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# Long-term outcomes in young patients with atrioventricular block of unknown aetiology

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## Aims

Atrioventricular block (AVB) of unknown aetiology is rare in the young, and outcome in these patients is unknown. We aimed to assess long-term morbidity and mortality in young patients with AVB of unknown aetiology.

## Methods and results

We identified all Danish patients younger than 50 years receiving a first pacemaker due to AVB between January 1996 and December 2015. By reviewing medical records, we included patients with AVB of unknown aetiology. A matched control cohort was established. Follow-up was performed using national registries. The primary outcome was a composite endpoint consisting of death, heart failure hospitalization, ventricular tachyarrhythmia, and cardiac arrest with successful resuscitation. We included 517 patients, and 5170 controls. Median age at first pacemaker implantation was 41.3 years [interquartile range (IQR) 32.7–46.2 years]. After a median follow-up of 9.8 years (IQR 5.7–14.5 years), the primary endpoint had occurred in 14.9% of patients and 3.2% of controls [hazard ratio (HR) 3.8; 95% confidence interval (CI) 2.9–5.1;  $P < 0.001$ ]. Patients with persistent AVB at time of diagnosis had a higher risk of the primary endpoint (HR 10.6; 95% CI 5.7–20.0;  $P < 0.001$ ), and risk was highest early in the follow-up period (HR 6.8; 95% CI 4.6–10.0;  $P < 0.001$ , during 0–5 years of follow-up).

## Conclusion

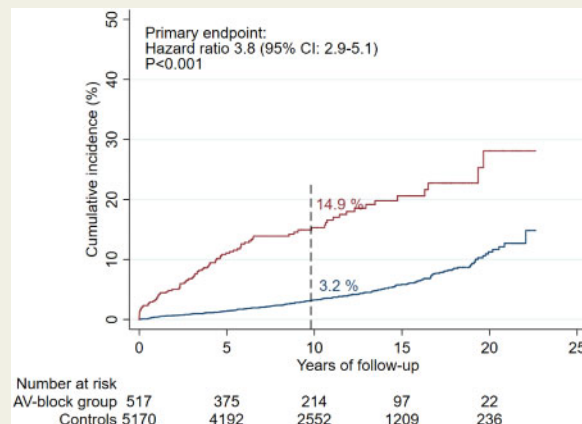
Atrioventricular block of unknown aetiology presenting before the age of 50 years and treated with pacemaker implantation was associated with a three- to four-fold higher rate of the composite endpoint of death or hospitalization for heart failure, ventricular tachyarrhythmia, or cardiac arrest with successful resuscitation. Patients with persistent AVB were at higher risk. These findings warrant improved follow-up strategies for young patients with AVB of unknown aetiology.

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## Graphical Abstract



Atrioventricular block of unknown aetiology presenting before the age of 50 years and treated with pacemaker implantation was associated with a three- to four-fold higher rate of the composite endpoint of death or hospitalization for heart failure, ventricular tachyarrhythmia, or cardiac arrest with successful resuscitation. CI, confidence interval.

## Keywords

Atrioventricular block • Long-term outcomes • Young • Pacemaker implantation • Unknown aetiology • Follow-up

## Introduction

Atrioventricular block (AVB) is the leading indication for pacemaker implantation.<sup>1</sup> When not accompanied by other cardiac diseases, AVB is reported to have a good prognosis with survival rates equal to that of the general population.<sup>2</sup> However, these findings apply to a typical pacemaker population, consisting mostly of elderly patients, in whom age-related fibrosis of the cardiac conduction system is considered the most frequent aetiology of AVB.<sup>3,4</sup> In contrast, other aetiologies dominate among young patients.<sup>5</sup> Prior studies have demonstrated that in approximately half of young patients, an underlying aetiology for AVB is not identified during the pre-implantation work-up.<sup>5,6</sup> It is likely that separate pathological mechanisms may be present in young patients. Whether this affects the long-term outcome is unknown. Therefore, this study aimed to assess long-term morbidity and mortality in young patients with AVB of unknown aetiology.

## Methods

### Study population

We conducted a nationwide retrospective cohort study of young patients with AVB of unknown aetiology treated on a clinical basis with pacemaker implantation. Consecutive patients who received their first pacemaker due to AVB before the age of 50 years between 1 January 1996 and 31 December 2015 were identified using the Danish Pacemaker and implantable cardioverter-defibrillator (ICD) Registry.<sup>1</sup> By reviewing medical records, we included patients with AVB of unknown aetiology. Using the Danish Civil Registration Registry and the Danish

National Patient Registry, a matched cohort consisting of 10 controls per case was generated from the Danish general population. The control cohort was matched based on age and gender. Moreover, controls also had to be alive and live in Denmark on the day of pacemaker implantation and could not have an ICD-10 code of pacemaker implantation (DZ950 or procedure code BFC) at any time prior to this date. Using national registries, we followed all patients and controls from the time of pacemaker implantation until a primary or secondary endpoint was reached, migration, or end of follow-up on 1 September 2018, whichever came first.

The study was approved by the Danish Data Protection Agency (record number: 2016-051-000001) and the Danish Patient Safety Authority (record number: 3-3013-1970/1/).

