Prevalence and Outcomes of Cardiac Amyloidosis in All-Comer Referrals for Bone Scintigraphy

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The prevalence of cardiac amyloidosis (CA) in the general population and associated prognostic implications remain poorly understood. We aimed to identify CA prevalence and outcomes in bone scintigraphy referrals. **Methods:** Consecutive all-comers undergoing ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic-acid (^{99m}Tc-DPD) bone scintigraphy between 2010 and 2020 were included. Perugini grade 1 was defined as low-grade uptake and grade 2 or 3 as confirmed CA. All-cause mortality, cardiovascular death, and heart failure hospitalization (HHF) served as endpoints. **Results:** In total, 17,387 scans from 11,527 subjects (age, 61 ± 16 y; 63.0% women, 73.6% cancer) were analyzed. Prevalence of ^{99m}Tc-DPD positivity was 3.3% (n = 376/11,527; grade 1: 1.8%, grade 2 or 3: 1.5%), and was higher among cardiac than noncardiac referrals (18.2% vs. 1.7%). In individuals with more than 1 scan, progression from grade 1 to grade 2 or 3 was observed. Among patients with biopsy-proven CA, the portion of light-chain (AL)-CA was significantly higher in grade 1 than grade 2 or 3 (73.3% vs. 15.4%). After a median of 6 y, clinical event rates were: 29.4% mortality, 2.6% cardiovascular death, and 1.5% HHF, all independently predicted by positive ^{99m}Tc-DPD. Overall, adverse outcomes were driven by confirmed CA (vs. grade 0, mortality: adjusted hazard ratio [AHR] 1.46 [95% CI 1.12–1.90]; cardiovascular death: AHR 2.34 [95% CI 1.49–3.68]; HHF: AHR 2.25 [95% CI 1.51–3.37]). One-year mortality was substantially higher in cancer than noncancer patients. Among noncancer patients, also grade 1 had worse outcomes than grade 0 (HHF/death: AHR 1.45 [95% CI 1.01–2.09]), presumably because of longer observation and higher prognostic impact of early infiltration. **Conclusion:** Positive ^{99m}Tc-DPD was identified in a substantial number of consecutive ^{99m}Tc-DPD referrals and associated with adverse outcomes.

Key Words: transthyretin; ATTR; diagnosis; mortality; heart failure

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Cardiac amyloidosis (CA) is a myocardial infiltrative disease and causes heart failure by deposition of amyloid fibrils. The 2 major amyloid proteins deposited in the myocardium are transthyretin (ATTR), which predominantly affects elderly individuals, and immunoglobulin light chain (AL), whereas other types of CA are very rare (*1*). If left untreated, CA leads to heart failure and death, both in ATTR and AL. Formerly believed to be a rare condition, recent diagnostic advances and disease awareness have resulted in a true renaissance of CA. Increased diagnosis of CA is mainly driven by excellent sensitivity and specificity of bone scintigraphy (e.g., ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid [^{99m}Tc-DPD]; ^{99m}Tc-pyrophosphate [^{99m}Tc-PYP]), in particular for ATTR (*1*). Broader use of bone scintigraphy for screening of ATTR-CA has unveiled a significant proportion of (coexisting) CA for various cardiac conditions (*2–5*). Attempts to estimate the prevalence of CA in the general population using bone scintigraphy yielded substantially lower proportions of affected patients (*6–8*). However, these studies were limited either by small sample size or failure to report on prognostic implications of CA. Current diagnostic criteria require strong cardiac tracer uptake (Perugini grade ≥ 2) for ATTR-CA, whereas the clinical significance of low uptake (Perugini grade 1) is not well studied (*9*). This diagnostic gap is of particular importance because ATTR-specific treatments might be more effective at earlier stages of disease (*10*). Yet, underlying pathology and outcomes of low-grade cardiac uptake are unclear.

The present study was designed to evaluate the prevalence of cardiac tracer uptake (grades 1–3) and to investigate associated outcomes in all-comers referred to bone scintigraphy.

MATERIALS AND METHODS

Study Population

This study included consecutive all-comer referrals for bone scintigraphy between January 2010 and August 2020 at the Vienna General Hospital, a university-affiliated tertiary center. Bone scintigraphy was performed using ^{99m}Tc-methylene diphosphate (^{99m}Tc-MDP) before April 2010, and ^{99m}Tc-DPD thereafter. Because ^{99m}Tc-MDP has been shown to lack sensitivity in the diagnosis of ATTR (*11*), patients evaluated with this tracer were excluded (Supplemental Fig. 1; supplemental materials are available at http://jnm.snmjournals.org). The remaining patients with available ^{99m}Tc-DPD scans and sufficient image quality were included in the final analysis. The institutional review board approved this retrospective study (EK 1557/2020), and the requirement to obtain informed consent was waived.

