Manuscript Details

Manuscript number	IJC_2019_4624_R1
Title	Sex differences in rates and causes of 30-day readmissions after cardiac electronic device implantations: insights from the Nationwide Readmissions Database.
Article type	Original article

Abstract

Background: Women undergoing cardiac implantable electronic device (CIED) implantation are at a higher risk of procedure-related complications. The present study examined sex differences in rates and causes of 30-day readmissions following CIED implantation. Methods: Using the United States Nationwide Readmissions Database (NRD), all adults who had undergone CIED implantation (cardiac resynchronization therapy (CRT), permanent pacemakers (PPM) and implantable cardioverter defibrillators (ICD)) between January 2010 and September 2015 were included. We compared rates, trends and causes of 30-day readmissions between sexes, and examined associations between sex and outcomes (adjusted odds ratios (aOR) and 95% confidence intervals (CI)) Results: Out of 1,155,992 index hospitalizations for CIED implantation, 43.1% of the patients were women. All-cause 30-day readmissions were persistently higher in women than men but declined in both sexes over the study period, more so in women (women vs. men; 2010: 15.0% vs. 14.1%; 2015: 13.7% vs.13.4%). Women were at higher odds of readmission due to cardiac (aOR 1.22, 95%CI 1.20-1.24) and device-related complications (aOR 1.18, 95%CI 1.15-1.20) compared to men, but no difference odds of all-cause readmission were found between sexes (women: aOR 0.998, 95%CI 0.997-1.008). The most common cardiac and non-cardiac causes of readmission were heart failure and infection, respectively, and these were similar in both sexes (men vs. women: 17.8% vs. 17.6% and 10.7% vs. 10.8%, respectively). Conclusion: Women are persistently at higher risk of readmission due to cardiac causes and device-related complications compared to men over a six-year period, but no difference in all-cause readmissions was found between sexes.

Keywords	Cardiac devices, CIED, pacemakers, defibrillators, cardiac resynchronization, sex, readmissions, outcomes
Taxonomy	Risk Factor, Electrophysiology, Epidemiology
Manuscript category	Original clinical research studies, basic science/translational research papers
Manuscript region of origin	Europe

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Submission Files Included in this PDF

File Name [File Type]

CIED Readmissions rebuttal cover letter.docx [Cover Letter]

Response to reviewers.docx [Response to Reviewers]

Highlights.docx [Highlights]

Abstract.docx [Abstract]

Title page IJC.docx [Title Page (with Author Details)]

CIED Gender Readmission paper IJC.docx [Manuscript File]

Figure 1A.tiff [Figure]

Figure 1B.tiff [Figure]

Figure 2a.tiff [Figure]

Figure 2b.tiff [Figure]

Figure 3.tiff [Figure]

Table 1a.docx [Table]

Table 1b.docx [Table]

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Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:
The authors do not have permission to share data

Keele Cardiovascular Research Group

Dear Professor Paolo G. Camici, Editor in Chief,

We thank the Editorial Committee and the Reviewer for their valuable comments on the manuscript entitled 'Sex differences in rates and causes of 30-day readmissions after cardiac electronic device implantations: insights from the Nationwide Readmissions Database.' We feel that these comments have improved the quality of our manuscript. We have attempted to answer all the comments fully as outlined in the rebuttal and tracked all new changes in the manuscript.

We hope that we have addressed all reviewers' comments sufficiently and hope that these changes will enable publication of our paper in the International Journal of Cardiology.

Yours sincerely

Dr Mohamed Mohamed and Prof. Mamas Mamas
On behalf of submitting authors

We list our reply to the reviewer's comments in the file entitled 'Response to Reviewers' as per journal instructions.

Response to reviewers

Reviewer 1

Well-written observational registry analysis of readmissions after CIED implantations, focusing on differences between sex. Females had more readmissions for cardiac causes, but not for all-causes in adjusted analysis.

Comment 1. Major: Why did the study period end in 2015? There is a trend towards declining readmission rates and differences between sexes being less over the period 2010-2015. Would strengthen the data very much to include contemporary data also.

Response: We thank the reviewer for their interest in our paper and for their comments. In the cases of national databases such as NRD, there is always have a 2-year between the time that hospitalizations surveyed and their public release for their purpose of research. The most recent NRD year accessible to researchers as of today is 2016 (link: https://www.distributor.hcup-us.ahrq.gov/Databases.aspx). However, starting from the final quarter of 2015, NRD has moved to a new coding system (ICD-10), which classifies certain comorbidities, procedures and complications in a different way to ICD-9, the coding system used in the present study. Therefore, other than the fact that we didn't have access to 2016, we also didn't consider using it for the purpose of this study so as to have a homogenous cohort using a unified coding system. We fully agree with the reviewer in that more longitudinal analysis would be useful and we hope to do this once more calendar years are available for research purposes.

Comment 2. Abstract: Must be clear that the OR's are from adjusted analysis. Otherwise, it is not easy to understand why female had more re-admissions, but the OR for all-cause readmissions was not different from 1.0.

Response: We have now updated the abstract to clarify that the OR's are adjusted (aOR).

Reviewer 2

This is an interesting article regarding Sex differences in rates and causes of 30-day readmissions after cardiac electronic device implantations: insights from the NRD by a team with an important experience in the field of big data.
There are some issues that should be clarified to improve the quality of the manuscript:

Comment 1.- Supp Fig 2: It looks like that ICD readmissions due to CV are higher in men that in women, how can we interpret this finding regarding to the results of CRT / PPM?

Response: As the reviewer kindly noted, Supplementary Figure 2 (soon to be a main figure as per the reviewer's second comment) illustrates readmission causes according to device subtype. We observe that CV readmission rates are higher in men in the ICD subgroup, but lower in the PPM and CRT-P groups, whereas no difference was found in the CRT-D group. The higher CV readmission rates in women in the PPM and CRT-P groups could be explained their higher prevalence of heart failure and AF as observed in our analysis of baseline characteristics according to device subgroups (now added to the supplements as Supplementary Table 3). Indeed we observe that readmissions due to arrhythmias and heart failure were higher in women in the PPM (9.2% vs. 6.6% and 15.4% vs. 12.4%, respectively) and CRT-P (6.7% vs. 5.7% and 25.6% vs. 23.8%, respectively) groups (Supplementary Table 4), although this was not statistically significant in the latter group, likely due to its small sample size. We have updated our results section to describe the differences in characteristics between device subgroups (quoted below). Our discussion has touched on this as quoted below.

Under Results:

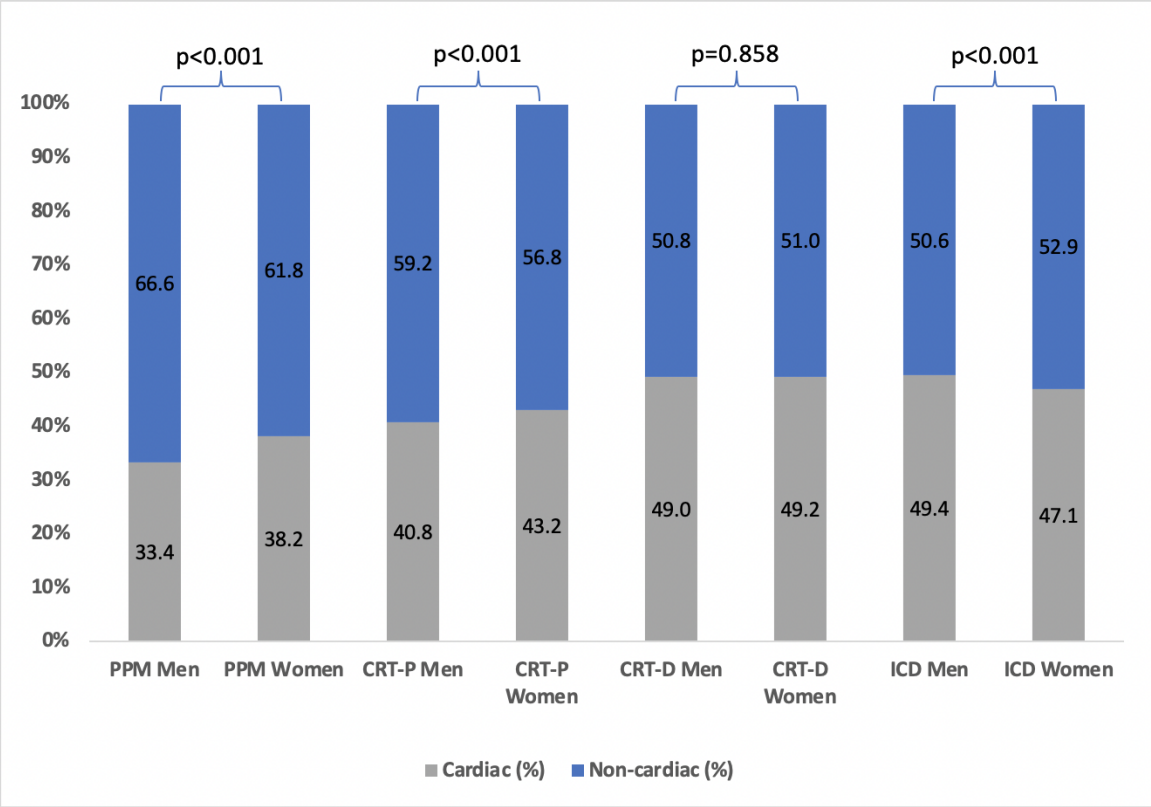
"Within the CIED subgroups in the readmitted cohort, women were older in the PPM group and younger in the CRT-D group, while no difference in age between sexes was found in the CRT-P and ICD groups. (Supplementary Table 3). Women in the PPM and CRT-P subgroups were more likely to have an urgent admission (vs. elective) or admission on a weekend compared to men, and had a higher prevalence of atrial fibrillation, chronic blood loss and deficiency anemias and heart failure but a lower prevalence of renal failure, coagulopathies and ventricular tachycardia.:

Under Discussion:

"Our analysis highlights a disparity between device groups with regard to sex differences in causes of cardiac readmission. For example, although no difference was found in heart failure readmissions in the total cohort, women who had undergone PPM implantation were more likely to be readmitted for heart failure while other device groups either demonstrated no sex difference or lower rates of heart failure readmission amongst women. This is likely due to the observed higher prevalence of heart failure in women compared to men in the PPM group who may have not fulfilled the criteria for CRT device eligibility and are, therefore, presenting with frequent heart failure decompensations. Furthermore, the response rates to CRT are reported to be better in women than in men and that might contribute to the lack of sex-difference in HF hospitalizations among those patients receiving CRT. Our analysis of the total cohort also demonstrated higher rates of arrhythmias and device-related complications in women compared to men and, although this was also true in most device groups, there was no sex difference in either condition in patients undergoing CRT-P implantation. The latter is likely due to the smaller sample size of the CRT-P group in comparison to other groups (2.9% of the readmission cohort), masking any possible sex differences in this device group."

Comment 2.- Please improve the presentation of Supplementary Figure 2: write the p value and modify the presentation of it. I think this figure should be included in the article and not only as suppl material.

Response: We thank the reviewer for this suggestion. We did initially want to include it in our main figures, but the journal submission rules restrict us from using more than 4 tables/figures combined in the main paper, which is why we had moved it to the supplements. We have added p-values to the figure itself and made improvements to its presentation (below) and it is now a main figure (Figure 1B). We hope that it is now satisfactory to the reviewer.



Comment 3.- Table 1a: all p-values of the second page are missing, please add it.

Response: Thank you. This has now been updated.

Comment 4.- Discussion: compare with other device implantation (TAVI, stent in the context of AMI), do we have the same results?

Response: We have updated the discussion with findings from studies that looked at sex differences in difference cardiovascular procedure cohorts (quoted below).