### Registries

All people living in Denmark are given a unique and permanent civil registration number upon time of birth or immigration. This allows crosslink of information from large nationwide, population-based registries.<sup>7,8</sup> In this study, we used data from the Danish Pacemaker and ICD Registry, the Danish Civil Registration Registry, the Danish National Patient Registry, the Danish Prescription Registry, and the Cause of Death Registry.

The Danish Pacemaker and ICD Registry is a national clinical database founded in 1982.<sup>1</sup> The implanting physician enters technical and clinical details of all device-related procedures prospectively into the database. The Registry therefore holds information on all pacemaker implantations in Denmark in the study period.

### Reviewing process

We retrieved all medical records from AVB patients identified in the Danish Pacemaker and ICD Registry fulfilling the study inclusion criteria. Atrioventricular block had to be documented by electrocardiogram (ECG), telemetric recording, loop recording, Holter monitoring, or a

description of one of these modalities in the medical record. Patients with missing medical records were excluded. In order to select only patients with AVB of unknown aetiology, we further excluded patients with identified causes of AVB according to the medical record. This comprised patients with AVB due to congenital heart disease<sup>9,10</sup> (congenitally corrected transposition, Steno-Fallot tetralogy, ventricular septal defect, or univentricular heart anatomy), iatrogenic causes (side-effects to antiarrhythmics or radiation therapy, planned His ablation, complications from cardiac surgery, radiofrequency ablation, or alcohol septal ablation), congenital AVB,<sup>11</sup> cardioinhibitory reflex, cardiomyopathy,<sup>12,13</sup> endocarditis, muscular dystrophy,<sup>14</sup> ischaemic heart disease, sarcoidosis,<sup>15</sup> borreliosis,<sup>16</sup> hereditary causes, amyloidosis, myocarditis, cardiac tumour, or if any other aetiology was reported as cause of AVB in the medical record.<sup>5</sup> To ensure a consistent review, all medical records were reviewed by the same physician (J.R.D., overseen by H.K.J.) and categorization of aetiologies was defined before reviewing patient data.

## Baseline characteristics

Baseline data were defined as the day of pacemaker implantation. Information about persistent or intermittent AVB at baseline was obtained through review of medical records and ECGs. If data on echocardiography were available in the medical records, left ventricular ejection fraction (LVEF) was registered. The data were only registered, if echocardiography was performed within 30 days prior to pacemaker implantation. Information about the type of device was obtained from the Danish Pacemaker and ICD Registry. Information about cardiovascular comorbidity was obtained from the Danish National Patient Registry and the National Prescription Database. Drug classes and ICD codes used to define comorbidities are available in [Supplementary material online, Table S1](#). Congestive heart failure was defined as a previous diagnosis of heart failure combined with treatment with loop diuretics. Patients were considered to suffer from hypertension if treated with a combination of at least two of the following antihypertensive drug classes prior to baseline:  $\alpha$ -adrenergic blockers, non-loop diuretics, vasodilators, calcium channel blockers, and renin-angiotensin system inhibitors.<sup>17</sup> Patients were considered to have diabetes mellitus if a prescription for glucose-lowering drugs was claimed prior to baseline. Hypercholesterolaemia was considered to be present if patients had either been registered with the diagnosis of hypercholesterolaemia or claimed a prescription for cholesterol-lowering drugs prior to baseline. Prior acute myocardial infarction (AMI) was considered to be present with a previous diagnosis of AMI. Patients were considered to have atrial fibrillation or atrial flutter with a previous diagnosis of atrial fibrillation or atrial flutter. Overall comorbidity of patients and controls was evaluated using the Charlson comorbidity index.<sup>18</sup> The Charlson comorbidity index was calculated at baseline using the ICD-8 and ICD-10 codes from the 10-year period prior to baseline.<sup>19</sup>

## Study outcomes

Information on all-cause death was obtained from the Danish Civil Registration Registry. Information on heart failure hospitalization, ventricular tachyarrhythmia, and cardiac arrest with successful resuscitation was collected from the Danish National Patient Registry and defined as the first admission to hospital, where an ICD-10 code of either heart failure (DI110, DI50), ventricular tachyarrhythmia (DI470, DI470C, DI472, DI472A, DI472B, DI472D, DI472H), or cardiac arrest with successful resuscitation (DI460) was given. Cardiovascular death was defined as code 23, 24, 25, 26, 27, 28, or 41 in the Cause of Death Registry.

The pre-specified primary outcome was a composite outcome consisting of (i) death from any cause, (ii) hospitalization due to heart failure, (iii) hospital admission for ventricular tachyarrhythmia, and (iv) hospital

admission for cardiac arrest with successful resuscitation. Due to the long follow-up, we also computed the hazard ratio (HR) of the primary outcome in the follow-up period from 0 to 5 years, 5 to 10 years, and from 10 years onwards. This was done to investigate any change in risk over time. Also, we wanted to explore whether having intermittent or persistent AVB at baseline was associated with different risks. Therefore, the HR for the primary endpoint was also computed separately for these two groups. Secondary endpoints were death from any cause, cardiovascular death, hospitalization due to heart failure, and hospitalization for ventricular tachyarrhythmia.

