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ORIGINAL ARTICLE

Recurrent syncope in patients with a pacemaker and bradyarrhythmia

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ABSTRACT

Background. Pacemakers are used to treat syncope in patients with bradyarrhythmia; however, the risk of recurrent syncope has only been investigated in few and smaller studies. *Objective*. The aim of this study was to investigate the risk of recurrent syncope after pacemaker implantation in patients with bradyarrhythmia and prior syncope. *Methods*. This retrospective, population-based cohort study included patients with a prior syncope and implantation of a pacemaker using data from the Danish nationwide registers from 1996 to 2017. Cumulative incidence and cox regression was used to estimate the 5-year incidence and the risk of recurrent syncope, respectively. *Results*. In total, 11,126 patients (median age: 78 years, interquartile range: 69–85, 56% male) were included and the 5-year cumulative incidence of recurrent syncope was 19.6% (95% confidence interval (CI): 18.8–20.3%). Sinus node dysfunction (hazard ratio [HR]: 1.29, 95%CI: 1.17–1.42) and unspecified type of bradyarrhythmia (HR: 1.32, 95%CI: 1.15–1.52) were associated with an increased risk of syncope compared to advanced atrioventricular (AV) block. Male sex (HR: 1.22, 95%CI: 1.22–1.34), cerebrovascular disease (HR: 1.17, 95%CI: 1.05–1.30), and prior number of syncopes were significantly associated with a higher HR of recurrent syncope. *Conclusion*. Almost one-in-five patients with bradyarrhythmia and prior syncope who had a pacemaker implanted had a recurrent syncope within five years. A higher risk of syncope was observed among patients with sinus node dysfunction and unspecified type of bradyarrhythmia compared to AV block. Male sex, cerebrovascular disease, and prior number of syncopes were associated risk factors of recurrent syncope.

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Pacing; pacemaker; sick sinus syndrome; syncope; recurrent syncope; bradyarrhythmia

Introduction

Cardiac pacing can be indicated in patients with bradyarrhythmia to prevent the recurrence of syncope [1]. The incidence of pacemaker implantation is rising, but despite pacemaker implantation, some patients continue to suffer from syncope, which has a negative impact on quality of life and increases the risk of traumatic falls [1–5]. Pacemakers also have potential side effects and while pacing in advanced AV (atrioventricular) block can improve survival, long-term survival in patients with sinus node dysfunction has not been prolonged with a pacemaker, indicating that cardiac pacing is implanted primarily to alleviate symptoms [1]. Despite pacemaker implantation after relevant indications, there are studies reporting recurrent syncope in some patients [3,4,6–8]. However, little is known about the patients experiencing recurrent syncope after pacemaker implantation as no randomized controlled studies or large-scale registries have systematically reported data on the risk of recurrent syncope after pacemaker implantation. Therefore, the aim of this study was first, to estimate the incidence of recurrent syncope within the first five years after device implantation, and second, to explore the impact of type of bradyarrhythmias, device type, and other clinical factors on the risk of recurrent syncope.

Methods

Data

All residents in Denmark acquire a unique personal identification number at birth or immigration, which is registered in the Danish National Registry. This enables linkage in all national registers such as The Danish National Patient Registry that contains information about hospital admissions and discharges since 1978 [9]. After each discharge from a hospital, a primary diagnosis and if applicable one or more secondary diagnoses are linked to the specific hospitalization. Diagnoses are given according to the International Classification of Diseases (ICD). Date of death, birth, and vital status were obtained from the Danish Registry of Causes of Death and the Central Personal Registry. Data on

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cause of death is reported in the Danish Registry of Causes of Death and cardiovascular death was defined by cardiovascular ICD-10 codes 'I'. Information on surgical procedures was extracted from the Nordic Medico-Statistical Committee (NOMESCO) Classification of surgical procedures (since 1996), which includes all patients who receive a pacemaker in Denmark [9]. The National Registry for Medicinal Statistics contains data on all dispensed prescriptions from Danish pharmacies since 1995 based on the Anatomical Therapeutic Chemical System (ATC). All Danish pharmacies are legally required to register all dispensed drug prescriptions [10].

