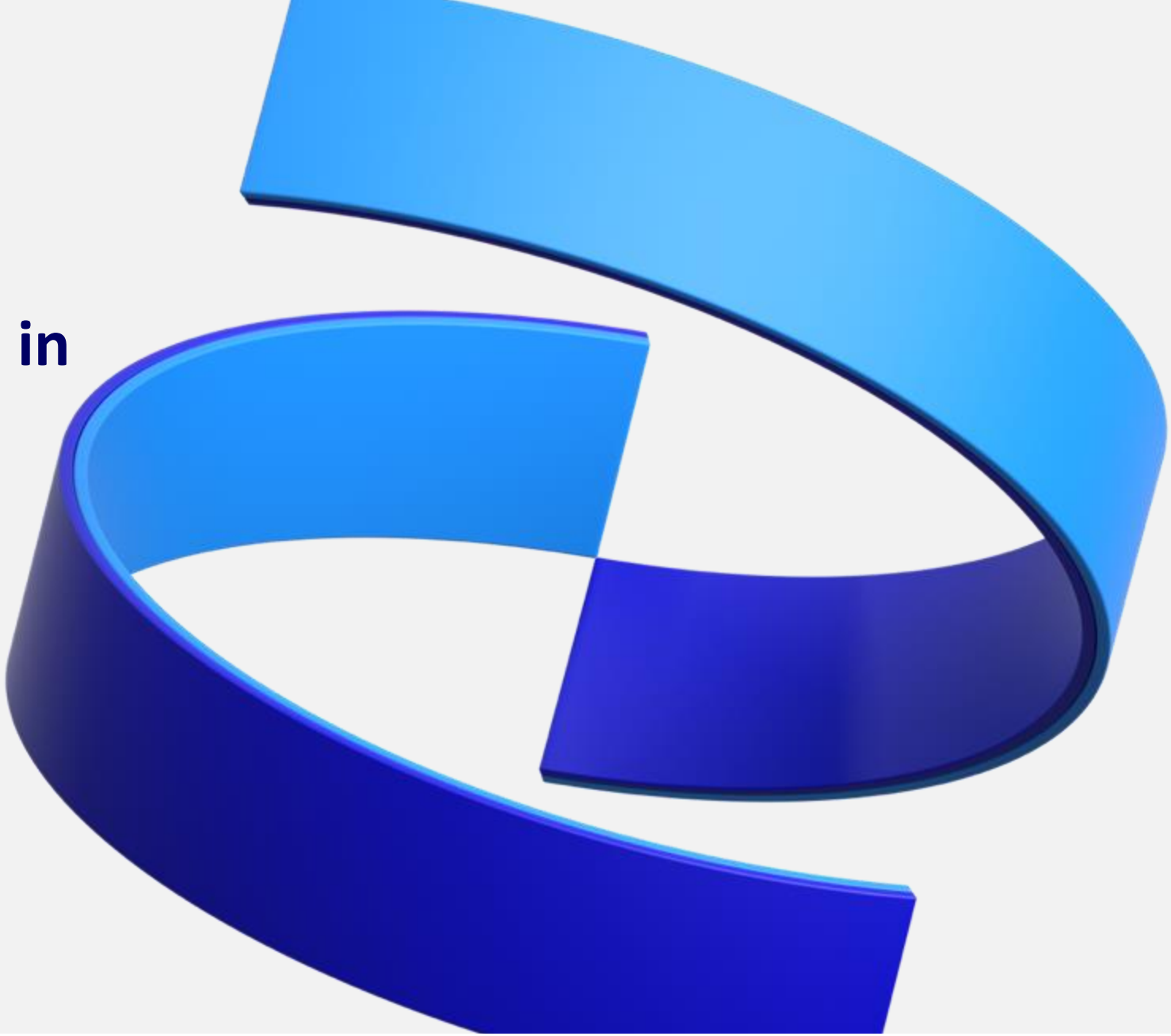
Suspecting and diagnosing transthyretin amyloid cardiomyopathy (ATTR-CM) in India: An Indian expert consensus



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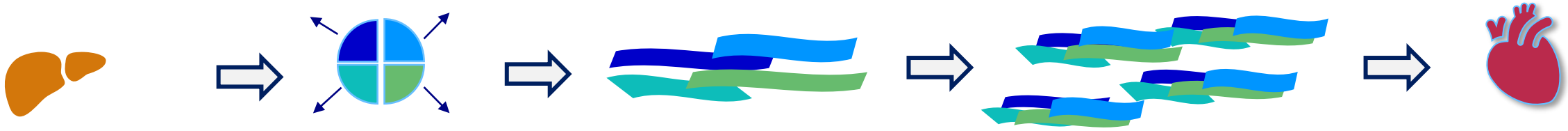
Introduction

Transthyretin cardiac amyloidosis (ATTR-CM): definition and pathogenesis

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a rare, life-threatening, progressive and infiltrative cardiomyopathy which is characterized by the aggregation of transthyretin-derived insoluble amyloid fibrils in the myocardium.