^{99m}Tc-DPD Bone Scintigraphy

All patients were scanned using either an Infinia Hawkeye 4 (GE Healthcare) or a Discovery 670 (GE Healthcare) hybrid γ-camera 3 h after intravenous administration of 700 MBq of ^{99m}Tc-DPD. Planar whole-body images were acquired at a scan speed of 10 cm/min using

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low-energy high resolution collimators (*12*). On clinical request, additional SPECT/CT of the chest was performed.

Image Analysis and Diagnosis of CA

All scans were analyzed by 2 experienced nuclear imaging scan readers masked to clinical data (e.g., age, sex, and referral diagnosis). Visual assessment according to the Perugini classification was applied (*11*), where grade 0 represents no cardiac uptake with normal bone uptake (i.e., negative, ^{99m}Tc-DPD [^{99m}Tc-DPD−]) and grades 1–3 represent increasing cardiac uptake (^{99m}Tc-DPD+) with increasing bone attenuation and soft-tissue uptake. Grade 1 was defined as low-grade uptake (Supplemental Fig. 2) and grade 2 or 3 uptake as confirmed amyloidosis. In the case of discrepant ^{99m}Tc-DPD grading between the 2 readers, which occurred in 12 borderline cases, a third nuclear imaging specialist was consulted, and final diagnosis was reached by consensus (Supplemental Fig. 3). Because of the retrospective study design, CA subtype was not consistently assessed. However, organ tissue biopsy including Congo red staining and immunohistochemical analysis was available in a subset of patients. Mass spectroscopy was sought in cases with indistinct amyloid subtyping on immunohistochemistry.

Data Acquisition

Clinical and laboratory data as well as hospitalizations for heart failure (HHF) were retrieved from medical records. All-cause mortality was captured from the Austrian-Death-Registry and served as primary study endpoint. Cardiovascular death (as determined from the cause of death in the Austrian-Death-Registry) and HHF were selected as secondary study endpoints. HHF was determined from 3 sources, covering hospitalizations in all Austrian hospitals: patient records of the Medical University of Vienna, Vienna-Health-Association data base, and the nationwide electronic health records. Outcome assessment was 100% complete. An internal expert committee adjudicated each event, masked to ^{99m}Tc-DPD results. The presence of monoclonal protein was defined as positivity of serum or urine immunofixation with or without elevated serum/urine levels of the corresponding light chain.

Statistical Analysis

All statistical analyses were computed using SPSS 27 (IBM SPSS). Continuous data are expressed as median and interquartile range (IQR), and categoric variables as numbers and percentages. Differences between groups were analyzed with the Kruskal–Wallis test. Post hoc analyses were performed using Dunn-Bonferroni tests for continuous variables. χ^2 tests or Fisher tests were used for categoric variables as appropriate. We calculated the prevalence of ^{99m}Tc-DPD+ and 95% CIs according to the Wilson's score method. Kaplan–Meier estimates and Cox regression analyses were used to evaluate the prognostic significance of ^{99m}Tc-DPD+. Multivariate adjustment (including age, sex, cardiovascular risk factors, and comorbidities as outlined in the respective outcome tables) was performed using a nonstepwise approach with a cutoff P value to enter the multivariate model of ≤ 0.05. The proportional hazards assumption was tested with the examination of Schoenfeld residuals. Multivariate binary logistic analysis was applied to evaluate the association of parameters with the presence of ^{99m}Tc-DPD+. A P value ≤ 0.05 was considered statistically significant.

RESULTS

Patient Population

In total, 17,387 consecutive ^{99m}Tc-DPD bone scintigraphy scans from 11,527 patients were analyzed and included in the final analysis (Supplemental Fig. 1). The median age of the study population was 63.6 y (IQR 51.3–73.0), with 63.0% women and 73.6% cancer patients.

Referral Diagnosis and Temporal Trends

Referral diagnoses for ^{99m}Tc-DPD were noncardiac (90.6%) and cardiac (9.4%). Precise breakdown of referral diagnoses is displayed in Supplemental Figure 4 and baseline characteristics stratified according to referral indication are displayed in Supplemental Table 1. The proportion of cardiac referrals among all-comers increased consistently over time (2010–2014: 0.5%; 2015–2016: 4.5%; 2017–2018: 19.7%; 2019–2020: 28.8%; $P < 0.001$).