Under discussion:

"There is a growing interest in the study of sex differences in readmissions after cardiovascular procedures such as PCI, TAVI and catheter ablation for AF. However, no study has examined these differences amongst those undergoing de novo CIED implantation. Despite the baseline differences in patients undergoing each type of procedure, sex disparities in rates and causes

of readmissions have been previously observed. In patients undergoing catheter ablation for AF, women were shown to have higher rates of all-cause, cardiac and arrhythmia-related (AF/atrial tachycardia) 30-day readmissions. In contrast, the rates of 30-day cardiac readmissions were higher in men compared to women after PCI in a national sample of more than 800,000 patients from the United States, and in a German registry analysis of patients undergoing TAVI, men were associated with increased odds of 1-year all-cause readmissions."

Comment 5.- Supplementary Table 5: do we have any data of a higher incidence / prevalence of AF due to the higher Acute stroke/TIA, %?

Response: We thank the reviewer for raising this point. Indeed the prevalence of AF was much higher in women compared to men, especially in the readmitted group (49.4% vs. 43.6%; Table 1a) and this may account for the higher stroke rates in this group, especially if their anticoagulation was interrupted prior to, or shortly after, CIED implantation (especially in the case of warfarin).

Comment 6.- Comment: This work constitutes part of a PhD for Dr Mohamed Mohamed that is supported by Medtronic Ltd. Dr Mohamed is not listed as author, please delete this comment.

Response: We are not sure why the authorship was not clarified, and we suspect it's because the journal operates with a double-blind review policy, however, Mohamed Mohamed (myself) is the first author of the paper. Since my PhD funding comes from Medtronic Ltd, I am under an obligation to acknowledge their funding in the manuscript. We hope that you find this justification acceptable and we thank you for your thorough review of our manuscript.

Highlights

- Largest study of sex differences in rates and causes of 30-day readmissions after CIED implantation.
- No difference in all-cause readmissions was found between sexes over a 6-year period.
- Women are at a greater risk of cardiac and device-related 30-day readmissions.
- Reduction of procedural complications in women may improve their rates of cardiac readmission.

Abstract

Background: Women undergoing cardiac implantable electronic device (CIED) implantation are at a higher risk of procedure-related complications. The present study examined sex differences in rates and causes of 30-day readmissions following CIED implantation.

Methods: Using the United States Nationwide Readmissions Database (NRD), all adults who had undergone CIED implantation (cardiac resynchronization therapy (CRT), permanent pacemakers (PPM) and implantable cardioverter defibrillators (ICD)) between January 2010 and September 2015 were included. We compared rates, trends and causes of 30-day readmissions between sexes, and examined associations between sex and outcomes (adjusted odds ratios (aOR) and 95% confidence intervals (CI))

Results: Out of 1,155,992 index hospitalizations for CIED implantation, 43.1% of the patients were women. All-cause 30-day readmissions were persistently higher in women than men but declined in both sexes over the study period, more so in women (women vs. men; 2010: 15.0% vs. 14.1%; 2015: 13.7% vs.13.4%). Women were at higher odds of readmission due to cardiac (aOR 1.22, 95%CI 1.20-1.24) and device-related complications (aOR 1.18, 95%CI 1.15-1.20) compared to men, but no difference odds of all-cause readmission were found between sexes (women: aOR 0.998, 95%CI 0.997-1.008). The most common cardiac and non-cardiac causes of readmission were heart failure and infection, respectively, and these were similar in both sexes (men vs. women: 17.8% vs. 17.6% and 10.7% vs. 10.8%, respectively).

Conclusion: Women are persistently at higher risk of readmission due to cardiac causes and device-related complications compared to men over a six-year period, but no difference in all-cause readmissions was found between sexes.

Key Words: Cardiac devices, CIED, pacemakers, defibrillators, cardiac resynchronization, sex, readmissions, outcomes

Sex differences in rates and causes of 30-day readmissions after cardiac electronic device implantations: insights from the Nationwide Readmissions Database.

Short Title: Sex differences in post-CIED readmissions.

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Word count (inc. abstract): 4560

Introduction

The rate of cardiac implantable electronic device (CIED) implantations, including permanent pacemakers (PPM), cardiac resynchronization therapy with pacemakers (CRT-P) or defibrillators (CRT-D) and implantable cardioverter defibrillators (ICD), has grown considerably over the past decade, as has the rate of complications resulting from these procedures. [1-4]

Unplanned hospital readmissions may occur as a consequence of such complications following CIED implantation, or may result in the sub-optimal provision of care during the index hospitalization.[5, 6] Hospital readmissions represent a significant burden for patients and healthcare systems, which may incur financial penalties as a result of high readmission rates, as they are frequently perceived as a measure of efficiency and quality of healthcare delivery.[7] Women have been shown to carry a higher risk of procedure-related complications following CIED implantation, partly due to their older age at the time of procedure, greater comorbid burden and anatomical differences compared to men.[8-11] Little is known about sex differences in unplanned readmissions, their temporal trends and causes in patients that have undergone CIED implantation.

The present study examined national-level trends, causes and predictors of 30-day readmissions after hospitalizations for de novo CIED implantation between January 2010 and September 2015, stratified by sex and CIED type.

Methods

Data Source

The Nationwide Readmissions Database (NRD) is a nationally representative sample of all-age, all-payer discharges from United States (U.S.) nonfederal hospitals sponsored by the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research

and Quality (AHRQ) and is a database of inpatient stays and readmissions that can be used to generate national estimates of readmissions. [12] The NRD dataset constitutes a stratified sample from 22 states with anonymized data from more than 17 million hospitalizations annually from 22 states and provides sampling weights to calculate national estimates that represent more than 50% of the U.S. population (approximately 36 million hospitalizations per annum).

Study Design and Population

All adults (aged ≥18 years) who underwent de novo CIED implantation (PPM, CRT-P, CRT-D, and ICD) in an index hospitalization between January and November of the years 2010 to 2014, and between January and August in 2015, were included, along with any records for readmission within 30 days of their index episode. We excluded index hospitalizations for CIED implantation in the last month of each study year (December in 2010-2014 and September in 2015) as these patients would not have not had 30-day follow-up and data was annualized and therefore impossible to track patients across years. Patient characteristics and in-hospital and readmission outcomes and procedures were extracted using the International Classification of Diseases, ninth revision (ICD-9) and Clinical Classification Software (CCS) diagnosis and procedural codes provided in the supplements (Supplementary Table 1). Causes of readmission were extracted using primary diagnoses CCS codes provided in Supplementary Table 2. The study cohort was stratified by gender into two groups; men and women. A flow diagram illustrating the selection process and missing variables in the present study is presented in Supplementary Figure 1. Cases excluded due to missing variables represented less than 0.14% (n=1170) of the original dataset. HCUP predefined discharge weights for each hospital were applied to the included records to produce the study population's discharge estimates.

Outcomes

We examined the difference in rates, trends and causes of 30-day readmissions between sexes and according to type of CIED, as well as the predictors of cardiac readmission. We also

examined sex differences in clinical outcomes of the readmitted cohort, including the rates of in-hospital mortality, acute stroke or transient ischemic attack (TIA), acute kidney injury (AKI), bleeding, device-related infection and device revision or removal.

Statistical Analysis

Statistical analysis was performed using SPSS version 24 (IBM Corp, Armonk, NY). 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.

Multivariable logistic regression models were constructed to assess the predictors of readmission from the index hospitalization variables, including female sex and type of CIED, measured by odds ratios (aOR, 95% confidence interval (CI)) adjusted for the following covariates: age, weekend admission, elective admission, primary expected payer, median household income, atrial fibrillation (AF), thrombocytopenia, ventricular tachycardia (VT) and fibrillation (VF), dyslipidemia, smoking status, previous AMI, previous coronary artery bypass graft (CABG), history of ischemic heart disease (IHD), previous PCI, previous cerebrovascular accidents (CVA) including stroke and TIA, family history of coronary artery disease (CAD), bed size of hospital, year of admission, Elixhauser comorbidities (acquired immune deficiency syndrome (AIDS), deficiency anemias, chronic blood loss anemia, rheumatoid arthritis/collagen vascular diseases, congestive heart failure, chronic pulmonary disease, coagulopathy, depression, diabetes (uncomplicated), diabetes with chronic complications, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, obesity, peripheral vascular disorders (PVD), psychoses, pulmonary circulation disorders, chronic renal failure, solid tumor without metastasis, peptic ulcer disease excluding bleeding, valvular heart disease, and weight loss), and complications during index admission (acute stroke or TIA, AKI, procedure-related

bleeding, thoracic and cardiac complications). Thoracic complications were defined as a composite of acute pneumothorax or hemothorax, with or without drainage, or thoracic vascular injury, while cardiac complications were defined as a composite of cardiac tamponade, hemopericardium, pericardiocentesis.

Results

A total of 1,155,992 hospitalizations for CIED implantation were recorded between January 2010 and August 2015. The percentage of women undergoing CIED implantation remained relatively stable through the study period (2010: 42.3% vs. 2015: 43.0%, $p<0.001$).

Several key differences in patient demographics and procedure-related outcomes were observed between men and women in the index hospitalization for CIED implantation (Table 1a). Overall, women were older, more likely to be admitted during a weekend, less likely to have an elective admission, and had a higher prevalence of previous CVA, concomitant AF, anemia (chronic and iron deficiency), hypertension, hypothyroidism, fluid and electrolyte disorders, and valvular heart disease. However, there was a higher prevalence of cardiovascular comorbidities amongst men such as heart failure, previous coronary-related disease and coronary intervention (previous MI, PCI and CABG), and diabetes. While these patterns of sex differences were observed in both the readmission and non-readmission groups, the prevalence of all comorbidities was much higher in the readmission group. Within the CIED subgroups in the readmitted cohort, women were older in the PPM group and younger in the CRT-D group, while no difference in age between sexes was found in the CRT-P and ICD groups. (Supplementary Table 3). Women in the PPM and CRT-P subgroups were more likely to have an urgent admission (vs. elective) or admission on a weekend compared to men, and had a higher prevalence of atrial fibrillation, chronic blood loss and deficiency anemias and heart failure but a lower prevalence of renal failure, coagulopathies and ventricular tachycardia.

There was no difference in the rate of PPM implantation between sexes although women were less likely than men to undergo implantation of other types of CIEDs (CRT-P: 42% vs. 58%, CRT-D: 27.9% vs. 72.1%, ICD: 28.1% vs. 71.9%).

30-day Readmissions

The overall rate of 30-day readmissions was 14.0% while the rate of cardiac readmissions was 5.6% (40 % of all readmissions), and both were observed to be higher in women than in men (overall: 14.4% vs. 13.6% and cardiac: 5.8% vs. 5.5%, $p<0.001$ for both). Women were more likely to be readmitted earlier than men (mean time: 12 vs. 13 days, $p<0.001$). The rates of 30-day readmission (all-cause, cardiac and device-related) declined in both sexes from 2010 to 2015 and, although the rates were higher in women in earlier years, this gap was progressively eliminated in later years (Figure 1). In multivariable analysis, female sex was independently associated with increased odds of readmission due to cardiac causes (aOR 1.22 95% CI 1.20 - 1.24, $p<0.001$), Supplementary Table 5, Figure 2A) and, more specifically, device-related complications (aOR 1.26 95% CI 1.19- 1.33, $p<0.001$), both of which persisted throughout the study period. (Figure 3A and Figure 3B). The odds for all-cause readmission for women were compared to men (aOR 0.998 95% CI 0.997 - 1.008, $p=0.660$).