As a *post hoc* analysis, we also investigated the association between AVB and atrial fibrillation or flutter.

## Statistical analysis

Baseline variables are expressed as absolute number (proportion) and median [interquartile range (IQR)]. To minimize the risk of surveillance bias, a 30-day blinding period was introduced when generating cardiovascular comorbidity at baseline. The 30-day blinding period was introduced to minimize risk of bias due to increased medical attention in the pacemaker cohort. When diagnosed with AVB, comorbidities such as hypertension, diabetes, and hypercholesterolaemia that would otherwise not have been discovered, could be revealed during the pre-implantation work-up programme. This would make the control cohort look healthier solely because they were not examined for these diseases. Comparisons of baseline characteristics were performed using the  $\chi^2$  test or the Mann-Whitney *U* test as appropriate.

Comparisons between groups were done using a stratified Cox regression model with stratification by the matching groups and thereby adjustment for the matching variables sex and age. Additional adjustment for Charlson comorbidity index groups ([Table 1](#)) was done by including the variable as covariate in the Cox regression model. For the secondary endpoints 'cardiovascular death' and 'ventricular tachyarrhythmia', the adjustments were done as Charlson score 0 or 1+ groups due to few events. Cumulative incidence proportions at 5, 10, and 15 years were calculated for the respective endpoints by the Aalen-Johansen method with death as a competing risk.<sup>20</sup> For outcomes including death, the Kaplan-Meier method was used. Results are illustrated by graphics of cumulative incidence in which death was accounted for as a competing risk in the non-fatal endpoints. Comparison of patients with intermittent and persistent AVB at baseline was done as a *post hoc* analysis.

Statistical analyses were performed using STATA version 15.1 software (Stata Corp., College Station, TX, USA).

## Results

We included 517 patients receiving their first pacemaker before the age of 50 years because of AVB of unknown aetiology, representing 50.3% of the total number of pacemaker recipients below 50 years in the study period, and 5170 controls from the general population in the study.<sup>5</sup> Since potential aetiologies of AVB could possibly have been diagnosed after the time of pacemaker implantation, we calculated the cumulative proportion of potential aetiologies of AVB (dilated or hypertrophic cardiomyopathy, sarcoidosis, muscular dystrophy, or amyloidosis) diagnosed during follow-up ([Supplementary material online, Table S2](#)). In total, 22 patients (4.3%) were diagnosed with one or more possible aetiology at a later point in time ([Supplementary material online, Table S2](#)).

**Table 1** Baseline characteristics

	AVB cohort <sup>a</sup> , n (%)	General population cohort <sup>b</sup> , n (%)	P-value
Total	517 (100)	5170 (100)	—
Male sex	299 (57.8)	2990 (57.8)	—
Median age	41.3 (IQR 32.7–46.2)	41.3 (IQR 32.7–46.2)	—
Age at baseline			
0–10	7 (1.6)	70 (1.6)	—
10–20	28 (5.4)	280 (5.4)	—
20–30	69 (13.3)	690 (13.3)	—
30–40	132 (25.5)	1320 (25.5)	—
40–50	281 (54.4)	2810 (54.4)	—
Device type			
Brady pacemaker	513 (99.2)	—	—
Biventricular pacemaker	4 (0.8)	—	—
LVEF			
>50%	351 (67.9)	—	—
50–40%	6 (1.2)	—	—
<40%	4 (0.8)	—	—
Missing/older than 30 days	156 (30.1)	—	—
Cardiovascular comorbidity			
Congestive heart failure	7 (1.4)	4 (0.1)	<0.001
Hypertension	64 (12.4)	300 (5.8)	<0.001
Diabetes mellitus	13 (2.5)	86 (1.7)	0.158
Hypercholesterolaemia	30 (5.8)	138 (2.7)	<0.001
Prior AMI	7 (1.4)	16 (0.3)	<0.001
AF/AFL	19 (3.7)	13 (0.3)	<0.001
Charlson comorbidity index			<0.001
0	421 (81.4)	4793 (92.7)	—
1	75 (14.5)	339 (6.6)	—
2–3	15 (2.9)	25 (0.5)	—
4+	6 (1.2)	13 (0.2)	—

AF, atrial fibrillation; AFL, atrial flutter; AMI, acute myocardial infarction; AVB, atrioventricular block; IQR, interquartile range; LVEF, left ventricular ejection fraction.

<sup>a</sup>Patients <50 years when receiving their first pacemaker due to AVB.