Outcomes

The primary outcome was an admission or emergency visit with recurrent syncope within five years. The validity of syncope (ICD code R55) has shown a sensitivity of 63%, a positive predictive value of 95.9%, a negative predictive value of 99.5%, and a specificity of 99.9% [11].

Study population

Patients with a previous diagnosis of a non-vasovagal syncope prior or in the same hospitalization to a first-time procedure of pacemaker implantation (excluding cardiac resynchronization therapy (CRT) devices and implantable cardioverter defibrillators) between 1996 to 2017 were included in the study. The cohort was stratified into type of bradyarrhythmias 30 days before and 5 days after the date of pacemaker implantation in the following order: sinus node dysfunction, advanced AV blocks (second- and third-degree AV block, and AV block with LBBB), and unspecified bradyarrhythmias (see Supplementary Table S1 for diagnosis codes). First-degree AV block was separated from second- and third-degree AV block due to the lack of recommendation for cardiac pacing in these patients. Patients who had an event or died within 5 days were excluded to avoid conditioning on the future. The information on device types: atrial (AAI), ventricular (VVI), or dual-chamber (DDD) were also noted [12]. Furthermore, patients aged under 18 years, with an unknown type of pacemaker, without a diagnosis of bradyarrhythmia, and patients with advanced AV block and AAI were excluded.

Covariates

Comorbidities before the date of pacemaker implantation were identified (Supplementary Table S1). Hypertension was defined as either when the patient had at least two antihypertensive prescriptions or a diagnosis of hypertension as previously done [13]. Diabetes was defined by any prescription of antidiabetic medication. Alcohol-related disease was defined as either prescription of anti-alcoholic medication or a diagnosis of alcohol abuse or alcohol-induced disease. Cardiac medications and medications with known side effects as syncope and orthostatic hypotension were identified based on prescriptions redeemed within 180 days prior to inclusion using Anatomical Therapeutic Chemical (ATC) codes. See Supplementary Table S1 for all ICD and ATC codes used in this study.

Statistical analyses

Baseline characteristics stratified by bradyarrhythmia for the study cohort for continuous data are presented as medians with first and third interquartile range (IQR), whereas absolute and relative frequencies are used to describe the categorical data. Cumulative incidence of 5-years was estimated for recurrent syncope with mortality as competing risk. Patients were followed from the date of pacemaker implantation plus five days to allow for further diagnosis of bradyarrhythmias and followed until date of event, immigration, death, or end of study (31st December 2018). A cause-specific cox proportional hazard regression model was used to determine the risk of recurrent syncope with mortality as competing risk with the covariates: type of bradyarrhythmia (reference = advanced AV block), type of pacemaker (reference = DDD), sex, age groups, and comorbidities (alcohol-related disease, myocardial infarction, diabetes, heart failure, hypertension, chronic kidney disease, cerebrovascular disease, and atrial fibrillation (AF)). Interaction analyses were done for age and sex. Explorative subgroup analyses were done stratifying on bradyarrhythmia, time from prior syncope to pacemaker implantation, and due to the definition of syncope update in 2001 by the European Society of Cardiology the year 1996–2001 and 2002–2017. Sensitivity analyses of recurrent syncope were done for 1-year follow-up and adjustment for number of prior syncopes. The assumptions of proportional hazard were tested using Schoenfeld residuals, and no violations were found. Relative risks are presented as hazard ratios (HR) with 95% confidence intervals (CI). P-values of <0.05 were considered significant. Data management was performed in Statistical Analysis System (SAS, version 9.4) (SAS Institute Inc., Cary, NC, USA), and statistical analyses were performed in R Statistical Software (version 3.6.1) [14].

Ethics

Approval from the ethics committees is not required for registered studies in Denmark, and data were anonymized. The Danish Data Protection Agency approved use of data for this study.