The signs and symptoms are non-specific and resembles the ones in other cardiac conditions, as a result, diagnosis is delayed and is considered under-recognized cause of heart failure (HF) in adults.

Pathogenesis



Liver produces a tetrameric transport protein, **transthyretin**

Transthyretin dissociates into monomer subunits

The monomers misfolds and reaggregates into toxic dimers and oligomers and form **insoluble amyloid fibrils**

The amyloid fibrils get deposited extracellularly in the interstitial space of the myocardium.

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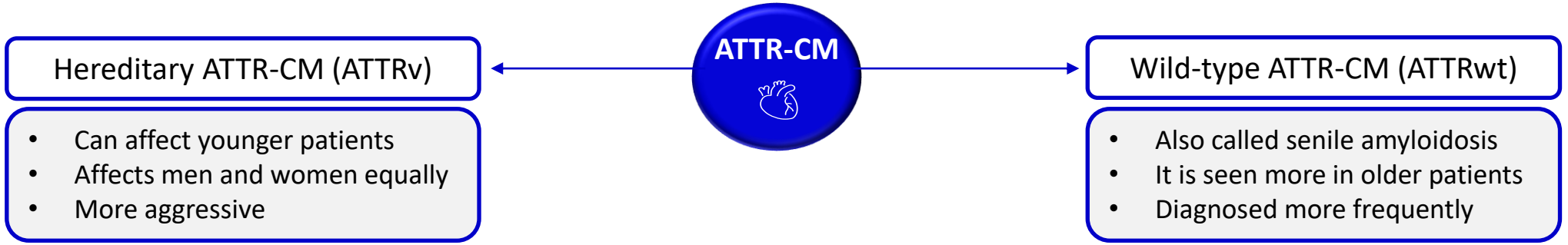
Transthyretin cardiac amyloidosis (ATTR-CM) : classification and burden



Disease burden

Epidemiology of ATTR-CM is not well characterized in India

Available case reports suggest that ATTR-CM is more prevalent in younger patients in India, compared with the West

Patients experience poor quality of life due to delay in diagnosis

Once diagnosed, life expectancy is as low as approximately 2 to 5 years which makes early diagnosis crucial

The hallmark features are not distinguished and seen in many other cardiac conditions thereby delaying the actual treatment

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Need for guiding tool for ATTR-CM in India

ATTR-CM is often diagnosed very late

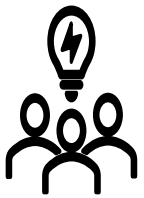
In India, there is limited region-specific literature available on ATTR-CM

Guidelines are lacking which are required for recognizing suspect cases and specific diagnosis

A series of specialized tests need to be performed which are available in select locations

These challenges draws attention to the urgent need for development of consensus on how to diagnose ATTR-CM

This will also help sensitize the doctors and regulatory bodies to increase awareness



To address this need, a list of recommendations was developed which will act as a guiding tool for the clinicians in diagnosing the patients of ATTR-CM

Focus of the consensus document – patient journey, common red flags in ATTR-CM, and the most recommended tools for diagnosis in the Indian context

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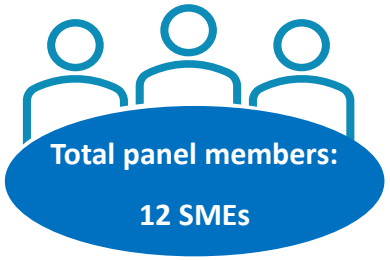
Methodology

Methodology for development of India specific diagnostic protocol



- Experts in cardiology, total, n = 7
- Expert in nuclear medicine, n = 4
- Experts in hematology, n = 4

- **Consensus recommendations on ATTR-CM from United States and Europe were reviewed and used as reference documents**
- **Below given topics were discussed in four sessions:**