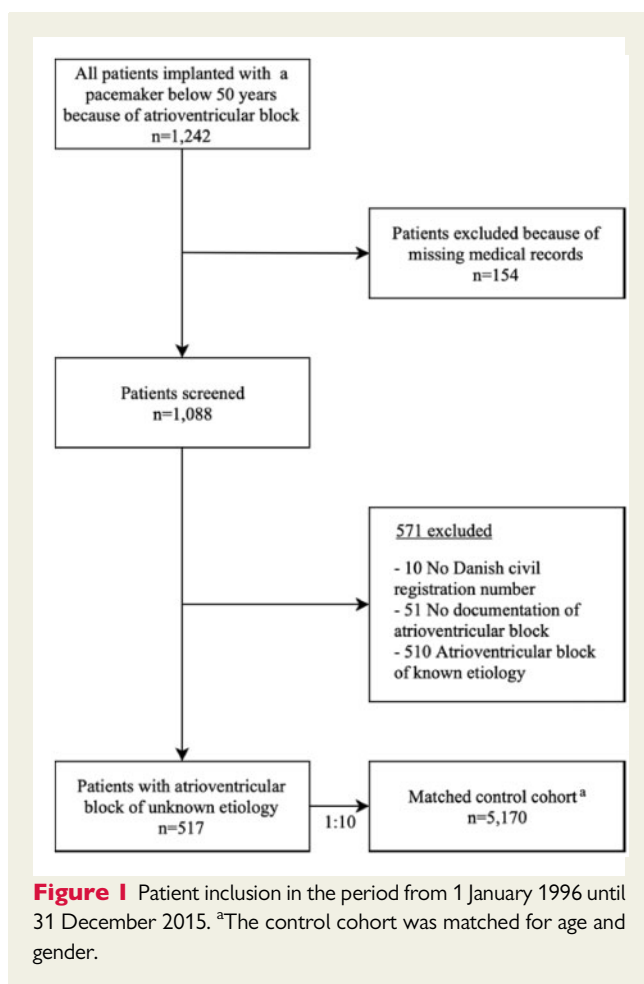
<sup>b</sup>Control cohort matched by age and gender.

Patient selection is shown in *Figure 1*. Median age at first pacemaker implantation was 41.3 years (IQR 32.7–46.2) and 299 (57.8%) were males. At baseline, the AVB cohort had more cardiovascular comorbidity and a higher Charlson comorbidity index than controls (*Table 1*). Data from pre-implantation echocardiography were available, and performed within the time window of 30 days prior to pacemaker implantation, in 361 (69.8%) patients. The data showed an LVEF >50% in 351 (97.2%) of these patients. A total of 513 (99.2%) patients received a conventional pacemaker and 4 (0.8%) received a biventricular pacemaker. In 438 (84.7%) patients, the AVB was intermittent, whereas 79 (15.3%) had persistent AVB. Besides a higher incidence of hypercholesterolaemia among patients with intermittent AVB, there was no difference in cardiovascular comorbidities between patients with intermittent and persistent AVB (*Supplementary material online, Table S3*). Right ventricular (RV) lead position was apical in 316 (61%) patients, septal in 197 (38%) patients, and epicardial in 4 (1%) patients. Cumulative incidence of reoperations due to lead malfunction was 0.9%, 3.3%, 6.5%, and 11.9% after 1, 5, 10, and 20 years, respectively. The cumulative incidence of reoperations due

to infection was 0.4%, 0.9%, 1.7%, and 4.7% after 1, 5, 10, and 20 years, respectively.

## Primary endpoints

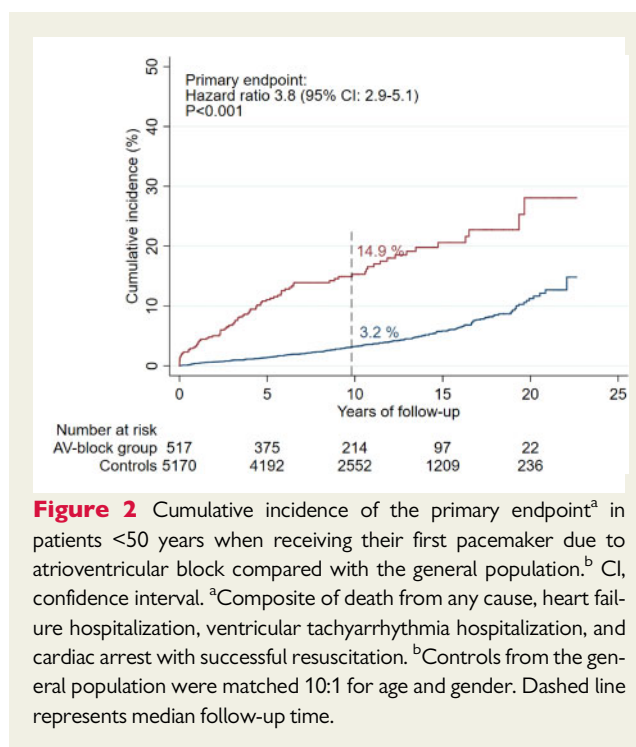
After a median follow-up of 9.8 years (IQR 5.7–14.5 years), the primary outcome had occurred in 14.9% [95% confidence interval (CI) 11.9–18.6] of AVB patients and in 3.2% (95% CI 2.6–3.7) of controls (adjusted HR 3.8; 95% CI 2.9–5.1;  $P < 0.001$ ) (*Figure 2*). The risk was relatively highest within the first 5 years after pacemaker implantation (adjusted HR 6.8; 95% CI 4.6–10.0;  $P < 0.001$ ) as opposed to the period between 5 and 10 years after the procedure (HR 2.6; 95% CI 1.4–4.9;  $P = 0.004$ ). After 10 years, there was no longer a significant difference in risk of the primary endpoint between the two groups (adjusted HR 1.8; 95% CI 1.0–3.3;  $P = 0.06$ ). The cumulative incidences after 5, 10, and 15 years are listed in *Table 2*. There was no statistically significant difference in HRs of the primary endpoint when comparing patients aged 0–40 years (HR 5.25; 95% CI 3.1–9.0;  $P < 0.001$ ) with patients aged 40–50 years (HR 3.45; 95% CI 2.5–4.8;  $P < 0.001$ ) ( $P = 0.19$ ).