Results

Baseline characteristics

We identified 14,943 patients with syncope who had subsequent pacemaker implantation with a diagnosis of bradyarrhythmia between 1996 and 2017. We excluded a total of 3,817 patients due to age under 18 ($n = 30$), death ($n = 62$) or syncope ($n = 998$) within 5 days of index date, without a diagnosis of bradyarrhythmia ($n = 2,639$), or patients with a diagnosis of both advanced AV block and implantation of

an AAI pacemaker ($n = 88$) (Figure 1). Our total study population consisted of 11,126 patients and the median time between first time diagnosed with syncope to pacemaker implantation was 101 days (IQR: 5–1219). Of the total cohort 852 (8%) had a pacemaker implantation on the day of the prior syncope diagnosis. The baseline characteristics of the population (median age: 78.1 years (IQR: 69.3–84.6), 55.5% males) stratified by type of bradyarrhythmia are presented in Table 1. The types of bradyarrhythmia included 5,520 (49.6%) patients with an advanced AV block (including nine patients with AV block and LBBB), 4,404 (39.6%) with sinus node dysfunction, and 1,202 (10.8%) had another or unspecified diagnosis of bradyarrhythmia. The distribution of type of pacemakers implanted was DDD 8,479 (76.2%), VVI 2,127 (19.1%), and AAI 520 (4.7%). Of prior syncope, 51.1% of the whole cohort had 1 prior admission with syncope, 23.2% had 2 prior admissions, and 25.2% had 3 or more admissions with syncope. The most common comorbidities were hypertension (45.8%), cerebrovascular disease (20.2%), and heart failure (18.0%). The most commonly prescribed medication was acetylsalicylic acid (40.4%), antihypertensive medication like RAS inhibitors (39.3%), and diuretics (33.4%). During a median follow-up

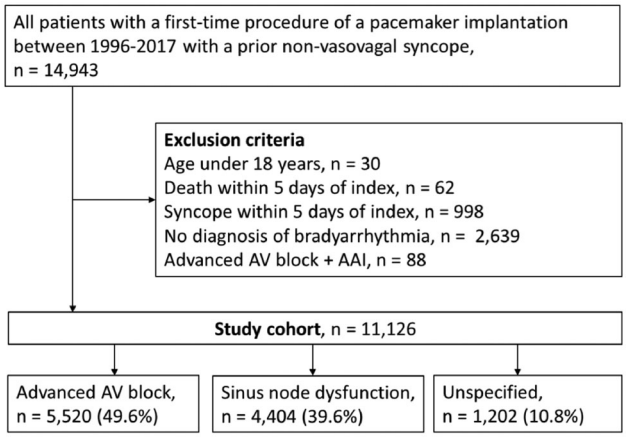

Figure 1. Flowchart of the study cohort. AAI: pacemaker with an atrial lead; AV: atrioventricular.

Table 1. Study population stratified by type of bradyarrhythmia.

