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DEVICES

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Hospitalization for permanent pacemaker implantation in the context of isolated sinus node dysfunction is associated with increased mortality compared with an outpatient strategy

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Abstract

Background: Permanent pacemaker (PPM) implantation is a well-established treatment for symptomatic sinus node dysfunction (SND). The optimal timing of this intervention is unclear, with atrioventricular blocks often prioritized in resource stressed waiting lists due to mortality concerns.

Methods: Mortality data was compared between patients receiving elective outpatient (OP) PPM implantation, and those presenting to hospital for urgent inpatient (IP) management for symptomatic SND. Survival analysis was conducted using Kaplan-Meier plots and compared using the log-rank test. Univariable and multivariable Cox regression, as well as propensity score matching analyses were performed to assess the prognostic effect on 30-day and 1-year all-cause mortality of inpatient implant.

Results: Of the 1269 patients identified with isolated SND, 740 (58%) had PPMs implanted on an OP and 529 (42%) on an IP basis. Mortality was significantly worse in patients where management was driven by hospital admission on an urgent basis (Log-Rank $\chi 2 = 21.6$, $p < 0.001$) and remained an independent predictor of 1-year all-cause mortality (HR 3.40, 95% CI 1.97–5.86, $p < 0.001$) on multivariable analysis.

Conclusions: SND is predominantly a disease associated with ageing and comorbid populations, where avoidance of deconditioning, hospitalization acquired infections, and polypharmacy is advantageous. Admission avoidance is therefore the preferable strategy.

Abbreviations: AV, atrioventricular; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; IP, inpatient; OP, outpatient; PPM, permanent pacemaker; PSM, propensity score matching; SND, sinus node dysfunction.

Alexander Sharp and Gareth Matthews contributed equally to this work.

KEYWORDS
admission avoidance, aging, frailty, permanent pacemaker, sick sinus syndrome, sinus node disease/dysfunction

1 | INTRODUCTION

Sinus node dysfunction (SND) incorporates a wide spectrum of pathology, including sinus bradycardia, sinoatrial block, chronotropic incompetence, and tachy-brady syndrome.[1,2] Permanent pacemaker (PPM) implant is a well-established treatment to reduce morbidity in symptomatic patients,[1–3] and represents the most common indication for PPM implant.[4,5] However, unlike in the context of higher degree atrioventricular (AV) block, PPM implant has not been shown to improve mortality in patients with SND.[1,2,6,7] Unfortunately, with healthcare systems seeking to optimize resource allocation, this often translates into individuals with SND "taking a backseat" to those with AV block with regards to urgency of PPM implant.

Symptomatic SND is not a benign condition. Common symptoms include shortness of breath on exertion, chronic fatigue, dizziness, pre-syncope, and syncope. Syncope is described in 50% of patients receiving a PPM for SND.[1,2] SND is associated with a higher risk of cardiovascular events including atrial fibrillation[8] and heart failure.[2] Additionally, the prevalence of SND is strongly correlated with aging.[9,10] In the elderly population, falls and deconditioning are leading drivers of morbidity and mortality.[11] PPM implantation has been associated with a reduced risk of falls and fall-related fractures,[12] hence the importance of timely intervention seems logical. Difficulties in showing mortality benefits in this group might be due to frequent non-cardiac competing causes of death in an elderly and comorbid population.[13,14]

The present study hypothesized that elective outpatient (OP) intervention before progression of symptoms to a stage necessitating hospital admission, reduces the overall negative impact of the disease and its management, thus reducing long-term mortality. Mortality, clinical, and demographic data were compared between patients receiving a PPM implant as an elective OP and urgent inpatient (IP) procedure.

2 | MATERIALS AND METHODS

2.1 | Study participants

This was a single centre, retrospective, observational study. Patients who had either a single or dual chamber PPM implanted for SND between 1st January 2016 and 1st November 2020 at the Norfolk and Norwich University NHS Foundation Hospitals Trust were included. The duration of the COVID-19 pandemic was therefore excluded as this may have influenced usual practices surrounding device implantation, particularly on an elective basis. Patients were excluded if they had any degree of AV block. There was no exclusion based on age or comorbidities.