When comparing patients with intermittent AVB with the corresponding controls, we found an HR of 2.9 (95% CI 2.1–4.1;  $P < 0.001$ ) of the primary endpoint. When comparing patients with persistent AVB with their controls, we found an HR of 10.6 (95% CI 5.7–20.0;  $P < 0.001$ ) of the primary endpoint (Figure 3).

## Secondary endpoints

Secondary endpoints are shown in Table 2 and cumulative incidences are graphically illustrated in Figure 4. After a median follow-up of 10.0 years (IQR 5.8–14.6), the cumulative incidence of death from any cause was 8.6% (95% CI 6.2–11.5%) in the AVB population compared with 2.4% (95% CI 1.9–2.9%) in controls (adjusted HR 2.2; 95% CI 1.5–3.2%). Cardiovascular deaths comprised 3.5% (95% CI 2.1–5.5%) in the AVB population and 0.2% (95% CI 0.1–0.4%) in the general population [median follow-up 10.0 (IQR 5.8–14.6) years] (adjusted HR 11.7; 95% CI 5.7–23.3). Heart failure hospitalization was observed in 7.7% (95% CI 5.4–10.4%) in the AVB population compared with 0.7% (95% CI 0.5–1.0%) in the general population [median follow-up 9.9 (IQR 5.7–14.5) years] (adjusted HR 8.6; 95% CI 5.4–13.8). When comparing patients with intermittent AVB with the corresponding controls, we found an HR of 8.0 (95% CI 4.9–13.0;  $P < 0.001$ ) of heart failure hospitalization. When comparing patients with persistent AVB with their controls, we found an HR of 15.5



(95% CI 6.9–35.0;  $P < 0.001$ ) of heart failure hospitalization (Supplementary material online, Figure S1). However, there was no statistically significant difference between the two HRs ( $P = 0.24$ ).

Ventricular tachyarrhythmia was also more common in the AVB population (2.8%; 95% CI 1.5–4.7%) compared with the general population (0.2%; 95% CI 0.07–0.3%) [median follow-up 9.9 (IQR 5.8–14.6) years]; however, absolute event numbers were low.

Atrial fibrillation or flutter was seen in 8.8% (95% CI 6.3–12.3) of AVB patients and in 1.2% (95% CI 0.9–1.6) of controls (adjusted HR 7.3; 95% CI 4.8–11.0;  $P < 0.001$ ) (Supplementary material online, Figure S2).

## Discussion

In the present long-term follow-up study, we observed a three- to four-fold increase in risk of the composite endpoint of death or hospitalization for heart failure, ventricular tachyarrhythmia, or cardiac arrest with successful resuscitation in patients with AVB of unknown aetiology, receiving their first pacemaker before the age of 50 years. The risk was highest during the first 5 years after pacemaker implantation and in patients with persistent AVB at time of pacemaker implantation.

The increased risk was primarily driven by an increased risk of death from any cause and by hospitalization for heart failure. The increased risk persisted after adjustment for higher baseline comorbidity among AVB patients.

The increased risk in patients with persistent AVB may relate to the risk of developing heart failure due to high-burden ventricular pacing. This was observed in the MOST study in which patients with sinus node dysfunction who received >40% ventricular pacing had a

**Table 2** Cumulative incidence and crude and adjusted hazard ratio for the primary and secondary endpoints in the general population and the atrioventricular block cohort

	Total number of events	5-year cumulative incidence (95% CI)	10-year cumulative incidence (95% CI)	15-year cumulative incidence (95% CI)	Crude hazard ratio (95% CI)	Adjusted hazard ratio <sup>a</sup> (95% CI)
Primary endpoint						
General population (reference)	219	1.4% (1.1–1.8%)	3.3% (2.7–3.9%)	5.9% (5.0–6.9%)	1.0	1.0
AVB cohort	84	11.1% (8.6–14.1%)	15.3% (12.2–19.1%)	20.6% (16.5–25.6%)	4.9 (3.7–6.3)	3.8 (2.9–5.1)
Death from any cause						
General population (reference)	170	1.0% (0.8–1.3%)	2.4% (1.9–2.9%)	4.4% (3.7–5.3%)	1.0	1.0
AVB cohort	46	5.7% (3.8–7.9%)	8.6% (6.2–11.5%)	11.4% (8.1–15.3%)	3.3 (2.3–4.6)	2.2 (1.5–3.2)
Heart failure hospitalization						
General population (reference)	51	0.3% (0.2–0.5%)	0.7% (0.5–1.0%)	1.3% (0.9–1.8%)	1.0	1.0
AVB cohort	45	5.0% (3.3–7.2%)	7.7% (5.4–10.4%)	11.1% (7.9–14.8%)	10.2 (6.6–15.7)	8.6 (5.4–13.8)
Cardiovascular death						
General population (reference)	15	0.1% (0.04–0.2%)	0.2% (0.1–0.4%)	0.4% (0–0.8%)	1.0	1.0
AVB cohort	19	2.4% (1.3–4.1%)	3.5% (2.1–5.5%)	4.6% (2.7–7.2%)	12.7 (6.4–24.9)	11.7 (5.7–23.3)
Ventricular tachyarrhythmia hospitalization						
General population (reference)	9	0.1% (0.03–0.2%)	0.2% (0.07–0.3%)	0.2% (0.1–0.4%)	1.0	1.0
AVB cohort	13	1.9% (0.9–3.4%)	2.8% (1.5–4.7%)	3.6% (1.8–6.3%)	14.4 (6.1–33.6)	14.6 (5.8–36.5)