Variable	Advanced AV block ($n = 5,520$)	Sinus node dysfunction ($n = 4,404$)	Unspecified ($n = 1,202$)	Total ($n = 11,126$)
Baseline characteristics				
Sex, male	3287 (59.5)	2130 (48.4)	762 (63.4)	6,179 (55.5)
Age (years)	78.6	77.8	76.9	78.1
median (IQR)	[69.5, 85.0]	[69.2, 84.3]	[68.1, 83.4]	[69.3, 84.6]
Age groups				
18–59	522 (9.5)	426 (9.7)	137 (11.4)	1,085 (9.8)
60–79	2336 (42.3)	1976 (44.9)	563 (46.8)	4,875 (43.8)
>=80	2662 (48.2)	2002 (45.5)	502 (41.8)	5,166 (46.4)
Type of pacemaker				
DDD	4,484 (81.2)	3,101 (70.4)	894 (74.4)	8,479 (76.2)
VVI	1036 (18.8)	833 (18.9)	258 (21.5)	2,127 (19.1)
AAI	0 (0.0)	470 (10.7)	50 (4.2)	520 (4.7)
Prior syncopes, *n* (%)				
1	2,988 (54.1)	2,210 (50.2)	534 (44.4)	5,732 (51.5)
2	1,287 (23.3)	1,012 (23.0)	286 (23.8)	2,585 (23.2)
3	1,245 (22.6)	1,182 (26.8)	382 (31.8)	2,809 (25.2)
Comorbidities				
Cerebrovascular disease	1100 (19.9)	915 (20.8)	233 (19.4)	2,248 (20.2)
Alcohol related disease	367 (6.6)	224 (5.1)	78 (6.5)	669 (6.0)
Heart failure	1026 (18.6)	767 (17.4)	210 (17.5)	2,003 (18.0)
Chronic kidney disease	407 (7.4)	246 (5.6)	78 (6.5)	731 (6.6)
Diabetes	758 (13.7)	444 (10.1)	144 (12.0)	1,346 (12.1)
Hypertension	2546 (46.1)	2053 (46.6)	492 (40.9)	5,091 (45.8)
Myocardial infarction	913 (16.5)	655 (14.9)	169 (14.1)	1,737 (15.6)
COPD	598 (10.8)	409 (9.3)	117 (9.7)	1,124 (10.1)
Atrial fibrillation	1,400 (25.4)	1,936 (44.6)	363 (30.2)	3,726 (33.5)
Orthostatic hypotension	106 (1.9)	102 (2.3)	27 (2.2)	235 (2.1)
Aortic stenosis	507 (9.2)	298 (6.8)	86 (7.2)	891 (8.0)
Concomitant medication				
Anticoagulation	618 (11.2)	938 (21.3)	198 (16.5)	1,754 (15.8)
ADPi	347 (6.3)	284 (6.4)	82 (6.8)	713 (6.4)
Acetylsalicylic acid	2238 (40.5)	1822 (41.4)	440 (36.6)	4,500 (40.4)
NSAID	752 (13.6)	555 (12.6)	156 (13.0)	1,463 (13.1)
Diuretics	1893 (34.3)	1463 (33.2)	363 (30.2)	3,719 (33.4)
Beta blockers	1408 (25.5)	1601 (36.4)	327 (27.2)	3,336 (30.0)
Calcium channel blockers	1405 (25.5)	1151 (26.1)	280 (23.3)	2,836 (25.5)
RAS inhibitors	2273 (41.2)	1628 (37.0)	466 (38.8)	4,367 (39.3)
Loop diuretics	1364 (24.7)	1040 (23.6)	232 (19.3)	2,636 (23.7)
Statins	1710 (31.0)	1341 (30.4)	393 (32.7)	3,444 (31.0)
Digoxin	419 (7.6)	571 (13.0)	126 (10.5)	1,116 (10.0)
Amiodarone	83 (1.5)	104 (2.4)	19 (1.6)	206 (1.9)

Baseline characteristics of the study population including comorbidities and concomitant medication.
AAI: pacemaker with an atrial lead; ADPi: adenosine diphosphate receptor inhibitor; AV: atrioventricular; COPD: chronic obstructive pulmonary disease; DDD: dual-chamber pacemaker; IQR: interquartile range; NSAID: nonsteroidal anti-inflammatory drug; RAS: renin angiotensin system; VVI: pacemaker with a ventricular lead.