Prevalence and Predictors of CA

Among all-comers the prevalence of ^{99m}Tc-DPD+ was 3.3% (95% CI 2.9–3.6, n = 376/11,527). Grade 1 was found in 1.8% (n = 209/11,527) and confirmed amyloidosis (grade 2 or 3) in 1.5% (n = 167/11,527) of patients. There was a significant increase in the prevalence of ^{99m}Tc-DPD positivity with incremental age: <60 y: 0.6% vs. 60–70 y: 2.2% vs. 70–80 y: 5.5% vs. >80 y: 12.4% ($P <$ 0.001). Age distribution of ^{99m}Tc-DPD+ according to referral indication is shown in Figure 1. As expected, ^{99m}Tc-DPD+ was more common among cardiac versus noncardiac referrals (18.2%, 95% CI 16.0–20.7, n = 197/1,081 vs. 1.7%, 95% CI 1.5–2.0, n = 179/10,446; $P < 0.001$). The distribution of disease burden differed significantly between cardiac and noncardiac patients. Most ^{99m}Tc-DPD+ cases among cardiac referrals displayed grade 2 or 3 uptake (62.9% grade 2 or 3 vs. 37.1% grade 1), whereas grade 1 uptake was predominantly observed among noncardiac referrals (24.0% grade 2 or 3 vs. 76.0% grade 1, P for differences according to referral diagnosis < 0.001).

Independent predictors for the presence of ^{99m}Tc-DPD+ by multivariate binary logistic regression analysis were history of carpal tunnel syndrome (odds ratio [OR], 8.06 [95% CI 4.50–14.46]), atrial fibrillation (OR, 2.61 [95% CI 2.01–3.39]), chronic heart failure (OR, 2.05 [95% CI 1.87–3.35]), male sex (OR, 1.86 [95%

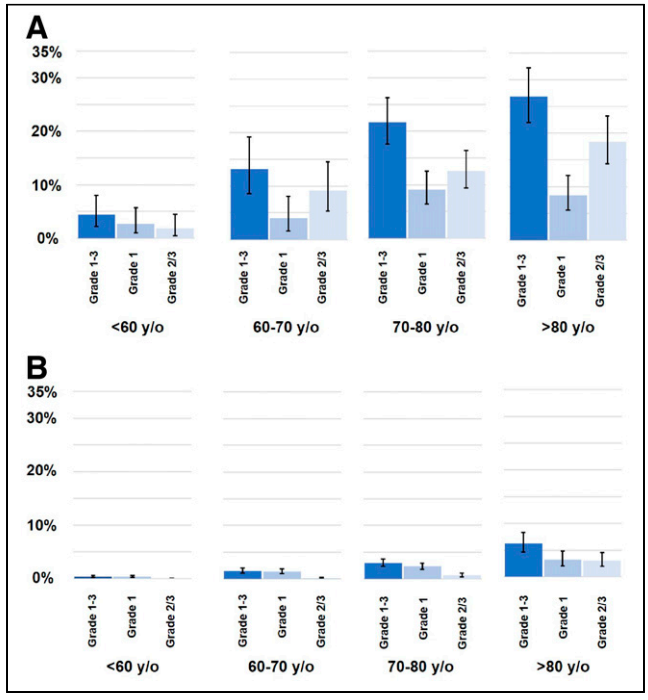

FIGURE 1. (A and B) Prevalence of cardiac uptake and breakdown of Perugini grading according to age levels in cardiac (A) and noncardiac referrals (B). y/o = year old.

CI 1.48–2.34]), and age (per year increase: OR, 1.08 [95% CI 1.07–1.09], all $P < 0.001$).

