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ORIGINAL ARTICLE

2024 Australia–New Zealand Expert Consensus Statement on Cardiac Amyloidosis

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Over the past 5 years, early diagnosis of and new treatments for cardiac amyloidosis (CA) have emerged that hold promise for early intervention. These include non-invasive diagnostic tests and disease modifying therapies. Recently, CA has been one of the first types of cardiomyopathy to be treated with gene editing techniques. Although these therapies are not yet widely available to patients in Australia and New Zealand, this may change in the near future. Given the rapid pace with which this field is evolving, it is important to view these advances within the Australian and New Zealand context. This Consensus Statement aims to update the Australian and New Zealand general physician and cardiologist with regards to the diagnosis, investigations, and management of CA.

Keywords Amyloidosis • Cardiac • Transthyretin • Hereditary • Heart failure with preserved ejection fraction • Heart failure • Genetics

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Box 1. The unmet need for CA diagnosis and management in Australia and New Zealand.

- Patients are often diagnosed late, with symptoms of advanced heart failure (HF).
- Amyloidosis is frequently misdiagnosed, with a median diagnostic delay of greater than 12-months and approximately 50% of patients visiting more than five physicians prior to diagnosis.
- Delays in diagnosis are associated with high early mortality.
- Specialised Australian Amyloidosis Network centres are limited in number and location; however, pathways at these centres do triage urgent referrals (https://aan.org.au/).
- With greater awareness, cardiologists can reduce diagnostic delay and improve access to therapy.
- Both the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) have updated their guidelines for amyloidosis in the past 2 years. These guidelines, however, do not reflect the Australian or New Zealand context.

Box 2. Key points about Cardiac Amyloidosis in 2024

- Cardiac amyloidosis (CA) results from misfolded proteins, termed amyloid fibrils, depositing in the myocardium, heart valves and conduction system (Figure 1).
- These fibrils can also deposit in other organ systems such as the peripheral nerves, kidneys, and gastrointestinal tract.
- Approximate life expectancy without treatment is 4 years for transthyretin (ATTR) amyloidosis), but as little as 3 months for advanced cardiac amyloid light chain amyloidosis (AL).
- 95% of CA is caused by ATTR or AL deposition.
- Appropriate subtyping between ATTR and AL is essential, as treatments vary, and prognosis differs.
- "Non-invasive" diagnosis of CA is now possible. This requires simultaneous bone scintigraphy and blood and urine tests to exclude AL.
- Equivocal results require patients to be referred to specialist centres for careful assessment and an invasive 'tissue' diagnosis.
- Tissue biopsy could be "on-target" (e.g., endomyocardial biopsy for primary cardiac disease) or "off target" (bone marrow, fat pad biopsy, salivary gland biopsy).
- All patients with confirmed ATTR-CA should have genetic testing for mutations.
- Treatments are now disease-modifying and targeted. In Australia, tafamidis will become available on the PBS; diflunisal is available through the Special Access Scheme at all Australian Amyloidosis Network (AAN) Centres. In New Zealand, these treatments are currently only accessible through inclusion in clinical trials.
- Patients should ideally be referred for multidisciplinary care.

Introduction

Cardiac amyloidosis (CA) is a devastating condition in which misfolded proteins, called amyloid fibrils, deposit in multiple organs including the heart. This leads to an increase in left ventricular (LV) wall thickness, diastolic dysfunction, valvular and conduction disturbance. This infiltrative condition leads most commonly to symptoms of heart failure, conduction block and arrhythmias. Unlike other cardiac pathology, CA exists within a multi-system disease. Amyloid fibril deposition can occur throughout the body, including in the nerves, kidneys, and gastrointestinal system. Therefore, evaluating the individual patient within this context is essential.

While previously only recognised in its late stages and treated with palliation, early diagnosis of and new treatments for CA have emerged over the past 5 years that hold promise for early intervention. These include disease modifying therapies which target the elimination of amyloid fibrils. Excitingly, in the past 12-months, CA has been one of the first types of cardiomyopathy to be treated with gene editing techniques. Although these therapies are not yet widely available to patients in Australia, this may change in the near future. Given the rapid pace with which this field is evolving, it is important to view these advances within the Australian and New Zealand context, and to update the Australian and New Zealand general physician and cardiologist with regards to background, diagnosis, investigations, and management of CA.

Background

The unmet need for early diagnosis of and co-ordinated management of CA in Australia and New Zealand is outlined in Box 1.

Methods

A collaborative interest group in CA was formed, and included the National Cardiac Amyloidosis Subcommittee, senior leadership of the Australian Amyloidosis Network, and representatives from across Australia and New Zealand.

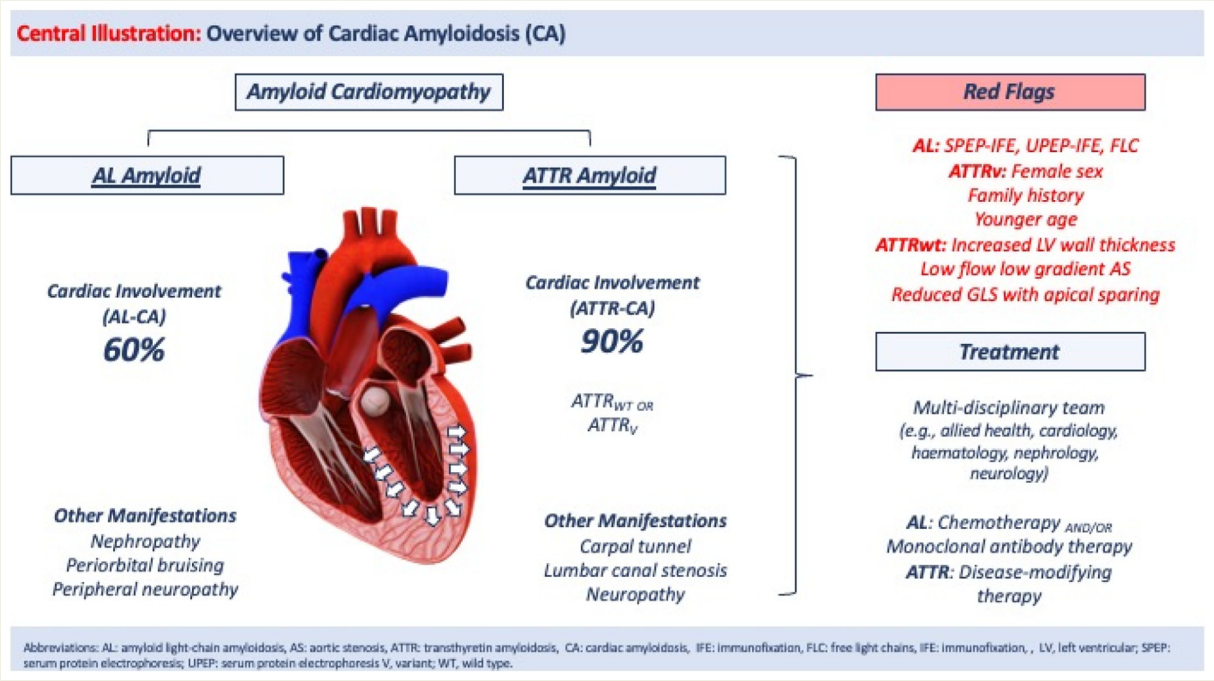

Figure 1 Central Illustration: An overview of cardiac amyloidosis (CA).

There was also patient and consumer input (Ms Patricia Neely).

Conflicts of Interest Process

Conflicts of interests were declared at the beginning of the writing process to the Cardiac Society of Australia and New Zealand (CSANZ), and to *Heart, Lung and Circulation*. This included a declaration of Funding sources for individual authors. See **Funding Sources** and **Conflicts of Interest** sections below.

Consensus Statement Scope

The group sought to respond to recent developments in the diagnosis, management, and prognosis of CA, as summarised in Box 2.

Definitions and Classifications

Definitions

Amyloidosis is a disease caused by abnormal folding of a variety of proteins resulting in the extracellular deposition of highly organised fibrillar aggregates in different organs, including the heart, kidneys, peripheral nerves, and gastrointestinal tract. This process causes cellular stress and deformation of the normal tissue architecture, leading to end-organ dysfunction.

Cardiac amyloidosis (CA) is caused by the deposition of abnormal amyloid fibrils in the myocardium, including the ventricular walls, valves, and conduction system. This infiltrative process typically causes heart failure with preserved ejection fraction (HFpEF) and, in more advanced stages, degenerates into heart failure with reduced ejection fraction (HFrEF).

Table 1 provides an overview of terminology related to amyloidosis, and in particular, cardiac amyloidosis.

Pathophysiology

In systemic amyloidosis, the amyloidogenic protein is synthesised in one tissue, circulates in the blood, and is finally deposited as amyloid fibrils at a distant site or sites such as the heart, kidneys, or nerves [2]. The process of amyloid formation sees a misfolded protein form prefibrillar aggregates and finally deposit as mature fibrils in the extracellular space. This is a complex process, involving not only the amyloidogenic protein but also extracellular chaperones and matrix components, shear forces, tissue proteolysis, and interactions with various cells. In terms of protein misfolding, a point mutation resulting in an amino acid substitution (e.g., ATTRv) or a unique amino acid sequence (e.g., AL) may destabilise the protein making it prone to misfold and aggregate. Alternately, because nucleation and fibril development are concentration-dependent processes, an increased plasma concentration of the parent protein may predispose to amyloid formation (e.g., AA or AL). Sometimes wild-type proteins may be intrinsically amyloidogenic (e.g., ATTRwt) and can, at a slow rate, form amyloid deposits that become symptomatic after many decades. Ageing also contributes to amyloid deposition, but the mechanism is uncertain.

Table 1 Overview of terminology.

Term	Definitions
Amyloid	• The term 'amyloid' and 'amyloid fibril' technically refers to any cross β-sheet fibril which can be both physiological and pathological. • The amyloid deposits are formed by 10-nanometre to 12-nanometre-wide nonbranching fibrils and display characteristic positive Congo red staining with birefringence under polarised light. • For clarity, in this Consensus Statement, amyloid will *only* be used to refer to pathological deposits of specific protein fibrils with distinct microscopic properties, particularly affinity for Congo red dye with typical birefringence under polarised light.
Amyloid fibril protein	• All amyloid fibril proteins are named by a standard convention as "A" for amyloid, followed by the specific protein as a suffix, e.g., AL (L=immunoglobulin light chain) or ATTR (TTR=transthyretin). • In the case of ATTR, the protein can be specified as wild-type (wt) or variant (v), e.g., ATTRwt or ATTRv. • Furthermore, in the case of variant proteins, the specific variant can replace "v", e.g., ATTRV30M [1].
Amyloidosis	• While amyloid is the deposited material, amyloidosis is the disease caused by amyloid fibrils or during the process of their formation. • Thus, the amyloid fibril protein is ATTRwt, and the disease is ATTRwt amyloidosis.
Systemic amyloidosis	• Systemic amyloidosis is amyloidosis that results when the production of the amyloid-forming protein is distant to the amyloid deposits (e.g., transthyretin produced in the liver but deposited in the heart as ATTR amyloid).
Localised amyloidosis	• In localised amyloidosis, amyloid deposits occur only at the site of amyloid protein production.
HFpEF	• Heart failure with preserved ejection fraction (HFpEF) is defined as: — Clinical symptoms with or without signs of heart failure — A measured ejection fraction (EF) of at least 50% and, — Objective evidence of either relevant structural heart disease or diastolic dysfunction without an alternative cause.
Left Ventricular (LV) hypertrophy	• This refers to the hypertrophy of cardiac muscle cells (cardiomyocytes), which is typically seen in hypertension.
Increased LV wall thickness	• This refers to an increase in LV wall thickness on echocardiography beyond 12mm. There is biographical variation, with women expected to have a smaller LV wall thickness. The pathology in CA is increased LV wall thickness rather than "LV hypertrophy" (defined above).

