WORLD HEART FEDERATION

WORLD HEART FEDERATION POLICY SUMMARY OF THE WHF CONSENSUS ON TRANSTHYRETIN AMYLOIDOSIS CARDIOMYOPATHY (ATTR-CM)

A WORLD HEART FEDERATION POLICY SUMMARY

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Writers: Dulce Brito, Irina Duarte and Constança Coelho

Design: MINT® designbymint.com

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WHAT IS ATTR-CM?

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive and fatal condition that requires early diagnosis, management, and specific treatment. The availability of new disease-modifying therapies has made successful treatment a reality. ATTR-CM can be either age-related (wild-type form) or caused by mutations in the TTR gene (genetic, hereditary forms). It is a systemic disease, and while the genetic forms may exhibit a variety of symptoms, a predominant cardiac phenotype is often present.

Amyloid cardiomyopathy may also be caused by light chain disease (AL-CM), a rare medical condition in which a clone of plasma cells in the bone marrow produce light chain proteins that deposit as amyloid fibrils in the heart and other organs. AL-CM can be clinically indistinguishable from ATTR-CM and the differential diagnosis between the two is essential to make the appropriate therapeutic decisions.

WHF assembled a panel of 20 expert clinicians specialized in TTR amyloidosis from 13 countries, along with a representative from the Amyloidosis Alliance, a patient advocacy group to develop a consensus of ATTR-CM amyloidosis focusing on cardiac involvement, which is the most critical factor for prognosis, available tools for early diagnosis and patient management, given that specific treatments are more effective in the early stages of the disease, and highlights the importance of a multidisciplinary approach and of specialized amyloidosis centres.

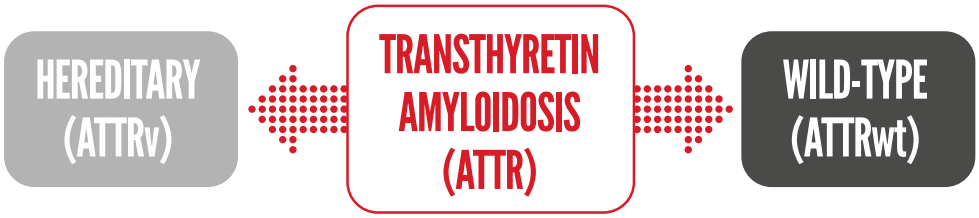
- **ATTR-CM stands for Transthyretin Amyloidosis (ATTR) Cardiomyopathy (CM). It is a rare and progressive form of heart disease characterized by the deposition of abnormal amyloid protein in the heart tissue, leading to heart failure.**
- **Transthyretin is a protein produced primarily in the liver and is involved in the transport of thyroid hormones and vitamin A. In ATTR-CM, the transthyretin protein becomes unstable and misfolds, forming insoluble amyloid fibrils. These fibrils accumulate in various organs, including the heart, leading to impaired cardiac function.**

WHY DOES ATTR-CM OCCUR?

There are two major types of ATTR-CM:

- **Hereditary ATTR-CM (also known as genetic or familial ATTR-CM): this form is caused by inherited mutations in the transthyretin gene. It typically affects multiple family members and often presents earlier in life.**
- **Wild-type ATTR-CM (previously known as senile ATTR-CM): this form is more common in older individuals, typically over the age of 60. It is not associated with inherited gene mutations but it is believed to result from the age-related deposition of wild-type transthyretin amyloid fibrils.**

The subtypes of Transthyretin Amyloidosis that affects the heart



WHY IS ATTR-CM IMPORTANT?

Overall, the importance of ATTR-CM lies in its impact on the individuals´ health, the need for early diagnosis, the genetic implications for families, the availability of treatment options, ongoing research, and public health considerations.

- **Disease impact:** ATTR-CM is a progressive and debilitating condition that affects the heart´s structure and function. It can lead to heart failure, arrhythmias, and reduced quality of life. If left untreated, it can significantly impact a person´s health and lifespan.
- **Underdiagnosis:** ATTR-CM is often underdiagnosed or misdiagnosed, leading to delayed and inadequate treatment. Increasing awareness about the disease is crucial to improve early detection and intervention, allowing for appropriate management and improved patient outcomes.
- **Genetic implications:** Hereditary ATTR-CM is caused by specific mutations in the transthyretin (TTR) gene. Understanding the genetic basis of the disease is important for identifying at-risk individuals within families and facilitating genetic counseling and testing.
- **Treatment options:** Recent advances in the treatment of ATTR-CM have emerged, offering new hope for patients. Medications known as TTR stabilizers (i.e. tafamidis) or TTR silencers can potentially slow down or halt the progression of the disease by reducing the deposition or the production of abnormal transthyretin protein.
- **Research and Development:** ATTR-CM has become an active area of research, leading to a better understanding of the disease´s underlying mechanisms, improved diagnostic techniques, and the development of novel treatment strategies. By studying ATTR-CM, researchers can also gain insights into amyloidosis and other related conditions.
- **Public Health Implications:** Raising awareness about ATTR-CM helps healthcare professionals identify and manage the condition effectively. It also facilitates the development of screening programs, guidelines, and support networks for individuals and families affected by ATTR-CM.

