Wild-type transthyretin amyloid cardiomyopathy (ATTRwt CM) is a more common disease than previously thought. Awareness of ATTRwt CM and its diagnosis has been challenged by its unspecific and widely distributed clinical manifestations and traditionally invasive diagnostic tools. Recent advances in echocardiography and cardiac magnetic resonance (CMR), non-invasive diagnosis by bone scintigraphy, and the development of disease-modifying treatments have resulted in an increased interest, reflected in multiple publications especially during the last decade. To get an overview of the scientific knowledge and gaps related to patient entry, suspicion, diagnosis, and systematic screening of ATTRwt CM, we developed a framework to systematically map the available evidence of (i) when to suspect ATTRwt CM in a patient, (ii) how to diagnose the disease, and (iii) which at-risk populations to screen for ATTRwt CM. Articles published between 2010 and August 2021 containing part of or a full diagnostic pathway for ATTRwt CM were included. From these articles, data for patient entry, suspicion, diagnosis, and screening were extracted, as were key study design and results from the original studies referred to. A total of 50 articles met the inclusion criteria. Of these, five were position statements from academic societies, while one was a clinical guideline. Three articles discussed the importance of primary care providers in terms of patient entry, while the remaining articles had the cardiovascular setting as point of departure. The most frequently mentioned suspicion criteria were ventricular wall thickening (44/50), carpal tunnel syndrome (42/50), and late gadolinium enhancement on CMR (43/50). Diagnostic pathways varied slightly, but most included bone scintigraphy, exclusion of light-chain amyloidosis, and the possibility of doing a biopsy. Systematic screening was mentioned in 16 articles, 10 of which suggested specific at-risk populations for screening. The European Society of Cardiology recommends to screen patients with a wall thickness \( \geq 12 \) mm and heart failure, aortic stenosis, or red flag symptoms, especially if they are \( > 65 \) years. The underlying evidence was generally good for diagnosis, while significant gaps were identified for the relevance and mutual ranking of the different suspicion criteria and for systematic screening. Conclusively, patient entry was neglected in the reviewed literature. While multiple red flags were described, high-quality prospective studies designed to evaluate their suitability as suspicion criteria were lacking. An upcoming task lies in defining and evaluating at-risk populations for screening. All are steps needed to promote early detection and diagnosis of ATTRwt CM, a prerequisite for timely treatment.

Keywords: Amyloidosis; Cardiomyopathy; Transthyretin; ATTRwt CM; Suspicion; Diagnosis; Screening

Introduction

Once regarded a rare condition, wild-type transthyretin amyloid cardiomyopathy (ATTRwt CM) is currently considered a more common cause of heart failure in the elderly.\(^1\) The disease is characterized by progressive deposits of transthyretin (TTR) amyloid in the extracellular myocardial matrix, with de-
velopment of an infiltrative cardiomyopathy that carries a poor prognosis.2

Wild-type transthyretin amyloid cardiomyopathy typically affects men over 60 years of age, though women can also be affected. Its genetic counterpart, variant ATTR (ATTRv) CM, is caused by mutations in the TTR gene, may appear at a younger age as compared with ATTRwt CM, and affects both genders equally.3 This review will focus on ATTRwt CM.

The early stages of ATTRwt CM can manifest as heart failure with preserved ejection fraction (HFpEF) and may mimic hypertensive heart disease or hypertrophic cardiomyopathy, which increases the risk of misdiagnosis.4,5 In more advanced stages, ATTRwt CM can present along other well-known cardiac conditions like atrial fibrillation, atrioventricular conduction disorders, or aortic stenosis.3

With the introduction of new effective treatment possibilities,6–8 the relevance of identifying patients with ATTRwt CM has increased, as has the development and evaluation of non-invasive tools to diagnose the disease. This enhanced interest has resulted in multiple publications on ATTRwt CM suspicion criteria, red flags, and diagnostic pathways over the last decade. As a natural next step in identifying and treating patients with ATTRwt CM, systematic screening of at-risk subpopulations has also received some attention lately.

With this review, we seek to systematically describe the recent scientific literature dealing with suspicion, screening, and diagnosis of ATTRwt CM. This is performed with the purpose of analysing the scientific evidence underlying the available ATTRwt CM recommendations, thereby enabling a discussion of potential data gaps and needs to further substantiate optimal detection of patients affected by this detrimental disease.

**Methods**

To assess the literature on suspicion of and screening for ATTRwt as well as on diagnostic pathways for ATTRwt CM, we conducted a systematic literature review. Based on our clinical and professional research experience, we developed a new framework for analysing the resulting articles. This novel approach is described in the following section and illustrated in Figure 1.

**Definitions and framework for the analyses**

*Patient entry* is defined as the clinical setting in which suspicion of ATTRwt CM is first raised. As illustrated in Figure 1, a patients’ journey to an ATTRwt CM diagnosis can begin with a referral from the general practitioner or be initiated from different departments in the secondary healthcare sector. Patient entry is a relevant parameter to investigate as it often reflects the reason for suspicion in the first place and might provide important clues on the degree of ATTRwt CM awareness in the different parts of the healthcare system.

