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ORIGINAL RESEARCH

HEART FAILURE AND CARDIOMYOPATHIES

Diagnostic, Therapeutic, and Prognostic Implications of Carpal Tunnel Syndrome and Spinal Stenosis in Wild-type ATTR-Cardiomyopathy

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ABSTRACT

BACKGROUND In wild-type transthyretin cardiac amyloidosis (ATTRwt-CM), the prognostic role of carpal tunnel syndrome (CTS) is unclear and that of lumbar spinal stenosis (SS) remains unexplored.

OBJECTIVES The aim was to examine the diagnostic, therapeutic, and prognostic relevance of bilateral CTS and SS in ATTRwt-CM, in relation to the tafamidis treatment.

METHODS Clinical characteristics of 1,449 patients with ATTRwt-CM were evaluated in a multicenter cohort. The primary endpoint was all-cause mortality. Cox multivariable regression was used to assess mortality in patients with and without CTS and SS.

RESULTS Preceding an ATTRwt-CM diagnosis, CTS and SS were present in 29% and 22% of patients, respectively, without sex-difference. CTS ($P < 0.001$), but not SS, was more prevalent among younger patients. Tenosynovial red flags and ATTRwt-CM diagnosis occurred approximately 4 years later in females vs males, with similar preceding time, suggesting later female ATTRwt-CM disease onset. Patients with vs without CTS and SS had lower National Amyloidosis Centre disease stage ($P \leq 0.001$), despite similar symptomatic status. During a mean follow-up of 2.3 ± 1.8 years, 73% (1,052/1,449) of patients were initiated on tafamidis and 28% (406) died. Tafamidis was initiated more in CTS positive vs negative patients (78% vs 71%; $P = 0.008$), on average 2.3 years earlier ($P < 0.001$). More SS positive than negative patients received tafamidis (78% vs 71%; $P = 0.018$), but at similar age ($P = 0.394$). CTS (HR: 0.70; 95% CI: 0.52-0.95) and SS (HR: 0.68; 95% CI: 0.48-0.97) predicted lower mortality.

CONCLUSIONS Both CTS and SS not only enable early ATTRwt-CM diagnosis and treatment initiation, but independently relate to improved survival, potentiating a role for opportunistic screening. (JACC Adv. 2026;5:102631)

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ABBREVIATIONS AND ACRONYMS

ATTR = transthyretin amyloid

ATTR-CM = transthyretin amyloid cardiomyopathy

ATTRwt-CM = wild-type transthyretin amyloid cardiomyopathy

CTS = carpal tunnel syndrome

eGFR = renal estimated glomerular filtration rate

LV = left ventricular

NAC = National Amyloidosis Centre

NT-proBNP = N-terminal pro-B-type natriuretic peptide

SS = lumbar spinal stenosis

TTR = transthyretin

Wild-type transthyretin (TTR) cardiac amyloidosis (ATTRwt-CM) is an age-related infiltrative disease, resulting from extracellular TTR amyloid (ATTR) fibril deposition in the myocardium of patients without TTR gene mutation. It is a progressive disorder with a dismal prognosis, evidenced by a median survival of 3-6 years, if left untreated.[1] Once considered to be rare and incurable, ATTRwt-CM is nowadays increasingly identified in 1 of 5 elderly, often male, patients with ventricular hypertrophy as the leading cause of heart failure, amenable to disease-modifying therapy.[2] In that respect, tafamidis (a tetrameric stabilizer) showed, in a placebo-controlled randomized trial, a notable 30% all-cause mortality benefit in symptomatic ATTRwt-CM heart failure patients (HR: 0.70; 95% CI: 0.51-0.96), with the highest benefit noted when the treatment was initiated at an earlier disease stage.[3,4] Therefore, early diagnosis of ATTRwt-CM is mandatory to assure optimal patient outcome.

According to recent recommendations, ATTR cardiomyopathy (ATTR-CM) should be suspected in patients with increased wall thickness, presenting with additional red flags, including bilateral carpal tunnel syndrome (CTS) and lumbar spinal stenosis (SS).[1,5] Intriguingly and contrary to all other proposed red flags, both tenosynovial disorders precede cardiac diagnosis by 5-15 years, representing the most common initial systemic ATTR symptom, often before cardiac symptom onset.[6-9] This renders them unique and clinically highly relevant sentinels, facilitating potential early preclinical ATTR-CM diagnosis.[9,10]

Although no studies have detailed the potential prognostic relevance of SS in ATTRwt-CM, only 3 single-center studies reported on CTS as prognosticator for all-cause mortality, showing conflicting results.[9,11,12] The diagnostic and potential prognostic value of CTS and SS in ATTRwt-CM patients, in relation to tafamidis treatment, remain unexplored to date. Therefore, we studied a large multicentric cohort of real-world ATTRwt-CM patients, aiming to: 1) describe the prevalence and diagnostic epidemiology of both bilateral CTS and SS; 2) evaluate therapeutic implications of their presence; and 3) explore their potential prognostic relevance, all in the context of a contemporary tafamidis disease-modifying treatment era. We hypothesized that bilateral CTS and SS may relate to all-cause mortality.

METHODS

PATIENT POPULATION. Patients that were diagnosed with ATTRwt-CM at 14 heart centers (10 Belgian, 1 French, 1 Austrian, 1 Romanian, and 1 Dutch) were collected from local ongoing cardiac amyloidosis data registries. All subjects with TTR gene mutation were excluded. ATTR-CM diagnosis was made as recommended: 1) TTR amyloid positive endomyocardial biopsy; 2) Perugini ≥2 intramyocardial radiotracer uptake on 99-technetium bone scintigraphy without monoclonality, based on serum and urine electrophoresis and immunofixation with serum-free light chain assay; and/or 3) extracardiac TTR positive tissue biopsy with suggestive noninvasive cardiac imaging findings.[5]

BASELINE AND FOLLOW-UP DATA. Baseline data were collected from electronic patient chart reviews. Arterial hypertension was defined by a documented history of antihypertensive drug treatment. Serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) and renal estimated glomerular filtration rate (eGFR) were used to compute the National Amyloidosis Centre (NAC) prognostic disease stage (stages 1-4),

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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based on validated cutoffs.[13] All patients underwent transthoracic echocardiography to document left ventricular (LV) wall thickness, ejection fraction and diastolic E/e', as recommended. CTS was defined by bilateral surgical release and/or electromyographically documented evidence in symptomatic patients. Lumbar SS was identified by causative surgical decompression and/or radiographic (computerized tomography or cardiac magnetic resonance imaging) documentation at the level of the lumbar spine in symptomatic individuals.

Patients were followed at the outpatient clinic every 6-12 months. Initiation of tafamidis (tetrameric stabilizer) was at the discretion of the treating physician, representing the single approved and reimbursed therapy for ATTRwt-CM in Europe at data closure. Few patients received other or additional disease-modifying therapies within the context of an ATTR-CM randomized controlled trial. All-cause mortality endpoint was assessed for all study subjects, as electronic patient files are automatically coupled with the governmental National Death Registers. Most patients provided written informed consent. Need for written informed consent in the remainder was waived by the respective ethical committees, due to the retrospective nature of the study.