1. **Patient journey and red flags**
2. **Tools for suspicion and diagnosis**
3. **Review of global and regional recommendations for diagnosis and management of ATTR-CM**
4. **Expert recommendations for development of India specific diagnostic approach protocol.**

- **For each topic, a set of question were addressed by the panelists and incorporated in the India specific diagnostic recommendations**

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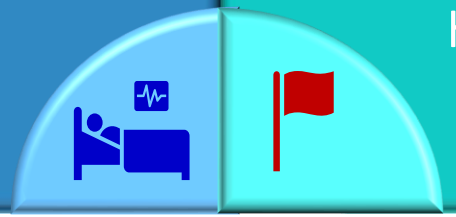
Discussion and recommendations

- **Patient journey and when to suspect ATTR-CM**

Patient journey and warning signals or red flags for ATTR-CM

Patient Journey

There is a strong need towards understanding the difficulties of patients in the journey to diagnosis to promote earlier intervention to not only improve the quality of life but also for better prognosis



Red flags or warning signals

The signs and/or symptoms that support a high degree of suspicion of ATTR-CM, many of which can be identified from an initial physical examination, assessment of patient history and routine investigations

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Warning signals or red flags for ATTR-CM

Cardiac	Extracardiac
Hypotensive or normotensive if previously hypertensive	• **Soft tissue infiltrations** - purpura (advanced disease), bilateral carpal tunnel syndrome/weakness or paresthesia of hands, atraumatic biceps tendon rupture, lumbar spinal stenosis
Atrial fibrillation together with conduction system disorders	
Increased LV wall thickness	
Arrythmias and conduction defects with HFpEF	• **Nervous system** – peripheral neuropathy and dysautonomia 
Infiltration of the atrioventricular and sinoatrial nodes	
Cardiac conduction abnormalities	
Low-flow and low-gradient aortic stenosis	• **Gastrointestinal tract** - diarrhea and/or constipation, nausea and vomiting, and early satiety, leading to weight loss 
Cardiogenic shock due to diffuse ischemia (although rare)	
Pseudo infarct pattern with low/decreased QRS voltage on ECG	
Disproportionally elevated NT-proBNP to degree of HF	• **Ophthalmological** - glaucoma, intravitreal deposition and scalloped pupils 
Persistently elevated troponin levels	
Increased valve thickness	
Subendocardial LGE	• **Liver and kidney** - hepatomegaly (advanced disease) and renal disease (rare) 
Abnormal gadolinium kinetics	
Increased extracellular volume	

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Key recommendations by panel on patient journey and red flags

1. ATTR-CM should be suspected in younger age group (≥40 years) with red flags considering the propensity of Indian people to develop heart conditions earlier as compared to western population
2. **Red flags:** HFpEF, left ventricular (LV) thickness (>11mm), global longitudinal strain (GLS), aortic stenosis, arrythmias, cardiac conduction abnormalities
3. **Important red flag:** “Thick walled non dilated hypokinetic ventricle” should be considered an
4. Suspect ATTR-CM with pseudo infarct pattern with low/decreased QRS voltage, increased left ventricular (LV) thickness, atrial fibrillation together with conduction system disorders examined in ECG/ECHO
5. **Extracardiac signs to suspect ATTR amyloidosis**: carpel tunnel syndrome (CTS), lumbar spinal stenosis (LSS), ophthalmological and neurological manifestations, liver and kidney disorders, edema and swelling
6. ATTR-CM should be actively looked for in HF patient (≥65 years), aortic stenosis, hypotension or normotensive if previously hypertensive, sensory involvement and autonomic dysfunction
7. CMR although should be reserved in case of ambiguity but it can provide important clues to suspect ATTR-CM

