

Evaluation of the cardiac amyloidosis clinical pathway implementation: a real-world experience

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Aims

The aim of this study is to evaluate the implementation of the cardiac amyloidosis (CA) clinical pathway on awareness among referring cardiologists, diagnostic delay, and severity of CA at diagnosis.

Methods and results

Patients with CA were retrospectively included in this study and divided into two periods: pre-implementation of the CA clinical pathway (2007–18; T1) and post-implementation (2019–20; T2). Patients' and disease characteristics were extracted from electronic health records and compared. In total, 113 patients (mean age 67.8 ± 8.5 years, 26% female) were diagnosed with CA [T1 (2007–18): 56; T2 (2019–20): 57]. The number of CA diagnoses per year has increased over time. Reasons for referral changed over time, with increased awareness of right ventricular hypertrophy (9% in T1 vs. 36% in T2) and unexplained heart failure with preserved ejection fraction (22% in T1 vs. 38% in T2). Comparing T1 with T2, the diagnostic delay also improved (14 vs. 8 months, $P < 0.01$), New York Heart Association Class III (45% vs. 23%, $P = 0.03$), and advanced CA stage (MAYO/Gillmore Stage III/IV; 61% vs. 33%, $P \leq 0.01$) at time of diagnosis decreased.

Conclusion

After implementation of the CA clinical pathway, the awareness among referring cardiologists improved, diagnostic delay was decreased, and patients had less severe CA at diagnosis. Further studies are warranted to assess the prognostic impact of CA clinical pathway implementation.

Keywords

Cardiac amyloidosis • Clinical pathway • Transthyretin • Light chain amyloid

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Introduction

Cardiac amyloidosis (CA) is a progressive, life-threatening disease, caused by the deposition of amyloid fibrils in the heart. In the majority of patients, two main precursor proteins are responsible for the deposition of amyloid fibrils. First, amyloid light (AL) chain amyloidosis, is caused by immunoglobulin light chain (kappa or lambda) overproduction by plasma cells.¹ Second, deposition of amyloid transthyretin (ATTR) amyloidosis is caused by a hereditary pathogenic variant in the TTR gene (ATTRv) or by wild-type TTR (ATTRwt) as a consequence of ageing.² Survival depends on the disease stage at diagnosis, and in patients with very advanced heart failure, the median survival for AL-CA is 6–12 months.³ For ATTR-CA, median survival is 2–6 years, although these numbers are based on data before the introduction of disease-modifying drugs.⁴

In recent years, several novel treatment options have become available, including TTR stabilizers and TTR gene silencing approaches for ATTR-CA.² Moreover, the treatment for AL-CA has improved significantly over the past decade.⁵ One disease-modifying treatment has been shown to improve outcomes, and a number of others are currently under investigation in Phase 3 trials (NCT03860935; NCT04153149; NCT03997383; NCT04136171).^{2,5} Nevertheless, the treatment for both ATTR-CA and AL-CA is, unsurprisingly, most beneficial in patients with early stages of CA, illustrating the importance of early diagnosis. Unfortunately, the diagnosis of CA is often delayed.^{6,7} Reasons for delayed diagnosis are unawareness of CA, misconception regarding diagnosis, the heterogenic and multi-systematic nature of CA, and/or non-specific symptoms in the early stages of CA.^{1,8}

To facilitate early diagnostic and effectively treat and support patients in our region, a multidisciplinary CA clinical pathway was introduced in the Amyloidosis Expertise Center Utrecht. The aim of this study is to evaluate the CA clinical pathway implementation on awareness among referring cardiologists, diagnostic delay, and severity of CA at diagnosis.

Methods

Study population

In this single-centre retrospective study, all patients from 2007 until 2020 referred to our university medical centre and who were diagnosed with CA were included. All participants provided written informed consent. The study was approved by the medical ethics committee of the University Medical Center Utrecht (non-WMO 19/222) and conducted in accordance with the Declaration of Helsinki. Patients' characteristics and clinical data were extracted from electronic health records. Final diagnosis of AL-CA was established if echocardiographic and cardiac magnetic resonance (CMR) criteria were present and systemic AL amyloidosis was confirmed by positive Congo red staining of abdominal fat pad/targeted organ biopsy, further demonstrated by positive immunohistochemistry for kappa or lambda light chain and negative staining for TTR. For ATTR-CA, final diagnosis was established by positive bone scintigraphy (Grade II or III) in the absence of laboratory evidence a plasma cell dyscrasia. Endomyocardial biopsy was only performed if a non-invasive diagnosis of ATTR-CA could not be established, demonstrated by positive Congo red and TTR staining according to current guidelines.⁹