STATISTICS. Continuous data were reported as mean and SD or median with IQR and categorical variables as frequencies and percentages. Independent *Student's* t-test or Wilcoxon rank-sum test was applied to compare continuous variables, as applicable. Categorical data were compared by chi-square -test or Fisher exact test, as appropriate.

First, the study cohort was stratified by baseline presence of CTS in one and by SS in another analysis, with baseline characteristics compared. Secondly, prevalence of CTS, SS, and prior heart failure hospitalization was compared between age categories (≤70 years, ≥90 years and per 5-year categories in between). Third, sex-specific age-onset of both tenosynovial red flags (CTS and SS) and consecutive ATTRwt-CM diagnosis with lag-time in between was compared. Fourth, the overall study population was further stratified within the CTS and SS stratification, respectively, depending on tafamidis initiation during follow-up, creating 4 groups. Baseline NAC prognostic stages as well as all-cause mortality since ATTRwt-CM diagnosis were compared between these groups for the baseline CTS and SS stratification, respectively. Finally, univariable Cox regression analysis for all-cause mortality was performed, including available variables of previously validated or potential prognostic interest: baseline age, gender, disease stage components (eGFR, NT-proBNP, and LV ejection fraction), heart failure therapies, and tafamidis initiation (as time-dependent covariate to avoid immortal time bias), in addition to presence of baseline CTS or SS, respectively. Variables with significant correlation at the univariable level ($P < 0.050$) were included in the multivariable analysis. We additionally evaluated effect modification by tafamidis by including multiplicative interaction terms between time-dependent tafamidis use and CTS or SS in separate Cox regression models, adjusting for clinically relevant covariates. Statistical analysis was performed on IBM SPSS Statistics (version 25); all tests were 2-sided with $P < 0.050$ regarded as statistically significant.

RESULTS

STUDY POPULATION. A total of 1,449 ATTRwt-CM patients (79% males, mean age 81 ± 7 years old, age range 45-98 years, 77% Belgian) comprised the study population. Subjects were diagnosed with ATTRwt-CM between October 2009 and November 2024, the vast majority of 95% (n = 1,377) since 2017 onward. Arterial hypertension was a common comorbidity in 66% of patients (**Table 1**). In total, 24% presented with NYHA functional class ≥ III symptoms and 29% had a prior heart failure hospitalization history. Mean LV septal wall thickness was 16.4 ± 3.6 mm. Up to 53% presented with NAC stage 1 and heart failure with preserved LV ejection fraction ≥50% was identified in 70% (n = 950). Baseline NT-proBNP and eGFR values were missing in 28% and 16%, respectively.

CARPAL TUNNEL SYNDROME DIAGNOSTIC CHARACTERISTICS. Before diagnosis, CTS history was present in 29% (n = 414), without sex-difference ($P = 0.186$) (**Central Illustration**, **Table 2**). Patients with vs without CTS were diagnosed with ATTRwt-CM on average 2.5 years earlier and presented at lower NAC disease stage (both $P < 0.001$), associated with lower prior heart failure hospitalization history ($P = 0.003$), despite overall comparable structural and functional remodeling on echocardiography and NYHA functional class symptoms (p = NS). Remarkably, lower age at ATTRwt-CM diagnosis coincided with a higher prevalence of preceding CTS red flag diagnosis ($P = 0.001$) and declining heart failure admission history ($P < 0.001$) (**Figure 1**). Notably, SS was more prevalent in patients with vs without baseline CTS (32% vs 18%, $P < 0.001$, respectively).

The exact date of CTS history was available in 82% (n = 339/414, 86 females and 253 males) patients.

TABLE 1 Baseline Characteristics (N = 1,449)

Demographics	
Age, y	[1,449] 81.0 ± 6.8
Male	1,142/1,449 (78.8%)
BSA, m^2	[1,397] 1.88 ± 0.20
BMI, kg/m^2	[1,397] 26.3 ± 4.0
Sinus rhythm	822/1,408 (58.3%)
SBP, mm Hg	[1,387] 133 ± 21
DBP, mm Hg	[1,387] 76 ± 13
Cardiovascular risk	
Smoking history	416/1,315 (31.6%)
Hyperlipidemia	820/1,402 (58.5%)
Arterial hypertension	949/1,446 (65.6%)
Diabetes mellitus	245/1,448 (16.9%)
Medication	
Beta-blocker	748/1,446 (51.7%)
ACEI/AIIRB/ARNI	664/1,449 (45.8%)
SGLT2-I	267/1,402 (19.0%)
MRA	514/1,442 (35.6%)
Loop diuretic	844/1,447 (58.3%)
Oral anticoagulant	816/1,448 (56.4%)
Oral antiplatelet	434/1,448 (30.0%)
History	
Heart failure hospitalization	417/1,442 (28.9%)
Coronary artery disease	402/1,446 (27.8%)
Atrial fibrillation	817/1,448 (56.4%)
Pacemaker	259/1,448 (17.9%)
CRT	76/1,438 (5.3%)
ICD	39/1,438 (2.7%)
Cardiac surgery	145/1,447 (10.0%)
Stroke or TIA	202/1,404 (14.4%)
Bilateral carpal tunnel syndrome	414/1,449 (28.6%)
Lumbar spinal stenosis	316/1,449 (21.8%)
Laboratory serum	
NT-proBNP, pg/mL	[1,046] 2,133 (795-4,520)
Hs-troponin I, ng/L	[131] 36 (22-62)
Hs-troponin T, ng/L	[899] 79 ± 337
eGFR, mL/min	[1,218] 57 ± 19
Symptoms and disease stage	
NYHA functional class	
I	299/1,403 (21.3%)
II	754/1,403 (53.7%)
III	324/1,403 (23.1%)
IV	26/1,403 (1.9%)
NAC stage	
I	511/963 (53.1%)
II	267/963 (27.7%)
III	99/963 (10.3%)
IV	86/963 (8.9%)
Echocardiography	
IVS thickness, mm	[1,368] 16.4 ± 3.6
PW thickness, mm	[1,290] 15.1 ± 4.6
LV EDD, mm	[1,325] 44 ± 8
LV ejection fraction, %	[1,349] 54 ± 11
E/E'	[1,060] 17 ± 9

Values are [n] means ± SD, [n] median (Q1-Q3), or n (%).

ACE-I = angiotensin converting enzyme inhibitor; AIIRB = angiotensin-2 receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BMI = body mass index; BSA = body surface area; CRT = cardiac resynchronization therapy device; DBP = diastolic blood pressure; Hs = high-sensitive; EDD = end-diastolic diameter; eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter defibrillator device; IVS = interventricular septal wall; LV = left ventricular; MRA = Mineralocorticoid receptor antagonist; NAC = National Amyloidosis Centre prognostic stage; NT-proBNP = N-terminal pro-brain natriuretic peptide; PW = posterior wall; SBP = systolic blood pressure; SGLT2-I = sodium-glucose cotransporter-2 inhibitor; TIA = transient ischemic attack.

