Canada's Drug and
Health Technology Agency

CADTH Reimbursement Request for Advice

Tafamidis Meglumine (Vyndaqel)

Sponsor: Pfizer Canada ULC

Therapeutic area: Transthyretin-mediated amyloidosis

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Abbreviations

AL	amyloid light chain
ATTR	TTR-mediated amyloidosis
ATTR-CM	TTR-mediated amyloidosis cardiomyopathy
CDEC	CADTH Canadian Drug Expert Committee
CMR	cardiac magnetic resonance
EMB	endomyocardial biopsy
MINDS	Medical Information Network Distribution Service
SPECT	single-photon emission computerized tomography
TTR	transthyretin (protein)
Tc-99m-DPD	technetium-99m-3, 3-diphosphono-1,2-propanodicarboxylic acid
Tc-99m-HMDP	technetium-99m hydroxymethylene diphosphonate
Tc-99m-PYP	technetium-99m pyrophosphate scintigraphy

Executive Summary

An overview of the Request for Advice for tafamidis is provided in Table 1.

Table 1: Overview of the Request for Advice

Item	Description
Drug	Tafamidis meglumine (Vyndaqel) 20 mg capsule
Indication	For the treatment of adult patients with cardiomyopathy due to transthyretin-mediated amyloidosis, wild-type or hereditary, to reduce cardiovascular mortality and cardiovascular-related hospitalization
Final CDEC Recommendation	Reimburse with conditions
NOC date	January 20, 2020
Sponsor	Pfizer Canada ULC

CDEC = CADTH Canadian Drug Expert Committee; NOC = Notice of Compliance.

Source: CADTH CDEC Final Recommendation for Tafamidis Meglumine (Vyndaqel), February 19, 2020.[1]

Context for Request for Advice

In 2020, the CADTH Canadian Drug Expert Committee (CDEC) recommended that tafamidis be reimbursed for the treatment of adult patients with cardiomyopathy due to transthyretin (TTR)-mediated amyloidosis (ATTR), wild-type or hereditary, to reduce cardiovascular mortality and cardiovascular-related hospitalization, but only if the conditions for reimbursement were met.[1] One of the conditions in the recommendation for initiating treatment was the presence of documented cardiac disease due to ATTR cardiomyopathy (ATTR-CM). The recommendation stated that documented ATTR-CM consists of the "presence of amyloid deposits in biopsy tissue (fat aspirate, salivary gland, median nerve connective tissue sheath, or cardiac),"[1] among other criteria. With the advent of newer diagnostic modalities that may detect the presence of amyloid deposits, the evolving role of biopsies may result in implementation challenges for jurisdictions.

The public drug plans are seeking advice on the role of biopsies and other modalities in diagnosing ATTR-CM. Specifically, the drug plans asked if biopsy is a necessary diagnostic modality for diagnosing patients with cardiomyopathy due to wild-type or hereditary ATTR, and which other alternative modalities (e.g., technetium-99m [Tc-99m] pyrophosphate [Tc-99m-PYP] scintigraphy would be acceptable for diagnosing patients with cardiomyopathy due to wild-type or hereditary ATTR for the purposes of providing reimbursement for treatment with tafamidis (Vyndaqel).

CADTH's approach for the Request for Advice consisted of collecting stakeholder feedback from the sponsor and patient groups, consulting 2 clinical experts, and conducting a literature search for relevant clinical practice guidelines. Pfizer Canada ULC and Canadian Organization for Rare Disorders provided input to CADTH.

Summary of Findings

The use of biopsy to confirm diagnosis is necessary only in select cases. The clinical expert panel and the 12 clinical guidelines reviewed as part of this Request for Advice all indicated that biopsies are necessary only if the Tc-99m-PYP scintigraphy results are equivocal, if clinical suspicion remains high despite negative results, or if the Tc-99m-PYP modality is unavailable. The clinical experts noted that the yield of non-cardiac biopsy, especially in wild-type ATTR, is highly variable and may be low, which also aligned with the findings presented in the guidelines.

Tc-99m-PYP scintigraphy is an acceptable modality for diagnosing ATTR-CM. The clinical experts and clinical guidelines suggest that Tc-99mm-PYP scintigraphy is a valid form of non-invasive diagnosis; however, single-photon emission computerized tomography (SPECT) imaging is necessary, as opposed to planar imaging alone, alongside the use of PYP scanning.

Patients reported valuing diagnostic modalities that are effective and low-risk, trusting their cardiologist to provide the best information and most appropriate care.

Background

CADTH 2020 Recommendation for Tafamidis Meglumine

CADTH conducted a reimbursement review for tafamidis for the treatment of adult patients with cardiomyopathy due to ATTR, wild-type or hereditary. The 2020 CADTH recommendation, conditions for reimbursement, reasons for the recommendation, and implementation considerations are reported in Table 2.

Table 2: CADTH 2020 Recommendation for Tafamidis Meglumine

Recommendation, conditions for reimbursement, reasons for recommendation, implementation considerations
CADTH recommendation for tafamidis meglumine (Vyndaqel)
The CADTH Canadian Drug Expert Committee (CDEC) recommends that tafamidis be reimbursed for the treatment of adult patients with cardiomyopathy due to transthyretin (TTR)-mediated amyloidosis, wild-type or hereditary, to reduce cardiovascular mortality and cardiovascular-related hospitalization only if the following conditions are met.
Conditions for reimbursement
Initiation criteria 1. Documented cardiac disease due to TTR-mediated amyloidosis cardiomyopathy (ATTR-CM) 1.1. Documented wild-type ATTR-CM consists of all of the following: absence of a variant TTR genotype; evidence of cardiac involvement by echocardiography with end-diastolic interventricular septal wall thickness of greater than 12 mm; presence of amyloid deposits in biopsy tissue (fat aspirate, salivary gland, median nerve connection tissue sheath, or cardiac); and TTR precursor protein identification by immunohistochemistry, scintigraphy, or mass spectrometry.

Recommendation, conditions for reimbursement, reasons for recommendation, implementation considerations
1.2. Documented hereditary ATTR-CM consists of all of the following: presence of a variant TTR genotype associated with cardiomyopathy and presenting with a cardiomyopathy phenotype; evidence of cardiac involvement by echocardiography with end-diastolic interventricular septal wall thickness of greater than 12 mm; presence of amyloid deposits in biopsy tissue (fat aspirate, salivary gland, median nerve connective tissue sheath, or cardiac) 2. Patients who have all of the following characteristics: 2.1. New York Heart Association (NYHA) class I to III 2.2. history of heart failure, defined as at least 1 prior hospitalization for heart failure or clinical evidence of heart failure that required treatment with a diuretic 2.3. have not received a heart or liver transplant 2.4. do not have an implanted cardiac mechanical assist device (CMAD) 2.5. not receiving other disease-modifying treatments for ATTR. **Discontinuation criteria** 1. Treatment with tafamidis should be discontinued for patients who: 1.1. progress to NYHA class IV, or 1.2. receive a heart or liver transplant, or 1.3. receive an implanted CMAD. **Prescribing conditions** 1. The patient must be under the care of a specialist with experience in the diagnosis and management of ATTR-CM. **Pricing conditions** 1. Price reduction.
Reasons for recommendation
1. In 1 double-blind, phase III, randomized controlled trial in patients with wild-type or hereditary ATTR-CM, treatment with tafamidis 80 mg was associated with reduced mortality and cardiovascular-related hospitalizations after 30 months compared with placebo. At month 30, more patients were alive in the tafamidis 80 mg group compared with the placebo group (69.3% versus 57.1%). There were also more cardiovascular-related hospitalizations in the placebo group compared with tafamidis 80 mg among patients who were alive at month 30 (mean: 0.46 per year versus 0.34 per year). Clinically important differences were also observed in favour of tafamidis at month 30 in health-related quality of life, as measured by the Kansas City Cardiomyopathy Questionnaire overall score (least squares mean difference for tafamidis 80 mg versus placebo: 13.5 points; 95% CI, 9.2 to 17.8), and disability progression, as measured by the 6-minute walk test (least squares mean change of −54.8 m versus −130.6 m). 2. There is an unmet clinical need due to the absence of effective alternative treatments for ATTR-CM. There are no other approved treatment options that address the underlying mechanism of the disease and are supported by robust evidence. 3. Patients classified as NYHA class IV (i.e., unable to carry on any physical activity without discomfort, symptoms of heart failure at rest, if any physical activity is undertaken discomfort increases) at baseline and those who had prior liver or heart transplant or an implanted CMAD were excluded from the study. If, during the study, a patient chose to accept a donor organ transplant or had implantation of a CMAD, the patient was discontinued from the study. Therefore, there is no evidence to support the use of tafamidis in these patients. 4. The sponsor-submitted price of tafamidis is $133.57 per 20 mg capsule. At a dose of tafamidis 80 mg daily, the cost of tafamidis is $534 daily and $195,012 annually. Based on a CADTH reanalysis of the sponsor-submitted economic model, the incremental cost-utility ratio (ICUR) for tafamidis compared with best supportive care is $443,694 per quality-adjusted life-year (QALY) gained. However, this estimate is associated with significant uncertainty due to limitations in the submitted model structure. Based on the CADTH reanalysis, a price reduction of more than 92% is required for tafamidis to achieve an ICUR of $50,000 per QALY.

Recommendation, conditions for reimbursement, reasons for recommendation, implementation considerations
Implementation considerations
• Diagnosis of hereditary or wild-type ATTR-CM requires specialized testing for amyloid protein, scintigraphy, or genetic testing, which are available at larger academic centres. • The classification of patients according to NYHA class depends on clinician judgment; there are no laboratory or imaging criteria that designate a patient as having transitioned from NYHA class III to NYHA class IV. This judgment will rely on clinical assessments only. • The prevalence of wild-type ATTR-CM is unknown, and some evidence indicates that wild-type ATTR may be underdiagnosed. The budget impact of tafamidis may be considerable, given the high cost of the drug. Even at a substantially reduced price, CDEC discussed that the budget impact of tafamidis could be even greater if the prevalence of wild-type ATTR is higher than currently recognized. The availability of an effective treatment may also stimulate diagnostic testing with further impact on health system resources. CDEC also discussed that the diagnostic accuracy of currently used tests among the broad spectrum of patients with restrictive cardiomyopathy is unknown.

6MWT = 6-minute walk test; ATTR-CM = TTR-mediated amyloidosis cardiomyopathy; BST = best supportive care; CDEC = CADTH Canadian Drug Expert Committee; CI = confidence interval; CMAD = cardiac mechanical assist device; ICUR = incremental cost-utility ratio; NYHA = New York Heart Association; TTR = transthyretin; QALY = quality-adjusted life-year.

Source: CADTH Recommendation for tafamidis meglumine (Vyndaqel).[1]

The primary conclusions from the 2020 CADTH reimbursement review of tafamidis were as follows:

- Based on a single double-blind, phase III RCT [randomized controlled trial] in patients with wild-type or hereditary ATTR-CM, treatment with tafamidis was associated with reduced mortality and hospitalizations after 30 months compared with placebo. Clinically important differences were also observed in favour of tafamidis at month 30 in HRQoL [health-related quality of life] and disability progression, as measured by the KCCQ [Kansas City Cardiomyopathy Questionnaire] overall score and 6MWT [six-minute walk test], respectively. Exploratory subgroup analyses suggested that treatment benefits are present for wATTR-CM [wild-type ATTR-CM], hATTR-CM [hereditary ATTR-CM], NYHA [New York Heart Association] class I/II and NYHA class III, although the benefits for patients in NYHA class III are less clear. The most common AEs [adverse events] were cardiac-related (i.e., atrial fibrillation and cardiac failure). The most common SAEs [serious adverse events] were cardiac-related or aggravation of condition and were experienced by a similar proportion of patients in the tafamidis and placebo groups. Thyroxine abnormality was higher in the tafamidis group, although this was anticipated to be of limited clinical significance. Further, the clinical experts consulted for this review agreed that tafamidis appears to be fairly well tolerated and monitoring requirements are anticipated to be minimal.
- The current management strategy for ATTR-CM is primarily supportive cardiac disease treatments, as there are very few options available that target the underlying disease process. The only other TTR stabilizer used for the treatment of ATTR-CM in Canada is diflunisal; however, this is used beyond the Health Canada indication in this patient population, is associated with numerous limitations, and is not supported by rigorous evidence. There is no comparative evidence of tafamidis versus diflunisal; however, the clinical experts consulted for this review acknowledged that tafamidis appears to meet an unmet need for patients with wild-type and hereditary ATTR-CM.[1]

Common Definitions of Diagnostic Procedures

The modalities discussed throughout this report are briefly described subsequently.

