Carpal Tunnel Syndrome in Patients Who Underwent Pacemaker Implantation and Relation to Amyloidosis, Heart Failure, and Mortality

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Advances in treatment warrant earlier diagnosis of cardiac amyloidosis (CA). Common cardiac and extracardiac manifestations of CA, such as pacemaker implantation and carpal tunnel syndrome (CTS), might provide screening opportunities for CA. However the association between CTS and CA in patients undergoing pacemaker implantation has not been well studied. This study examined the association between previous CTS surgery and adverse cardiovascular outcomes in patients who underwent pacemaker implantation. Using Danish nationwide registries, we identified all patients ≥50 years who underwent first-time pacemaker implantation during 2000 to 2018, examining the association between previous CTS surgery and adverse cardiovascular outcomes 5 years after pacemaker implantation. Cumulative incidence functions and Cox proportional hazard models were used to assess the differences. Among 57,315 patients who underwent pacemaker implantation, 2.2% (n = 1,266) had previous CTS surgery. Patients in the CTS cohort were older, more often female, and had more co-morbidities than patients without CTS. The cumulative 5-year mortality was higher among patients with CTS (44.6% [41.1% to 47.9%] versus 40.2% [39.7% to 40.6%], p = 0.04). In the adjusted models, previous CTS surgery was not associated with increased 5-year mortality, but it was associated with an increased rate of hospitalization for new-onset heart failure, (hazard ratio 1.32 [1.11 to 1.57], p = 0.002) and a higher risk of amyloidosis diagnosis after pacemaker implantation (hazard ratio 7.72 [2.96 to 20.10], p <0.0001), compared with no previous CTS surgery. In patients who underwent pacemaker implantation, adjusted models showed that previous CTS surgery was associated with a higher incidence of hospitalization for new-onset heart failure and amyloidosis diagnosis after pacemaker implantation. Screening for CA may be considered in patients undergoing pacemaker implantation. **(Am J Cardiol 2022;177:121−127)**

There is a major unmet need of population-based data on disease progression in cardiac amyloidosis (CA). The presence of both cardiac and extracardiac manifestations of amyloidosis might provide opportunities for screening for CA, and the association between bilateral carpal tunnel syndrome (CTS) and CA is well known.[1] Furthermore, atrioventricular (AV) conduction abnormalities are common in CA. In a large retrospective study, Donnellan et al reported that 9.5% of patients with transthyretin (ATTR)-CA had a high degree AV block at the time of CA diagnosis, requiring pacemaker implantation. Another 10% to 12% of patients developed high degree AV block during the mean follow-up of 28 months.[2] A large registry study by Fosbøl et al[3] showed that CTS surgery was not only associated with increased risk of future amyloidosis but also increased the risk of future pacemaker implantation. We set out to explore the impact of CTS in patients who underwent pacemaker implantation, hypothesizing that previous CTS surgery would be associated with increased risk of CA and its final manifestations: heart failure (HF) and death.

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See page 126 for disclosure information.

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Methods

The study is in accordance with the Declaration of Helsinki. Ethical approval is not required for registry studies in Denmark. The study has been approved by the Danish Data Protection Agency (approval number: P-2019-348).

Data were extracted from Danish national registries, in which all hospitalizations, procedures, and drug prescriptions are cataloged. The specifics and high validity of these registries have been reported previously.[4–8] All Danish residents have a unique personal identifier, which enables linkage of nationwide registries on an individual level.

All patients ≥50 years who underwent pacemaker implantation between January 1, 2000 and December 31, 2018 were evaluated for inclusion in the study. Patients with missing crucial data (e.g., date of pacemaker implantation) were excluded. Baseline was defined as the date of pacemaker implantation. Patients were divided into 2 groups on the basis of the presence of CTS surgery before baseline.

Pacemaker implantation was defined as a record of any of the Danish procedural codes (BFCA0, BFCA01-08). Implantable cardioverter defibrillators were not included in the codes used. The exposure of interest was CTS surgery (Danish procedure codes KACC51, KACC61). Study subjects were followed up from baseline (i.e., the date of pacemaker implantation) until (1) HF, (2) amyloidosis, (3) all-cause mortality, (4) emigration, (5) 5 years of follow-up, or (6) end of study period (December 31, 2018). The outcomes were: hospitalization due to new-onset HF (International Classification of Diseases [ICD]-10 codes I42, I50, I110, I130, I132, J819) and new-onset amyloidosis (ICD-10 code E85) after baseline. Mortality was assessed for the entire study population, whereas new-onset HF and new-onset amyloidosis were only assessed for patients who did not already have the disease in question at baseline.