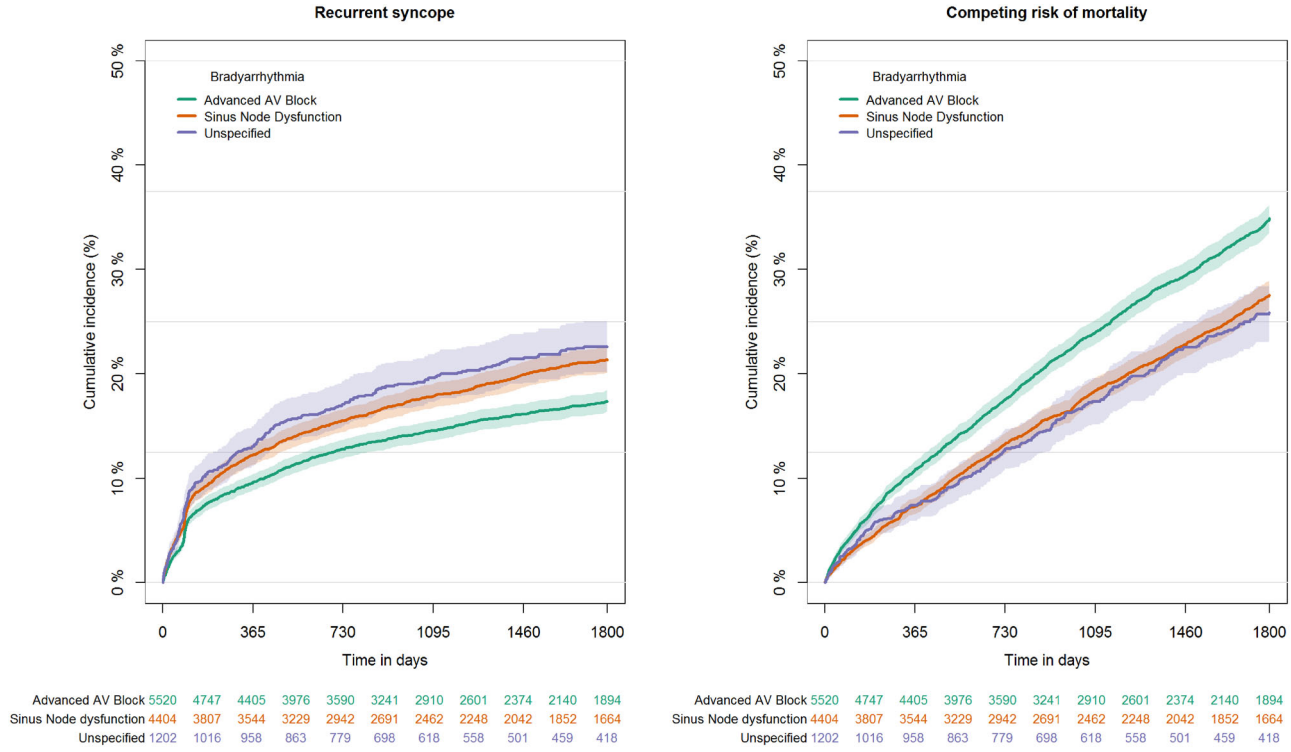

Figure 2. Five-year cumulative incidence of recurrent syncope stratified by bradyarrhythmia with competing risk of mortality. AV: atrioventricular.

of 4.5 years (1,653 days), 2,069 patients experienced a recurrent syncope and 3,871 patients died. Deaths were mostly due to cardiovascular disease ($n = 2{,}518$). During follow-up for patients who had a recurrent syncope, 24 had a device alteration, 19 had a replacement and 1 had a revision. Patients who did not experience an event had a similar number of alterations of 26, with 14 replacements, 11 revisions, and 1 upgrade within 5 years of follow-up.

Incidence of recurrent syncope

The five-year cumulative incidence of recurrent syncope was 19.6% (95%CI: 18.8–20.3), and the competing event of mortality was 31.3% (95%CI: 30.4–32.2), while 1-year cumulative incidence was 11% (95%CI: 10.5–11.6). When stratifying the cumulative incidence of recurrent syncope according to type of bradyarrhythmia, the highest recurrence rate of 22.6% (95%CI: 20.1–25.0) was in those with unspecified type of bradyarrhythmia, and the lowest recurrence rate was in patients with advanced AV block of 17.5% (95%CI: 16.4–18.5) (Figure 2**).** The recurrence rate of syncope in patients with sinus node dysfunction was 21.4% (95%CI: 20.1–22.7). When stratified according to type of pacemaker the cumulative incidence of recurrent syncope was highest in the group of patients with an AAI pacemaker of 24.5% (95%CI: 20.8–28.1) and lowest in the group of patients with a VVI pacemaker of 16.6% (95%CI: 14.9–18.2). Patients with a DDD pacemaker had a recurrence rate of 20.0% (95%CI: 19.1–20.9).