Grade 0 versus Low-Grade Uptake Versus Confirmed Amyloidosis

Differences in baseline characteristics according to Perugini grade are displayed in Table 1. From ^{99m}Tc-DPD− to grade–1 to confirmed CA, a stepwise increase in age, male sex, and history of carpal tunnel syndrome was found (P all < 0.001). Conversely, the proportion of cancer declined from no CA to confirmed CA ($P < 0.001$). Comorbidities typically associated with age, such as arterial hypertension, coronary artery disease, and impaired kidney function, were more prevalent in ^{99m}Tc-DPD+ patients (all $P < 0.001$). Furthermore, atrial fibrillation and chronic heart failure were more common in ^{99m}Tc-DPD+ than in ^{99m}Tc-DPD− patients (all $P < 0.001$). Accordingly, cardiac serum markers displayed a stepwise increase in ^{99m}Tc-DPD− patients versus low-grade uptake versus confirmed CA: high-sensitive troponin T, 19 ng/mL (IQR 10–41) versus 49 (IQR 25–148) versus 60 (IQR 33–104); N-terminal pro-brain natriuretic peptide, 655 pg/mL (IQR 185–2,311) versus 2,117 (IQR 848–6,364) versus 3,043 (IQR 1,562–6,556); all $P < 0.001$. The presence of monoclonal protein was more prevalent in grade 1 than in ^{99m}Tc-DPD− and grade 2 or 3 ($P = 0.001$). Among patients who underwent echocardiography, a stepwise increase of left ventricular wall thickness from ^{99m}Tc-DPD− to low-grade uptake to confirmed CA was observed: 13 mm (IQR 11–15) versus 14 (IQR 13–17) versus 20 (IQR 17–23). Also, left and right heart dimensions were increased and left ventricular function was decreased in ^{99m}Tc-DPD+ compared with ^{99m}Tc-DPD− (P for all < 0.001).

^{99m}Tc-DPD Grading Trajectories

Repeated scans were available for 2,136 patients and yielded identical Perugini grades in most cases (98.9%). However, 23 patients experienced a change in cardiac tracer uptake 3.4 y (IQR 1.3–5.9) after their previous scan (Supplemental Fig. 5): grade 0 to grade 1 ($n = 15$), grade 0 to grade 2 ($n = 1$), grade 1 to grade 2 or 3 ($n = 4$), grade 0 to grade 1 to grade 2 or 3 ($n = 1$), decline in grading because of excessive bone metastasis ($n = 2$).

SPECT

Among patients with a positive scan result on planar imaging, additional SPECT of the chest was available for 19.1% ($n = 72/376$). Cardiac origin of tracer uptake was verified by SPECT in 89% ($n = 64/72$), which was markedly higher among patients with grade 2 or 3 (100%, $n = 52/52$) than grade 1 by planar imaging (60%, $n = 12/20$, Supplemental Fig. 6).

Tissue Biopsy

Organ tissue samples for amyloid detection and subtyping among patients with a positive scan result were available in 7.7% of grade 1 and in 16.8% of grade 2 or 3 (Supplemental Table 2). Confirmation rates of amyloid tissue presence were 93.8% and 92.9% for grade 1 and 2 or 3, respectively. Negative samples were derived from kidney biopsies (1 grade 1, 1 grade 2 or 3) and abdominal fat tissue aspirate (1 grade 2 or 3), whereas amyloid was confirmed in 100% of endomyocardial biopsies ($n = 33/33$). Among those with confirmed amyloid on biopsy, the portion of ATTR was significantly higher in grade 2 or 3 (76.9%, $n = 20/26$) than in grade 1 patients (26.7%, $n = 4/15$; $P < 0.01$). Hence, AL

TABLE 1
Baseline Characteristics

Characteristic	Grade 0 (n = 11,151 [96.7%])	Grade 1 (n = 209 [1.8%])	Grade 2 or 3 (n = 167 [1.5%])	P
Age (y)	63 (51–73)	75 (68–80)*	80 (74–84)†,‡	<0.001
Sex, male (%)	36.1	53.1*	74.3†,‡	<0.001
BMI (kg/m^2)	25.7 (22.8–29.4; 10,747)	27.5 (24.8–32.1; 198)*	25.3 (23.4–28.3; 163)‡	<0.001
Cardiac referral (%)	7.9	34.9*	74.3†,‡	<0.001
Cancer (%)	74.6	56.5*	25.7†,‡	<0.001
Myeloma (%)	1.0	5.3*	1.2‡	<0.001
Arterial hypertension (%)	40.2	70.8*	49.9†,‡	<0.001
Diabetes (%)	12.1	24.9*	12.6‡	<0.001
Atrial fibrillation (%)	8.1	29.7*	50.3†,‡	<0.001
Past stroke (%)	5.5	7.2	10.2†	0.019
CAD (%)	12.1	38.8*	31.1†	<0.001
Previous MI (%)	1.7	7.7*	3.0	<0.001
Chronic heart failure (%)	7.2	26.3*	38.9†,‡	<0.001
PAD (%)	1.5	4.3*	1.2	0.004
COPD (%)	7.2	11.5*	10.8	0.015
CTS (%)	0.8	3.8*	6.6†	<0.001