2.2 | Data collection

Patient demographics, comorbidities, implant indication, and complications were entered at the time of implant into our institution's electronic records database. This system is linked to the Office for National Statistics mortality records allowing us to subsequently extract all necessary data for analysis. All data utilized in this study was anonymized and collected as part of a service evaluation project registered with our local clinical effectiveness and audit department (ID Card_2021-22_a14).

2.3 | Statistical analysis

The primary outcome measure was 30-day and 1-year all-cause mortality. Mortality at 30-days might be expected to reflect index admission and peri-implant death, whereas 1-year mortality provides an intermediate term measure. All patients were followed up for 1-year. Survival analysis was conducted using Kaplan-Meier curves to illustrate the association of IP and OP implant with survival, and the log-rank test used to assess for the presence of differences. Univariable Cox proportional hazard regression analysis was used to assess the prognostic value of pre-specified demographic, symptom, comorbidity, and implant related metrics. All variables were then passed into a multivariable Cox proportional hazard regression model utilizing the backward conditional method as the number of variables was less than the total number of patients. Some patients presented with more than one symptom, and these are each included in the subsequent analysis, rather than attempting to retrospectively choose which was the most important.

An alternative method of correction for confounding, propensity score matching (PSM), which allows a quasi-experimental design was also employed to ensure statistical outcomes were robust, and not due to violation of underlying assumptions required in the analysis. Some studies have suggested superiority of PSM to other multivariable approaches although others have shown no consequential difference.[15] PSM was conducted in SPSS (IBM SPSS Statistics for Macintosh, Version 28.0.1.0, Armonk, NY: IBM Corp) and the R integration package for SPSS to generate propensity matched scores and balanced cohorts. Following this, groups were compared using the average treatment effect for the treated (ATT) with 95% confidence intervals.

Continuous data was tested for normality by assessment of histograms and use of Shapiro-Wilk tests. Parametric continuous variables are expressed as mean ± standard deviation. Categorical data was presented as the number of subjects and percentage. Parametric continuous variables were compared using an unpaired Student's

TABLE 1 Characteristics of the study population.

	Outpatients (*n* = 740)	Inpatients (*n* = 529)	*p*-value
Age (years)	76 ± 9	77 ± 11	0.12
Female sex	338 (46%)	245 (46%)	0.82
Nature of Sinus Node Dysfunction			
Sick sinus syndrome	448 (61%)	346 (65%)	0.08
Tachy-brady syndrome	292 (40%)	183 (35%)	0.08
Symptoms			
Syncope	269 (36%)	303 (57%)	<0.001*
Presyncope	345 (47%)	218 (41%)	0.06
Palpitations	89 (12%)	43 (8%)	0.02*
Fatigue	65 (9%)	22 (4%)	<0.001*
Chest pain	4 (< 1%)	13 (2%)	0.003*
Co-morbidities			
Hypertension	319 (43%)	246 (46%)	0.23
Hypercholesterolemia	53 (7%)	36 (7%)	0.81
Chronic kidney disease	44 (6%)	28 (5%)	0.62
Previous myocardial infarction	70 (9%)	45 (9%)	0.56
Previous coronary artery bypass	22 (3%)	19 (4%)	0.54
Underlying structural heart disease			
Normal	632 (85%)	432 (82%)	0.07
Ischemic cardiomyopathy	36 (5%)	56 (11%)	<0.001*
Dilated cardiomyopathy	7 (< 1%)	2 (< 1%)	0.23
Hypertrophic cardiomyopathy	5 (< 1%)	6 (1%)	0.38
Valvular heart disease	24 (3%)	21% (4%)	0.49

**p*-value < 0.05. Some patients presented with > 1 symptom hence the total percentage in the symptom category is > 100%.

t-test. Categorical variables were compared using Pearson's Chi-square test, or Fisher's Exact test where appropriate, depending on the sample number. MedCalc Statistical Software version 19.2.6 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020) was used for statistical analysis. All statistical tests were two-sided and the significance level (α) was set at < 0.05.

3 | RESULTS

3.1 | Baseline characteristics

Two thousand seven hundred and twenty-one patients had PPM implants during the specified date range. Of these 1269 (47%) were for isolated SND and included in the analysis. Seven hundred and forty implants (58%) for SND were performed as an elective (OP) and 529 (42%) as an urgent (IP) case.