The process whereby amyloid formation causes organ dysfunction is not fully understood. Certainly, a major cause of cardiac dysfunction is due to the mass effect of extracellular amyloid deposits with disruption of tissue structure [3]. Cellular cytotoxicity can be caused by both amyloid fibrils, pre-fibrillar aggregates and the soluble circulating protein [4]. In the case of AL amyloidosis, amyloidogenic light chains can exert direct toxic effects on myocardial cells, as noted in *in vitro* and animal models [5–7].

Cardiac amyloid deposition is most common in the myocardium resulting in increased bi-ventricular wall thickness, ventricular stiffness, and symptomatic HF from a restrictive cardiomyopathy (Figure 1). Atrial infiltration is also common and likely contributes to the high prevalence of atrial fibrillation (AF) and increases the risk of atrial thrombus formation and thromboembolism, even in sinus rhythm [8]. Pericardial involvement is common and leads to pericardial effusion, and endocardial involvement may result in thickening and dysfunction of the heart valves. Epicardial vessels are typically spared, but microvascular involvement is common, resulting in angina, or rarely, myocardial infarction [9]. Coronary flow reserve abnormalities by positron emission tomography have been reported in patients with microvascular amyloid infiltration [10].

Types of Cardiac Amyloidosis (CA)

Over 30 proteins can form amyloid deposits in humans, however only about 10 cause cardiac disease (Table 2). The vast majority of CA are caused by either ATTR or AL deposition. Table 3 summarises the types of cardiac involvement.

Epidemiology

ATTR–CA

The true epidemiology of ATTRwt CA is uncertain and is the subject of ongoing research. Historically, it was considered a 'rare disease', however modern diagnostic methodologies have now unmasked a large burden of previously undiagnosed cases. Anecdotally, ATTRwt-CA is now the commonest reason for referral to Australian and New Zealand amyloidosis clinics. The prevalence of ATTR-CA is highest in

Table 2 Proteins in amyloidosis that can cause cardiac disease.

ATTR amyloidosis	Transthyretin (TTR) was previously known as pre-albumin and is composed of four ß-sheet rich monomers. These circulate as a tetramer and carry thyroxine and retinal binding protein (i.e., transports thyroxine and retinol). It is produced predominantly in the liver, but also in the choroid plexus and retina. If the TTR tetramer becomes unstable and dissociates into monomers, the monomers have the endogenous molecular capacity to misfold and to then form amyloid. The mechanism that causes dissociation of the TTR tetramer in age-related wild-type transthyretin amyloidosis (ATTRwt) is poorly defined. In hereditary ATTR (ATTRv), the mutated "variant" TTR tetramer is unstable and dissociates into amyloidogenic monomers.
ATTRwt	Wild-type transthyretin amyloidosis (ATTRwt) most commonly deposits in tenosynovial tissues and the heart. ATTRwt has a predilection for the connective tissues, and this usually precedes the diagnosis of cardiac involvement by many years. For instance, carpal tunnel syndrome is diagnosed in ≈40%–50% of patients, on average 10 years before the diagnosis of ATTRwt [11]. Spinal canal stenosis can occur from deposition of amyloid in the ligamentum flavum causing spinal cord compression, canal stenosis, and nerve root compression. In some instances, rupture of the biceps tendon in the forearm can precede cardiac involvement by many years. The pace of the amyloid deposition is slow, and some patients may never develop cardiac disease. Approximately 9% may develop a mild peripheral sensory neuropathy [11]. The kidney is not affected by ATTRwt, however cardiac dysfunction can cause a low output state and resultant renal failure.
ATTRv	Variant transthyretin amyloidosis (ATTRv) is caused by pathogenic variants in the TTR gene that is located on the long arm of chromosome 18. Variants are inherited in an autosomal dominant manner. Prognosis, age of onset and symptoms depend on variant type and position. Note that for these patients the recommended terminology is, "hereditary" rather than "familial" by the International Society of Amyloidosis (ISA), and we have endorsed this in these consensus guidelines.
AL Amyloidosis	Amyloid light chain (AL) amyloidosis occurs when bone marrow plasma cells produce monoclonal free light chains which circulate, misfold and deposit as amyloid fibrils in any tissue of the body except the central nervous system. The heart is involved in 60%–70%, and those with cardiac involvement carry the worst prognosis.
AA amyloidosis	AA amyloidosis occurs in patients with chronic inflammation, which drives the accumulation of amyloid protein. It was previously more prevalent, however due to better treatment of chronic inflammatory conditions, it now accounts for <5% of cardiac cases. AA amyloidosis is associated with renal failure, proteinuria, gastrointestinal problems.
Fibrinogen Aα (AFib):	Fibrinogen Aα (AFib) amyloidosis is inherited in an autosomal dominant manner due to variants in the FGA gene that encodes fibrinogen Aα-chain. Presents with renal disease and often progresses to end-stage renal failure.
Apolipoprotein A-1 (AApoA1):	Apolipoprotein A-1 amyloidosis is inherited in an autosomal dominant manner due to variants in the APOA1 gene. This can lead to deposition of amyloid within the heart, liver, kidneys, testis, nerves, larynx, and skin.
Apolipoprotein A-II (AApoAII)):	AApoAII amyloidosis is inherited in an autosomal dominant manner and is associated with renal disease. Note that ApoAII is one of the major components of plasma high-density lipoprotein.
Apolipoprotein (A-IV):	AApoAIV amyloidosis is Inherited in an autosomal dominant manner and is associated with renal disease. Rarest form of the Apolipoprotein A group.
β2-microglobulin (Aβ2M):	Associated with excessive accumulation of β-2 microglobulin (Aβ2M) in patients with end-stage renal failure being supported on dialysis. Aβ2M deposits in the tenosynovial tissues, spine, gastrointestinal tract and uncommonly the heart. Improved dialysis technology has almost eliminated this disease.
Gelsolin (AGel):	Inherited in an autosomal dominant manner, and is associated with a triad of ophthalmological, neurological, and dermatological signs and symptoms. Cardiac involvement is increasingly being recognised in this rare entity.
Isolated atrial amyloidosis (AANP):	Unlike the other forms of CA in this article, AANP amyloidosis is not a form of systemic amyloidosis but, instead, amyloid deposition is limited to the atrium. The amyloid fibril is formed from atrial natriuretic peptide. AANP is more common in women and in patients with AF. Its exact role in AF pathogenesis is yet to be defined but studies have suggested that it may be a precipitating factor for AF or alternately may be produced as part of the atrial remodelling associated with this arrhythmia [12].

certain risk groups including those with HF (predominantly HFpEF), low flow low gradient aortic stenosis (AS), and those with concomitant extra-cardiac manifestations such as carpal tunnel syndrome or biceps tendon rupture (Table 2).

Insights into disease prevalence have come from studies of bone scintigraphy. In one study of 3,472 hydroxymethylenediphosphonate (HMDP or HDP) bone scans from Brisbane, Queensland, Australia [13], abnormal cardiac uptake was not observed in anyone aged less than 65 years. The prevalence of cardiac uptake consistent with ATTR-CA in individuals aged 65 years and over was 1.44% in males and 0.17% in females, increasing with age to reach

Table 3 Types of cardiac involvement.

Fibril protein	Precursor protein	Systemic (S) vs Localised (L)	Acquired (A) vs Hereditary (H)	Frequency of clinical organ involvement				
				Heart	Kidney	Liver	Nerves	Other
COMMON CAUSE OF CARDIAC AMYLOIDOSIS								
ATTRwt	Transthyretin, wild type	S	A	+++	–	–	+	Carpal tunnel syndrome, spinal stenosis, ligaments, tenosynovium
AL	Immunoglobulin light chain	S	A	+++	+++	+	++	Macroglossia, Factor X deficiency
LESS COMMON CAUSE OF CARDIAC AMYLOIDOSIS								
ATTRv	Transthyretin, variant	S	H	+++	+		+++	Vitreous opacities, leptomeningeal involvement
AANP	Atrial Natriuretic Peptide	L	A	+++ (atria)	–	–	–	
UNCOMMON CAUSE OF CARDIAC AMYLOIDOSIS								
AFib	Fibrinogen α, variants	S	H	rare	+++	+	–	
AA	Serum amyloid A	S	A	+	+++	+	–	
AApoAI	Apolipoprotein A I, variants	S	H	+	+++	++	+	Larynx, skin
AApoAII	Apolipoprotein A II, variants	S	H	+	+++			
AApoAIV	Apolipoprotein A IV wild type	S	A	Poorly understood	++			Striking microvasculature involvement
AGel	Gelsolin, variants	S	H	++	–	–	+++ (cranial neuropathy)	Corneal lattice dystrophy
Aβ2M	β2-Microglobulin, wild type	S	A	Variable	–	–	–	Bone cysts, joint synovium

6.15% in males and 1.69% in females aged 85 years and older. Given the Australian population over 65 years of age is approximately 2.1 million, this would suggest that up to 33,000 Australians may have ATTRwt-CA. These estimates of ATTR-CA prevalence are like those reported in European countries [14]. Alternate epidemiological data can be inferred from studies of patients with HFpEF. In an autopsy study of LV specimens from patients with ante-mortem diagnosis of HFpEF without clinically apparent amyloid [15], moderate or severe interstitial transthyretin deposition consistent with ATTRwt as the primary aetiology of HFpEF, was present in 5% of patients >70 years and 80% were male. In a study of 120 consecutive patients ≥60 years with HFpEF and LV hypertrophy (≥12 mm), DPD scintigraphy demonstrated that 13% had ATTR-CA [16]. There was no difference in age or gender between ATTR-CA and other causes of HFpEF. If we assume that about half of the estimated 480,000 Australian adults with HF have HFpEF [17], then, by this estimate, 8,000 to 12,000 Australians may have ATTRwt-CA. Table 4 summarises distinct patient populations with a higher prevalence of ATTRwt cardiomyopathy.

AL Amyloidosis

An epidemiological study of amyloidosis based on biopsy proven cases identified an incidence of 12 cases per million person years [24]. Given most of these cases are presumed to be AL amyloidosis (a monoclonal gammopathy was identified in 72%) and about 70% of AL amyloidosis cases have cardiac involvement, the incidence of AL amyloidosis cardiomyopathy would be expected to be in the order of 7 cases per million.