*Suspicion* of ATTRwt CM is defined as the physician’s substantiated conjecture that an individual patient may have ATTRwt CM. Suspicion of ATTRwt CM is raised by a clinical evaluation initiated because of patient symptoms, abnormal
imaging findings (which may be accidental) or cardiac biomarker levels, a relevant medical history, or a combination of these.

**Screening** for ATTRwt CM is defined as a systematic examination for ATTRwt CM in a population of patients defined as being at increased risk of ATTRwt CM. The screening entry criteria can be based on the presence of certain factors such as previous medical history, biomarkers, imaging findings, demographics, or a combination of these.

**Diagnosis** of ATTRwt CM is defined as the specific examinations recommended or required to confirm or reject a diagnosis of ATTRwt CM, including the order of these examinations and relevant thresholds or cut-off levels.

Thus, while suspicion relates to the clinician’s assessment of the individual patient based on clinical findings and the patient’s symptoms and medical history, screening is a systematic assessment of a patient population who meet some predefined entry criteria. **Figure 1** illustrates the analytical framework developed to analyse the articles included in this review.

### Databases and search strategy

The two electronic databases Embase and MEDLINE were searched using the PubMed platform. The searches were conducted in September 2021 and covered the period from 2010 to August 2021. This systematic review was carried out following the principles of the PRISMA guidelines.9

The search string was constructed of two clusters covering search terms relating to the ATTRwt CM population and diagnostic guideline terms, respectively (see Supporting Information, Table S1, for the search strings tailored to the applied databases). References cited in recently published articles or other relevant articles were screened to confirm that the search captured all relevant articles.

### Review process and eligibility criteria

Title and abstracts of all identified articles were reviewed for eligibility. Eligible articles were defined by a set of inclusion and exclusion criteria. Eligible articles were proceeded to full-text review, and articles failing to meet the inclusion criteria were excluded. The review process was performed independently by two investigators. In the event of disagreement about the eligibility of an article, consensus was reached through discussion with a third investigator.

Inclusion criteria were as follows: articles describing a part of or a full diagnostic pathway, including but not limited to suspicion, screening, or diagnosis of ATTRwt CM. Articles were considered to report a diagnostic pathway if they graphically or visually presented an order of tests recommended to diagnose ATTRwt CM. Exclusion criteria were as follows: (i) articles not written in English and (ii) case reports or conference abstracts.

### Data extraction

Extracted data included general information about the articles, information about suspicion and screening of ATTRwt CM (if addressed), information about clinical testing and diagnosing of ATTRwt CM, thresholds or cut-off levels, and origin of the pathway (Table 1). Extracted suspicion criteria were not limited to symptoms or findings defined in the articles as suspicion criteria but included all symptoms or findings that could be interpreted as suspicion criteria, such as ‘red

| Table 1 Data extraction categories and variables |
|------------------------------------------------|
| **Category** | **Variables** |
| General information | Publication year, Country of research, Journal, Type of article (review, original research), Objective, Methodology, Main results, Conclusion |
| Patient entry | Healthcare sector of initial contact |
| Suspicion | Is suspicion addressed? (yes or no), Nature of suspicion criteria (e.g. specific symptoms, clinical findings, and medical history), Characteristics of suspicion criteria (e.g. their cut-off values and evidence level) |
| Screening | Is screening addressed? (yes or no), Patient populations suggested for screening, Underlying evidence for suggested screening |
| Clinical testing and diagnosing | Cardiac investigations and thresholds, Diagnostic tools in suggested order, Definite diagnose/rule out of ATTRwt, Underlying evidence for suggested diagnostic elements |
| Origin of pathway | New pathway or modified from already published pathway |
flags’, ‘clinical presentation’, ‘clinical clues’, ‘clinical features’, ‘common symptoms’, or ‘typical manifestations’.

To further evaluate the level of evidence underlying the suspicion, screening, and diagnosis of ATTRwt CM, relevant data from original prospective or retrospective studies referred to in the included articles were extracted. Only original studies including more than 20 patients with ATTRwt CM were included.

Data analysis

A descriptive analysis was performed to give a historical overview of the development of the published literature describing diagnostic pathways for ATTRwt CM. Pathways in the included articles were assessed in four subanalyses: (i) patients’ entrance into the diagnostic pathways, (ii) suspicion of ATTRwt CM, (iii) systematic screening for ATTRwt CM, and (iv) establishment of the ATTRwt CM diagnosis. The analyses comprised a quantitative summary of extracted data and a qualitative assessment.

Results

From the two searches, 1706 articles were identified. Following removal of duplicates, 1318 articles were screened on titles and abstracts. Of these, 1225 articles were excluded, as they did not meet the inclusion criteria. A total of 93 articles were fully reviewed and assessed for eligibility. Finally, 48 articles describing a diagnostic pathway for ATTRwt were included in this systematic literature review. Two additional relevant articles not captured in the primary literature search were included, resulting in a total of 50 articles (Figure 2).

Characteristics of the included articles

Among the 50 articles containing a diagnostic pathway for ATTRwt CM, 36 articles were review studies. The 14 remaining articles were consensus recommendation papers, cohort studies, or guidelines. The majority of the identified articles were not country or regional specific.

Eighteen articles focused specifically on ATTRwt CM or on ATTRwt CM plus ATTRv CM (in the following referred to as ATTR-CM), while the rest covered CA in general, including ATTR-CM.