Continued in the next column

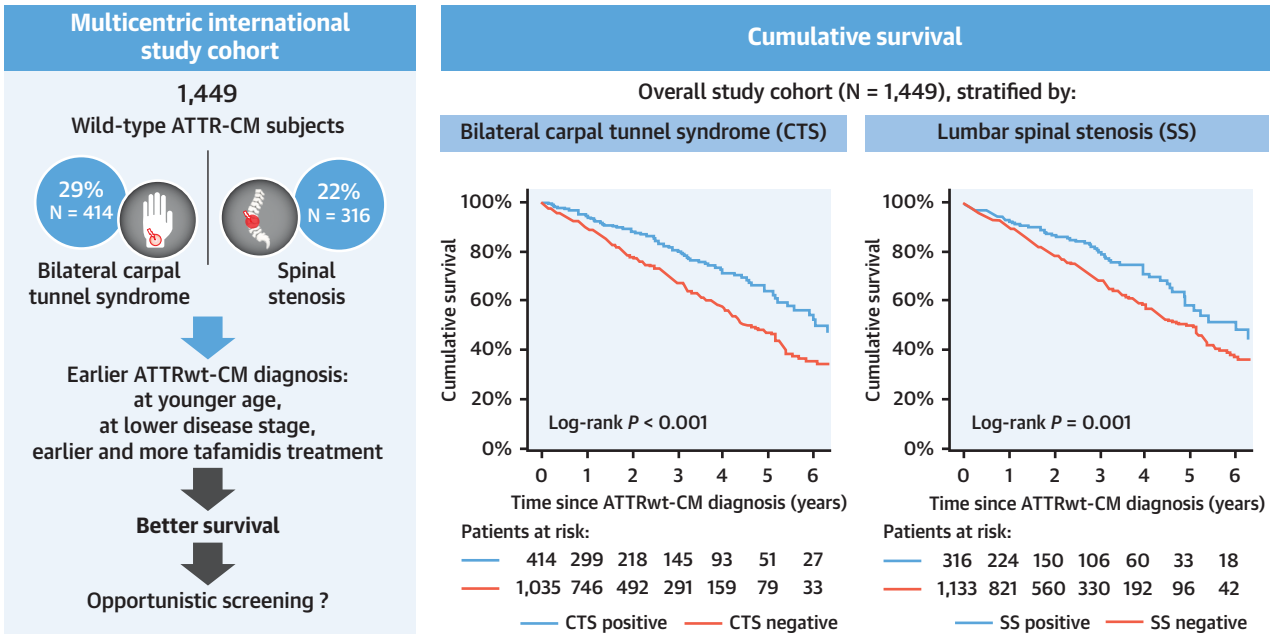
At time of preceding CTS diagnosis, females were on average 3.7 years older than males (73.0 ± 9.9 vs 69.3 ± 9.2 years; $P = 0.002$), with average preceding time between CTS onset and ATTRwt-CM diagnosis being similar (8.9 ± 7.1 vs 9.1 ± 6.5 years; $P = 0.874$, respectively) (Figure 2). In this patient group, females were on average 3.5 years older at ATTRwt-CM diagnosis ($P < 0.001$).

SPINAL STENOSIS DIAGNOSTIC CHARACTERISTICS. Before diagnosis, SS was present in 22% of patients (n = 316), no sex-difference noted ($P = 0.346$). Contrary to CTS, age at ATTRwt-CM diagnosis was comparable between patients with vs without SS ($P = 0.968$) and prevalence was equally distributed between age categories ($P = 0.354$) (Central Illustration, Figure 1, Table 2). Nevertheless, SS patients presented at lower NAC disease stage ($P = 0.001$) with a trend toward less prior heart failure hospitalization history ($P = 0.052$), lower LV wall thickness ($P = 0.044$), but similar NYHA functional class symptoms ($P = 0.221$). CTS was more prevalent in patients with vs without baseline SS (42% vs 25%; $P < 0.001$, respectively) in total 9% of patients (n = 133) presented with both CTS and SS, without sex-difference ($P = 0.283$).

The date of prior SS was available in 89% (n = 282/316, 62 females and 220 males) patients. At preceding SS diagnosis, females were on average 3.6 years older than males (77.2 ± 8.6 vs 73.6 ± 9.4 years; $P = 0.008$), although the average preceding time between SS onset and ATTRwt-CM diagnosis was similar (7.2 ± 7.3 vs 6.5 ± 5.7 years; $P = 0.453$, respectively) (Figure 2). In this patient group, females were on average 4.2 years older at ATTRwt-CM diagnosis ($P < 0.001$).

THERAPEUTIC CHARACTERISTICS. In total 73% (n = 1,052) of patients were treated with tafamidis on average 217 ± 413 days after ATTRwt-CM diagnosis, more in 78% (n = 321/414) with vs 71% (n = 731/1,035) without preceding CTS ($P = 0.008$). Importantly,

CENTRAL ILLUSTRATION **Carpal Tunnel Syndrome and Spinal Stenosis Implications in Wild-Type Transthyretin Amyloid Cardiomyopathy**



Bilateral carpal tunnel syndrome (HR: 0.69, 95% CI: 0.51-0.93, $P = 0.016$) and spinal stenosis (HR: 0.69, 95% CI: 0.48-0.97, $P = 0.035$) relate to lower mortality, independent of age, sex cardiac disease burden, and disease-modifying therapies.

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ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRwt-CM = wild-type transthyretin amyloid cardiomyopathy.

tafamidis was initiated earlier in subjects with vs without CTS, being on average 2.3 years younger (79.1 ± 6.8 vs 81.4 ± 6.6 years old, $P < 0.001$). NAC disease stage at the start of tafamidis therapy was available in 64% (n = 674/1,052) of subjects. The presence of CTS associated to tafamidis treatment at lower NAC disease stage than without CTS history, both at baseline ($P < 0.001$) and at the start of treatment ($P = 0.001$) (Figure 3). Likewise, more patients with SS history received tafamidis (n = 246/316, 78%) than without (n = 806/1,133, 71%; $P = 0.018$). Contrary to patients with CTS history, patients with vs without SS history were of similar age (81.0 ± 6.6 vs 80.7 ± 6.8, respectively; $P = 0.394$) at tafamidis initiation. Nevertheless, the presence of SS also related to lower NAC disease stage than without SS history, both at baseline ($P = 0.021$) and at the start of tafamidis treatment ($P = 0.003$).

In addition, few patients (n = 60/1,449, 4%) were included in an (nontafamidis) ATTR-CM disease-modifying therapy randomized controlled trial; 5% (n = 51/1,052) of patients with and 2% (n = 9/397) of patients without concomitant tafamidis treatment. Subjects with prior CTS were more included in such trial than patients without (8% vs 3%; $P < 0.001$), but not SS patients (5% vs 4%; respectively, $P = 0.117$).