Implementation of the pathway

Cardiac amyloidosis requires interdisciplinary input and collaboration to accurately diagnose and effectively treat and support patients.¹⁰ In order to achieve this, we developed a multidisciplinary CA clinical pathway in our Amyloidosis Expertise Center, Utrecht. This pathway was implemented in 2018, the same year in which our centre was recognized as national Amyloidosis Expertise Center. The Amyloidosis Expertise Center Utrecht is one of the two national amyloidosis expertise centres in the Netherlands.

The pathway was implemented between June 2018 and December 2018 using a three-phase framework (grounded in the Knowledge-to-Action framework and ADAPTE Collaboration methodology for guideline adaptation) to support pathway development and dissemination.¹¹ This included: (i) facilitating clinical owner and stakeholder engagement, (ii) developing a protocol on diagnosis, treatment, and follow-up based on existing literature, and (iii) developing a plan for dissemination and impact assessment. More information on the clinical pathway is shown in the [Supplementary material online, Text S1](#).

Assessment of the clinical pathway

The clinical pathway was evaluated by comparing the period before (2007–18; T1) and after implementation (2019–20; T2) on awareness of referring physicians, diagnostic delay, and severity of CA.

Awareness of physicians was measured by the number of patients referred by cardiologist, the number of patients referred with cardiac signs suspected of CA and the total number of patients with CA. The rationale behind these measurements is that, with a relatively stable number of patients with CA in the general population, increasing awareness will result in an increasing amount of referrals to our Amyloidosis Expertise Center, thereby leading to more patients diagnosed with CA.

Parameters leading to the suspicion of CA were extracted from the referral letters based on current guidelines,⁴ which included: unexplained left ventricular hypertrophy, defined as interventricular septal (IVS) thickness or left ventricular posterior thickness ≥ 12 mm, with at least one of the following cardiac characteristics: (i) heart failure with preserved ejection fraction (HFpEF) in patients aged ≥ 65 years, (ii) right ventricular hypertrophy (RVH), (iii) aortic stenosis in patients aged ≥ 65 years, and electrocardiogram abnormalities including (iv) decreased QRS voltage, (v) pseudo Q waves on electrocardiogram, and (vi) atrioventricular block.

Diagnostic delay was defined as the time in months between the first cardiac symptoms and the final diagnosis of CA. The severity of CA was subdivided into New York Heart Association (NYHA) class at diagnosis, CA stage at diagnosis, and wall thickness measured by transthoracic echocardiography. Depending on the type of CA, different staging criteria were used. For AL-CA the MAYO-criteria were used and for ATTR-CA the Gillmore criteria.^{3,12} As left ventricular wall thickness increases with progression of CA, echocardiographic data were collected. The wall thickness was divided into IVS thickness and left ventricular posterior wall (LVPW) thickness.

Statistics

For descriptive statistics, patients were stratified by total patients included, T1 or T2. Nominal variables were expressed as number and percentage. Continuous variables were expressed as mean \pm standard deviation (SD) for normally distributed variables and median [interquartile range (IQR)] if not normally distributed. Statistical analyses to compare dichotomous variables were performed by chi-square or, in case of small numbers (i.e. <5), the Fisher's exact test. For comparison of continuous variables, a t-test or, if not normally distributed, a Mann–Whitney U test was carried out. A *P*-value <0.05 was considered statistically

significant. Data were extracted to IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA) for statistical analysis.

Results

Patient population

A total of 113 patients were diagnosed with CA between 2007 and 2020 at the Amyloidosis Expertise Center Utrecht, of which 56 patients were diagnosed in T1 (2007–18) and 57 patients in T2 (2019–20). AL-CA was diagnosed in 70/113 (62%) patients, consisting of 44 patients (79%) in T1 and 26 patients (44%) in T2. The number of ATTR-CA patients increased over time from 12 patients (22%) in T1 to 31 patients (54%) in T2 (Figure 1). As shown in Table 1, mean age was 67.8 ± 8.5 years in the total CA population, 75% were male. As expected, patients with ATTR-CA were generally older (73.0 ± 6.0 years vs. 64.6 ± 8.3) and were more often male (86% vs. 66%) compared to patients with AL-CA.

