thinner right ventricle walls as well smaller size of coronary sinuses increasing the likelihood of cardiac perforation. [8, 9, 27, 28] It is possible that use of cephalic vein cutdown, ultrasound of vascular access, careful use of fluoroscopy or potentially ultrasound to guide true septal placement of right ventricular leads and his bundle pacing in lieu of coronary sinus or traditional right ventricular apical pacing may decrease this risk. In the right clinical scenarios, use of subcutaneous ICD instead of the traditional transvenous ICD or leadless pacemakers instead of the traditional single lead pacemakers, may further mitigate these risks. Whilst we observed a trend towards worse

outcomes in procedure-related complications (bleeding, thoracic and cardiac) in the CRT-P group, these were not statistically significant that could be due to its small sample size (2.3% of total CIED cohort) compared to all other device subgroups, which may mask any sex differences of potential statistical significance.

Limitations

There are several limitations to our study. First, the administrative nature of the NIS database, as with any such database has limitations around the accuracy of coding with no external validation. However, the use of administrative data has been previously validated for the purpose of cardiovascular research 29, and for capturing CIED-related complications.30 Furthermore, the NIS database has a comparable capture of patient demographics and superior geographic capture of hospitalizations in more than 25 diagnosis groups in comparison to large multistate electronic health record databases.31 Secondly, since the NIS dataset does not provide information on pharmacotherapy, indication for each CIED device (e.g. type of arrhythmia and primary vs. secondary prevention in CRT-D and ICD procedures), subtype of device wherever applicable (e.g. single versus dual chamber pacemaker, subcutaneous ICD, His-bundle pacemaker) and operator experience, we were unable to adjust for the differences in these covariates between the study groups. However, pacemaker type and indication were shown to have an insignificant effect in a large analysis of ICD outcomes in women. 5 Furthermore, due to the observational nature of these data, the results should not be interpreted as causal, but rather relate to associations that require further research. Finally, the NIS dataset only reports in-hospital outcomes and, therefore, the present findings are not be applicable to longer term outcomes.

Conclusion

In our temporal analysis of almost 3 million hospitalizations for de novo CIED implantation over an 11-year period, we demonstrate that women were at an increased risk of in-hospital adverse procedural outcomes compared to men, and that there has been a worsening trend in outcomes for women over the study period. Our findings also show no difference in the risk of all-cause mortality between sexes, although there was a trend towards a lower risk of death in women compared to men. These findings emphasize the need for further research to investigate the exact mechanisms of these sex differences and develop new approaches to neutralize the inherent risk of complications in women undergoing CIED implantation.

Conflicts

DB is paid by Medtronic for educational sessions. Other co-authors have no disclosures and no relationships with the pharmaceutical industry.

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Statement

The manuscript has neither been published nor is currently under consideration for publication by any other journal. All authors have approved the final version of the manuscript.

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Figure Legends:

Figure 1. Proportion of women undergoing CIED implantation procedures according to type of CIED (2004-2014)

Legend: p-values are for trends

Figure 2a. In-hospital outcomes of total CIED cohort according to sex

Legend: p<0.001 for all outcomes; MACE: Composite of mortality, thoracic and cardiac complications, and device-related infection

Figure 2b. In-hospital outcomes of CIED subtypes according to sex

Legend: § non-significant; **†** p<0.05; **‡** p<0.001; **ICD**: automated implantable cardioverter-defibrillator; **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively; **MACE**: Composite of all-cause mortality, thoracic and cardiac complications, and device-related infection; **PPM:** permanent pacemaker.

Figure 3a. Adjusted odds ratio (aOR) of major adverse cardiovascular events (MACE) in women (reference is men).

Legend: ***p<0.01; **† p<0.001**; ICD**: automated implantable cardioverter-defibrillator; **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively; **MACE**: Composite of all-cause mortality, thoracic and cardiac complications, and device-related infection; **PPM:** permanent pacemaker.

Figure 3b. Adjusted odds ratios (aOR) of all-cause mortality and procedure-related complications in women (reference is men)

Legend: † p<0.001**; §** non-significant**; ICD**: automated implantable cardioverter-defibrillator; **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively; **PPM:** permanent pacemaker

Figure 4a. Trend of adjusted odds ratios (aOR) of MACE in women compared with men (2004-2014)*

Legend: *p<0.001 for trend; **MACE**: Composite of all-cause mortality, thoracic and cardiac complications, and device-related infection

Figure 4b. Trend of adjusted odds ratios (aOR) of all-cause mortality and procedure-related complications in women compared with men (2004-2014)*

