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Sex differences in Cardiac electronic device implantation: Outcomes from an Australian multi-centre clinical quality registry

David Eccleston [a,d,*], Daniel Cehic [b], Glenn Young [b], Tina Lin [a], Steven Pavia [c], Enayet K. Chowdhury [d,e], Christopher Reid [d,e], Danny Liew [d], Ben King [f], Isabel Tan [f], Karen Phillips [c], David O'Donnell [a], for the GenesisCare Outcomes Registry Investigators

[a] Warringal Private Hospital, Melbourne, Australia
[d] School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia
[b] Wakefield Hospital, Adelaide, Australia
[c] Wesley Hospital, Brisbane, Australia
[e] Curtin University, Perth, Australia
[f] Mount Hospital, Perth, Australia

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ABSTRACT

Background: There is uncertainty regarding whether outcomes after Cardiac Implantable Electronic Devices (CIED) differ between women and men. There are no prospectively collected data regarding Australian CIED outcomes. This study aimed to determine whether the characteristics and outcomes of Australian patients undergoing CIED implantation differ by sex.

Methods: We prospectively followed 5,360 patients undergoing CIED implantation between 2015 and 2019 in a large multi-centre Australian registry. Patient characteristics, procedural data, medications and clinical outcomes to 1 year were analysed.

Results: The mean age was 76.2 + 11.2 years, and 2022 (37.7%) were female. Women were older than men at device implantation (77.0 ± 11.6 years vs. 75.5 ± 10.9 years, $p < 0.001$). Most implants were de novo (79.7%). Pacing was more commonly for sick sinus syndrome in women than men (54.4% vs. 47.2%, $p < 0.001$) and less often for A-V block (28.3% vs. 35.1%, $p < 0.001$). Adverse events at 30 days were low compared to international cohorts, for mortality (0.06%) and major complications (0.6%). There were no significant sex differences (women vs. men) for death (HR 1.33, 95% CI 0.58–3.13, $p = 0.49$) or major complications (HR 1.41, 95% 95% CI 0.65–3.03, $p = 0.39$). At 1-year, there was no difference in major complications or risk-adjusted all-cause mortality (HR 1.05, 95% CI 0.70–1.29, $p = 0.77$) between women and men.

Conclusions: Clinical practice and 30-day outcomes after CIED implantation in Australia are consistent with international reports. There were no differences in procedural complication rates or clinical outcomes at 1-year between women and men, regardless of age or CIED system implanted.

1. Introduction

Sex differences are increasingly recognised in cardiovascular disease, particularly regarding pathophysiology, clinical presentation, treatment and outcomes in coronary artery disease [1]. Women develop ischaemic heart disease at a later age compared to men, present later with acute coronary syndromes and have a higher likelihood of complications and a higher mortality related to coronary revascularisation procedures than men [2]. The preva-

Abbreviations: CIED, Cardiac implantable electronic device; PM, Pacemaker; ICD, Implantable cardioverter-defibrillator; CRT-P, Cardiac Resynchronisation therapy pacemaker; NCDR, National Cardiovascular data registry; GCOR, GenesisCare Cardiovascular Outcomes Registry; A-V, Atrio-ventricular; DDD, Dual chamber sensing and pacing; VDD, Ventricular sensing dual chamber pacing; VVI, Ventricular sensing and pacing; HF, Heart failure; MI, Myocardial infarction; CABG, Coronary artery bypass graft; PCI, Percutaneous coronary intervention; NOAC, Non-Vitamin K-dependent Oral Anticoagulant; AF, Atrial fibrillation; EPS, Electrophysiological study; OR, Odds ratio; ILR, Implantable loop recorder; VT/VF, Ventricular tachycardia/fibrillation.

* Corresponding author at: Warringal Private Hospital, Heidelberg, VIC 3084, Australia.
E-mail address: david.eccleston@genesiscare.com (D. Eccleston).

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lence of heart failure with preserved ejection fraction is greater in women than men [1].

