IJC Heart & Vasculature 33 (2021) 100741

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.journals.elsevier.com/ijc-heart-and-vasculature

The association of prior carpal tunnel syndrome surgery with adverse cardiovascular outcomes and long-term mortality after aortic valve replacement

Oscar Westin [a,*], Marie D. Lauridsen [a], Søren Lund Kristensen [a], Lars Køber [a], Christian Torp-Pedersen [b], Gunnar Gislason [c,d,e,f], Lars Søndergaard [a], Mathew S. Maurer [g], Birgitte Pernille Leicht [h], Finn Gustafsson [a], Emil L. Fosbøl [a]

[a] The Heart Center, University Hospital of Copenhagen, Rigshospitalet, Denmark
[b] Department of Cardiology and Clinical Research, Nordsjællands Hospital, Hillerød, Denmark
[c] Department of Cardiology, Copenhagen University Hospital Herlev and Gentofte, Denmark
[d] The Danish Heart Foundation, Copenhagen, Denmark
[e] Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[f] The National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark
[g] Columbia University Irving Medical Center, New York, NY, United States
[h] Gildhøj Privathospital, Copenhagen, Denmark

ARTICLE INFO

Article history:
Received 27 December 2020
Received in revised form 27 January 2021
Accepted 9 February 2021

Keywords:
Carpal tunnel syndrome
Aortic valve replacement
Cardiac amyloidosis

ABSTRACT

Aims: Patients undergoing aortic valve replacement (AVR) for severe aortic stenosis have a 6–16% prevalence of occult cardiac amyloidosis. Carpal tunnel syndrome (CTS) is common in cardiac amyloidosis, but whether prior CTS surgery has a prognostic impact in patients undergoing AVR is unknown. This study examined the association between prior CTS surgery and adverse cardiovascular outcomes in patients treated with AVR.

Methods and results: Using Danish nationwide registries, we retrospectively identified patients undergoing first-time AVR from 2005 to 2018, examining the association between previous CTS and adverse cardiovascular outcomes the following 5 years after the AVR procedure. Cumulative incidence functions and adjusted Cox proportional hazard models were used to assess differences. Among 19,211 patients undergoing AVR, 2.5% (n = 472) had prior CTS surgery. Patients in the CTS-cohort were significantly older (median age 75.7 [IQR 68.1–82.3] vs 73.7 [IQR 66.0–79.6]), more often female and had more comorbidities. Prior CTS surgery was not associated with differences in hospitalization for heart failure (11.2% [95% CI 8.3–14.7] vs 9.4% [95% CI 9.0–9.9]), atrial fibrillation (11.1% [95% CI 8.2–14.5] vs 11.2% [95% CI 10.8–11.7]) or pacemaker implantation (6.2% [95% CI 4.0–9.0] vs 5.1% [95% CI 4.8–5.5]). The 5-year mortality (32.8% [27.6–38.0] vs 25.2% [24.5–25.9]) was higher in the CTS-cohort. CTS was significantly associated with increased 5-year mortality (HR 1.27 [1.05–1.53]) in crude models, however, after multivariable adjustment prior CTS surgery was not associated with adverse cardiovascular outcomes.

Conclusion: Previous CTS surgery was not associated with increased risk for adverse cardiovascular outcomes after AVR.

1. Introduction

Occult cardiac amyloidosis (CA) is prevalent in 6% to 16% of elderly patients undergoing surgical or transcatheter aortic valve replacement (AVR) [1,2]. It has been suggested that CA may be an important disease modifier in aortic stenosis (AS), causing poorer outcomes [1,3], as well as higher risk of procedural complications and more frequent need for pacemakers among patients undergoing AVR [4]. Previous studies on larger cohorts are sparse and recent data implies that the differences are insignificant [5–7].

It is well known that patients with CA may present with symptoms of carpal tunnel syndrome (CTS) years prior to their cardiac

* Corresponding author at: Hjertemedicinsk Klinik, 2142, Rigshospitalet, Blegdamsvej 9, Copenhagen 2100, Denmark.
E-mail address: oscar.mikael.westin@regionh.dk (O. Westin).

https://doi.org/10.1016/j.ijcha.2021.100741
2352-9067/

impairment [8]. Indeed, CTS has been described as the most common initial symptom of wild-type transthyretin amyloidosis (wtATTR), present in more than 2/3 of patients at time of diagnosis [9]. A recently published registry study of 56,000 CTS patients and age-gender matched counterparts from the general population, showed that previous medical history of CTS was significantly associated with a higher risk of amyloidosis (hazard ratio (HR) 12.12 [95% CI: 4.37–33.60]) and adverse cardiovascular outcomes [10].

We hypothesized that a medical history of CTS might be associated with worse outcome in AVR-patients. To address this hypothesis, we used Danish registries to compare adverse cardiovascular outcomes and mortality in a nationwide sample of patients undergoing AVR according to prior CTS surgery.