*DPD grade 1 vs. grade 0: $P \leq 0.05$.
†DPD grade 2 or 3 vs. grade 0: $P \leq 0.05$.
‡DPD grade 2 or 3 vs. grade 1: $P \leq 0.05$.
BMI = body mass index; CAD =coronary artery disease; MI = myocardial infarction; PAD = peripheral artery disease; COPD = chronic obstructive pulmonary disease; CTS = carpal tunnel syndrome.
Parenthetical data indicate number of patients with available data for parameter if not identical to column total.

was the predominant amyloid subtype in grade 1 (73.3%, $n = 11/15$). Furthermore, the presence of combined ATTR/AL-CA was diagnosed in 2 grade 2 or 3 patients with endomyocardial biopsy and confirmed by mass spectroscopy.

Mortality

After a median follow-up of 6.0 y (IQR 2.8–8.9), 29.4% ($n = 3,385/11,527$) had died. Cardiovascular death accounted for 8.9% of mortality ($n = 302/3,385$). Among all-comers, ^{99m}Tc-DPD+ was significantly associated with mortality by Cox regression analysis (crude hazard ratio [HR] 1.76 [95% CI 1.49–2.08]), which applied for both grade 1 (vs. grade 0: HR 1.61 [95% CI 1.29–1.99], and grade 2 or 3 (vs. grade 0: HR 2.02 [95% CI 1.57–2.60], all $P < 0.001$). After multivariate adjustment, ^{99m}Tc-DPD+ remained significantly associated with mortality (Table 2), driven by confirmed CA but not low-grade uptake (adjusted HR [AHR] with ^{99m}Tc-DPD− as reference: 1.20 [95% CI 1.01–1.43] for ^{99m}Tc-DPD+, $P = 0.036$; AHR, 1.46 [95% CI 1.12–1.90] for confirmed CA, $P = 0.006$; AHR, 1.09 [95% CI 0.87–1.35] for low-grade uptake, $P = 0.5$). Results remained unchanged after exclusion of 3 grade 1 patients with documented myocardial infarction within 1 mo before scintigraphy. Also, results were consistent when cardiovascular death was analyzed separately (AHR with ^{99m}Tc-DPD− as reference: 1.79 [95% CI 1.26–2.54] for ^{99m}Tc-DPD+, $P = 0.001$; AHR, 2.34 [95% CI 1.49–3.68] for confirmed CA, $P < 0.001$; AHR, 1.31 [95% CI 0.78–2.20] for low-grade uptake, $P = 0.3$; Supplemental Table 3). The proportional hazard assumption was satisfied, and we did not detect a significant collinearity in the multivariate models. Kaplan–Meier curves illustrate increased all-cause mortality in confirmed CA versus grade 1 (log-rank, $P = 0.039$; Fig. 2).

Overall, mortality rates at 1 y were more than doubled in cancer versus noncancer patients (13.4% vs. 6.0%, $P < 0.001$). Unadjusted death rates for ^{99m}Tc-DPD− versus ^{99m}Tc-DPD+ patients were higher among both cancer (HR, 1.59 [95% CI 1.29–1.98]) and noncancer patients (HR, 3.94 [95% CI 3.03–5.11], both $P < 0.001$). After multivariate adjustment, ^{99m}Tc-DPD+ remained significantly associated with mortality only for noncancer (AHR, 1.41 [95% CI 1.06–1.89], $P = 0.017$), but not for cancer patients (AHR, 0.94 [95% CI 0.75–1.19], $P = 0.6$).

HHF

During follow-up, 1.5% of patients ($n = 178/11,527$) were hospitalized for heart failure. ^{99m}Tc-DPD + independently predicted the occurrence of HHF (AHR, 2.25 [95% CI 1.51–3.37], $P < 0.001$). Again, patients with low-grade uptake versus ^{99m}Tc-DPD− performed equally (AHR, 1.18 [95% CI 0.61–2.26], $P = 0.6$), whereas confirmed CA was associated with a 3.5 times higher risk of future HHF than was ^{99m}Tc-DPD− (AHR, 3.57 [95% CI 2.19–5.80], $P < 0.001$, Supplemental Table 4).