However, whether women are equally likely to receive cardiac implantable electronic devices (CIEDs), and whether their outcomes are equivalent to those of men is unclear [4–6]. Women are under-represented in clinical trials, and patients with Pacemakers (PM) and Cardiac Resynchronisation Therapy-Pacemakers (CRT-P) are not well studied and are not included in national registries such as the National Cardiovascular Data Registry (NCDR) [4,7], Women have been reported to experience lower efficacy yet more complications with Implantable Cardioverter-Defibrillators (ICD) than men [2,3,8] Conversely, CRT-Ds may have enhanced efficacy in women according to some, but not all, reports [8]. Lack of sex-specific evidence potentially affects clinical decision making, health system planning and has payor and regulatory implications, hence there is a need to gather "real-world" evidence to inform optimal patient care [4–8].

The GenesisCare Cardiovascular Outcomes Registry (GCOR) is a multi-centre clinical quality registry that collects data regarding all CIED implants performed by a large practice group in private hospitals across Australia. Participation in this registry is an integral component of quality assurance and is mandatory for all procedures, leading to high compliance with documentation and data completeness above 95%.

The aim of this study was to determine whether procedural, 30 day and 1-year clinical outcomes after CIED implantation in Australia vary by sex by analysing the GCOR database.

2. Methods

The database of the prospective multi-centre GCOR CIED registry, the first of national scope in Australia, was evaluated for patients enrolled between August 30, 2015 to July 31, 2019. With ethics approval de-identified data was collected on consecutively enrolled patients into an electronic database that is managed centrally at Monash University (Prahran, Melbourne). This study compared the procedural, 30-day and 1-year clinical outcomes of patients receiving CIEDs stratified by sex. Parameters evaluated include age, sex, pacing indication, type of device, procedural and fluoroscopy time, pacing threshold, and measured amplitudes for atrial and ventricular leads. Major complications comprised asystole, ventricular fibrillation, pneumothorax requiring intervention, haemothorax requiring intervention, pericardial effusion/tamponade requiring intervention, haematoma requiring drainage, lead dislocation, device infection requiring drainage or extraction, stroke and death.

2.1. Statistics

Data were collected using a standardised questionnaire and further analysed. The proportion of missing data were < 1% for all variables. We used descriptive analysis (frequency /sample proportions or mean with standard deviations) to summarise patients baseline demographic and clinical characteristic, risk factors and procedural characteristics overall, and also stratified by sex. Student *t*-test, ANOVA or Chi-square tests were used to compare the distributions of patients' characteristics including procedural and/or risk factors by sex. A Cox proportional hazard regression model was used to compare clinical outcome at 30 days and 1-year between women and men. The model was adjusted for patient baseline characteristics including admission diagnosis, history of myocardial infarction, coronary revascularisation, valvular surgery, heart failure and device type. All statistical analyses were performed using Stata 15.1 for Windows. P values of < 0.05 were considered to be statistically significant.

3. Results

3.1. Patients and indications

A total of 5,360 patients undergoing cardiac device implantation were enrolled from August 30, 2015 to July 31, 2019, of which 2022 (37.7%) were female. The mean age of the patient cohort was 76.2 ± 11.2 years (range 43–102 years). Women were older than men at device implantation (77.0 ± 11.6 years vs. 75.6 ± 10.9 years, p < 0.001), with a larger proportion of CIED patients aged over 80 years being women than men (80–89 years 38.1% vs. 33.1% p = 0.001, >90 years 14.6% vs 10.0% p < 0.001, Fig. 1). However, women were less likely to have a history of myocardial infarction, coronary artery revascularisation, valvular heart disease surgery or heart failure than men (Table 1).

The average number of devices implanted at the 14 centres was 286.1 ± 176.8 per annum; almost without exception these cardiologists perform additional CIED implants at public and university hospitals that are not included in this registry.

The indication for device implantation was based on ACC/AHA and ESC guidelines for CIED (PM, CRT and ICD) implantation [8,9]. Most patients underwent de novo CIED implants (73.7%). The indication for pacing was more commonly sick sinus syndrome or vasovagal syncope in women than men (54.4% vs. 47.2%, p < 0.001), whereas A-V block was less prevalent (28.3% vs. 35.1%, p < 0.001) (Table 2).