Subgroup analyses according to the type of CIED demonstrated significantly higher rates of cardiac readmission in women who have undergone PPM and CRT-P implantation (38.2% vs. 33.4% and 43.2% vs. 40.8%, respectively, $p<0.001$ for both) compared to men, and lower rates of cardiac readmission in women who have undergone ICD implantation (47.1% vs. 49.4%, $p<0.001$). (Figure 1B) There were no sex differences in patients who had undergone CRT-D implantation (men: vs. women: 49.0% vs. 49.2%, $p=0.850$).

The top non-cardiac causes of readmission were due to infectious, respiratory, PVD, renal, gastrointestinal and stroke/TIA diagnoses. (Table 1b) Women were more likely to be readmitted for respiratory and gastrointestinal conditions but less likely to be readmitted for

renal and PVD-related presentations. However, there was no difference between sexes in readmissions due to infection and stroke/TIA.

Overall, heart failure was the most common cardiac cause of readmission. While there was no difference in heart failure readmissions between sexes in the total CIED cohort (men 17.8% vs. women 17.6%, p=0.242) (Table 1b, Supplementary Figure 2) and across most CIED subtypes (CRT-P, CRT-D and ICD), women were more likely to be readmitted due to heart failure in the PPM group (Supplementary Table 4). Arrhythmias and device-related complications were the next most common cardiac causes of readmission and were both higher in women (9.1% vs. 8.5% and 3.5% vs. 3.0%, respectively, p<0.001 for both) in the total CIED cohort. (Table 1b, Supplementary Figure 2). This pattern was observed across all CIED subtypes for device-related complications, however, women in the PPM and CRT-P were more likely to be readmitted for arrhythmias compared to men, while those in the CRT-D and ICD groups were less likely to be readmitted for arrhythmias compared to men. (Supplementary Table 4)

Regression analysis was performed to identify predictors of readmission due to cardiac causes from variables related to the index admission. In comparison to PPM, all complex types of CIED were associated with increased odds of cardiac readmission with the highest being CRT-D and ICD groups (aOR CRT-P: 1.19 95% CI 1.13 - 1.25, CRT-D: 1.46 95% CI 1.42 - 1.50, ICD: 1.46 95% CI 1.43 - 1.50). (Figure 2B) All in-hospital procedure-related complications (AKI, acute stroke, thoracic and cardiac complications and post-procedural hemorrhage) were also associated with increased odds of cardiac readmission, the highest being cardiac complications (aOR 1.42 95% CI 1.24 - 1.62) and AKI during index admission (aOR 1.29 95% CI 1.26 - 1.32) (Figure 2B). Other variable associated with increased odds of cardiac readmission included previous history of heart failure, VT, AF, deficiency anemias, AIDS, chronic pulmonary disease, coagulopathy and lymphoma. (Supplementary Table 5, Figure 2A)

Readmission episode in-hospital outcomes

The rates of all-cause mortality and device revision or removal in the 30-day readmissions episodes were 4.9% and 5.2%, respectively, with no difference between sexes (Supplementary Table 6, Figure 6). Women were more likely to experience acute stroke/TIA during the readmission episode (2.4% vs. 1.9%) but less likely to experience all other complications (AKI: 13.7% vs. 15.6%, bleeding: 4.9% vs. 5.2%, and device-related infection: 2.8% vs. 3.7%).

Discussion

The present study is the largest to examine national-level sex differences in trends and predictors of 30-day readmissions in over 1 million patients with de novo CIED implantations and provides several novel findings. We report a decline in the rates of all-cause and cardiac 30-day readmissions in both sexes over time, more so in women who were at a much higher risk of readmission in earlier years compared to men. We show that women have increased odds of cardiac readmission and are more likely to be readmitted with device-related complications compared to men throughout the study duration. Finally, we show that there was no sex difference in in-hospital mortality amongst those readmitted and that women were less likely to experience adverse events in their readmissions. The requirement for device revision or extraction, was however similar in both sexes.

There is a growing interest in the study of sex differences in readmissions after cardiovascular procedures such as PCI, TAVI and catheter ablation for AF. [13-15] However, no study has examined these differences amongst those undergoing de novo CIED implantation. Despite the baseline differences in patients undergoing each type of procedure, sex disparities in rates and causes of readmissions have been previously observed. In patients undergoing catheter ablation for AF, women were shown to have higher rates of all-cause,

cardiac and arrhythmia-related (AF/atrial tachycardia) 30-day readmissions.[15] In contrast, the rates of 30-day cardiac readmissions were higher in men compared to women after PCI in a national sample of more than 800,000 patients from the United States, [14] and in a German registry analysis of patients undergoing TAVI, men were associated with increased odds of 1-year all-cause readmissions. [13]

To the best of our knowledge, the present study is the first to examine trends of readmissions following CIED implantation according to sex. Pasupula et al. reported a reduction in 30-day readmissions (14% to 13%) after CIED implantation over a five-year period (2010 to 2014).[16] However, their descriptive analysis did not compare sex differences in readmission trends, particularly given that sex has previously been shown to be an independent risk factor for procedure-related complications. [8] Our analysis shows a downward trend of 30-day all-cause readmissions over a five-year horizon in both sexes and that women were more likely to be readmitted after CIED implantation, although the gap between sexes has narrowed in later years. This reduction in overall rate of readmission in both sexes, especially women, could be attributed to improvements in the quality of care and discharge planning offered to patients undergoing CIED implantation. However, a concerning finding is the persistent increased risk of cardiac and device-related readmissions amongst women throughout the study period despite advancements in implantation techniques in recent years (e.g. ultrasound guidance, dedicated training fellowships for operators). [9, 17-19] We believe that this is likely due to the higher rate of procedure-related complications in women during the index admission as demonstrated in our study as well as in previous reports. [8]

One of the key aspects of our analysis was the comparison of sex differences in cardiac and non-cardiac causes of 30-day readmission. While previous studies have looked at readmissions following CIED implantation, no study has examined the trend and overall causes of these readmissions according to sex and type of CIED. [8, 20-22] In a national registry analysis of CIED implantations in Australia and New Zealand, Moore et al. reported no

difference in hospitalizations for device-related complications between sexes as part of their secondary outcomes (women: 3.4% vs. men: 3.5%, OR 1.05 [0.97, 1.13]) in over 80000 patients.[8] However, their analysis was based on a much smaller cohort with a lower proportion of women (37.9% vs. 43.1%) and patients in receipt of complex pacing (CRT and ICD: 24.2% vs. 36.6%) compared to our study and only focused on hospitalizations for device-related complications. In contrast, our analysis provides insight into the common cardiac and non-cardiac causes of 30-day readmission after CIED implantation. Although we report a similarity in the most common cardiac (heart failure) and non-cardiac (infection) causes of readmission between sexes, we show that other common cardiac causes of readmission such as arrhythmias and device-related complications are more likely to occur in women. Even after adjustment for baseline and procedural differences (device type and complications in the index episode), women remained at increased odds of 30-day readmissions for cardiac (aOR 1.22 [1.20, 1.24]) and device-related causes (aOR 1.26 [1.19, 1.33]) compared to men.

Our analysis highlights a disparity between device groups with regard to sex differences in causes of cardiac readmission. For example, although no difference was found in heart failure readmissions in the total cohort, women who had undergone PPM implantation were more likely to be readmitted for heart failure while other device groups either demonstrated no sex difference or lower rates of heart failure readmission amongst women. This is likely due to the observed higher prevalence of heart failure in women compared to men in the PPM group who may have not fulfilled the criteria for CRT device eligibility and are, therefore, presenting with frequent heart failure decompensations. Furthermore, the response rates to CRT are reported to be better in women than in men and that might contribute to the lack of sex-difference in HF hospitalizations among those patients receiving CRT.[23] Our analysis of the total cohort also demonstrated higher rates of arrhythmias and device-related complications in women compared to men and, although this was also true in most device groups, there was no sex difference in either condition in patients undergoing CRT-P implantation. The latter is

likely due to the smaller sample size of the CRT-P group in comparison to other groups (2.9% of the readmission cohort), masking any possible sex differences in this device group. A further possible explanation to the variation in causes of readmission between device groups may be related to differences in baseline risk profile between sexes undergoing each type of device or differences in the receipt of evidence-based therapy between sexes (e.g. angiotensin converting enzyme inhibitors in heart failure and beta-blockers or amiodarone in patients with ventricular arrhythmias).[24-26] These findings emphasize the importance of incorporating sex as well as device type when risk assessing patients undergoing CIED therapy.

Our multivariable analysis identifies several important baseline and procedure-related predictors of cardiac readmission other than sex. Complex device groups (CRT and ICD) were associated with significantly increased odds of cardiac readmission (19-46%) compared to PPM, as were complications during the index admission (cardiac, thoracic, bleeding complications and AKI) and comorbidities such as heart failure, arrhythmias (VT and AF), and chronic pulmonary disease. The present findings emphasize the importance of timely follow up of women and other high-risk patients undergoing CIED implantation, as recommended by current guidelines, which may have a positive impact on their short-term readmission rates.

Limitations

There are several limitations to our study. First, the administrative nature of the NRD database is subject to coding inaccuracies and potential misclassification bias. However, the use of ICD-9 codes from such databases has been previously validated for the purpose of cardiovascular research as well as for capturing CIED complications. [27, 28] Secondly, the NRD dataset does not provide information on the indication for CIED implantation (e.g. type of arrhythmia and primary vs. secondary prevention in CRT-D and ICD procedures) and operator experience, and therefore 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. [29] Thirdly, we were only able to analyze the first eleven months of every calendar year in order to examine 30-day readmissions within that year since NRD does not allow tracking of individual patients over multiple years. Finally, NRD does not capture post discharge mortality, which acts as a competing risk for readmission. Nevertheless, we believe that the present study provides a valuable insight into the sex differences in trends and causes of 30-day readmissions following CIED implantation in a nationwide cohort.

Conclusion

In a nationwide analysis of CIED implantations we find that women were at a higher risk of all-cause 30-day readmissions and that this risk has gradually declined to a similar rate compared to men over the study years. We also conclude that women were at a persistently higher risk of cardiac and device-related readmissions compared to men over a six- year period. This may be partly due to the higher risk of complications in women after CIED implantation, which was also an independent predictor of readmission in our analysis. These findings emphasize the need for further work on strategies to reduce the risk of procedure-related complications in women, which may have a positive impact on their rates of cardiac and device-related readmissions. The present study reports important predictors of cardiac readmission, including CIED type and procedure-related complications during index admission, and provides insight into those individuals at higher risk when discharging and arranging follow-up after CIED implantation.

Conflicts

None the co-authors have any disclosures of interest or relationships with the pharmaceutical industry.

Funding

This work constitutes part of a PhD for Dr Mohamed Mohamed that is supported by Medtronic Ltd. Medtronic Ltd. was not involved in the conceptualization, design, conduct, analysis, or interpretation of the current study.AG is a consultant to Medtronic Ltd. and has received grant support from them for 2 projects in the past year. AG also previously received limited honoraria from Medtronic, St Jude (Abbott), and Boston Scientific for lectures (less than $2500). DB is paid by Medtronic for educational sessions. Other co-authors have no disclosures and no relationships with the industry.