Biopsy

In the context of ATTR-CM, different types of biopsies may be considered in the diagnostic algorithm. Tissue is obtained from the heart (i.e., endomyocardial biopsy), or from peripheral tissue (i.e., extracardiac biopsy), such as fat aspirate, salivary gland, skin, or median nerve connection tissue sheath.[2] There is variation in the sensitivity and specificity of biopsies of different tissues for detecting amyloidosis,[2] with endomyocardial biopsy (EMB) being 100% sensitive.[3] Amyloid fibres can be specifically typed with immunohistochemistry and mass spectrometry to determine the specific amyloid-forming protein (e.g., ATTR or amyloid light chain [AL] amyloidosis).[4]

Nuclear Scintigraphy Scan

Radionuclide scanning uses the radiation released by radionuclides to produce images, where a radionuclide, usually Tc-99m, is combined with different compounds to form a radiopharmaceutical that localizes to a particular structure (target tissue) and images are captured using gamma cameras.[5-7] Tc-99m-PYP, Tc-99m-3, 3-diphosphono-1,2-propanodicarboxylic acid (Tc-99m-DPD) or Tc-99m-hydroxymethylene diphosphonate (Tc-99m-HMDP) are 3 of the tracers that have been evaluated for ATTR, with varying degree of availability across jurisdictions.[8] To aid visualization, SPECT or planar images are obtained.[7] Uptake is typically assessed using a 4-point visual grading scale ranging from 0 to 3 based on myocardial uptake relative to the ribs (i.e., the Perugini grade).[9,10] It can also be assessed using a heart-to-contralateral lung-uptake ratio.

Request for Advice

CDEC recommended that tafamidis be reimbursed for the treatment of adult patients with cardiomyopathy due to ATTR, wild-type or hereditary, to reduce cardiovascular mortality and cardiovascular-related hospitalization only if the conditions for reimbursement are met.[1] One of the conditions for initiating tafamidis was "documented cardiac disease due to ATTR-CM."[1] As per the recommendation, documented wild-type and documented hereditary ATTR-CM consisted of the "presence of amyloid deposits in biopsy tissue (fat aspirate, salivary gland, median nerve connection tissue sheath, or cardiac),"[1] among other criteria. With the advent of new modalities that may be capable of diagnosing ATTR-CM, the evolving role of biopsies may result in implementation challenges for jurisdictions.

The public drug plans are requesting that CADTH provide advice regarding the following:

- Is biopsy a necessary modality for diagnosing patients with cardiomyopathy due to wild-type or hereditary TTR-mediated amyloidosis?
- What alternative modalities (e.g., Tc-99m-PYP scintigraphy) would be acceptable for diagnosing patients with cardiomyopathy due to wild-type or hereditary TTR-mediated

amyloidosis for the purposes of providing reimbursement for treatment with tafamidis (Vyndaqel)?

CADTH Approach to the Request for Advice

To address the questions in the Request for Advice submitted by the drug plans, CADTH reviewed the clinical guidelines on the diagnostic pathway for ATTR-CM, particularly the role of biopsy and bone scintigraphy and their place in the diagnostic landscape.

CADTH considered the following sources of information to determine existing best practices for the diagnosis of hereditary or wild-type ATTR-CM:

- input from 2 clinical experts with experience in treating patients with ATTR-CM
- input from 1 patient group, Canadian Organization for Rare Disorders, about testing and issues important to patients
- input from the sponsor
- relevant clinical practice guidelines (from a literature search)

Stakeholder Perspectives

Patient Group Input

The Canadian Organization for Rare Disorders provided input to this Request for Advice. The full patient group input is included in the Stakeholder Input section of this report. The patient group obtained patient-relevant information from a discussion group with 6 patients and family members. All 6 discussion participants resided in Canada, 5 of 6 were male, and all 6 were diagnosed with ATTR-CM. The patient group reported collecting no data on treatment status and experience with tafamidis meglumine. The following is a summary of the information provided by the patient group.

- Not all patients and family members were aware of the potential use of extracardiac biopsies to confirm diagnosis of ATTR-CM for eligibility to receive tafamidis; however, all were aware of the requirement for an EMB. The patients and family members indicated receiving information about the risks of a cardiac biopsy but were not presented with an alternative to a biopsy. All patients and family members indicated accepting the risks compared with the benefit of qualifying for treatment, and they expressed confidence in their cardiologists to provide the best information and appropriate care. No patients reported experiencing adverse events from EMB.
- Based on their previous knowledge or exposure, patients and family members had mixed reactions about the requirement by the public drug plans for a tissue biopsy of fat, salivary gland, or nerve tissue (i.e., extracardiac biopsies) to approve reimbursement of tafamidis. All felt that the use of or requirement for biopsy from sites other than the heart was not appropriate. In their experience with ATTR-CM, no patients or family members had ever been asked to provide extracardiac biopsies.

- Patients and family members indicated they would endorse an alternative to cardiac biopsy, specifically bone scintigraphy, for the treatment and reimbursement of tafamidis if the new procedure was equally effective and less risky. Patients and family members added that it was important to communicate reimbursement changes to the cardiologist and patient community. Some patients and family members recommended ongoing monitoring and evaluation of any new procedures to ensure patients are accurately diagnosed and those who might benefit from tafamidis are not excluded.

Clinical Expert Input

The information in this section is a summary of the input provided by the 2 clinical experts consulted by CADTH. The clinical experts responded to a questionnaire about the current diagnostic pathway, the role of biopsies, and alternative modalities for diagnosing ATTR-CM. Overall, the clinical experts indicated that a Tc-99m-PYP scan is the first-line technique for diagnosing patients with cardiomyopathy due to wild-type or hereditary ATTR. Furthermore, the clinical experts maintained that confirming amyloid tissue deposits by biopsy is suggested only when non-invasive evaluation is equivocal, unavailable, or discordant with clinical suspicion.

Current Diagnostic Pathway

The clinical experts outlined that when systemic amyloidosis is suspected based on clinical evaluation and preliminary investigations, the initial step for clinicians is to typically exclude AL amyloidosis. The diagnostic techniques used initially include echocardiogram and/or cardiac MRI, cardiac biomarkers (i.e., troponin, N-terminal-pro-B-type natriuretic peptide), electrocardiogram and other standard tests. While these tests can demonstrate features that are characteristic of amyloid cardiomyopathy, they do not differentiate by subtype (i.e., AL versus ATTR) or confirm the diagnosis. Once AL is excluded, the next recommended test is a Tc-99m-PYP scan. If this is positive, then genetic testing is recommended to differentiate wild-type from hereditary ATTR. If the PYP results are equivocal, the test is unavailable, or suspicion of ATTR remains high, then cardiac biopsy is recommended. If the PYP scan is negative, the search for an alternate diagnosis is initiated.

The Role of Biopsies

The clinical experts advised that it is not necessary to confirm the presence of amyloid deposits in a tissue biopsy to diagnose patients with cardiomyopathy due to wild-type or hereditary ATTR; rather, confirming amyloid tissue deposits by biopsy is recommended only when the non-invasive evaluation (i.e., PYP scan) is equivocal, unavailable, or discordant with clinical suspicion (i.e., ATTR is highly suspected clinically despite a negative PYP scan, although the clinical experts maintain this scenario is exceptionally rare). In patients requiring biopsy, the clinical experts suggest that cardiac biopsy is generally preferred but any form of tissue biopsy is acceptable. However, the clinical experts noted that the yield of non-cardiac biopsy, especially in wild-type, is highly variable and may be low.

The clinical experts expressed concern over the use of biopsies to diagnose ATTR-CM. Particularly, the clinical experts were concerned that ATTR-CM patients are generally older and may have other comorbidities, which puts patients at a relatively higher risk of complications from the biopsy procedure. In patients with atrial fibrillation and cardiac amyloidosis who are on oral anticoagulants, the clinical experts expressed concern that the interruption of anticoagulant medication for the purpose of conducting a biopsy puts patients at risk for thromboembolic complications, such as stroke. The clinical experts shared that they observed serious (i.e., life-threatening) complications at their treatment centres after performing an EMB to confirm a non-invasive diagnosis. The experts also added that complications arising from confirmatory biopsies might be a concern at other treatment centres.

The clinical experts also shared that some of their patients have refused treatment when faced with the prospect of undergoing a confirmatory invasive diagnostic procedure (e.g., biopsy) after some indication of ATTR-CM through non-invasive procedures.

Scintigraphy

The clinical experts maintained that PYP scanning has generally replaced the need to perform a biopsy when diagnosing ATTR-CM, except when the evaluation is equivocal, unavailable, or discordant with clinical suspicion. The clinical experts clarified that, for example, an equivocal PYP scan result (i.e., grade 1) would be considered a reason to conduct a biopsy.

The clinical experts suggest that SPECT imaging should be required alongside PYP scanning as opposed to planar imaging alone. Specifically, the experts noted that false positives may arise from mistaking blood pool uptake (i.e., left ventricular chamber cavity) for true myocardial uptake, which is what confirms the diagnosis. This limitation can be corrected using SPECT imaging during a PYP scan, as opposed to planar imaging alone. The experts added that SPECT imaging can demonstrate uptake localized to the myocardium and referenced the American Society of Nuclear Cardiology, which now recommends SPECT be performed as part of PYP scans for this indication.

The clinical experts were concerned about the availability of PYP scanning, which they suggested is improving but there are communities without access. The clinical experts added that these communities, in general, also do not have access to tissue biopsies; however, PYP availability may now be better than biopsy availability.

Additionally, the experts highlighted how evolving clinical standards for the diagnosis of ATTR-CM may have impacted the design of the transthyretin amyloidosis cardiomyopathy clinical trial (ATTR-ACT).[11] Specifically, the experts highlighted that when the ATTR-ACT trial was designed, PYP scanning had not yet become the clinical standard for diagnosis of ATTR-CM and, therefore, the ATTR-ACT participant inclusion criteria (i.e., requiring biopsy confirmation) used an outdated diagnostic approach. The experts also emphasized that making the biopsy confirmation of amyloid deposits a requirement for public reimbursement eligibility puts patients and clinicians in the difficult position of pursuing either non-cardiac biopsy sites, which may be lower yield, or

conducting an EMB, which may come with a relatively higher risk of serious complications.

Sponsor Input

The sponsor submitted input for this Request for Advice that generally aligned with the clinical expert input. The full sponsor input is included in the Stakeholder Input section of this report. The sponsor indicated that biopsy (cardiac or extracardiac) is no longer a necessary modality for diagnosing patients with wild-type or hereditary ATTR-CM and, instead, has been superseded by Tc-99m-PYP) scanning. As per the sponsor, the medical community internationally accepts bone scintigraphy as sufficient to diagnose ATTR-CM without biopsy when: cardiac amyloidosis is suspected based on standard heart failure workup, monoclonal proteins are absent as assessed by serum and urine protein electrophoresis with immunofixation and serum free light chain assay, or a radionuclide scan with Tc-99m-PYP shows grade 2 or 3 cardiac uptake.

The sponsor also commented on the ACT-ATTR trial design, which was reviewed as part of the CADTH reimbursement review for tafamidis (Vyndaqel). Per the sponsor, if the ATTR-ACT trial were to be conducted today, it would not require biopsy as an inclusion criterion. As an example, the sponsor points to the amendment of the ATTR-ACT study protocol (April 16, 2014) to include scintigraphy as a diagnosis technique. Additionally, the sponsor cited the inclusion criteria of an ongoing phase III clinical trial, the CARDIO-TTRansform study that was initiated in March 2020,[12] examining the efficacy of new molecules for the treatment of ATTR-CM. The trial accepts either the use of cardiac or non-cardiac biopsy or Tc-99m-PYP imaging showing grade 2 or 3 cardiac uptake in the absence of an abnormal light-chain ratio for a confirmation of ATTR-CM for patient inclusion.