ATTR-CM IS A GLOBAL DISEASE

- While the prevalence of ATTR-CM varies across different regions, it has been identified in populations worldwide. Hereditary ATTR-CM can be found in various ethnic groups and regions, where specific genetic mutations associated with the disease are present. For example, certain mutations in the TTR gene are more prevalent in certain populations, such as the V50M mutation in individuals of Portuguese, Japanese, and Swedish descent, and the V142I mutation in populations of African, Afro-Caribbean, and African-American descent. On the other hand, given the ageing population, the diagnosis of wild-type ATTR-CM has also been made much more frequently in diverse populations globally.
- Because accurate prevalence data has been challenging to procure due to underdiagnosis of the condition, ATTR-CM has been considered a rare disease. However, due to growing awareness of the disease, and advances in diagnostic techniques, increased recognition and diagnosis of the disease is becoming commonplace. As a result, the understanding of the global prevalence of ATTR-CM is continually evolving. Wild-type ATTR-CM is thought to be more prevalent than hereditary ATTR-CM.
- It is worth noting that prevalence estimates can vary depending on factors such as population demographics, access to healthcare, and awareness among healthcare providers. Therefore, regional or country-specific studies may provide more accurate information on the prevalence of ATTR-CM in specific regions.

WHY IS AN EARLY DIAGNOSIS OF ATTR-CM IMPORTANT?

ATTR-CM manifestations (left ventricular hypertrophy, heart failure, arrhythmias) may overlap or even coexist with other much more common conditions affecting the heart, being a reason why the diagnosis is often delayed for several years. However, early diagnosis of ATTR-CM is important for several reasons:

- **Treatment initiation:** While currently there is no cure for ATTR-CM, certain medications have been developed to slow down the progression of the disease and manage its symptoms. At present, only one medication (tafamidis), a TTR stabilizer, has been approved for the treatment of both variant and wild-type ATTR-CM. Other novel therapies under investigation for the treatment of ATTR-CM include TTR silencers (RNAi) and gene therapy (CRISPR), which will hopefully become available to eligible patients in the coming years. Starting appropriate treatment early can help to reduce the burden of disease on patients and their primary caregivers, and improve quality of life.
- **Disease management:** Managing ATTR-CM involves a multidisciplinary approach, including cardiologists, neurologists, genetic counselors and other specialists. The deposition of amyloid fibrils does not occur only in the heart but may involve several other organs, making the diagnosis and the management a true challenge. Early diagnosis allows for comprehensive disease management planning, including regular monitoring of cardiac function and the implementation of lifestyle modifications, such as a heart-healthy diet and exercise, to optimize overall health and well-being.
- **Genetic counseling and family screening:** In the case of hereditary ATTR-CM, identifying the specific gene mutation responsible for the disease allows other at-risk family members to undergo genetic testing and counseling. Early detection in family members facilitates proactive monitoring and intervention if necessary.
- **Clinical trial participation:** Early diagnosis increases the likelihood of patients being eligible for enrollment in clinical trials studying novel treatments for ATTR-CM. Participation in clinical trials can provide access to experimental therapies and contribute to the advance of scientific knowledge and treatment options for the disease.
- **Emotional and psychological support:** An early diagnosis provides patients and their families with an opportunity to seek emotional and psychological support. Coping with a rare and progressive disease can be challenging, and having a support network in place from an early stage can be beneficial in managing the emotional impact of the diagnosis.

Early diagnosis of ATTR-CM allows for timely intervention, appropriate treatment initiation, genetic counselling, family screening, potential participation in clinical trials, and the provision of emotional support. Collectively, these factors contribute to better disease management and improved outcomes for individuals with ATTR-CM.

HOW TO DO AN EARLY DIAGNOSIS OF ATTR-CM?

An earlier diagnosis of ATTR-CM involves a combination of clinical suspicion, appropriate screening, and diagnostic tests.