Half of the patients had a preserved ejection fraction [left ventricular ejection fraction (LVEF) at least 50%], a mildly reduced ejection fraction (LVEF 41–49%) was seen in 24%, an ejection fraction <40% (HFrEF) was seen in 29 (26%) patients. In 44 patients (39%), one or more guideline-directed heart failure drugs were prescribed.¹³ Diuretics were prescribed the most (59%), followed by mineralocorticoid receptor antagonists (39%) and, beta blockade (34%). Anticoagulants were prescribed in almost half of the CA patients, which did not change over time. Before the correct diagnosis was established, 52 patients (46%) consulted more than two different physicians.

Implementation of the clinical pathway

Awareness

After implementation of the clinical pathway, an increase of patients diagnosed with CA at the Amyloidosis Expertise Center was

observed (Figure 1), rising from an average of 5 patients/year (T1) to 28 patients/year (T2). Ninety-three percent of the patients lived within a radius of 70 km of the expertise centre. As expected, the use of endomyocardial biopsy as a diagnostic test for ATTR-CA decreased over time, the use of bone scintigraphy increased (Table 1). The most important reasons for referral are summarized in Supplementary material online, Figure S1A and B. In total, 79 patients (70%) were referred by cardiologists, which showed an increase in T2 (T1: 50% vs. T2: 68%, $P < 0.05$). The remaining 34 patients (30%) had mainly non-cardiac symptoms at presentation, and amyloidosis was diagnosed by a haematologist (66%), neurologist (18%), nephrologist (12%), or gastroenterologists (4%). These patients were referred to our centre for screening of cardiac involvement. There was no difference in percentages of patients presenting with non-cardiac symptoms before and after the implementation of the clinical pathway (T1: 32% vs. T2: 27%).

After implementation of the clinical pathway, the referring cardiologist more often reported at least one cardiac sign in the referral letter compared to post-implementation [T1: 22 (39%) vs. T2: 37 (65%)]. Especially RVH [T1: 5 (9%) vs. T2: 20 (36%)] and patients ≥ 65 years with a preserved ejection fraction [T1: 5 (15%) vs. T2: 14 (37%)]. Surprisingly, in none of the 95 patients ≥ 65 years, aortic stenosis was reported as reason for referral.

Diagnostic delay

Compared to T1, diagnostic delay decreased by 6 months at T2 after clinical pathway implementation ($P < 0.01$), illustrated by a change in diagnostic delay from 14 months (IQR 6–24) to 8 months (IQR 4–11) (Figure 2A). Interestingly, the decrease in median diagnostic delay was most notable in patients with ATTR-CA [T2: 8 months (IQR 4–13) vs. T1: 18 months (IQR 7–36); $P \leq 0.01$] (Figure 2B). In patients with AL-CA, median diagnostic delay decreased with 5 months [T2: 6 (IQR 3–9) vs. T1: 11 months (IQR 6–19); $P \leq 0.01$] (Figure 2B).

