Chest pain and coronary artery disease in cardiac amyloidosis: Prevalence, mechanisms, and clinical implications

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ABSTRACT Amyloidosis is a systemic disease affecting multiple organs, and often presents with cardiac involvement, with 2 primary underlying pathologies: amyloid light chain- and transthyretin cardiac amyloidosis. Chest pain can occur in both types with variable clinical presentations. This narrative review describes the relationship between cardiac amyloidosis (CA) and chest pain. A PubMed search (June 03. 2024) identified 393 articles related to chest pain in CA. Twenty-eight studies, in English and with full text, were selected. Articles included were case reports, reviews, perfusion- and autopsy studies. In CA patients 10%-20% report chest pain as the initial symptom preceding the diagnosis, and the overall prevalence of chest pain is 38% of patients with CA and it is related to an increased risk of heart failure hospitalization. The mechanisms leading to chest pain in CA patients include increased left ventricular diastolic pressure, infiltration of amyloid fibrils inside and around coronary arteries, and amyloid compression of the microvasculature. The mechanisms commonly lead to elevations of plasma troponin levels, which are higher in amyloid patients with chest pain compared to amyloid patients without chest pain. Symptomatic treatment of chest pain can be challenging due to the low tolerability of medical therapy and poor outcomes of coronary interventions in alleviating the pain and with a higher rate of complications. Our review underscores the importance of recognizing chest pain as a CA symptom, particularly in the elderly. Persistent troponin elevation without coronary artery disease could indicate CA. Screening-based and longitudinal studies are crucial for understanding the relationship between chest pain and CA. Acknowledging the significance of chest pain in CA may facilitate early intervention and improve patient outcomes. (Am Heart J 2025;280:52–59.)

Background

Cardiac amyloidosis (CA) generally is a result of amyloid light chain amyloidosis (AL-CA) or transthyretin amyloidosis (ATTR-CA). CA is often diagnosed late, and the prognosis is poor.[1,2] Due to heightened awareness of the disease and advances in diagnostic methods, the prevalence of CA is higher than previously anticipated.[3] Symptomatology associated with CA often mimics those of other more common cardiac diseases with symptoms such as dyspnea, fatigue, edema, and dizziness. Additionally, extracardiac symptoms are common and typically involve tenosynovial manifestations, such as lumbar spinal stenosis, carpal tunnel syndrome, and spontaneous rupture of the bicep tendon.[4] Another important symptom is chest discomfort or -angina. Chest pain is previously reported in patients with CA[5] and it can be the initial symptom preceding CA diagnosis, but a consensus regarding its etiology and a systematic approach to evaluation or management has not been established. Elevations of troponin as a marker for myocardial injury are common in CA patients,[6–11] but the efficacy of coronary interventions are low and related with higher rate of complications from the procedure.[12,13] Early diagnosis of CA is essential, as treatment with disease-modifying drugs is more effective if started in earlier stages of the disease, leading to a better prognosis.[4] Furthermore, understanding the underlying mechanism of symptoms of CA is important from the patient's perspective as this may enable rational symptomatic treatment, which is significant in addition to disease-modifying treatment as the quality of life of patients with CA is significantly affected.[14]

In the following narrative review, we explore the relationship between chest pain and CA by describing the available information about pathophysiology and propose a diagnostic approach and management strategy.

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https://doi.org/10.1016/j.ahj.2024.11.004

Methods

We conducted a Pubmed search for articles related to chest pain in CA, with the search performed on June 03, 2024. The search string included the following:

> ("amyloidosis" OR "AL amyloidosis" OR "ATTR amyloidosis") AND ("chest pain" OR "thoracic pain" OR "heart pain" OR "cardiac pain" OR "ischemia" OR "angina" OR "angina pectoris" OR "coronary circulation")

We only included articles in the English language, and those with full-text availability, encompassing observational cohort studies, case reports, reviews, and studies reviewing autopsies.