2. Material and methods

2.1. Data sources

Data were retrospectively extracted from Danish national registries, where all admissions, prescriptions and hospital procedures are registered since 1978, 1995 and 1996, respectively. The registries have been validated and described in detail previously [11–14].

2.2. Study subjects

All patients undergoing an AVR – either as surgical aortic valve replacement (SAVR) with biological or mechanical valve, or transcatheter aortic valve replacement (TAVR) - from 2005 to 2018 were assessed for inclusion in the study. Index date was set to the day of the first AVR-procedure. To be considered a part of the CTS population, a procedural code for CTS surgery before the index date was required. Among CTS patients, those with a previous distal radius fracture were excluded, as this might be a cause of secondary CTS (i.e. not related to amyloidosis). Patients under 18 years or over 100 years at the time of AVR were also excluded.

2.3. Exposure, follow-up, and outcomes

The study population comprised all patients treated with AVR (Danish procedure codes KFMD00, KFMD11, KFMD12 and KFMD14) during the time period 01/01/2005–31/12/2018, and the exposure of interest was CTS surgery (Danish procedure codes KACC51, KACC61). The patients were followed until each outcome of interest or 1) death, 2) emigration, 3) 5 years of follow up, or 4) end of study period (31.12.2018), whichever came first. The cardiovascular outcomes were hospitalization with heart failure (International classification of Diseases (ICD)-10 codes I42, I50, I110, I130, I132, J819) or atrial fibrillation (ICD-10 code I48), or pacemaker implantation (Danish procedure code BFCA0). Heart failure has been validated in the Danish registries with a high specificity of 99% and a positive predictive value of 81% [15].

2.4. Study covariates

Preexisting comorbidities were assessed during the 10 years prior to the admission date for the AVR-procedure, via hospital admissions and outpatient diagnoses. Concomitant pharmacotherapy was assessed through redeemed prescriptions 6 months prior to admission for the AVR-procedure. See appendix for the used ICD- and Anatomical Therapeutic Chemical Classification System (ATC)-codes.

3. Theory/calculations

Descriptive statistics of AVR patients with and without previous CTS were presented as percentages for categorical variables, and as medians and interquartile ranges for continuous variables. Differences were tested with Chi-squared test and Kruskal Wallis-test where appropriate. Comparative incidences of admission due to heart failure, atrial fibrillation, and pacemaker implantation were assessed using cumulative incidence functions, accounting for competing risk of death. Crude and adjusted Cox proportional hazard models were used to estimate hazard ratios (HR) comparing AVR patients with and without CTS. The Cox models were adjusted for age, sex, type of AVR-procedure, heart failure, ischemic heart disease, hypertension, diabetes mellitus, nephropathy, and chronic obstructive pulmonary disease (COPD). For all Cox models, the proportional hazards assumption was assessed graphically by plotting log(-log (survival function)) vs. time for all exposure variables and found valid. Age did not fulfil linearity assumptions, why it was categorized. The potential of effect modification by sex, age or type of AVR was not present. Statistical analyses were performed using the SAS statistical software (version 9.4, Cary, NC, USA) as well as R statistical software (R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.P-project.org/.). Level of statistical significance was defined as a p-value below 0.05.

4. Results

A total of 19,211 AVR patients were included in the study, of whom 472 (2.5%) had previous CTS (Fig. 1). Table 1 shows baseline characteristics of the study population by CTS status. The median age of CTS patients was 75.5 years (interquartile range (IQR) 68.1–82.3), compared with 73.7 years (IQR: 66.0–79.6) in those without previous CTS. Among CTS patients, 52% were men, compared with 64% in the no-CTS group. Hypertension, diabetes mellitus, and COPD were significantly more prevalent among CTS patients, and concomitant pharmacotherapy was generally more extensive among the CTS patients. Table 2 shows procedural characteristics for CTS surgery.

4.1. Comparative cardiovascular outcomes

The cumulative incidences of admissions for heart failure (11.2% [95% CI: 8.3–14.7] vs 9.4% [95% CI 9.0–9.9]), admissions for atrial fibrillation (11.1% [95% CI 8.2–14.5] vs 11.2% [95% CI 10.8–11.7]) or pacemaker implantation (6.2% [95% CI 4.0–9.0] vs 5.1% [95% CI 4.8–5.5]) did not differ significantly between patients with or without previous CTS, but the 5-year mortality (32.8% [95% CI 27.6–38.0] vs 25.2% [95% CI 24.5–25.9]) was higher among patients with previous CTS (Supplementary Table 1 & Fig. 2).

In crude models, CTS was significantly associated increased 5-year mortality (HR 1.27 [95% CI 1.05–1.53]). After adjustment for age, this association disappeared. Upon adjustment for age, sex, type of AVR and comorbidities, CTS was not significantly associated with any adverse cardiovascular outcomes or mortality; admission for heart failure (HR 1.10 [95% CI 0.81–1.49]), admission for atrial fibrillation (HR 0.99 [95% CI 0.74–1.34]), pacemaker implantation (HR 1.14 [95% CI 0.75–1.73]), or 5-year mortality (HR 1.03 [95% CI 0.86–1.25]) (Fig. 3).