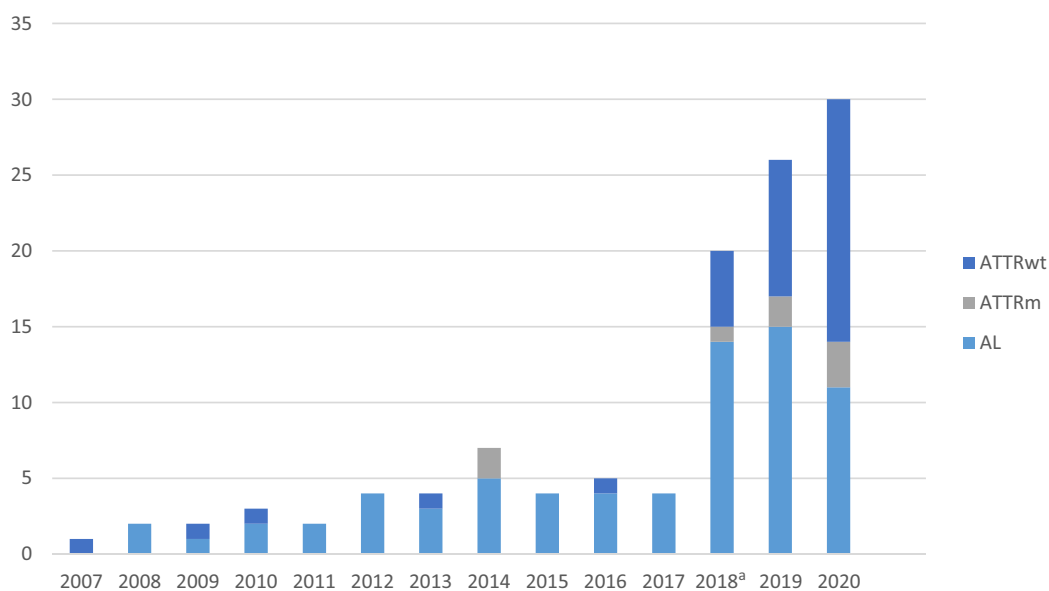


Figure 1 Number of patients diagnosed per year. ^aIn June 2018, the cardiac amyloidosis clinical pathway was implemented. In August 2018, the ATTR-ACT study was published.

Table 1 Baseline characteristics of patients with cardiac amyloidosis, diagnosed between 2007–18 vs. 2019–21 (n = 113)

	Total (n = 113)	Diagnosed 2007–8 (n = 56)	Diagnosed 2019–20 (n = 57)
Demographics			
Mean age in years ± SD	67.8 ± 8.5	66.4 ± 8.7	69.3 ± 8.0
Male sex, n (%)	85 (75)	39 (64)	46 (87)
Comorbidities			
Hypertension, n (%)	37 (33)	18 (30)	19 (35)
COPD or asthma, n (%)	11 (10)	4 (7)	7 (13)
Diabetes mellitus, n (%)	9 (8)	4 (7)	5 (9)
Amyloidosis non-cardiac symptoms			
Carpal tunnel syndrome, n (%)	26 (23)	13 (22)	13 (24)
Polyneuropathy, n (%)	20 (18)	8 (14)	12 (22)
Orthostatic hypotension, n (%)	20 (18)	11 (19)	9 (17)
Syncope/dizziness, n (%)	43 (38)	22 (37)	21 (39)
Gastrointestinal problems, n (%)	26 (23)	16 (27)	10 (18)
Unexplained weight loss, n (%)	21 (18)	14 (24)	7 (13)
Cardiac history			
Atrial fibrillation, n (%)	36 (32)	17 (29)	19 (35)
Acute coronary syndrome, n (%)	15 (13)	5 (8)	10 (18)
Angina, n (%)	45 (40)	24 (41)	21 (39)
History of cardiac interventions			
Pacemaker implantation, n (%)	9 (8)	3 (5)	6 (11)
ICD or CRTD implantation, n (%)	6 (5)	4 (7)	2 (4)
Cardiac ablation, n (%)	5 (4)	2 (3)	3 (6)
Cardiac surgery, n (%)	6 (5)	2 (3)	4 (7)
PCI, n (%)	8 (7)	2 (3)	6 (11)
Echocardiography			
Left ventricular hypertrophy, n (%)	113 (100)	56 (100)	57 (100)
Left and right ventricular hypertrophy, n (%)	75 (66)	37 (63)	38 (70)
LVEF <40%	29 (26)	17 (30)	12 (21)
LVEF 40–49%	26 (23)	10 (18)	16 (28)
LVEF ≥50%	58 (51)	29 (52)	29 (51)
Median IVS thickness in mm (25th–75th percentiles)	15 (14–18)	16 (14–19)	15 (14–17)
Median LVPW thickness in mm (25th–75th percentiles)	15 (14–18)	16 (14–18)	14 (13–16)
Electrocardiogram			
Low voltages ECG, n (%)	48 (42)	28 (47)	20 (38)
Atrioventricular block, n (%)	23 (20)	12 (20)	11 (21)
Bundle branch block, n (%)	19 (17)	14 (24)	5 (9)
Laboratory results			
Median Troponine µg/L (25th–75th percentiles)	0.05 (0.03–0.11)	0.06 (0.03–0.15)	0.05 (0.03–0.11)
Natriuretic peptides			
Median NT-proBNP ^a pg/mL (25th–75th percentiles)	3259 (1797–6780)	3365 (2940–8805)	3115 (1765–5792)
Median BNP ^a pmol/L (25th–75th percentiles)	119 (78–285)	133 (86–345)	83 (38–114)
Symptoms of heart failure			
Dyspnoea, n (%)	83 (73)	47 (80)	36 (67)
Oedema, n (%)	51 (45)	28 (47)	23 (43)
Tiredness, n (%)	70 (62)	44 (75)	26 (48)
Medication			
Loop diuretics, n (%)	67 (59)	35 (59)	32 (59)
Mineralocorticoid receptor antagonist, n (%)	44 (39)	21 (35)	23 (42)
ACE inhibitor, n (%)	25 (22)	16 (27)	9 (17)
Angiotensin II receptor blocker, n (%)	9 (8)	6 (10)	3 (6)
Beta blocker, n (%)	38 (34)	20 (34)	18 (33)
Anticoagulants, n (%)	52 (46)	26 (42)	26 (48)
Statins, n (%)	32 (28)	15 (25)	17 (31)