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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Figures and Legends:

Figure 1A. Trends of all-cause, cardiac and device-related 30-day readmissions according to sex
Caption: $p<0.001$ for trend; *2015: January to August only

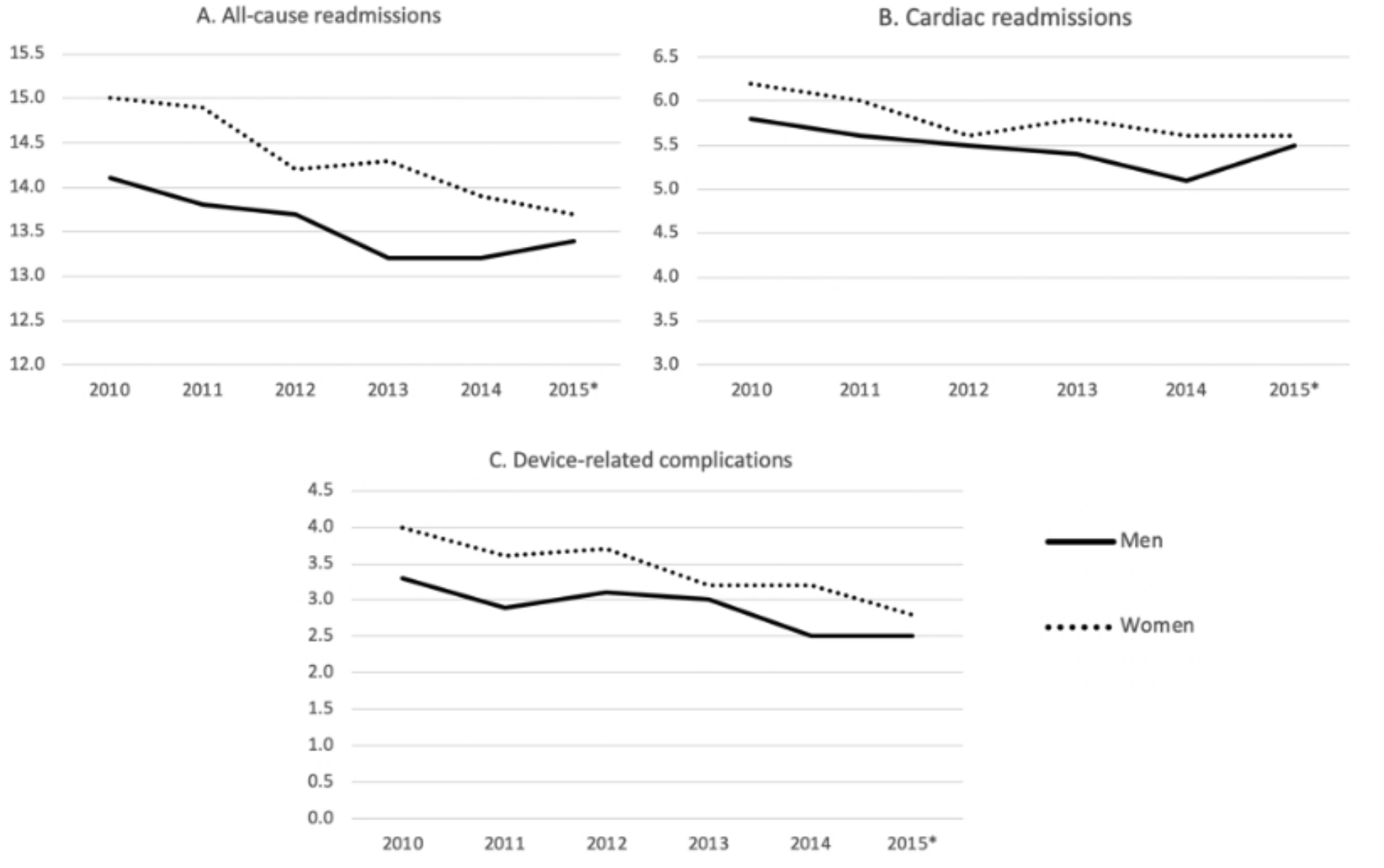
Figure 1B. Proportion of cardiac (vs. non-cardiac) readmissions according to sex and CIED type

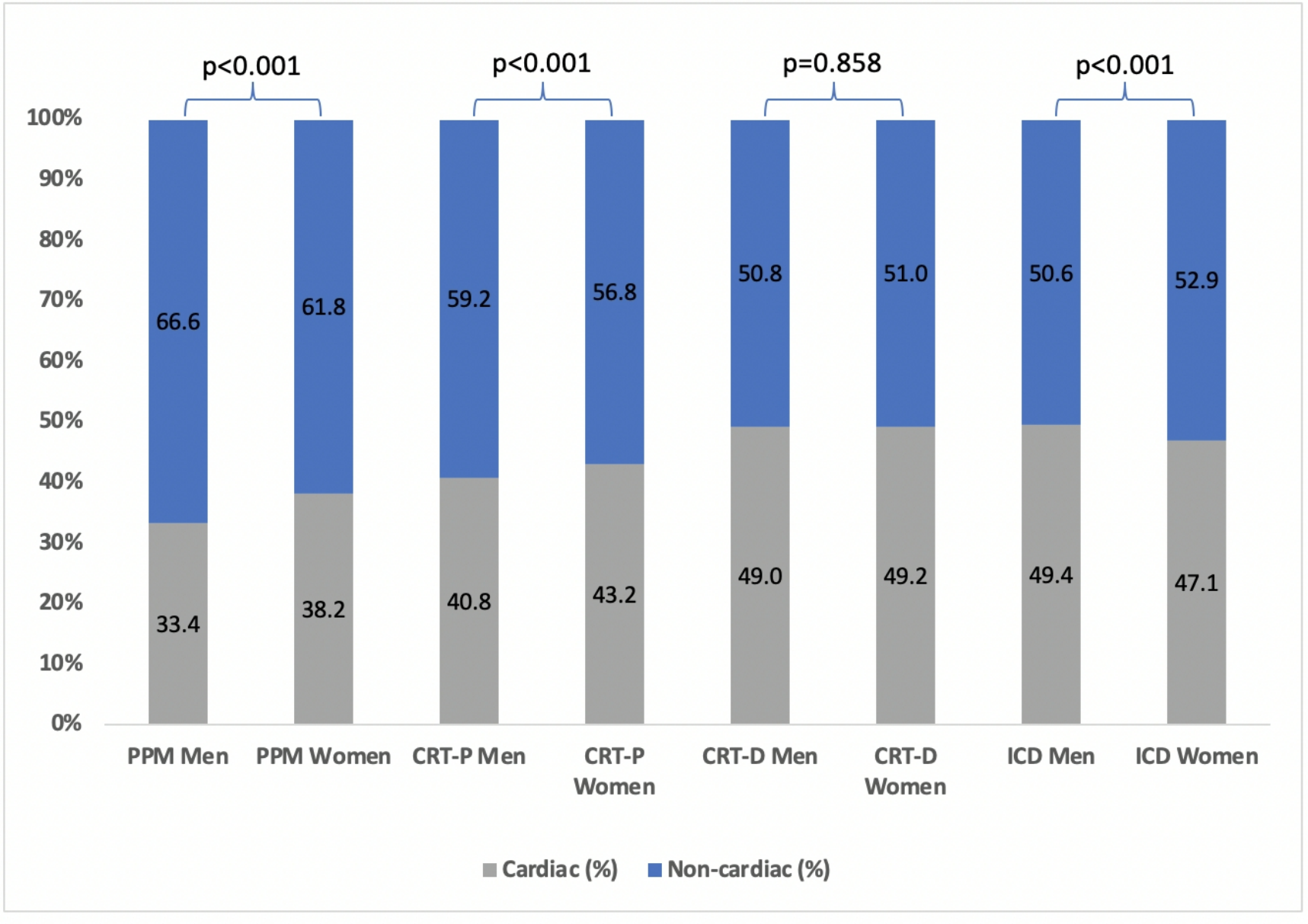
Figure 2. A) Baseline and B) Index procedure-related predictors of 30-day cardiac readmissions*

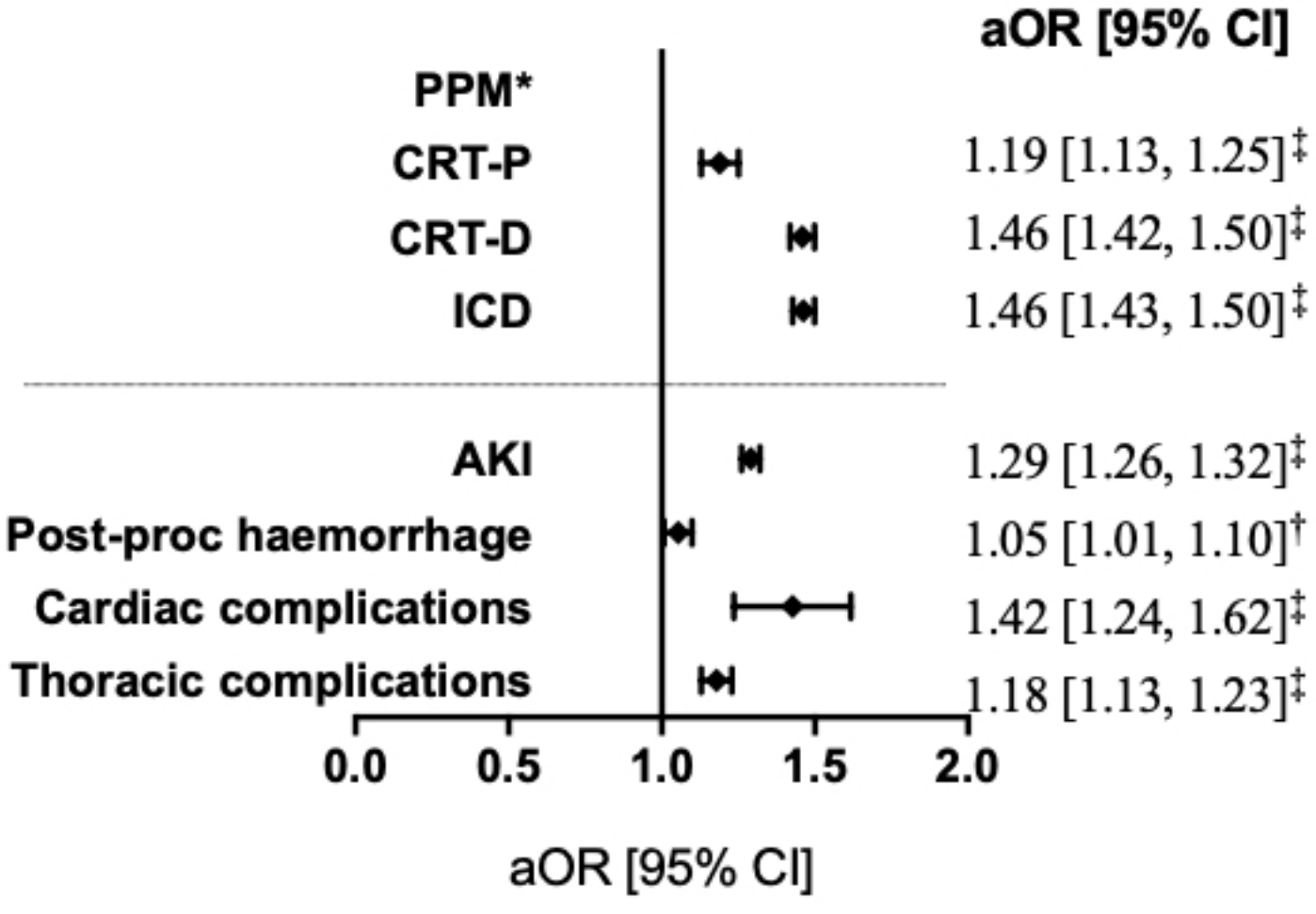
Caption: * all predictors generated from a single multivariate regression model; § non-significant; † $p<0.01$; ‡ $p<0.001$;

Figure 3. Temporal trend of adjusted odds ratio (aOR) of 30-day readmissions due to A) cardiac causes and B) device-related complications in women compared to men