Risk factors of recurrent syncope

Patients with sinus node dysfunction had an increased associated risk of syncope compared to patients with advanced AV block (HR: 1.29, 95%CI: 1.17–1.42), as did patients with an unspecified type of bradyarrhythmia (HR: 1.32, 95%CI: 1.15–1.52) in the main adjusted analysis. Furthermore, no significant differences were observed between the different device types when comparing DDD to AAI or VVI, or when comparing AAI to VVI (HR: 0.92, 95%CI: 0.74–1.14) (Figure 3). The implantation of AAI pacemakers has been steadily declining (Supplementary Figure S1) and our analysis excluding AAI pacemakers from the cohort found no differences in the associated risk factors from the main analysis. Male sex (HR: 1.22, 95%CI: 1.11–1.34) and cerebrovascular disease (HR: 1.17, 95%CI: 1.05–1.30) were associated with a higher risk of recurrent syncope. The HR of syncope was decreased in patients with AF (HR: 0.77, 95%CI: 0.70–0.86). The short-term follow-up of 1-year showed no differences from the main results (Supplementary Table S2). Sex stratified analyses showed higher cumulative incidences for males stratified by bradyarrhythmia while unspecified bradyarrhythmia were insignificant in females (HR 1.14, 95%CI: 0.89–1.46) (Supplementary Figure S2). No interactions were found between type of bradyarrhythmia and age groups ($p = 0.3265$), sex ($p = 0.3092$), or AF ($p = 0.73$).

Sensitivity and subgroup analyses

Prior number of syncopes as per one increase was associated with an increased risk of recurrent syncope (HR 1.10 95%CI: 1.08–1.12), and compared to one prior syncope, the HR were 1.19, 95%CI: 1.06–1.33 and 1.69, 95%CI: 1.53–1.87 for the groups two and three or more prior syncopes, respectively (Supplementary Table S3). Subgroup analyses of type of bradyarrhythmia showed similar results as the