AVB, atrioventricular block; CI, confidence interval.

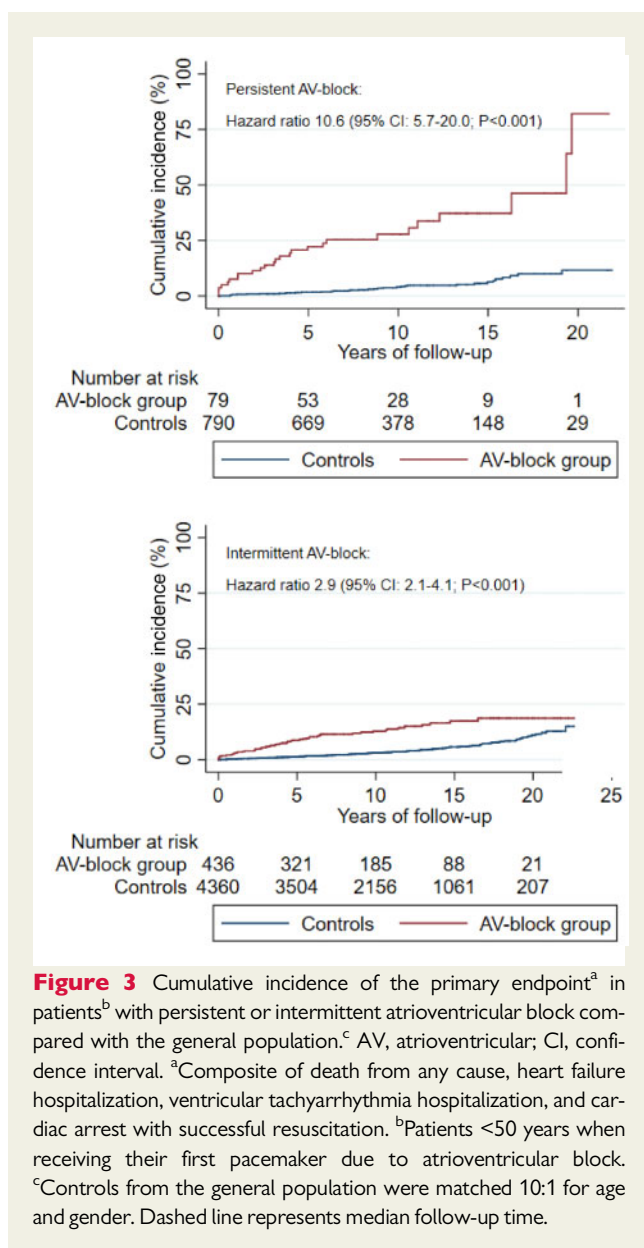
<sup>a</sup>Hazard ratios were adjusted for the matching variable sex and age and for the Charlson comorbidity index.

2.6-fold higher risk of heart failure hospitalization compared with patients who received  $\leq 40\%$  ventricular pacing.<sup>21</sup> However, studies in patients with AVB have not demonstrated uniform results. While some studies demonstrate an even lower threshold, where pacing burden  $>20\%$  was associated with an increased risk of pacing-induced cardiomyopathy,<sup>22,23</sup> others did not show a difference in the risk of declining left ventricular systolic function when comparing high- and low-burden RV pacing in AVB patients with normal LVEF.<sup>24</sup> It is important to bear in mind that these studies were conducted in typical pacemaker cohorts with a mean age of 69, 76, and 73 years, respectively, i.e. in considerable older patients than the patients in our study. It is likely that the pathogenesis of AVB differs among young and elderly AVB patients, which may also affect the response to ventricular pacing. This hypothesis may be supported by a cohort study of 6994 patients with AVB and suspected high-burden RV pacing in which the highest relative risk of heart failure hospitalization was observed among patients younger than 55 years.<sup>25</sup> Furthermore, a single-centre study of 286 patients who underwent atrioventricular junction ablation with subsequent RV pacing showed that these patients did not experience significant change in LVEF after 20 months of follow-up.<sup>26</sup> Nor did the DANPACE trial show any difference in heart failure hospitalizations between 1384 patients with sick sinus syndrome randomized to either AAIR or DDDR pacing.<sup>27</sup> This finding may indicate that RV pacing alone is not the solitary factor contributing to the poor clinical outcome seen in younger AVB patients. Undiagnosed disease possibly plays a role in our findings and, in some cases, AVB may just be the initial manifestation of a more severe underlying disease. Previous studies of young and middle-aged patients with initially unexplained AVB demonstrated that subsequent myocardial biopsy or cardiac imaging revealed