4.2. Sensitivity analyses

Subgroup analysis of the impact of CTS in TAVR versus SAVR yielded no significant associations with adverse cardiovascular

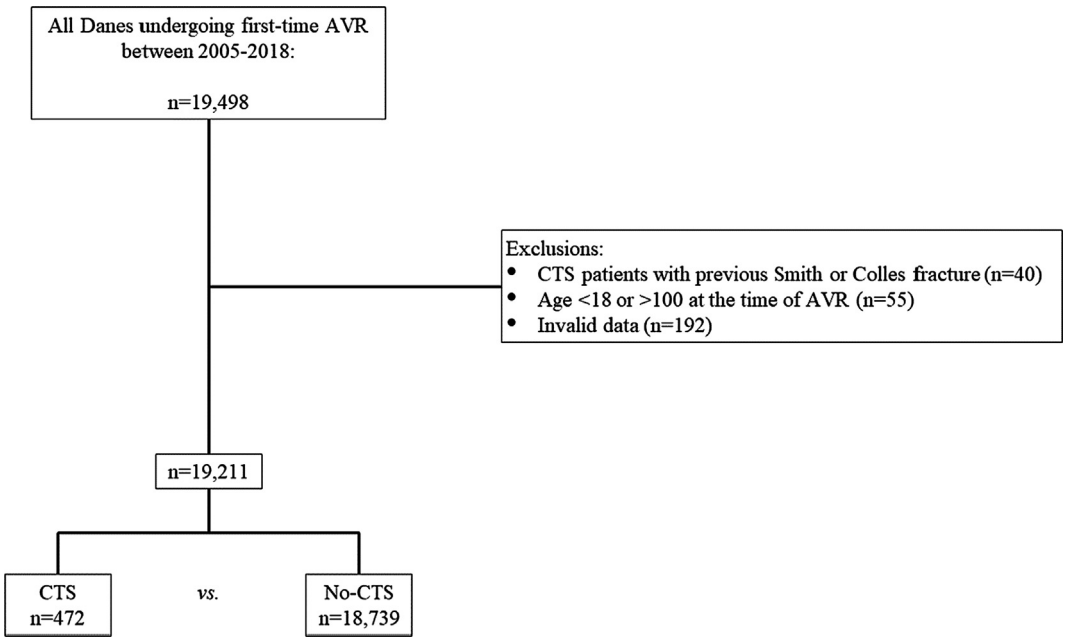

Fig. 1. Flow chart of patient selection.

Table 1
Baseline characteristics.

	CTS N = 472	No-CTS N = 18739	p-value
Demographics			
Median age, years (IQR)	75.5 (68.1–82.3)	73.7 (66.0–79.6)	<0.0001
Median age at time of CTS surgery (IQR)	70.0 (59.5–76.8)		
Male	52.3	64.8	<0.0001
Comorbidity			
Hypertension	54.7	46.8	0.0007
IHD	47.7	44.5	0.1743
Myocardial infarction	12.5	10.8	0.2347
Heart failure	20.3	20.0	0.8539
Atrial fibrillation	25.9	24.1	0.3898
PVD	6.1	5.4	0.4545
Stroke	8.3	7.5	0.5546
COPD	13.1	9.8	0.0151
Renal disease	7.8	6.8	0.3529
Diabetes mellitus	28.4	18.6	<0.0001
Cancer	12.3	11.8	0.7477
Bleeding	16.3	15.0	0.4210
Pacemaker	5.3	4.3	0.2713
Pharmacotherapy 6 months prior to index			
Statins	62.9	55.7	0.0019
ASA	52.5	47.1	0.0185
ADP	14.4	11.5	0.0531
Anticoagulants	24.6	19.2	0.0036
Antidiabetics	24.2	15.6	<0.0001
Beta blockers	43.9	42.3	0.5058
ACE-I	51.5	46.2	0.0220
MRCA	7.2	6.6	0.6065
Digoxin	11.0	8.1	0.0221
Furosemide	37.7	32.3	0.0131
Thiazides	20.3	18.1	0.2152
Calcium antagonists	30.1	28.8	0.5568
Type of AVR			
SAVR; biological valve	51.3	61.4	
TAVR	35.0	21.5	<0.0001
SAVR; mechanical valve	13.8	17.1	

Values are gives as % unless otherwise indicated.
CTS = carpal tunnel syndrome; IHD = ischemic heart disease; PVD = peripheral vascular disease; COPD = chronic obstructive pulmonary disease; ASA = acetylsalicylic acid; ADP = adenosine diphosphate receptor inhibitors; ACE-I = angiotensin-converting-enzyme inhibitors; MRCA = mineralocorticoid antagonists; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

Table 2
Procedural characteristics for CTS surgery.