Caption: *2015: January to August only


A. All-cause readmissions
15.5
15.0
14.5
14.0
13.5
13.0
12.5
12.0
2010
2011
2012
2013
2014
2015*
B. Cardiac readmissions
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2010
2011
2012
2013
2014
2015*
C. Device-related complications
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2010
2011
2012
2013
2014
2015*
Men
Women


p<0.001
p<0.001
p=0.858
p<0.001
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
66.6
61.8
59.2
56.8
50.8
51.0
50.6
52.9
33.4
38.2
40.8
43.2
49.0
49.2
49.4
47.1
PPM Men
PPM Women
CRT-P Men
CRT-P Women
CRT-D Men
CRT-D Women
ICD Men
ICD Women
Cardiac (%)
Non-cardiac (%)


aOR [95% CI]
PPM*
CRT-P
CRT-D
ICD
AKI
Post-proc haemorrhage
Cardiac complications
Thoracic complications
1.19 [1.13, 1.25]‡
1.46 [1.42, 1.50]‡
1.46 [1.43, 1.50]‡
1.29 [1.26, 1.32]‡
1.05 [1.01, 1.10]†
1.42 [1.24, 1.62]‡
1.18 [1.13, 1.23]‡
0.0
0.5
1.0
1.5
2.0
aOR [95% CI]

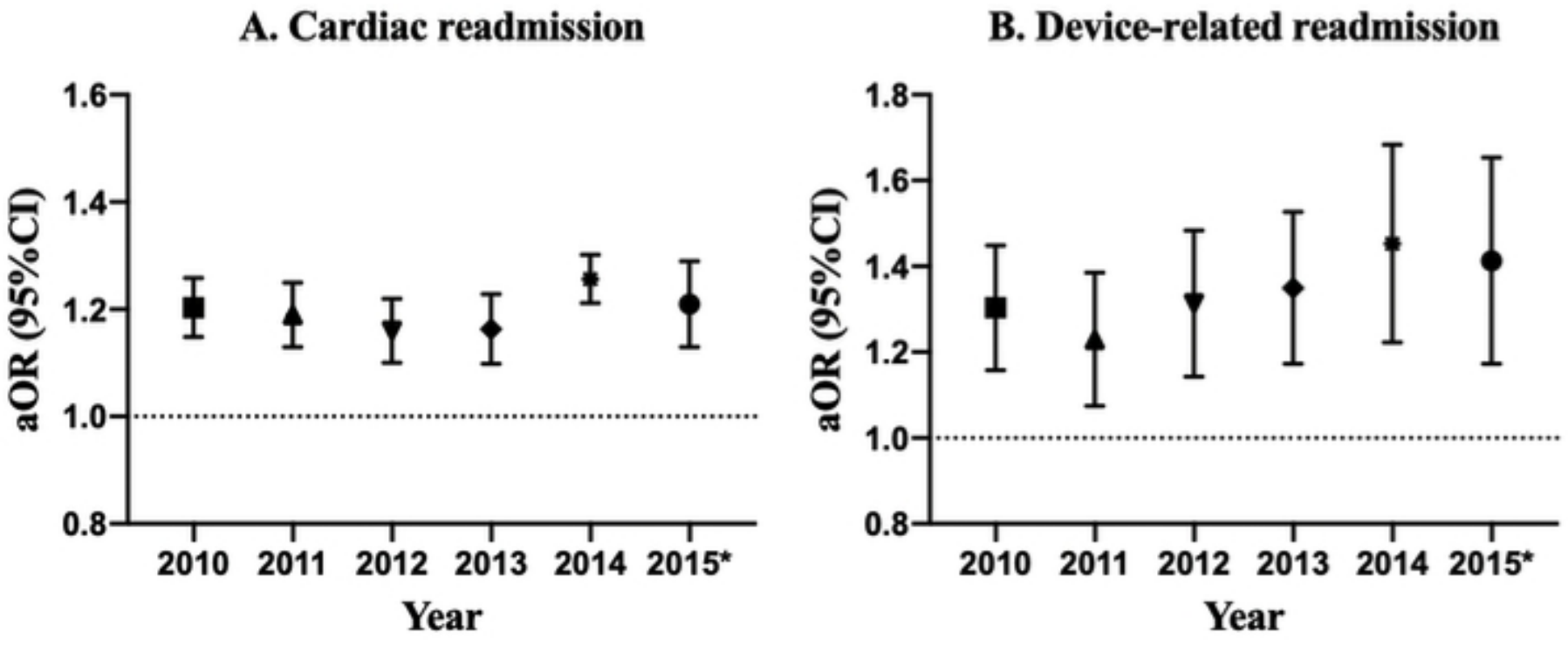

A. Cardiac readmission
aOR (95%CI)
1.6
1.4
1.2
1.0
0.8
2010
2011
2012
2013
2014
2015*
Year
B. Device-related readmission
aOR (95%CI)
1.8
1.6
1.4
1.2
1.0
0.8
2010
2011
2012
2013
2014
2015*
Year

Table 1a. Patient characteristics of study groups

Variable/Group (%)	Not readmitted				Readmitted			
	Men (57.8)	**Women (42.2)**	**Total**	**p-value**	**Men (55.8)**	**Women (44.2)**	**Total**	**p-value**
Number of weighted discharges	454856	332759	787615	<0.001	205574	162803	368377	<0.001
Type of CIED, %				<0.001				<0.001
PPM	59.5	78.1	67.4		54.0	74.4	63.0	
CRT-P	2.6	2.5	2.5		2.8	2.9	2.9	
CRT-D	14.3	7.5	11.4		17.2	8.4	13.3	
ICD	23.6	11.9	18.6		25.9	14.4	20.8	
Age (years), median (IQR)	73 (64, 81)	77 (68,84)	75 (65,83)	<0.001	74 (64,82)	78 (68,85)	76 (66,83)	<0.001
Elective Admission, %	26.7	22.1	24.8	<0.001	22.0	18.3	20.3	<0.001
Weekend admission, %	16.6	18.4	17.4	<0.001	18.3	19.9	19.0	<0.001
Primary expected payer, %				<0.001				<0.001
Medicare	71.2	79.3	74.6		76.5	83.1	79.4	
Medicaid	4.6	4.4	4.5		6.3	5.6	6.0	
Private Insurance	19.4	13.7	17.0		13.4	9.3	11.6	
Self-pay	1.9	1.2	1.6		1.5	1.0	1.2	
No charge	0.2	0.2	0.2		0.2	0.1	0.2	
Other	2.7	1.2	2.1		2.2	0.9	1.6	
Median Household Income (Percentile), %				<0.001				<0.001
0-25th	26.0	28.0	26.9		28.9	30.0	29.4	
26-50th	25.7	26.1	25.9		25.4	26.0	25.7	
51-75th	24.4	24.2	24.3		23.7	23.6	23.7	
76-100th	23.8	21.7	22.9		21.9	20.3	21.2	
Cardiac Arrest, %	4.4	4.0	4.2		4.2	4.3	4.3	
Ventricular Tachycardia, %	9.2	5.2	7.5		11.7	6.4	9.3	
Ventricular Fibrillation, %	4.4	2.9	3.7		4.1	2.8	3.5	
Comorbidities, %								
Dyslipidemia	55.5	50.4	53.3	<0.001	53.0	48.9	51.2	<0.001
Smoking	29.9	17.8	24.8	<0.001	28.8	17.8	24.0	<0.001
Atrial Fibrillation	36.3	39.8	37.8	<0.001	43.6	49.4	46.1	<0.001
Thrombocytopenia	5.1	3.6	4.4	<0.001	6.1	4.6	5.4	<0.001
Previous AMI	15.2	7.5	12.0	<0.001	16.4	9.5	13.3	<0.001

Variable/Group (%)	Not readmitted				Readmitted			
	Men (57.8)	Women (42.2)	Total	p-value	Men (55.8)	Women (44.2)	Total	p-value
History of IHD	54.9	34.4	46.2		61.5	43.5	53.6	
Previous PCI	13.7	7.7	11.2		14.2	9.5	12.1	
Previous CABG	16.9	6.4	12.5		18.0	8.3	13.7	
Previous CVA	7.2	8.2	7.6		8.4	9.5	8.9	
Family history of CAD	4.2	3.8	4.0		3.1	2.6	2.9	
AIDS	0.1	0.0	0.0		0.1	0.0	0.1	
Alcohol abuse	3.3	0.8	2.3		3.8	0.9	2.5	
Deficiency anemias	12.7	16.4	14.3		21.2	25.2	23.0	
Chronic Blood loss anemia	1.5	3.8	2.4		1.8	4.7	3.1	
RA/collagen vascular diseases	0.4	0.6	0.5		0.8	1.1	0.9	
Heart Failure	41.5	35.0	38.8		56.6	51.6	53.3	
Chronic pulmonary disease	18.0	18.4	18.2		25.9	26.0	26.0	
Coagulopathy	6.6	4.9	5.9		8.6	6.7	7.8	
Depression	5.5	9.9	7.4		7.4	12.2	9.5	
Diabetes	27.2	24.3	26.0		30.8	28.9	30.0	
Diabetes with complications	5.3	4.6	5.0		8.7	7.7	8.2	
Drug abuse	1.4	0.8	1.2		2.0	1.2	1.6	
Hypertension	71.0	73.5	72.1		72.4	75.0	73.6	
Hypothyroidism	9.2	23.3	15.1		10.7	24.1	16.6	
Liver disease	1.4	1.1	1.3		2.3	1.6	2.0	
Lymphomas	0.7	0.6	0.7		1.1	0.9	1.0	
Fluid and electrolyte disturbances	18.4	23.4	20.5		26.7	32.0	29.0	
Metastatic cancer	0.4	0.4	0.4		0.8	0.7	0.7	
Other neurological disorders	6.3	7.5	6.8		8.1	9.4	8.7	
Obesity	12.1	12.9	12.4		12.7	14.7	13.6	
Paralysis	1.6	1.7	1.6		2.5	2.6	2.6	
Peripheral vascular disease	10.4	8.0	9.4		14.9	11.5	13.4	
Psychoses	1.9	2.5	2.1		2.9	3.6	3.2	
Pulmonary circulation disorder	0.6	0.9	0.8		1.2	1.9	1.5	
Renal failure (chronic)	20.0	17.0	18.8		32.5	27.3	30.2	

Variable/Group (%)	Not readmitted				Readmitted			
	Men (57.8)	Women (42.2)	Total	p-value	Men (55.8)	Women (44.2)	Total	p-value
Solid tumor without metastases	1.5	0.9	1.2		2.2	1.3	1.8	
Valvular heart disease	1.4	1.9	1.6		2.5	3.0	2.7	
Weight loss	2.2	2.6	2.3		3.9	4.4	4.1	
Dementia	1.6	2.2	1.9		2.1	2.7	2.4	
Hospital bed size, %								
Small	8.2	9.0	8.5		7.3	8.1	7.6	
Medium	20.9	22.0	21.4		20.4	21.7	21.0	
Large	70.9	69.0	70.1		72.3	70.2	71.4	

PPM: permanent pacemaker**; CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively; **ICD:** implantable cardioverter-defibrillator; **IQR:** interquartile range; **AMI:** acute myocardial infarction; **IHD:** ischemic heart disease; **CABG:** coronary artery bypass graft; **PCI:** percutaneous coronary intervention; **CAD:** coronary artery disease; **CVA**: cerebrovascular accidents.