AANP (Isolated Atrial) Amyloidosis

Atrial amyloid deposition is a common finding at autopsy, particularly in elderly patients [25]. It was found in 16% of consecutive cardiac biopsy specimens obtained during cardiac surgery, mostly from patients with chronic rheumatic heart disease [26].

Table 4 Distinct patient populations with higher prevalence of ATTRwt cardiomyopathy.

Patient population	Prevalence
HF patients aged >60 years	On bone scintigraphy 13% of patients hospitalised with HFpEF found to have ATTRwt-CA [16].
Patients with concomitant AS	ATTRwt-CA found in 6%–16% of patients with AS [18–20].
Non-obstructive hypertrophic cardiomyopathy phenotype	5% of patients with unexplained hypertrophy found to have a TTR variant. Unexplained septal hypertrophy found in up to 25% of patients with ATTR-CA.
Carpal tunnel syndrome	Up to 50% of patients with ATTR have bilateral carpal tunnel syndrome. Peripheral nerve symptoms begin 5–10 years prior to ATTRwt-CA [21].
Lumbar spinal canal stenosis	Amyloid deposits in ligamentum flavum may be an early manifestation of systemic ATTR disease [22].
Biceps tendon rupture	Biceps tendon rupture is not uncommon with up to 44% of patients being affected [23].

Investigations

Patients may present with a constellation of symptoms that overlap with other cardiovascular conditions. These symptoms include shortness of breath, palpitations, pre-syncope, syncope, postural hypotension, and chest pain.

There are certain cardiac, and extracardiac "red flags" that should alert the physician to considering amyloidosis as a differential diagnosis (Figure 2). Cardiac flags include down-titration of antihypertensives in a previously hypertensive patient, symptoms and signs of heart failure including pleural effusions and peripheral oedema, AF, and conduction disease.

Within cardiovascular patients, there are certain high-risk groups who require particular attention. These include patients with aortic valve disease, particularly degenerative AS, low-flow low gradient AS, and those referred for transcatheter aortic valve replacement (TAVI). High risk groups according to biomarkers include those with a persistently elevated troponin level ("troponinemia") and those with a disproportionately elevated serum NT-pro BNP level. Finally, patients with unexplained LV 'hypertrophy', including those with a historical diagnosis of hypertrophic cardiomyopathy, should be considered.

Extra-cardiac red flags include multisystem involvement and require a detailed history and clinical exam. These include neurological signs, particularly bilateral carpal tunnel syndrome and spinal canal stenosis, autonomic neuropathy including orthostatic hypotension, sexual dysfunction and sweating abnormalities, and gastrointestinal symptoms including alternating diarrhoea and constipation.

12-Lead Electrocardiogram (ECG)

All patients with suspected CA should have a 12-lead electrocardiogram (ECG). This may demonstrate typical features but has limited sensitivity and specificity. LV hypertrophy by ECG criteria is often present [27], but is non-specific; more typical for CA is reduced QRS voltage that is discordant with the degree of increased LV wall thickening on echocardiogram [28]. There are findings suggestive of pseudo-infarction [28], without associated regional wall motion abnormality. Conduction abnormalities are common, with sinus node dysfunction, and atrioventricular conduction delay or bundle branch blocks, particularly left bundle branch block [29]. Comparison with prior ECGs may be of use to evaluate disease progression.

Transthoracic Echocardiogram (TTE)

Typical features on transthoracic echocardiogram (TTE) include increased LV wall thickness, which is usually symmetric in nature [30]. The increase in LV wall thickness is associated with a small LV cavity and a consequent reduction in LV stroke volume, which is considered a hallmark of CA [3]. Increased myocardial echogenicity or 'speckling' is a feature of CA but is not a sensitive marker [31,32]. Systolic function measured by LV ejection fraction (EF) is relatively preserved till more advanced disease, but an early reduction in LV global longitudinal strain has been reported [30,33] (Figure 3). There is, additionally, regional variation in segmental LV strain with reduction in basal segmental strain with a relative apical sparing pattern [34]. However, relative apical sparing is not specific for CA, and is now recognised in other hypertrophic phenotypes.

Diastolic dysfunction is common and often advanced, with evidence of restrictive filling (Grade 3 diastolic dysfunction). In addition, there is often evidence of elevated LV filling pressure present with an elevated E/average e' [35,36]. Increased thickness of the right ventricular free wall is noted and is often used to differentiate CA from hypertensive heart disease [30]. An associated reduction in right ventricular free wall strain has also been reported [37,38].

Bi-atrial enlargement is common and has been described as "owl eyes". Atrial enlargement is consequent to diastolic dysfunction. There is often coexistent thickening of the interatrial septum and atrial dysfunction which is likely due to amyloid deposition in the atrial myocardium [29]. Left atrial reservoir and contractile strain may be significantly impaired regardless of left atrial volume or LVEF in CA [39]. Valve leaflet thickening is reported, but valvular regurgitation is largely mild or at most, moderate in severity [30]. A pericardial effusion is not an uncommon finding [30].

Low flow low gradient AS is increasingly being recognised in conjunction with CA. ATTR-CA was present in 16% of patients with AS requiring TAVI [19]. Both conditions cause LV wall thickening with diastolic dysfunction. When ATTR-CA is concomitantly present, the symptomatic response to treatment

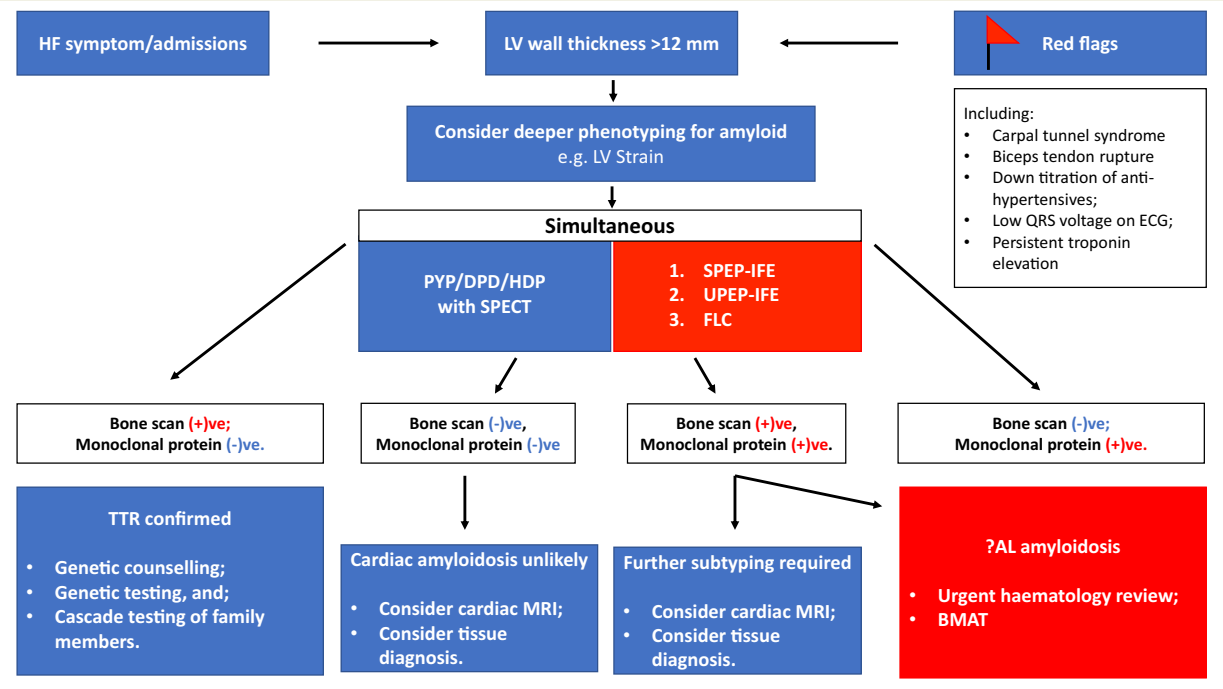

Figure 2 Proposed algorithm for work up of CA.
Abbreviations: AL, amyloid light chain; CMR, cardiac magnetic resonance; FLC, free light chains; IFE, immunofixation; LV, left ventricle; NT-pro BNP, N-terminal pro b-type natriuretic peptide; SPEP, serum electrophoresis protein; TTR, transthyretin; UPEP, urine protein electrophoresis.

and survival benefit is less. Echocardiographic features suggesting underlying ATTR-CA include severe LV wall thickening or LV wall thickening disproportionate to the degree of AS and marked diastolic dysfunction [40]. Markedly abnormal LV strain with an apical sparing strain pattern is also noted when CA is associated with AS, whereas a non-specific patchy reduction in regional strain is observed in instances with isolated AS. Right ventricular (RV) wall thickening and/or significant pulmonary hypertension is often present [40].

A variety of echocardiographic parameters that identify CA have been recently described and combine various TTE parameters. The LVEF to strain ratio (EFSR) could discriminate hypertrophic cardiomyopathy from CA [41]. The increased wall thickness (IWT) score is a multiparametric score, that can differentiate AL-CA from other hypertrophic cardiomyopathies [42]. However, this score is complex and has been subsequently simplified to the relative wall thickness/ E/e' (AMYLoidosis Index [AMYLI] score) [43]. More recently, the LV mass to strain ratio (MSR) was proposed as a tool to differentiate AL-CA from ATTR-CA [44]. These scores are still complex and time consuming for the clinician but may become useful tools with the uptake of machine learning models.

Box 3 summarises key points about ECG and Echocardiology in CA.

Laboratory Investigations

Routine investigations should include a full blood count, assessment of biochemistry, kidney function and liver function tests. Cardiac biomarkers, including NT-pro-BNP and high sensitivity troponin, are important in staging cardiac disease and will be discussed elsewhere. All patients should be screened for a monoclonal protein. This should include serum and urine protein electrophoresis with immunofixation as well as an immunoglobulin free light chain (FLC) assay for k and λ immunoglobulin light chains. This combination of tests should detect a monoclonal protein in nearly all cases of AL amyloidosis [45]. Approximately two-thirds of patients have positivity on serum protein electrophoresis with immunofixation [46]. Monoclonality is determined by the presence of an abnormal kappa to lambda FLC ratio rather than raised absolute kappa or lambda FLC levels [47]. Results must be interpreted with caution in patients with renal failure given the circulating free light chains are normally cleared by the kidneys. It is important to note that kappa to lambda ratios may be elevated three-fold in patients with renal insufficiency when using the Freelite FLC assay whereas when using the N Latex assay, the kappa to lambda ratio is not affected by renal function [48]. A more recent analysis of the Freelite assay, from the iStopMM study in Iceland, proposed estimated glomerular filtration rate (eGFR)-based reference intervals [49,50]. As a rough rule of thumb, in renal failure, the kappa and lambda free lights chains are often elevated proportionately, giving a normal ratio.