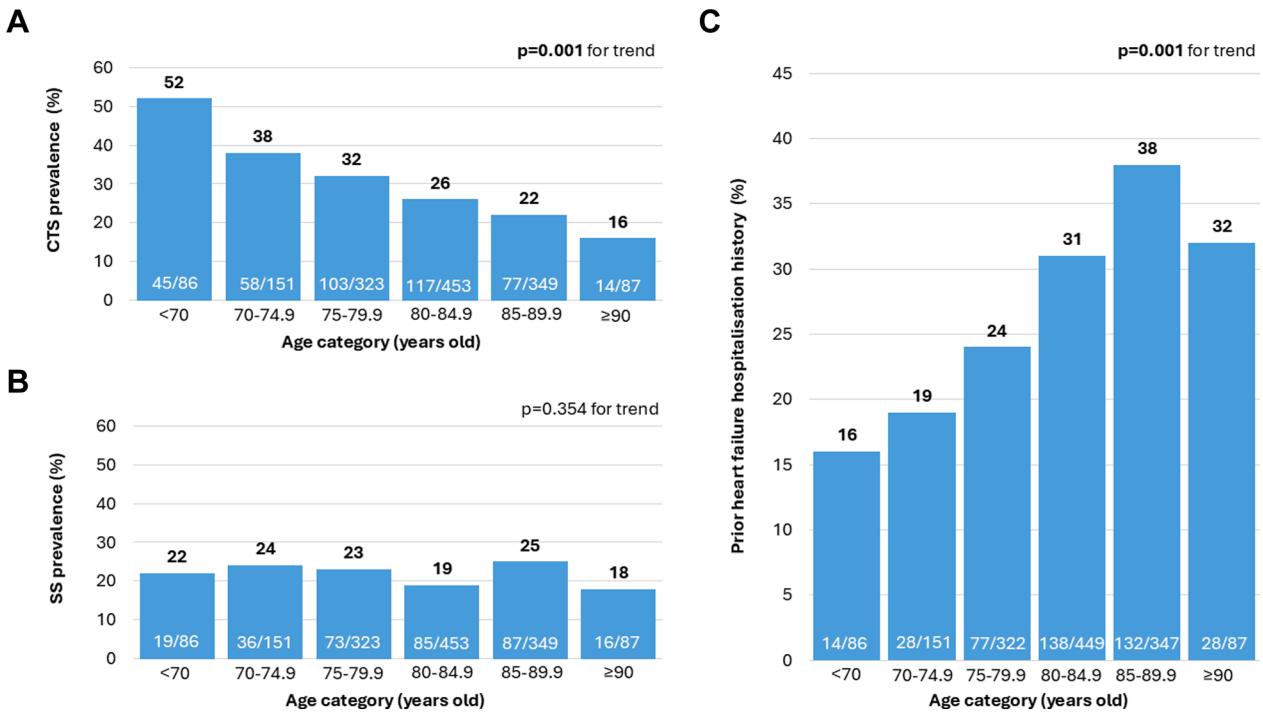
PROGNOSTIC CHARACTERISTICS. During a mean follow up of 2.3 ± 1.8 years, 28% (n = 406) of patients died: 21% (n = 86) with and 31% (n = 320) without prior CTS, 21% (n = 65) with and 30% (n = 341) without prior SS. Overall, 1-, 3-, and 5-year cumulative mortality in subjects with vs without baseline CTS was 5%, 20%, and 36% vs 10%, 32%, and 52%, respectively ($P < 0.001$). Lower cumulative 1-, 3-, and 5-year mortality of 6%, 20%, and 41% vs 9%, 31%, and 49%, respectively, was also noted in patients with vs without baseline SS history ($P = 0.001$) (Central illustration). Both baseline CTS and SS history patients had better cumulative survival with vs without tafamidis therapy ($P < 0.001$) and under the disease-modifying therapy trial inclusion ($P < 0.001$ for CTS and $P = 0.016$ for SS history patients) (Figure 4).

TABLE 2 Baseline Characteristics, Stratified by Bilateral Carpal Tunnel Syndrome and Lumbar Spinal Stenosis at Cardiomyopathy Diagnosis