Continued

Table 1 Continued

	Total (n = 113)	Diagnosed 2007–8 (n = 56)	Diagnosed 2019–20 (n = 57)
Diagnostic tests			
Endomyocardial biopsy	22 (19)	20 (36)	2 (3)
Bone scintigraphy	41 (36)	6 (11)	35 (61)

ACE, angiotensin-converting enzyme; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; LVPW, left ventricular posterior wall; IVS, interventricular septal; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PCI, percutaneous coronary intervention.

^aTwenty-nine percentage of BNP values and 71% NT-proBNP values.

Severity of cardiac amyloidosis

Severity of CA at diagnosis improved considerably over time, as measured by NYHA class and CA stage (Figure 3A and B). At T2, the percentage of patients with NYHA Class III symptoms at diagnosis was lower compared with T1 (45% vs. 23%; $P = 0.03$). A similar trend was seen when looking at CA disease stage at diagnosis, showing a lower number of patients with advanced disease at T2 (MAYO/Gillmore Stage III or IV; 33% vs. 61%; $P < 0.01$). In line with NYHA class and CA disease stage, wall thickness at diagnosis also improved after the clinical pathway implementation at T2 (Table 1, Supplementary material online, Figure S2A–D). In ATTR-CA patients, IVS thickness decreased from 20 mm (IQR: 18–22) in T1 to 15 mm (IQR: 15–18) in T2, which was also seen for LVPW thickness [T1: 18 (IQR: 17–20) vs. T2: 15 (IQR 13–17)] (Supplementary material online, Figure S2B and D). In AL-CA patients, IVS thickness decreased from 18 mm (IQR: 17–20) to 14 mm (IQR 13–16), and for LVPW thickness from 15 mm (IQR 14–18) to 14 mm (IQR: 13–15) (Supplementary material online, Figure S2B and D). Although not statistically significant, the amount of patients with a severely reduced ejection fraction at diagnosis decreased post-implementation (30% vs. 21%; $P = 0.28$).

Discussion

With the implementation of the CA clinical pathway, a positive impact was seen on awareness among Dutch cardiologists, diagnostic delay, and severity of CA (Figure 4). Importantly, an increase in the total amount of patients diagnosed with CA at the Amyloidosis Expertise Center was observed (5 vs. 28 patients/year) and cardiac signs for suspicion of CA were more often reported as the reason for referral. In parallel, diagnostic delay decreased by 6 months, which is the largest decrease in ATTR-CA patients (10 months). Furthermore, disease severity was reduced leading to less patients presenting with NYHA Class III at diagnosis (45% vs. 23%) and less patients with an advanced disease stage (MAYO/Gillmore Stage III or IV; 33% vs. 61%). In line with these observations, wall thickness at diagnosis also improved post-implementation.

Although awareness of CA has increased among Dutch cardiologists, aortic stenosis in patients aged ≥ 65 years was underrepresented. It is well known that ATTR-CA is associated with aortic stenosis ($\sim 10\%$), especially in male patients aged > 70 years.¹⁴ This is particularly interesting considering the fact that more and more elderly patients undergo (percutaneous) intervention on the aortic

valve, which suffers from many comorbidities. It remains to be seen whether outcome in patients with and without underlying ATTR-CA will be different, although it was recently suggested that prognosis is similar in both patient groups.¹⁴ As CA shares several signs and symptoms with severe aortic stenosis, it is of clinical importance to identify the presence of a concomitant CA.^{15,16} Therefore, CA diagnosis might be further increased when aortic stenosis patients are actively screened in the future, which is currently under investigation in several trials (NCT04899180, NCT04869631, NCT04061213).