Physicians must also be aware that several manufacturers produce FLC assays that may produce variable results for patients. Where possible, for serial measurements, the same

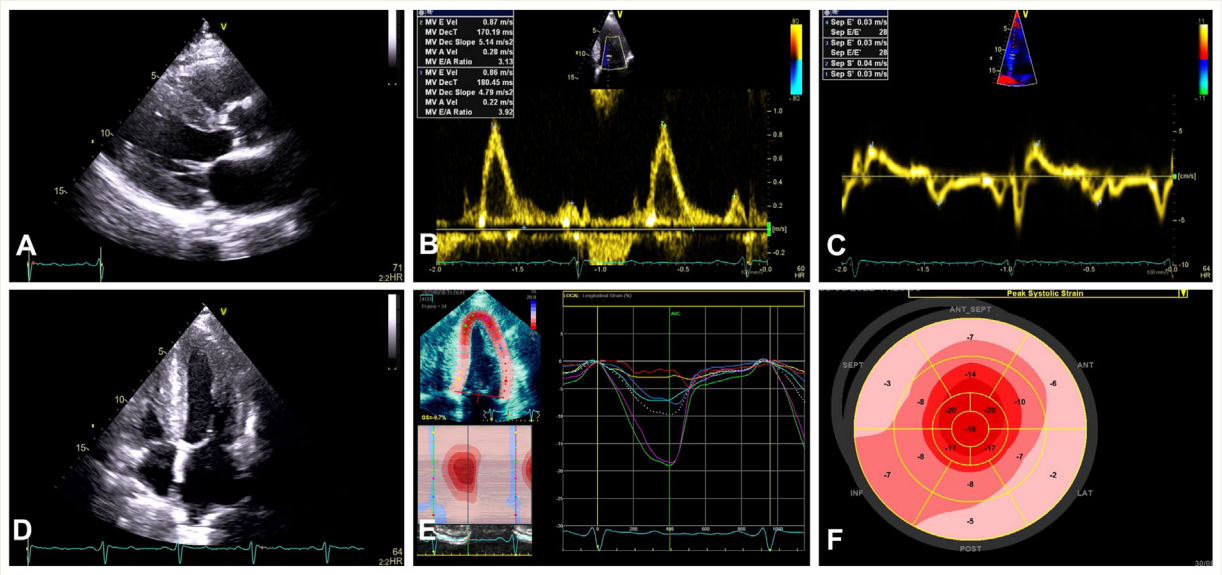

Figure 3 Typical echocardiographic features of CA. A. Parasternal long axis view demonstrating increased LV wall thickness. B. Transmitral flow showing restrictive filling (Grade 3 diastolic dysfunction). C. Reduced mitral annular e' velocity. D. Apical 4 chamber view with myocardial speckling, increased thickness of the RV free wall and enlarged atria. E. Apical 4 chamber global longitudinal strain which is reduced. F. Typical "cherry-on-top" segmental strain pattern.

manufacturer and laboratory should be used. These factors need to be carefully considered when assessing for a monoclonal light chain in patients with AL amyloidosis. This is particularly relevant to the proportion (~20%) of AL amyloidosis patients that present with low level free light chains (FLC) [51]. Where the suspicion for a monoclonal protein is high in the context of AL amyloidosis and serum assays have not been definitive, bone marrow biopsy to assess for a clonal plasma cell population may be considered.

Bone Scintigraphy

The observation that certain bone scintigraphy tracers localise to amyloid deposits in the heart has revolutionised the diagnostic algorithm for cardiac amyloidosis. While iodine-123 (^{123}I) labelled serum amyloid P (SAP) scintigraphy has been used to assess organ amyloid involvement, it is of little use for assessment of cardiac disease due to intrinsic washout kinetics. However, technetium-99m labelled radionuclide bisphosphonate derivatives including 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), pyrophosphate (PYP), or hydroxymethylenediphosphonate (HMDP or HDP) have been demonstrated to localise in the myocardium of subjects with ATTR-CA, and less frequently in subjects with AL-CA, although the precise mechanism of uptake has not been clearly identified [52,53]. At present, DPD is not approved by the Therapeutic Goods Administration or readily available in Australia.

The degree of myocardial uptake in amyloidosis can be graded semi quantitatively by visually comparing myocardial to bone (rib) uptake on a scale of 0–3 (Table 5), according to the method described by Perugini [54], or quantitatively using the heart (myocardial) to contralateral lung ratio (H/CL), with a PYP H/CL ratio ≥1.5 at 1 hour, or ≥1.3 at 3 hours, being consistent with the presence of CA [55]. In studies showing planar uptake, single photon emission computed tomography (SPECT) imaging should be obtained at 3 hours after administration of tracer to avoid confounding by the presence of persistent blood pool activity [52]. The combination of planar and SPECT imaging reduces false positivity due to blood pool uptake [52]. A visual myocardial grade of 2 or more, in the absence of a monoclonal protein in serum or urine, has demonstrated specificity and positive predictive value for a non-invasive diagnosis of ATTR-CA of almost 100% [53]. It is important to note that >20% of patients with AL-CA may demonstrate Grade 2 or 3 uptake, so exclusion of a monoclonal protein is crucial before making a diagnosis of ATTR-CA. False negative scintigraphy myocardial uptake is rare and usually low-grade, but has been reported and may occur in certain ATTRv-CA.

The use of positron emission tomography for identification of CA, in particular 18F-labelled tracers, is being actively evaluated and may hold promise, but for now are regarded as investigational only. Box 4 summarises key points about scintigraphy in investigating CA.

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMR) is an excellent modality for the diagnosis and monitoring of CA. Complementary to TTE and nuclear scintigraphy, CMR provides highly accurate and reproducible structural and functional information as well as offering tissue characterisation and the ability to quantify amyloid burden (Figure 5). These CMR

Box 3. Key points about ECG and Echo in CA

- A 12-lead electrocardiogram and echocardiography are cheap and widely available screening tools. They lack specificity for diagnosis of CA.
- Echocardiographic global and regional strain has improved sensitivity compared to traditional parameters and could also be utilised in longitudinal follow up.
- Multiparametric measurements may be useful particularly with the advent of machine learning and artificial intelligence.

characteristics make it particularly useful in the differentiation of CA from other causes of myocardial thickening or infiltration.

Morphological findings

Characteristic CMR findings seen in CA include typical morphological features such as thickening of LV and RV walls, valve leaflet thickening and the presence of pericardial effusion. Typically concentric and symmetric in CA, the pattern of LV wall thickening can be easily assessed with CMR but is not particularly helpful in differentiating CA from other pathologies, with a range of different patterns including asymmetric thickening frequently present [56].

Tissue characterisation

Tissue characterisation using T1 mapping (pre- or post-contrast), T2 mapping, late gadolinium enhancement (LGE) and the assessment of myocardial extracellular volume (ECV) have proven to be very useful. Typically, CA presents with a diffuse subendocardial or transmural pattern of LGE, with the latter more common in subjects with ATTR-CA [57]. Due to gadolinium contrast accumulation in the extracellular space, traditional post-contrast LGE imaging shows typical difficulty with "nulling" the myocardial signal relative to blood pool. Newer, but widely available, phase-sensitive inversion recovery LGE techniques have been useful, improving reproducibility of LGE assessment.

Table 5 Visual scintigraphic score. Adapted from Perugini et al. [54].

Visual Grade	Myocardial Scintigraphic Uptake
0	Absent myocardial uptake and normal bone uptake
1	Mild uptake but less than bone
2	Moderate uptake equal to bone
3	High uptake greater than bone

Box 4. Key points about Scintigraphy in CA

- We recommend simultaneous screening with technetium-99m PYP, DPD, HMDP bone scintigraphy and blood and urine testing for a monoclonal protein (Figure 4).
- Non-invasive diagnosis of ATTR-CA is now possible with positive bone scintigraphy (grade 2 or 3) and no evidence of a monoclonal protein on blood or urine.
- Where a monoclonal protein is detected, and AL amyloidosis is suspected, urgent haematology referral for work up of AL amyloidosis including bone marrow biopsy is recommended.
- Planar bone scintigraphy has a higher false positive rate as uptake is often by blood pool, whereas planar with SPECT bone scintigraphy is more specific for myocardial tracer uptake.

The use of T1 mapping techniques offer the ability to quantify the extent of myocardial amyloidosis with or without the use of contrast. A high native myocardial T1 time in patients with clinical suspicion of amyloid has been shown to be useful to diagnose and differentiate amyloid from other causes of LV hypertrophy and can be particularly useful in subjects where avoidance of gadolinium contrast may be desirable, such as severe renal failure [58,59]. One limitation of T1 assessment is a lack of standardisation across different sequences and hardware.

The addition of post-contrast T1 time allows the calculation of myocardial extracellular volume (ECV), which has shown good diagnostic accuracy for amyloidosis and could allow the assessment of response to treatment [60]. A global ECV value of >0.40 has been suggested as a useful diagnostic threshold for the presence of amyloidosis [61]. Both native T1 time and ECV have been shown to have prognostic value [62].

In the diagnostic algorithm, CMR is used when the first-line non-invasive pathway is inconclusive, for example a negative or equivocal bone scintigraphy result with negative blood and urine immunofixation with a strong clinical suspicion of CA. It can also be used with negative bone scintigraphy and at least one abnormal monoclonal protein to confirm cardiac involvement [52]. Finally, in AL amyloidosis there is increasing evidence that sequential monitoring of ECV on CMR can be important in monitoring treatment response [63].

CMR has some limitations. Importantly, it is still prohibitively expensive for some patients as CA is not currently listed as an item for reimbursement in the Medicare Benefits Scheme

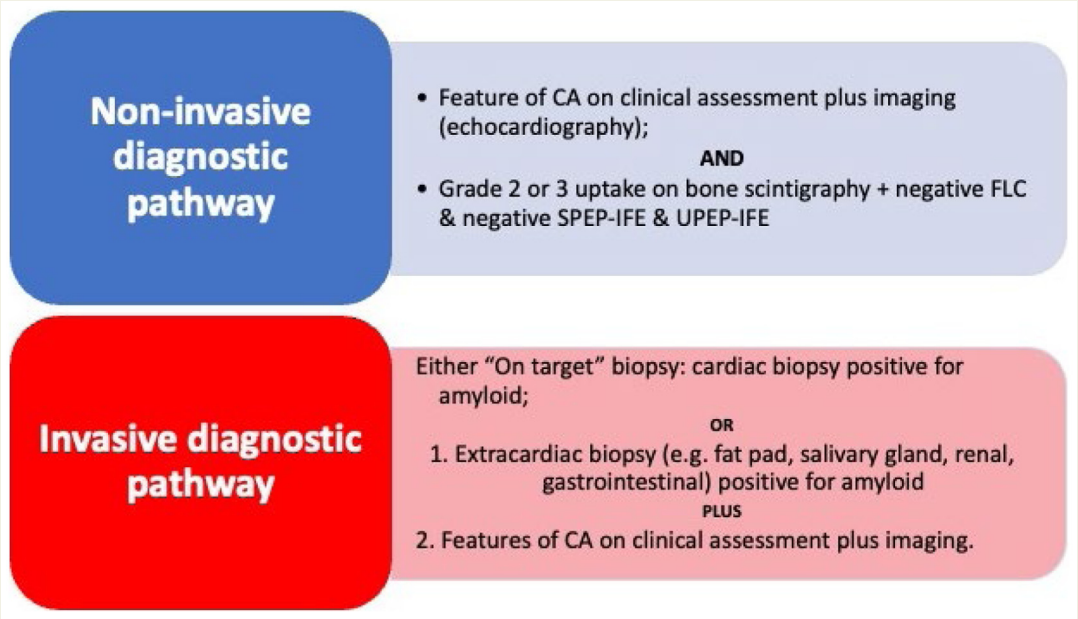

Figure 4 Non-invasive vs invasive diagnosis of CA.
Abbreviations: CA, cardiac amyloidosis; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; IFE, immunofixation; FLC, free light chains.

in Australia. In addition, there are currently no techniques that categorically differentiate between AL-CA and ATTR-CA. Box 5 summarises key points about CMR in CA.