Legend: *p<0.001 for all 4 trends

Table 1. Patient characteristics according to sex

Variable/Group (%)	Male (58.1)	Female (41.9)	Total	p-value
Number of weighted discharges	1637121	1178492	2815613	<0.001
Type of CIED, %				<0.001
PPM	53.2	74.7	62.2	
CRT-P	2.4	2.3	2.3	
CRT-D	16.7	8.7	13.3	
ICD	27.7	14.2	22.1	
Age (years), median (IQR)	73 (63, 81)	77 (68,84)	75 (65,82)	<0.001
Ethnicity, %				<0.001
White	79.9	77.6	78.9	
Black	8.8	10.8	9.6	
Hispanic	6.4	6.6	6.5	
Asian/Pacific Islander	1.8	2.1	1.9	
Native American	0.5	0.5	0.5	
Other	2.6	2.3	2.5	
Elective Admission, %	33.5	26.9	30.8	<0.001
Weekend admission, %	14.1	16.6	15.1	<0.001
Primary expected payer, %				<0.001
Medicare	71.2	78.6	74.3	
Medicaid	4.2	4.5	4.4	
Private Insurance	20.4	14.2	17.9	
Self-pay	1.9	1.3	1.7	
No charge	0.2	0.2	0.2	
Other	2.0	1.1	1.6	
Median Household Income (Percentile), %				<0.001
0-25th	24.9	27.0	25.8	
26-50th	26.3	26.9	26.6	
51-75th	24.8	24.0	24.5	

Variable/Group (%)	Male (58.1)	Female (41.9)	Total	p-value
76-100th	24.0	22.1	23.2	
Shock, %	1.5	1.2	1.4	<0.001
All-cause infection, %*	2.5	2.4	2.5	0.198
Cardiac Arrest, %	3.7	3.7	3.7	0.612
Ventricular Tachycardia, %	20.1	10.2	16.0	<0.001
Ventricular Fibrillation, %	3.8	2.5	3.2	<0.001
Comorbidities, %				
Dyslipidaemia	43.9	39.7	42.1	<0.001
Smoking	8.8	5.5	7.4	<0.001
Atrial Fibrillation	36.0	41.3	38.2	<0.001
Thrombocytopaenia	3.7	2.8	3.3	<0.001
Previous AMI	16.9	8.8	13.5	<0.001
History of IHD	57.6	37.5	49.2	<0.001
Previous PCI	11.7	7.1	9.8	<0.001
Previous CABG	18.5	7.5	13.9	<0.001
Previous CVA	4.1	4.9	4.5	<0.001
Family history of CAD	2.8	2.5	2.7	<0.001
AIDS	0.1	0.0	0.1	<0.001
Alcohol abuse	2.8	0.6	1.9	<0.001
Deficiency anaemias	11.3	15.4	13.0	<0.001
Chronic Blood loss anaemia	0.6	0.9	0.7	<0.001
RA/collagen vascular diseases	1.2	3.2	2.1	<0.001
Heart Failure	46.3	40.2	43.8	<0.001
Chronic pulmonary disease	19.1	19.1	19.1	0.103
Coagulopathy	4.8	4.0	4.5	<0.001
Depression	4.3	8.0	5.8	<0.001
Diabetes	25.7	23.9	24.9	<0.001
Diabetes with complications	4.6	4.4	4.5	<0.001

Variable/Group (%)	Male (58.1)	Female (41.9)	Total	p-value
Drug abuse	1.1	0.6	0.9	<0.001
Hypertension	62.5	67.0	64.3	<0.001
Hypothyroidism	7.6	20.0	12.8	<0.001
Liver disease	1.2	1.0	1.1	<0.001
Lymphomas	0.7	0.6	0.6	<0.001
Fluid and electrolyte disturbances	15.3	20.7	17.5	<0.001
Metastatic cancer	0.5	0.4	0.5	<0.001
Other neurological disorders	5.4	6.9	6.0	<0.001
Obesity	8.2	9.4	8.7	<0.001
Paralysis	1.5	1.6	1.5	<0.001
Peripheral vascular disease	9.8	7.6	8.9	<0.001
Psychoses	1.5	2.1	1.8	<0.001
Pulmonary circulation disorder	0.5	0.8	0.6	<0.001
Renal failure (chronic)	17.0	14.7	16.0	<0.001
Solid tumour without metastases	1.5	0.9	1.2	<0.001
Valvular heart disease	1.2	1.7	1.4	<0.001
Weight loss	1.9	2.3	2.0	<0.001
Dementia	1.7	2.7	2.1	<0.001
Hospital bed size, %				<0.001
Small	8.5	9.2	8.8	
Medium	21.3	22.6	21.8	
Large	70.2	68.2	69.4	
Hospital Region, %				<0.001
Northeast	21.5	21.1	21.4	
Midwest	23.3	24.0	23.6	
South	37.0	37.8	37.3	
West	18.1	17.1	17.7	
Location/ Teaching status, %				<0.001

Variable/Group (%)	Male (58.1)	Female (41.9)	Total	p-value
Rural	6.0	7.4	6.6	
Urban non-teaching	40.1	41.8	40.8	
Urban- teaching	53.9	50.8	52.6	

* **All-cause infection**: Composite of septicaemia, viraemia and bacteraemia; **HRF:** High-risk frailty; **IRF:** Intermediate-risk frailty; **LRF:** Low-risk frailty.