The sponsor also commented on the risks associated with EMB use and the poor detection rates of extracardiac biopsies. The sponsor indicated that the current reimbursement criterion related to the mandatory tissue biopsy at initiation may not be in the best interest of patients because EMB is associated with an approximate 1% risk of major complications, which include cardiac perforation, severe arrythmias, valvular trauma, and death.[13] The sponsor indicated that, anecdotally, Canadian clinicians are concerned about performing an EMB in their patients with atrial fibrillation and cardiac amyloidosis, as the interruption of the oral anticoagulant increases the risk of stroke and systemic embolism in this high-risk population, or could increase the risk of bleeding if the oral anticoagulant is not withheld long enough. The sponsor also shared that it has been made aware of patients refusing treatment in the face of having to undergo an invasive procedure, despite having a confirmed diagnosis by PYP imaging. The sponsor added that biopsies from extracardiac sites have either low or undocumented detection rates for wild-type ATTR-CM, stating that it represents the predominant form of ATTR-CM (95% of cases) in Canada,[14] and that many clinicians must often go to great lengths to identify an individual with sufficient training to perform biopsy types with relatively higher detection rates. The sponsor also commented on the resource use of EMBs. The sponsor noted that cardiac biopsies are usually performed in cardiac catheterization laboratories under fluoroscopic guidance, and the need for patient monitoring (heart

rhythm, non-invasive blood pressure, and blood oxygen saturation monitoring).[13] As per the sponsor, clinicians have anecdotally shared that the number of requests for cardiac biopsies has increased and caused congestion at cardiac catheterization laboratories, which has an impact on all patients waiting for the cardiac procedures these laboratories regularly perform (i.e., angioplasty, angiogram, ablation). Furthermore, the sponsor suggests that EMB requires maintenance of procedural skill, which is only feasible at larger Canadian centres.

The sponsor highlighted that tafamidis is the only therapy available in Canada for ATTR-CM, and most countries do not require a mandatory biopsy at treatment initiation. As per the sponsor, compared with most public drug programs in Canada, the clinical initiation criteria for tafamidis for the province of Quebec and for most private insurers is more flexible and aligned with clinical guidelines, referencing the 2020 Institut national d'excellence en santé et en services sociaux (INESSS) report for tafamidis meglumine (Vyndaqel).[15]

Literature Search for Clinical Practice Guidelines

A limited literature search was conducted by an information specialist on key resources, including MEDLINE and Embase, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Vyndaqel (tafamidis) and ATTR. CADTH-developed search filters were applied to limit retrieval to clinical guidelines. Where possible, retrieval was limited to the human population. The search was conducted on January 14, 2022 and limited to English. Retrieval was not limited by publication date. One CADTH clinical reviewer screened the search results for clinical practice guidelines describing the diagnostic algorithm for both wild-type and hereditary ATTR-CM.

A total of 12 clinical guidelines from various jurisdictions were identified from the limited literature search.[2,4,16-27] Seven of 12 guidelines were authored by medical societies, including 1 from 2 Canadian societies, while the remaining 5 were authored independently across various international jurisdictions. All guidelines generally suggest that the diagnostic workup should start with serum and urine immunofixation and free light chain assays. If monoclonal paraprotein is detected, a further hematologic workup should be performed to confirm or reject AL amyloidosis. If no monoclonal immunoglobulin is detected, the next step is to perform bone scintigraphy with Tc-99m-PYP, Tc-99m-DPD, or Tc-99m-HMDP. If bone scintigraphy is strongly positive, then ATTR is confirmed. If the bone scintigraphy is indeterminate or clinical suspicion remains high, a biopsy is required to exclude or confirm ATTR-CM, followed by genetic testing to confirm its type.

All 12 guidelines, including any available diagnostic algorithm and recommendations pertaining to the role of biopsies and bone scintigraphy, are summarized subsequently.

Canadian Cardiovascular Society/Canadian Heart Failure Joint Position Statement

The *Canadian Cardiovascular Society/Canadian Heart Failure Joint Position Statement on the Evaluation and Management of Patients with Cardiac Amyloidosis* was published in 2020.[19] The aim of the joint position statement was to provide a reasonable and practical approach to care for specialists and allied health professionals. Fine et al., 2020, did not describe the methods used to produce this guideline, although it appeared to be formed through a review of the literature and clinical experience.

This guideline suggested that serum and urine protein electrophoresis with immunofixation and a serum free light chain assay be performed first in all patients with suspected cardiac amyloidosis to evaluate for possible AL amyloidosis or other plasma cell dyscrasia. ATTR amyloidosis is suspected when monoclonal protein is absent. After exclusion of AL, the guideline then suggested performing nuclear scintigraphy with a bone-seeking radiotracer (if available) to evaluate for cardiac involvement. In the presence of a positive result, defined as an update of Perugini grade 2[9] or higher (greater than or equal to bone uptake), or a heart-to-contralateral lung-uptake ratio of 1.5 or greater, a diagnosis of ATTR cardiac amyloidosis was suggested, without the need for a tissue biopsy. The guideline suggested performing an EMB for diagnosis and subtyping with mass spectrometry or immunohistochemistry or immunofluorescence (if available) when the existing diagnostic workup for cardiac amyloidosis is equivocal or negative despite high clinical suspicion. The definition of equivocal was not described. The authors described that the identification of subtypes requires techniques (i.e., mass spectrometry or immunohistochemistry, immunofluorescence) that are not widely available and should only be performed in laboratories with significant expertise. The authors indicated that direct biopsy of a clinically involved organ has the highest sensitivity and EMB remained the diagnostic gold standard for all subtypes.

Both suggestions made by the authors of the guidelines regarding the use of scintigraphy and the use of biopsies were labelled as "strong;" however, there was no formal definition. In terms of the quality of the evidence used to inform the guideline suggestions, the recommendation made regarding the use of scintigraphy was labelled as "moderate quality," while the recommendation made regarding the use of biopsy was labelled as "low quality;" however, in both cases, no definitions were presented by the authors on what they considered to be moderate- or low-quality evidence.

Overall, the guidelines had a clearly described scope and purpose, and the suggestions for clinical practice were presented clearly. The guideline writing group was multidisciplinary, and the target user of the guidelines was clearly defined. Although the guidelines were peer-reviewed, specific methods were not described and it was unclear whether a systematic search for evidence was undertaken. Despite the authors reporting on the quality of the evidence and the strength of the suggestion, there is no additional description of how this evidence was critically appraised or what defined "moderate quality" versus "low quality." Furthermore, the authors did not report any conflicts of interest.

Multi-Societal Expert Consensus Recommendation for Multimodality Imaging in Cardiac Amyloidosis

The American Society of Nuclear Cardiology, American Heart Association, American Society of Echocardiography, European Association of Nuclear Medicine, Heart Failure Society of America, International Society of Amyloidosis, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine and Molecular Imaging Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis guidelines were published in 2021.[16,17] Findings from all publications are discussed herein. Dorbala et al., 2021, reported forming a panel of 7 clinical experts to develop expert consensus on criteria for the diagnosis of cardiac amyloidosis through histologic, imaging, and cardiac biomarkers, and the panel engaged in an exercise using the modified Delphi technique. The aim of these guidelines was to determine which diagnostic modalities might be reasonable for a specific indication rather than to identify 1 test that is best. All suggestions were scored by the panel on "appropriateness," assessing benefits and risks and the need to conduct further research.

The guidelines emphasized that no single existing diagnostic tool could provide information on cardiac involvement in amyloidosis and confirm the etiologic subtype, necessitating a multimodality cardiac imaging approach. If cardiac amyloidosis is suspected clinically or based on echocardiography or cardiac magnetic resonance (CMR) imaging according to defined criteria,[17] blood and urine should be analyzed for evidence of a monoclonal protein and cardiac scintigraphy should be considered using Tc-99-m-PYP, Tc-99m-DPD or Tc-99m-HMDP. If both blood and scintigraphy tests are negative, then cardiac amyloidosis is very unlikely. In the presence of a positive (Perugini grade 2 or 3)[9] Tc-99m-PYP, -DPD, or -HMDP cardiac scintigraphy without evidence of monoclonal proteins in blood and urine, a diagnosis of ATTR-CM can be made without a biopsy (specificity and positive predictive value > 98%).[28] For those patients with evidence of a plasma cell dyscrasia, a histological diagnosis is still required because the presence of low-grade uptake on a Tc-99m-PYP, -DPD, or -HMDP scan is not 100% specific for ATTR-CMs.[28] Substantial uptake (Perugini grade 2 or 3)[9] has been reported in more than 20% of patients with AL cardiac amyloidosis.[28]

Per the guidelines, a histological diagnosis of ATTR can be achieved by EMB or extracardiac biopsy with typical cardiac imaging (e.g., echocardiogram, CMR, positron emission tomography) features described in the guideline. An EMB is positive for cardiac amyloidosis with Congo red staining with apple-green birefringence under polarized light, typing by immunohistochemistry, and/or mass spectrometry at specialized centres.

The guideline emphasized the importance of excluding monoclonal plasma cell dyscrasia with serum or urine immunofixation and a serum free light chain assay in all patients with suspected amyloidosis. Additional key considerations for radionuclide imaging in this guideline are included in Table 3.

Table 3: Additional Considerations for Radionuclide Imaging

Additional considerations for radionuclide imaging, as per the multi-societal expert consensus recommendation for multimodality imaging in cardiac amyloidosis
• Tc-99m-PYP, -DPD, and -HMDP are highly sensitive and specific to the diagnosis of ATTR-CM and, in the appropriate clinical context, may aid in its early detection. • Grade 2 myocardial uptake of Tc-99m-PYP, -DPD, or -HMDP is indicative of ATTR-CM, averting the need for EMB, in the absence of a light-chain clone. • Tc-99m-PYP, -DPD, and -HMDP scanning should be considered in patients with unexplained increased left ventricle wall thickness, heart failure with preserved ejection fraction, familial amyloid polyneuropathy, family history of amyloidosis, degenerative aortic stenosis with low-flow low gradient in the elderly, and a history of bilateral carpal tunnel syndrome. • ^{123}I-meta-iodobenzylguanidine can detect cardiac denervation in patients with hereditary ATTR.

ATTR = TTR-mediated amyloidosis; ATTR-CM = TTR-mediated amyloidosis cardiomyopathy; Tc-99m = technetium-99m; Tc-99m-DPD = Tc-99m-3, 3-diphosphono-1,2-propanodicarboxylic acid; Tc-99m-HMDP = technetium-99m hydroxymethylene diphosphonate; Tc-99m-PYP = technetium-99m pyrophosphate scintigraphy; TTR = transthyretin.

Source: [Multi-societal] Expert Consensus Recommendation for Multimodality Imaging in Cardiac Amyloidosis (part 1 and 2).[16,17]

In an addendum published after the guidelines, the multi-societal writing group clarified that for Tc-99m-PYP, -DPD, and -HMDP acquisition and interpretation, SPECT imaging is important.[18] Specifically, SPECT is required in all studies irrespective of the time between injection and scan to enable directly visualizing tracer uptake in the myocardium. The authors also stated that 1-hour planar-only imaging is not recommended.

Overall, the guidelines had a clearly described scope and purpose, and suggestions were presented clearly. The guideline development group included individuals from all relevant professional groups and the target user of the guidelines was clearly defined. Experts with extensive imaging expertise were reportedly excluded from the panel to prevent bias in the scoring process. The guidelines clearly described the methods and the quality of evidence was reportedly appraised using study designs. Suggestions were based on moderate-quality evidence from 1 or more well-designed, well-executed non-randomized studies, observational studies, registries, or meta-analyses of such studies, and the positron emission tomography recommendations were based on more limited data.[17] Furthermore, the authors are not free of competing interests, and it is unclear if the expert panel was free of competing interests. One or more authors reported a conflict of interest pertaining to the sponsor.

Japanese Circulation Society Guideline

The Japanese Circulation Society published a guideline on the diagnosis and treatment of cardiac amyloidosis in 2020.[23] The aim of this guideline was to help promote appropriate treatment for patients with cardiac amyloidosis. The authors used literature searches and accompanied every suggestion in the guideline with a class, level of evidence, and Medical Information Network Distribution Service (MINDS) grades of recommendations and MINDS levels of evidence.[29]

In this guideline, all possible diagnoses of ATTR are placed into either “probable” or “definite” categories. To obtain a definite diagnosis of systemic wild-type ATTR or hereditary ATTR, the defined diagnosis criteria pertaining to biopsy results must be met,

as outlined in Table 4. However, meeting biopsy-related criteria is not required for probable diagnosis; instead, meeting the criteria that rely on a scintigraphy scan is acceptable (Table 4).