Genetic Counselling and Testing

Genetic testing has a key role in the diagnostic work-up of CA (Figure 2). Identifying a causative genetic variant has implications for affected patients and their families and may inform prognosis and management.

Genetic testing has a Class I indication in international consensus guidelines and is typically undertaken at the end of the diagnostic pipeline in all patients who have been diagnosed with ATTR-CA. Genetic testing is needed in affected individuals irrespective of clinical presentation or family history, in order to differentiate between the age-related wild-type form of ATTR (ATTRwt) and the heritable (ATTRv) forms [27,64,66–68].

The usual method for genetic testing involves targeted sequencing of the coding sequences of the TTR gene. This can be organised through most clinical cardiac genetic services, although availability and costs may vary. Multigene panel or exome/genome sequencing may be useful to exclude other genetic causes of ventricular hypertrophy and arrhythmias, although this is not part of standard practice presently.

Variant interpretation

Interpretation of genetic test results is not always straightforward and needs to be done by experienced genetics personnel. Not all variants in the TTR gene are necessarily deleterious and variant curation needs to be carefully performed in accordance with standard American College of Medical Genetics and Genomics criteria [69]. Factors to consider include whether the variant is predicted to disrupt transthyretin structure and function, the frequency with which the variant occurs in ethnically-matched reference populations, and whether it has previously been reported as disease-associated in variant databases (such as ClinVar). There are several common variants that are characteristic of certain geographical regions or phenotypes [66,68,70]. These include p.Val1122Ile, that manifests predominantly as cardiomyopathy. This variant is present in ~3%–4% of black Americans and up to 10% of black Americans who present with heart failure aged >60 years. The variant p.Thr60 Ala is associated with a mixed phenotype and occurs in ~1% of people in north-western Ireland, while p.Val30Met is often associated with polyneuropathy but may also cause late-onset cardiomyopathy. Apart from these well-described common variants, there are numerous rare variants associated with ATTRv. Rare variants may be uniquely seen in single probands or families and evidence for disease-association may be less robust than for common variants. Some genotype–phenotype correlations for rare variants have been proposed [66], but further work is needed to confirm these findings. Whether pathogenic variants cluster in certain protein domains has yet to be determined. Caution is needed for determining the clinical significance of TTR variants that arise as incidental findings in patients who have genetic testing for unrelated indications, and follow-up clinical and genetic evaluation by experienced personnel is required in this context.

Family screening and genetic counselling

A major outcome of genetic testing is the capacity to undertake predictive testing in relatives. This is becoming increasingly important with the emergence of new therapies that hold promise for attenuating or preventing disease progression. For

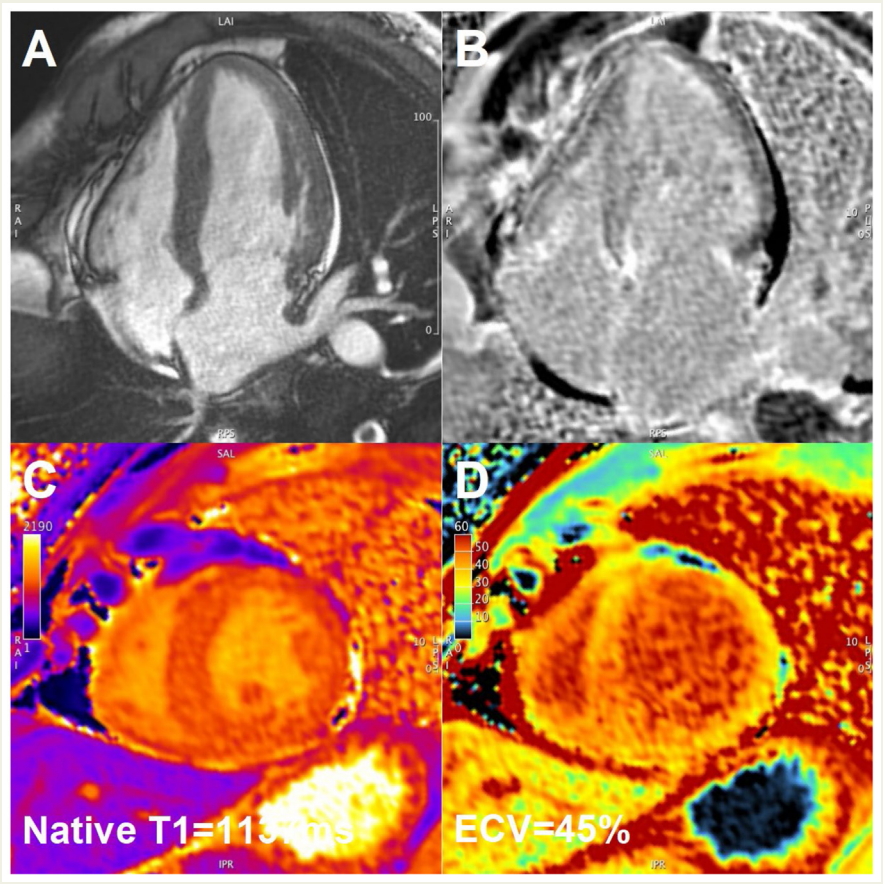

Figure 5 Typical CMR features of CA. (A) four chamber cine sequence with diffuse wall thickening and small pericardial effusion; (B) phase sensitive inversion recovery (PSIR) late gadolinium enhancement (LGE) image showing diffuse myocardial uptake with subendocardial predominance; (C) native T1 map showing diffuse elevation of myocardial T1 time; (D) extracellular volume (ECV) myocardial map with elevated myocardial extracellular volume.

index cases confirmed to carry a pathogenic or likely-pathogenic TTR variant, a three-generation family history needs to be obtained with cascade clinical and genetic screening offered to all first-degree relatives. This is ideally undertaken in a multi-disciplinary clinic that includes clinicians, clinical geneticists, allied health personnel and genetics counsellors [68,70,71]. The potential psychosocial impact of receiving a positive result should not be under-estimated, particularly if this occurs many decades before expected disease onset. Predictive testing of asymptomatic relatives may also have insurance and/or employment implications. For these reasons, family members need to be fully informed about the potential outcomes of genetic testing, provide informed consent, and undergo both pre-test and post-test genetic counselling [68,70,71]. To minimise harm and maximise cost-efficacy, it has been suggested that clinical and genetic screening is delayed until approximately 10 years or so before the usual age of disease manifestation in each family [27,68,70,71]. The optimal frequency of follow-up screening in genotype-positive, phenotype-negative relatives and the choice of methods to be used are the subject of ongoing investigations [27,64,68,70,71]. Identification of the most sensitive markers of early disease should facilitate pre-emptive interventions and further research is urgently needed.

Tissue Diagnosis

A tissue biopsy with amyloid deposits demonstrated by Congo red staining is the gold standard for diagnosing amyloidosis. This now is only required in approximate 30% of patients where a non-biopsy diagnosis is not possible. This is because non-biopsy diagnosis of ATTR-CA in patients without a monoclonal protein using bone scintigraphy has a high degree of specificity [53] (Figure 4). In suspected AL amyloidosis, the first step is a bone marrow aspirate and trephine, avoiding invasive organ biopsy. The biopsy can be "on target", which means sampling the organ where the clinical suspicion lies; in the case of ATTR-CA, this involves a cardiac biopsy. It can also be "off-target", in which case to make the diagnosis of ATTR-CA there must be features of cardiac involvement on cardiac biomarker, TTE and CMR.

Endomyocardial biopsy

For suspected CA, a cardiac biopsy is the most specific, and with an adequate biopsy sample, the diagnostic accuracy is

Box 5. Key points about CMR in CA

- CMR is useful for tissue characterisation in CA.
- Typical features include diffuse subendocardial or transmural pattern of LGE with poor "nulling".
- It is useful in those whom the diagnosis is indeterminate on the basis of TTE and scintigraphy results (i.e., Grade 0 or 1 uptake), with negative paraprotein screen but with high clinical suspicion [64].
- CMR is also useful in patients in whom a diagnosis of monoclonal gammopathy or systemic amyloidosis has been made and there is a need to clarify cardiac involvement [65].

close to 100%. This is an invasive procedure in which 4 x 4–5mm samples are taken from the endomyocardium at the mid-RV septum. The procedure does not involve a general anaesthetic and patients are discharged on the same day. This procedure needs to be performed at a specialist centre, as complications rarely include pericardial effusion or haematoma and pneumothorax.

Bone marrow biopsy

Bone marrow biopsy with haematology oversight should be the standard of care in all patients with suspected AL amyloidosis. This test will show plasma cell dyscrasia in over 80% of patients and amyloid deposits in approximately 60% [72].

Fat pad biopsy

Fat pad biopsies have variable sensitivity depending on the type of amyloidosis and the load of disease ranging from only 15% sensitivity in ATTRwt to 100% sensitivity in advanced AL amyloidosis with a high burden of disease [73].

Careful clinical assessment and review of imaging needs to be undertaken to determine a site with a high burden of disease, that has the greatest potential yield from an invasive tissue biopsy. Other extracardiac sites where a tissue diagnosis can be made include a renal biopsy, nerve biopsy, salivary gland biopsy, or histopathology taken at the same time as colonoscopy/endoscopy, laminectomy, or carpal tunnel release. If this is considered, the surgeon and testing laboratory needs to be informed to ensure the correct samples and staining occurs.

For patients presenting with amyloid on a tissue biopsy the critical next step is accurate subtyping of the amyloid. Traditionally immunohistochemistry has been utilised with variable diagnostic sensitivity [74,75]. Given the many different types of amyloidosis, cross reactivity of some antibodies and nonspecific binding and staining, the utility of immunohistochemistry is limited. In settings where an extensive antibody panel is available, and the histopathology expertise is present the diagnostic accuracy can approach 100% [76]. Due to these limitations, liquid chromatography tandem mass spectrometry (LC-MS/MS) has become the gold standard for subtyping amyloidosis and should be utilised when readily available or considered in cases where traditional typing methods fail [77,78].

Staging of ATTR Amyloidosis

ATTR-CA is a progressive condition but has a better short to medium prognosis than the more aggressive AL-CA. There are two internationally validated staging systems that are endorsed in this consensus document, the National Amyloidosis Centre (NAC) staging system [79], and the Mayo Clinic staging system [66].

