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RESEARCH ARTICLE

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# The Prevalence of Coronary Artery Disease in Amyloidosis Is 23%

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## ABSTRACT

**Purpose:** This observational cross-sectional analysis evaluates the prevalence of coronary artery disease in TTR and non-TTR amyloidosis.

**Methods:** Amyloidosis cases were identified in a large multi-center medical database using defined criteria. The presentation of CAD was determined through ICD codes for cardiac catheterization records and other precisely identifiable data, such as the history of stenting or bypass graft operations. TTR and non-TTR amyloidosis groups were compared regarding their baseline demographics, clinical, laboratory, and imaging presentations.

**Results:** Out of 5273 subjects in the study, 79 had TTR, and 5194 had non-TTR amyloidosis. On average, non-TTR patients are significantly older than TTR patients (70.39±13.26 vs. 63.09±19.40, *p=.0013*).

Overall, CAD was present in 1221 (23.16%) subjects. The prevalence of CAD was comparable between the non-TTR and TTR amyloid groups (23.2% vs. 22.8%, *p>0.05*). However, hypertension was more present in the non-TTR group than in TTR (32% vs. 12%, *p=.0001*). Race, gender, diabetes, and hyperlipidemia did not differ between the two groups (*p>0.05*).

**Conclusion:** CAD prevalence in TTR and non-TTR is around 23%. The type of amyloidosis does not impact the prevalence of CAD.

## ARTICLE HISTORY

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## KEYWORDS

Amyloidosis, Transthyretin amyloidosis, Non-transthyretin amyloidosis, Coronary artery disease.

## Background

Cardiac amyloidosis (CA) is characterized by the extracellular accumulation of insoluble misfolded fibrillar proteins that infiltrate the heart [1]. Cardiac involvement is the leading cause of morbidity and mortality in patients with systemic amyloidosis, regardless of the underlying pathogenesis of amyloid production [2,3]. Two types of amyloid proteins predominantly infiltrate the heart: Transthyretin (TTR) amyloid and light chain (AL) amyloid (non-TTR). TTR amyloid can be caused by mutations in the transthyretin gene (TTRm) or acquired through wild-type transthyretin protein (TTRwt) aggregation [4]. The infiltrative process results in biventricular wall thickening in a concentric and diffuse pattern, thickening of the interatrial septum, and thickening of the cardiac valves, each of which can be seen on echocardiography [5]. Amyloid infiltration reduces end-diastolic volume, leading to a reduction in stroke volume and cardiac output [2,5].

CA is becoming more commonly recognized. Between 2000 and 2012, the incidence was 4746 among Medicare beneficiaries, and the prevalence was 15737 in 2012. Also noted was an increase in the prevalence rate (8-17 per 100,000 person-years) and incidence rate (18-55 per 100,000 person-years) from 2000 to 2012, most notable after 2006 [6].

Other researchers noted that the incidence rates of probable amyloidosis increased from 1.38 to 3.69 per 100,000 person-years, and the prevalence rates increased from 3.42 to 14.85 per 100,000 person-years between 2004 and 2018. (*P trend < .0001*) [7]. Among patients aged >40 years referred with an initial diagnosis of hypertrophic cardiomyopathy, CA was the most common unrecognized mimic (9% prevalence). It increased with age (from 1% at ages 40–49 to 26% at age >80 years between 2014- 2017) [8].

Due to the ongoing destruction of cardiomyocytes, patients with CA often present with angina or heart failure (HF) symptoms with elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) and elevated troponin levels. This elevation often leads to further workup with cardiac catheterization [9,10]. Anecdotally, interventional cardiologists have noted a lower prevalence of severe atherosclerotic coronary artery disease

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(CAD) among patients with CA, inconsistent with age and risk factors. Older heart failure patients with cardiac amyloidosis had less calcified lesions, less ostial involvement, and reduced anterograde coronary blood flow [9]. However, there has been a paucity of studies describing the prevalence of CAD and risk factors for CAD among patients with CA. Notwithstanding, there have been reports of a recurrent acute coronary syndrome in cardiac amyloidosis and amyloidosis in general with unobstructed coronary arteries [11]. Therefore, we aim to contribute to this literature by reporting the prevalence of severe CAD in confirmed amyloidosis cases presenting to and being treated for coronary artery disease in the hospitals of a healthcare corporation.

## Methods

The Institutional Review Board of Graduate Medical Education at Mountainview Hospital reviewed and made the application exempt. All patient data were de-identified. The study was performed per institutional ethical guidelines and was in compliance with the Declaration of Helsinki.