Table 4: Japanese Circulation Society Diagnostic Criteria for Systemic Amyloidosis

Type	Possible criteria	Definite category	Probable category
ATTR hereditary	A. Clinical signs and laboratory findings: Clinical signs or laboratory findings due to each type of amyloidosis are present. B. Pathological examination findings: Amyloid deposits exhibiting positive staining with Congo red under a light microscope and showing apple-green birefringence under a polarizing microscope in biopsy tissue are observed. Amyloid can be detected in abdominal fat pad needle aspiration biopsy, skin biopsy, gastrointestinal biopsy, lip biopsy, peripheral nerve biopsy, myocardial biopsy, and so forth. Since amyloid deposits are often found on the vascular wall of the gastrointestinal submucosa, it is recommended that a gastrointestinal biopsy be performed down to the submucosal layer. If the disease is strongly suspected due to clinical signs or other laboratory findings, it needs to be detected by a repeated biopsy taken from each tissue site. C. Amyloid typing: Amyloid deposits show positive staining for TTR. ATTR (+), ALκ (−), ALλ (−), and AA (−) should be confirmed by immunostaining or the amyloid precursor protein should be identified using LMD and LC-MS/MS in biopsy tissue samples. D. Scintigraphy: Intensely diffuse myocardial uptake on Tc-99m-PYP scintigraphy is confirmed with visual grading method using frontal planar images taken 3 hours later (grade 0 = no accumulation in the heart, grade 1 = mild accumulation in the heart weaker than the ribs, grade 2 = moderate degree in the heart equivalent to the ribs accumulation, grade 3 = higher accumulation in the heart than the ribs, grade 2 or higher is positive), or a quantitative validation method using planar images taken 1 hour later (H/CL ratio ≥ 1.5) should be used for evaluation. E. Genetic testing: A pathogenic mutation leading to a change of amino acids in the *TTR* gene.	A + B + E or A + D + E	A + B + C + E
ATTR wild-type	A. Clinical signs and laboratory findings: Clinical signs or laboratory findings due to each type of amyloidosis are present.	A + B + C + E + G1	A + D + E + F + G2

Type	Possible criteria	Definite category	Probable category
	B. Pathohistological findings: In biopsied myocardium or other tissues, there are amyloid deposits exhibiting positive staining with Congo red under a light microscope and showing apple-green birefringence under a polarizing microscope. In the case of wild-type ATTR, the detection rate is low for amyloid in abdominal fat pad needle aspiration biopsy, skin biopsy, gastrointestinal biopsy, lip biopsy, and so forth. Therefore, if amyloid deposits are not detected at these biopsy sites, a myocardial biopsy should be planned. If the disease is strongly suspected due to clinical signs or other laboratory findings, it needs to be detected by repeated biopsy from each tissue site. Amyloid deposition in wild-type ATTR shows weak staining with Congo red and weak apple-green birefringence under polarized light. If it is difficult to judge at one's own facility; a consultation with the research group or specialized facilities is recommended. C. Amyloid typing: Amyloid deposits show positive staining for TTR. ATTR (+), ALκ (−), ALλ (−), and AA (−) should be confirmed by immunostaining, or the amyloid precursor protein should be identified using LMD and LC-MS/MS in biopsy tissue samples. D. Scans intensely diffusing myocardial uptake on Tc-99m-PYP scintigraphy is confirmed. Visual grading method using frontal planar images taken 3 hours later (grade 0 = no accumulation in the heart, grade 1 = mild accumulation in the heart weaker than the ribs, grade 2 = moderate degree in the heart equivalent to the ribs accumulation, grade 3 = higher accumulation in the heart than in the ribs, and grade 2 or higher is positive), or using a quantitative validation method that uses planar images taken 1 hour later (heart-to-contralateral ratio ≥ 1.5) should be used for evaluation. E. Genetic testing: No pathogenic mutations involve amino acid alterations in the *TTR* gene. F. M protein is not detected. No abnormalities in the immunoglobulin-free light chain kappa to lambda ratio. In addition, no M protein in serum or urine immunofixation electrophoresis. G. Differential diagnosis G1. Localized wild-type ATTR amyloidosis, which is limited to tendon and ligament tissues, should be excluded. G2. Other diseases that cause clinical signs or laboratory findings (under "A") should be		

Type	Possible criteria	Definite category	Probable category
	excluded. However, it should be noted that wild-type ATTR can be complicated with other diseases causing cardiac hypertrophy.		

AA = amyloid A; AL = amyloid light chain; ALλ = amyloid of lambda light chain origin; ALκ = amyloid of kappa light chain origin; ATTR = transthyretin-mediated amyloidosis; H/CL = heart-to-contralateral ratio; LC-MS/MS = liquid chromatography tandem mass spectrometry; LMD = laser microdissection; Tc-99m-PYP = technetium-99m pyrophosphate; TTR = transthyretin.

Source: Japanese Circulation Society Guideline.

In the diagnostic pathway, results from M protein detection and Tc-99m-PYP scintigraphy can provide confirmation of ATTR. Specifically, the guideline suggests that grade 2 and 3 uptake and a negative M protein indicate a high possibility of ATTR. For scintigraphy, the guideline suggested adding SPECT along with planar imaging, when possible, because it enables a more accurate assessment of uptake in the myocardium. It also suggested that fusion imaging is as effective as SPECT in visual diagnosis.

This guideline suggested confirming amyloid deposits in biopsy tissue (cardiac or non-cardiac) as a requirement for the appropriate administration of tafamidis in patients with TTR cardiac amyloidosis.

Overall, the guidelines had a clearly described scope and purpose and suggestions were presented clearly. The target user of the guidelines was clearly defined. It was unclear whether the literature searches were systematic; however, a critical appraisal of the retrieved evidence was provided. Every suggestion in this guideline was accompanied with a class of recommendation, level of evidence, MINDS grades of recommendations, and MINDS levels of evidence.[29] The authors reported conflicts of interest and there appeared to be competing interests. One or more authors reported a conflict of interest pertaining to the sponsor.

European Society of Cardiology Working Group on Myocardial and Pericardial Diseases Position Statement

The European Society of Cardiology Working Group on Myocardial and Pericardial Diseases published a position statement on the diagnosis and treatment of cardiac amyloidosis in 2021.[20] The aim of this guideline was to help cardiologists and other physicians recognize, diagnose, and treat patients with cardiac amyloidosis. The methods used to produce this guideline were not described, although the methods appeared to be a review of the literature.

In this statement, the group emphasized that non-invasive diagnostic criteria are accepted for ATTR. In a patient with typical echocardiographic or CMR findings (as defined in the guidelines), ATTR-CM would be diagnosed when Tc-99m-PYP, -DPD, or -HMDP scintigraphy shows grade 2 or 3 myocardial uptake[28] of the radiotracer, and clonal dyscrasia is excluded by all the following tests: serum free light chain assay and serum and urine protein electrophoresis with immunofixation. The guideline suggests proceeding with genetic testing to differentiate between wild-type and hereditary ATTR. As per this guideline, the use of biopsies is only suggested in the following scenarios:

- Scintigraphy does not show cardiac uptake and assessments for monoclonal proteins are negative, but clinical suspicion persists. CMR should be followed by EMB or extracardiac biopsy, as bone scintigraphy could be negative in some hereditary ATTR mutations (tracer uptake depends on TTR fibril composition) and in rare subtypes of cardiac amyloidosis.
- Scintigraphy shows cardiac uptake and assessments for monoclonal proteins are negative. Histological confirmation is also required in the case that cardiac uptake is grade 1 (it could be an extracardiac biopsy).
- Scintigraphy shows cardiac uptake and at least 1 of the monoclonal protein tests is abnormal. The diagnosis of cardiac amyloidosis, in this case, requires histology with amyloid typing, usually through EMB.

Overall, the guideline had a clearly described scope and purpose and suggestions were presented clearly. The target user of the guideline was clearly defined. Although the guideline was peer-reviewed, the authors did not describe the methods used to compile them and it is unclear whether systematic methods were used to search for evidence. It is unclear if the quality of evidence was appraised. Furthermore, conflicts of interest were declared, and the authors were not free of competing interests.

German Cardiac Society Position Statement

The German Cardiac Society published a position statement on the diagnosis and treatment of cardiac amyloidosis in 2021.[27] The aim of the guideline was to detect cardiac amyloidosis in a timely and reliable manner, determine its extent and underlying subtype, and ultimately enable treatment. Yimaz et al., 2021, described the use of a systematic review and quality of evidence appraisal in preparing the guideline.

This guideline outlined a diagnostic pathway emphasizing that the implementation of the path would be dependent on the available options onsite. Per the guidelines, if cardiac amyloidosis was suspected, 1 of the following would follow for further clarification: free light chains and immunofixation (from serum and 24-hour urine) for the determination of light chains, multi-parametric CMR study and local expertise in CMR (including late gadolinium enhancement imaging and T1 mapping) and/or Tc-99m-PYP scintigraphy. The pathway enables a scintigraphy-based diagnosis of ATTR if monoclonal protein studies (in serum and urine) are negative and scintigraphy is positive. A diagnosis could be made with positive multi-parametric CMR study findings and negative monoclonal protein study findings only if there is suspicion of ATTR and there is additional workup with EMB. Per the guidelines, this ATTR confirmation should be followed up with genetic testing.

Regarding the role of scintigraphy for ATTR, the authors proposed that it be mandatory to exclude AL amyloidosis with the absence of monoclonal proteins in the serum and urine electrophoresis. SPECT imaging was suggested only in the case of positive planar imaging (illustrated in the guideline). The authors described 2 approaches that can be used for image interpretation: a semi-quantitative visual analysis using the Perugini score (a point scale of 0 to 3, where 0 = no cardiac uptake and normal bone uptake, 1 = mild cardiac uptake less than bone uptake, 2 = moderate cardiac uptake and relatively

equal bone uptake, and 3 = high cardiac uptake and only mild or absent bone uptake), or a semi-quantitative analysis that determines the ratio of tracer uptake between the heart and contralateral half of the lung, referred to as the heart-to-contralateral (H/CL) ratio.

Pertaining to the role of biopsies, the guideline maintained that EMB remains the gold standard. Because the sensitivity for the detection of wild-type ATTR is low in extracardiac biopsy, the authors recommend EMB, which has a significantly higher sensitivity if there is no unequivocal diagnosis made from non-invasive testing. Per the guidelines, decisions to use EMB should be evaluated case by case, and the advantages of diagnosis and therapy implementation must be weighed against the availability of non-invasive information using modern imaging techniques and the complication risks of invasive EMB. For patients with heart failure, the guidelines suggested EMB if it is necessary to confirm diagnosis, and results would have direct therapeutic consequences.[30] The authors described some circumstances under which they considered EMB to be unnecessary:

- In cases where unequivocal echocardiographic, CMR, or scintigraphy findings of cardiac amyloidosis are available, the presence of monoclonal bands has been ruled out, and/or a specific drug therapy for ATTR is not considered.
- In younger patients (younger than age 50) with a family history of and/or a symptom complex that clearly indicates systemic hereditary ATTR amyloidosis, a genetic examination with or without extracardiac biopsy can be performed.
- If EMB is not technically possible, not desired by the patient, or is not purposeful, an extracardiac biopsy (fat aspirate biopsy) can be considered despite a significantly lower sensitivity.

Overall, the guidelines had a clearly described scope and purpose and suggestions were presented clearly. The target user of the guidelines was clearly defined. The authors reported conducting systemic searches and screening and reported conducting a critical appraisal of the included literature. Strengths and limitations of cited literature, including cohort studies and trials, were discussed throughout the guidelines. The authors reported conflicts of interest and there appear to be competing interests. One or more authors reported competing interests pertaining to the sponsor.

Heart Failure Association, Heart Failure Society of America, and Japanese Heart Failure Society Position Statement

The Heart Failure Association, Health Failure Society of America, and Japanese Heart Failure Society published a position statement on EMB in 2021.[13] This statement did not include a diagnostic pathway for ATTR-CM, but it did provide insight on the role of biopsies. The aim of the guideline was to provide an overview of the practical approach to EMB. Literature searches informed the development of the guidelines. The authors indicated that EMB is highly sensitive and specific for cardiac amyloidosis, and that it may be considered if a non-invasive assessment provides inconclusive or discordant results (e.g., an abnormal serum free light chain assay and a positive Tc-99m-DPD scintigraphy), or ambiguous imaging results in patients with plasma cell dyscrasia.[31-33]

Guidelines Produced by Other Authors

All guidelines produced by the authors, independent of medical societies, aligned with the diagnostic pathway described in the medical society guidelines. These guidelines supported that scintigraphy can be used for the confirmation of ATTR-CM after excluding AL amyloidosis, and biopsies should be used in cases with equivocal results or when clinical suspicion remains high.[2,4,21,22,24]

Benson et al.