Clinical assessment with New York Heart Association (NYHA) functional status carries prognostic information. In the ATTR-ACT open label extension trial; patients in NYHA functional class I–II, the 5-year survival in those on continuous tafamadis, and placebo then tafamadis, were 61.4% and 40.3% respectively. In those in NYHA III functional class survival was 35% with continuous tafamadis treatment and 18% in the placebo then tafamadis group [80].

Cardiac Biomarker Staging

The National Amyloid Centre (NAC) have proposed a staging system using biomarkers: the N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and estimated glomerular filtration rate (eGFR) [79]:

Stage I NT-proBNP <3000 ng/L and eGFR >45mL/min/1.73m^2,
Stage II: either NT-proBNP <3000 ng/L and eGFR >45mL/min/1.73m^2, but not both,
Stage III was defined as NT-proBNP >3000 ng/L and eGFR <45mL/min/1.73m^2.

Another staging system was developed by the Mayo Clinic that used specifically cardiac biomarkers, TroponinT and NT-proBNP [81]:

Stage I: Troponin T <0.05ng/mL and NT-proBNP <355pmoL/L but not both,
Stage II: either Troponin T <0.05ng/mL and NT-proBNP <355pmoL/L but not both,
Stage III Troponin T >0.05ng/mL and NT-proBNP >355pmoL/L.

Finally, there is the modified Mayo score which includes NT-proBNP, Troponin T and renal function (eGFR), updated as the former two biomarkers can be influenced by renal function [82].

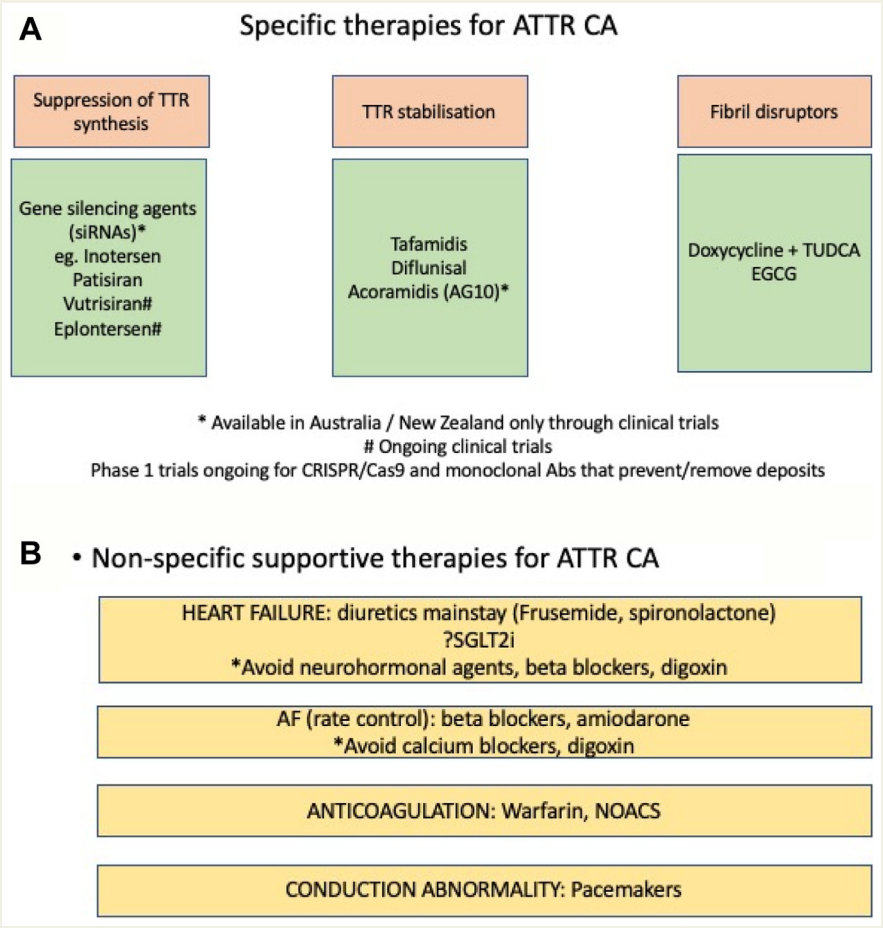

Figure 6 (A) Specific therapies for treatment of CA. (B) Non-specific and supportive therapies for treatment of CA. Abbreviations: CA, cardiac amyloidosis; ATTR, transthyretin amyloid: TTR, transthyretin; siRNA, small interfering RNA; TUDCA, tauroursodeoxycholic acid (a bile acid); EGCG, epigallocatechin gallate (a polyphenol); CRISPR/Cas9, clustered regularly interspaced palindromic repeats/Cas 9; Abs, antibodies; AF, atrial fibrillation; NOACS, non-vitamin K antagonist oral anticoagulants; SGLT2i, sodium-glucose cotransporter-2 inhibitors.

Overall, average (50%) survival for ATTRwt-CA was shown to be 6 years for stage I, 4 years for stage II and 2 years for stage III [79,81]. In the NAC population, survival tended to be less for those with ATTRv-CA.

It is recommended to uses cardiac biomarkers to guide discussion on patient prognosis, and that biomarkers be repeated every 6 to 12 months to provide a guide on disease progression [27].

Treatment of ATTR CA

Longitudinal Assessment and Follow Up

The management of ATTR-CA includes systemic therapy which helps manage the symptoms and complications of disease, and TTR-specific therapy to modify disease course and attenuate further progression (see Figure 6).

Importantly, ATTR-CA is a chronic and progressive disease. Longitudinal assessment is needed to determine individual patient response (progression, stability, or improvement) to current and future therapies [83]. The evaluation tools must be validated for use in both disease phenotypes (ATTRwt CA vs ATTRvCA), and for all stages of the disease. An accurate baseline assessment remains crucial and includes the initial disease staging and relevant biomarkers levels [84,85]. Clinical examination, NYHA functional class assessment, ECG and circulating biomarkers levels should be conducted at baseline and in regular 6 monthly intervals.

A new multiparametric approach, that includes a set of 11 measurable items across three separate domains: 1) clinical and functional endpoints; 2) biomarkers and laboratory markers, and 3) imaging and electrocardiographic parameters, has been proposed by the European Society of Cardiology (ESC) consensus panel [64]. One marker from each of the three domains provides the minimum requirements for disease progression.

As stated above, Domain 1 includes clinical and functional assessment tools. An increase in HF–related hospitalisation, an increase in NYHA class, a decline in quality-of-life measure (QoL) scores on standard questionnaires (5 to 10 points

Box 6. Key points about Heart Rhythm Management in CA

- Anticoagulation in patients with ATTR-CA and AF, regardless of CHA2DS2-VASc, is now a Class I indication.
- AF has been demonstrated in case series from 10% up to 71% of ATTRwt-CA and 9% to 26% AL-CA amyloid, and often causes clinical decompensation.
- Conduction disease is commonly encountered in patients with ATTR-CA.
- Standard indications for pacing are recommended.
- There is limited utility of ICDs for primary prevention, however secondary prevention indications for ICD implantation are accepted.

on the Kansas City Cardiomyopathy questionnaire or 10% on EuroQol group questionnaire) or six-minute walk test (6MWT) (by 30 to 40 metres) have been included as the key measurable outcomes in patients with ATTR-CA. It is important to remember that many of patients with ATTR-CA develop other age-related cardiac and extracardiac conditions, which impact their symptoms, and functional performance with resulting QoL scores, and often lead to progressive frailty [64].

Box 7. Key points about CA Management and Cardiac Transplantation.

- We advocate for referral to specialist amyloidosis centres with multi-disciplinary teams for the assessment and management of ATTR-CA.
- The Australian Amyloidosis Network (AAN) website (https://aan.org.au/) provides information for patients and clinicians.
- Patients should have a basic work up and should be referred early for subtyping and treatment.
- Cardiac transplantation for patients with ATTR-CA is possible in select cases, if the patients are identified and referred early.
- The recommended age limit for cardiac transplantation is ~70 years, so patients with ATTRwt-CA are often diagnosed too late.
- Careful assessment for, and treatment of, extracardiac manifestations such as peripheral or autonomic neuropathy is important in the perioperative period.

Domain 2 encompasses laboratory biomarkers. Reproducibility of certain measurements, such as natriuretic peptides and troponin levels that are evaluated over multiple timepoints may be more meaningful than those used at specific cut-off values. An arbitrary 30% increase in serum levels should be robust enough to identify patients with progression of underlying cardiomyopathy and not coexistent diseases. Advance in ATTR stage based on rise of cardiac biomarkers levels or reduction in eGFR could also be considered as a marker of disease [64].

Domain 3 includes cardiac imaging and ECG. TTE or CMR should be performed annually unless there is a significant clinical deterioration, or a new therapeutic strategy is implemented. Increase in LV wall thickness (by 2mm), increase in diastolic dysfunction grade, reduction in LV EF (by more than 5%), in stroke volume (by more than 5 mL) or a 1% deterioration in global longitudinal strain, constitute an indicator for disease progression. Minimising interobserver variability by performing serial measurements by dedicated technicians is advisable. The emergence of new conduction abnormality (atrioventricular or bundle branch block) suggests progressive TTR deposition [64].

As mentioned previously, in patients carrying TTR variants, the age of onset of symptomatic disease in the proband family member should be established. This varies according to typical age of onset for a particular variant. Once the predicted age of onset is identified, annual monitoring should begin 10 years before this date. The assessment is adjusted to the expected phenotypic presentation for the specific variant and in general includes clinical questionnaire and examination (both cardiac and neurological) and relevant cardiac and neurophysiological tests needed to detect organ involvement [5].

Any future long-term studies should also explore global measurements of frailty, stratifying patients by age, severity, and ATTR-CA phenotype. Ideally, multidimensional assessment of frailty should be incorporated into ongoing holistic assessment of ATTR-CA patients.

Heart Failure

Amyloid TTR deposition leads to a progressive restrictive cardiomyopathy characterised by decreased myocardial compliance, elevated filling pressure, reduced stroke volume and cardiac output. Studies directly addressing the benefit of traditional HF medical therapy for ATTR-CA remain limited. In the absence of definitive data, expert consensus opinion currently guides clinical practice. Excessive fluid and salt intake should be avoided as this would contribute to worsening of oedema and symptoms [86,87]. Loop diuretics are used preferably for maintaining fluid balance in ATTR-CA. The risk of over diuresis resulting in organ hypoperfusion, and acute kidney injury is higher than in other HF patient populations and requires close attention. Frusemide remains

Box 8. Key diseases-modifying treatment classes.