The validity of cardiovascular diagnosis codes and procedural codes is high in the used registries: the positive predictive value (PPV) for pacemaker implantation is 100% and the PPV for HF is 81%, which ensured that the patients included in this study has had a pacemaker implanted and provided a valid measure of the end point HF.[9,10]

Demographics were described at the baseline. Co-morbidities were registered using in- and outpatient diagnoses for the past 10 years before baseline. Pharmacotherapy was assessed using filled prescriptions up to 180 days before baseline. See Supplementary Materials for used ICD and Anatomical Therapeutic Chemical Classifications System codes.

Baseline characteristics for study subjects with and without previous CTS surgery were presented as medians and interquartile ranges (IQRs) for continuous variables and as percentages for categoric variables. Chi-square test and Wilcoxon test were used to assess differences, as appropriate. Cumulative incidence functions were used to compare incidences of outcomes, incorporating competing risk of death. Hazard ratios (HRs)were calculated using crude and adjusted Cox proportional hazard models. The Cox models were adjusted for gender, age group, calendar year, hypertension, ischemic heart disease, diabetes mellitus, chronic obstructive pulmonary disease, and chronic renal failure. The proportional hazards assumption was examined graphically using log (−log[survival function]) versus time plots for the exposure variable and found valid. Age did not meet linearity assumptions and was categorized. Statistical analyses were made using SAS statistical software (version 9.4, Cary, North Carolina). A $p < 0.05$ was considered statistically significant.

Results

The study population included 57,315 patients, 2.2% (n = 1,266) of whom had previous CTS surgery. The median follow-up time was 7.7 years (IQR 3.6 to 12.7). Figure 1 shows a flow chart of patient selection. In patients with previous CTS surgery, the median age and the frequency of women was higher than in patients without previous CTS surgery. Co-morbidities (e.g., atrial fibrillation, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, chronic renal failure) and pharmacotherapy were more extensive in patients with CTS than in patients without previous CTS. Diagnosed amyloidosis was more prevalent at baseline in the CTS cohort than in the no CTS cohort (0.8% vs 0.1%, $p < 0.0001$) and Table 1 shows the baseline characteristics among study subjects with and without previous CTS surgery.

The most frequently implanted types of pacemakers were transvenous cardiac pacemaker with atrial and ventricular lead (59.4%) and transvenous cardiac pacemaker with ventricular lead (21.3%). There was no difference in pacemaker type between the 2 groups. See Supplementary Table 1 for distribution of pacemaker types. The median time from previous CTS surgery to subsequent pacemaker implantation was 5.7 years (IQR 2.8 to 9.9).

Among patients without HF at baseline, previous CTS surgery was significantly associated with increased risk of the combined end point of hospitalization for new-onset HF and 5-year mortality (crude HR 1.19 [1.07 to 1.32], $p = 0.002$, adjusted HR 1.15 [1.04 to 1.28], $p = 0.01$) compared with no previous CTS surgery.

Among patients without HF at baseline, previous CTS surgery was significantly associated with increased risk of subsequent hospitalization for new-onset HF after pacemaker implantation (crude HR 1.28 [1.08 to 1.52], $p = 0.004$, adjusted HR 1.32 [1.11 to 1.57], $p = 0.002$) compared with no previous CTS surgery. The median time from previous CTS surgery to new-onset HF was 7.8 years (4.7 to 12.5). The 5-year cumulative incidence of hospitalization for HF among patients with previous CTS surgery was 18.1% (95% confidence interval [CI] 15.3 to 21.0) compared with 14.6% (95% CI 14.2 to 14.9, $p = 0.008$ Gray test) in patients with without previous CTS surgery. Cumulative incidence curves of new-onset HF can be seen in Figure 2.