Historical development

We found an overall increase in the rate of published articles suggesting a diagnostic pathway for ATTRwt CM from 2010 to August 2021, particularly since 2019 when also articles reproducing an already published diagnostic pathway started to appear (Figure 3)

Figure 2. PRISMA chart. *Identified in connection with the analysis of the included articles.
Analyses of the diagnostic pathways

Patients’ entrance into the diagnostic pathways
Of the 50 identified articles for ATTRwt CM, three explicitly mentioned the importance of the primary care providers. The remaining 47 articles did not report the initial contact with the healthcare system. The speciality areas of the journals publishing the included articles can be considered an indicator of the clinical societies focusing on ATTRwt CM patients. Notably, 43 of 50 articles were published in a journal within cardiology or haematology, while the remaining seven articles were published in papers of general or internal medicine or oncology. No articles were published in journals within neurology or orthopaedics.

Suspicion of wild-type transthyretin amyloid cardiomyopathy
All included articles, except three, described an initial suspicion of ATTRwt CM based on clinical presentation and red flags. Table 2 lists the typical suspicion criteria as described in the identified articles, divided into cardiac symptoms/diagnoses, extracardiac manifestations, cardiac biomarkers, and findings based on electrocardiography (ECG), echocardiography (ECHO), and cardiac magnetic resonance (CMR). Most of the suspicion criteria did not show any historical trend in that they appeared throughout the investigated period. Exceptions were, however, the apical sparing global longitudinal strain pattern on ECHO, which was not described in the included articles until 2015, and aortic stenosis and lumbar spinal stenosis, which were not included as suspicion criteria until 2016 and 2017 respectively.

Evaluation of the evidence for selected suspicion criteria
The most prevalent suspicion criteria for each of the categories listed in Table 2 were evaluated in terms of underlying evidence, except for ‘Symptoms of heart failure’ due to its diffuse expression and its intrinsic linkage to ATTRwt CM. Original studies referred to and relevant results are listed in Tables 3 and 4 and outlined in short in the succeeding text.

Heart failure with preserved ejection fraction
Thirty articles mentioned HfPmEF as a suspicion criterion for wild-type ATTRwt CM, or at least for CA. Prospective studies referred to reported between 6% and 18% of patients with HfPmEF to have ATTRwt. Some articles raised the awareness that while HfPmEF can be a sign of ATTRwt CM, studies have reported 30–50% of patients with ATTRwt CM to have heart failure with reduced ejection fraction (HFrEF).

Carpal tunnel syndrome
All, except eight articles, mentioned carpal tunnel syndrome (CTS) as a common and very early finding in patients with ATTRwt. Three prospective studies investigated the frequency of amyloid and/ or ATTRwt CM in patients undergoing surgery for CTS. One registry study showed that while patients undergoing CTS surgery have a low risk of being diagnosed with amyloidosis (0.10% incidence within 10 years of surgery), the risk was still 12 times higher than for people without CTS.

Lumbar spinal stenosis
Sixteen articles mentioned lumbar spinal stenosis (LSS) as a disease often associated to ATTRwt CM. Original studies referred to included two relatively small prospective studies investigating for amyloid in ligamentum flavum samples from patients undergoing LSS surgery and reporting the presence of TTR amyloid in, respectively, 33% and 45% of the samples.

Neuropathy
Autonomic and peripheral neuropathy was included as a typical symptom in 35 articles. Most arti-
Atrial fibrillation Twenty-four articles mentioned atrial fibrillation as a typical feature of ATTRwt CM.2,5,10,11,13,14,18–20,22,24–26,29,30,32–34,36,42,43,46–48,56 Original studies referred were all retrospective and documented a high occurrence (27–67%) of atrial fibrillation in ATTRwt CM patients. No studies were designed to investigate the prevalence of ATTRwt CM in patients with atrial fibrillation.

Aortic stenosis Aortic stenosis was mentioned in 23 articles,2,3,10,20–22,24,32,35,37–40,42–44,46–51,56,57 21 of which were published after 2019. The increased attention of aortic stenosis in patients with ATTRwt CM is based on the original studies referred to, which are all prospective and have been published in 2016 or later.81–85 Two of the studies suggested that patients with concomitant ATTRwt CM and aortic stenosis had a worse prognosis.81,84

Electrocardiography The most typical ECG findings mentioned were atrial fibrillation (discussed earlier), conduction abnormalities, pseudo-infarction pattern, low QRS voltage, and a discordance between QRS voltage on ECG and ventricular wall thickness on ECHO. Original studies referred to described ECG patterns in patients diagnosed with ATTRwt CM or compared ECG characteristics in the different types of CA or in CA and other cardiac diseases. None of the studies were designed to investigate the prevalence of ATTRwt CM in patients with specific ECG features. Notably, although a criterion like low voltage QRS was mentioned often, it was also characterized as a low sensitive criterion for ATTRwt CM and more typical of amyloid light-chain (AL) amyloidosis. Articles referred to in this context were retrospective.3,87,88