- TTR synthesis suppressors, e.g., patisiran, inotersen.
- TTR stabilisers, e.g., tafamidis (61 mg daily), diflunisal (250 mg b.d.), acoramidis.
- Fibril disruptors, e.g., epigallocatechin-3-gallate (EGCG; green tea extract) 600–800 mg daily, doxycycline, tauroursodeoxycholic acid, and ursodeoxycholic acid.
- Acoramidis and TTR synthesis suppressors have proven benefit but are not yet available in Australia or New Zealand.
- Liver transplantation no longer has a role in treatment of ATTR-CA.

the first-line diuretic, but for those with limited response, bumetanide or intravenous formulation offer greater potency and bioavailability. The aldosterone antagonist, spironolactone, could be often added as adjunctive therapy for potassium sparing effect [86,87]. The analysis of patients with ATTR-CA-like phenotypes in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) study suggests that spironolactone use could result in meaningful reduction in hospitalisation and mortality; however, this has not been demonstrated in ATTR-CA patients [88]. Addition of thiazide diuretic and metolazone enhances natriuresis but at the same time increases the risk of kidney hypoperfusion. The administration of intravenous diuretics is effective in ATTR-CA patients with suboptimal response to oral regimens. In majority of cases the intravenous therapy would necessitate hospitalisation, however the recent study of ambulatory intravenous diuretics use showed no excess of symptomatic hypotension or severe kidney injury, with significant decrease in emergency department visits and inpatient admissions [89]. The increase in the dose requirement not only reflects the emergence of diuretic resistance but also serves as a surrogate of disease progression and worse outcome [90]. The use of salt-poor albumin infusions can be considered as an adjunct to allow effective diuresis in fluid overloaded patients.

The use of ambulatory pulmonary artery pressure monitoring in patients with HF results in reduction in HF-related hospitalisations, but its use has not been assessed in ATTR-CA. Theoretically this could result in similar outcomes, particularly since the risk of over diuresis is high [91].

Excessive neurohormonal stimulation is present in all patients with HFrEF and particularly in those with ATTR-CA [92]. Pharmacological treatments directed to block such activity have led to significant reduction in morbidity and mortality of patients with HFrEF but unfortunately not in ATTR-CA (Figure 6B). The use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers increases the risk of postural hypotension and has not been associated with improved survival in this group, irrespective of the degree of LV impairment or concomitant use of mineralocorticoid antagonist [93]. Data regarding the use of angiotensin receptor neprolysin inhibitors and sodium-glucose cotransporter 2 inhibitors in ATTR-CA are lacking. Abnormalities in passive ventricular filling and altered ventricular-vascular coupling result in fixed reduction in stroke volume, hence patients with ATTR-CA rely on appropriate heart rate to maintain cardiac output [94]. Gradual reduction in dose and even cessation of beta-blockers (BB) should be considered in all patients, particularly in those with symptomatic hypotension and slow heart rates. A recent study showed patients who discontinued beta blocker use appear to have improved survival irrespective of the stage of ATTR-CA and LV EF [93]. Beta blockers may still be required for rate control of atrial arrhythmias, but the lowest effective dose is recommended. The use of standard HF therapy in ATTR-CA, including sodium-glucose cotransporter 2 inhibitors [95], is anticipated and likely to evolve with more experience and diagnoses at earlier stages.

Postural hypotension is common in patients with ATTR-CA, especially in those with abnormal TTR variant and coexistent autonomic neuropathy [96]. Pharmacological treatment with midodrine or pyridostigmine with use of compression stockings may be helpful [97].

Aortic Stenosis

Aortic stenosis (AS) is an increasingly recognised complication of ATTR-CA that is prevalent among older patients. CA is found in as many as 6%–16% of patients with AS [18–20]. Older patients with known or undiagnosed ATTR-CA represent an increasing proportion of referrals for TAVI consideration, resulting in a greater focus on screening of older AS patients for concurrent ATTR-CA. While there has been concern that ATTR-CA patients may represent a higher risk population for adverse outcomes following TAVI, recent evidence suggests that selected ATTR-CA patients with AS derive survival benefit from TAVI compared with medical therapy alone [20]. While further research is needed to optimise risk stratification for ATTR-CA patients referred for TAVI, this report suggests that current approaches used for selection of non-ATTR-CA patients for TAVI may also be effective for ATTR-CA patients. Of note, frailty assessment is an important and recommended component of evaluation of patients referred for TAVI.

Atrial Fibrillation

Atrial fibrillation (AF) is common in patients with ATTR-CA [15], and its prevalence increases with stage of ATTR-CA (stage 1—61%, stage 3—76%). AF is more frequent in patients with ATTRwt-CA (76%) than in those with ATTRv-CA (54%) disease [98,99]. The presence of AF in ATTR-CA patients is associated with worse outcomes and maintenance of

sinus rhythm improves overall 5-year survival (65% if sinus rhythm is maintained vs 49% if not maintained). Unfortunately, the freedom from recurrent AF at 30 days varies between the stages of the disease from ~90% in stage 1 to <50% in stage 3 [99]. Direct current cardioversion success rates under transoesophageal echocardiographic guidance in ATTR-CA are similar to rates in the general population but the procedure carries a significantly higher cancellation and procedural complication rate in ATTR-CA patients. The main reasons are an intracardiac thrombus and stroke [83].

Medications commonly used for heart rate-control are often poorly tolerated (e.g., beta blockers), or contraindicated (e.g., calcium channel blockers which have been associated with increased risk of local myocardial tissue toxicity and heart block). Low dose amiodarone has been advocated for patients who are intolerant of beta blockers [100]. The role of digoxin in the management of AF in patients with ATTR-CA remains controversial. There are concerns that digoxin may bind with amyloid fibrils leading to increased risk for toxicity. However, in patients with low blood pressure, uncontrolled heart rate and no other alternative, a judicious use of low dose digoxin with close monitoring could be trialled [101]. Catheter ablation for AF is generally ineffective due to significant amyloid deposition in atrial wall.

The use of oral anticoagulant is imperative in patients with ATTR-CA and AF (now a Class I indication). The presence of ATTR-CA is a predictor of incident thromboembolism independent of the CHA2DS2-VASc score and left atrial volume index. The combination of hypercoagulability, disrupted endocardium, and altered haemodynamics may predispose to left atrial thrombosis and embolism, even in the presence of sinus rhythm or therapeutic anticoagulation therapy. In one echocardiographic study, 27% of patients had an identifiable thrombus. Interestingly, 20% of them had no documented AF [102]. The presence of intracardiac thrombi remains significantly higher in patients with severe biventricular systolic dysfunction (stroke volume, $p<0.01$; EF, $p<0.05$; mitral annular plane systolic excursion, $p<0.01$; tricuspid annular plane systolic excursion, $p<0.01$; and, global longitudinal strain, $p<0.01$), atrial dilatation (left atrium, $p<0.05$; right atrium, $p<0.01$), and more severe degree of amyloid infiltration (ECV, $p<0.01$) [103]. Intracardiac thrombi are associated with higher levels of NT pro-BNP ($p<0.01$) and AF ($p<0.05$) [104].

Devices

Conduction disease is commonly encountered in patients with ATTR-CA. Standard indications for pacing are recommended.

The role of implantable cardioverter-defibrillators (ICD) in ATTR-CA remains controversial [67]. Ventricular arrhythmias, especially asymptomatic non-sustained ventricular tachycardia, are commonly detected in patients with ATTR-CA. Sudden cardiac death is thought to be uncommon. A survival benefit from ICD therapy has not been proven; however, among ATTR-CA patients with an ICD, appropriate shocks/therapies have been reported. There is limited utility of ICDs for primary prevention of sudden cardiac death. Features limiting potential benefit in primary prevention include: 1) patients' reduced life expectancy, commonly of less than a year; 2) sudden death due to pulseless electrical activity (PEA) rather than arrhythmia; and 3) high defibrillator thresholds due to amyloid infiltration which reduces effectiveness [105]. Secondary prevention indications for ICD implantation are accepted [106].

Box 6 summarises heart rhythm management in CA.

Referral to a Specialist Amyloidosis Centre

We advocate for early referral to a specialist amyloidosis centre for advanced testing and therapy, and active enrolment into clinical trials. Amyloidosis is a truly multi-system disease and isolated cardiac involvement is uncommon. Therefore, amyloidosis patients' need to be worked up and assessed systematically by a multidisciplinary team, ideally involving a cardiologist, neurologist, haematologist, genetic counsellor, palliative care physician, and HF nurse. This has become the standard of care in the USA and Europe. Quaternary amyloidosis clinics may offer patients advanced investigations such as endomyocardial biopsy or mass spectrometry. In probands with pathogenic or likely-pathogenic TTR variants, cascade testing to inform relevant family members of their risk should be accompanied by genetic counselling. Finally, these centres should have available clinical trials with disease modifying therapy.

Several of these specialised centres exist across Australia and New Zealand and are open for referrals. Further details can be found on the Australian Amyloidosis Network (AAN) website (https://aan.org.au/) which provides information for clinicians and patients.

Quaternary amyloidosis programs are also active in providing patient support and clinician education programs including the annual amyloidosis education day, which attracts international speakers and can be an important source of information for physicians and trainees.

Referral for Transplantation

Patients with end-stage HF due to ATTR-CA can undergo cardiac transplantation with excellent survival rates. The International Consortium on CA Transplantation group reported 95% 3-year survival in those with ATTRv, and 83% with ATTRwt deposition. Survival does not seem to differ with respect to gender, type of variant, or concomitant liver transplantation.

Heart transplantation has been often limited by the advanced age of the patients with ATTR-CA (international transplant guidelines recommend an age cut-off of 70 years for transplantation). In addition, patients need extensive evaluation of the extent of extracardiac amyloid involvement, which can limit quality of life post- transplantation. Note that even following successful heart transplantation, 55% of patients develop evidence of progressive extracardiac TTR deposition in nervous system and gastrointestinal tract, unless treated with TTR stabiliser [107].

Mechanical circulatory support options for patients with ATTR-CA are challenging, due to poor anatomy (small LV cavity size), arrhythmias and diastolic dysfunction. Therefore, it is important that patients with ATTR-CA are identified and referred for transplantation early.

Box 7 summarises the recommended approach to Managements of CA, including the role of Cardiac Transplantation.

Nutrition

Gastrointestinal (GI) symptoms and malnutrition are common in patients with ATTR. In the Transthyretin Amyloidosis Outcomes Survey (THAOS), gastrointestinal symptoms were reported in 63% of patients with ATTRv and in 15% of patients with ATTRwt [108]. Several mechanisms contribute to gastrointestinal manifestations in patients with ATTR-CA. Significant amyloid fibrils are typically distributed in the mucosa and neuromuscular layer of the gastrointestinal tract. The infiltration is responsible for increased friability and erosions which, in conjunction with the acquired bleeding diathesis, result in risk of gastrointestinal bleed. Factors contributing to the increased risk includes abnormal clotting, hepatic dysfunction, or iatrogenic medications (anticoagulation for AF). Patients with congestive heart failure have additional bowel oedema and hypoperfusion contributing to their gastrointestinal dysfunction. Autonomic dysfunction can be a significant component of some ATTRv with symptoms present in 50%–80% of patients [109]. Dysmotility disturbances arise from the autonomic dysfunction. Gastrointestinal symptoms frequently reported include early satiety (25%), weight loss (28%), diarrhoea/constipation (23%), faecal incontinence (6%), and intestinal pseudo-obstruction with culmination in cachexia and malnutrition [110].