### Patient Selection

Patients were included in the present study if they were

1) >18 years of age
2) Admitted to one of 180 HCA healthcare hospitals across the USA between Oct 1, 2015, and December 31st, 2020
3) Carried an International Classification of Diseases (ICD) code for amyloidosis (E85.0):

a. (E85.0) Non-neuropathic heredofamilial amyloidosis
b. (E85.2) Heredofamilial amyloidosis, unspecified
c. (E85.4) Organ-limited amyloidosis
d. (E85.81) Light chain amyloidosis
e. (E85.82) Wild-type transthyretin-related (TTRwt) amyloidosis
f. (E85.89) Other amyloidosis
g. (E85.9) Amyloidosis, unspecified

4) Had a diagnostic code for CAD: I200, I 201, I 208, I209, I2109, I2119, I2129, I213, I214, I219, I21A1, I222, I241, I248, I249, I2510, I25110, I25118, I25119, I252, I254, I255, I25810, I25811, I2582, I2583, I2584, I259.

### Data Collection and Definitions

All cross-sectional variables were collected from the HCA healthcare patient database. Chart abstraction during the index hospitalization and hospitalizations before and after were used.

The demographic variables were age, sex, body mass index (BMI in kg/m$^2$), and race/ethnicity (Black, White, other). Clinical variables collected were HF symptoms (dyspnea, lower extremity edema, pulmonary edema, and increased jugular venous pressure) documented during either hospitalization. Risk factors for CAD were collected from the history (diabetes, hypertension, family history of CAD, tobacco use, and hyperlipidemia). Reduced left ventricular ejection fraction (<50%, ICD-10 code I50-2) was documented. Laboratory variables collected were Troponin-I in ng/l, NT-proBNP in pg/ml, BNP in pg/ml, serum and urine protein electrophoresis (SPIE & UPIE), and serum-free light chain (FLC). The timing of these tests was random and could have been recorded in any of the hospitalizations. Severe CAD was diagnosed with ICD codes, as mentioned above.

## Statistical Analysis

Descriptive statistics of baseline demographics, clinical, laboratory, and imaging presentations were computed. Means with standard deviations were reported for continuous variables, and numbers with percentages were reported for categorical variables. TTR and non-TTR groups were compared in terms of their baseline demographics, clinical, laboratory, and imaging presentations using independent two-sample t-tests for continuous variables and Fisher Exact tests for categorical variables using SAS statistical software (www.sas.com). The statistical significance threshold for all analyses is 0.05.

## Results

Of the 5375 patients who met the inclusion criteria, 102 were excluded for missing or conflicting data, leaving 5273 patients in the final sample (Figure 1). Seventy-nine patients had TTR amyloidosis, compared to 5194 patients with Non-TTR.

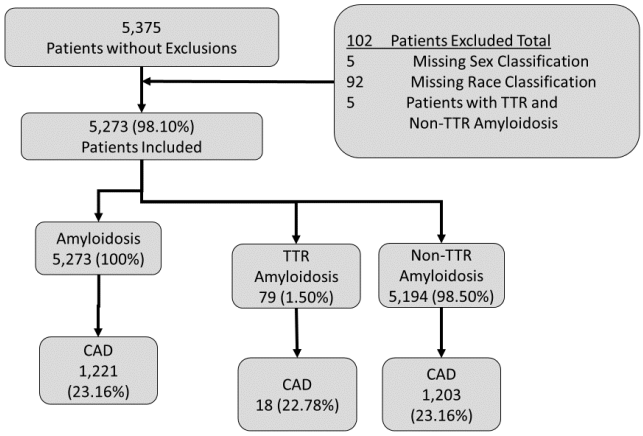


**Figure 1:** (Central Illustration) Description of Patients Included in the Final Analysis.

On average, non-TTR patients are significantly older than TTR patients (70.39±13.26 vs. 63.09±19.40, *P=.0013*). Race and gender did not differ between the two groups (*p>0.05*) (Table 1).

**Table 1:** Baseline characteristics of patients with non-TTR and TTR cardiac amyloidosis.

| Variable | Non-TTR n=5194 | TTR n=79 | P-value |
|---|---|---|---|
| CAD n (%) | 1,203 (23.16%) | 18 (22.78%) | >0.9999 |
| Age mean (SD) | 70.3910 (13.2596) | 63.0886 (19.3981) | 0.0013 |
| Race | | | |
| Black | 1,003 (19.31%) | 20 (25.32%) | |
| White | 3,647 (70.22%) | 54 (68.35%) | 0.2505 |
| Other | 544 (10.47%) | 5 (6.33%) | |
| Sex, Males n (%) | 2,773 (53.39%) | 37 (46.84%) | 0.2576 |
| Diabetes Type 2 N (%) | 1,241 (23.89%) | 12 (15.19%) | 0.0826 |
| Hypertension N (%) | 1,664 (32.04%) | 10 (12.66%) | 0.0001 |
| Hyperlipidemia N (%) | 2,095 (40.34%) | 27 (34.18%) | 0.2990 |

The prevalence of CAD was comparable between the non-TTR and TTR groups (23.2% vs. 22.8%, *p>0.05*), but hypertension was

more present in the non-TTR group (32% vs. 12%, *P=.0001).* The groups did not have statistically significant differences in diabetes or hyperlipidemia (*p>0.05*) (Table 1).