Patients undergoing procedure, n	472
Initial procedure	
Left hand	33.1
Right hand	33.5
Both hands	0.4
Side not reported	33.0
Patients undergoing > 1 procedure	38.8
No. of procedures	1 (1,2)

Values are n, % or median (5th, 95th percentiles).
CTS = carpal tunnel syndrome.

outcomes or mortality in adjusted models. When stratifying the cumulative incidences by sex, male patients with previous CTS had the highest cumulative incidences of all adverse outcomes, while CTS did not seem to have the same effect on cumulative incidences in women (Supplementary Fig. 1). However, following adjustments, there was no significant interaction between CTS and sex, age or type of AVR.

5. Discussion

This study examined the prognostic impact of previous CTS in AVR patients. We had three main findings; 1) the prevalence of CTS among AVR patients was 2.5%; 2) CTS patients were older, had more comorbidities and more extensive pharmacotherapy; and 3) CTS was associated with increased 5-year mortality in crude analyses, but not after multivariable adjustment.

First, the prevalence of CTS among AVR patients in our cohort was 2.5%, which is comparable to that of the general European population, where studies typically report a 1–7% prevalence [16], but the usually observed 2:1 female:male ratio among CTS-patients [17,18] was not seen in our cohort. Instead, the ratio was reversed, with male patients being in majority. Interestingly, the phenomenon has recently been described by Milandri et al. in their study on the prevalence of CTS among patients with amyloidosis [19]. In the study, the reversed ratio was interpreted as a strong implication that CTS in amyloidosis is not idiopathic, but a

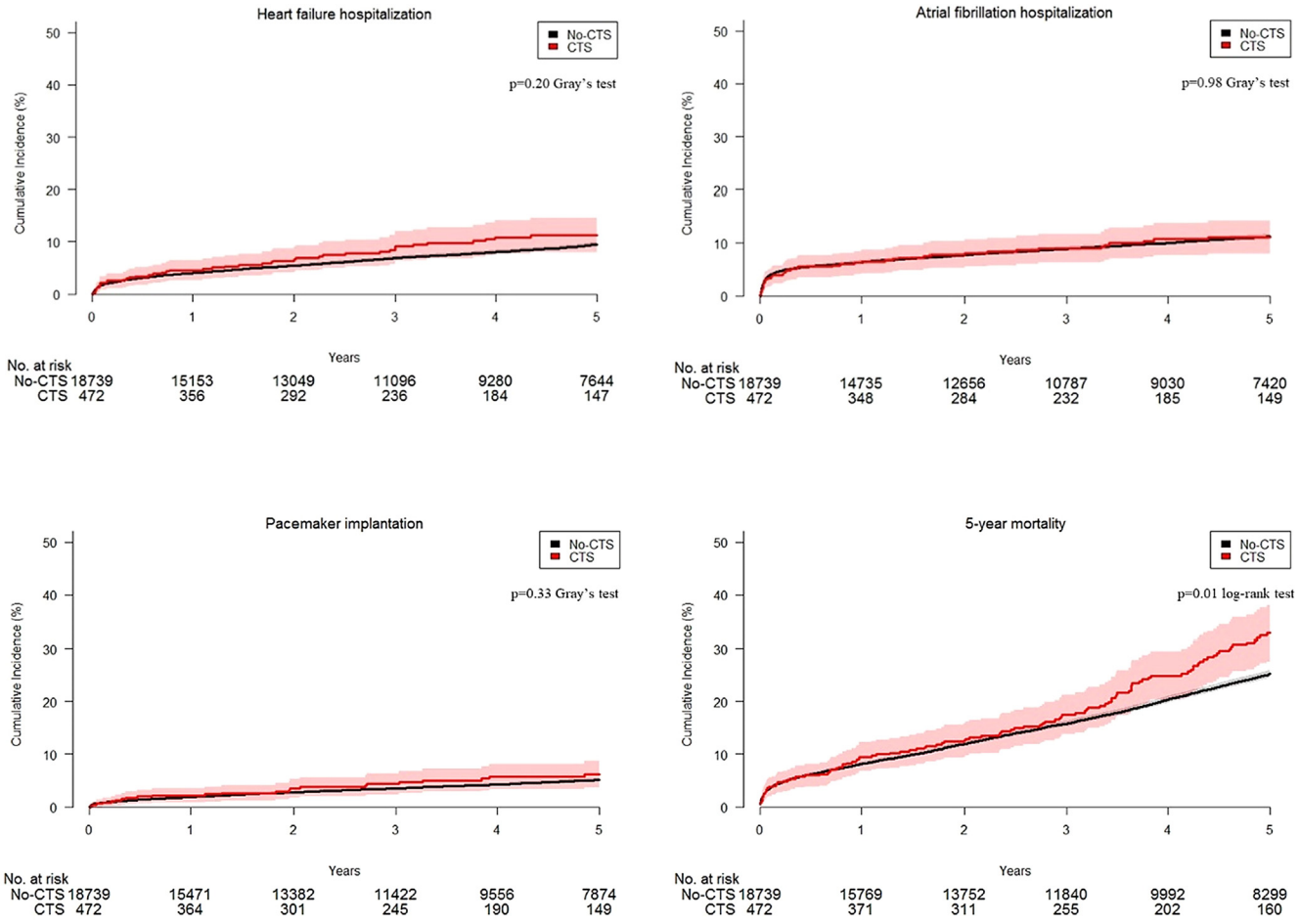

Fig. 2. Cumulative incidence curves of endpoints.