Outcomes of Noncancer Patients with Low-Grade Uptake

Importantly, among noncancer patients, also grade 1 was associated with worse outcomes compared with grade 0 with a higher hazard of HHF (HR, 4.89 [95% CI 2.34–10.24]), cardiovascular (HR, 3.84 [95% CI 2.01–7.36]), and all-cause mortality (HR, 3.56 [95% CI 2.47–5.15], all $P < 0.001$). Results for the composite endpoint of HHF or death remained significant after multivariate adjustment for patients with grade 1 (vs. grade 0: AHR, 1.45 [95% CI 1.01–2.09], $P = 0.04$), and grade 2 or 3 (vs. grade 0: AHR, 1.40 [95% CI 1.01–1.97], $P = 0.049$).

DISCUSSION

In this large-scale study we analyzed all-comer bone scintigraphy referrals for the presence of ^{99m}Tc-DPD positivity and report a prevalence of 1-in-50 among noncardiac and 1-in-5 among cardiac referrals. Repeated scans revealed an increase in the burden of cardiac

TABLE 2
Cox Regression Analyses Assessing the Association of Parameters with Mortality

	Univariate		Multivariate	
Parameter	Hazard ratio	*P*	Hazard ratio	*P*
Age, per 10-y increase	1.547 (1.498–1.598)	<0.001	1.346 (1.298–1.396)	<0.001
Male sex	2.223 (2.077–2.379)	<0.001	2.097 (1.951–2.253)	<0.001
Cancer	2.515 (2.272–2.783)	<0.001	2.907 (2.620–3.225)	<0.001
Arterial hypertension	1.884 (1.761–2.016)	<0.001	1.137 (1.052–1.230)	0.001
Diabetes	1.758 (1.610–1.919)	<0.001	1.161 (1.055–1.278)	0.002
Atrial fibrillation	2.096 (1.903–2.310)	<0.001	1.095 (0.981–1.221)	0.104
Chronic heart failure	2.005 (1.808–2.225)	<0.001	1.261 (1.117–1.423)	<0.001
CAD	2.119 (1.945–2.307)	<0.001	1.065 (0.957–1.185)	0.251
Previous MI	1.633 (1.291–2.066)	<0.001	0.919 (0.718–1.177)	0.504
Past stroke	2.034 (1.812–2.284)	<0.001	1.231 (1.086–1.395)	0.001
PAD	1.837 (1.461–2.309)	<0.001	0.915 (0.722–1.159)	0.460
COPD	2.185 (1.975–2.417)	<0.001	1.585 (1.425–1.763)	<0.001
DPD positivity	1.758 (1.488–2.077)	<0.001	1.152 (1.004–1.323)	0.036

BMI = body mass index; CAD =coronary artery disease; MI = myocardial infarction; PAD = peripheral artery disease; COPD = chronic obstructive pulmonary disease; CTS = carpal tunnel syndrome.

Data in parentheses are 95% CI.

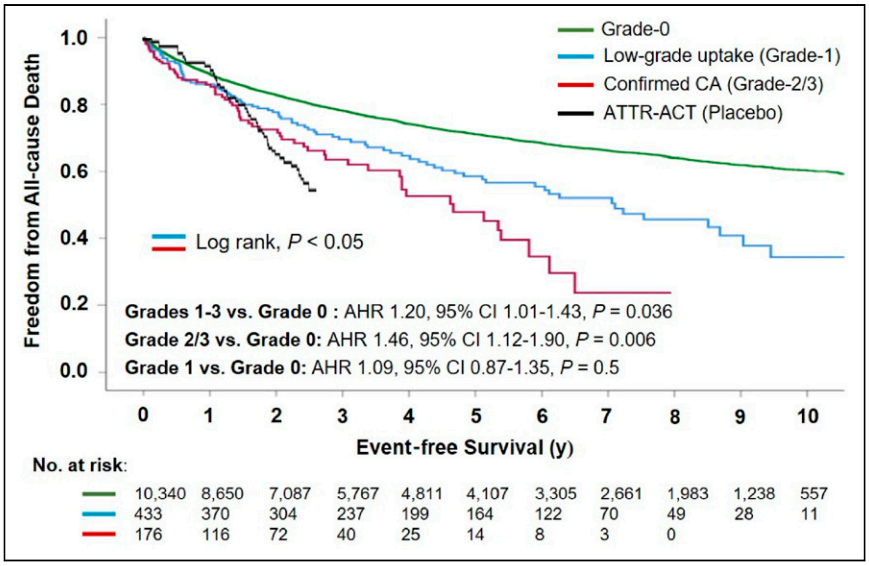

FIGURE 2. Association of CA with mortality. Among all-comers, grade 2 or 3 but not grade 1 was associated with increased adjusted mortality as compared with grade 0. Two-year survival rates of confirmed CA were comparable to those for patients in the placebo arm of the ATTR-ACT trial (data adapted from (10)).