Full details of each cohorts' baseline characteristics are presented in Table 1. Both cohorts showed similar age, sex, nature of SND, and co-morbidities (hypertension, hypercholesterolemia, chronic kidney disease, previous myocardial infarction, and previous coronary artery bypass). Ischemic cardiomyopathy was more prevalent in the IP cohort. Symptoms of syncope and chest pain were more prevalent in the IP cohort, whilst palpitations and fatigue were more prevalent in the OP cohort.

3.2 | Survival analysis

Overall, all-cause mortality at 1-year was 5.2%. Figure 1 shows the Kaplan-Meier curves for IP and OP implant groups, and demonstrates significantly worse survival in the IP cohort ($p <$ 0.0001).

3.3 | Predictors of 30-day all-cause mortality

Using the Cox proportional hazards univariable analysis only age (HR 1.18, 95% CI 1.04–1.33, $p = 0.008$) and the presence of diabetes (HR 5.71, 95% CI 1.15–28.31, $p = 0.033$) were predictors of mortality at 30-days. In the Cox proportional hazards multivariable model both age (HR 1.22, 95% CI 1.03–1.45, $p = 0.023$) and diabetes (HR 7.32, 95% CI 1.07–49.90, $p = 0.042$) remained significant with no other significant variables.

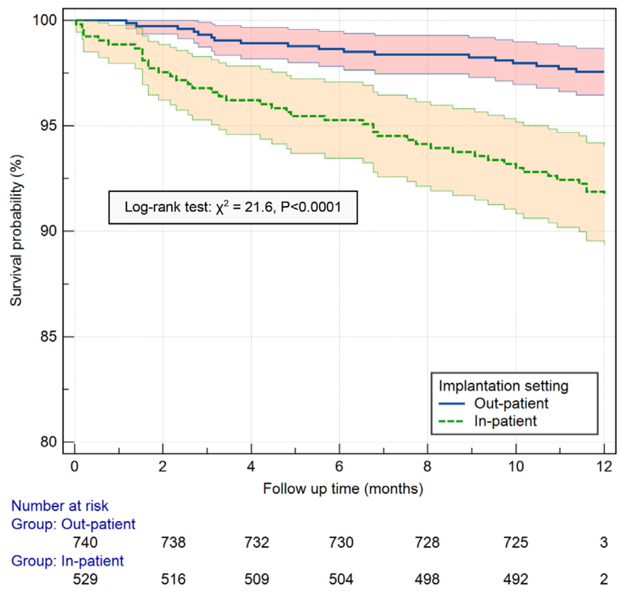

FIGURE 1 Kaplan Meier survival curves. [Color figure can be viewed at wileyonlinelibrary.com]

3.4 | Predictors of 1-year all-cause mortality

Cox proportional hazards univariable analysis (Table 2) revealed that in addition to established prognostic factors, such as age, ischemic cardiomyopathy, and dilated cardiomyopathy, IP implant was a predictor of 1-year all-cause mortality (HR 3.25, 95% CI 1.92–5.50, $p < 0.001$). On multivariable analysis (Table 2), IP implant remained an independent predictor of 1-year mortality (HR 3.40, 95% CI 1.97–5.86, $p < 0.001$) along with age, female gender, and fatigue as a presenting symptom, whilst both ischemic and dilated cardiomyopathy did not remain significant. Palpitations as a presenting symptom were protective on univariable analysis but did not remain significant in the multivariable model.

3.5 | Propensity score matching (PSM) analysis

Results were checked with PSM as an alternative correction method. Propensity score was calculated using logistic regression including all demographics and comorbidities collected. Subsequent matching via the nearest neighbor method gave OP and IP groups with 484 patients each (total $n = 968$). Cohorts were well balanced with an absolute standardized difference in means of ≤ 0.1 (see supplementary material). Between the groups, an IP pacing strategy was associated with a non-significant 1.03% (95% CI: 0.13–1.93%, $p = 0.062$) increased mortality at 30-days and a significant 6.40% (95% CI: 3.45–9.36%, $p < 0.001$) increase at 1-year compared with OP implant. IP pacing reduced the average survival by 0.23 (95% CI: 0.017–0.43, $p = 0.035$) days at 30-days of follow-up and by 13.3 (95% CI: 6.69–19.52, $p < 0.001$) days at 1-year follow-up.