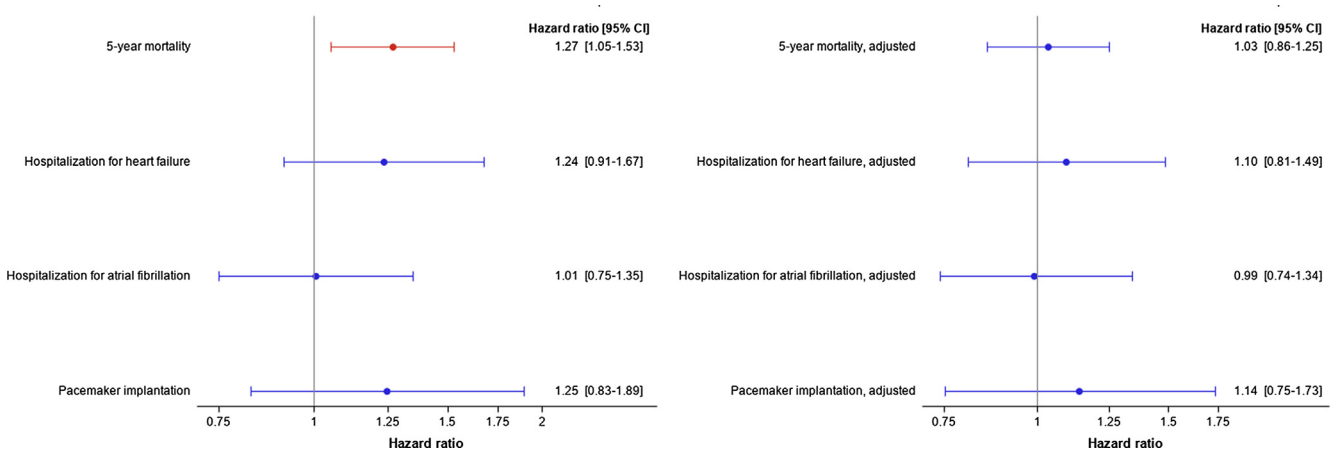

Fig. 3. Forest plot - Cause specific hazard ratios on the impact of previous CTS surgery on endpoints, crude and adjusted models.

manifestation of amyloidosis. The reflection of the same reversed ratio in our cohort is intriguing, and maybe an indication of the presence of occult amyloidosis among AVR patients. On the other hand, it could just be a result of the overall AVR population being largely male. Indeed, the male predominance in AVR has been described previously [20–22]. With an incidence of 1–2% [23], bicuspid aortic valve (BAV) is three times more frequent among males [24], thus contributing to the sex related differences in AVR, where the frequency of BAV is even higher [25,26]. Studies have also implied that differences in referral patterns and diagnostic testing between the sexes might be present [20,27].

Secondly, patients with CTS were older, had more comorbidities and more extensive pharmacotherapy. While age, female sex and diabetes are known risk factors for CTS [19], the role of smoking/COPD in CTS is more elusive, as meta-analyses have shown an association in cross-sectional studies but not in case-control

studies or cohort studies [28]. The observed increased age and comorbidities among CTS-patients in our cohort corresponds to what was previously concluded in female AVR-patients, as presented by Chaker et al. in their large retrospective study on sex differences in AVR [29]. In their study, Chaker et al. showed that female patients undergoing AVR were older, had a higher prevalence of hypertension, diabetes mellitus, COPD, atrial fibrillation/flutter and anemia, as well having higher in-hospital mortality, compared with propensity matched male patients. More advanced age and more advanced disease at referral, more cardiovascular risk factors, as well as anatomical factors (e.g., patient-prosthetic mismatch due to smaller aortic annulus) have been suggested as reasons for females having higher cardiac morbidity after AVR [27]. This was however not apparent in our study.

Lastly, CTS was associated with increased 5-year mortality in crude analyses, but this was not evident after multivariable adjustment. Furthermore, interaction analyses showed that the effect of CTS on outcomes did not differ between the sexes or type of AVR.

Thus, when faced with a patient referred for AVR, careful evaluation of risk factors is important, but presence of prior CTS surgery should not influence the decision whether or not to proceed with AVR.