Among patients without amyloidosis at baseline, previous CTS surgery was significantly associated with increased risk of subsequent amyloidosis diagnosis after pacemaker implantation (crude HR 6.81 [2.67 to 17.39], $p < 0.0001$, adjusted HR 7.72 [2.96 to 20.10], $p < 0.0001$) compared with no previous CTS surgery. Cumulative 5-year incidence curves of diagnosed amyloidosis can be seen in Figure 2. The total number of patients new-onset amyloidosis during the entire study period was low: 0.4%

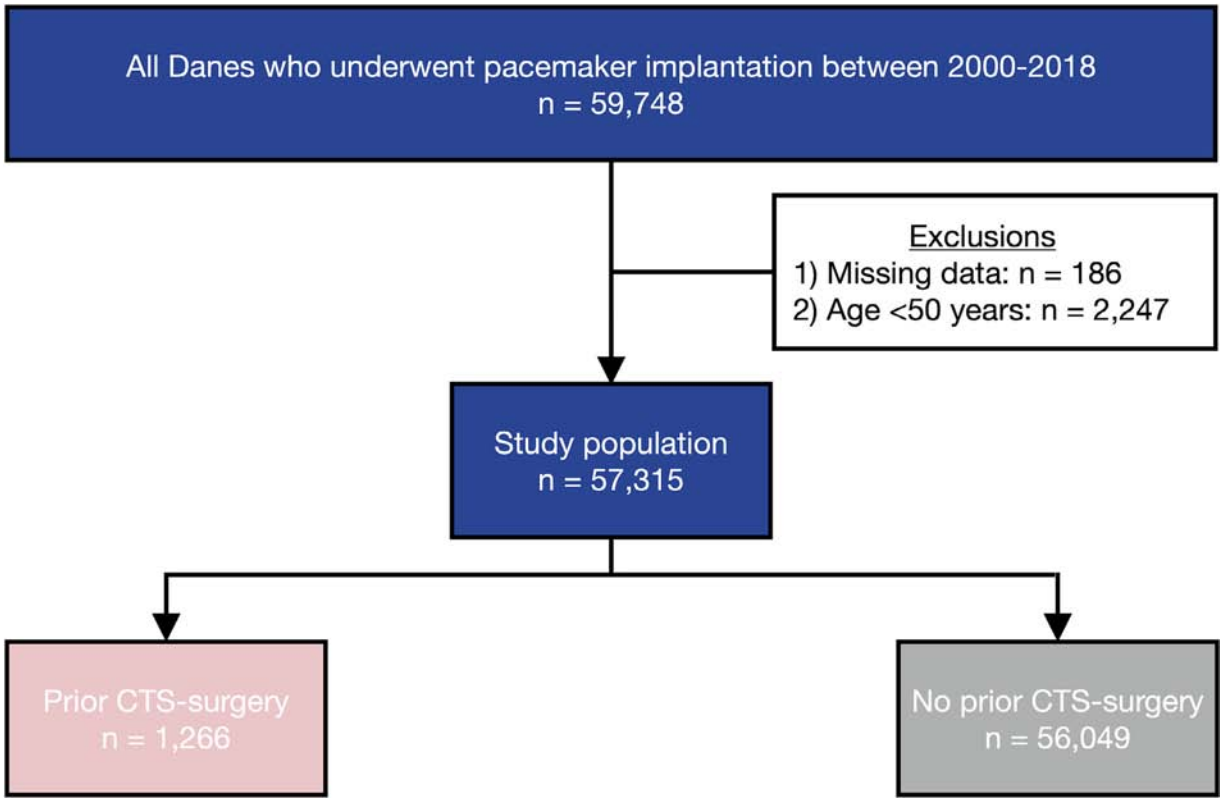

Figure 1. Flow Chart of patient selection. All patients ≥50 years who underwent pacemaker implantation between 2000 and 2018 were identified in Danish nationwide registries using procedural codes. Baseline was defined as the date of pacemaker implantation. Patients were divided into 2 groups, based on the presence of CTS surgery before baseline. A total of 57,315 patients were identified, of which 2.2% (n = 1,266) had previous CTS surgery.

(n = 5, 1 woman, 4 men) in patients with previous CTS surgery compared with 0.08% (n = 44, 15 women, 29 men) in patients without previous CTS surgery (p <0.0036 Fisher exact test). The median time elapsed between CTS surgery and subsequently diagnosed amyloidosis after pacemaker implantation was 6.3 years (IQR 4.9 to 13.4).