4 | DISCUSSION

Our real-world data highlights that PPM implant during hospitalization in SND is associated with significantly increased 1-year all-cause mortality on both multivariable and PSM analysis. Whilst there was a trend towards an increase in 30-day mortality, it was not significant, and the effect size was small. Nearly half of PPM implants for SND occurred in patients following a hospital admission in this tertiary hospital cohort.

The overall 1-year mortality rate associated with SND is relatively high and in keeping with previous studies.[14,16] In our center, nearly half of all implantable cardiac devices were indicated for isolated SND, again reflective of previously reported practice.[4,5] The present data are therefore likely to be widely applicable. Diabetes was a significant risk factor for 30-day mortality but not 1-year mortality suggesting that it increases the risk of acute rather than chronic complications. The role of diabetes as a risk factor in mortality following PPM implant has been previously noted.[17]

SND itself cannot be a direct cause of the increased long-term mortality in the hospitalized population post-PPM as it has been definitively treated. Furthermore, syncope, an advanced symptom of SND, was not associated with higher mortality. The present study does not directly inform the reason for the increased mortality in the IP group; however, several potential explanations exist. Previous studies have reported the prevalence of “frailty syndrome” in patients with SND requiring a PPM to be 16%.[18] Poorer baseline functional status associated with increasing frailty is likely to increase the likelihood of hospital admission due to difficulty managing symptoms within the community. The present IP cohort had a higher prevalence of ischemic cardiomyopathy, which has previously been shown to be a poor prognostic marker,[14] but did not have higher rates of other common comorbidities such as hypertension and CKD. In addition, ischemic cardiomyopathy was not an independent risk factor for mortality at 1-year in the multivariable model and the statistical conclusions were robust following PSM of baseline characteristics.

Secondly SND is more common in the elderly[9] and this is a patient cohort at higher risk of deconditioning preceding, during and following hospital admission.[19] In older patients, over 80% of hospital admission time is spent lying down,[20] and 35% have a decline in activities of daily living from baseline to discharge.[21] Hospital acquired infections,[22] pressure injuries,[23] and polypharmacy[24] are more common in the elderly. Preventing admission in the elderly population is therefore of paramount importance. The retrospective nature of this study limits conclusions about whether aggressive earlier intervention as an OP would have improved mortality, this would require a randomized control trial. However, the data does suggest that the frailty “hit[25]” associated with IP management has lasting detrimental effects and thus an early intervention strategy would seem sensible.

Adopting such an approach to managing deconditioning in SND patients involves identifying those most at risk. In our study, the mean age of IP and OP cohorts was similar, implying we cannot use age as a sole marker for intervention, although age was predictably associated

TABLE 2 Cox proportional hazards univariable and backward conditional multivariable models for mortality at 1-year post implant.

	Univariable			Multivariable		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Inpatient implant	3.25	1.92–5.50	<0.001*	3.40	1.97–5.86	<0.001*
Age (years)	1.11	1.08–1.15	<0.001*	1.11	1.07–1.15	<0.001*
Female gender	1.36	0.82–2.27	0.24	1.81	1.08–3.04	0.025*
Indication						
Sick sinus syndrome	1.22	0.73–2.04	0.45			
Tachy-brady syndrome	0.82	0.49–1.37	0.45			
Symptoms						
Syncope	1.29	0.79–2.11	0.32			
Presyncope	1.13	0.69–1.86	0.62			
Palpitations	0.34	0.11–1.11	0.07*			
Fatigue	1.79	0.81–3.93	0.15	3.37	1.50–7.55	0.003*
Chest pain	0.049	0.00–692.49	0.536†			
Co-morbidities						
Hypertension	0.49	0.29–0.83	0.008*	0.44	0.26–0.76	0.003*
Hypercholesterolaemia	0.44	0.11–1.79	0.25			
Diabetes mellitus	0.83	0.41–1.67	0.60			
Chronic kidney disease	0.26	0.04–1.87	0.18			
Previous myocardial infarction	1.08	0.46–2.50	0.86			
Previous coronary artery bypass	1.55	0.48–4.93	0.46			
Underlying structural heart disease						
Normal	0.65	0.36–1.18	0.16			
Ischaemic cardiomyopathy	2.23	1.10–4.51	0.027*			
Dilated cardiomyopathy	5.47	1.34–22.36	0.018*			
Hypertrophic cardiomyopathy	0.049	0.00– 7009.17	0.62†			
Valvular heart disease	0.44	0.06–3.21	0.42			
Congenital Heart Disease	0.049	0.00–140742.00	0.69†			