	CTS History (n = 414)	No CTS History (n = 1,035)	*P* Value	SS History (n = 316)	No SS History (n = 1,133)	*P* Value
Demographics						
Age, y	[414] 79.3 ± 7.0	[1,035] 81.8 ± 6.6	**<0.001**	[316] 81.0 ± 6.7	[1,035] 81.1 ± 6.9	0.968
Male	317/414 (76.6%)	825/1,035 (79.7%)	0.186	243/316 (76.9%)	899/1,133 (79.3%)	0.346
BSA, m^2	[407] 1.90 ± 0.20	[990] 1.88 ± 0.20	0.062	[308] 1.90 ± 0.19	[1,089] 1.88 ± 0.21	**0.022**
BMI, kg/m^2	[407] 26.6 ± 3.9	[990] 26.1 ± 4.1	**0.034**	[308] 26.8 ± 3.9	[1,089] 26.1 ± 4.0	**0.007**
Sinus rhythm	257/407 (63.1%)	565/1,001 (56.4%)	0.184	206/307 (67.1%)	616/1,101 (55.9%)	**0.003**
SBP, mm Hg	[404] 135 ± 21	[983] 133 ± 21	0.057	[301] 136 ± 22	[1,086] 133 ± 21	**0.022**
DBP, mm Hg	[404] 76 ± 13	[983] 75 ± 13	0.340	[301] 76 ± 14	[1,086] 76 ± 12	0.978
Cardiovascular risk						
Smoking history	133/376 (35.4%)	283/939 (30.1%)	0.065	105/280 (37.5%)	311/1,035 (30.0%)	**0.017**
Hyperlipidemia	244/393 (62.1%)	576/1,009 (57.1%)	0.088	178/300 (59.3%)	642/1,102 (58.3%)	0.737
Arterial hypertension	263/413 (63.7%)	686/1,033 (66.4%)	0.324	213/315 (67.6%)	763/1,131 (65.1%)	0.400
Diabetes mellitus	77/414 (18.6%)	168/1,034 (16.2%)	0.281	60/315 (19.0%)	185/1,133 (16.3%)	0.255
Medication						
Beta-blocker	210/414 (50.7%)	538/1,032 (51.1%)	0.628	172/314 (47.5%)	576/1,132 (50.9%)	0.222
ACE-I/AIIRB/ARNI	212/414 (51.2%)	452/1,035 (43.7%)	**0.009**	150/316 (47.5%)	514/1,093 (45.4%)	0.507
SGLT2-I	69/397 (17.4%)	198/1,005 (19.7%)	0.319	61/309 (19.7%)	206/1,093 (18.8%)	0.724
MRA	147/410 (35.9%)	367/1,032 (35.6%)	0.917	111/313 (35.5%)	403/1,129 (35.7%)	0.940
Loop diuretic	217/412 (52.7%)	627/1,035 (60.6%)	**0.006**	157/314 (50.0%)	687/1,133 (60.6%)	**0.001**
Oral anticoagulant	205/413 (49.6%)	611/1,035 (59.0%)	**0.001**	160/315 (50.8%)	656/1,133 (57.9%)	**0.024**
Oral antiplatelet	126/413 (30.5%)	308/1,035 (29.8%)	0.778	107/315 (34.0%)	327/1,133 (28.9%)	0.080
History						
Heart failure hospitalization	95/409 (23.2%)	211/1,033 (31.2%)	**0.003**	77/314 (24.5%)	340/1,128 (30.1%)	0.052
Coronary artery disease	98/413 (23.7%)	304/1,033 (29.4%)	**0.029**	86/315 (27.3%)	316/1,131 (27.9%)	0.823
Atrial fibrillation	208/414 (50.2%)	609/1,034 (58.8%)	**0.003**	151/315 (47.9%)	666/1,133 (58.8%)	**0.001**
Pacemaker	64/407 (15.5%)	195/1,034 (18.9%)	0.127	41/315 (13.0%)	218/1,133 (19.2%)	**0.011**
CRT	31/407 (7.6%)	45/1,031 (4.4%)	**0.013**	17/313 (5.4%)	59/1,125 (5.2%)	0.896
ICD	18/407 (4.4%)	21/1,031 (2.0%)	**0.012**	8/313 (2.6%)	31/1,125 (2.8%)	0.847
Cardiac surgery	32/412 (7.8%)	113/1,035 (10.9%)	0.072	29/315 (9.2%)	116/1,132 (10.2%)	0.586
Stroke or TIA	56/393 (14.2%)	146/1,011 (14.4%)	0.927	44/31 (14.6%)	158/1,103 (14.3%)	0.898
Bilateral carpal tunnel syndrome	414/414 (100.0%)	0/1,035 (0.0%)	na	133/316 (42.1%)	281/1,133 (24.8%)	**<0.001**
Lumbar spinal stenosis	133/414 (32.1%)	183/1,035 (17.7%)	**<0.001**	316/316 (100.0%)	0/1,133 (0.0%)	na
Laboratory serum						
NT-proBNP, pg/mL	[324] 1,683 (636-3,366)	[722] 2,432 (907-5,023)	**<0.001**	[238] 1,493 (586-3,260)	[808] 2,374 (915-5,003)	**<0.001**
Hs-Troponin I, ng/L	[44] 32 (17-59)	[87] 39 (24-68)	0.406	[38] 31 (13-58)	[93] 39 (24-67)	0.159
Hs-Troponin T, ng/L	[287] 59 ± 90	[612] 89 ± 404	0.212	[206] 51 ± 36	[693] 88 ± 84	0.173
eGFR, mL/min	[368] 60 ± 18	[850] 56 ± 19	**<0.001**	[260] 59 ± 18	[958] 57 ± 19	0.122
Symptoms and disease stage						
NYHA functional class			0.324			0.221
I	94/407 (23.1%)	205/996 (20.6%)		76/309 (24.6%)	223/1,094 (20.4%)	
II	213/407 (52.3%)	541/996 (54.3%)		165/309 (53.4%)	589/1,094 (53.8%)	
III	96/407 (23.6%)	228/996 (22.9%)		65/309 (21.0%)	259/1,094 (23.7%)	
IV	4/407 (1.0%)	22/996 (2.2%)		3/309 (1.0%)	23/1,094 (2.1%)	
NAC stage			**<0.001**			**0.001**
I	196/307 (63.8%)	315/656 (48.0%)		136/216 (63.0%)	375/747 (50.2%)	
II	75/307 (24.4%)	192/656 (29.3%)		55/216 (25.5%)	212/747 (28.4%)	
III	20/307 (6.5%)	79/656 (12.0%)		17/216 (7.9%)	82/747 (11.0%)	
IV	16/307 (5.2%)	70/656 (10.7%)		8/216 (3.7%)	78/747 (10.4%)	
Echocardiography						
IVS thickness, mm	[393] 16.7 ± 3.7	[975] 16.3 ± 3.5	0.464	[293] 16.1 ± 3.6	[1,075] 16.5 ± 3.6	**0.044**
PW thickness, mm	[378] 15.4 ± 5.3	[912] 15.0 ± 4.3	0.258	[268] 15.0 ± 4.3	[1,022] 15.2 ± 4.7	**0.040**
LV EDD, mm	[383] 44 ± 8	[942] 45 ± 8	0.286	[279] 45 ± 10	[1,046] 44 ± 8	0.177
LV ejection fraction, %	[390] 54 ± 12	[959] 54 ± 11	0.341	[295] 55 ± 11	[1,054] 54 ± 11	0.096
E/E'	[314] 16 ± 9	[746] 17 ± 9	0.475	[239] 16 ± 9	[821] 17 ± 9	0.214

Values are [n] means ± SD, [n] median (Q1-Q3), or n (%). **Bold** means statistically significant, $P < 0.05$.
CTS = carpal tunnel syndrome; other abbreviations as in Table 1.

FIGURE 1 Baseline Characteristics Prevalence Within Age Categories at Wild-Type Transthyretin Amyloid Cardiomyopathy Diagnosis



(A) Bilateral carpal tunnel syndrome (CTS). (B) Lumbar spinal stenosis (SS). (C) Prior heart failure hospitalization.

In tafamidis naive patients, mortality was lower in patients with vs without prior CTS history ($P = 0.040$) or SS history ($P = 0.021$).