The cumulative 5-year mortality was 44.6% (95% CI 41.1% to 47.9%) in patients with CTS compared with 40.2% (95% CI 39.7% to 40.6%) in patients without previous CTS (p = 0.04 Log-rank test) (Figure 2). In crude Cox models, previous CTS surgery was significantly associated with increased 5-year mortality (HR 1.11 [1.01 to 1.22], p = 0.04) compared with no previous CTS surgery, but the association disappeared after adjustment for age (HR 1.02 [0.93 to 1.13], p = 0.65). Figure 3 shows a forest plot of HRs for new-onset HF and mortality.

Interaction analyses showed no significant interaction between gender and previous CTS surgery. Subgroup analyses of men showed hospitalization for new-onset HF (HR 1.53 [1.22 to 1.93], p = 0.0003) and subsequent amyloidosis diagnosis (HR 10.14 [3.43 to 30.01], p <0.0001) in adjusted models. Interaction analyses showed a significant interaction between previous third-degree AV block and previous CTS surgery regarding hospitalization because of new-onset HF and new-onset amyloidosis. In patients with previous third-degree AV block, previous CTS surgery carried a slightly higher HR (1.55 [1.18 to 2.03], p = 0.0015) for hospitalization because of new-onset HF, and the association to new-onset amyloidosis was greatly increased (HR 33.45 [10.75 to 104.03], p <0.0001). Subgroup analysis of men-with previous third-degree AV block showed the highest HR (40.19 [10.12 to 159.65], p <0.0001) for new-onset amyloidosis. Cumulative incidences of end points in the subgroup of patients with previous third-degree AV block can be found in Supplementary Figures 1 to 3. Figure 3 shows a forest plot of HRs for new-onset amyloidosis, stratified by presence of previous third-degree AV block and male gender.

Discussion

This study examined the prognostic impact of previous CTS surgery in patients who underwent pacemaker implantation. We had 3 main findings: (1) the characteristics of patients with CTS who underwent pacemaker implantation agree with current knowledge on CTS, (2) previous CTS surgery was associated with increased risk of new-onset HF and diagnosed amyloidosis after pacemaker implantation but (3) was not associated with increased 5-year mortality.

First, previous CTS surgery was present in 2.2% of patients who underwent pacemaker implantation, comparable with the frequency in the general population.[11] The characteristics of the patients with CTS included in this study are in line with previous reports on CTS, allowing for easier comparison with other published work on CTS populations.

Second, previous CTS surgery was significantly associated with increased risk of hospitalization because of new-

Table 1
Baseline characteristics

Variable	CTS* (n = 1266)	No CTS (n = 56049)	p-Value
Median age, (years) (IQR)	79.5 (71.7 − 85.4)	78.0 (70.4-84.3)	<0.001
Female	53.1%	42.5%	<0.001
Hypertension	52.5%	40.3%	<0.001
Coronary heart disease	32.9%	32.0%	0.48
Myocardial infarction	11.8%	11.2%	0.52
Heart failure	22.8%	21.1%	0.13
Atrial fibrillation	39.0%	36.3%	0.04
Stroke	10.2%	9.8%	0.68
Chronic obstructive pulmonary disease	12.4%	9.6%	<0.001
Renal disease	9.5%	6.1%	<0.001
Diabetes mellitus	24.1%	17.8%	<0.001
Cancer	15.9%	13.4%	0.01
Amyloidosis	0.8%	0.1%	<0.001
3rd degree AV†-block	25.4%	29.9%	<0.001
Pharmacotherapy			
Statins	46.7%	35.4%	<0.001
ASA‡	41.0%	39.1%	0.17
ADP§	9.7%	7.2%	<0.001
Anticoagulants	30.9%	24.7%	<0.001
Antidiabetics	19.8%	14.5%	<0.001
Beta blockers	40.0%	36.1%	0.004
ACE-I¶	54.3%	46.9%	<0.001
MRA**	11.8%	9.2%	0.002
Digoxin	13.0%	13.2%	0.89
Furosemide	37.4%	29.7%	<0.001
Burinex	1.7%	0.8%	0.001
Thiazides	16.4%	18.4%	0.08
Calcium antagonists			
Dihydropyridine	27.3%	23.4%	0.001
Non-dihydropyridine	2.9%	3.8%	0.10

* Carpal tunnel syndrome.
† Atrioventricular.
‡ Acetylsalicylic acid.
§ Adenosine diphosphate receptor inhibitor.
¶ Angiotensin-converting enzyme inhibitor.
** Mineralocorticoid receptor antagonist.