Theoretically, we had expected that males with previous CTS would have the highest prevalence of occult CA, as wtATTR is vastly more common among males (between 25 and 50:1 male:female ratio [30]). We had also expected that previous CTS, as a surrogate measure of CA, would have a prognostic impact among AVR-patients, a population of patients where occult CA has been shown to be high [1,2]. The prognostic impact of CA in AS has been described in a retrospective study on 113 patients by Cavalcante et al., where they showed that suspected CA (by cardiovascular magnetic resonance) was prevalent in 25% of male patients >80 years with severe AS. The study showed that AS-patients with suspected CA often had low-flow, low-gradient physiology (78%) and was associated with higher all-cause mortality after adjustment for comorbidities and confounders, including AVR [31]. Nonetheless, our study could not show any significant associations between previous CTS and adverse cardiovascular outcomes after multivariable adjustment. Our findings are in line with those of a recently published study by Scully et al. on 200 patients with severe AS referred for TAVR. In this study, a blinded bone scintigraphy was performed prior to TAVR, identifying CA in 13% of patients. CA patients treated with TAVR experienced significantly improved outcome compared to those receiving medical management only ($p = 0.03$), and at median follow-up of 19 months (10–27), there was no difference in mortality between CA patients and non-CA patients ($p = 0.71$). Furthermore, the periprocedural complication rates were the same ($p = 0.78$) [5]. Newly published studies on outcomes in coexisting severe aortic stenosis and CA by Nitsche et al. and Rosenblum et al. showed that neither ATTR-CA or amyloid light chain (AL)-CA affected mortality after TAVR [6,7], although an increased rate of heart failure hospitalizations was seen at 1 and 3 years post TAVR [7]. This however was not evident in our data.

6. Conclusions

Prior CTS surgery was not associated with any adverse cardiovascular outcomes or mortality in AVR. While previous studies provided some ground for suspecting worsened prognosis among CTS patients in AVR, through mediation of risk from occult CA, newer studies are suggesting that the coexistence of CA and severe AS does not increase the mortality after AVR. Further studies on the prognostic importance of CA in cardiovascular disease are needed.

7. Strengths and limitations

Utilizing nationwide registries minimizes selection bias and allows for essentially complete follow-up. The procedure codes and diagnosis codes in the registries are validated and have high positive predictive values (PPV): the PPV for heart failure is 81%, the PPV for atrial fibrillation is >90%, the PPV for pacemaker implantation is 100% [13,14,32]. Due to the observational nature of the study, causal relationships cannot be assessed. Efforts to minimize confounding were taken, however residual and/or unmeasured confounding cannot be excluded. Important information such as body mass index, smoking, family history, LVEF, EKG readings and blood samples was not available for analysis. Although the registries include all Danish patients diagnosed CTS, we chose to only include the ones who underwent surgery for CTS. This was done in order to increase the likelihood of the patient actually having a clinically relevant degree of CTS. The Danish population is almost entirely Caucasian which may influence the results, as the prevalence of hATTR is much higher in certain other populations, for instance African-Americans who have a 4% prevalence of V122I [33].

Conflicts of interest

Dr. Westin reports grants from Erik og Susanna Olesens Almenvelgørende Fond, during the conduct of the study; grants from Pfizer, grants from Arvid Nilssons Fond, grants from Højmosegårdlegatet, grants from Frimodt-Heineke Fonden, and grants from Hjertecentrets forskningsudvalg, Rigshospitalet, outside the submitted work.

Dr. Dam Lauridsen, Dr. Fosbøl, Dr. Lund Kristensen, Dr. Søndergaard, Dr. Leicht, Dr Gislason and Dr. Torp-Pedersen have nothing to disclose.

Dr. Maurer reports grants from Pfizer, grants and personal fees from Alnylam, grants and personal fees from Ionis, personal fees from Ackea, personal fees from Prothena, personal fees from Intellia, outside the submitted work.

Dr. Køber reports personal fees from Speakers honorarum from Novartis, AstraZeneca, Novo and Boehringer, outside the submitted work.

Dr. Gustafsson reports personal fees from Abbott, personal fees from Astra-Zeneca, personal fees from Orion Pharma, other from Corvia, personal fees from Pfizer, personal fees from Boehringer-Ingelheim, personal fees from Novartis, outside the submitted work.

Declaration of Helsinki

The study complies with the Declaration of Helsinki. Registry studies do not require ethical approval in Denmark. The study has received the mandated approval by the Danish Data Protection Agency (approval number: P-2019-348).

Funding

Funding: This work was supported by a grant from "Erik og Susanna Olesens Almenvelgørende Fond" to [OW].

Appendix A

ICD-codes

Ischemic heart disease: ICD10: I20, I21, I22, I23. ICD8: 410, 411, 412, 413, 414.

Heart failure: ICD10: I42, I50, J819, I110, I130, I132. ICD8: 425, 428, 4270, 4271.