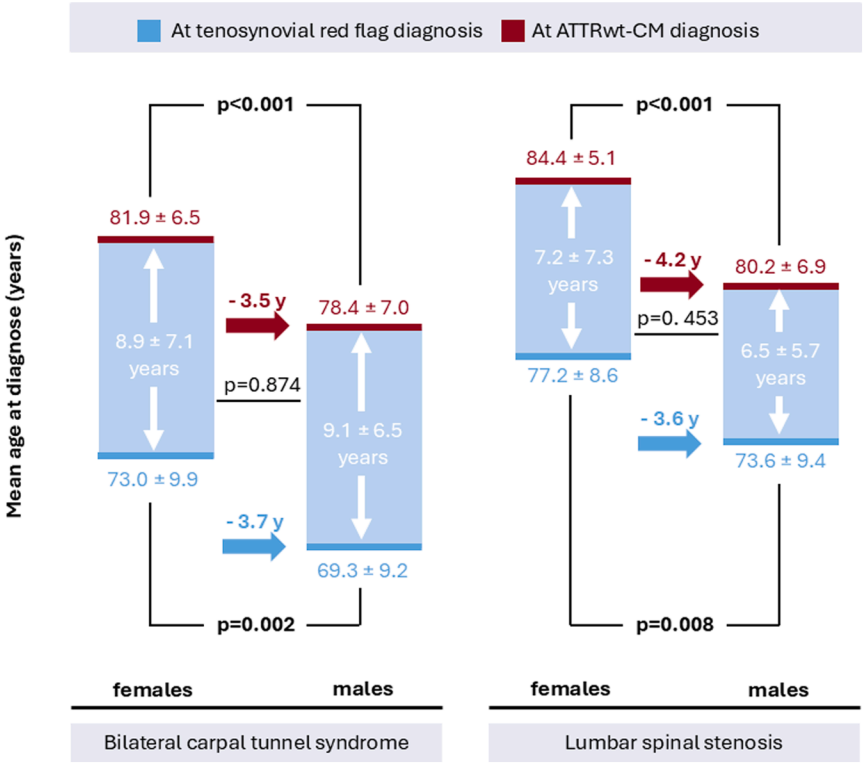
Cox regression analysis identified both CTS ($P < 0.001$) and SS history ($P = 0.001$) to be related to improved survival (**Table 3**). Importantly, after correction for age, disease stage components (eGFR, NT-proBNP, and LV ejection fraction), baseline cornerstone heart failure therapy, and disease-modifying therapies (including tafamidis), all related to ATTRwt-CM prognosis, both prior CTS history (HR: 0.70; 95% CI: 0.52-0.95; $P = 0.024$) and SS history (HR: 0.68; 95% CI: 0.48-0.97; $P = 0.032$) remained independently predictive for lower mortality. A significant interaction was observed for CTS with tafamidis (HR: 0.47; 95% CI: 0.26-0.84; $P = 0.010$), indicating its prognostic association differed according to tafamidis exposure, whereas the interaction with SS was not significant (HR: 0.70; 95% CI: 0.35-1.38; $P = 0.298$).

DISCUSSION

DIAGNOSTIC RELEVANCE. Many small studies reported the presence of CTS in 25 to 60% of ATTRwt-CM patients, related to ATTR deposition in the transverse carpal ligament with median nerve compression, with 48% of patients having bilateral CTS history in a large study, including 553 ATTRwt-CM patients.[6,8,9,12,14,15] Our data expand this knowledge to 1,449 ATTRwt-CM patients, indicating bilateral CTS affects 29% of subjects. Similarly, the SS presence in ATTRwt-CM individuals, related to ATTR deposition-induced ligamentum flavum hypertrophy compressing the spinal cord, has been demonstrated in 13 to 40%, compared to the 22% demonstrated in the current larger patient cohort.[8,12,15,16] The prevalence of bilateral CTS and SS in ATTRwt-CM by far exceeds that of up to 4% to 10% and 11%, respectively, found in the general population.[9,17-19] Our data, therefore, confirm the sentinel diagnostic value of presence of bilateral CTS or SS as red flags, to suspect ATTR-CM in patients presenting with hypertrophy, as justifiably advocated by recent recommendations.[5]

In addition, and contrary to other smaller series, our data indicated that the presence of bilateral CTS (but not SS) leads to subsequent ATTRwt-CM diagnosis approximately 3 years earlier than in those without.[9,12] Particularly when evaluating younger patients with ventricular hypertrophy, bilateral CTS

FIGURE 2 Age-Related Sex-Differences Between Tenosynovial Red Flags



ATTRwt-CM = wild-type transthyretin amyloid cardiomyopathy.

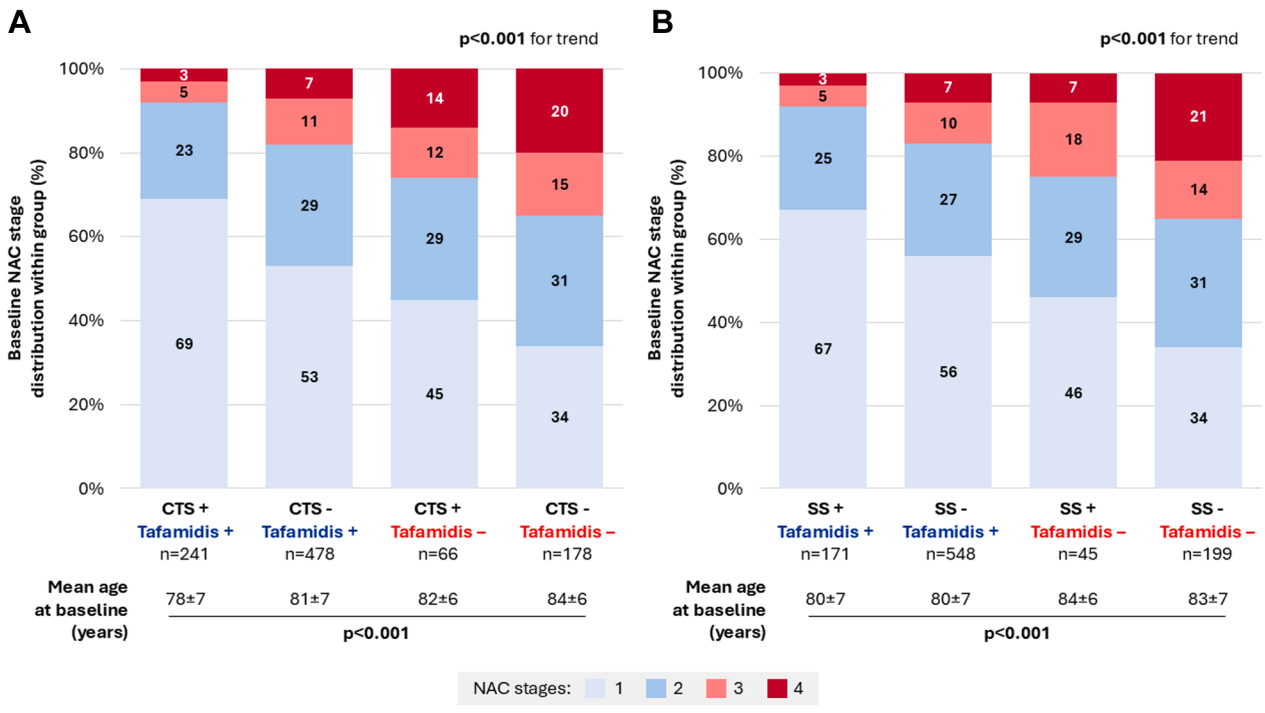
(rather than prior heart failure hospitalization) may be the most relevant red flag to suspect underlying ATTR-CM. Indeed, we demonstrated a progressive increase of bilateral CTS prevalence in younger patients, with over 50% of ATTRwt-CM diagnosed <70 years old presenting with such history. In general, however, CTS affects more younger patients, with a peak incidence between 40 and 60 years old, which may partly account for the effect noted in our study population.[20]

Despite the higher general female CTS incidence, we found equal gender distribution within the ATTRwt-CM study population.[20] In addition, SS is characterized by an age-related increase in prevalence, but we found equal presence between age categories.[17] Both findings strengthen a disease-related relationship between CTS and ATTRwt-CM, being an intrinsic systemic disorder, rather than reflecting an idiopathic finding.[9,21]