cardiac sarcoidosis in between 25% and 34% of patients.<sup>6,15</sup> Patients with cardiac sarcoidosis have a high risk of adverse cardiac events,<sup>28</sup> thus cardiac sarcoidosis should be acknowledged up front and primary defibrillator implantation considered. In recent guidelines, there has been an increased awareness that young patients with AVB may benefit from a more comprehensive pre-implantation work-up, and in the most recent American guidelines investigation for cardiac sarcoidosis is recommended in AVB patients  $<60$  years.<sup>29</sup> Due to the risk of immortal time bias, we did not use in the analysis a later diagnosis of sarcoidosis or other diseases that could be possible aetiologies of AVB.

Whether a more physiological pacing mode as an alternative to RV pacing may lead to better clinical outcomes is debated, and results are conflicting. The BLOCK HF trial<sup>30</sup> showed that implantation of a biventricular pacemaker for patients with AVB and LVEF  $<50\%$  reduced the incidence of the composite primary endpoint (all-cause mortality, urgent heart failure visits, or  $\geq 15\%$  increase in left ventricular end-systolic volume index) compared to conventional RV pacing. However, the PREVENT-HF<sup>31</sup> did not demonstrate any clinical or echocardiographic benefits from biventricular pacing over RV pacing in AVB patients with preserved LVEF. His-bundle pacing (HBP) or left bundle branch (LBB) pacing may preserve LVEF better than RV pacing.<sup>32,33</sup> However, with HBP battery drain is significantly higher and risk of lead failure is increased compared with RV pacing, and no randomized controlled data support that HBP is superior or even non-inferior to DDD pacing in AVB on long-term follow-up.<sup>33,34</sup> Experience with LBB pacing is still very limited.

In our study, despite the vast majority of patients had LVEF  $>50\%$ , the cumulative incidence of heart failure hospitalization was 7.7% (5.4–10.4%) after 10 years. Compared with the DANPACE trial,<sup>27</sup>



this is a relatively high incidence having the difference in age and comorbidity in mind. DANPACE patients had a mean age >70 years and much higher burden of comorbidity than our patients but only 12% experienced heart failure hospitalizations after a mean follow-up of 8.9 years. Moreover, our cohort had an increased risk of all-cause mortality. We found a more than two-fold increase in risk of all-cause death in our cohort, even after adjustment for a slightly higher Charlson comorbidity index at baseline. This finding supports the hypothesis that undiagnosed cardiac disease may play a role in our findings.

We observed that the risk of the primary endpoint was highest within the first 5 years after pacemaker implantation and declined thereafter. This pattern does not support a dose–response relationship, where the rate of complications rises with increasing duration of pacing. Instead, this may indicate that only some patients are vulnerable to pacing in which case these patients develop manifest disease

within the first years after pacemaker implantation. The reason for this observation is unknown and there is no current knowledge on how to predict who will or will not deteriorate. This finding also adds to the hypothesis that existence of undiagnosed underlying cardiac disease may progress and lead to a poor clinical outcome if untreated. This is supported by the 5-year cumulative incidence of death from any cause of 5.7% (95% CI 3.8–7.9%), which is high in a young and healthy cohort with >95% having a Charlson comorbidity index of 1 or 0.

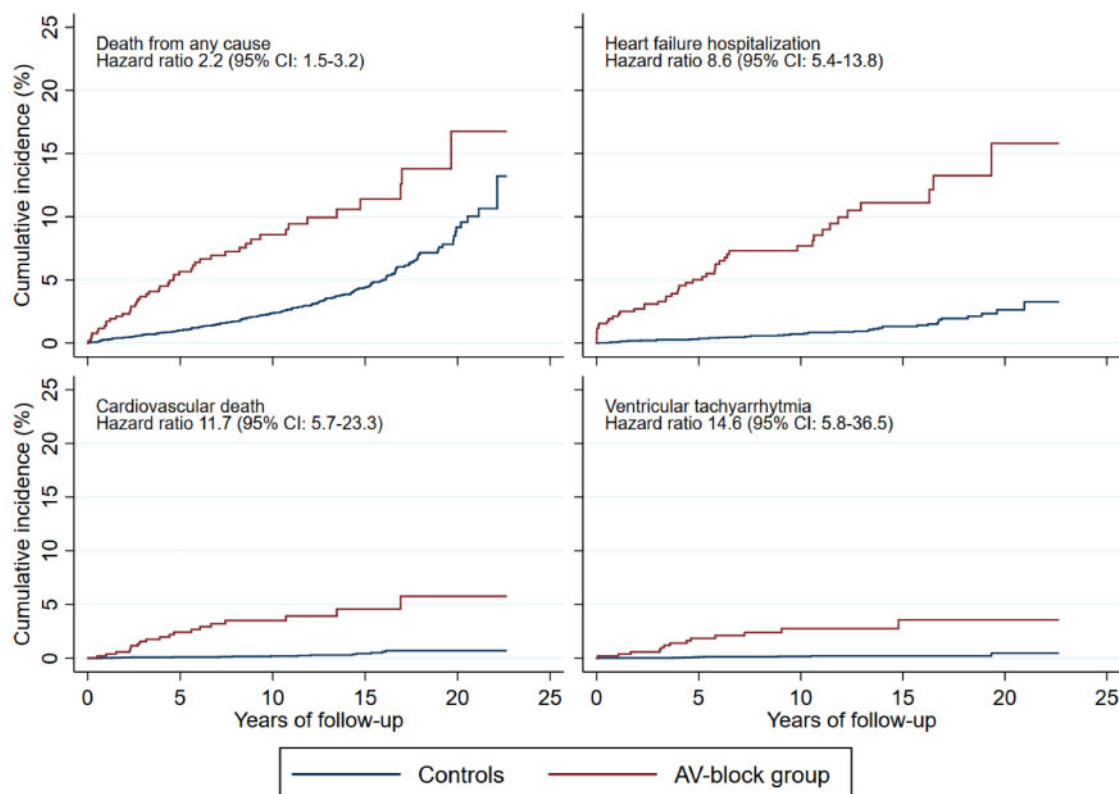
Although recent guidelines address the importance of a thorough pre-implantation work-up, our findings indicate that young AVB patients are not sufficiently addressed in current guidelines when it comes to follow-up strategy.<sup>29,35</sup> In particular, our findings show that young pacemaker-treated AVB patients are at increased risk and may require special attention. A better follow-up strategy in patients with persistent AVB or perhaps increasing pace burden could potentially enable physicians to detect early stage heart failure or arrhythmogenic cardiomyopathy and initiate relevant treatment, which may in turn improve outcome.