Acute myocardial infarction: ICD10: I21-I22. ICD8: 410.
Atrial fibrillation: ICD10: I48, ICD8: 42794, 42793.
Ischemic stroke: ICD10: I63, I64. ICD8:430, 431, 432, 433, 436.
Diabetes mellitus: ICD10: E10-E14. ICD8: 250.
Chronic obstructive pulmonary disease: ICD10: J42, J43, J44. ICD8: 490, 491, 492.
Malignancy: ICD10: C00-C97. ICD8: 140-209.
Chronic renal disease: ICD10: 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. ICD8: 403, 404, 581, 582, 584, 25002, 40039, 59009, 59320, 75310, 75311, 75319
Hypertension: ICD10: I10, I15.
Distal radius fracture: ICD10: S525

ATC codes

Statins: C10A
Angiotensin converting enzyme inhibitors: C09
Mineralocorticoid antagonists: C03D
Thiazides: C03A
Calcium channel blockers: C08
Beta blockers: C07
Clopidogrel: B01AC04
Prasugrel: B01AC22
Ticagrelor: B01AC24
Acetylic salicylic acid: B01AC06
Digoxin: C01AA05
Anti-diabetics: A10
Furosemide: C03CA01
Vitamin K antagonists: B01AA
Direct oral anticoagulants: B01AE, B01AF

Procedural codes

TAVR: KFMD11, KFMD12, KFMD14.
SAVR: KFMD00, KFMD10.
CTS surgery: KACC51, KACC61.
Pacemaker implantation: BFCA0

Abbreviations

AS: aortic stenosis
ACEi: angiotensin converting enzyme inhibitor
ARB: angiontensin II receptor blocker
ATTR: transthyretin amyloidosis
wtATTR: wild type transthyretin amyloidosis
hATTR: hereditary transthyretin amyloidosis
AL: amyloid light chain
AVR: aortic valve replacement
BAV: bicuspid aortic valve
CA: cardiac amyloidosis
COPD: chronic obstructive pulmonary disease
CTS: carpal tunnel syndrome
CVD: cerebrovascular disease
HF: heart failure
HFpEF: heart failure with preserved ejection fraction
HFrEF: heart failure with reduced ejection fraction
HR: hazard ratio
IHD: ischemic heart disease
LVEF: left ventricular ejection fraction
PVD: peripheral vascular disease
SAVR: surgical aortic valve replacement
TAVR: transcatheter aortic valve replacement

Appendix B. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2021.100741.