tracer uptake from low- to high-grade uptake in a subgroup of patients over time, highlighting the progressive nature of the disease. Outcomes were worse in ^{99m}Tc-DPD+ patients, without differences in event-free survival between grade 1 and grade 0 in the overall cohort. However, 1-y mortality was twice as high in cancer than in noncancer patients. After the exclusion of cancer patients from the analysis, grade 1 patients experienced worse outcomes than those with no uptake, presumably because of the longer observation time/life expectancy with a higher prognostic impact of early ATTR infiltration. On the basis of these results, we conclude that, particularly, patients with grade 1 tracer uptake should be examined thoroughly and receive close follow-up, as an early diagnosis may offer a window of opportunity for timely initiation of novel CA-specific treatments to prevent adverse outcomes.

We also report a 10-times higher prevalence of ^{99m}Tc-DPD positivity in cardiac than noncardiac scintigraphy referrals. Active CA screening of patients with conditions typically associated with myocardial thickening, such as severe aortic stenosis and heart failure with preserved ejection fraction, have unveiled a prevalence of concomitant/underlying CA of ≥ 10% (*2,3*). Among elderly patients (≥80 y) without these conditions, CA proportions ranging from less than 1% to 5% have been reported (*6–8*). The present data indicate an even higher CA prevalence among noncardiac patients older than 80 y of 6%.

In clinical routine, CA is generally suspected when symptoms of heart failure are reported in combination with imaging features typical for infiltrative cardiomyopathies (e.g., markedly increased wall thickness). Hence, cardiac ^{99m}Tc-DPD referrals have a much higher likelihood of CA, and on average, showed more advanced disease (grade 2 or 3) than noncardiac patients, who mostly displayed grade 1 uptake. This likely relates to the clinical course of the disease. If detected incidentally, CA may be caught at an early stage where it is clinically unapparent. Conversely, the onset of clinical symptoms and transition to overt HF is more common in cases with advanced amyloid deposition (grade 2 or 3).

To our knowledge, for the first time we also report progressive amyloid deposition over time, as indicated by an increase in the amount of cardiac tracer uptake observed in subjects with multiple scans. Most importantly, this included cases with progression from low-grade uptake to confirmed CA (grade 2 or 3). Moreover, ATTR was confirmed in approximately 25% of grade 1 patients with biopsy-proven CA. However, most grade 1 patients receiving myocardial biopsy had monoclonal protein, and tissue sampling was sought to rule out AL-CA. Hence, the proportion of ATTR among all patients with low-grade uptake on bone scintigraphy (not only in those with a likelihood of AL) might in fact be considerably higher than indicated by our data. These findings highlight the importance to recognize subtle tracer uptake as potential ATTR-CA (*4,9*)—especially in the absence of a plasma cell dyscrasia. In patients with monoclonal protein with or without a positive bone scan result, novel nuclear imaging tracers (e.g., ^{18}F-florbetaben) show promise to diagnose AL or reliably differentiate between AL and ATTR or mimicking conditions, respectively (*13*). Distribution of late enhancement patterns by cardiac MR (CMR) may support the establishment of a CA diagnosis. Importantly, the addition of SPECT to planar imaging is recommended to discriminate cardiac from other sources of tracer uptake (e.g., ribs, residual blood-pool activity; Supplemental Fig. 6) (*14*). SPECT is of particular relevance in cases with subtle uptake on planar imaging to avoid false-positive results. One recent study using PYP and a 1-h imaging protocol reported false positivity in two thirds of patients with subtle uptake on planar imaging when compared with SPECT as a reference standard (*15*). In the present series, where scans were performed at 3 h—and therefore presumably more accurate in the verification of myocardial tracer origin—false positivity of grade 1 planar imaging was 40%, whereas grade 2 or 3 was 100% accurate. Given that SPECT was available only for a subset of patients with low-grade uptake, we assume that a relevant proportion of grade 1 patients was diagnosed because of blood pooling effects. In the case of suspected AL, endomyocardial biopsy OR extracardiac biopsy in combination with typical imaging features (echocardiography, CMR) are necessary to confirm the diagnosis (*16*). However, recent important improvements in cardiac imaging as outlined above have nurtured the hope that a CA diagnosis can be established purely noninvasively, thereby avoiding potential risks inherent to cardiac biopsy. Yet, on the basis of our data, grade 1 uptake currently requires comprehensive work-up (e.g., echo, CMR, SPECT, laboratory light-chain assessment, myocardial biopsy if indicated) to unmask early CA cases.