Initially, the search yielded 393 articles. In total 28 studies were selected for inclusion which were comprised of studies followed by the search and their relevant references. The search and study collection were performed by N.N.

Prevalence of chest pain and coronary artery disease in cardiac amyloidosis

Prevalence of chest pain in cardiac amyloidosis

A report from 1984 [15] highlighted chest pain as an initial prodromal symptom in CA patients, and more sporadic case reports have subsequently described this phenomenon (Table 1).[16–26] Nine out of eleven case reports involved patients diagnosed with AL-CA, but more recent reports have described chest pain in patients with ATTR-CA.[24,25] A common feature is the delay in diagnosis, with some patients experiencing chest pain years before receiving a CA diagnosis, leading to severe adverse outcomes in certain cases [20,24,27] and 1 fatal outcome.[19] The overall number of CA patients who initially present with chest pain is reported to be 10%-20%.[28] A recent observational, retrospective study included a mixed population of 174 patients with ATTR-CA or AL-CA and reported a prevalence of chest pain in 38% of the population.[5] Conversely, a prospective study explored a population aged over 18 years (n = 43) experiencing chest pain without significant stenosis findings on coronary CT arteriogram (CTA), showed that 3 (7%) had a diagnosis of amyloidosis. All 3 cases were verified through endomyocardial biopsy. The study did not differentiate between types of amyloidosis.[29] A summary of findings regarding the prevalence of chest pain among patients with CA is presented in Table 2.

Prevalence of coronary artery disease in patients with cardiac amyloidosis

Among the included case reports presented in Table 1, only 2 out of 11 patients were diagnosed with significant obstruction of the coronary vessels after coronary angiography (CAG). In a larger retrospectively collected study, the prevalence of obstructive coronary artery disease (CAD) and its prognostic significance was explored in 133 ATTR-CA patients.[28] Overall, 72 patients underwent investigations for CAD, and 30 (42%) with a median age of 79 ± 7 years were found to have significant coronary obstruction. Another study reported obstructive CAD in 38% of ATTR-CA patients (14 out of 38), with an average age of 75 years (interquartile range: 71-80). In ATTRwt patients with suspicion of acute coronary syndrome (ACS), 53% had obstructive CAD.[5] In AL-CA, the prevalence was remarkedly lower as only 1 out of eleven (9%) with suspicion of ACS displayed obstructive CAD on CAG.[5] Overall data on CAD in patients with CA is sparse, and the available large clinical trials in CA did not report information on CAD at baseline.[9–11,30] A summary of findings regarding the prevalence of CAD among patients with CA is presented in Table 2.

Pathophysiology and mechanisms of ischemia and chest pain in CA

The leading etiology of symptoms of myocardial ischemia in CA patients is believed to be intramural microvascular amyloid fibril deposition leading to microvascular myocardial ischemia. This has predominantly been associated with AL-CA.[17,21,28,31] To explore the etiology of chest pain in CA patients, Mueller et al. examined autopsies from 11 patients with evidence of amyloid in the small intramural coronary arteries and this was associated with myocardial ischemic changes.[21] All patients had experienced angina pectoris, and angina was the primary symptom of 6 of the 11 patients. Up to 2-thirds of patients had significant intramural coronary amyloid deposits, many associated with microscopic focal changes of ischemic injury.[28,32] The fibrils can be found in all layers of the coronary arteries (intima, media, and adventitia), with the adventitia being more affected.[32] This widespread infiltration can lead to wall thickening and luminal stenosis, contributing to ischemic symptoms. In addition to amyloid deposition, increased left ventricular (LV) mass and elevated LV filling pressure may contribute to the ischemic pattern seen in CA.[33,34] This can be attributed to several underlying mechanisms. Increased wall thickness and diastolic dysfunction may lead to higher end-diastolic pressures, which in turn reduces coronary perfusion pressure. This reduction in perfusion pressure can result in decreased blood flow to the subendocardial layers, causing ischemic chest pain. This may imply an inverse relationship between coronary microvascular function and LV mass, as well as the link between increased diastolic filling pressures and subclinical systolic dysfunction.[33,34] Furthermore, imaging findings can suggest ischemic patterns in CA patients even without evident CAD.[33,34]