## Discussion

About 20.1 million adults aged 20 and older in the US had CAD in 2020 (7.2% general prevalence) [12]. The prevalence is different in the age groups. Recent data from the Centre for Disease Control showed the prevalence of heart disease in the age groups of 18 to 44, 45 to 64, and over 65 to be 0.9%, 5.9%, and 18.2%, respectively [13]. In adults older than 70, the prevalence is rising by over 30% [13]. Autopsy has shown obstructive CAD in 50% of older women and 70-80% of men (over 75) [14]. Therefore, the mean prevalence is estimated to be around 60% in people over 70 years old (The same age at which most amyloidosis cases occur). However, severe CAD resulting in myocardial infarction is less common [15].

The incidence of amyloidosis is not well documented but probably falls between 5 and 13 per million per year. Amyloidosis prevalence data are scarce, but one UK study indicates that about 20 per million inhabitants live with the condition [16]. Another study found that the prevalence of non-TTR increased significantly between 2007 and 2015, from 15.5 cases per million in 2007 to 40.5 in 2015, an annual percentage change (APC) of 12% (*P<.001*). The incidence ranged from 9.7 to 14.0 cases per million person-years with no statistically significant increase (APC 3%; *p=.114*). Therefore, there was an increase in non-TTR prevalence over nine years coupled with stable incidence rates [17].

Reports of CAD in amyloidosis have been around since the 1970s [18]. Coronary microvascular dysfunction is related to abnormalities in myocardial structure and function in cardiac amyloidosis [19]. One might think coronary artery microvascular deficiencies might increase or enhance the number and severity of CAD cases. However, although amyloidosis involves the vasculature of the heart and causes vasculopathy, it is through presumably different mechanisms [19,20]. This is likely the exact mechanism that microvascular disease can predispose to Alzheimer's disease [20]. Nevertheless, this is not the mechanism of atherosclerosis that causes CAD. This could be one reason for not having more CAD in amyloidosis patients [21].

Beyene and colleagues recently Evaluated 110 patients with heart failure for CA [9]. 55 patients had CA, and 55 did not. However, the groups were somewhat different, with more hypertension and smoking in the non-CA group (*P=0.001, P=0.006*). Despite the older age of the CA group, there was less coronary calcification and CAD in that group. This is compatible with our findings in this study. They analyzed the angiographic cohorts in detail and found less calcification and reduced antegrade coronary blood flow [9].

An older study of 58 patients with CA shows that amyloid was present in 97% of the epicardial coronary arteries [22]. Layers of intima, media, and adventitia were all affected, especially the adventitia. However, there was no intraluminal coronary obstruction in any patients [22]. This is again compatible with our findings and augments the discussion that there is less CAD in the amyloidosis age group.

Our perspective is that there might be a decrease in CAD in amyloidosis. Could this be a reflection that amyloidosis and the presence of amyloid prevent CAD formation? Does amyloidosis inhibit the development of CAD in patients with similar risk factors? Further studies are needed to prove such a concept. What are the likely mechanisms? Is amyloid precipitation in vessels prevent the deposition of lipids? Or is it preventing it through a molecular or hormonal mechanism? Can we treat coronary atherosclerosis if we discover and reproduce this mechanism? That would be an exciting perspective and help us treat atherosclerosis more efficiently. Future research in this area should be vital and enlightening.

This data might also be significant because the elevated troponin levels in amyloidosis cases can be considered less significant, with no need for a coronary angiogram to evaluate them. TTR and non-TTR have less CAD and no need for aggressive measures and evaluations. Therefore, time and resources would be saved by paying attention to the unique characteristics of this subset of patients [23]. Troponin sensitivity, specificity, and the appropriate setting for its measurement have continuously been evolving and reconsidered. Amyloidosis is another caveat for it [24,25].

Our study seems to be the first to evaluate the prevalence of CAD in the amyloidosis group, which is 23%. This number seems lower than expected in the 70 years old age group that harbors amyloidosis and does not follow that general population pattern.

## Conclusion

TTR and non-TTR amyloidosis have a CAD prevalence of around 23%. The type of amyloidosis does not impact the prevalence rate of CAD.

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