Benson et al., 2020, presented a review of the literature on the current understanding of the ATTR disease process, diagnostic and surveillance approaches, treatment modalities, and future directions.[4] The review methods were not described, although it appeared to be a literature search.

In this diagnostic pathway, suspicion of amyloidosis was followed by the need to rule out AL amyloidosis. As per the guideline, the following laboratory tests were recommended: serum free light chains, serum protein electrophoresis and urine protein electrophoresis with immunofixation, and a urinalysis to look for proteinuria. Once AL amyloidosis was excluded in patients, either a biopsy or non-biopsy diagnosis approach was suggested. A non-biopsy approach consisted of nuclear scintigraphy scan using Tc-99m-PYP, Tc-99m-DPD, or Tc-99m-HMDP. If the nuclear scan was positive and showed more uptake of tracer in the heart than the bone, this would be suggestive of a diagnosis. The guideline suggested following the positive scan with genetic testing. If a known pathologic mutation in TTR were found, the diagnosis would be hereditary ATTR. Alternatively, if the DNA analysis was normal, the diagnosis would be wild-type ATTR. Alternatively, cardiac biopsy could be performed to make a diagnosis of amyloidosis. If ATTR was confirmed through biopsy, the guideline suggested that this should be followed by genetic testing.

Overall, the guideline had a clearly described scope and purpose and suggestions were presented clearly. The target user of the guideline was clearly defined. The methods were not described, and it was unclear whether the searches were systematic, or whether a critical appraisal of the evidence was conducted. The authors reported conflicts of interest and there appear to be competing interests. One or more authors reported competing interests pertaining to the sponsor.

Bistola et al.

Bistola et al., 2020, presented practical recommendations for the diagnosis and management of ATTR-CM.[2] The methods were not described, although it appeared to be a literature search.

In this diagnostic pathway, the authors suggested that patients should start with serum and urine immunofixation and free light chain assays to exclude AL amyloidosis. Once AL amyloidosis was excluded, the authors suggested bone scintigraphy with Tc-99m-PYP, -DPD, or -HMDP. If the scan was positive (defined as Perugini grade 2 or 3), then ATTR was confirmed. If the scan was indeterminate, the authors suggested that EMB

would be required. In all confirmed ATTR cases, the authors suggested the use of genetic testing to establish the ATTR subtype.

Overall, the guideline had a clearly described scope and purpose, and suggestions were presented clearly. The target user of the guideline was clearly defined. The methods were not described, and a critical appraisal of the evidence was not found. The authors reported conflicts of interest and there appear to be competing interests. One or more authors reported competing interests pertaining to the sponsor.

Gertz et al.

Gertz et al., 2020, presented consensus recommendations for general practitioners for the suspicion of and diagnosis of ATTR-CM.[21] The methods were described in detail and consisted of a series of development and review cycles by an international working group of specialists. The authors also reported the details of a literature search, with a list of key search terms and databases.

In this diagnostic pathway, which was contextualized to general practitioners, defined light chain abnormality, cardiac symptoms and peripheral neuropathy symptoms should lead to further diagnostic testing. The pathway suggested that cardiac symptoms should be followed by echocardiogram, electrocardiogram, cardiac MRI and scintigraphy, and peripheral neuropathy symptoms should be followed by *TTR* genetic testing. Diagnostic testing would be followed by referrals for cardiology or neurology and genetic counselling, while a light chain abnormality would indicate a referral to hematology. The guideline emphasized that tracer uptake may be low or absent in patients with ATTR-CM with rare mutations, citing *TTR* Phe64Leu as an example. When PYP is used as the bone tracer, false-positive myocardial uptake (score of 1) of planar images can occur due to the blood pool effect such that SPECT imaging is necessary. Furthermore, the guideline specified that the sensitivity of non-cardiac tissue biopsy, particularly abdominal fat biopsy, is low in patients with wild-type ATTR-CM.

Overall, the guideline had a clearly described scope and purpose and suggestions were presented clearly. The target user of the guidelines was clearly defined. The methods were described; however, it was unclear whether a critical appraisal of the evidence was conducted. The authors reported conflicts of interest and there appear to be competing interests. One or more authors reported competing interests pertaining to the sponsor.

Inomata et al.

Inomata et al., 2021, presented a diagnostic pathway for wild-type ATTR-CM based on discussions from an advisory board held in Tokyo, Japan in 2019.[22]

In this diagnostic pathway, suspicion of amyloidosis with defined criteria was followed by Tc-99m-PYP scanning and monoclonal protein detection tests to exclude AL amyloidosis and grade the cardiac uptake. The guideline suggested following positive findings with a tissue biopsy, amyloid typing, and *TTR* genetic testing to differentiate between wild-type and hereditary ATTR-CM. This guideline discussed the role of false positives in planar imaging for Tc-99m-PYP scanning and the subsequent use of SPECT imaging for a more accurate assessment of uptake.

Biopsies were also discussed in this guideline. Biopsies were described as necessary for confirming amyloid deposits and the type of amyloidosis definitively, typically following the confirmation of a grade 2 or 3 myocardial uptake score in the Tc-99-PYP scanning. Per this guideline, the rate of amyloid detection was described as sufficiently high for biopsy at less invasive sites (e.g., lip salivary glands, stomach or duodenum, and skin) for hereditary ATTR-CM; however, biopsies other than EMB were described as insufficient for detecting wild-type ATTR-CM. Specifically, the sensitivity of abdominal fat pad biopsy was described to be highly variable and the guideline suggested performing a repeated biopsy test when results are strongly suggestive of wild-type ATTR-CM. The guideline described that when amyloid deposits are not detected in these tissues, EMB should be considered. The guideline also discussed the safety of EMB, specifically suggesting that EMB can be safely enforced with a less than 1% incidence of serious cardiac complications and should be performed for differentiation of wild-type ATTR-CM from monoclonal gammopathy of undetermined significance or AL amyloidosis, because its sample error rate was described to be low.

Overall, the guidelines had a clearly described scope and purpose and suggestions were presented clearly. The target user of the guidelines was clearly defined. The methods were described; however, they did not appear to be systematic, and it was unclear whether a critical appraisal of the evidence was conducted. The authors reported conflicts of interest and there appear to be competing interests. The sponsor reportedly funded the advisory board that informed the guidelines, and 1 or more authors reported competing interests pertaining to the sponsor.

Korosoglou et al.

Korosoglou et al., 2021, presented a diagnostic pathway that considered clinical data, cardiovascular imaging, and myocardial biopsy.[24] The methods were not described, although it is likely a literature search.

In this pathway, the first step after suspicion (i.e., defined red flags), was for patients to undergo screening for monoclonal gammopathy in blood and urine samples including free light chains and immunofixation. If AL amyloidosis was excluded through negative findings in the light-chain analysis, the next step was a bone scintigraphy. Moderate or strong tracer uptake (i.e., Perugini score 2 or 3) was suggestive of confirming ATTR-CM, and an EMB was not required due to the high specificity and positive predictive value. In the case of equivocal findings (e.g., absent monoclonal gammopathy with absent or mild tracer uptake by bone scintigraphy), an EMB was suggested to be necessary. An ATTR diagnosis was followed by further genetic testing to confirm or exclude a variant in the *TTR* gene.

Overall, the guidelines had a clearly described scope and purpose and suggestions were presented clearly. The target user of the guidelines was clearly defined. The methods were not described, and it was unclear whether they were systematic and whether a critical appraisal of the evidence was conducted. The authors reported no conflicts of interest.

Conclusion

Overall, the clinical experts and guidelines reviewed by CADTH indicated that the use of biopsy to confirm diagnosis is only necessary in select cases. The clinical expert panel and the 12 clinical guidelines reviewed as part of this Request for Advice all indicated that biopsies are only necessary in the case that results from Tc-99m-PYP scintigraphy are equivocal, that clinical suspicion remains high despite negative results, or if the Tc-99m-PYP modality is unavailable. The clinical experts noted that the yield of non-cardiac biopsy, especially in wild-type, is highly variable and may be low, which also aligned with the findings presented in the guidelines. Tc-99m-PYP scintigraphy is an acceptable modality for diagnosing ATTR-CM. The clinical experts and the clinical guidelines suggest that Tc-99mm-PYP is a valid form of non-invasive diagnosis, maintaining that SPECT is necessary alongside the use of PYP scanning as opposed to planar imaging alone.

The guidelines generally suggested that once AL is excluded through standard testing, the next recommended test is a Tc-99m-PYP scan. In the presence of a positive scintigraphy result, defined as an uptake of grade 2 or higher (greater than or equal to bone uptake), or a heart-to-contralateral lung-uptake ratio 1.5 or greater, and excluding monoclonal protein, a diagnosis of ATTR cardiac amyloidosis can be made. Although still the gold standard for the diagnosis of ATTR, given the inherent risks of performing biopsies on high-risk patients, along with the increased suitability of scintigraphy, the guidelines suggested that biopsies should be reserved for instances of equivocal PYP results, unavailability of PYP, or when clinical suspicion for ATTR remains high. Genetic testing, followed by positive findings in scintigraphy or biopsy, enables the differentiation between wild-type and hereditary ATTR.

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Appendix 1: Relevant Guidelines Retrieved From the Literature Search

Note that this appendix has not been copy-edited.

Table 5: Guidelines Reviewed in Request for Advice

Author (Publication year)	Title
Medical societies	
Dorbala, S., et al. (2021)	ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis: Part 1 of 2-Evidence Base and Standardized Methods of Imaging ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis: Part 2 of 2-Diagnostic Criteria and Appropriate Utilization Addendum to ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: Part 1 of 2-evidence base and standardized methods of imaging
Fine, N.M., et al. (2020)	Canadian Cardiovascular Society/Canadian Heart Failure Society Joint Position Statement on the Evaluation and Management of Patients with Cardiac Amyloidosis
Garcia-Pavia, P., et al. (2021)	Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases
Kitaoka, H., et al. (2020)	JCS 2020 Guideline on Diagnosis and Treatment of Cardiac Amyloidosis
Rapezzi, C., et al. (2013)	Diagnostic work-up in cardiomyopathies: Bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases
Seferovic, P.M., et al. (2021)	Heart Failure Association of the ESC, Heart Failure Society of America, and Japanese Heart Failure Society Position statement on endomyocardial biopsy
Yilmaz, A., et al. (2021)	Diagnosis and treatment of cardiac amyloidosis: position statement of the German Cardiac Society
Other authors	
Benson, M.D., et al. (2020)	Diagnosis and Screening of Patients with Hereditary Transthyretin Amyloidosis (hATTR): Current Strategies and Guidelines
Bistola, V., et al. (2021)	Practical recommendations for the diagnosis and management of transthyretin cardiac amyloidosis
Gertz, m., et al. (2020)	Avoiding misdiagnosis: expert consensus recommendations for the suspicion and diagnosis of transthyretin amyloidosis for the general practitioner
Inomata, T., et al. (2021)	Diagnosis of wild-type transthyretin amyloid cardiomyopathy in Japan: red-flag symptom clusters and diagnostic algorithm
Korosoglou, G., et al. (2021)	Diagnostic Work-Up of Cardiac Amyloidosis Using Cardiovascular Imaging: Current Standards and Practical Algorithms

Appendix 2: Stakeholder Input

Patient Input: Canadian Organization for Rare Disorders

Response to CADTH Request for Input on: Biopsy vs technetium-99 m pyrophosphate scintigraphy for diagnosis of transthyretin cardiac amyloidosis for reimbursement of tafamidis (Vyndaqel)

Context

The Canadian Organization for Rare Disorders, having conducted patient survey and provided input to the original CADTH review of tafamidis for patients with cardiomyopathy due to wild-type or hereditary ATTR-CM is pleased to provide a brief submission to the question of alternatives to biopsy for diagnosing ATTR-CM patients as a requirement for reimbursement of tafamidis (Vyndaqel).

Approach to Question

We have rephrased the question to focus specifically on 2 modalities. Is technetium-99 m pyrophosphate scintigraphy an acceptable modality to replace biopsy for diagnosing wild-type (wATTR) or hereditary ATTR (hATTR) in patients with confirmed cardiomyopathy to provide reimbursement of tafamidis?