With increasing age, the proportion of dual chamber systems, both pacemaker and ICD, declined (Fig. 1). In patients aged over 80, women received a significantly lower proportion of dual-chamber devices than men, with pacing more commonly for bradycardias with atrial fibrillation rather than A-V block. Women were also less likely to receive Cardiac Resynchronization Therapy than men (8.3% vs. 13.8%, p = 0.004).

Implant procedure time and fluoroscopy time did not differ significantly between women and men for either single (Table 3). Women were less likely to have leads placed by the cephalic approach men (14.7% vs. 17.7%, p = 0.04).

3.2. Outcomes at 30 days

Overall, CIED-related major and minor complications at 30 days follow-up were uncommon at 0.6% and 3.9% respectively (Table 4). Major and minor complication events were similar between women and men, irrespective of age or pacing system implanted (all p > 0.05). Similarly, cumulative all-cause mortality at 30-days post-device implant was low overall at 0.06% and did not differ between women and men (0.7% vs. 0.64% adjusted Hazard ratio [HR] 1.33, 95% CI 0.58–3.13, p = 0.49). However, all-cause readmission 30 days post-procedure was more common in women than men, after adjusting for baseline variables (7.2% vs. 5.4%, adjusted HR 1.38, 95% CI: 1.08–1.77, p = 0.01)

3.3. Outcomes at 1 year

Between 30 days and 1-year post-device implantation, device-related complications were 0.9% and 1.6% respectively, and did not differ by sex (Fig. 2). All-cause mortality 1-year post-procedure was 4.1%, and statistically did not differ between women and men (4.2% vs. 4.0%, adjusted HR 1.05, 95% CI: 0.70–1.29, p = 0.77) (Fig. 3). Readmission for any reason was similarly more frequent 1-year post-CIED implant in women than men (19.8% vs. 16.6%, adjusted HR 1.20, 95% CI: 1.04–1.39, p = 0.02).