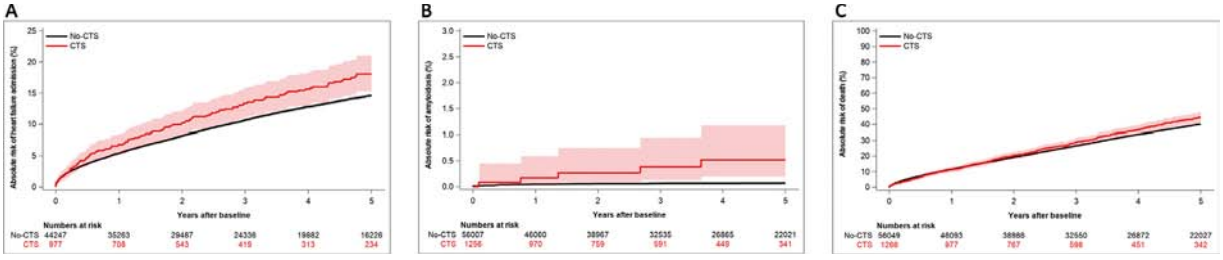

Figure 2. (A) Cumulative incidence of hospitalization because of new-onset HF, by presence of previous CTS surgery. The incidence of hospitalizations due to new-onset HF was described using cumulative incidence functions, incorporating competing risk of death. The 5-years cumulative incidence of hospitalization for HF among patients with previous CTS surgery was 18.1% (95% CI 15.3 to 21.0), compared with 14.6% (95% CI 14.2 to 14.9), p = 0.008 Gray's test, in patients with without previous CTS surgery. (*B*) Cumulative incidence of diagnosed amyloidosis after pacemaker implantation, by presence of previous CTS surgery. The incidence of diagnosed amyloidosis was described using cumulative incidence functions, incorporating competing risk of death. The 5-years cumulative incidence of amyloidosis among patients with previous CTS surgery was 0.5% (95% CI 0.2 to 1.2), compared with 0.07% (95% CI 0.05 to 0.09), p <0.001 Gray's test, in patients with without previous CTS surgery. (*C*) Cumulative 5-years mortality after pacemaker implantation, by presence of previous CTS surgery. The mortality was described using cumulative incidence functions. The cumulative 5-years mortality was 44.6% (95% CI 41.1% to 47.9%) in patients with previous CTS surgery, compared with 40.2% (95% CI 39.7% to 40.6%) in patients without previous CTS surgery, p = 0.04 Log-rank test.