Keys approaches to facilitate early detection:

- **Clinical suspicion:** Healthcare providers need to maintain a high index of suspicion for ATTR-CM, especially in individuals presenting with heart failure symptoms, particularly if they are older or there is a family history of cardiomyopathy. Raising awareness among healthcare professionals about the disease can aid in early recognition.
- **Comprehensive evaluation:** A thorough evaluation of patients should include a detailed medical history, physical examination and assessment of symptoms, identifying specific red flags or features that raise suspicion for ATTR-CM and that can guide further investigations. Complaints may include not only heart failure symptoms/signs and/or arrhythmias (e.g. atrial fibrillation, heart blocks) but also hypotension ("no longer need treatment for previous hypertension"), presence of calcified aortic stenosis in older patients, unexplained peripheral neuropathy, history of carpal tunnel syndrome, spinal stenosis, hip or knee replacement, or unstable bowel habits, among other features.
- **Biomarker testing:** Blood tests can be helpful in the diagnostic workup. Serum cardiac troponin and N-terminal pro-B-type natriuretic peptide (NT-proBNP) can be elevated and aid in the diagnosis.
- **ECG and imaging studies:** ECG is frequently abnormal and cardiac imaging may reveal characteristic findings due to myocardial infiltration. These include increased myocardial thickness, diastolic dysfunction, decreased global longitudinal strain (often with apical sparing), and biatrial enlargement on echocardiogram; extracellular volume expansion and diffuse gadolinium enhancement on cardiac magnetic resonance imaging.
- **Biopsy or non-invasive imaging:** In some cases, a tissue biopsy of affected organs may be necessary to confirm the presence of amyloid deposits. This occur when there are doubts regarding the type of amyloidosis in particular if light-chain (AL) amyloidosis cannot be excluded by specific laboratory tests. However, when AL amyloidosis is excluded newer non-invasive imaging techniques such as technetium-labeled bone-seeking agents (scintigraphy) may allow for the detection of ATTR-CM without the need for a biopsy.
- **Genetic testing:** In all cases of TTR-CM diagnosis, genetic testing is important to identify/exclude mutations in the TTR gene. If a mutation is identified, genetic testing can be extended to at-risk family members for early detection and intervention.

Collaboration between cardiologists and several other specialists experienced in the diagnosis of amyloidosis is crucial for achieving an early and accurate diagnosis of ATTR-CM.

WHY SHOULD THE WORLD HEART FEDERATION CARE ABOUT ATTR-CM

The World Heart Federation (WHF) should care about ATTR-CM for several reasons:

- **Global impact on cardiovascular health:** ATTR-CM, as a form of cardiomyopathy, contributes to the burden of cardiovascular disease worldwide. The WHF, as a global organization dedicated to promoting cardiovascular health, should be concerned about all conditions that affect heart health, including ATTR-CM.
- **Awareness and education:** The WHF plays a vital role in raising awareness about cardiovascular diseases and educating the public, healthcare professionals, and policymakers. By including ATTR-CM in their awareness campaigns and educational initiatives, the WHF can increase understanding of the disease, promote early diagnosis, and improve management strategies.
- **Advocacy for equitable access to care:** The WHF advocates for equitable access to healthcare services and interventions for cardiovascular diseases. Given the challenges in diagnosing and managing ATTR-CM, which can lead to disparities in access to specialized care and treatments, the WHF can work towards ensuring that individuals with ATTR-CM have fair and equitable access to appropriate healthcare resources and interventions.
- **Collaboration and knowledge exchange:** The WHF serves as a platform for collaboration and knowledge exchange among researchers, healthcare professionals, and organizations involved in cardiovascular health. By including ATTR-CM in their conferences, research programs, and collaborations, the WHF can foster advances in research, facilitate the exchange of best practices, and encourage international cooperation in addressing this disease.
- **Advocacy for research and innovation:** The WHF can advocate for research funding and support for ATTR-CM, encouraging studies that focus on understanding the disease, developing effective treatments, and improving patient outcomes. By promoting research and innovation, the WHF can contribute to advancing the field of ATTR, identifying new strategies to tackle the disease.
- **Policy influence:** as a global organization with influence on health policies, the WHF can advocate for policies that address the challenges associated with ATTR-CM. This includes policies related to early diagnosis, access to specialized care, reimbursement of treatments, and genetic counselling services. By engaging with policymakers, the WHF can help shape policies that improve the care and outcomes for individuals with ATTR-CM.

By addressing ATTR-CM, WHF can contribute to reduce the CVD burden and improve the lives of individuals affected by this condition.

CHALLENGES OF ATTR-CM IN LOW AND MIDDLE-INCOME COUNTRIES.

Research on ATTR-CM in low and middle-income countries (LMICs) is limited and there remains a significant gap in diagnosis in certain populations. However efforts are being made to improve awareness, diagnosis, and management of this condition globally.