*p-value < 0.05. †Only a single event in these groups occurred at 1 year follow-up hence the wide 95% CI.

with increased mortality in multivariable analysis. Previous studies have also shown that mortality rate in patients over 85 years but with good functional status at the time of PPM implant is similar to that of younger patients.[26] Similarly, female gender was similar in both IP and OP groups and was not significant as a risk factor alone. However, in multivariable analysis, female gender become a significant risk factor. Perhaps surprisingly, fatigue as a presenting symptom, which is often felt to be a "softer" indication for PPM compared with syncope was associated with a significantly increased risk of 1-year mortality in multivariable but not univariable analysis, and this was despite more of the OP group presenting with fatigue. This would suggest that when adjusted for other factors, fatigue is not a benign symptom. The present study does not inform whether this related directly to the presence of SND or to another serious underlying undiagnosed pathology where the SND was more of a bystander. Screening for other underlying conditions would certainly be prudent in the IP cohort.

Hypertension was interestingly a protective factor for mortality in both uni- and multivariable analysis. Hypotension has previously been found to be associated with increased mortality in the elderly, whilst hypertension was not.[27] Aggressive blood pressure control in the elderly remains controversial with potential reductions in heart failure but at a cost of other deleterious effects, notably an increased risk of syncope.[28] This has resulted in heterogeneous blood pressure control targets in guidelines and likely reflects further complex interplay with frailty.[29] Possible explanations for result of this study are that hypertensive patients might be better able to compensate for brief interruptions in cardiac output and may therefore come to less harm with SND. Hypotension might additionally occur in more advanced levels of heart failure. An additional confounding factor might be that patients with hypertension are more frequently followed-up in primary care, driven by quality improvement metrics. This might result in an increased health surveillance and subsequent referrals into secondary care in the hypertensive, but not normo- or hypotensive groups. As a pragmatic point however, if an aggressive blood pressure control strategy is planned, the data from this study might suggest that it should be cautioned in SND until after a PPM has been implanted.

4.1 | Limitations

The study was limited to a single center and had the inherent limitations of being observational and retrospective in design. As with any non-randomized study it is only possible to consider identified confounders within the subsequent multivariable and PSM analysis, and therefore other factors not accounted for may have affected the groups at baseline. Data on the indication for hospital admission was not available, meaning some patients may have received IP PPM implant on an incidental basis unrelated to their admission. However, if qualifying for an IP procedure, rather than awaiting an elective OP implant, it would be expected that they had a high symptom burden. In addition, this issue would be expected to bias the conclusion away from the present finding of increased 1-year mortality from awaiting hospitalization for implant. Some factors, such as chest pain, hypertrophic cardiomyopathy and congenital heart disease had very low event rates and are thus under-powered in the subsequent statistical analysis.

5 | CONCLUSIONS

In conclusion, in this large cohort of patients undergoing PPM implant for SND, IP admission was associated with greater mortality. Identification and early treatment of patients with SND at increased risk of hospitalization, especially in the elderly, women and those with fatigue may ultimately improve mortality, deconditioning and IP resource utilization.

AUTHOR CONTRIBUTIONS

Alexander Sharp, Gareth Matthews, Pankaj Garg, and Wei Yao Lim were involved in conceptualization, data analysis and interpretation. AS conducted the data extraction. Alexander Sharp, Gareth Matthews, Nikolaos Papageorgiou, Richard Till, Daniel Raine, Ian Williams, Cairistine Grahame-Clarke, Santosh Nair, Omar Abdul-Samad, Vassilios Vassiliou, Pankaj Garg, and Wei Yao Lim were all involved in manuscript drafting and critical analysis. All authors approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

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INFORMED CONSENT

Not applicable.

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