Endoscopic biopsy with the histological demonstration of amyloid deposition in the gastrointestinal tract represents the gold standard for the diagnosis of gastrointestinal amyloidosis. The frequency of amyloid deposition varies according to the type of amyloidosis with the highest diagnostic detection in the duodenum, followed by the stomach, colorectum and oesophagus [111]. Consideration of prokinetic agents such as metoclopramide, and judicious use of laxative, can assist with symptom control in addition to treatment of the underlying disease process. Ensuring iron repletion to counter iron deficiency anaemia associated with frequent gastrointestinal bleeding can improve cardiac morbidity. Early evaluation of nutritional status and referral to dietitian services is recommended.

Psychological Impact

The psychological aspect of being diagnosed with CA can be profound due to disease burden, chronicity, and life expectancy. Patients with CA report significant impairment to their quality of life. A recent study from a French national survey of amyloidosis patients showed that 69% of patients believed that amyloidosis severely affected their quality of life with high levels of tiredness (67%), pain (56%), disturbed sleep (56%) and loss of appetite (46%), in addition to the typical symptoms at presentation, including breathlessness [112]. Fifty-eight percent (58%) of patients reported anxiety and depression. Seventy-two percent (72%) reported decrease in sexual desire. Amyloidosis also has a broader impact on families, carers, and society. One in three patients working at diagnosis had to stop work, and one in 10 had to modify their work due to amyloidosis. Family members assisted 31% of patients daily, and 16% occasionally [112].

ATTRv-CA can have devastating impact with some variants, such as the p.Val30Met TTR, demonstrating a lifetime penetrance approaching 100%. There is severe sensory–motor and autonomic neuropathy typically occurring after the 2nd decade of life with serious multi-system dysfunction and disability and death within a mean duration of 11 years. Many patients are raised knowing, and witnessing, the impact of the disease on family and community members. The psychological distress reported amongst asymptomatic and symptomatic p.Val30Met TTR carriers was higher than in the general population. Female gender, duration of disease, and having offspring were associated with higher levels of psychological disorder. Twenty-five percent (25%) of carriers had lost an affected parent by the age of 14 years, and this was a predictor for higher somatisation, anxiety, phobic anxiety, interpersonal sensitivity, obsession–compulsion, paranoid ideation, and psychoticism [113]. It is recommended that psychosocial support and individual education about their own disease, including an overview of who is on their treatment team, be offered to patients when the treatment plan is explained and, also throughout their illness, as needed.

Referral to Supportive Care

As in managing all chronic diseases, patients' wishes must be sought and respected, and early referral to supportive care is vital. Though a plethora of disease modifying therapies are available, they are not without travel time, hospital visits and costs. In addition, patients are often diagnosed late in life, and may opt for conservative treatment. Supportive care referral can help with symptom control, particularly breathlessness and postural symptoms. In addition, it can help support patients with end-of-life planning and comfort measures.

Disease-Modifying Therapies

Disease-modifying treatment to slow or stop the progression of ATTR-CA can be broadly divided into three groups: 1) TTR synthesis suppressors; 2) TTR stabilisers; and 3) fibril disruptors (Figure 6A). Box 8 summarises the key disease-modifying treatment classes in ATTR-CA.

TTR synthesis suppressors

Patisiran and inotersen are TTR synthesis suppressors that are based on RNA interference and antisense oligonucleotide mediated TTR mRNA degradation, respectively [114,115]. Patisiran is administered by intravenous infusion once every

3 weeks. Dosing is based on actual body weight, with a recommended dose of 0.3 mg/kg for a patient under 100 kg. Inotersen is administered via subcutaneously once weekly.

These parenteral agents consistently reduce peripheral blood TTR levels by ~80%. Patisiran and inotersen have both been shown to stabilise peripheral neuropathy and quality of life compared with placebo in patients with ATTRv amyloidosis [114,115]. The Apollo-B study (NCT03997383) evaluated patisiran in patients with ATTR-CA and has recently met its primary endpoint of statistically significant improvement in 6-minute walk test (6MWT) compared with placebo. Trials investigating second-generation TTR synthesis suppressors, such as vutrisiran (HELIOS A and B) and eplontersen are ongoing.

TTR stabilisers

Tafamidis is an orally administered selective TTR tetramer stabiliser that inhibits tetramer dissociation into amyloidogenic monomers by native state kinetic stabilisation [116]. In a double-blind, placebo-controlled study of patients with ATTRv amyloidosis with polyneuropathy, tafamidis failed its coprimary end points, and demonstrated a significant reduction in neurological deterioration [117,118]. However, a similar trial in ATTR-CA demonstrated that 18 months of tafamidis therapy reduced all-cause mortality and rates of cardiovascular-related hospitalisation compared to placebo [119]. Tafamidis appears to be very well tolerated and has received a positive recommendation from the Pharmaceutical Benefits Advisory Committee in Australia and will soon be available for ATTR-CA patients in NYHA class 1 and 2. Tafamidis remains a high-cost drug, and prescriptions will only be limited to cardiologists and amyloidosis specialists in Australia but will not be readily available to patients in New Zealand. There have been no head-to-head trials comparing tafamidis and diflunisal.

Diflunisal is a relatively affordable, oral non-steroidal anti-inflammatory drug that is a non-selective TTR stabiliser [120]. In a double-blind trial of ATTRv amyloidosis with polyneuropathy, diflunisal at a dose of 250 mg twice daily significantly slowed the deterioration rate of both neuropathy and quality of life when compared with placebo [121]. In ATTRwt amyloidosis, only retrospective studies have been conducted, however these also suggest disease-modifying and survival benefits [122]. Diflunisal is associated with renal dysfunction in up to 20% of cases, thus renal function needs to be reviewed at least every 6 months, along with a clinical assessment. A proton pump inhibitor to prevent gastric ulceration is recommended. In Australia, diflunisal is available through the Special Access Scheme and at all Australian Amyloidosis Network (AAN) Centres.

Acoramidis (AG10) is an oral TTR stabiliser designed to mimic the protective p.Thr119Met TTR variant that reduces the dissociation rate of tetrameric TTR and protects carriers from the disease. It is the newest TTR tetramer stabiliser [123]. A phase 3 trial (ATTRIBUTE-CM) included 632 patients in a 2:1 randomised double-blinded fashion, receiving acoramidis HCl (dose 800 mg b.d.) (n=421) or placebo (n=211). The primary endpoint, a hierarchical analysis consisting of all-cause mortality, cumulative frequency of cardiovascular-related hospitalisation, change from baseline NT-proBNP, and change from baseline in 6-minute walk distance had an overall win ratio favouring acoramidis (win ratio 1.77, 95% confidence interval [CI] 1.42–2.22; $p<0.0001$). This drug is, as yet, not available in Australia and New Zealand.

Fibril disruptors

Fibril disruptors that may have clinical benefit in ATTR-CA include: epigallocatechin-3-gallate (EGCG; green tea extract) [124,125], doxycycline [126], tauroursodeoxycholic acid [127], and ursodeoxycholic acid [128]. While these agents are typically well tolerated and affordable, prospective, randomised controlled studies are still needed in this area.

As the majority of transthyretin is produced in the liver, liver transplantation has historically been used in those with hereditary disease. While retrospective analyses initially suggested survival benefit from this surgical therapy, long-term follow-up has shown post-transplant progression of both CA and neuropathy, due to the continued deposition of wild-type TTR produced by the transplanted liver. Liver transplantation is, thus, no longer recommended.

Finally, resorptive therapies of established amyloid deposits are still in early phase clinical trials but offer some promise of reversibility of ATTR disease.

Future Directions

Gene Editing (CRISPR/Cas9)

Clustered, regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated enzyme (Cas9) can achieve *in vivo* gene editing and thus the potential to provide curative therapy. NTLA-2001 (Intellia Therapeutics, Cambridge, MA, USA, and Regeneron Pharmaceuticals, Tarrytown, NY, USA), an intravenous infusion, is being evaluated in a phase 1 study in patients with hereditary ATTR with polyneuropathy (NCT04601051). It comprises a lipid nanoparticle encapsulating messenger RNA for Cas9 protein and a single guide RNA targeting TTR. It is designed to treat ATTRv by reducing the concentration of TTR in serum. The initial experience with the systemic administration of NTLA-2001 to six patients with ATTRv amyloidosis polyneuropathy has recently been reported with sustained reductions in the serum TTR protein concentration [79]. The effect of NTLA2001was dose-dependent, with greatest reductions in TTR concentration among patients who received higher doses. These effects of NTLA-2001 were reproducible across patients at each dose level, with TTR reductions at day 28, ranging from 47% to 56% in the lower-dose group and from 80% to 96% in the higher-dose group. The results follow similar outcomes of data from cell lines and *in vivo* data on potency in animals, which showed a deep and permanent

reduction in serum TTR protein concentrations [79]. Data from studies of RNA-targeting gene silencing agents have shown observed reductions in serum TTR protein, that may translate into clinical benefits relative to placebo. As with current standard-of-care agents that reduce TTR availability, vitamin A supplementation is required to compensate for the loss of TTR, which has a normal physiological role in vitamin A transport. Complications of this treatment would include risk of unintended genotoxicity or oncogenic transformation that would require long term safety monitoring of changes detected in primary human hepatocytes modified by the DNA structural variants.

Human Monoclonal Antibodies

Human Monoclonal antibodies (mAbs) have the potential to bind to 'pathogenic' forms of the protein and perform targeted therapy to prevent or remove deposits. Phase I studies are underway which target misfolded forms of the TTR protein (NCT03336580). In addition, trials are underway with combination receptor ligand technology with antisense oligonucleotide (AKCEA-TTR-LRx) [113,129].

Conclusions

CA is characterised by progressive diastolic, and then systolic, ventricular dysfunction, accompanied by valvular and conduction system disease. In Australia, the true prevalence of CA is unknown, and it is important for the general cardiologist to recognise the signs, symptoms, and "red flags". That trigger appropriate investigations and referral to a specialist amyloidosis centre. Non-invasive diagnosis of CA is now possible with the use of bone scintigraphy and blood and urine tests to identify absence of a monoclonal protein; however, some patients still need to undergo diagnostic biopsy.

Historically, CA was considered an untreatable condition with patients having limited life expectancy and treated by palliation. In contrast, in the present era, we have a plethora of treatment options that are disease modifying by directly reducing production or increasing elimination of the amyloid fibril. In the future, gene therapy may be available for patients with hereditary amyloidosis, and so gene testing has also now become a vital part of the ATTR work up.

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Conflicts of Interest

NB: Novartis, Pfizer—research, Bristol Myers Squibb—advisory board. JLH: Pfizer—advisory board, clinical trials involvement. SDJG: Pfizer, BridgBio, Alexion/Astrazeneca, Ionis, Intellia, Attralus—honoria for speaking engagements, advisory board or steering committee payments, clinical trials involvement. PM: Jansen, Pfizer—research funding/clinical trials involvement. LT: Boehringer Ingelheim, Novartis, Sanofi Genzyme—advisory board, Jansen, Pfizer, Bayer—research funding.

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