ATTR-CM poses several challenges in LMICs:

- **Limited awareness and knowledge:** One of the primary challenges is the lack of awareness and knowledge about ATTR-CM among healthcare professionals in LMICs. This can result in underdiagnosis or misdiagnosis, leading to delayed or inadequate treatment;
- **Limited access to specialized diagnostic imaging:** Accurate diagnosis of ATTR-CM often requires specialized imaging techniques such as CMR imaging and nuclear scintigraphy. However, these imaging modalities may not be readily available or accessible in many healthcare settings in LMICs, making it challenging to confirm the diagnosis;
- **Cost and availability of genetic testing:** Genetic testing plays a crucial role in identifying specific mutations associated with ATTR-CM in the hereditary form of the disease. However, genetic testing can be expensive and may not be covered by healthcare systems in LMICs. Additionally, the availability of genetic testing facilities and expertise may be limited in certain regions;
- **Limited treatment options:** Treatment for ATTR-CM includes disease-modifying therapies, such as TTR stabilizers or potentially gene silencers, as well as symptomatic management of HF. However, access to these treatments may be limited or non-existent in LMICs due to factors such as high costs, lack of reimbursement, and regulatory challenges related to drug availability;
- **Healthcare infrastructure and resources:** LMICs often face resource constraints, including limited healthcare infrastructure, shortage of trained healthcare professionals, and inadequate healthcare funding. These challenges can hinder the timely diagnosis, management, and follow-up of patients with ATTR-CM;
- **Socioeconomic factors:** The socioeconomic factors prevalent in LMICs, such as poverty, limited access to healthcare services, and competing healthcare priorities, can further impact the diagnosis and treatment of ATTR-CM. Affordability of medications, transportation to specialized centres, and patient adherence to treatment plans can be significant challenges.

Increased investment in healthcare infrastructure, training programs, and research initiatives can help mitigate these challenges and improve outcomes for patients with ATTR-CM in low and middle-income countries.

EQUITABLE AND STANDARDISED ATTR-CM PATIENT MANAGEMENT

WHF believes that every human being should have access to the information, care and treatment they need to keep their heart healthy, regardless of race, nationality, gender, age, education or income. At the World Heart Federation, we work tirelessly to ensure the global population is provided with accurate and up to date details and data on CVD.

By adopting these health policy attitudes in concert, multiple countries can work together to manage patients with ATTR-CM more uniformly and equitably, improving diagnosis, access to care, and treatment outcomes for individuals living with this condition.

Some key considerations:

- **Standardised diagnostic guidelines:** Developing and implementing standardized diagnostic guidelines for ATTR-CM can help ensure consistent and accurate diagnostic criteria across countries. These guidelines should address the clinical criteria, biomarker testing, and imaging modalities necessary for diagnosis. Collaboration between international cardiovascular societies and experts can contribute to the development of these guidelines.
- **Education and awareness campaigns:** International collaboration is crucial in raising awareness about ATTR-CM among healthcare professionals, patients, and the general public. Collaborative efforts can include educational campaigns, symposia, and conferences that focus on increasing the knowledge about the disease, its symptoms, and the importance of early diagnosis and appropriate treatment.
- **Access to specialized centers:** Establishing specialized centers of excellence for the diagnosis and management of ATTR-CM can ensure that patients have access to expert care. These centers can provide comprehensive services, including multidisciplinary care teams, genetic counselling, and access to innovative therapies. Ensuring equitable access to these centers, particularly in regions with limited resources, should be a priority.
- **Collaboration in research and clinical trials:** Encouraging international collaboration in research and clinical trials can enhance the understanding of ATTR-CM and expedite the development of effective treatments. Collaboration can involve sharing patient registries, data, and resources to facilitate research, as well as coordinating multicenter clinical trials to evaluate new therapies and interventions.
- **Patient support and advocacy:** International collaboration can facilitate the establishment of patient support networks and advocacy groups dedicated to ATTR-CM. These organizations can provide resources, support, and a collective voice for patients and their families. Health policy attitudes should promote patient-centered care and involve patient representatives in policy discussions and decision-making processes.
- **Health technology assessment and reimbursement:** Collaborative efforts in health technology assessment (HTA) can help evaluate the effectiveness and cost-effectiveness of diagnostic tools, treatments, and interventions for ATTR-CM. Sharing HTA findings and best practices can inform reimbursement decisions and ensure equitable access to innovative therapies across countries.
- **Data sharing and registries:** Collaboration in data sharing and the establishment of international registries for ATTR-CM can contribute to a better understanding of the disease, its epidemiology, and treatment outcomes. Sharing anonymized patient data and collaborating on research can enhance knowledge and inform evidence-based policies and clinical practices.
- **Policy harmonization:** Harmonizing policies related to ATTR-CM diagnosis, treatment and reimbursement can ensure consistency and equity in patient care across countries. Collaboration between health policymakers can help identify common challenges, share best practices, and work towards aligning policies to optimize patient outcomes.

IMPROVING ATTR-CM

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WORLD HEART FEDERATION
32 rue de Malatrex
1201 Geneva
Switzerland
+41 22 512 06 95
info@worldheart.org
www.worldheart.org

World Heart
@worldheartfed
World Heart Federation
@worldheartfederation