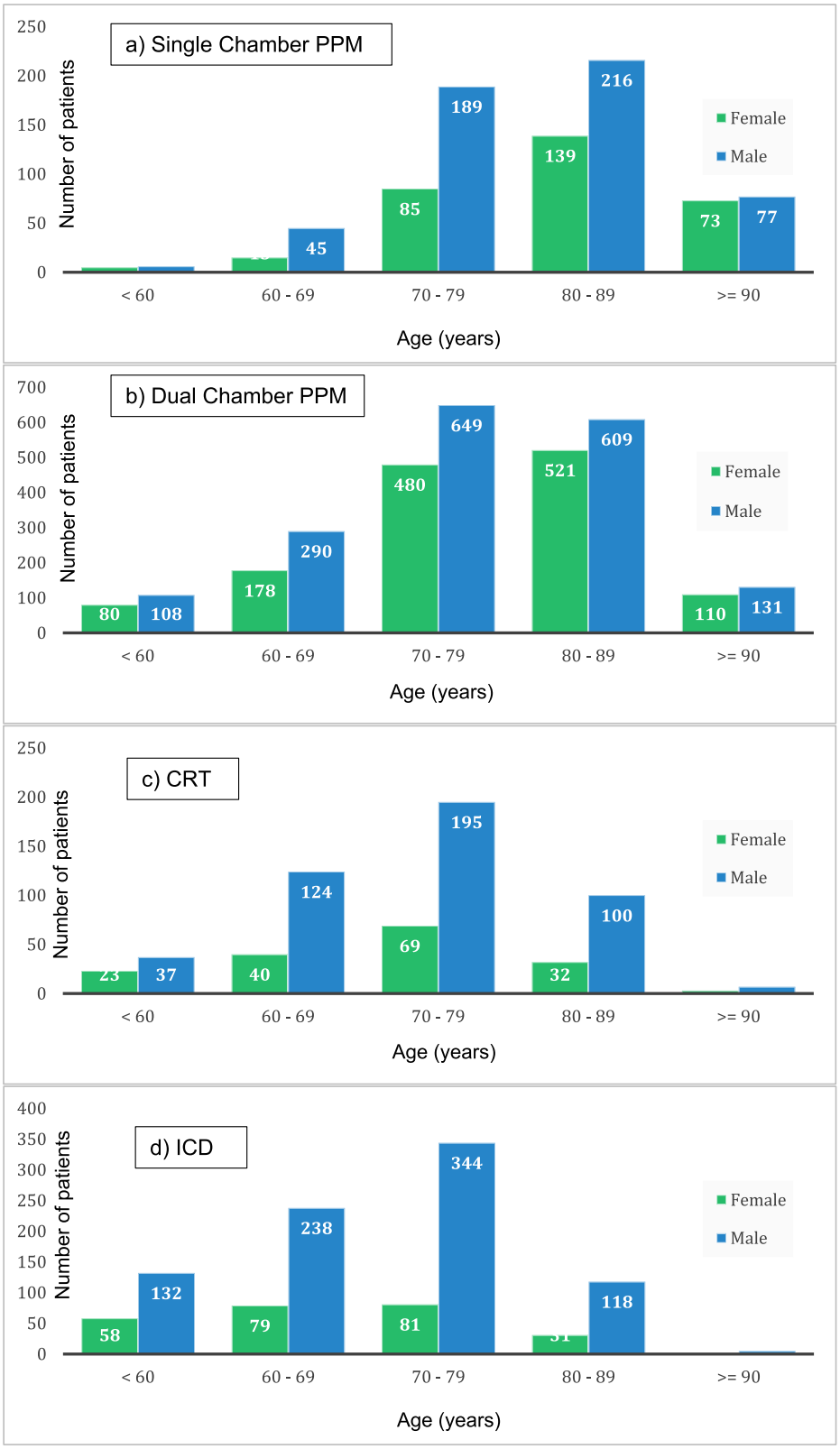

Fig. 1. Number of A) Single chamber PPM, B) Dual chamber PPM, C) CRT, D) ICD implants according to sex and age decade.

4. Discussion

This is the first large scale, multicentre, prospective evaluation of long-term outcomes after CIED implantation to assess sex-specific complication rates and patient survival in Australia. Overall, more men than women received CIEDs of any type. Women were older at the time of device implantation and less frequently received dual-chamber or CRT devices and were less likely to have a history of cardiovascular disease or intervention than men. Despite these baseline clinical and procedural differences, after

Table 1
Patient characteristics and discharge medications by sex.

Characteristic N	Female 2022	Male 3335	p-value
Age, in yr. mean (SD)	77.0 ± 11.6	75.6 ± 10.9	<0.001
Admission Status			0.09
Elective	1457 (78.4%)	2542 (80.4%)	
Emergency	402 (21.6%)	599 (19.6%)	
History and risk factors			
Atrial Fibrillation	1048 (54.3%)	1681 (53.3%)	0.49
MI	152 (8.1%)	622 (20.1%)	<0.001
CABG	83 (4.4%)	596 (19.1%)	<0.001
PCI	156 (8.3%)	600 (19.2%)	<0.001
Valvular Surgery	173 (9.2%)	394 (12.7%)	<0.001
Heart Failure	423 (22.5%)	953 (31.2%)	<0.001
Device used			
ICD	250 (12.4%)	837 (25.1%)	<0.001
Pacemaker	1772 (87.6%)	2498 (74.9%)	<0.001
Discharge medication			
Antiplatelet Drugs	469 (26.5%)	1174 (39.9%)	<0.001
Warfarin	227 (12.8%)	379 (12.8%)	0.99
NOAC	583 (32.9%)	950 (32.1%)	0.56

Table 2
Pacing & ICD Indications by sex.

Indication - Pacemaker N	Female 1772	Male 2498	p-value
Sinus node dysfunction	964 (54.4%)	1179 (47.2%)	<0.001
AV Block	501 (28.3%)	877 (35.1%)	<0.001
Fascicular Block	35 (2.0%)	66 (2.6%)	0.16
Cardiac Resynchronisation Therapy	60 (3.4%)	124 (5.0%)	0.012
Other	212 (11.9%)	252 (10.1%)	0.019
Indication - ICD N	Female 250	Male 837	p-value
Primary prevention	133 (53.2%)	403 (48.1%)	0.16
Syncope with VT at EPS	2 (0.8%)	9 (1.1%)	0.70
Syncope with LV dysfunction	2 (0.8%)	10 (1.2%)	0.60
Secondary prevention for VT/VF	56 (22.4%)	196 (23.4%)	0.74
Resynchronisation Therapy with ICD	48 (19.2%)	174 (20.8%)	0.58
Other	9 (3.6%)	45 (5.4%)	0.26

Table 3
Implant parameters by sex.