Echocardiography Ventricular wall thickening was mentioned in all studies discussing ECHO findings. Other typical ECHO findings are listed in Table 2. Original studies referred to described ECHO patterns in patients diagnosed with ATTRwt CM or compared characteristics in the different types of CA or in CA and other cardiac diseases. Conclusions from these studies were that ECHO, and especially apical sparing global longitudinal strain pattern, is indeed useful for raising

| Table 2 Frequency of the most prevalent suspicion criteria/red flags mentioned in the identified articles |
|-----------------------------------------------------------|
| Clinical symptoms and medical history                      |
| Symptoms of heart failure                                  | 34 |
| HFpEF                                                      | 30 |
| Carpal tunnel syndrome                                    | 42 |
| Lumbar spinal stenosis                                    | 29 |
| Neuropathy (peripheral or autonomic)                       | 35 |
| ECG findings                                               |
| Discordance between QRS voltage on ECG and wall thickness on ECHO | 32 |
| Atrial fibrillation                                       | 24 |
| Low QRS voltage                                            | 30 |
| Conduction abnormality (AV block, left and right bundle block) | 25 |
| Pseudo-infarction pattern                                 | 27 |
| ECHO findings                                              |
| Ventricular wall thickening                                | 44 |
| Apical sparing global longitudinal strain pattern          | 36 |
| Small pericardial effusion                                | 28 |
| Reduced global longitudinal strain                         | 28 |
| Bialtrial enlargement/dilatation                           | 27 |
| Granular sparkling appearance of myocardium                | 25 |
| Aortic stenosis                                            | 23 |
| CMR findings                                               |
| Late gadolinium enhancement                               | 43 |
| Increased extracellular volume                             | 36 |
| Elevated native T1 mapping sequences                      | 33 |
| Diffuse subendocardial or transmural late gadolinium enhancement | 30 |
| Cardiac biomarkers                                         |
| Abnormal troponin levels                                  | 26 |
| Abnormal NT-proBNP level                                  | 21 |

AV, atrioventricular; CMR, cardiac magnetic resonance imaging; ECG, electrocardiography; ECHO, echocardiography; HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.
### Table 3: Original studies referred to in relation to suspicion criteria in the form of symptoms and diagnoses

| Suspection criteria | Study type | Prospective | Retrospective | Autopsy | Registry |
|---------------------|------------|-------------|---------------|---------|----------|
| HFpEF               | ATTRwt CM 13% of patients admitted with HFpEF and wtt ≥ 12 mm<sup>1</sup> | Broad description of ejection fraction in patients with ATTRwt CM<sup>60</sup> | 5% of patients with HFpEF had ATTRwt CM as the primary reason for HFpEF<sup>61</sup> | | |
|                     | ATTRwt CM 18% of patients >65 years with HFpEF<sup>78</sup> | | | | |
|                     | ATTRwt CM 6% of patients with HFpEF as evaluated by myocardial biopsy analysis<sup>59</sup> | | | | |
|                     | TTR amyloid in tenosynovial tissue from patients undergoing CTS surgery was found in 34% (no check for amyloid in the heart<sup>62</sup> | CTS prevalence of 20–60% reported in patients with ATTRwt CM<sup>65–74</sup> | | Risk of ATTRwt CM 12x increased in patients undergoing CTS surgery<sup>75</sup> |
| Carpal tunnel syndrome | TTR amyloid in tenosynovial tissue from patients undergoing CTS surgery was found in 10.2% (cardiac involvement confirmed in one patient)<sup>63</sup> | | | | |
|                     | Confirmed ATTRwt CM was reported in 0.85% of patients undergoing CTS surgery<sup>64</sup> | | | | |
| Lumbar spinal stenosis | TTR amyloid found in 33% of LSS surgery samples, no check for cardiac symptoms<sup>56</sup> | 14% of patients with ATTRwt CM had a history of LSS<sup>87</sup> | | | |
|                     | TTR amyloid found in 45% of LSS surgery samples, no cardiac symptoms found<sup>77</sup> | | | | |
| Neuropathy          | | Of ATTRwt CM patients, 12% had neuropathic pain, 12% had numbness, and 13% had tingling CM<sup>65–78</sup> | | | |
|                     | | 12% of patients with ATTRwt MS had autonomic neuropathy, manifesting as orthostasis<sup>70</sup> | | | |
| Atrial fibrillation | ATTRwt CM was reported in 6% of patients undergoing SAVR<sup>81</sup> | Atrial fibrillation was reported in 27–67% patients with ATTRwt CM<sup>5,60,66,70,79,80</sup> | | | |
| Aortic stenosis     | ATTRwt CM was reported in 12–16% in patients undergoing TAVR<sup>82–84</sup> | ATTRwt CM was reported in 12% of patients undergoing SAVR or TAVR<sup>85</sup> | | | |

ATTRwt CM, wild-type transthyretin amyloid cardiomyopathy; CTS, carpal tunnel syndrome; HFpEF, heart failure with preserved ejection fraction; LSS, lumbar spinal stenosis; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; TTR, transthyretin.