Few prospective CA registries have reported on predictors of survival (*17–19*). However, outcome implications of CA in the general population remain largely unknown. Here, we first describe CA as an independent predictor of clinical endpoints. After adjustment for (cardiovascular) risk factors, ^{99m}Tc-DPD positivity was associated with a 20% increase in all-cause mortality, an 80% increase in cardiovascular death, and a more than 2-fold risk for HHF. Overall, adjusted risk for adverse outcomes was only increased in confirmed CA, with 2-y survival rates comparable to those for patients in the placebo arm of the ATTR-ACT trial (Fig. 2) (*10*). However, the present cohort comprised individuals

with a high prevalence of malignancy and, hence, substantially increased 1-y mortality rates. Thus, the impact of CA—in particular of grade 1 CA—may be much stronger in the general population, and over a longer follow-up period. Accordingly, among noncancer patients, who had a significantly longer life expectancy than those with cancer, both grade 2 or 3 and low-grade uptake predicted outcomes, as previously reported in a preliminary analysis (*20*). Of note, inclusion of a relevant number of grade 1 patients with blood pooling may in fact underestimate the severity of outcomes in grade 1 patients with true myocardial uptake in the present series. Hence, low-grade uptake may represent a window of opportunity for timely diagnosis and initiation of novel CA-specific treatments. In ATTR, such treatments include agents that stabilize the tetrameric TTR protein (tafamidis) or reduce TTR serum levels (inotersen, patisiran). Tafamidis is the only drug currently approved for the treatment of ATTR-CA and has been shown to improve survival compared with placebo (*10*). However, subgroup analysis indicated fewer benefits for those with more advanced disease (NYHA class III), where placebo was superior to Tafamidis in the prevention of cardiovascular hospitalization. Treatment should, therefore, be initiated early in the disease process to achieve prognostic improvements. Future randomized trials are necessary to clarify whether ATTR-specific drugs will improve outcomes in grade 1 ATTR-CA patients.

This study has limitations. CA subtype was not consistently assessed given the retrospective study design. Yet, available results from cardiac biopsies emphasize the importance to recognize grade 1 cardiac uptake as potential ATTR-CA. Additional SPECT/CT of the chest was not uniformly available. Grade 1 may therefore comprise a proportion of patients with blood pooling effects and outcomes of low-grade patients with true myocardial tracer origin may in reality be even worse than shown here. Also, the presence of bone metastases in this population with a high rate of malignancy may have led to an underdiagnosis of low-grade amyloid deposition because of tracer competition with other compartments (Supplemental Fig. 5). Laboratory values (including monoclonal protein assessment) were not available for all patients and therefore excluded from outcome analysis. Finally, whereas a selection bias must be considered because of the single-center nature of our study, we followed an identical protocol for ^{99m}Tc-DPD bone scintigraphy, ensuring consistency of data throughout the more than 10-y study period.

CONCLUSION

CA is prevalent in elderly patients undergoing bone scintigraphy, both among noncardiac and even more so among cardiac referrals. Overall, the presence of confirmed CA (Perugini grade 2 or 3) was independently associated with adverse clinical outcomes. Grade 1—which we show can progresses to confirmed CA over time—had increased mortality only among noncancer patients because of longer life expectancy and potentially higher prognostic impact of early ATTR infiltration. If diagnosed and treated early, outcomes of CA patients may potentially improve significantly.

DISCLOSURE

This study received financial support from Pfizer. Christian Nitsche reports speaker fees from Pfizer. No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: How prevalent is CA among all-comers referred for bone scintigraphy and is it associated with worse outcomes?

PERTINENT FINDINGS: ^{99m}Tc-DPD+ affects 1-in-50 noncardiac and 1-in-5 cardiac patients referred for bone scintigraphy. Confirmed CA (grade 2 or 3) has increased mortality (all-cause and cardiovascular) and risk for future heart failure; grade 1 may represent both ATTR- and AL-CA and is likewise associated with a poor prognosis if observed for a longer period.

IMPLICATIONS FOR PATIENT CARE: Grade 1 may offer the possibility for early CA diagnosis and treatment with new amyloid-targeting therapies.

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