Table 1b. Causes of readmission according to sex

Group (% within category)	Men	Women	Total	p-value
Number of weighted readmissions	104358	83554	187912	
A. Cause of readmission				0.755
Cardiac, %	40.4	40.3	40.3	
Non-cardiac, %	59.6	59.7	59.7	
B. Specific Non-cardiac causes, %				
Infectious	10.7	10.8	10.7	0.538
Respiratory	5.1	6.2	5.6	<0.001
Bleeding	2.2	2.1	2.2	0.360
Peripheral Vascular Disease	3.8	3.3	3.5	<0.001
Renal	3.4	2.9	3.2	<0.001
Genitourinary	2.2	2.2	2.2	0.596
Gastrointestinal	4.6	5.0	4.8	<0.001
TIA/Stroke	2.7	2.8	2.8	0.137
Trauma	1.7	2.3	2.0	<0.001
Endocrine/Metabolic	1.5	1.7	1.6	0.002
Neuropsychiatric	2.9	2.6	2.7	<0.001
Hematology-Oncology	2.3	2.1	2.2	0.006
Rheumatology	0.2	0.1	0.1	<0.001
ENT	0.3	0.4	0.3	0.261
Dermatological	0.2	0.1	0.1	0.049
Poisoning	0.2	0.3	0.3	0.237
Syncope	1.5	1.4	1.5	0.121
C. Specific cardiac causes, %				
Device-related complications	3.0	3.5	3.2	<0.001
Arrhythmia	8.5	9.1	8.8	<0.001
Heart failure	17.8	17.6	17.7	0.242
Chest pain	2.2	2.3	2.3	0.161
Conduction disorders	0.3	0.3	0.3	0.873
Valve disorders	0.6	0.6	0.6	0.982
Circulatory disorder (hypo- or hypertension)	2.0	2.1	2.0	0.751
Pericarditis	1.3	1.5	1.4	<0.001
Coronary artery disease (including angina)	2.6	1.5	2.1	<0.001
Acute myocardial infarction	1.9	1.8	1.9	0.010

CRediT author statement

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Author Agreement Form – International Journal of Cardiology

Manuscript Title: Sex differences in rates and causes of 30-day readmissions after cardiac electronic device implantations: insights from the Nationwide Readmissions Database.

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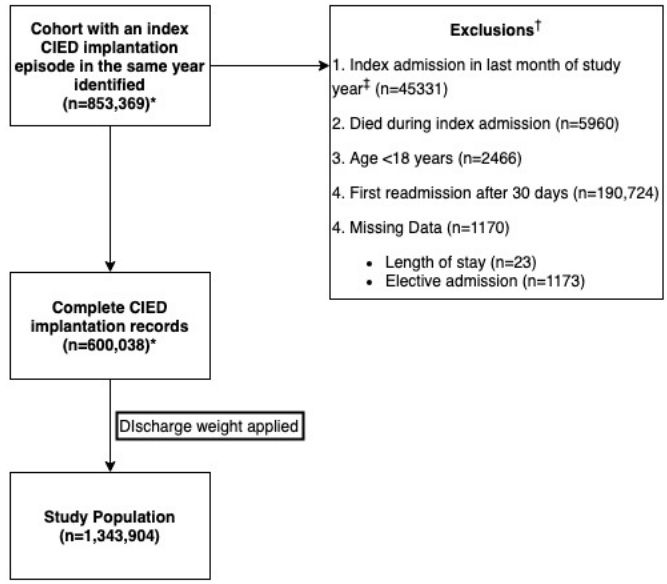
This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology*.

We attest that the article is the Authors' original work, has not received prior publication and is not under consideration for publication elsewhere. We adhere to the statement of ethical publishing as appears in the International of Cardiology (citable as: Shewan LG, Rosano GMC, Henein MY, Coats AJS. A statement on ethical standards in publishing scientific articles in the International Journal of Cardiology family of journals. Int. J. Cardiol. 170 (2014) 253-254 DOI:10.1016/j.ijcard.2013.11).

On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission. Any changes to the list of authors, including changes in order, additions or removals will require the submission of a new author agreement form approved and signed by all the original and added submitting authors.

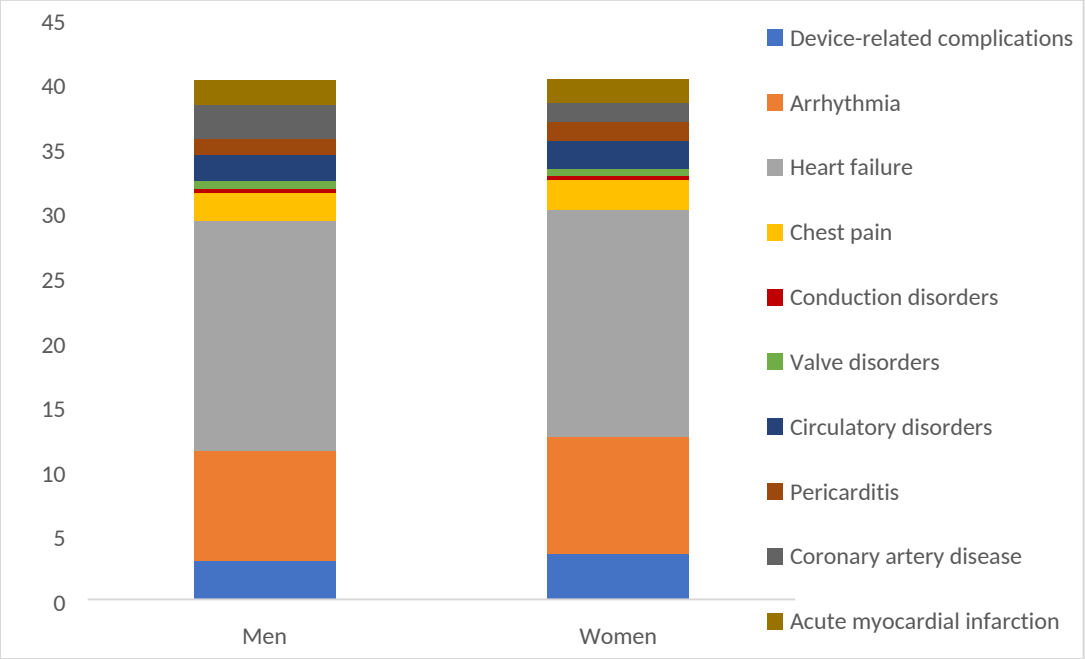
All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. If there are no conflicts of interest, the COI should read: “The authors report no relationships that could be construed as a conflict of interest”.

Supplementary Figure 1. Flow chart of cohort selection



* Number of records (unweighted)
† There was an overlap between cases excluded either for missing data or for not fulfilling study criteria
‡ December in years 2010-2014 and September in 2015

Supplementary Figure 2. Top 10 causes of cardiac readmission stratified by sex in the overall CIED cohort



Supplementary Table 1. ICD-9 diagnosis and procedure codes

Variable	Source	Diagnostic (D)/ Procedural (P)	Codes
Diagnoses			
Dyslipidemia	CCS	D	53
Smoking Status	ICD-9	D	V15.82, 305.1
AF	ICD-9	D	427.31
History of IHD	ICD-9	D	414.00-07, 414.2-9
Previous MI	ICD-9	D	412
Previous PCI	ICD-9	D	V45.82
Previous CABG	ICD-9	D	V45.81
Family history of CAD	ICD-9	D	V17.3
Previous CVA (TIA and Stroke)	ICD-9	D	V12.54
Dementia (Presenile, Senile, Vascular and Alzheimer's)	ICD-9	D	290.10-13, 290.20-21, 290.40-43, 294.10-11, 331.0
Thrombocytopenia	ICD-9	D	287.5,287.49
Heart Failure	ICD-9, CCS	D	428.x plus CCS: 108, 7.2.11.1, 7.2.11.2
Ventricular Tachycardia/Fibrillation	ICD-9	D	427.1 (VT – paroxysmal and/or sustained), 427.41 (VF)
In-hospital procedures and outcomes			
PPM	ICD-9	P	[37.70 or 37.71 or 37.72 or 37.73] + [37.80 or 37.81 or 37.82 or 37.83]
CRT-P	ICD-9	P	00.50
CRT-D	ICD-9	P	00.51
ICD	ICD-9	P	37.94 or (37.95+37.96)
Acute ischemic stroke/transient ischemic attack	ICD-9	D	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 435.0-1, 435.8-9, 436
Acute hemorrhagic stroke (subarachnoid, intracerebral hemorrhage)	ICD-9	D	431,432.x, 430
Post-procedural hemorrhage	ICD-9	D	998.11, 285.1
Acute kidney injury	ICD-9	D	584*
Shock during admission	ICD-9	D	785.51
Hemopericardium	ICD-9	D	423.0
Pericardiocentesis	ICD-9	P	37.0
Cardiac tamponade	ICD-9	D	423.3
Coronary dissection	ICD-9	D	414.12
Pneumothorax	ICD-9	D	512.89, 512.1, 860.0-1
Hemothorax	ICD-9	D	860.2-3
Chest Drain Insertion	CCS	P	39
Cardiac Arrest	ICD-9	D	427.5
Device related infection	ICD-9	D	996.61
Fever	ICD-9	D	780.60-64
Bacteraemia/Viremia	ICD-9	D	790.7/790.8
Septicemia	ICD-9	D	038.x
Thoracic/Upper Limb Vascular injury	ICD-9	D	901.x, 903.1, 903.8-9, 900.1

Supplementary Table 2: Clinical classification software codes for Readmissions Causes

Causes of readmission	CCS code	Diagnosis
Respiratory	127	Chronic obstructive pulmonary disease and bronchiectasis
	128	Asthma
	130	Pleurisy, pneumothorax, pulmonary collapse
	131	Respiratory failure, insufficiency and arrest
	132	Lung disease due to external agents
	133	Other lower respiratory disease
	134	Other upper respiratory disease
	221	Respiratory distress syndrome
Infection	1	Tuberculosis
	2	Septicemia
	3	Bacterial infection
	4	Mycoses
	5	HIV infection
	6	Hepatitis
	7	Viral infection
	8	Other infection
	9	Sexually transmitted infection
	76	Meningitis
	77	Encephalitis
	78	Other CNS infection and poliomyelitis
	90	Inflammation or infection of eye
	122	Pneumonia
	123	Influenza
	124	Acute and chronic tonsillitis
	125	Acute bronchitis
	126	Other upper respiratory infections
	129	Aspiration pneumonitis
	135	Intestinal infection
	197	Skin and subcutaneous tissue infections
	201	Infective arthritis and osteomyelitis (except that caused by tuberculosis or sexually transmitted disease)
Bleeding	60	Acute posthaemorrhagic anemia
	153	Gastrointestinal hemorrhage
	182	Hemorrhage during pregnancy; abrutio placenta; placenta previa
Peripheral vascular disease	114	Peripheral and visceral atherosclerosis
	115	Aortic, peripheral and visceral artery aneurysms
	116	Aortic and peripheral arterial embolism or thrombosis
	117	Other circulatory disease
	118	Phlebitis, thrombophlebitis and thromboembolism
	119	Varicose veins of lower extremities
Genitourinary	159	Urinary tract infection
	160	Calculus of the urinary tract

	161	Other diseases of kidney and ureters
	162	Other diseases of bladder and urethra
	163	Genitourinary symptoms and ill-defined conditions
	164	Hyperplasia of prostate
	165	Inflammatory conditions of the male genital organs
	166	Other male genital disorders
	170	Prolapse of female genital organs
	175	Other female genital disorders
	215	Genitourinary congenital anomalies
Renal disease	156	Nephritis; nephrosis; renal sclerosis
	157	Acute and unspecified renal failure
	158	Chronic kidney disease
Gastrointestinal	138	Esophageal disorders
	139	Gastroduodenal ulcer (except hemorrhage)
	140	Gastritis and duodenitis
	141	Other disorders of stomach and duodenum
	142	Appendicitis and other appendiceal conditions
	143	Abdominal hernia
	144	Regional enteritis and ulcerative colitis
	145	Intestinal obstruction without hernia
	146	Diverticulosis and diverticulitis
	147	Anal and rectal conditions
	148	Peritonitis and intestinal abscess
	149	Biliary tract disease
	150	Liver disease; alcohol-related
	151	Other liver diseases
	152	Pancreatic disorders (not diabetes)
	154	Noninfectious gastroenteritis
	155	Other gastrointestinal disorders
	214	Digestive congenital anomalies
	222	Hemolytic jaundice and perinatal jaundice
	250	Nausea and vomiting
	251	Abdominal pain
TIA/stroke	109	Acute cerebrovascular disease
	110	Occlusion of stenosis of precerebral arteries
	111	Other and ill-defined cerebrovascular disease
	112	Transient cerebral ischemia
	113	Late effects of cerebrovascular disease
Trauma	207	Pathological fracture
	225	Joint disorders and dislocations; trauma-related
	226	Fracture of neck of femur (hip)
	227	Spinal cord injury
	228	Skull and face fractures
	229	Fracture of upper limb
	230	Fracture of lower limb