The mechanisms above disrupt normal vascular structures and can result in impaired perfusion leading to ischemic manifestations observed in these patients even without evident CAD. However, it is also important to note that CA patients can have coexisting CAD and the

Table 1. Case reports examining patients with cardiac amyloidosis experiencing chest pain

	Saltissi et al.	Ogawa et al.	Yamano et al.	Cantwell et al.	Whitaker et al.	George et al.	Singh et al.	Nguyen et al.	Tew et al.	Morgado et al.	Vaxman et al.
Year	1984	2001	2002	2002	2004	2015	2019	2020	2021	2021	2023
Type of [1]CA	AL	AL	AL	AL	AL	AL	ATTR	AL	AL	ATTR	AL
Age	32	69	76	43	65	75	69	72	53	64	63
Sex	Male	Female	Female	Male	Male	Male	Male	Male	Male	Male	Male
CAD	No	No	No	No	No	No	Yes	No	No	No	+ (CAG)
CAD risk factor	No	No	T2DM + HTN	T2DM	HC	No	T2DM, HTN and HC	No	No	HTN, dyslipidemia	Smoking + obesity
ECG	ST depr	AV block	Negative T wave	Negative T wave	ST depr	ST depr	AFLI	RBBB	Negative T wave	LBBB and AV block	+ (unspecific)
Troponin	NA	NA	NA	+	+	+	+	+	+	NA	-
CKMB	NA	NA	NA	+	NA	NA	NA	-	NA	NA	NA
BNP	NA	NA	NA	NA	NA	+	+	NA	NA	NA	+
Echocardiography											
1) Restrictive pattern	-	-	-	-	NA	-		+	+	NA	NA
2) Increased Wall thickness	+	-	-	-	NA	+	+	+	+	+	NA
3) Hypokinesis	-	-	-	-	NA	-	+	+	+	+	NA
4) Other findings		LVEF 38% and LVEDP 23 mmHg	Normal		Mild global LV dysfunction		Apical sparing pattern. Biatral enlargement			Biatrial enlargement and severe mitral and tricuspid insufficiency	
Histology											
1) Myocardium		+		+	-	NA	NA			+	NA
2) Endocardium		+			-	NA	NA			-	NA
3) Epicardial coronary arteries		-	-	-	-	NA	NA			-	NA
4) Intramural coronary arteries	+	+	+	+	+	NA	NA			-	NA

CA, Cardiac Amyloidosis; AL, Amyloid Light Chain; ATTR, Amyloid Transthyretin; CAD, Coronary artery disease; CAG, Coronary Angiography; T2DM, Type 2 Diabetes Mellitus; HC, Hypercholesterolemia; HTN, Hypertension; NA, Not Applicable; LVEF, Left Ventricular Ejection Fraction; LVEDP, Left Ventricular End Diastolic Pressure.

Table 2. Studies reporting the prevalence of Chest Pain and Coronary Artery Disease in Cardiac Amyloidosis

Category	Study type	Sample Size	Type of Amyloidosis	Prevalence and comments
Chest Pain in CA	Retrospective study (De Michieli et al., 2023)	174	ATTR-CA (n=104) and AL-CA (n=70)	38% of the patients experienced chest pain.
Chest Pain in CA	A prospective study (Palmisano et al., 2022)	43	ATTR-CA	7% had CA among 43 patients with initially suspected ACS (Assessed without significant stenosis on coronary CTA.
CAD in CA	Retrospective study (Hassan et al., 2023)	133 (72 assessed)	ATTR-CA	42% had CAD with a median age of 79±7 years
CAD in CA	Case reports with chest pain as initial symptom (Table 2)	11	ATTR-CA (n=9) and AL-CA (n=2)	18% had obstructive CAD (2 out of 11) distributed in 1 ATTR-CA and 1 AL-CA.
CAD in CA patients with ACS suspicion	Retrospective study (De Michieli et al., 2023)	49	ATTR-CA (n=38) and AL-CA (n=11)	The prevalence of CAD was 53% in ATTR-CA and 9% in AL-CA.