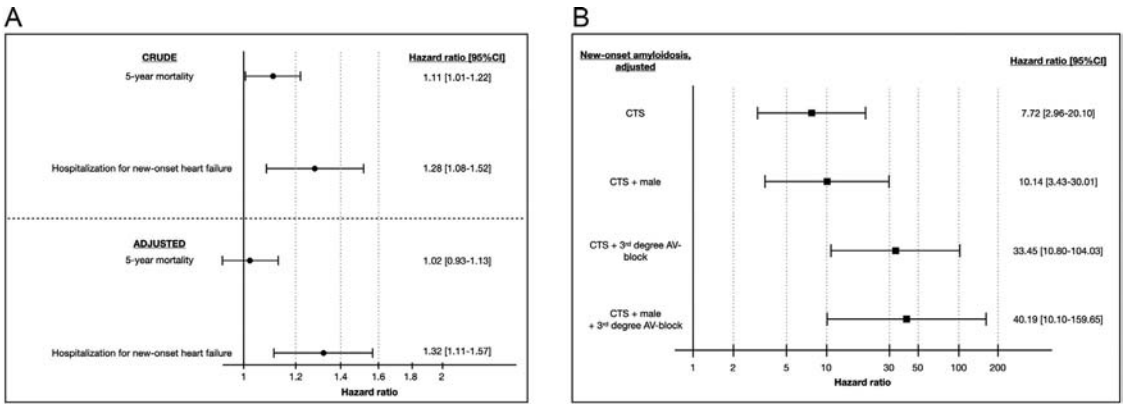

Figure 3. (*A*) Forest plot with 5-years hazard ratios for mortality and hospitalization for new-onset HF. Among patients without HF at baseline, previous CTS surgery was significantly associated with increased risk of subsequent hospitalization for new-onset HF after pacemaker implantation, crude HR 1.28 (1.08 to 1.52), p = 0.004, adjusted HR 1.32 (1.11 to 1.57), p = 0.002, compared with no previous CTS surgery. In crude Cox models, previous CTS surgery was significantly associated with increased 5-y mortality (HR 1.11 [1.01 to 1.22], p = 0.04) compared with no previous CTS surgery, but the association disappeared after adjustment for age (HR 1.02 [0.93 to 1.13], p = 0.65). The models were adjusted for gender, age group, calendar year, hypertension, ischemic heart disease, diabetes mellitus, chronic obstructive lung disease and chronic renal failure. (*B*) Forest plot with adjusted 5-years hazard ratios for new-onset amyloidosis, by presence of previous CTS, previous third-degree AV block and male gender. Among patients without amyloidosis at baseline, previous CTS surgery was significantly associated with increased risk of subsequent amyloidosis diagnosis after pacemaker implantation, compared with no previous CTS surgery. Male gender and the presence of third-degree AV block increased the associated hazard ratios further. The highest hazard ratio was seen in males with third-degree AV block before pacemaker implantation: HR 40.19 (10.10 to 159.65), p <0.0001. The models were adjusted for age group, calendar year, hypertension, ischemic heart disease, diabetes mellitus, chronic obstructive lung disease and chronic renal failure.

onset HF and increased risk of diagnosed amyloidosis after pacemaker implantation. The same association between CTS, HF, and amyloidosis has been reported previously by Fosbøl et al in a nationwide sample of patients with CTS.[3] The results support the hypothesis of undiagnosed CA being present in the population. The ICD codes used do not guarantee that the type of amyloidosis being diagnosed is CA; however, the coexistence of pacemaker implantation and diagnosed amyloidosis is highly suggestive of CA.[9] Reviewing patient records in patients with an ICD code for amyloidosis between 2016 and 2021 (n = 242), we assessed the PPV for CA, defined as any ICD code for amyloidosis + a record of pacemaker implantation, and found that this definition yielded a PPV of 85.2%. However, this assessment was performed on patient records from a single center (Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark), and the possibility to extrapolate the findings to a national scale is uncertain. No significant interaction between gender and CTS could be established. Although, epidemiologically, there is a reason to investigate the associated risks for male patients only because wild type ATTR (ATTRwt) is a predominantly male disease.[12] Subgroup analyses of men showed accentuated HRs for all outcomes. Although not statistically appropriate, the results are interesting and in line with current knowledge about CA. Although the entire cardiac conduction system has been reported to be affected by amyloid infiltration, AV block is more common than sinoatrial disease in CA.[10] Therefore, subgroup analyses of patients with a code for third-degree AV block before pacemaker implantation was performed and showed further accentuation of the results. In men with previous third-degree AV block, the associated risk of a future amyloidosis diagnosis was 40 times higher than in men without previous CTS surgery. These findings support that previous CTS in men undergoing pacemaker implantation is indicative of a higher risk of CA.

Third, no association between previous CTS surgery and increased mortality could be established. This may be because the absolute number of subjects with CA was insufficient in the CTS cohort to show statistical significance. Although CA is certainly underdiagnosed, cases of undiagnosed CA would still be reflected in mortality. An alternative interpretation could be that the severity of CA at time of pacemaker implantation was low—meaning that there is time for early treatment should screening reveal undiagnosed CA among these patients. This interpretation is in line with results from the recently published study by Donnellan et al, in which advanced AV block was not associated with increased mortality in patients with ATTR-CA, whereas disease severity was.[2] If conduction abnormalities are indeed early manifestations of CA, a 5-year follow-up might be too short to observe increased mortality. This is, however, partially contradicted by the high median age observed in the described population, as CA would be expected to be manifested at this age. At this age, nonetheless, there are certainly competing risks for mortality in addition to CA.