In this study, 51% of the CA patients presented with a preserved ejection fraction, and 26% of the patients with a severely reduced ejection fraction. The observed number of patients with a reduced ejection fraction is lower than in a previous study where approximately one-third of the patients presented with reduced ejection fraction.¹⁷ Based on our data, this could well be explained by the improvement in CA disease severity. After implementation of the clinical pathway, patients presented with a less severe CA stage (CA Stage I–II: T1: 39% vs. T2: 67%).

Previous studies on diagnostic delay included CA patients diagnosed before 2018 and did not describe diagnostic delay separately per year.^{7,18–22} Therefore, we could not compare our findings directly with other studies. However, it is known that the reasons for diagnostic delay are multifactorial and include symptom overlap with other conditions, low disease awareness, the historical need for invasive diagnosis in ATTR-CA, and until recently, the lack of a disease-modifying treatment in ATTR-CA.⁶ A recent simplified, diagnostic non-invasive algorithm for ATTR-CA may have the potential to increase disease awareness and reduce the diagnostic delay.^{12,23} Nevertheless, there is evidence that uptake of new methods for the diagnosis of CA is slow outside expertise centres.⁶ An analysis from the Transthyretin Amyloidosis Outcomes Survey (THAOS) found that despite the rising use of scintigraphy in diagnosis, half of ATTR wild-type CA patients experienced diagnostic delay > 4.7 years.²⁴ The observed improvement in diagnostic delay in our study, may partly be explained by the new drug treatment in ATTR-CA launched in 2018, leading to an increase in scientific papers, presentations on (inter)national congresses, revision of diagnostic algorithms and the help of pharmaceutical industry with flyers and symposia.^{23,25} As CA in general, including AL-CA, was in the spotlights, this probably also contributed to an improvement in the diagnostic delay. However, it is known that there is a gap between clinical science and clinical practice.²⁶ For example, with an estimated 7619