In addition, to the best of our knowledge, we are the first to demonstrate that both bilateral CTS and SS patients are diagnosed approximately 4 years later in females than males, with comparable lag time until subsequent ATTRwt-CM diagnosis, again 4 years later in females. These results are in line with the higher prevalence of ATTRwt-CM noted in elderly females.[22,23] Moreover, this finding additionally suggests a later or slower female ATTRwt-CM disease onset, providing indirect evidence to support a significant sex-hormone-specific (estrogens, androgens) and premenopausal protective effect, as suggested before.[22]

Finally, both bilateral CTS and SS are early red flags in ATTRwt-CM, preceding cardiac diagnose on average 7-9 years, in line with the 5-15 years noted in previous reports. Importantly, they appeared in concert with lower baseline NAC disease stage, a novel finding, offering real-world evidence of the unequivocal opportunity for early ATTRwt-CM diagnosis.[9,21] A mechanic-enzymatic pathway (related to repetitive stress) may contribute to the unexplained tissue tropism and likely reflects a systemic amyloidogenic activity that may mirror the tempo of subsequent myocardial infiltration, rather than representing purely age-related changes.[7,8,10]

FIGURE 3 Baseline National Amyloidosis Centre Prognostic Stage Distribution



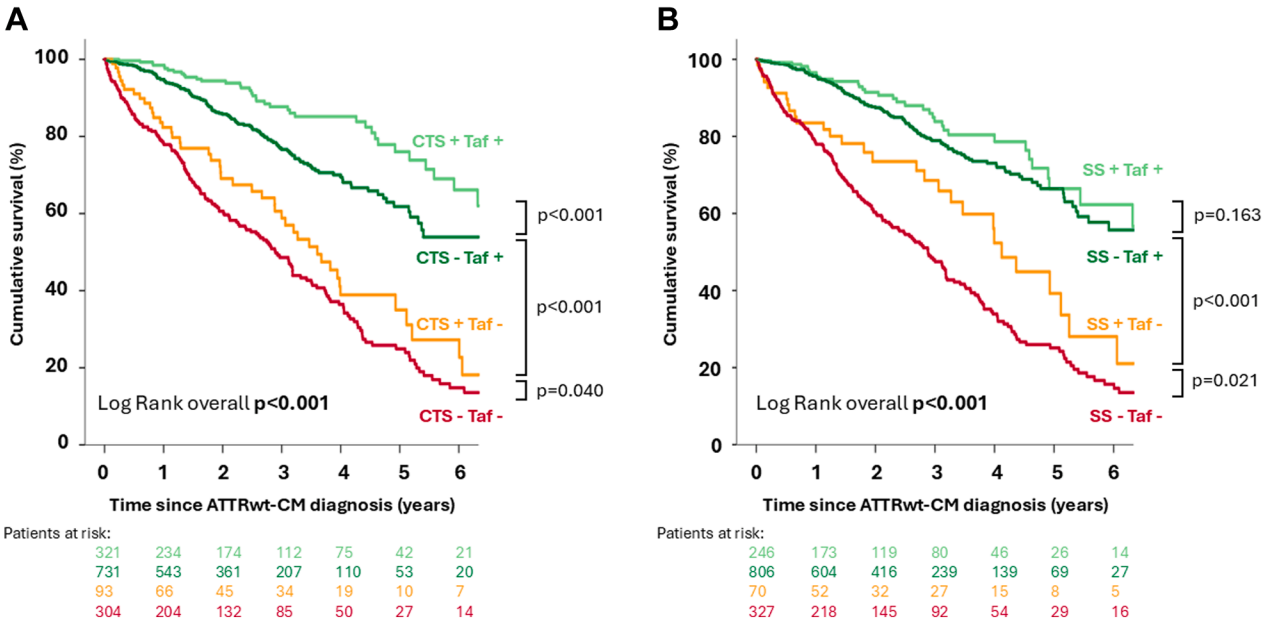
(A) Stratified by baseline carpal tunnel syndrome and tafamidis treatment initiation during follow-up. (B) Stratified by baseline lumbar spinal stenosis and tafamidis treatment initiation during follow-up. CTS = carpal tunnel syndrome; SS = spinal stenosis; NAC = National Amyloidosis Centre; - = negative; + = positive. *Baseline NAC stages available for 963 patients.*

THERAPEUTIC RELEVANCE. Current study represents the largest reported multicentric data set of real-world tafamidis-treated ATTRwt-CM patients (1,052 of 1,449) to date, demonstrating that both bilateral CTS and SS relate to both higher tafamidis treatment initiation and at an earlier disease stage (lower NAC disease stage, both at baseline and at the start of treatment). Bilateral CTS (but not SS)-positive subjects were even started on tafamidis on average 2.3 years earlier than patients without. These findings may partly account for the survival benefit under tafamidis treatment in patients with baseline bilateral CTS and/or SS and comply with randomized studies using tetrameric stabilizers (tafamidis and acoramidis), showing better outcomes when started earlier at less advanced cardiac disease.[3,4,24]

PROGNOSTIC RELEVANCE. The prognostic relevance of (bilateral) CTS in ATTRwt-CM is poorly studied in few small single-center studies, presumably all in tafamidis naive patients. One study on 253 ATTRwt patients (25% bilateral and 60% unilateral CTS history) found no survival difference between subjects with vs without CTS (67 vs 63 months, $P = 0.450$), similar to another report on 206 ATTRwt-CM subjects (34% CTS, $P = 0.100$).[11,12] Milandri et al[9] reported that CTS independently predicted higher mortality in ATTRwt-CM subjects (HR: 3.62; 95% CI: 1.24-10.3; $P = 0.016$), corrected for NYHA functional class symptoms and eGFR. This study, however, included 107 ATTRwt-CM patients only (25% with bilateral CTS), all recruited before June 2017. One study on 206 ATTRwt-CM patients (8% SS prevalence) mentioned similar mortality between patients with vs without SS, lacking further details.[11]

Current study on 1,449 ATTRwt-CM subjects is the largest analysis on CTS and the first evaluating SS, showing both relate to better survival, partly attributed to the younger age, lower disease stage components, and earlier (and more) disease-modifying therapy initiation in these patients. The interaction between CTS and tafamidis suggests that patients with CTS may derive greater survival benefit from tafamidis, consistent with CTS representing an early or prodromal manifestation of ATTR-CM that identifies individuals likely to benefit from earlier tafamidis therapy, acting as an effect modifier rather than a simple mediator. In contrast, SS may develop

FIGURE 4 Cumulative Survival for All-Cause Mortality



(A) Stratified by baseline carpal tunnel syndrome and tafamidis treatment initiation during follow-up. (B) Stratified by baseline lumbar spinal stenosis and tafamidis treatment initiation during follow-up. Taf = tafamidis treatment; other abbreviations as in Figures 2 and 3.