López-Sainz et al published a study in 2019, in which 115 patients ≥60 years who underwent pacemaker implantation were screened for CA, reported a 2% prevalence of ATTRwt.[13] Although the authors discerned that the found prevalence might be too small to justify systemic screening, they suggest that unexplained advanced conduction disturbances should still be regarded as a red flag for ATTRwt. Future studies to define a set of robust factors with a high PPV will be essential to delineate an effective viable screening strategy. Such factors would likely include echocardiographic measurements, cardiac biomarkers, common extracardiac manifestations of CA, age, gender, and

pacemaker indication. The presence of extracardiac manifestations of CA (bilateral CTS, lumbar spinal stenosis, bicep tendon rupture, deafness), older age, male gender, and pacemaker implantation because of AV block would be possible signs of ATTRwt.

The major limitation of observational studies is that causal relations cannot be surveyed. Although efforts were made to minimize confounding, any residual confounding cannot be rejected. The Danish registries provide virtually complete follow-up on all patients and the use of a nationwide sample minimizes selection bias. The cardiovascular diagnosis codes have high PPVs in the registries, as do the procedural codes.[4−8] Although the registries contain information on all diagnosed CTS, we choose to use previous CTS surgery because this is more specific (i.e., the diagnosis is verified by a surgeon, finding indication for operation). The increased specificity comes with the price of reduced sensitivity because patients with milder, conservatively treated CTS are missed. Clinical parameters (e.g., echocardiography, cardiac biomarkers, BMI) are not available in the registries used. The associations with amyloidosis are likely underestimated because CA is underdiagnosed.

In conclusion, in patients ≥50 years who underwent pacemaker implantation, previous CTS surgery was associated with a higher risk of hospitalization for new-onset HF and amyloidosis diagnosis after pacemaker implantation. Previous CTS surgery was not associated with increased 5-year mortality after pacemaker implantation. These results suggest that screening for CA may have a place in patients with previous CTS undergoing pacemaker implantation.

Acknowledgment

Statistics Denmark provided the data underlying this article, with permission from the Danish Data Protection Agency. If permitted by the Danish Data Protection Agency, data will be shared upon request to the corresponding author.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.04.059.

	ICD Codes
Amyloidosis:	E85
Ischemic heart disease:	I20, I21, I22, I23, 410, 411, 412, 413, 414
Heart failure:	I42, I50, J819, I110, I130, I132, 425, 428
Acute myocardial infarction:	I21-I22, 410
Atrial fibrillation:	I48, 42,794, 42,793
Ischemic stroke:	I63, I64, 430, 431, 432, 433, 436
Diabetes mellitus:	E10-E14, 250
Chronic Obstructive Pulmonary Disease:	J42, J43, J44, 490, 491, 492
Malignancy:	C00-C97, 140−209
Hypertension:	I10, I15
Chronic renal disease:	N02, N03, N04, N05, N06, N07, N08, N11, N21, N14, N18, N19, N26, N158, N159, N160, N162, N163, N164, N168, Q612, Q613, Q615, Q619, E102, E112, E132, E142, I120, M300, M313, M319, T858, T859, Z992, 403, 404, 581, 582, 584, 25,002, 40,039, 59,009, 59,320, 75,310, 75,311, 75,319
3rd degree atrioventricular block	I442
ATC codes	
Statins:	C10A
Angiotensin-converting enzyme inhibitors:	C09
Mineralocorticoid antagonists:	C03D
Thiazides:	C03A
Calcium channel blockers:	C08
Dihydropyridine calcium channel blockers	C08CA
β blockers:	C07
Clopidogrel:	B01AC04
Prasugrel:	B01AC22
Ticagrelor:	B01AC24
Acetylic salicylic acid:	B01AC06
Digoxin:	C01AA05
Antidiabetics:	A10
Furosemide:	C03CA01
Bumetanide	C03CA02
Vitamin K antagonists:	B01AA
Direct oral anticoagulants:	B01AE, B01AF
Amiodarone:	C01BD01
Procedural codes	
CTS surgery:	KACC51, KACC61
Pacemaker implantation:	BFCA0, BFCA01-08

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