Methods

A. Literature review (selected)

B. Development of questionnaire/discussion guide (to optimize informed reflections on question)

C. Presentation on individual basis to small cohort (n=6) patients and family members, some who had previously provided input to tafamidis consultation and others newly recruited.

A. Standard of care/best practice guidelines literature review

We complied the findings from the literature review around key questions.

Q1: Is biopsy of fat, tissue or gland a recommended procedure to accurately confirm a diagnosis of ATTR-CM?

- No, not sufficient to confirm CM ATTR.

Q2: Is endomyocardial biopsy (EMD) a recommended procedure to accurately confirm a diagnosis of ATTR-CM?

- Yes, it is highly accurate
- No, as an invasive procedure with inherent risks, it is not preferred if there is alternative

Q3: Is technetium-99 m pyrophosphate scintigraphy (aka bone scintigraphy with specific tracer) a recommended (sufficient) procedure to confirm diagnosis of wATTR or hATTR?

- Yes, it is highly (99-100%) accurate
- Yes, it is a non-invasive procedure with a low risk of adverse effects
- If unavailable or nonconclusive results, conduct EMD

B. Discussion protocol

We formulated the findings into questions for the participants.

1. Are you aware of the CADTH recommendation and public drug plan protocol to require a biopsy (using fat, gland, tissue, or cardiac tissue) to confirm diagnosis of ATTR-CM for eligibility to receive tafamidis?
2. Biopsy of tissue from an affected organ (for example, kidney, liver, or heart) is the best confirmation of amyloidosis at that site. Biopsy of tissue from alternative sites, such as abdominal fat, bone marrow, or salivary gland may be effective for other organs but not the heart. How do you feel about the requirement of tissue biopsy of fat, salivary gland, or nerve tissue by the public drug plans to approve tafamidis?
3. Biopsies of any organ can have adverse effects; however, biopsy is especially risky for the heart. How do you feel about requirement for biopsy of cardiac tissue to approve tafamidis?
4. Standards of care and best practice guidelines, including joint guidelines of the Canadian Cardiovascular Society and the Canadian Heart Failure Society recommend that patients with suspected TTR cardiac amyloidosis (based on heart failure workup) be tested with an alternative nuclear imagining procedure known as bone scintigraphy with a radiotracer that is non-invasive (requires no tissue removal) and is highly accurate (99-100%). How do you feel about this as the alternative procedure to diagnosis ATTR-CM for treatment and reimbursement of tafamidis?
5. What other questions or comments do you wish to share.

Summary of Responses

Demographics: All 6 reside in Canada; 5 are male and 1 is female; all diagnosed with ATTR-CM. We did not ask age or treatment status.

1. Are you aware of biopsy requirement?
   Not all participants were aware of potential for biopsy with other tissue, but all were aware of requirement of a biopsy (cardiac tissue) to confirm diagnosis of ATTR-CM to qualify to receive tafamidis. None had experienced any adverse effects or were aware of others who had.
2. How do you feel about the requirement of tissue biopsy of fat, salivary gland, or nerve tissue?
   Participants had mixed reactions based on their previous knowledge or exposure, but all agreed that the use of or requirement for biopsy from sites other than the heart was not appropriate. However, none had asked to provide, and they did they have knowledge of biopsies performed on tissue from alternative sites.
3. How do you feel about requirement for biopsy of cardiac tissue to approve tafamidis?
   Participants said they had received information about the risks of a cardiac biopsy. None had been informed about an alternative to a biopsy and they accepted the risk-benefit to qualify for treatment. All expressed confidence in their cardiologists to provide the best information and appropriate care.
4. How do you feel about this as the alternative procedure to diagnosis ATTR-CM for treatment and reimbursement of tafamidis?
   All participants indicated that they would indeed endorse an alternative to cardiac biopsy if it were equally effective and less risky. They overwhelmingly endorsed a change to the requirement and also to making the information known to the cardiologists and especially to the patient community. None based on the summary information presented expressed any reservation about the change in protocol, but some did recommend ongoing monitoring and evaluation to assure that all patients who were accurately diagnosed (no one missed and denied treatment). Not excluding those who might benefit was a greater concern than potentially including those who were not ATTR-CM.
5. There were numerous other comments as to the importance of treatment.

Respectfully submitted,
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21 January 2022

Sponsor Input

Overview

1. **Is biopsy a necessary modality for diagnosing patients with cardiomyopathy due to wild-type or hereditary TTR-mediated amyloidosis?**

   No, biopsy is not a necessary modality for diagnosing patients with cardiomyopathy due to wild-type or hereditary TTR-mediated amyloidosis (ATTR-CM). This fact is supported by the following key clinical points:

   - The treatment and management of ATTR-CM has evolved since the initial design of the ATTR-ACT trial, when cardiac biopsy was the only definitive way to diagnose ATTR-CM. Technetium-99m pyrophosphate scintigraphy (^{99m}Tc-PYP) imaging is now recognized as the technique for confirming the diagnosis of a patient suspected of having ATTR-CM. Canada was the first jurisdiction to publish a position statement recommending ^{99m}Tc-PYP imaging as a first-line diagnostic technique patients with ATTR-CM, other countries followed shortly thereafter. *(Please refer to Scientific Rationale, Question 1, Section 1.1 and Question 2, Section 2.1).*
   - The Canadian Cardiovascular Society (CCS)/Canadian Heart Failure (CHFS) Joint Position Statement recommends that endomyocardial biopsy be performed only when non-invasive evaluation yields equivocal results or clinical suspicion remains high despite a negative workup.(1) *(Please refer to Scientific Rationale, Question 1, Section 1.1).*
   - As illustrated by the amendment to the ATTR-ACT study protocol (April 16, 2014) to include ^{99m}Tc-PYP imaging as a diagnosis technique, if the ATTR-ACT trial were to be conducted today, it would not require biopsy as an inclusion criterion. Ongoing phase III clinical trials examining the efficacy of new molecules for the treatment of ATTR-CM permit the use of cardiac or non-cardiac biopsy **OR** ^{99m}Tc-PYP imaging with grade 2 or 3 cardiac uptake in the absence of abnormal light chains ratio for a confirmation of ATTR-CM for patient inclusion within the trial. (2, 3) *(Please refer to Scientific Rationale, Question 1, Section 1.2).*
   - Extracardiac biopsies have either low or undocumented detection rates for wild-type ATTR-CM which represents the predominant (95%) form of ATTR-CM in Canada.(4) As such, they have limited clinical utility for detection of amyloid since if the results are negative, but a high index of suspicion still exists, cardiac biopsy is still required. *(Please refer to Scientific Rationale, Question 1, Section 1.4).*
   - Cardiac biopsy is an invasive procedure with documented risks of complications, which provides added concern in frail elderly patients with multiple comorbidities that are suspected of having ATTR-CM. Compared with ^{99m}Tc-PYP imaging, cardiac biopsies are also resource intensive procedures that require time in a catherization lab as well as interventionalists with a high level of specialized training to maintain competency. *(Please refer to Scientific Rationale, Question 1, Sections 1.3 and 1.6).*
   - Based on the recommendations from the current CCS/CHFS diagnostic algorithm for the evaluation of suspected cardiac amyloidosis, clinicians can accurately confirm, without putting patients at unnecessary risk of further complications, an ATTR-CM diagnosis by following the diagnosis algorithm (see Figure 3 p.3).(1) Biopsy is not a necessary modality for diagnosing patients with cardiomyopathy due to wild-type or hereditary ATTR-CM.

2. **What alternative modalities (e.g., technetium-99m pyrophosphate scintigraphy) would be acceptable for diagnosing patients with cardiomyopathy due to wild-type or hereditary TTR-mediated amyloidosis for the purposes of providing reimbursement for treatment with tafamidis (Vyndaqel)?**

   Overall, only 2 modalities are considered acceptable to diagnose ATTR-CM, 1 of them being biopsy. The alternative modality that would be acceptable for the diagnosis of ATTR-CM, as aligned with the most current clinical practice recommendations is ^{99m}Tc-PYP imaging. *(Please refer to Scientific Rationale, Question 2, Section 2.1).*

   - The application of non-invasive imaging with ^{99m}Tc-PYP has transformed the diagnostic pathway for patients, and reduced the risks and delays associated with the historical requirement for endomyocardial biopsy.(5, 6)
   - ^{99m}Tc-PYP imaging has been established as the first-line diagnostic technique for ATTR-CM in Canada through the CCS/CHFS Joint Position Statement.(1) This is similar to the standards of practice in various jurisdictions around the world.
   - The 2016 study by Gillmore et al. (6) demonstrated the combined findings of grade 2 or 3 myocardial radiotracer uptake on bone scintigraphy and the absence of a monoclonal protein in serum or urine had a specificity and positive predictive value for ATTR-CM of 100%.
   - Significant advances have been made in the use of ^{99m}Tc-PYP imaging in diagnosing patients suspected of having ATTR-CM since the initial trial design of ATTR-ACT. More recently, the Canadian Association of Nuclear Medicine published PYP Imaging Guidelines to standardize the acquisition procedure, image interpretation and reporting.(7)

   Overall, the medical community internationally accepts bone scintigraphy sufficient to diagnose ATTR-CM without biopsy when: 1) cardiac amyloidosis is suspected based on standard heart failure work-up; 2) monoclonal proteins are absent as assessed by serum and urine protein electrophoresis with immunofixation and serum free light chain assay; 3) a radionuclide scan with ^{99m}Tc-PYP shows grade 2 or 3 cardiac uptake.(1)

Recommendation

Pfizer recommends that the CADTH Conditions for Reimbursement, Initiation Criteria, Section 1, be revised to reflect advancements in clinical practice. Revisions to the original text are **noted in bold**. Please note that bullet points 1.1 and 1.2 have been merged into bullet point 1.1 to simplify the documentation of cardiac disease due to ATTR-CM.

1. Documented cardiac disease due to TTR-mediated amyloidosis cardiomyopathy (ATTR-CM):

   1.1. Documented wild-type or hereditary ATTR-CM consists of all of the following: absence or presence of a variant TTR genotype **(not necessary for initiation, however, genetic testing to differentiate between wild-type and hereditary subtypes should be undertaken)** (refer to section Scientific Rationale, Section 3.1) evidence of cardiac involvement by echocardiography with end-diastolic interventricular septal wall thickness of greater than 12 mm; and either:

      1.1.1. Presence of amyloid deposits in biopsy tissue (fat aspirate, salivary gland, median nerve connection tissue sheath, or cardiac) followed by TTR precursor protein identification by immunohistochemistry or mass spectrometry; **or**

      1.1.2. **Bone scintigraphy (with grade 2 or 3 cardiac uptake in the absence of abnormal light chains ratio confirmed by serum and urine protein electrophoresis with immunofixation and serum free light chain assay).**

2. Patients who have all of the following characteristics:

    2.1. New York Heart Association (NYHA) class I to III

    2.2. History of heart failure, defined as at least 1 prior hospitalization for heart failure or **documented** clinical evidence of heart failure that required treatment with a diuretic (refer to Scientific Rationale, Section 3.3.)

    2.3. have not received a heart or liver transplant

    2.4. do not have an implanted cardiac mechanical assist device (CMAD)

    2.5. not receiving other disease-modifying treatments for ATTR.

Scientific Rationale

1. Is biopsy a necessary modality for diagnosing patients with cardiomyopathy due to wild-type or hereditary TTR-mediated amyloidosis?

Specialist clinicians with experience in the diagnosis and management of ATTR-CM can accurately confirm an ATTR-CM diagnosis by following the CCS/CHFS diagnostic algorithm for the evaluation of suspected cardiac amyloidosis (see Figure below).(1) Biopsy is not a necessary modality for diagnosing patients with ATTR-CM.