### Table 4: Original studies referred to in relation to suspicion criteria in the form of imaging findings and cardiac biomarkers

| Imaging technique/ biomarker | Study type | Prospective | Descriptive | Comparative |
|-----------------------------|------------|-------------|-------------|-------------|
| ECG                         | Applicability of ECG and ECHO in diagnosing CA, not specifically ATTRwt CM<sup>86</sup> | Description of ATTRwt CM in specific<sup>86</sup> | Comparison of ECG in different types of CA<sup>5,79–90</sup> | Comparison between CA and other diseases<sup>91</sup> |
| Echocardiography            | Description of ATTRwt CM in specific<sup>90</sup> | | | | |
| CMR                         | Comparison of ECHO in different types of CA<sup>88,92–95</sup> | | | | |
| Cardiac biomarkers          | Comparison between CA and other cardiac diseases<sup>101–105</sup> | Comparison of CMR between different types of CA<sup>106–109</sup> | Comparison of high-sensitivity cardiac troponin T levels between CA and other causes of cardiac hypertrophy<sup>110</sup> | | |

ATTRwt CM, wild-type transthyretin amyloid cardiomyopathy; CA, cardiac amyloidosis; CMR, cardiac magnetic resonance; ECG, electrocardiography; ECHO, echocardiography.
the suspicion of CA.\textsuperscript{96–99} There were no prospective studies evaluating the prevalence of ATTRwt CM in patients with specific ECHO features, the closest being a study investigating the prevalence of ATTRv CM in patients with a ventricular wall thickness $\geq 15$ mm.\textsuperscript{112}

Cardiac magnetic resonance The most typical CMR findings suggestive of CA are listed in Table 2. Original studies referred to were comparative and investigated the use of CMR in distinguishing between CA and other cardiac diseases or between the different types of CA. Native myocardial T1 mapping and extracellular volume appear to be good indicators of ATTRwt CM.\textsuperscript{101–103} One study found that a native T1 < 1,036 ms was associated with 98\% negative predictive value for CA whereas a native T1 > 1,164 ms was associated with 98\% positive predictive value for CA and argued that the application of these thresholds can limit the use of gadolinium contrast to those with intermediate T1 levels.\textsuperscript{101} No prospective studies were referred to that evaluated the prevalence of ATTRwt CM in patients with specific CMR features.

Cardiac biomarkers—troponin and N-terminal pro-brain natriuretic peptide Cardiac biomarkers in the form of troponin or N-terminal pro-brain natriuretic peptide (NT-proBNP) were mentioned as a marker of suspicion in 13 papers.\textsuperscript{4,5,11–13,21,22,24,32,33,45,46,49} Generally, troponin and NT-proBNP are considered non-specific markers of myocardial injury or heart failure, and only one article was referred to which investigated the value of high-sensitivity cardiac troponin T levels in discriminating between CA and other causes of cardiac hypertrophy.\textsuperscript{110} Rather, their role as prognostic markers for patients already diagnosed with ATTR-CM was widely discussed, based primarily on three original studies.\textsuperscript{60,113,114}

Systematic screening for wild-type transthyretin amyloid cardiomyopathy Sixteen articles used wording regarding systematic screening for ATTRwt CM.\textsuperscript{4,5,11,18,21–23,25,32,33,43,44,49–51} Most of these were published in 2019 or later.\textsuperscript{4,5,18,21,23,33,43,44,49–51} Discussed themes included the worsening of disease outcomes associated with delayed diagnosis, the importance of systematic screening in enabling early disease identification and thereby maximizing the benefit of therapy, and the existing knowledge gaps that complicate the implementation of systematic screening. Ten of the articles suggested specific at-risk patient populations who could be relevant for ATTRwt CM screening, such as elderly patients with neuropathy, patients with aortic stenosis, patients with established or suspected non-cardiac amyloidosis, patients with monoclonal gammopathy, and older adults with heart failure and a history or symptoms of CTS, LSS, or spontaneous rupture of the distal biceps tendon.\textsuperscript{4,5,11,18,21,23,25,33,50,51} Witteles et al. (2019) discussed in detail how to best screen for ATTRwt CM in everyday practice and specifically suggested, based on data, that men $>65$ years and women $>70$ years with heart failure or one or more specific red flags and a wall thickness $\geq 14$ mm should be screened for ATTRwt CM. Likewise, in the position statement from the European Society of Cardiology (ESC), it was recommended that individuals with a wall thickness $\geq 12$ mm and heart failure, aortic stenosis, or red flag symptoms should be screened for ATTRwt CM, especially if they are older than 65 years.\textsuperscript{51} The red flags mentioned included many of the suspicion criteria listed in Table 2, and the evidence underlying the specific suggestions overlapped substantially with the original studies described earlier.\textsuperscript{4,51} Thus, while many articles discussed the need for systematic screening of certain populations, no prospective screening studies of at-risk populations were referred to.

Establishment of the wild-type transthyretin amyloid cardiomyopathy diagnosis Essential diagnostic tools to reach a conclusive ATTRwt CM diagnosis include serological and in some cases bone marrow examinations to exclude AL amyloidosis, bone scintigraphy, myocardial biopsy, and genetic test. In alignment with this, one or more of these tools are included in all the diagnostic algorithms reviewed. Whether all types of tests are needed typically depends on the results of the other tests. Figure 4 provides an overview of the most prevalent test result combinations that according to the reviewed literature are required to reach a conclusive ATTRwt CM diagnosis.