CA, cardiac amyloidosis; ATTR, amyloid transthyretin; AL, amyloid light chain; ACS, acute coronary syndrome; CTA, computed topography angiography; CAD, coronary artery disease.

Table 3. Key findings from studies investigating the pathophysiology of chest pain in patients with cardiac amyloidosis

Study	Key findings
Mueller et al.	Intramural amyloid deposits caused severe obstruction in eleven patients with AL amyloidosis, with minimal or no epicardial CAD.
Neben-Wittich et al.	Amyloid deposition was present in epicardial coronary arteries of 56/58 patients with AL amyloidosis without causing intraluminal obstruction, with the tunica adventitia and vasa vasorum most affected.
Yamano et al.	76-year-old female with chest pain, normal coronary angiography, later diagnosed with AL amyloidosis. Autopsy showed complete obstruction of intramural coronary arteries by amyloid deposits.
Wittich et al.	In 96 patients with AL amyloidosis and cardiac involvement, 63 (66%) had severe epicardial coronary artery narrowing due to amyloid deposits, with 54 (86%) showing microscopic evidence of myocardial ischemia.
Chacko et al.	In 93 CA patients (41 AL-CA, 52 ATTR) undergoing stress perfusion CMR, stress myocardial blood flow was significantly reduced compared to both obstructive and non-obstructiveCAD controls.
Dorbala et al.	In 21 CA patients without coronary artery disease, 57% showed an ischemic pattern on stress PET CT, while none of the 10 patients with left ventricular hypertrophy did. Both rest and stress mean blood flow were lower in CA patients. All patients had coronary artery disease excluded prior to the examination. Autopsies revealed perivascular amyloid burden in 5 out of 8 CA patients
Beyene et al.	In a retrospective study of 55 patients with heart failure with CA versus 55 patients without CA, the heart failure without CA group had more severe and diffuse coronary calcification.
De Michieli et al.	Analyzed biopsies from 10 CA patients with chest pain (5 AL-CA and 5 ATTR-CA) revealed significant CAD in 3 ATTR-CA patients. In 1 ATTR-CA patient (20%), amyloid vascular involvement was observed. Among AL-CA patients (all without significant CAD), 4 out of 5 (80%) showed vascular or perivascular amyloid deposition. For comparison, biopsies from 2 AL-CA patients without chest pain showed no signs of vascular or perivascular amyloid involvement.

AL, amyloid light-chain; CAD, coronary artery disease; CA, cardiac amyloidosis; ATTR, amyloid transthyretin; CMR, cardiac magnetic resonance
PET, positron emission tomography.

amyloid deposits may accelerate an existing CAD, and thereby worsen potential ischemic heart disease.[26,28,35] The possible mechanism leading to chest pain in patients with CA is presented in Figure 1. A summary of key findings from studies reporting the pathophysiological link between CA and chest pain is presented in Table 3.