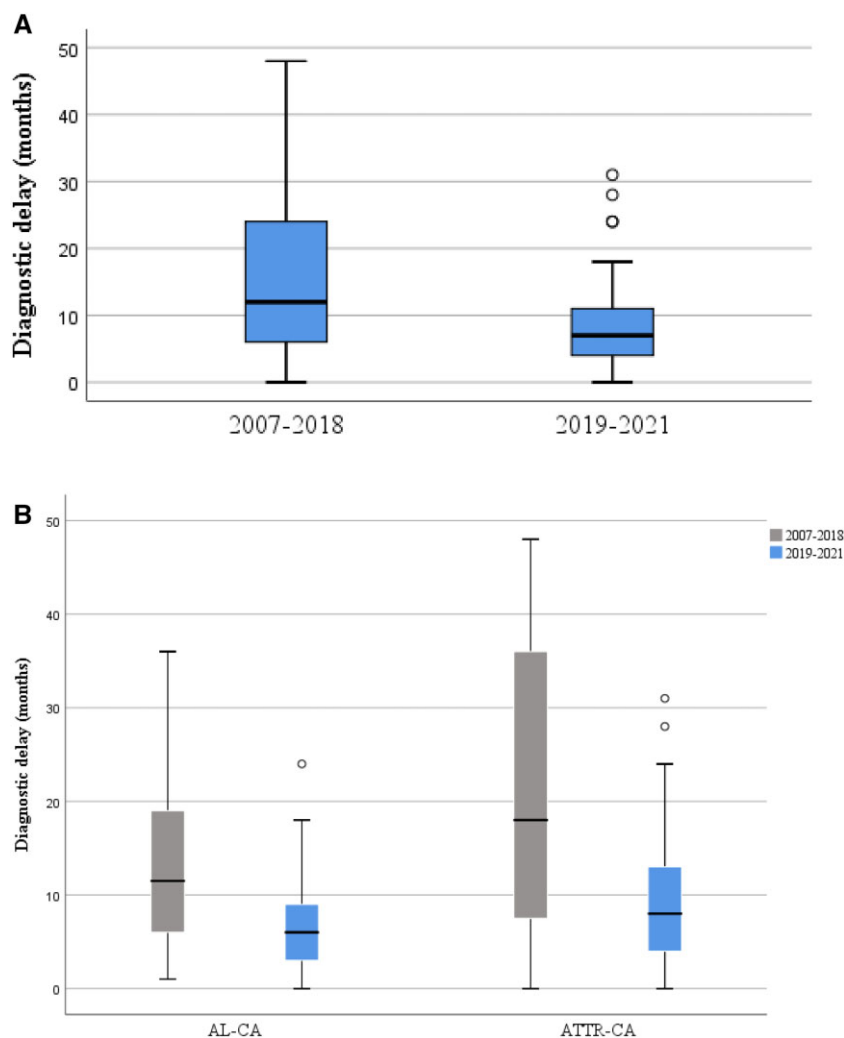


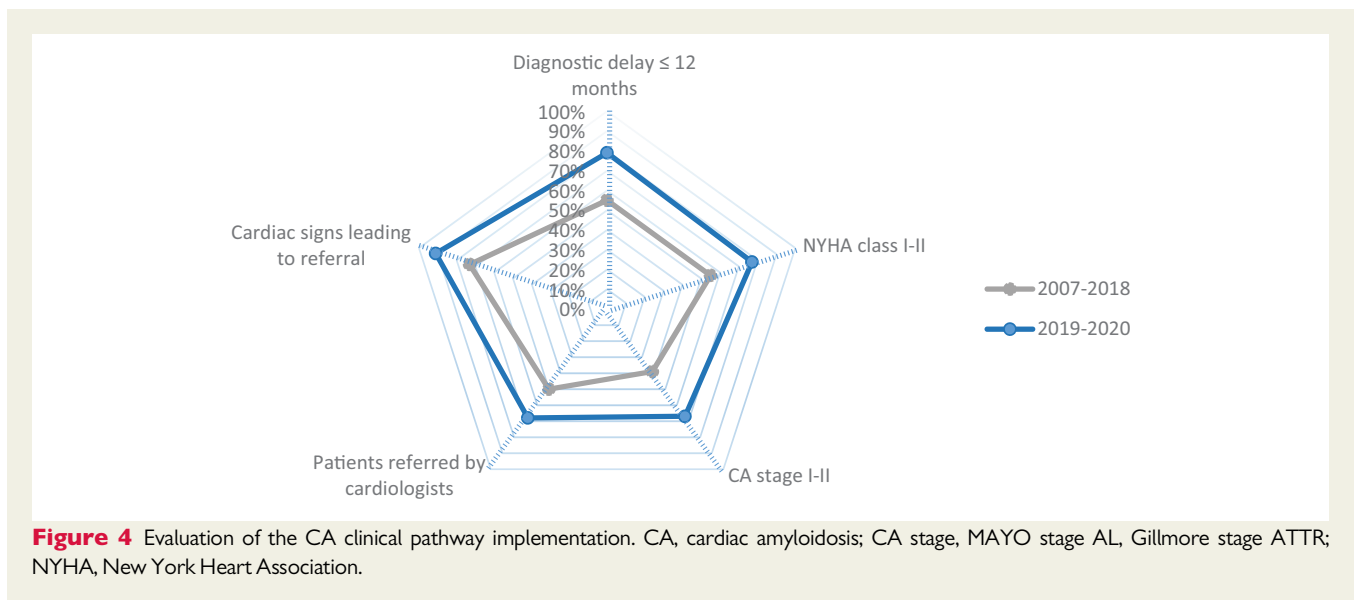
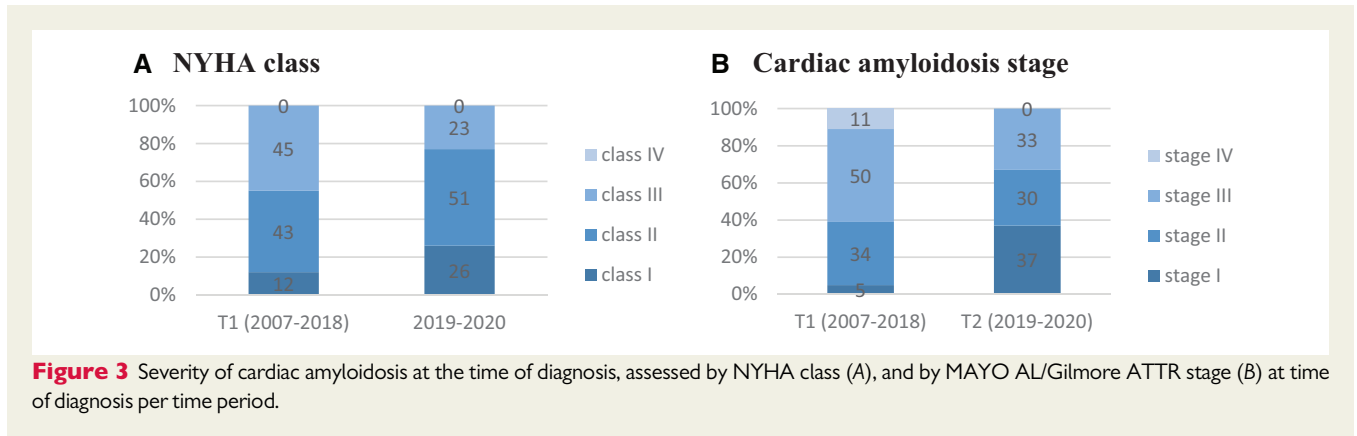
Figure 2 Diagnostic delay (in months), comparing T1 and T2 in all cardiac amyloidosis patients (A) and in AL-CA and ATTR-CA separately (B).