1.1. Current Clinical Practice

The CCS/CHFS Joint Position Statement recommends that endomyocardial biopsy be performed only when non-invasive evaluation yields equivocal results or clinical suspicion remains high despite a negative workup.(1) Biopsy is not a necessary modality for diagnosing patients with cardiomyopathy due to wild-type or hereditary ATTR-CM. This recommendation is aligned with recommendations from other jurisdictions including Europe, US and an international joint expert consensus recommendation document for multimodality imaging in cardiac amyloidosis published by American Society of Nuclear Cardiology (ASNC), American Heart Association (AHA), American Society of Echocardiography (ASE), European Association of Nuclear Medicine (EANM), Heart Failure Society of American (HFSA), International Society of Amyloidosis (ISA), Society for Cardiovascular Magnetic Resonance (SCMR), Society of Nuclear Medicine and Molecular Imaging (SNMMI).(8)

The CCS/CHFS recommendation is based on a multi-centre study published in 2016 by Gillmore et al. (6) that analyzed the diagnostic value of bone scintigraphy for diagnosing ATTR-CM. Bone scintigraphy images and biochemical investigations were analyzed from 1,217 patients with suspected cardiac amyloidosis referred for evaluation in specialist centres. The results demonstrated that myocardial radiotracer uptake on bone scintigraphy was > 99% sensitive and 86% specific for ATTR-CM, with false positives almost exclusively from uptake in patients with cardiac light chain amyloidosis (AL). Importantly, the combined findings of grade 2 or 3 myocardial radiotracer uptake on bone scintigraphy and the absence of a monoclonal protein in serum or urine had a specificity and positive predictive value for ATTR-CM of 100% (positive predictive value CI, 98.0–100). Importantly, this study also posited a diagnostic algorithm that recommended the utilization of PYP imaging before biopsy to establish a diagnosis of ATTR-CM and TTR genotyping after a diagnosis of ATTR-CM had been made to differentiate between wild-type and hereditary subtypes. This diagnostic algorithm played a central role in the diagnostic algorithm recommended by cardiology societies across the world including the CCS, the CHFS, the ASNC, the AHA, and the European Society of Cardiology (ESC).(1, 8-10)

Figure 1: Diagnostic Algorithm for the Evaluation of Suspected Cardiac Amyloidosis

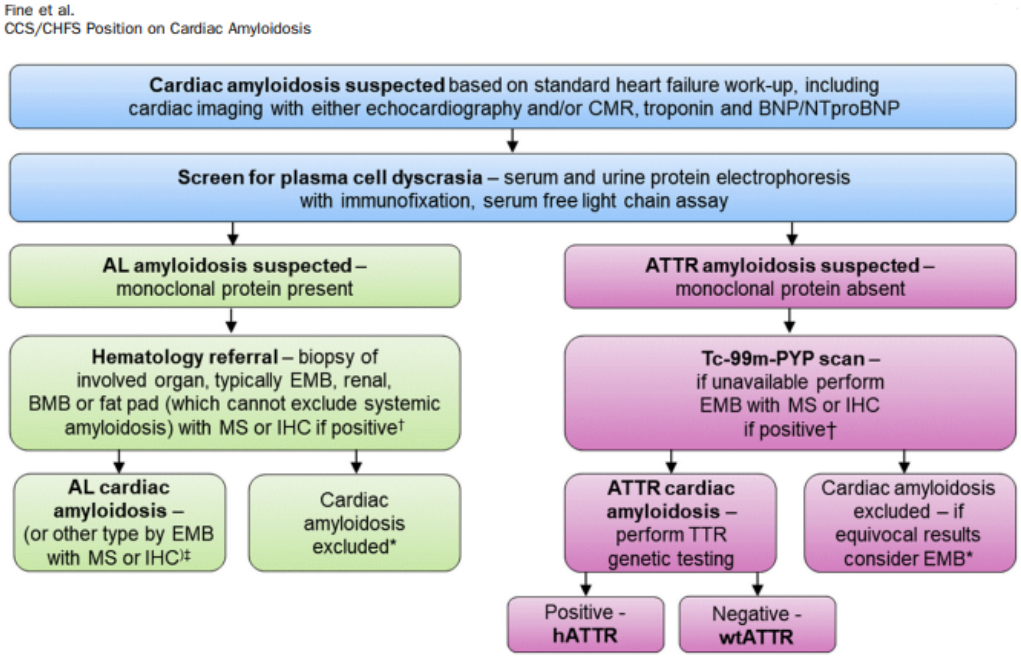

Figure 3. Diagnostic algorithm for the evaluation of suspected cardiac amyloidosis. * Endomyocardial biopsy should be performed if noninvasive evaluation is equivocal or negative despite a high index of clinical suspicion. † Tissue biopsy analysis includes Congo red staining for amyloid deposits. ‡ A diagnosis of AL cardiac amyloidosis should prompt urgent hematology referral. AL, light chain amyloidosis; ATTR, transthyretin amyloidosis; BMB, bone marrow biopsy; BNP, B-type natriuretic peptide; CMR, cardiovascular magnetic resonance imaging; EMB, endomyocardial biopsy; hATTR, hereditary transthyretin amyloidosis; IHC, immunohistochemistry; MS, mass spectrometry; NTproBNP, N-terminal pro-B-type natriuretic peptide; PYP, pyrophosphate; wtATTR, wild type transthyretin amyloidosis.

Overall, Gillmore et al. 2016 publication, provided the first diagnostic algorithm that suggested that ^{99m}Tc-PYP nuclear scintigraphy should precede endomyocardial biopsy in the diagnosis of ATTR-CM.(6) Since then, guidelines and position statements have emerged in various jurisdictions including Canada that highlight why biopsy is no longer necessary for the definitive diagnosis of ATTR-CM.

1.2. The ATTR-ACT Trial

As it stands today, the current initiation criteria established by CADTH for tafamidis are identical to the inclusion criteria of the pivotal phase III ATTR-ACT study. Patient enrolment in the ATTR-ACT trial was initiated in 2013 and was completed in August 2015.(11) At this time, the standard of care for diagnosing ATTR-CM was via confirmation of presence of transthyretin amyloid deposits in biopsy tissue as the 2016 multicenter study by Gillmore et al. (6), that established the viability of ^{99m}Tc-PYP imaging for the diagnosis of ATTR-CM, had yet to be published. As such, all patients in the ATTR-ACT trial underwent a cardiac biopsy as per the original inclusion criteria. However, a protocol amendment was made on April 16, 2014 to add scintigraphy as a diagnosis technique to better reflect clinical practice. It is also important to note that Gillmore et al.(6) recommended the use of bone scintigraphy well before the results from the ATTR-ACT trial were published. Hence, this recommendation is predicated strictly on the benefits that bone scintigraphy offers over endomyocardial biopsy. If the ATTR-ACT trial was to be conducted today, biopsy would not be required for enrolment. The shift in clinical practice is reflected in the design of the ongoing phase III clinical trials sponsored by other pharmaceutical companies that are looking to investigate the efficacy of emerging molecules for the treatment of ATTR-CM. One such study is the CARDIO-TTRansform study that was initiated in March 2020. The

CARDIO-TTRansform trial allows for the confirmation of ATTR-CM by cardiac or non-cardiac biopsy or ^{99m}Tc-PYP imaging with grade 2 or 3 cardiac uptake in the absence of abnormal light chains ratio.(2)

ATTR-CM is associated with mean progression to death within 2-3 years of diagnosis for the hereditary form and up to 3.5 years for the wild-type form.(12) Recent data from the ongoing long-term extension of the ATTR-ACT trial (13) showed that, for a median follow-up of approximately 58 months, patients initially treated with tafamidis in the ATTR-ACT trial had substantially better survival (a reduction of 41% of deaths) compared with patients first treated with placebo before transitioning to tafamidis, thus highlighting the importance of early and timely diagnosis and treatment.

1.3. Clinical Safety Perspective: Complications Associated with Endomyocardial Biopsies

In addition, the current reimbursement criterion related to the mandatory tissue biopsy at initiation is not considered to be in the best interest of patients. A recent Joint Position Statement on endomyocardial biopsy published in collaboration by Heart Failure Association, HFSA and Japanese Heart Failure Society noted that endomyocardial biopsy is associated with an approximated 1% risk of major complications which include cardiac perforation, severe arrythmias, valvular trauma, and death.(14) Furthermore, hemodynamically unstable patients with acute or advanced heart failure (NYHA class III to IV (15)) and those with dilated ventricles may be at a higher risk of cardiac perforation, tamponade and malignant arrythmias.(14) In the ATTR-ACT trial (16), though NYHA class IV patients were excluded, considering that 32% of patients were classified as NYHA class III, ATTR-CM patients represent a population that is inherently at a higher risk of cardiac biopsy complications. This Joint Position Statement on the endomyocardial biopsy (14) reinforced the same course of clinical action as the CCS/CHFS Joint position statement on cardiac amyloidosis (1) endomyocardial biopsy should be performed only when non-invasive evaluation yields equivocal results or clinical suspicion remains high despite a negative workup.(1)

Consideration should also be given to the fact that the population of patients with cardiac amyloidosis also have a high prevalence of atrial fibrillation (up to 69%) (17) which consequently leads to a significant utilization of oral anticoagulant to prevent stroke and systemic embolism. Indeed, according to literature, long-term anticoagulation is recommended in all patients with cardiac amyloidosis and atrial fibrillation in the absence of a prohibitively high bleeding risk, regardless of CHA2DS2-VASc score.(18-20) According to the Canadian guidelines on the management of atrial fibrillation (20), when an invasive procedure such as an endomyocardial biopsy is to be performed, the oral anticoagulant should be interrupted (duration varies according to the bleeding risk of the patient). Canadian clinicians shared that they are concerned about performing an endomyocardial biopsy in their patients with atrial fibrillation and cardiac amyloidosis as the interruption of the oral anticoagulant increases the risk of stroke and systemic embolism in this high-risk population or could increase the risk of bleeding if the oral anticoagulant is not withheld long enough.

The risk of complications arising from invasive biopsies weighs heavily on the minds of patients and clinicians alike. Indeed, Pfizer Canada ULC has been made aware of instances where patients have refused treatment in the face of having to undergo an invasive procedure despite having a confirmed diagnosis by PYP imaging.

1.4. Extracardiac Biopsies

Though the current CADTH criteria do allow for confirmation of TTR deposition via extracardiac biopsies, it is important to note that biopsies from these sites have either low or undocumented detection rates for wild-type ATTR-CM which represents the predominant (95%) form of ATTR-CM in Canada.(4) For example, though abdominal fat pad biopsy has been documented to have a detection rate of 45-67% in hereditary ATTR patients, the detection rate in wild-type ATTR patients is believed to be approximately only 15%. In contrast, though lip salivary gland biopsies are believed to have a high detection rate in hereditary ATTR (91-100%), their accuracy in wild-type ATTR patients remains to be studied.(21) Secondly, as these biopsy techniques are rarely used in clinical practice, many clinicians often must go to great lengths to identify an individual with sufficient training to perform salivary gland biopsies. As such, while extracardiac biopsies

do present an alternative to cardiac biopsies, they are limited by their detection rates, or lack thereof, and provide very little meaningful information if negative.

1.5. Maintenance of Procedural Skill and Resource Utilization

Given their invasive nature, endomyocardial biopsies require a significant amount of health care resources and maintenance of procedural skill. The recent Joint Position Statement on endomyocardial biopsy published in collaboration by Heart Failure Association, HFSA and Japanese Heart Failure Society recommends a range of 20-50 procedures per operator, per year may be reasonable to maintain procedural skill.(14) Similarly, the American College of Cardiology Competency Management Committee recommends 50 endomyocardial biopsies be performed per operator, per year to maintain procedural skill. This referral volume is typically seen at larger Canadian centres that accept referrals from across the province or city. From a laboratory resource perspective, cardiac biopsies are also usually performed in cardiac catheterization laboratories, under fluoroscopic guidance. Patient monitoring (heart rhythm, non-invasive blood pressure, and blood oxygen saturation monitoring) is mandatory during the procedure.(14) Anecdotally, clinicians have shared that the number of requests for cardiac biopsies have increased significantly thus creating congestion of the cardiac catheterization labs. This has had an overall impact on all patients that are awaiting cardiac procedures regularly performed in these labs (i.e., angioplasty, angiogram, ablation).

2. What alternative modalities (e.g., technetium-99 m pyrophosphate scintigraphy) would be acceptable for diagnosing patients with cardiomyopathy due to wild-type or hereditary TTR-mediated amyloidosis for the purposes of providing reimbursement for treatment with tafamidis (Vyndaqel)?