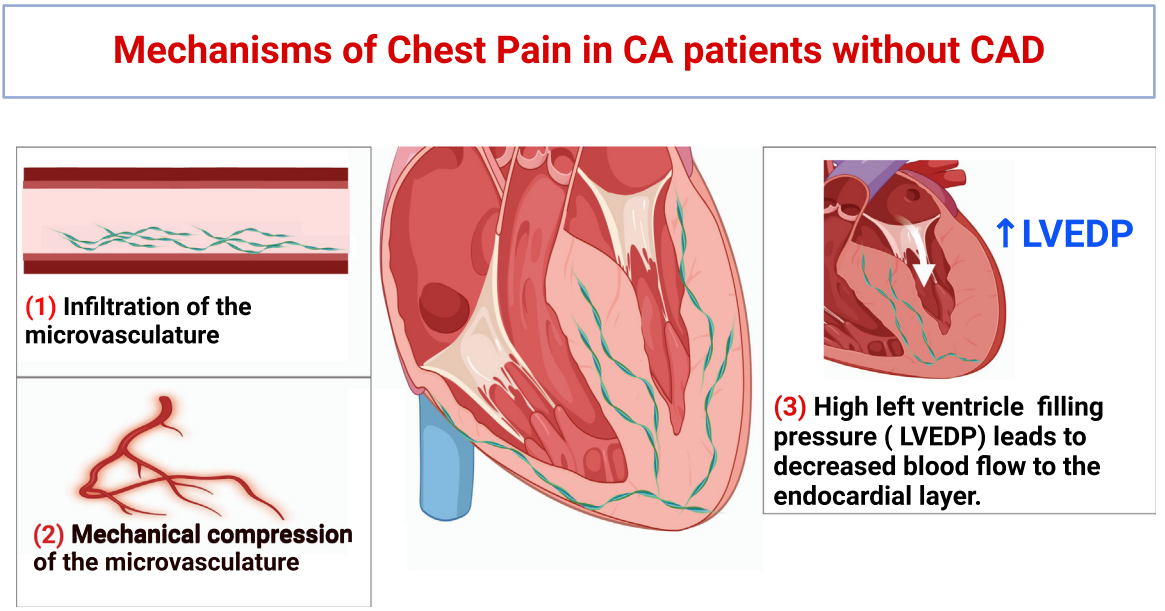
Biomarkers -Troponin, CKMB, and BNP in CA patients with chest pain

High prevalence and persistent elevated troponin levels in CA patients have been reported in the previous large landmark trials.[9,10,36]

In the case reports, troponin levels were elevated in 5 out of 6 cases with available measurements. In the study by De Michieli et al. the overall mean Troponin I level was 81 ng/L (IQ 41-159). In CA patients with chest pain, the mean level of Troponin I was 101 ng/L (IQ 45-219) while the level in non-chest pain CA patients was 65 ng/L (IQ 41-129). The difference was statistically significant, but it is important to recognize that levels were also above the normal range in patients without angina. In the study by Hassan et al., wtATTR patients (n = 116) displayed a mean level of Troponin T at 63 ng/L (IQ 49-92). When comparing ATTR-CA patients with and without concurrent CAD, patients with ATTR and CAD had higher overall mean Troponin T levels, but the difference was not statistically significant.[5]

In the included case reports (Table 1), only 2 subjects had measurements of creatine kinase-myoglobin binding (CKMB) where 1 patient had an elevated level, and the

Figure 1. Possible mechanisms of chest pain in patients with cardiac amyloidosis (Besides coronary artery disease). (A) Infiltration of amyloid fibrils within the microvasculature, leading to luminal stenosis. (B) Perivascular amyloid deposits compressing the coronary arteries, resulting in ischemic pain. (C) Elevated left ventricular end-diastolic pressure causing compression of the microvasculature in the subendocardial layers. Created in BioRender. Noory, N. (2024) https://BioRender.com/s23g545



other a normal value of CKMB.[5] In the study by Mueller et al., 4 out of the eleven AL-CA patients included had increased levels of serial creatine kinase associated with myocardial injury.[21] It is important to note that CKMB is sparsely reported in the literature in CA patients, and overall, it has limited sensitivity and specificity in diagnosing cardiac injury compared to Troponin.[37]

Among the included case reports (Table 1), brain natriuretic peptide (BNP) was measured in only 2 cases and was found to be elevated in both. In the cohort from Di Michieli et al.[5] the average BNP level in CA patients experiencing chest pain (n = 66) was 597 ng/L (IQ: 278-1675). This was significantly higher when compared to CA patients without chest pain, who had a mean level of BNP at 407 ng/L (IQ 203-653).