References

[1] Thomas A. Treibel, Fontana Marianna, Janet A. Gilbertson, et al., Occult Transthyretin Cardiac Amyloid in Severe Calcific Aortic Stenosis, Circul. Cardiovasc. Imag. 9 (2016).
[2] A. Castaño, D.L. Narotsky, N. Hamid, et al., Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement, Eur. Heart J. 38 (2017) 2879–2887.
[3] F. Nietlispach, J.G. Webb, J. Ye, et al., Pathology of Transcatheter Valve Therapy, J. Am. Coll. Cardiol. Intv. 5 (2012) 582–590.
[4] A. Castaño, S. Bokhari, M.S. Maurer, Could Late Enhancement and Need for Permanent Pacemaker Implantation in Patients Undergoing TAVR Be Explained by Undiagnosed Transthyretin Cardiac Amyloidosis?, J. Am. Coll. Cardiol. 65 (2015) 311–312.
[5] P.R. Scully, K.P. Patel, T.A. Treibel, et al., Prevalence and outcome of dual aortic stenosis and cardiac amyloid pathology in patients referred for transcatheter aortic valve implantation, Eur. Heart J. 41 (2020) 2759–2767.
[6] C. Nitsche, S. Aschauer, A.A. Kammerlander, et al., Light-chain and transthyretin cardiac amyloidosis in severe aortic stenosis: prevalence, screening possibilities, and outcome. Eur. J. Heart Failure n/a. Doi: 10.1002/ejhf.1756.
[7] H. Rosenblum, A. Masri, D.L. Narotsky, et al., Unveiling outcomes in coexisting severe aortic stenosis and transthyretin cardiac amyloidosis. Eur. J. Heart Failure n/a. Doi: 10.1002/ejhf.1974.
[8] A. Ikram, B. Sperry, B. Reyes, et al., Carpal Tunnel Syndrome and Amyloid Cardiomyopathy, J. Cardiac Fail. 23 (2017) S11–S12.
[9] M. Nakagawa, Y. Sekijima, M. Yazaki, et al., Carpal tunnel syndrome: a common initial symptom of systemic wild-type ATTR (ATTRwt) amyloidosis, Amyloid 23 (2016) 58–63.
[10] E.L. Fosbøl, R. Rørth, B.P. Leicht, et al., Association of Carpal Tunnel Syndrome With Amyloidosis, Heart Failure, and Adverse Cardiovascular Outcomes, J. Am. Coll. Cardiol. 74 (2019) 15–23.
[11] D. Gaist, H.T. Sørensen, J. Hallas, The Danish prescription registries, Dan. Med. Bull. 44 (1997) 445–448.
[12] M. Schmidt, S.A.J. Schmidt, J.L. Sandegaard, et al., The Danish National Patient Registry: a review of content, data quality, and research potential, Clin. Epidemiol. 7 (2015) 449–490.
[13] K. Adelborg, J. Sundbøll, T. Munch, et al., Positive predictive value of cardiac examination, procedure and surgery codes in the Danish National Patient Registry: a population-based validation study, BMJ Open 6. Epub ahead of print 9 December 2016. Doi: 10.1136/bmjopen-2016-012817.
[14] J. Sundbøll, K. Adelborg, T. Munch, et al., Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study, BMJ Open 6 (2016).
[15] T. Kümler, G.H. Gislason, V. Kirk, et al., Accuracy of a heart failure diagnosis in administrative registers, Eur. J. Heart Fail. 10 (2008) 658–660.
[16] S.D. Middleton, R.E. Anakwe, Carpal tunnel syndrome. BMJ 349. Epub ahead of print 6 November 2014. Doi: 10.1136/bmj.g6437.
[17] A. Farioli, S. Curti, R. Bonfiglioli, et al., Observed Differences between Males and Females in Surgically Treated Carpal Tunnel Syndrome Among Non-manual Workers: A Sensitivity Analysis of Findings from a Large Population Study, Ann. Work Expo Health 62 (2018) 505–515.
[18] S. Mattioli, A. Baldasseroni, S. Curti, et al., Incidence rates of in-hospital carpal tunnel syndrome in the general population and possible associations with marital status, BMC Public Health 8 (2008) 374.
[19] A. Milandri, A. Farioli, C. Gagliardi, et al., Carpal tunnel syndrome in cardiac amyloidosis: implications for early diagnosis and prognostic role across the spectrum of aetiologies. Eur. J. Heart Fail. n/a. DOI: 10.1002/ejhf.1742.
[20] D.S. Bach, J.I. Radeva, H.G. Birnbaum, et al., Prevalence, referral patterns, testing, and surgery in aortic valve disease: leaving women and elderly patients behind?, J. Heart Valve Dis. 16 (2007) 362–369.
[21] Y. Elhmidi, N. Piazza, D. Mazzitelli, et al., Sex-Related Differences in 2197 Patients Undergoing Isolated Surgical Aortic Valve Replacement, J. Card. Surg. 29 (2014) 772–778.
[22] A. Kulik, B.-K. Lam, F.D. Rubens, et al., Gender differences in the long-term outcomes after valve replacement surgery, Heart 95 (2009) 318–326.
[23] F.A. Rajput, R. Zeltser, Aortic Valve Replacement, in: StatPearls. Treasure Island (FL), StatPearls Publishing, http://www.ncbi.nlm.nih.gov/books/NBK537136/ (2020, accessed 24 February 2020).
[24] M. Vignac, B. Gaye, H.M. Björck, et al., Gender Differences In Patients With Bicuspid Aortic Valves, Atherosclerosis 287 (2019).
[25] R.S. Hira, S. Vemulapalli, Z. Li, et al., Trends and Outcomes of Off-label Use of Transcatheter Aortic Valve Replacement: Insights From the NCDR STS/ACC TVT Registry, JAMA Cardiol. 2 (2017) 846–854.
[26] Hayashida Kentaro, Bouvier Erik, Lefèvre Thierry, et al., Transcatheter Aortic Valve Implantation for Patients With Severe Bicuspid Aortic Valve Stenosis, Circul. Cardiovasc. Intervent. 6 (2013) 284–291.

[27] A.I. Duncan, J. Lin, C.G. Koch, et al., The Impact of Gender on In-Hospital Mortality and Morbidity After Isolated Aortic Valve Replacement, Anesth. Analg. 103 (2006) 800–808.
[28] M.-H. Pourmemari, E. Viikari-Juntura, R. Shiri, Smoking and carpal tunnel syndrome: a meta-analysis, Muscle Nerve 49 (2014) 345–350.
[29] Chaker Zakeih, Badhwar Vinay, Alqahtani Fahad, et al. Sex Differences in the Utilization and Outcomes of Surgical Aortic Valve Replacement for Severe Aortic Stenosis. J. Am. Heart Assoc. 6 e006370.
[30] A. Martinez-Naharro, P.N. Hawkins, M. Fontana, Cardiac amyloidosis, Clin. Med. (Lond.) 18 (2018) s30–s35.
[31] J.L. Cavalcante, S. Rijal, I. Abdelkarim, et al., Cardiac amyloidosis is prevalent in older patients with aortic stenosis and carries worse prognosis, J. Cardiovasc. Magn. Reson. 19 (2017) 98.
[32] S.K. Thygesen, C.F. Christiansen, S. Christensen, et al., The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients, BMC Med. Res. Method. 11 (2011) 83.
[33] L.H. Connors, T. Prokaeva, A. Lim, et al., Cardiac amyloidosis in African Americans: comparison of clinical and laboratory features of transthyretin V122I amyloidosis and immunoglobulin light chain amyloidosis, Am. Heart J. 158 (2009) 607–614.