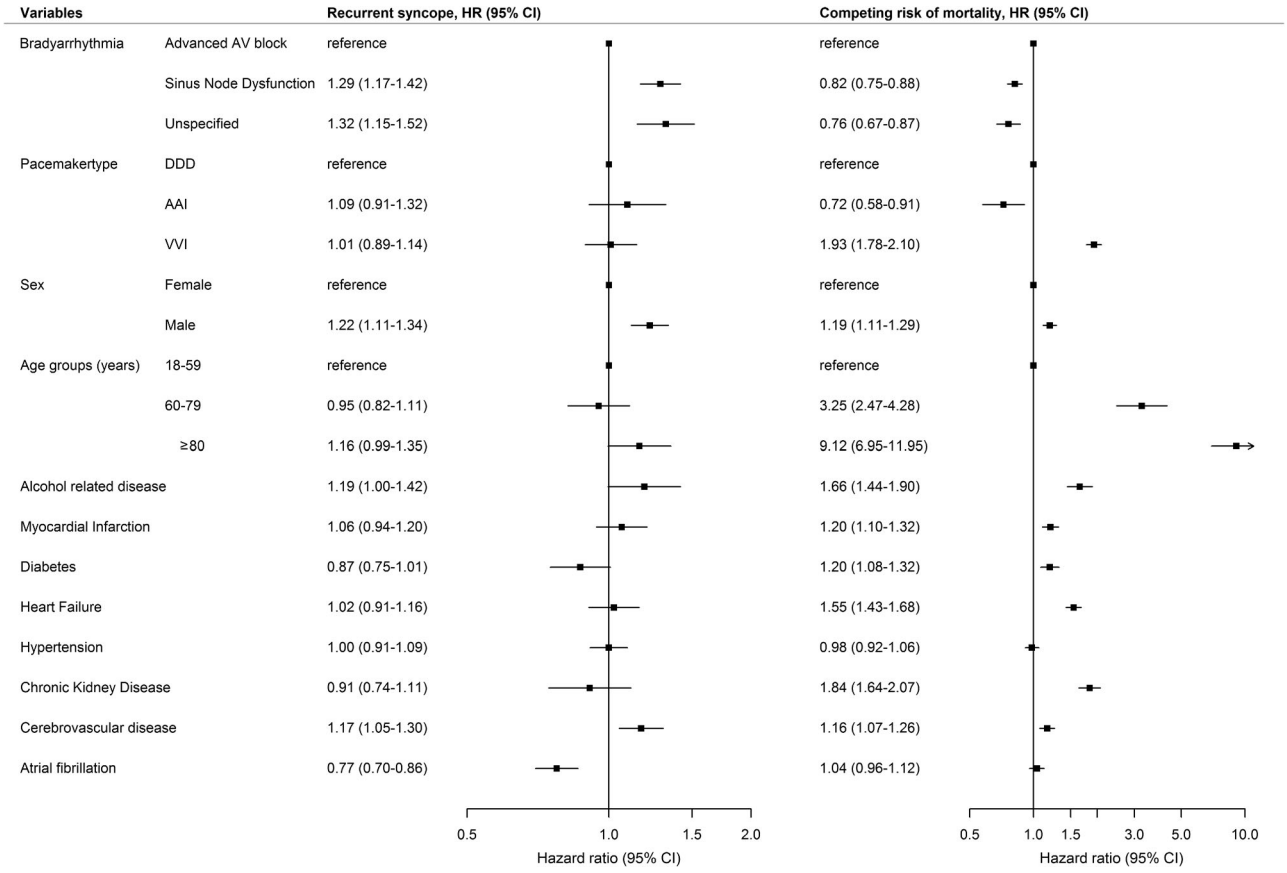

Figure 3. Risk of recurrent syncope with competing risk of mortality. AAI: pacemaker with an atrial lead; AV: atrioventricular; CI: confidence interval; DDD: dual-chamber pacemaker; HR: hazard ratio; VVI: pacemaker with a ventricular lead.

primary analyses. In the subgroup analyses for the short and long period from prior syncope to pacemaker implantation, defined as equal and below or after the median of 101 days, respectively, found similar results to the main analysis (Supplementary Table S4). Stratifying before and after the guideline update by 1996–2001 and 2002–2017 of pacemaker implantation showed overall similar results as the main analysis, though in 1996–2001 unspecified bradyarrhythmia were insignificant (HR 1.05, 95% CI: 0.72–1.53) compared to advanced AV block.

Discussion

In this nationwide retrospective cohort study, we found that syncope after pacemaker implantation in patients with bradyarrhythmia and prior syncope affected one-in-five of the cohort. Patients with sinus node dysfunction and unspecified type of bradyarrhythmia had an increased associated risk of recurrent syncope compared to advanced AV block. Male sex, cerebrovascular disease, and prior number of syncopes were associated risk factors of recurrent syncope, while a lower association was seen in patients with AF.

Bradyarrhythmia and the incidence and risk of recurrent syncope

Syncope is a common cause of hospitalization and in patients with a pacemaker, recurrent syncope is reported in about 16% of patients [3,8,15]. Our syncope recurrence rate of 21% for patients with sinus node dysfunction supports the findings of a randomized clinical trial in a real-life nationwide cohort [3]. A retrospective study have reported a lower 5-year incidence of syncope of 8% in patients with sinus node dysfunction after implantation of a pacemaker, however, this proportion increased to 20% for the subgroup of patients in whom the main indication for cardiac pacing was syncope [4]. Contrary to our findings of a recurrent syncope rate of 17.5% in patients with AV block, a lower rate has been shown in prior studies of notably smaller scale (including 115 and 229 patients) and a more heterogeneous cohort including less than 50% with a prior syncope [7,8]. Whereas a recent study reported, in line with our study, a recurrent syncope risk of 13.6% in patients with AV block, while finding a lower recurrent risk in patients with sinus node dysfunction of 12.5% [15]. The various incidence of recurrent syncope in patients with pacemakers depending on the underlying bradyarrhythmia demonstrates the importance of accurate diagnostics and highlights the need of larger real-life studies comparing recurrent syncope in patients with different bradyarrhythmias.

Compared to AV block, a higher risk of recurrent syncope was seen for patients with sinus node dysfunction and unspecified bradyarrhythmias. Pacing in symptomatic sinus node dysfunction is based on evidence level class I by European Society of Cardiology (ESC) guidelines; however, patients with sinus node dysfunction are generally old and

frequently have concomitant heart disease, which could potentially explain the observed higher risk. While the patients with unspecified bradyarrhythmias in our study was likely a heterogeneous group, they all had a clinical presentation adjudicated severe enough to indicate pacing without having a well-defined bradyarrhythmia diagnosis, which is not always possible to achieve in a clinical setting. Furthermore, the importance of a clear cause-effect relationship of syncope and bradyarrhythmia for recurrent syncope has recently been emphasized in a study, where patients with a presumed bradyarrhythmic origin of the syncope had the highest risk compared to patients with a definite bradyarrhythmia diagnosis [16].