While most published algorithms feature both a bone scintigraphy and tests to exclude AL amyloidosis, the order of these tests differs. Thus, 25 articles suggest to exclude AL amyloidosis before carrying out a bone scintigraphy,\textsuperscript{5,10,12,14–16,19,21–25,29,32,35–37,41,42,44–46,49,56} while nine articles suggest the reverse order.\textsuperscript{13,15,20,33,38,47,48,52,53,55} Whether a biopsy is also needed depends on the outcome of the other tests. Also, whether this should be an endomyocardial biopsy (EMB) or an extracardiac biopsy is discussed in many articles.

The history, diagnostic role, and underlying evidence for each of the tools are outlined in the succeeding text.

Exclusion of amyloid light-chain amyloidosis The relevance of excluding AL amyloidosis when diagnosing ATTRwt CM was reflected in the suggested diagnostic algorithms throughout the studied period, and all but three articles\textsuperscript{26,31,54} included it as a part of the diagnostic pathway.

Especially, the 18 articles focusing on ATTR-CM in specific\textsuperscript{4,5,10,11,13,17,19,21,25,32,35,37,39,40,45,49,52,53} (rather than CA in general) underlined the importance of excluding AL amyloidosis and agreed that the required tests are immunofixation electrophoresis (IFE) of serum and urine and the serum free light-chain (FLC) assay. Still, only few\textsuperscript{25,39,44,45,51,53} referred to original studies providing evidence for using these tests. Original studies referred to include an article in which the serum reference intervals for
free κ light chains, free λ light chains, and the κ/λ ratio were
defined. Especially the latter is used in relation to exclusion of
AL amyloidosis and is calculated to be 0.26–1.65 as based on
measurement of 282 serum samples. Also, two articles
were referred to which investigated new mass spectrometry
(MS)-based methodologies that may eliminate the need for
FLC assays in the future. Finally, in connection with
discussing the tests required to exclude AL amyloidosis,
awareness of monoclonal gammopathy of undetermined sig-
nificance (MGUS) was often mentioned, because patients
with MGUS present with abnormal values in the tests used
to exclude AL amyloidosis. The original study primarily re-
ferred to in this connection reported an MGUS prevalence
of 39% in patients with ATTR-CM.

Bone scintigraphy The earliest articles did not include the
use of bone scintigraphy in their diagnostic algorithm. However, since 2014, the method has gained ground and
was included in all reviewed articles beginning with Hutt
et al. (2014).

The evidence underlying the use of bone scintigraphy came from multiple studies that have evaluated the applica-
bility of different technetium (99mTc)-labelled radiotracers in
diagnosing ATTR-CM. The studied radiotracers referred to
in the included articles are 99mTc-3,3-diphosphono-1,2-
propanodicarboxylic acid (99mTc-DPD), 99mTc-pyrophosphate
(99mTc-PYP), and 99mTc-hydroxymethylene diphosphonate
(99mTc-HMDP). Retrospective studies were referred to which
all reported that 99mTc-DPD had a high sensitivity for cardiac
amyloid in patients with ATTR-CM, as had 99mTc-
PYP and 99mTc-HMDP. Importantly, prospective
studies reached similar results, and in line with the in-
dividual studies, a meta-analysis from 2018 referred to
concluded that bone scintigraphy using 99mTc-labelled radio-
tracers provides very high diagnostic accuracy in the assess-
ment of ATTR-CM. Of note, clinical studies suggesting that
bone scintigraphy can detect cardiac amyloid at a very early
stage were also referred to.

There was a general consensus among the included articles
to use the visual scoring system developed by Perugini et al.
(2005) and ranging from 0 (absent cardiac uptake and normal
bone uptake) to 3 (strong cardiac uptake with mild/ab-
sent bone uptake) to evaluate the results of the bone scintig-
raphy, with a score ≥2 suggesting an ATTR-CM diagnosis. By
use of the Perugini scoring system, the largest prospective
study referred to reported a sensitivity of bone scintigraphy
for cardiac TTR amyloid of >99%. Meanwhile, the specific-
ity was somewhat lower (86%), which could be explained
by the cardiac uptake of 99mTc-labelled radiotracers in some
patients with AL amyloidosis. This underlines the importance
of combining bone scintigraphy with tests to exclude AL am-
yloidosis, and by doing this, Gillmore et al. (2016) reached a
specificity and positive predictive value for ATTR-CM of 100%.

Biopsies All but four articles included a biopsy as a part of
their diagnostic pathway. As illustrated in Figure 3, 20 of these articles argued that a biopsy is needed in case
of inconclusive results from the bone scintigraphy and/or ab-
normal results from the tests conducted to exclude AL
amyloidosis.2,4,12,13,15–18,20–23,25,27,33,35–41,43,45–51,53,55,56 Also, 28 articles suggested that one way to diagnose ATTR-CM is with a biopsy after a positive monoclonal protein test (Figure 3). Biopsy types mentioned included fat tissue, bone marrow, involved organ, and in some cases an endomyocardial biopsy if less-invasive biopsies are negative, but suspicion remain. Twelve of these 28 articles only suggested conducting a cardiac biopsy if bone scintigraphy was unavailable.2,5,10,14,19,21,24,36,44–46,49

The evidence underlying the choice of tissue for biopsy included original studies investigating the suitability of endomyocardial biopsies132–135 as well as extracardiac biopsies for the detection of amyloid in patients with ATTR-CM.136–141 These studies reported amyloid detection rates of ~100% in cardiac tissue,132,133 14–45% in fat tissue,138–140 30% in bone marrow,139 and 44% in gastrointestinal tract and subcutaneous tissue combined141 in patients with ATTR-CM.