TABLE 3 Univariable and Multivariable Cox Regression Analysis for All-Cause Mortality

	Univariable			Multivariable					
				Bilateral CTS			Spinal Stenosis		
	HR	95% CI	*P* Value	HR	95% CI	*P* value	HR	95% CI	*P* Value
Tenosynovial red flag									
Bilateral carpal tunnel syndrome	0.57	0.45-0.73	**<0.001**	0.70	0.52-0.95	**0.024**	-	-	-
Lumbar spinal stenosis	0.65	0.50-0.84	**0.001**	-	-	-	0.68	0.48-0.97	**0.032**
Demographics									
Age, per year	1.10	1.08-1.12	**<0.001**	1.08	1.05-1.11	**<0.001**	1.08	1.06-1.11	**<0.001**
Male gender	1.11	0.86-1.44	0.411						
Disease stage components									
NT-proBNP, per pg/mL	1.00	1.00-1.00	**<0.001**	1.00	1.00-1.00	**<0.001**	1.00	1.00-1.00	**<0.001**
eGFR, per mL/min/1.73 m^2	0.97	0.97-0.98	**<0.001**	0.99	0.97-0.99	**0.001**	0.99	0.98-0.99	**0.001**
LVEF, per %	0.97	0.97-0.98	**<0.001**	0.98	0.97-0.99	**<0.001**	0.98	0.97-0.99	**<0.001**
Baseline cornerstone heart failure therapy									
Beta-blocker	1.13	0.93-1.37	0.239						
ACE-I/AIIRB/ARNI	0.89	0.73-1.08	0.234						
SGLT2-I	0.58	0.41-0.83	**0.003**	0.69	0.43-1.09	0.111	0.69	0.43-1.10	0.117
MRA	1.30	1.07-1.59	**0.009**	1.12	0.85-1.48	0.433	1.10	0.83-1.45	0.510
ICD	0.87	0.52-1.46	0.595						
CRT	0.84	0.54-1.30	0.437						
Disease modifying therapy									
Tafamidis initiation[a]	0.61	0.50-0.75	**<0.001**	0.69	0.52-0.90	**0.007**	0.69	0.52-0.90	**0.007**
ATTR-CM trial inclusion	0.23	0.11-0.47	**0.001**	0.26	0.10-0.72	**0.009**	0.25	0.09-0.69	**0.007**

Bold means statistically significant, $P < 0.05$. [a]As time-dependent covariate.
ATTR-CM = transthyretin amyloid cardiomyopathy; LVEF = left ventricular ejection fraction; other abbreviations as in Tables 1 and 2.

later in the disease course or be less specific to early ATTR-CM, which may explain the absence of a detectable interaction with tafamidis. Interestingly, however, a survival benefit was noted, independent of those predictors, including tafamidis naive patients. We speculate that the presence of bilateral CTS and/or SS may represent a subset of patients characterized by a more indolent, less aggressive natural disease course, allowing time to develop ATTR deposition-related tenosynovial disorders many years before, ultimately contributing to a survival benefit.[11,21] Although longitudinal studies would be required to test this hypothesis, indirect supportive evidence comes from light-chain amyloid cardiomyopathy patients, characterized by a more aggressive and detrimental natural course, with both CTS and SS being identified far less than in ATTRwt-CM, comparable to the general populations' prevalence.[8] Nevertheless, ascertainment or lead-time bias cannot be excluded and multivariable modeling does not infer causality, implying CTS and SS may represent risk stratifiers and diagnostic sentinels, rather than protective factors per se.

CLINICAL IMPLICATIONS. First, our data lend support to prioritize ATTR-CM in the differential diagnosis of hypertrophic heart disease in elderly (>60 years old), especially when bilateral CTS and/or SS coexist, and irrespective of coinciding hypertensive disease.[1,5] Their presence implies opportunities for early diagnosis (at younger age, earlier disease stage) with more and timely disease-modifying treatment initiation, conveying prognostic benefit.

Second, as both CTS and SS precede ATTRwt-CM by many years and independently predict better survival, opportunistic clinical screening strategies should be considered to facilitate early ATTRwt-CM diagnosis.[16] Indeed, increased future ATTRwt-CM risk at 10 years of 30-fold after bilateral CTS surgery and 2-fold in patients with SS was recently reported.[7,25] Direct evidence is provided by screening studies showing high prevalence of ATTR deposits in the transverse carpal ligament in 7% to 34% of CTS surgery patients and 21% to 66% in the ligamentum flavum during SS surgery, with coexistent ATTRwt-CM during diagnostic work up in 1% to 14% and 0% to 10%, respectively.[9,10,16,26-35] The serial follow-up of such patients with ATTR positive biopsy eventually leads to additional ATTRwt-CM diagnoses.[9,16] As no clinical, biochemical or echocardiographic characteristics discriminated between those CTS or SS patients with and without ATTR-CM at baseline, routine tenosynovial biopsy during surgery remains essential and has been adopted in several centers.[10,35] Given the high overall prevalence of tensosynovial ATTR deposits, most likely reflecting a rather age-related local phenomenon in most, providing ATTRwt-CM workup to those presenting with a high burden of ATTR deposits could maximize diagnostic specificity and cost-efficiency, thereby avoiding unnecessary diagnostic testing and patient anxiety, as has been proposed and undergoing current multicentric evaluation (ALCATTRASS, NCT06101108).[30]

STUDY LIMITATIONS. Potential confounders to our results may relate to its observational nature. In addition, the true prevalence of bilateral CTS and SS may be underestimated as not all patients underwent systematic screening for their presence and secondary to intercenter detection pathway variability, implying potential ascertainment bias. Finally, although our multivariable model reflects established ATTR-CM-specific prognosticators, alternative covariate selection strategies could yield different estimates.

CONCLUSIONS

Real-world data support the high prevalence of both bilateral CTS and SS in ATTRwt-CM patients, preceding cardiac diagnose by many years, representing principal sentinels for early ATTR-CM diagnosis (at younger age and lower disease burden) and subsequent earlier tafamidis treatment, all contributing to better patient survival. In addition, both bilateral CTS and SS relate to better prognosis, independent of these predictors, legitimizing opportunistic screening in patients with ventricular hypertrophy that present with these tenosynovial disorders, even in the absence of cardiac signs or symptoms.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In all elderly patients presenting with ventricular hypertrophy and/or heart failure, preceding CTS and/or SS presence should be questioned, prioritizing ATTRwt-CM in the differential diagnosis, irrespective of the hypertensive disease presence. CTS and SS are key sentinels, offering unequivocal opportunity for early ATTRwt-CM diagnosis and timely treatment initiation, related to improved survival, as we demonstrated in a large real-life cohort for the first time.

TRANSLATIONAL OUTLOOK: The prognostic relevance of both CTS and SS legitimizes and potentiates a role for opportunistic screening for ATTRwt-CM in elderly (>60 years) during decompression surgery, based on tenosynovial tissue biopsy. Given the high prevalence of ATTR deposits at tenosynovial biopsy, future study is needed to refine such screening to maximize ATTRwt-CM diagnostic specificity.

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