Diagnostic work up

As emphasized, chest pain is a common symptom in patients with CA.[5,22] In clinical experience, the chest discomfort in CA patients is not infrequently atypical angina, for instance presenting as sharp pain rather than oppression, but studies of pain quality and characteristics in this cohort are lacking. The presence is associated with an increased risk of heart failure hospitalization even after adjustment for types of CA and the presence of CAD. However, it is not associated with higher mortality.[5] More ATTRwt patients have co-existing CAD compared to AL-CA, and this may be due to their older age and the fact that the amyloid fibrils may accelerate coexisting CAD.[5,28]

This combination may challenge clinicians as perfusion imaging may not be reliable enough to exclude possible CAD, as it can also be abnormal in a high proportion of CA patients without CAD.[33,34] To finally exclude CAD in patients with CA and anginal-type chest pain, we therefore clearly suggest performing CAG or CTA.

Drug therapy and coronary revascularization

The high prevalence of chest pain and CAD findings in ATTRwt challenge clinical management, as usual, antiischemic treatment (i.e., calcium antagonists, nitrates, and beta blockers) is often not well tolerated in CA patients.[38]

Beta-blockers are used with caution in CA as poor tolerability has frequently been reported. A recent review including 4002 CA patients from 8 observational studies reported that beta blockers were prescribed in 53% of the patients but were discontinued by 26% due to adverse events (hypotension, bradycardia, and fatigue). The study analyzed the use of beta blockers and all-cause mortality but did not find any association.[39] This is in contrast with another recent study focusing on the tolerability and effectiveness of heart failure therapies in CA patients.[40] In this study, no associations were reported during follow-up regarding hospitalization and the use of beta-blockers. The study concluded that beta-blockers

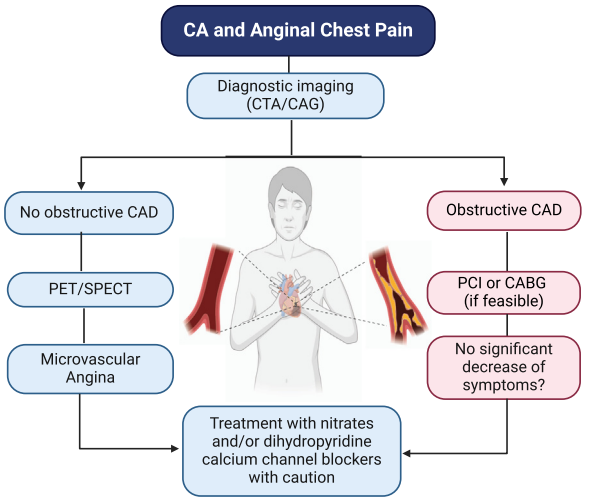
could be safely used but did not improve mortality or hospitalization. However, in a large cohort of ATTR-CM, low-dose beta-blockers have been reported to reduce mortality among patients with reduced ejection fraction (LVEF $\leq$ 40%).[41] Di Michieli et al.[5] reported that in 50 out of 66 cases with patients experiencing chest pain, the physicians prescribed more anti-ischemic medications (beta blockers or nitrates) compared to those without chest pain. The study did not report the tolerability and efficacy of the drugs. Percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) are commonly performed coronary intervention followed evident coronary artery disease, but outcomes after the procedure in patients with CA are sparse. Patients with concomitant CA and ST-elevation myocardial infarction (STEMI) have a higher risk of cardiovascular and renal complications, including cardiogenic shock, dialysis requiring acute kidney injury, and post-PCI bleeding compared to CA patients without STEMI. Neither coronary angiography, CABG nor PCI showed significant improvement in mortality in STEMI patients versus non-STEMI patients after adjustments for baseline comorbidities.[12] As the study was based on administrative registries, no information about the potential decrease in symptom burden was obtained.