Parameter	Female	Male	p-value
Single chamber implant, n	**317**	**533**	
Procedural duration, in min. mean (SD)	29.8 (14.4)	29.8 (14.0)	0.97
Fluoroscopy, in min. mean (SD)	2.3 (2.3)	2.5 (3.2)	0.39
Dual chamber implant, n	**1369**	**1787**	
Procedural duration, in min. mean (SD)	36.7 (18.4)	36.5 (17.3)	0.86
Fluoroscopy, in min. mean (SD)	3.1 (4.7)	3.0 (3.2)	0.65
Lead access, n	**1074**	**1777**	0.04
Cephalic	158 (14.7)	315 (17.7)	
Subclavian	916 (85.3)	1462 (82.3)	

Table 4
Device-related Complications at 30 days by sex.

	Female 1823	Male 3008	p-value
Any complication	**85 (4.7%)**	**133 (4.4%)**	**0.70**
Major complications	**12 (0.7%)**	**18 (0.6%)**	**0.80**
Arrhythmia Required Intervention	9 (0.5%)	8 (0.2%)	0.20
Tamponade Required Intervention	1 (0.1%)	0 (0.0%)	0.20
Pneumothorax - requiring Intervention	0 (0.0%)	2 (0.1%)	0.27
Pericardial Effusion, no intervention	0 (0.0%)	1 (0.03%)	0.44
Air Embolism	1 (0.1%)	0 (0.0%)	0.20
Arrhythmia Required Intervention	9 (0.5%)	8 (0.2%)	0.20
Infection requiring re-operation/ extraction	0 (0.0%)	4 (0.1%)	0.12
Stroke	0 (0.0%)	2 (0.1%)	0.27
Death	1 (0.07%)	2 (0.06%)	0.76
Minor complications	**73 (4.0%)**	**115 (3.8%)**	**0.75**
Haematoma	23 (1.3%)	31 (1.0%)	0.46
Pneumothorax – no intervention	1 (0.1%)	3 (0.1%)	0.60
Infection requiring antibiotics	7 (0.4%)	17 (0.56)	0.39
Subclavian Vein Thrombosis	2 (0.1%)	4 (0.1%)	0.82
Lead Dislodgement	13 (0.7%)	16 (0.5%)	0.43
Phrenic Nerve Stimulation, conservative	1 (0.1%)	6 (0.2%)	0.20
Bleeding	0 (0.0%)	1 (0.03%)	0.44
Other	26 (1.4%)	37 (1.2%)	0.56

risk-adjustment women had similar device-related complication rates at 30 days and all-cause mortality at 1-year to men. However, women were more likely to be readmitted to hospital both at 30 days and 1 year than men.

Although randomized clinical trials have reported outcomes of men and women receiving ICDs for specific conditions women are under-represented in randomised clinical trials, and there is limited data regarding those receiving CRT devices and in patients under 65 years of age. (9–12) Existing registries report differing outcome measures. The NCDR collects data from the US Medicare population (i.e., only patients aged > 65 years) receiving ICDs for primary prophylactic indications, but not pacemakers [11]. In contrast, the National Implant Sample includes patients from all payers, but only those coded for inpatient hospitalisation, and lacks some critical clinical data such as left ventricular ejection fraction. Neither registry performs longitudinal assessment as performed here [11,12]. This cohort study of consecutive patients fulfils an important need to gather real-world evidence, especially when randomized trial data are limited and generalisability to clinical practice questionable [13]. Given clinical trial randomisation on a sex-specific base would be unethical, large, observational data are particularly important to inform sex-specific treatment effects in patients with CIEDs. Further, while previous studies have focused on in-hospital outcomes this report contributes to improved understanding of sex-related long-term clinical outcomes after CIED implantation.

This large consecutively enrolled unselected cohort had similar baseline characteristics to international reports, with high procedural success rates and low rates of major complications including mortality [5,11,14]. Albeit older, women have less comorbidities and were implanted with simpler devices. These differences are important since may explain the reported findings.