Risk factors of recurrent syncope

We found cerebrovascular disease a significant risk factor of recurrent syncope, which could be explained by mediation of post-stroke sequelae, such as orthostatic hypotension, new-onset arrhythmias, and seizures [17–19]. Furthermore, AF was associated with a decreased risk of recurrent syncope, and while the exact mechanism is unknown, we can speculate that in patients with both bradyarrhythmia and AF, pacing could allow for better treatment of tachyarrhythmia. Alternatively, the increased competing risk of mortality in patients with AF observed in this study could in part explain the lower risk. Confirming previous studies investigating history of prior syncope episodes in risk of syncope, our study found an increasing number of syncopes a significant risk factor [3,4,16]. When comparing devices, no associated differences were found for recurrent syncope supported by another study [3]. While knowledge of pacemaker implantation and pacing mode due to arrhythmias has improved in recent years, specifically, studies of the trajectory of syncope with or without cardiac pacing are warranted.

Clinical implications

Our findings suggest that recurrent syncope is common in patients with a pacemaker and it is clinically imperative to do a meticulous diagnostic workup to establish a specific bradyarrhythmia diagnosis correlated to the syncope and not overlook other possible contributing causes of syncope especially in the elderly patients who often have several comorbidities and use multiple concurrent medications. Clinical presentation is emphasized in the current ESC guidelines of pacemakers, and our study provides insight to novel risk factors of which sex differences have not been explored prior to this extent. [12] Number of prior syncopes and cerebrovascular disease could facilitate the understanding of the etiology behind recurrent syncope, and future studies in different cohorts are warranted to highlight the impact of different risk factors. With the current evidence, clinicians and patients need to be conscious that syncope might reoccur after pacemaker implantation and higher level evidence of the indication of treatment with pacemakers for syncope are warranted to reduce the burden of recurrent syncope.

Strengths and limitations

Limitations include the observational and retrospective nature of the study and the lack of clinical parameters. The strength of this study is the large number of unselected patients included from nationwide registers liberating us from a possible recall bias and the ability to cross-link data on medication, comorbidities, and surgical procedures, in which we validated findings from prior smaller and older studies.

The true incidence of recurrent syncope may be higher as we did not have access to data from the primary sector. We cannot eliminate the possibility of patients with syncope being discharged with another primary diagnosis resulting in an underestimation of syncope or if a proportion of vasovagal syncopes were misdiagnosed as syncope and collapse, this misclassification could cause a regression towards the null, which is contrary to our findings. When looking at mimics of syncope such as pre-syncope, dizziness, epilepsy etc. Ruwald et al. demonstrated the code to be accurate. [11] However, about one-third of patients hospitalized or admitted to the emergency department with a syncope received another discharge diagnosis reflecting either the underlying etiology (most commonly sick sinus syndrome) or more observational codes (Z033 observation on suspicion of neurological disease). [11] The definition of syncope was redefined in 2001 by ESC and the risk of misdiagnosis due to syncope mimics may be increased in our cohort as we included patients from 1996. However, all patients with syncope also had a subsequent bradyarrhythmia diagnosis and pacemaker implantation, which strongly suggests a more severe etiology of syncope and our subgroup analyses, stratified by cut-off of guideline implementation year before and after were comparable.

Our study was unable to demonstrate the underlying etiology of the recurrent syncope. Previously orthostatic hypotension and reflex syncope have been reported as the most common causes of recurrent syncope, while tachyarrhythmias, structural heart disease, and device failure were less significant causes [4,15,20]. Furthermore, causes of syncope in patients with a pacemaker remain unexplained in approximately 26–30% of patients even after thorough workup [4,15].

Conclusion

Almost one-in-five patients with bradyarrhythmia and prior syncope who had a pacemaker implanted had a recurrent syncope within five years. In particular, patients receiving a device due to unspecified type of bradyarrhythmia or sinus node dysfunction had a higher risk of recurrence compared to AV block. Male sex, cerebrovascular disease, and prior number of syncopes were associated as significant risk factors of recurrent syncope. Careful consideration is advised before and after pacemaker implantation, since the threshold

for giving a pacemaker includes patients who will experience recurrent syncope and knowing the risk is important for informing patients.

Disclosure statement

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Data availability statement

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study.

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