2.1. The Emergence and Role of ^{99m}Tc-PYP Imaging

The application of non-invasive imaging with nuclear scintigraphy has transformed the diagnostic pathway for patients, and reduced the risks and delays associated with the historical requirement for endomyocardial biopsy.(5, 6)

^{99m}Tc-PYP imaging has been established as the first-line diagnostic technique for ATTR-CM in Canada through the CCS/CHFS Joint Position Statement as well as in other jurisdictions around the world. Bone scintigraphy is a type of imaging technique that uses phosphonate radiotracers that were originally developed to study metastatic bone disease but overtime, were also found to bind calcium in myocardial tissue affected by infarction and more recently from TTR amyloid deposition.(22) Of the 3 most studied radiolabelled phosphonates (HMDP: hydroxymethylene diphosphonate; DPD: 3,3-diphosphono-1,2-propanodicarboxylic acid; PYP: pyrophosphate), PYP is the only one available for use in Canada. It is remarkably sensitive for ATTR-CM, has a higher myocardial retention for ATTR compared with light chain amyloidosis, can reliably distinguish ATTR-CM from other entities that mimic cardiac amyloidosis, such as hypertrophic cardiomyopathy and has been shown to be able to detect ATTR in patients with HFpEF.(5, 6, 8, 22). As discussed in Question 1, the 2016 study by Gillmore et al. (6) demonstrated the combined findings of grade 2 or 3 myocardial radiotracer uptake on bone scintigraphy and the absence of a monoclonal protein in serum or urine had a specificity and positive predictive value for ATTR-CM of 100%. Secondly, a US consensus study (n = 229) examined the sensitivity and specificity of ^{99m}Tc-PYP cardiac imaging as a diagnostic tool for ATTR-CM.(23) The analysis included 121 patients with ATTR-CM. Results showed an overall sensitivity and overall specificity of 91% and 92%, respectively, for ^{99m}Tc-PYP cardiac imaging to confirm ATTR-CM. Finally, a recent meta-analysis of 6 selected studies on bone scintigraphy in ATTR-CM including 529 patients found that bone scintigraphy using 99mTc-labelled radiotracers provides very high diagnostic accuracy (sensitivity 92.2% (95% CI 89–95%) and specificity 95.4% (95% CI 77–99%)), in the non-invasive assessment of ATTR-CM.(24)

Overall, these studies demonstrated that bone scintigraphy is sufficient to diagnose ATTR-CM without biopsy when: 1) cardiac amyloidosis is suspected based on standard heart failure work-up; 2) monoclonal proteins are absent as

assessed by serum and urine protein electrophoresis with immunofixation and serum free light chain assay; 3) a radionuclide scan with ^{99m}Tc-PYP shows grade 2 or 3 cardiac uptake.(1)

More recently, the Canadian Association of Nuclear Medicine published PYP Imaging Guidelines to standardize the acquisition procedure, image interpretation and reporting(7). Significant advances have been made in the use of ^{99m}Tc-PYP imaging in diagnosing patients suspected of having ATTR-CM since the initial trial design of ATTR-ACT. Clinical diagnosis has shifted away from biopsy as the modality for diagnosis. It is recommended that CADTH reimbursement criteria s also reflect this advancement in clinical practice

In addition, it is worth noting that 99mTc-PYP imaging does not require as many health care resources as biopsy and is also expected to be substantially less expensive than a biopsy-based diagnosis. Thus, a benefit to not only the patient, yet the health care system as well.

3. Additional Considerations

3.1. Genetic Testing at Initiation

On a related note, it is also important to highlight that, although the criterion related to biopsy confirmation of ATTR-CM is a significant contributor for the delays associated with treatment initiation, it is not the sole factor. The requirement for genetic testing prior to tafamidis initiation is an additional limiting factor as some patients are unable to get timely access to therapy given the disparity of access to genetic testing across Canada. The CCS/CHFS Joint Position Statement on the Evaluation and Management of Patients with Cardiac Amyloidosis recommends that genetic testing be performed, to differentiate hereditary from wild-type ATTR once a patient has a confirmed diagnosis of ATTR cardiac amyloidosis.(1) This recommendation is predicated on the fact that tafamidis, the only approved medication for the treatment of ATTR-CM, has been shown to be effective in treating both wild-type and hereditary ATTR-CM. Indeed, the reduction in all-cause mortality with tafamidis compared with placebo was not different between wild-type ATTR-CM (hazard ratio: 0.706 [95% CI: 0.474–1.052]; p = 0.0875) and hereditary ATTR-CM (hazard ratio: 0.690 [95% CI: 0.408–1.167]; p = 0.1667).(25) As such, the mandatory requirement of subtyping via genetic testing prior to treatment initiation is not consistent with tafamidis' clinical profile, Health Canada indication, and the current clinical practice recommendations; nor is it in the best interest of Canadians with ATTR-CM and as such should be reconsidered. Removing genetic testing at initiation would not change the population targeted by the recommendation conditions. Genetic testing and counselling can still be carried out during the treatment of the condition as it is part of standard practice.(1)

3.2. Inequitable Access to Tafamidis for Canadian Patients

Tafamidis, is the only therapy available in Canada for the treatment of cardiac amyloidosis, a rare disease. Equitable access is a paramount foundational principle that must be evaluated. To our knowledge, the vast majority of countries do not require mandatory biopsy at treatment initiation. Also, compared with most public drug programs in Canada, the clinical initiation criteria for tafamidis in Quebec (26), and that of most private insurers, is more flexible and aligned with clinical guidelines.

At initiation, the patient must:

- have a diagnosis confirmed by a genetic confirmation of ATTR-CM
- a confirmation of ATTR-CM by bone scintigraphy **or** by cardiac biopsy
- have a medical history of heart failure including previous hospitalization or clinical manifestations which required treatment with a diuretic

- not have New York Heart Association (NYHA) class IV heart failure.

This initiation criteria allows for access to therapy in a timelier manner and considers the appropriate use of health care resources. As discussed in the previous paragraphs, time is a key factor since the data in the literature demonstrate that it is important to diagnose and treat patients as quickly as possible to optimize patient outcomes from treatment.(13)

3.3. Limitations on NYHA Class I ATTR-CM Patients

Finally, although the main concern presently for access to treatment is the biopsy requirement, the current CADTH initiation criteria stipulate that at initiation, the patient must have a medical history of heart failure including previous hospitalization or clinical manifestations which require treatment with a diuretic. Inadvertently, this restricts access to tafamidis for patients who may not have been hospitalized or treated with diuretics that could have either have another therapy prescribed or documentation of high suspicion of ATTR-CM based on clinical workup. More specifically, it restricts heart failure with preserved ejection fraction (HFpEF) patients in NYHA class I category (NYHA class I is defined as asymptomatic heart failure patients (27)) as their disease is in early stages and may not have progressed to the point where hospitalization or diuretics are required, despite the fact that the TTR plaques are progressively impacting cardiac function. To initiate treatment, NYHA class I patients need to wait until their condition progresses further to warrant a hospitalization or use of diuretic which is not aligned with the Health Canada indication. It is also contrary to the goal of treatment with tafamidis – to slow down disease progression and reduce cardiovascular hospitalizations and mortality. The importance of earlier diagnosis and treatment to optimize patient outcomes has been demonstrated in several studies.

The current (2017) Canadian Cardiovascular Society Guidelines for Management of Heart Failure discuss the role of diuretics (mineralocorticoid receptor antagonists (MRA) and loop diuretics) as well as other standard medications for the treatment and management of HFpEF patients.(27) They recommend that loop diuretics be used to control symptoms of congestion and peripheral edema (strong recommendation; moderate-quality evidence) and MRA diuretics such as spironolactone be considered for use in patients with serum potassium < 5.0 mmol/L, and an eGFR > 30 mL/min, with close surveillance of serum potassium and creatinine (weak recommendation; moderate-quality evidence). The guidelines also caution clinicians that excessive diuretic use can lead to decreased cardiac output and compromise renal function. Every attempt should be made to use the lowest possible dose of diuretic to achieve and maintain euvolemia. Besides diuretics, the Canadian Heart Failure Guidelines recommend that candesartan and antihypertensive medications be used to manage HFpEF patients and reduce heart failure hospitalization. As such, given that NYHA class I patients have asymptomatic heart failure, they may be managed with medications besides diuretics as diuretics may not be warranted yet, leading to tafamidis being withheld. Considering that it is now recognized that HFpEF is a multiorgan, systemic syndrome made up of multiple pathophysiological abnormalities above and beyond left ventricular diastolic dysfunction (28), the CCS Guidelines for Management of Heart Failure designate the first principle of management of HFpEF patients to be the identification and treatment of underlying etiological factors implicated in the development of HFpEF.(27) ATTR-CM is one such etiology and as such prioritizing and optimizing the management of ATTR-CM would align with the current guidelines, improve patient outcomes, and reduce costs to the Canadian health care system in the long run.

3.4. Wait Times and Impact of COVID-19

Research has repeatedly indicated that wait times for medically necessary treatment are not benign inconveniences. Wait times can, and do, have serious consequences such as increased pain, suffering, and mental anguish. In certain instances, they can also result in poorer medical outcomes – transforming potentially reversible illnesses or injuries into chronic, irreversible conditions, or even permanent disabilities. In many instances, patients may also have to forgo their

wages while they wait for treatment, resulting in an economic cost to the individuals themselves and the economy in general.(29)

Advancements in clinical practice, as the evidence evolves, which support the efficient use of health care resources should be encouraged. Eliminating or limiting the need for biopsy as a modality for diagnosing patients with wild-type or hereditary ATTR-CM is a robust example of advancement in care supported by evidence.

The undue harm of wait times is evident in the best of times yet is exacerbated in the current times of the continuous COVID-19 pandemic in Canada. Given the backlog of referrals, the lockdown and suspension of non-essential medical services, a vast number of patients across many disease areas are negatively impacted across the country.

For the ATTR-CM patient, where time is of the essence to access a treatment, there is a solution to minimize the time from suspicion to diagnosis to treatment. That solution is to revise the CADTH reimbursement initiation criterion related to mandatory biopsy at initiation of treatment with tafamidis.

Summary

Pfizer agrees with the Canadian Cardiology community in recognizing that biopsy (cardiac or extracardiac) is no longer a necessary modality for diagnosing patients with wild-type or hereditary ATTR-CM for the following reasons:

- The CCS/CHFS Joint Position Statement on the Evaluation and Management of Patients with Cardiac Amyloidosis defines the clinical management of ATTR-CM patients in Canada and recommends that biopsy be considered secondary to ^{99m}Tc-PYP in cases with equivocal results.(1).
- The treatment and management of ATTR-CM has evolved well past the days when cardiac biopsy was the only definitive way to diagnose ATTR-CM. This wave of change which established PYP imaging as a diagnosis technique of ATTR-CM has been led by the cardiology community in both Canada, which was the first jurisdiction to publish a position statement on the diagnosis and management of ATTR-CM patients, and around the world.
- The requirement of a cardiac biopsy to confirm the diagnosis is an artifact of inclusion criteria that were designed nearly 9 years ago.
- The decision to utilize cardiac biopsy should only be made clinically as it is an invasive procedure with documented risks of major complications, especially in frail patients such as those affected by ATTR-CM. Compared with ^{99m}Tc-PYP imaging, cardiac biopsies are also resource intensive procedures that require time in a catheterization lab as well as interventionalists with an appropriate amount of training.
- Given their invasive nature, endomyocardial biopsies require a significant amount of health care resources and maintenance of procedural skill.

As part of this Request for Advice process, Pfizer also encourages CADTH to consider these additional elements:

- The requirement for genetic testing prior to tafamidis initiation is an additional limiting factor as some patients are unable to get timely access to therapy given the disparity of access to genetic testing across Canada. In addition, the CCS/CHFS Joint Position Statement recommends that genetic testing be performed to differentiate hereditary from wild-type ATTR once a patient has a confirmed diagnosis of ATTR-CM.
- The difference in reimbursement criteria across provinces (mainly Quebec versus rest of Canada) and those patients that are covered by private insurers has resulted in inequitable differences in the ability of Canadians to access tafamidis based on their geographical disposition.
- The initiation criterion related to medical history of heart failure including previous hospitalization or clinical manifestations which required treatment with a diuretic restricts NYHA class I patients from accessing tafamidis until their condition

progresses further to warrant a hospitalization or use of diuretic which is not aligned with the Health Canada indication and contrary to the goal of treatment with tafamidis.

- Given the current impact of COVID-19 and the significant backlog of elective procedures noted across the country, many patients, including ATTR-CM patients are facing longer wait times to initiate treatment. For patients with ATTR-CM, these delays can significantly alter the course of their disease as the goal of treatment with tafamidis is to slow down disease progression and reduce cardiovascular hospitalizations and mortality.

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