Additionally, when compared to patients with other infiltrative or storage diseases (hemochromatosis and sarcoidosis), amyloidosis has the poorest outcome after percutaneous coronary intervention with an increased risk of stroke, major bleeding, and mortality.[13]

Suggestion of management strategy of chest pain and CAD in CA

Before any intervention, patients should be thoroughly informed about potential adverse events, side effects of medical therapy, and the general poot outcomes associated with coronary interventions. In general, patients with CA and typical anginal type chest pain should undergo CT angiography or CAG and be offered PCI if feasible, particularly because anti-anginal treatments may be poorly tolerated. A PET or SPECT scan may be performed if no obstructive CAD is found to determine if microvascular dysfunction is causing the symptoms. If perfusion abnormalities suggest microvascular angina, we recommend cautious treatment with nitrates, and dihydropyridine calcium channel blockers should be considered. In AL-CA, special caution is advised when using dihydropyridine calcium channel blockers as they carry a risk of inducing bradycardia and exerting negative inotropic effects.[42] Ranolazine has shown potential in relieving anginal pain without significantly impacting heart rate, blood pressure or myocardial perfusion and might be useful in patients with microvascular angina.[43] However, data there is a limited data on its efficacy and tolerability in CA patients. Verapamil and diltiazem have no role in the treatment regimen of CA patients and should be avoided, especially in AL-CA. An overview of management in patients with CA experiencing chest pain is presented in Figure 2.

Figure 2. The figure displays recommendations for managing patients who experience chest discomfort or chest pain alongside a diagnosis of cardiac amyloidosis. Created in BioRender. Noory, N. (2024) https://BioRender.com/z36r786



Gaps in evidence

Studies so far focusing on chest pain in CA patients have been restricted to case reports or retrospective cohorts. Prospectively collected studies with a focus on chest pain preceding CA diagnosis as well as studies to understand the interplay between CAD and CA are highly warranted. Patients with ATTRwt and AL-CA experiencing chest pain seem to have significant differences in the prevalence of CAD and histological studies of larger samples are highly warranted to explore this phenomenon. Apart from case reports, only registry-based studies exist on the outcomes of coronary interventions, and studies on the efficacy of anti-anginal treatments in CA are lacking. Prospective studies are needed to establish and provide evidence for treatment efficacy and safety of both medical therapies and coronary interventions in this population.

Conclusions

Chest pain in patients with CA is frequent and associated with increased heart failure hospitalization, but not mortality. The tolerability of anti-ischemic treatment remains unclear, and CA patients have poor outcomes after coronary interventions. CAD is more prevalent among ATTRwt patients compared to AL-CA. However,

the pathophysiological significance of CAD in patients with ATTRwt remains unclear.

Conflict of interest

Mathew Maurer reports grant support from NIH R01HL139671 and AG081582 and grants from Alnylam, BridgeBio, Attralus, Intellia, and Ionis; and personal fees from Alnylam, Novo-Nordisk, Roche, Prothena Astra Zeneca, and Intellia.

FG: Personal fees from Alnylam, Ionis, Astra-Zeneca, Bayer, Novartis, Abbott.

OW: Independent research grant from Pfizer, advisory board for Astra-Zeneca.

NN: Supported by an independent research grant from "Erik og Susanna Olesens Almenvelgørende Fond".

No extramural funding was used to support this work. The remaining authors have nothing to disclose.

The authors are solely responsible for the drafting and editing of the paper and its final contents.

CRediT authorship contribution statement

Navid Noory: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Oscar Westin:** Writing – review & editing, Methodology. **Mathew S. Maurer:** Writing – review & editing, Supervision, Methodology. **Emil Fosbøl:** Writing – review & editing, Supervision, Conceptualization. **Finn Gustafsson:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

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