Table 2. Clinical outcomes of total cohort according to sex

Variable/Group (% of cohort)	Male (58.1)	Female (41.9)	Total	p-value
In-hospital MACE, %*	4.5%	5.6%	5.0%	<0.001
In-hospital all-cause mortality, %	0.9%	1.0%	1.0%	<0.001
In-hospital procedure-related bleeding, %	2.7%	3.2%	2.9%	<0.001
In-hospital thoracic complications, %	2.4%	3.8%	3.0%	<0.001
In-hospital cardiac complications, %	0.3%	0.5%	0.4%	<0.001
Device-related infection, %*	1.1%	0.6%	0.9%	<0.001

* **MACE:** Composite of mortality, thoracic complications, cardiac complications, and device-related infection.

Table 3. Clinical Outcomes according to sex and type of CIED

Outcome/Study Group	Male	Female	Total	p-value
In-hospital MACE, %*				
PPM, %	4.6%	5.8%	5.2%	<0.001
CRT-P, %	7.3%	6.6%	7.0%	0.001
CRT-D, %	4.7%	5.1%	4.8%	<0.001
ICD, %	4.0%	4.8%	4.2%	<0.001
In-hospital all-cause mortality, %				
PPM, %	1.0%	1.2%	1.1%	<0.001
CRT-P, %	1.6%	1.0%	1.4%	<0.001
CRT-D, %	0.8%	0.6%	0.8%	<0.001
ICD, %	0.6%	0.7%	0.6%	<0.001
Procedure-related bleeding, %				
PPM, %	3.3%	3.4%	3.4%	<0.001
CRT-P, %	3.6%	3.3%	3.4%	0.041
CRT-D, %	1.8%	2.1%	1.9%	<0.001
ICD, %	2.0%	2.5%	2.2%	<0.001
In-hospital thoracic complications, %				
PPM, %	2.6%	4.0%	3.3%	<0.001
CRT-P, %	4.1%	4.4%	4.2%	0.090
CRT-D, %	2.3%	3.3%	2.6%	<0.001
ICD, %	2.0%	2.9%	2.2%	<0.001
In-hospital cardiac complications, %				
PPM, %	0.3%	0.4%	0.4%	<0.001
CRT-P, %	0.4%	0.6%	0.5%	0.026
CRT-D, %	0.3%	0.6%	0.3%	<0.001
ICD, %	0.3%	0.6%	0.4%	<0.001
Device-related infection, %*				
PPM, %	0.9%	0.5%	0.7%	<0.001
CRT-P, %	1.8%	1.1%	1.5%	<0.001
CRT-D, %	1.6%	0.9%	1.4%	<0.001
ICD, %	1.3%	0.8%	1.2%	<0.001

*__MACE:__ Composite of mortality, thoracic complications, cardiac complications and device-related infection; **ICD**: implantable cardioverter-defibrillator; **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively; **PPM:** permanent pacemaker.

Table 4. Adjusted odds of adverse outcomes in women

Frailty Risk Group/Outcome	**MACE***		**All-cause Mortality**		**Procedure-related Bleeding**		**Thoracic Complications**		**Cardiac Complications**	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Total										
Male**	-	-	-	-	-	-	-	-	-	-
Female	1.17 [1.16, 1.19]	<0.001	0.96 [0.94, 1.00]	0.198	1.13 [1.12, 1.15]	<0.001	1.42 [1.40, 1.44]	<0.001	1.44 [1.38, 1.50]	<0.001
PPM										
Male**	-	-	-	-	-	-	-	-	-	-
Female	1.25 [1.23, 1.27]	<0.001	1.01 [0.98, 1.05]	0.367	1.10 [1.08, 1.12]	<0.001	1.49 [1.46, 1.52]	<0.001	1.37 [1.30, 1.44]	<0.001
CRT-P										
Male**	-	-	-	-	-	-	-	-	-	-
Female	0.91 [0.85, 0.97]	0.005	0.70 [0.60, 0.82]	<0.001	1.01 [0.92, 1.11]	0.872	1.04 [0.95, 1.12]	0.424	1.06 [0.84, 1.35]	0.610
CRT-D										
Male**	-	-	-	-	-	-	-	-	-	-
Female	1.06 [1.02, 1.10]	0.003	0.72 [0.66, 0.80]	<0.001	1.21 [1.15, 1.28]	<0.001	1.38 [1.32, 1.45]	<0.001	1.65 [1.47, 1.85]	<0.001
ICD										
Male**	-	-	-	-	-	-	-	-	-	-
Female	1.07 [1.04, 1.10]	<0.001	1.05 [0.97, 1.13]	0.252	1.23 [1.18, 1.28]	<0.001	1.28 [1.23, 1.33]	<0.001	1.59 [1.46, 1.73]	<0.001

*__MACE:__ Composite of mortality, thoracic complications, cardiac complications and device-related infection; **ICD**: implantable cardioverter-defibrillator; **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively; **PPM:** permanent pacemaker.