As regards the method used for analysing the type of amyloid present in the biopsy samples, there was a general consensus that MS is superior to immunohistochemistry (IHC). Indeed, the superiority of MS was mentioned throughout the study period, beginning with Kapoor et al. (2011).30 Studies referred to in this connection included a study documenting the risk of false positive immunostaining for TTR amyloid in patients with AL amyloidosis,142 and studies documenting a high diagnostic accuracy of laser dissection MS.143–145 One study reported that IHC had a diagnostic accuracy of 76% while using laser dissection MS increased this to 96%,143 and a recent study based on 700 biopsies also concluded that laser dissection MS is superior to IHC for identifying the specific type of amyloid.144 The study mostly referred to documented a 100% specificity and sensitivity in a training set of 50 cases of amyloidosis and 98% in a validation set composed of 41 cases of CA.145

Genetic testing All but three11,15,52 of the included articles mentioned the need for genetic testing in their diagnostic algorithm. Most state that distinguishing between ATTRv CM and ATTRwt CM is important in terms of treatment options, screening of family members, and improved assessment of prognosis. No original articles were referred to in relation to the importance of genetic testing.

Consensus recommendation papers and guidelines

Six of the identified consensus recommendation papers were from national and international academic societies.2,45–48,51,57 The Canadian Cardiovascular Society/Canadian Heart Failure Society (CCS/CHFS) published a joint position statement providing recommendations that support the early recognition and optimal diagnostic approach for patients with CA,46 the American Heart Association (AHA) published a scientific statement intended to guide clinical practice and cover current diagnostic strategies in ATTR-CM,45 and a collaboration of multiple American and European societies within imaging techniques and cardiovascular disease (ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI) published recommendations for multimodality imaging in CA.47,48 Most recently, both the ESC and the German Cardiac Society (DGK) published position statements with the purpose of assisting cardiologists and other physicians in recognizing, diagnosing, and treating patients with CA.2,51 One guideline was also identified, namely, a guideline from the Japanese Circulation Society (JCS) on diagnosis and treatment of CA.57

In accordance with the majority of review articles identified, these position papers conclude that modern cardiac imaging techniques, including bone scintigraphy, allow accurate non-invasive diagnosis of ATTR-CM without the need for confirmatory cardiac biopsies.2,45–48,51 CCS/CHFS only suggests conducting an EMB if bone scintigraphy is unavailable,46 while AHA also suggests conducting a cardiac biopsy in case of a negative monoclonal protein test and a negative bone scintigraphy if suspicion of ATTR-CM remains high.45 DGK and ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI argue that a cardiac biopsy remains necessary in the context of equivocal imaging or the coexistence of a monoclonal gammopathy.2,47,48 ESC clearly distinguishes between invasive and non-invasive diagnostic possibilities and supports both.51

Discussion

Historical development

The number of articles suggesting a diagnostic pathway for ATTR-CM has increased substantially over the studied period (Figure 3). This reflects the augmented interest in the disease spurred by the development of new effective treatments for ATTR-CM.6–8 The use of bone scintigraphy in enabling a non-invasive diagnosis of ATTR-CM is among the most important clinical advancements within the suspicion, screening, and diagnosis of ATTRwt CM since 2010.52,53,55 Also, this period of time has offered the development of more sensitive imaging analyses like native myocardial T1 mapping and extracellular volume in CMR,101–103 and apical sparing global longitudinal strain pattern in ECHO,96–98 which together with bone scintigraphy has improved the possibilities of suspecting ATTRwt CM significantly.

Patient entrance

Patient entrance received very little attention in the reviewed literature. Patients with extracardiac symptoms like CTS, LSS,
or neuropathy typically enter the healthcare system via orthopaedics or neurology, an entry that could enable an early ATTRwt CM diagnosis if processed properly. Still, this was not in focus in the identified literature. Combined with the fact that none of the included articles were published in journals within neurology or orthopaedics, this could raise the concern that patients debuting with extracardiac symptoms are not identified as early as they could be. That said, recent papers published in orthopaedics and surgical journals suggest that focus on ATTRwt CM is increasing outside of cardiology as well.

Suspicion

While multiple red flags exist for ATTRwt CM, none of them are specific for the disease. Most findings and symptoms overlap substantially with those of AL amyloidosis and other cardiac disease. The red flags might, however, differ in their suitability of detecting ATTRwt CM at an early stage. While CTS and LSS belong in the category of medical history and can be seen years before cardiac involvement, native T1 mapping on CMR was described as enabling early detection of ATTR-CM as was bone scintigraphy. Also, HFrEF progresses into HFrEF as disease advances, while low voltage may primarily be found in late-stage disease.