In this report, women were older with mean age at primary pacemaker implantation averaging 79.6 years, 3.9 years older than that for men. This age distribution is in close accordance with European registries such as in Denmark and Sweden, in which the mean ages for women were 77.0 and 79.9 years and for men were 74.8 and 76.0 years respectively [15,16].

Patient characteristics were consistent with findings from single centre German, Swedish and Danish pacemaker cohorts in terms of age and co-morbidities, although the incidence of a history of atrial fibrillation was higher in this cohort than in some reports [15–18]. However, as would be expected this population differed considerably from a National Cardiovascular Data Registry (NCDR) ICD population. Although patients were older in an NCDR report restricted to those over 65 years (women 79.6 ± 11.3 vs. 74.1 ± 6.0 years, men 75.7 ± 9.9 vs. 74.0 ± 6.0 years), the GCOR cohort patients were far less likely to have a history of heart failure (women 22.5% vs. 76.9%, men 31.2% vs. 83.4%) or prior MI (women 8.1% vs. 52.2%, men 20.1% vs. 65.9%) [11].

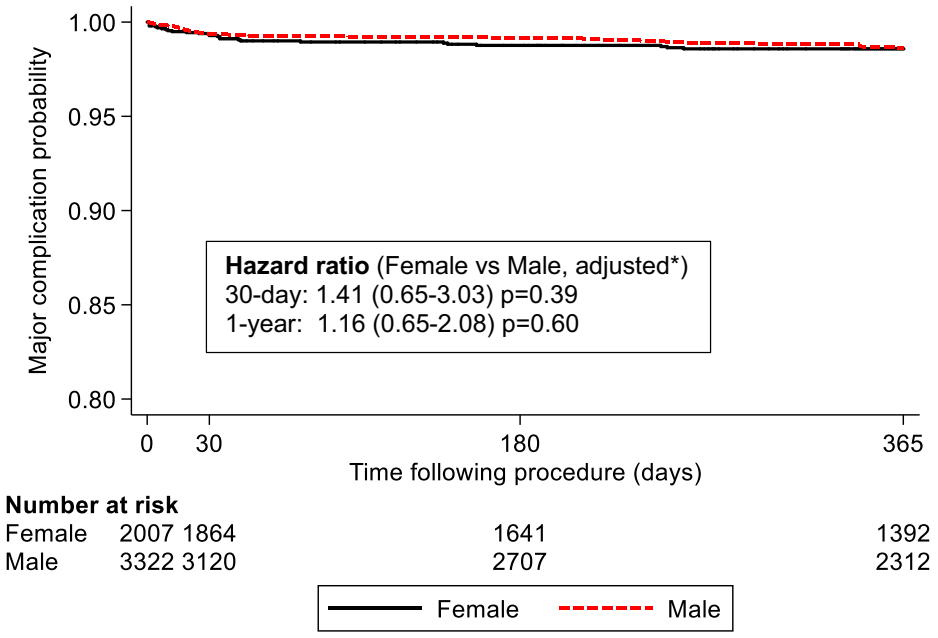

Fig. 2. Kaplan-Meier curve for cumulative incidence of major complications at 1 year after device implantation by sex. *Adjusted for age, admission diagnosis, history of MI, CABG, PCI, Heart failure and device type (Pacemaker vs ICD).