	231	Other fractures
	232	Sprains and strains
	233	Intracranial injury
	234	Crushing injury or internal injury
	235	Open wounds of head; neck; and trunk
	236	Open wounds of extremities
	239	Superficial injury; contusion
	244	Other injuries and conditions due to external causes
	260	All (external causes of injury and poisoning)
Endocrine/metabolic	48	Thyroid disorders
	49	Diabetes mellitus without complication
	50	Diabetes mellitus with complication
	51	Other endocrine disorders
	53	Disorders of lipid metabolism
	58	Other nutritional and endocrine/metabolic disorders
	186	Diabetes or abnormal glucose tolerance complicating pregnancy; childbirth or the puerperium
Neuropsychiatric	650	Adjustment disorders
	651	Anxiety disorders
	652	Attention-deficit, conduct, and disruptive behavior disorders
	653	Delirium, dementia, and amnestic and other cognitive disorders
	654	Developmental disorders
	655	Disorders usually diagnosed in infancy and childhood or adolescence
	656	Impulse control disorders, NEC
	657	Mood disorders
	658	Personality disorders
	659	Schizophrenia and other psychotic disorders
	660	Alcohol-related disorders
	661	Substance-related disorders
	662	Suicide and intentional self-inflicted injury
	663	Screening and history of mental health and substance abuse codes
	670	Miscellaneous mental health disorders
	79	Parkinson's disease
	80	Multiple sclerosis
	81	Other hereditary and degenerative nervous system conditions
	82	Paralysis
	83	Epilepsy, convulsions
	84	Headache including migraine
	85	Coma, stupor and brain damage
	95	Other nervous system disorders
	216	Nervous system congenital anomalies
	650	Adjustment disorders
	651	Anxiety disorders
	652	Attention-deficit, conduct, and disruptive behavior disorders
	653	Delirium, dementia, and amnestic and other cognitive disorders

	654	Developmental disorders
	655	Disorders usually diagnosed in infancy and childhood or adolescence
	656	Impulse control disorders, NEC
	657	Mood disorders
	658	Personality disorders
	659	Schizophrenia and other psychotic disorders
	660	Alcohol-related disorders
	661	Substance-related disorders
	662	Suicide and intentional self-inflicted injury
	663	Screening and history of mental health and substance abuse codes
	670	Miscellaneous mental health disorders
Hematological/ neoplastic	11	Cancer of head and neck
	12	Cancer of esophagus
	13	Cancer of stomach
	14	Cancer of colon
	15	Cancer of rectum and anus
	16	Cancer of liver and intrahepatic bile ducts
	17	Cancer of pancreas
	18	Cancer of other GI organs, peritoneum
	19	Cancer of bronchus, lung
	20	Cancer of other respiratory and intrathoracic
	21	Cancer of bone and connective tissue
	22	Melanoma of skin
	23	Other non-epithelial cancer of skin
	24	Cancer of breast
	25	Cancer of uterus
	26	Cancer of cervix
	27	Cancer of ovary
	28	Cancer of other female genital organs
	29	Cancer of prostate
	30	Cancer of testis
	31	Cancer of other male genital organs
	32	Cancer of bladder
	33	Cancer of kidney and renal pelvis
	34	Cancer of other urinary organs
	35	Cancer of brain and nervous system
	36	Cancer of thyroid
	37	Hodgkin's disease
	38	Non-Hodgkin's lymphoma
	39	Leukaemias
	40	Multiple myeloma
	41	Cancer, other and unspecified primary
	42	Secondary malignancies
	43	Malignant neoplasm without specification of site

	44	Neoplasm of unspecified nature or uncertain behaviour
	46	Benign neoplasm of uterus
	47	Other and unspecified benign neoplasm
	59	Deficiency and other anemias
	61	Sickle cell anemia
	62	Coagulation and hemorrhagic disorders
	63	Disease of white blood cells
	64	Other hematologic conditions
Rheumatology problem	54	Gout and other crystal arthropathies
Opthalmology problem	86	Cataract
	87	Retinal detachment defects, vascular occlusion and retinopathy
	88	Glaucoma
	89	Blindness and vision defects
	91	Other eye disorders
ENT problem	92	Otitis media and related conditions
	93	Conditions associate with dizziness or vertigo
	94	Other ear and sense organ disorder
Non-specific chest pain	102	Non-specific chest pain
Oral health problem	136	Disorders of teeth and jaw
	137	Diseases of mouth; excluding dental
Obstetric admission including pregnancy	174	Female infertility
	176	Contraceptive and procreative management
	177	Spontaneous abortion
	178	Induced abortion
	179	Postabortion complication
	180	Ectopic pregnancy
	181	Other complications of pregnancy
	184	Early or threatened labor
	185	Prolonged pregnancy
	187	Malposition; malpresentation
	188	Fetopelvic disproportion; obstruction
	189	Previous C-section
	190	Fetal distress and abnormal forces of labor
	191	Polyhydramnios and other problems of amniotic cavity
	192	Umbilical cord complication
	193	OB-related trauma to perineum and vulva
	194	Forceps delivery
	195	Other complications of birth; puerperium affecting management of mother
	196	Other pregnancy and deliver including normal
	218	Liveborn
	219	Short gestation; low birth weight; and fetal growth retardation
	220	Intrauterine hypoxia and birth asphyxia
	223	Birth trauma

	224	Other perinatal conditions
Dermatology problem	198	Other inflammatory condition of skin
	199	Chronic ulcer of skin
	200	Other skin disorders
Poisoning	241	Poisoning by psychotrophic agents
	242	Poisoning by other medication and drugs
	243	Poisoning by nonmedical substances
Syncope	245	Syncope
Other non-cardiac	10	Immunization and screening for infectious disease
	45	Maintenance chemotherapy, radiotherapy
	52	Nutritional deficiencies
	55	Fluid and electrolyte disorders
	56	Cystic fibrosis
	57	Immunity disorder
	120	Hemorrhoids
	121	Other diseases of veins and lymphatics
	167	Nonmalignant breast conditions
	168	Inflammatory disease of female pelvic organs
	169	Endometriosis
	172	Ovarian cyst
	173	Menopausal disorders
	202	Rheumatoid arthritis and related disease
	203	Osteoarthritis
	204	Other non-traumatic joint disorders
	205	Spondylosis; intervertebral disc disorders; other back problems
	206	Osteoporosis
	208	Acquired foot deformities
	209	Other acquired deformities
	210	Systemic lupus erythematosus and connective tissue disorders
	211	Other connective tissue disease
	212	Other bone disease and musculoskeletal deformities
	217	Other congenital anomalies
	237	Complication of device; implant or graft
	238	Complications of surgical procedure or medical care
	240	Burns
	246	Fever of unknown origin
	247	Lymphadenitis
	248	Gangrene
	252	Malaise and fatigue
	253	Allergic reactions
	254	Rehabilitation care; fitting of prostheses; and adjustment of devices
	255	Administrative/social admission
	256	Medical examination/evaluation
	257	Other aftercare
	258	Other screening for suspected conditions (not mental disorders or infectious disease)

	259	Residual codes; unclassified
Heart failure	108	Congestive heart failure non-hypertensive
Arrhythmia	106	Cardiac dysrhythmia
	107	Cardiac arrest and ventricular fibrillation
Conduction disorder	105	Conduction disorders
Valve disorders	96	Heart valve disorder
Hyper/hypotension	98	Essential hypertension
	99	Hypertension with complications and secondary hypertension
	183	Hypertension complicating pregnancy; childbirth and the puerperium
	249	Shock
Pericarditis	97	Peri-, endo- and myocarditis, cardiomyopathy
Coronary artery disease including angina	101	Coronary atherosclerosis and other heart disease
Acutemyocardial infarction	100	Acute myocardial infarction
Others (cardiac)	103	Pulmonary heart disease
	104	Other and ill-defined heart disease
	213	Cardiac and circulatory congenital anomalies

Supplementary Table 3. Patient characteristics of readmitted patients according to CIED subtype

	PPM			CRT-P			CRT-D			ICD		
Variable/Group (%)	**Men (47.4)**	**Women (52.6)**	**p-value**	**Men (56.4)**	**Women (43.6)**	**p-value**	**Men (72.1)**	**Women (27.9)**	**p-value**	**Men (69.9)**	**Women (30.1)**	**p-value**
Number of weighted discharges	56531	62664	-	3011	2327	-	17372	6719	-	27445	11845	-
Age (years), median (IQR)	78 (69, 85)	80 (72,86)	<0.001	78 (70, 85)	78 (70,84)	0.058	72 (63, 79)	71 (62,78)	0.01	66 (56,75)	66 (55,75)	0.063
Elective Admission, %	10.5	8.6	<0.001	11.1	9.3	0.031	12.0	12.0	0.898	8.7	8.8	0.703
Weekend admission, %	23.3	24.1	0.002	23.2	25.6	0.040	22.5	23.3	0.205	22.8	23.0	0.674
Primary expected payer, %			<0.001			<0.001			<0.001			<0.001
Medicare	82.4	87.1		81.9	84.8		75.9	75.0		62.2	63.7	
Medicaid	4.0	3.7		3.0	4.6		6.7	9.1		13.3	15.7	
Private Insurance	10.7	7.5		11.8	7.9		14.1	12.9		18.4	16.6	
Self-pay	0.9	0.7		0.6	0.9		0.9	1.5		2.6	2.3	
No charge	0.1	0.1		0.0	0.1		0.2	0.1		0.4	0.2	
Other	1.8	1.0		2.7	1.7		2.2	1.4		3.1	1.4	
Median Household Income (Percentile), %			<0.001			<0.001			<0.001			<0.001
0-25th	26.6	28.0		23.2	31.4		29.4	34.3		33.9	37.3	
26-50th	26.0	26.1		26.6	22.7		26.2	26.9		23.8	25.2	
51-75th	24.2	24.5		26.9	21.8		22.7	21.7		22.4	20.6	
76-100th	23.1	21.4		23.3	24.1		21.7	17.2		19.9	16.9	
Cardiac Arrest, %	0.8	0.9	0.492	0.7	0.9	0.401	1.4	0.8	<0.001	1.0	1.0	0.570
Ventricular Tachycardia, %	2.7	1.6	<0.001	4.5	2.6	<0.001	9.8	7.6	<0.001	10.8	9.8	0.002
Ventricular Fibrillation, %	0.5	0.4	<0.001	0.6	0.5	0.582	1.8	2.1	0.280	2.7	2.8	0.619