The suitability of specific ECHO and CMR findings in raising a suspicion of ATTRwt CM seems indisputable. These imaging tools have been widely investigated for their ability to diagnose ATTRwt CM, and while they do not possess this quality due to too much overlap with AL amyloidosis, they are indeed able to distinguish between CA and other causes of thick hearts. In many cases, an ECHO will be sufficient to raise the suspicion of ATTRwt CM. However, the ability of CMR to distinguish between CA, hypertensive heart disease, and hypertrophic cardiomyopathy, which are all characterized by increased wall thickness on an ECHO, makes a CMR useful in some cases.

The diversity and lack of specificity of ATTRwt CM symptoms indeed complicates the development of a structured approach to how to detect ATTRwt CM patients in the first place and renders the initial suspicion of the disease the weak link in ATTRwt CM patients’ journey to diagnosis. Indeed, a recent British study demonstrated substantial delays in establishing the ATTR-CM diagnosis following presentation with cardiac symptoms by documenting a delay of more than 4 years in more than 40% of the patients. The reviewed articles are characterized by listing numerous typical symptoms, but only few translate these lists into a more guided approach of how to define at-risk patients. An exception worth mentioning is the combination of increased wall thickness and one or more red flags in people of advanced age, as suggested by Witteles et al. (2019) and in the ESC consensus statement (2021).

In general, the suggested red flags are not specific and have not been evaluated prospectively in terms of their sensitivity, specificity, and positive predictive value. Rather, data are based on observations, experience, and consensus among experts.

Screening

To enable further progression towards solid recommendations and workable guidelines for when to suspect ATTRwt CM, large prospective studies investigating the suitability of specific red flag combinations in identifying the right patients are needed. This would also be the natural step towards implementing systematic screening for the disease. To the best of our knowledge, none of such studies are available at present. While the screening discussion is currently at a premature stage, newer articles highlighted the need to raise awareness for ATTRwt CM and to identify straightforward and cost-effective tools and algorithms for large-scale screening of populations at risk. This possibility is expected to unfold in coming years as a natural consequence of ATTR-CM treatments becoming increasingly available. Indeed, a search on clinicaltrials.gov for ongoing screening studies identified trials with titles like Global prevalence of ATTR-CM in participants with HFrEF (NCT04424914), Screening for amyloidosis before aortic valve elective replacement (NCT04869631), and Prevalence of Amyloidosis in Patients With Lumbar Spinal Stenosis or Carpal Tunnel Syndrome (NCT03966105).

Diagnosis

There was a high degree of consensus among the identified articles, including the recommendation papers from academic societies, on how to diagnose ATTR-CM once the suspicion has been raised. Bone scintigraphy and tests to exclude AL amyloidosis are central and inevitable tools, as is the need for a cardiac biopsy in inconclusive cases.

Multiple recommendations were, however, provided for (i) whether to conduct the bone scintigraphy or the tests to exclude AL amyloidosis first and (ii) when to make a biopsy and which biopsy to choose. As for (i), the rationale behind starting with the tests to exclude AL amyloidosis is that the bone scintigraphy might be unnecessary in patients, for whom the AL amyloidosis test results point towards an AL amyloidosis diagnosis. Conversely, tests to exclude AL amyloidosis are always needed, regardless of the results of the bone scintigraphy, because a bone scintigraphy can never be used to rule out AL amyloidosis. As for (ii), the time point and type of biopsy likely reflect that the complete clinical picture should always be considered in inconclusive cases as should the pros and cons of biopsy types. Hence, the high diagnostic value as well as the risk (though minor) of perform-
ing an invasive EMB should be compared with both the advantage of avoiding an EMB by performing a less-invasive extracardiac biopsy (of low diagnostic value), and the disadvantage of having to perform both an extracardiac biopsy and an EMB in case of a negative extracardiac biopsy.

The underlying evidence referred to for strengths and possible pitfalls of the individual diagnostic tools seemed strong for bone scintigraphy and biopsies, but somewhat limited for tests to exclude AL amyloidosis. The reason for this is unknown but may relate to a limited interest in these somewhat simple laboratory tests among cardiologists. The need for a correct interpretation of the FLC assay results should, however, not be overlooked, especially as the reference range referred to deviate in patients with renal problems, which can constitute a significant part of patients with suspected ATTRwt CM.

Conclusions

Wild-type transthyretin amyloid cardiomyopathy is an underdiagnosed disease that fortunately has gained interest, primarily due to an improvement in the diagnostic tools and the discovery and approval of disease-modifying medical treatment. The comparison of diagnostic pathways described in 50 different articles shows that diagnostic pathways are similar, albeit with minor differences, and should ensure a fairly stringent diagnostic process across the world.

Meanwhile, this systematic review has identified some significant knowledge gaps. Firstly, patient entry receives little if no attention in the literature. More focus on initial patient contact and increased awareness among general practitioners and relevant non-cardiological specialties could shorten the way to diagnosis and minimize the risk of misdiagnosis and improper treatment. Secondly, a major challenge lies in raising the initial suspicion of the disease. While multiple red flags are described, there is a general lack of high-quality prospective studies designed to evaluate the sensitivity and specificity of specific red flags or red flag combinations, not to mention their mutual ranking. Thirdly, a task lies in defining relevant at-risk screening populations. This should be performed by prospectively evaluating the value of systematic screening in predefined populations. This would lead the way to detection of ATTRwt CM at an early stage, a prerequisite for timely and relevant treatment.

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Conflict of interest

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Search string used for Embase and MEDLINE.

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