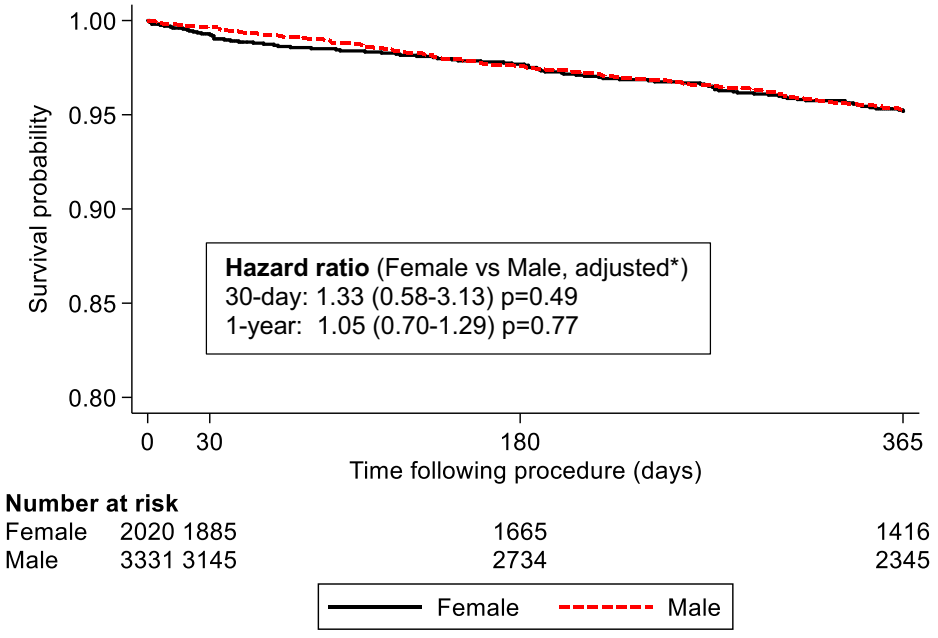

Fig. 3. Kaplan-Meier curve for cumulative all-cause mortality at 1 year following device implantation by sex. *Adjusted for age, admission diagnosis, history of MI, CABG, PCI, Heart failure and device type (Pacemaker vs ICD).*

In terms of patient outcomes, direct comparison with published data regarding device-related complications is somewhat problematic, due to a lack of standardisation of definitions for major complications, segregation of procedures and of optimal time-points for outcome measurement, which range from 30 and 90 days to as much as 6 months in one report [11]. The present study reported 30-day device-related complications, and 30-day and 1-year readmission and mortality rates as these are typical intervals for clinical review of patients after interventions such as device implants [4,6–16] Additionally, most studies detail only major device-related complications, however in this study minor complications were also reported, as these may impact patient reported outcomes such as quality of life, prolong hospitalisation, and also increase cost to patients and payors. Incorporating these measures into routine outcome monitoring could inform and benefit both patients and healthcare providers. A further point to note when benchmarking these results is that we are presenting outcomes for pacemakers, CRT and ICD devices, however unlike some reports excluded procedures with low complication rates such as Implantable Loop Recorders while including those known to have a higher risk of complications such as CRT implants and revision procedures [16].

To benchmark these data, they were contrasted with international registries rather than randomised controlled trials, as these

are more comparable and representative of real-world experience. Specifically, we looked to outcomes from The Cleveland Clinic Heart and Vascular Institute, a nationwide Danish of CIEDs, a US population-based study evaluating CIEDs, and the US National Cardiovascular Data Registry, (NCDR) although this records data only for ICDs [17–21].

In comparison to these studies, 30-day mortality in the GCOR cohort at 0. 6% (women 0.7%, men 0. 6%) was lower than the Danish (1.4%) group and NCDR ICD studies (women 1.45%, men 1.05%), and lower than the inpatient mortality in the US CIED study (0.75–1.86%), even though the GCOR group were older than the Danish and NCDR cohorts (average 76.8 ± 11.5 vs.74.0 ± 6.0 years). A retrospective study in 161,470 patients (27% women) undergoing ICD implantation from the NCDR ICD Registry revealed that women had a higher rate of any adverse events than men (4.4% vs. 3.3%; $P < 0.001$), however the prospective GCOR study did not find a significant difference in overall complications at 30 days (women 4.7% vs. men 4.4%, $p = 0.7$), and the NCDR cohort had a two-fold higher in-hospital mortality rate than the GCOR group (0.42% vs. 0.2%) [11].

In addition, 30-day major complication rates were lower at 0.6% than in these international cohorts (Danish 5.6%, NCDR 8.36%, Cleveland Clinic 3.08%), with no significant difference between women and men (0.7% vs. 0.6%, $p = 0.80$). (11, 15, 17, 18) In a large ICD study, older women had significantly more complications than did younger women [3]. Hematoma and lead dislodgement were the most common complications. Individual complications predominant in women included cardiac perforation, conduction block, coronary venous dissection, lead dislodgment, haemothorax, pneumothorax, deep phlebitis, and pericardial tamponade, however in our cohort only pneumothorax was more common in women than men (1.07% vs. 0.35%, $p < 0.01$), although there was no significant difference in the rate of pneumothorax requiring chest tube insertion. These rates are consistent with Cleveland Clinic (0.69%), Danish (0.09%) and a large US administrative dataset analysis (0.66 – 1.04%) reports, however are much lower than in US ICD population where patients were significantly younger yet had higher rates of ischaemic heart disease [19–22].