### Study limitations

The main strengths of this study include the large, nationwide cohort of well-characterized, consecutive, AVB patients and population-based controls as well as the almost complete long-term follow-up.<sup>36</sup> However, there are a number of limitations. Patients were identified from the Danish Pacemaker and ICD Registry. Consequently, patients who died from bradyarrhythmia before receiving a pacemaker were not included in the study, which might have introduced selection bias. Likewise, 154 (12.4%) patients were excluded due to missing medical records. However, their age and sex distributions were similar to that of the included patients and they were evenly distributed among hospitals. Selection of patients with AVB of unknown aetiology was retrospective over a 20-year period and based on review of medical records. It is possible that a systematic, prospective pre-implantation work-up, where all patients underwent the same protocolled series of diagnostic tests, would have uncovered an underlying cardiac pathology in a higher proportion of patients. While today cardiac magnetic resonance is used in many Danish centres for young patients with AVB, this imaging modality was not part of a routine work-up of AVB patients in most of the study period. Also, genetic testing has only been used in a very limited proportion of the study population. Therefore, we cannot exclude that some patients with myocardial diseases like sarcoidosis or genetic mutations in LMNA or other genes were undiagnosed during the pre-implantation work-up. This is clearly a limitation to the study and should be considered when interpreting the results. However, during long-term follow-up, only a small proportion of patients were diagnosed with other potential aetiologies of AVB.

Furthermore, data on LVEF measured within 30 days prior to pacemaker implantation were only available in 361 (69.8%) patients. This is probably due to the retrospective, nationwide design and the long study period as echocardiography has been a standard procedure in patients with AVB throughout the study period. However, we observed no clustering of age groups, sex, calendar time, or hospitals, leading to believe that the LVEF available should differ from the missing LVEF data. We did not have information about RV pacing percentage. The higher risk of the primary endpoint observed in the





**Figure 4** Cumulative incidence of secondary endpoints among patients<sup>a</sup> and the general population.<sup>b</sup> AV, atrioventricular; CI, confidence interval. <sup>a</sup>Patients <50 years when receiving their first pacemaker due to atrioventricular block. <sup>b</sup>Controls from the general population were matched 10:1 for age and gender. Deaths were considered competing risk in the non-fatal endpoints. Non-cardiovascular deaths were considered competing risk in the cardiovascular death endpoint.

subgroup of patients with persistent AVB may indicate that the percentage of RV pacing affects outcome in our cohort. However, this could not be evaluated in the present study since these data have not been collected in the Danish Pacemaker and ICD registry.

Additionally, LVEF was not available during follow-up, and therefore our study cannot elucidate whether the increased risk of the primary endpoint was driven by patients developing pacing-induced heart failure. Also, valid data on QRS width or morphology were not available from the Danish Registries during the study period, and therefore we cannot investigate whether these parameters were associated with outcome.

Lastly, there is a risk that an increased medical attention among pacemaker patients may have led to surveillance bias due to a higher probability of being diagnosed with heart failure, episodes ventricular tachyarrhythmia, or atrial fibrillation/flutter.

## Conclusion

Atrioventricular block of unknown aetiology presenting before the age of 50 years and treated with pacemaker implantation was associated with a three- to four-fold higher rate of the composite endpoint of death or hospitalization for heart failure, ventricular

tachyarrhythmia, or cardiac arrest with successful resuscitation. Patients with persistent AVB were at higher risk. These findings warrant improved follow-up strategies for young patients with AVB of unknown aetiology.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

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