	PPM			CRT-P			CRT-D			ICD		
Variable/Group (%)	**Men (47.4)**	**Women (52.6)**	**p-value**	**Men (56.4)**	**Women (43.6)**	**p-value**	**Men (72.1)**	**Women (27.9)**	**p-value**	**Men (69.9)**	**Women (30.1)**	**p-value**
Cardiogenic Shock, %	1.1	0.8	<0.001	1.4	2.1	0.047	3.0	2.9	0.576	2.7	2.2	0.010
Comorbidities, %												
Dyslipidemia	47.1	44.2	<0.001	48.0	42.4	<0.001	49.0	44.8	<0.001	48.0	42.7	<0.001
Smoking	23.5	14.2	<0.001	22.5	17.0	<0.001	25.3	17.7	<0.001	28.5	21.1	<0.001
Atrial Fibrillation	43.4	51.2	<0.001	56.7	62.0	<0.001	43.6	39.8	<0.001	34.9	29.7	<0.001
Thrombocytopenia	5.2	3.5	<0.001	5.0	3.7	0.019	5.7	4.5	<0.001	4.8	3.8	<0.001
Previous AMI	9.9	6.9	<0.001	12.2	8.2	<0.001	18.5	13.3	<0.001	20.6	16.3	<0.001
History of IHD	52.2	39.4	<0.001	65.4	45.5	<0.001	71.8	54.3	<0.001	67.4	55.4	<0.001
Previous PCI	11.1	7.9	<0.001	11.9	9.5	0.005	15.3	12.2	<0.001	17.8	13.0	<0.001
Previous CABG	16.9	8.2	<0.001	22.3	10.2	<0.001	26.0	11.8	<0.001	20.4	13.1	<0.001
Previous CVA	9.1	9.4	0.101	9.1	9.8	0.410	7.4	7.1	0.459	7.0	7.8	0.009
Family history of CAD	1.6	1.6	0.659	1.5	2.1	0.140	2.4	2.2	0.237	2.5	2.3	0.391
AIDS	0.1	0.0	<0.001	0.1	0.1	0.796	0.1	0.0	0.112	0.3	0.2	0.192
Alcohol abuse	2.4	0.5	<0.001	2.0	0.3	<0.001	2.4	1.0	<0.001	4.4	1.6	<0.001
Deficiency anemias	28.4	30.9	<0.001	28.1	28.9	0.530	25.6	30.2	<0.001	24.1	29.8	<0.001
Chronic Blood loss anemia	1.8	4.5	<0.001	2.0	3.8	<0.001	1.7	4.3	<0.001	1.5	5.0	<0.001
RA/collagen vascular diseases	1.6	1.6	0.212	1.2	1.7	0.136	0.8	1.1	0.038	1.0	1.3	0.009
Heart Failure	42.3	48.4	<0.001	71.5	74.6	0.011	83.5	84.3	0.166	70.2	70.2	0.971
Chronic pulmonary disease	24.9	24.8	0.741	27.1	29.0	0.122	28.8	30.3	0.017	27.1	29.6	<0.001
Coagulopathy	7.6	5.5	<0.001	7.1	5.8	0.062	8.7	7.1	<0.001	7.5	6.1	<0.001
Depression	7.9	11.8	<0.001	8.2	13.9	<0.001	7.6	12.7	<0.001	7.9	14.1	<0.001
Diabetes	28.8	27.4	<0.001	31.5	27.8	0.003	34.2	34.3	0.905	32.0	31.3	0.216
Diabetes with complications	8.3	6.7	<0.001	9.8	5.6	<0.001	8.2	8.0	0.601	8.6	9.7	<0.001
Drug abuse	1.1	0.8	<0.001	0.8	0.5	0.146	1.7	1.4	0.157	3.6	3.0	0.002

	PPM			CRT-P			CRT-D			ICD		
Variable/Group (%)	**Men (47.4)**	**Women (52.6)**	**p-value**	**Men (56.4)**	**Women (43.6)**	**p-value**	**Men (72.1)**	**Women (27.9)**	**p-value**	**Men (69.9)**	**Women (30.1)**	**p-value**
Hypertension	70.1	72.1	<0.001	64.3	69.8	<0.001	65.1	65.6	0.467	67.5	66.9	0.204
Hypothyroidism	12.2	25.1	<0.001	12.9	27.7	<0.001	12.2	21.1	<0.001	7.9	16.9	<0.001
Liver disease	2.3	1.7	<0.001	2.6	0.9	<0.001	2.7	1.5	<0.001	2.8	2.5	0.117
Lymphomas	1.3	1.0	<0.001	1.3	0.4	0.001	1.0	0.9	0.316	0.8	0.9	0.153
Fluid and electrolyte disturbances	30.2	34.2	<0.001	33.9	31.5	0.067	31.3	34.7	<0.001	28.4	32.0	<0.001
Metastatic cancer	1.6	0.8	<0.001	1.6	1.2	0.336	0.4	0.6	0.027	0.3	0.5	0.001
Other neurological disorders	10.1	9.4	<0.001	7.8	8.0	0.731	4.5	4.8	0.295	4.8	6.3	<0.001
Obesity	8.8	11.4	<0.001	9.5	11.5	0.015	11.0	15.0	<0.001	12.3	16.0	<0.001
Paralysis	2.9	2.6	0.005	3.1	2.2	0.057	1.3	1.9	<0.001	1.9	1.8	0.423
Peripheral vascular disease	12.8	10.0	<0.001	13.4	8.2	<0.001	13.3	9.4	<0.001	12.3	9.9	<0.001
Psychoses	3.3	3.3	0.818	2.2	2.2	0.936	2.4	2.8	0.165	3.6	4.3	0.004
Pulmonary circulation disorder	4.2	5.6	<0.001	6.2	5.8	0.523	3.4	5.0	<0.001	3.1	4.1	<0.001
Renal failure (chronic)	32.1	27.8	<0.001	39.3	30.3	<0.001	41.9	33.1	<0.001	33.2	28.8	<0.001
Solid tumor without metastases	2.8	1.3	<0.001	1.9	1.0	0.005	1.0	1.1	0.254	1.3	0.8	<0.001
Valvular heart disease	11.7	12.2	0.002	12.3	11.8	0.576	8.8	10.5	<0.001	6.5	7.6	<0.001
Weight loss	6.7	6.4	0.113	7.6	9.3	0.031	5.2	5.0	0.426	4.9	4.9	0.842
Dementia	3.6	3.3	0.004	2.4	1.2	0.002	0.9	0.9	0.999	0.7	0.6	0.981
Hospital bed size, %			<0.001			0.073			0.628			0.005
Small	10.5	10.9		9.6	7.8		8.3	8.3		7.9	7.3	
Medium	22.3	23.3		24.8	24.7		21.4	20.8		20.0	21.2	
Large	67.1	65.8		65.6	67.5		70.3	70.9		72.0	71.5	

Supplementary Table 4. Cardiac causes of readmission according to type of device and sex

	PPM			CRT-P			CRT-D			ICD		
Group (% within category)	**Men (47.8)**	**Women (52.2)**	**p-value**	**Men (55.6)**	**Women (44.4)**	**p-value**	**Men (72.1)**	**Women (27.9)**	**p-value**	**Men (69.5)**	**Women (30.5)**	**p-value**
Device-related complications	2.7	3.4	<0.001	2.3	2.4	0.647	3.2	4.2	<0.001	3.3	3.8	0.028
Arrhythmia	6.6	9.2	<0.001	5.7	6.7	0.136	9.4	8.3	0.01	12.1	9.7	<0.001
Heart failure	12.4	15.4	<0.001	23.8	25.6	0.126	26.2	26.0	0.743	23.2	23.2	0.975
Chest pain	2.3	2.3	0.826	1.2	2.1	0.016	1.7	2.6	<0.001	2.6	2.4	0.456
Conduction disorders	0.2	0.2	0.899	0.3	0.1	0.135	0.3	0.5	0.001	0.3	0.4	0.119
Valve disorders	0.9	0.8	0.005	0.9	0.8	0.661	0.2	0.2	0.629	0.3	0.2	0.122
Circulatory disorder (hypo- or hypertension)	1.7	2.0	<0.001	2.2	1.8	0.320	2.8	2.5	0.262	2.3	1.9	0.004
Pericarditis	1.4	1.5	0.128	0.9	0.9	0.880	1.2	1.8	<0.001	1.1	1.6	<0.001
Coronary artery disease (including angina)	2.9	1.4	<0.001	1.6	1.0	0.056	2.3	1.2	<0.001	2.5	2.0	0.001
Acute myocardial infarction	2.1	1.8	<0.001	1.8	1.3	0.168	1.7	1.7	0.881	1.7	1.9	0.123

Supplementary Table 5. Predictors of cardiac cause 30-day readmission*

Variable	aOR [95% CI]	p-value
Women	1.22 [1.20, 1.24]	<0.001
Index admission related variables		
PPM (reference)	-	-
CRT-P	1.19 [1.13, 1.25]	<0.001
CRT-D	1.46 [1.42, 1.50]	<0.001
ICD	1.46 [1.43, 1.50]	<0.001
Acute kidney injury	1.29 [1.26, 1.32]	<0.001
Post-procedural hemorrhage	1.05 [1.01, 1.10]	0.014
Cardiac complications	1.42 [1.24, 1.62]	<0.001
Thoracic complications	1.18 [1.13, 1.23]	<0.001
Baseline predictors		
Age in years at admission	0.99 [0.99, 1.00]	0.173
Elective admission	0.80 [0.79, 0.82]	<0.001
Weekend admission	1.06 [1.04, 1.08]	<0.001
VT	1.26 [1.22, 1.29]	<0.001
Dyslipidemia	0.93 [0.91, 0.95]	<0.001
Smoking	0.98 [0.97, 1.00]	<0.001
AF	1.42 [1.40, 1.44]	<0.001
History of ischemic heart disease	1.31 [1.28, 1.34]	<0.001
Previous percutaneous coronary intervention	1.04 [1.02, 1.07]	<0.001
Acquired immune deficiency syndrome	1.63 [1.26, 2.11]	<0.001
Deficiency anemia	1.17 [1.15, 1.20]	<0.001
Chronic blood loss anemia	1.01 [0.97, 1.06]	0.587
Rheumatoid arthritis/collagen vascular diseases	0.95 [0.86, 1.04]	0.244
Heart failure	1.40 [1.37, 1.43]	<0.001
Chronic pulmonary disease	1.25 [1.23, 1.28]	<0.001
Coagulopathy	1.18 [1.12, 1.25]	<0.001
Depression	1.03 [1.00, 1.06]	0.080

Diabetes, uncomplicated	1.07 [1.05, 1.09]	0.000
Diabetes with chronic complications	1.09 [1.05, 1.12]	0.000
Hypertension	0.99 [0.97, 1.01]	0.136
Hypothyroidism	1.01 [0.99, 1.04]	0.223
Liver disease	1.05 [0.99, 1.12]	0.088
Lymphoma	1.30 [1.20, 1.41]	<0.001
Fluid and electrolyte disorders	1.20 [1.18, 1.23]	<0.001
Other neurological disorders	0.92 [0.89, 0.96]	<0.001
Obesity	1.02 [0.99, 1.04]	0.15
Peripheral vascular disorders	1.07 [1.04, 1.09]	<0.001
Psychoses	1.02 [0.97, 1.07]	0.457
Pulmonary circulation disorders	1.02 [0.95, 1.10]	0.607
Chronic renal failure	1.39 [1.36, 1.42]	<0.001
Solid tumor without metastasis	1.00 [0.93, 1.07]	0.922
Valvular disease	0.95 [0.90, 1.01]	0.072

*All predictors are derived from index admission records; **PPM:** permanent pacemaker**; CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively; **ICD:** implantable cardioverter-defibrillator

Supplementary Table 6. Clinical outcomes of 30-day readmission episode according to sex

Variable/Group (% of cohort)	Men (55.8)	Women (44.2)	Total	p-value
All-cause mortality, %	4.9	5.0	4.9	0.384
Acute stroke/TIA, %	1.9	2.4	2.1	<0.001
Acute kidney injury, %	15.6	13.7	14.7	<0.001
Bleeding, %	5.2	4.9	5.0	0.004
Device-related infection, %	3.7	2.8	3.3	<0.001
Device revision or removal, %	5.3	5.2	5.2	0.269