Overall, in this study rates of major complications such as stoke, tamponade requiring intervention, cardiac perforation, haematoma requiring transfusion or evacuation, device-related infection requiring intervention and mechanical complications requiring revision were zero or low in comparison to other registries such as the NCDR cohort [11,22].

5. Limitations

This study included predominantly privately insured patients, with a small number of Medicare patients, treated in private hospitals, so the results may not be generalizable to all hospital settings. However, the present study involves a large, nation-wide cohort, which, although restricted to patients treated in private hospitals nevertheless mirrors the mix of device types, sex and age distribution, and overall survival post CIED-implant observed in other national registries. This cohort shares similar detailed patient characteristics, comorbidities and CIED indications with those described in those other registry studies including the US Medicare and other populations [11–14,17–19]. Although the current study found no sex-related differences in outcomes other than readmission, the number of women receiving a CRT device was small and proportionately lower than in men, so a difference in outcome for these devices may not be evident, although this will be monitored as enrollment grows with time. Although we accounted for a wide range of baseline clinical variables, the possibility of residual unmeasured confounding cannot be excluded. It is also unclear why women seem to receive ICDs at a more advanced stage of illness.

In a previous NCDR ICD study, men were slightly more likely to receive non–evidence-based ICDs than women [20]. In the current study, all individuals receiving ICDs during the censor period were included, and the question of possible non–evidence-based ICD implantation was not examined in order to capture real-world experience, and as all centres adhere to clinical guidelines. Although the possibility that sex differences in non-indicated devices may have influenced the results cannot be excluded, prior investigation has demonstrated that these differences were minimal.

The prevalence of a history of HF in this study was 23.5%, which appears somewhat low in comparison to ICD Registries, yet consistent with registries that encompass all CIED types, including PM while excluding ILRs. It is possible that documentation of HF may be limited in some medical records, and abstractors might have difficulty identifying a history of heart failure class based on symptoms in the medical record. This is less likely in this study as annual GCOR Registry audits demonstrate an average data accuracy of 97.2%. However, variability in documentation of some data elements does represent a potential limitation of registry studies.

6. Conclusions

This study supports growing evidence that women derive equal survival benefit and are no more at risk of device-related complications than men from CIED implantation. Although the indications for CIED therapy are the same in women and men, this study found that in Australia women are less likely to have CIED and particularly ICD implantation. Women receiving a Cardiac Implantable Electronic Device in Australia had similar 30-day complication and 1-year mortality rates to men, despite differing baseline characteristics. The lower rate of cephalic access in women compared to men provides the potential to further reduce lead access site-related complications in women by pursuing cephalic lead insertion where feasible.

The lack of sex-specific data for cardiovascular devices, which have potentially differing safety and effectiveness profiles in women compared to men, has had clinical and health system implications [1,5]. These findings suggest that decisions regarding the potential benefit of and indications for CIED implantation should not differ between men and women. Given the potential value of these findings to inform patient care, ongoing surveillance of clinical practice for potential modulators of CIED efficacy and clinical outcomes with particular focus on potential sex differences to expand evidence from randomised trials is recommended. These findings may help to reduce disparities in care related to sex when considering patients for CIED therapy.

7. Perspective

7.1. Translational outlook

This report indicates the importance and value of real-world monitoring of practice and outcomes through large-scale clinical quality registries. This is particularly so where clinical trials may have demonstrated the benefit of a new treatment or device, such as implantable cardioverter-defibrillators (ICDs) for the primary prevention of sudden cardiac death in selected high-risk individuals, yet where the small numbers of patient sub-groups, in this case women, enrolled in these trials means that outcomes for women after hospital discharge have not been well described [19]. This is also the case where single centre or small scale reports, such as data regarding the effect of sex on pacemaker implantation, are

inconsistent [5]. Continued development of large-scale cardiovascular outcome registries should remain a priority for health care providers, payors and government.

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Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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