hits on heart failure articles in English published per year between 2017 and 2019 on PubMed, and global scientific output doubling every 9 years,²⁷ it cannot be assumed that this vast research knowledge will automatically result in improvements in clinical practice that will benefit patients. In 2020, the 2016 European guideline on acute and chronic heart failure was still not fully adopted into daily practice when looking at the number of prescribed heart failure medication.²⁸ Therefore, the observed improvement in awareness, diagnostic delay and severity will not be solely explained by the increase in scientific output. The implementation of the clinical pathway has contributed to faster implementation of scientific knowledge in CA in our expertise centre, resulting in the growing number of diagnoses, referrals, and reduction in the often very delayed time to treatment initiation in CA patients. As >90% of the referring hospitals are within a radius of 70 km, this can be considered as a regional effect seen after pathway implementation including dissemination of disease-specific knowledge and (regional) education.

In line with a previous study on diagnostic delay, the NYHA class at diagnosis was lower in patients with a shorter diagnostic delay.²⁰ Whether clinical pathway implementation improves patient prognosis, will be a subject of interest in the future, as T2 was completed very recently. However, an effect on prognosis is likely given the observed improvement in diagnostic delay after pathway implementation as disease stage at diagnosis is the most important predictor of prognosis. Similar to the recently published London survival data, an increase in the number of CA cases reflects greater awareness and earlier recognition.²⁹ Especially in light of the recently published long-term tafamidis efficacy data, earlier recognition (i.e. symptoms <NYHA III) will lead to a survival benefit compared to >NYHA II as disease-modifying therapy can be initiated.³⁰

Study limitations

A gold standard for the development of clinical pathways does not exist. Therefore, the framework proposed by Flores *et al.*



2019¹¹ was used as a guideline for the development which fitted well into our daily practise. The time difference might have influenced both the structural and functional parameters obtained by echocardiography. Therefore, we used both echocardiographic parameters (wall thickness, ejection fraction) and non-echocardiographic parameters (NYHA class, CA staging) to assess CA severity.

As the current retrospective observational study could not investigate a direct causal relationship between the increased number of referrals and implementation of the clinical pathway, other factors may also have played a role. As CA has been in the spotlights recently, this probably contributed to an improvement in referrals. However, it is known that it takes years to implement results from randomized clinical trials (i.e. tafamidis treatment based on the ATTR-ACT study³¹) for which clinical pathways can function as a catalyser. This is further supported by the fact that we clearly observed improvement in NYHA class and disease stage, next to an

increased number of referrals, and mainly from referring centres within our own region.

Conclusion

After implementation of the CA clinical pathway a positive effect on awareness among cardiologists, diagnostic delay, severity of CA at diagnosis was observed. Further studies are warranted to assess the prognostic impact of CA clinical pathway implementation, although a survival benefit seems likely given the increasing therapeutic opportunities when diagnosed in an early stage.

Data availability

The data used to support the findings of this study are available from the corresponding author upon any reasonable request.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Lead author biography



Maaïke Brons, RN, MSc, earned a Master of Science in Nursing from the University of Utrecht, The Netherlands. She is a nurse scientist and business analyst at the Department of Cardiology at the University Medical Center Utrecht and she is currently completing her PhD at this department. Her research interests include disease management programmes and clinical pathways in cardiology and eHealth in cardiology.

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