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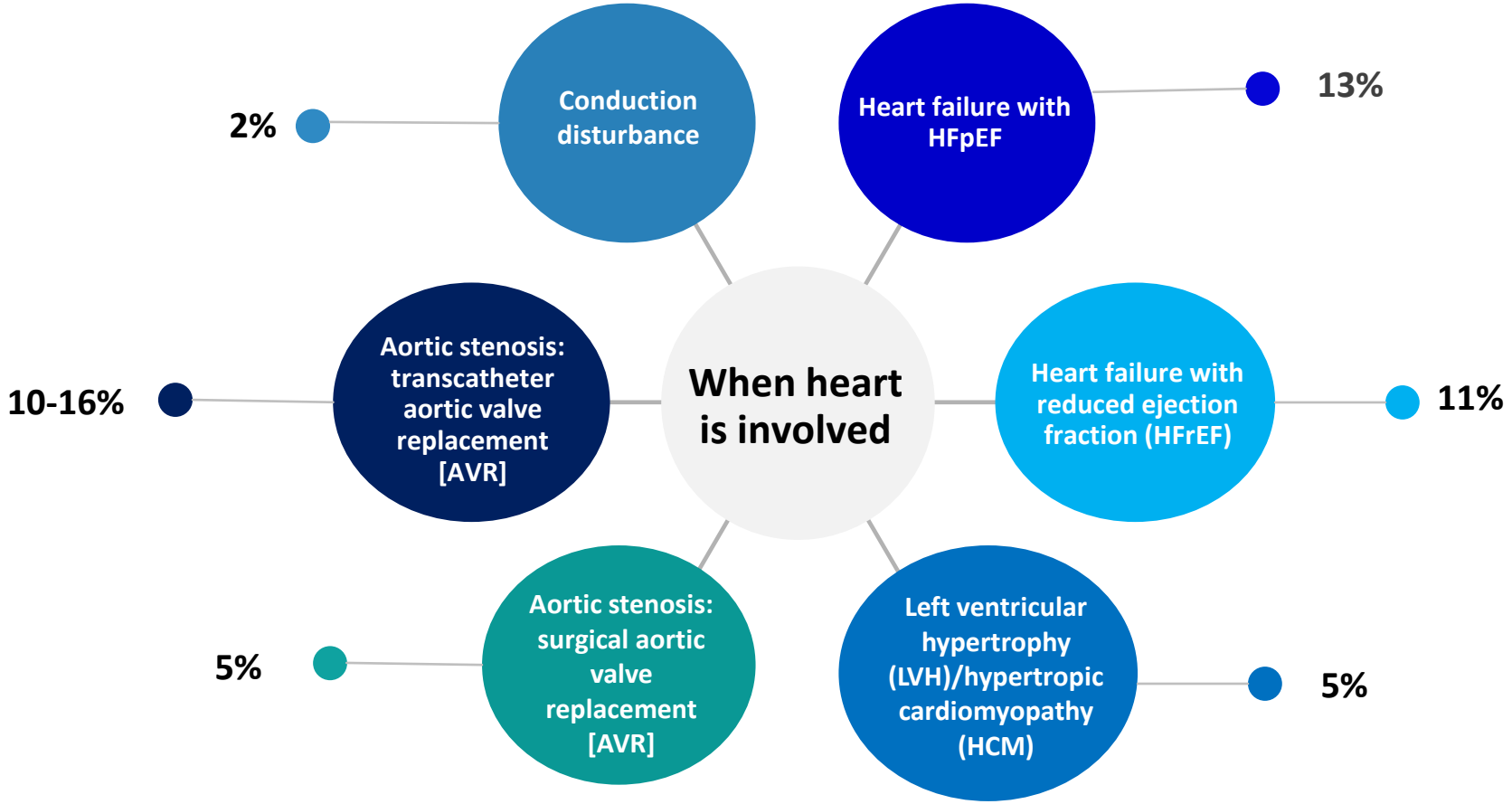
Discussion and recommendations

- **Stepwise diagnostic approach**

ATTR presentation

- ATTR can present in many ways depending on the organ system involved
- When heart is involved, ATTR may mimic the following conditions



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Criteria for diagnosis

If ATTR-CM is suspected based on history, physical examination and findings on investigations like: **Chest X-ray**, **Electrocardiogram** (ECG), **Echocardiography** (ECHO), **Cardiac magnetic resonance** (CMR)

CONFIRMATION

Non-invasive or **invasive** methods which includes
- Cardiac or extracardiac
- Biopsy or fat aspiration biopsy.

CMR

Generally reserved if ECHO findings are ambiguous or inconclusive. However, it can raise suspicion of ATTR-CM before confirmation of diagnosis. It cannot distinguish ATTR-CM from amyloid light-chain (AL) amyloidosis.

Radiotracers

Used in **nuclear scintigraphy** and have high sensitivity
- Tc-99m-DPD (3,3-diphosphono-1,2-propanodicarboxylicacid)
- Tc-99m-HMDP (hydroxy methylene diphosphonate)
- Tc-99m-PYP (pyrophosphate)

Mechanism:
tracers collect in the area of body that needs examination and release energy in the form of gamma rays which is detected

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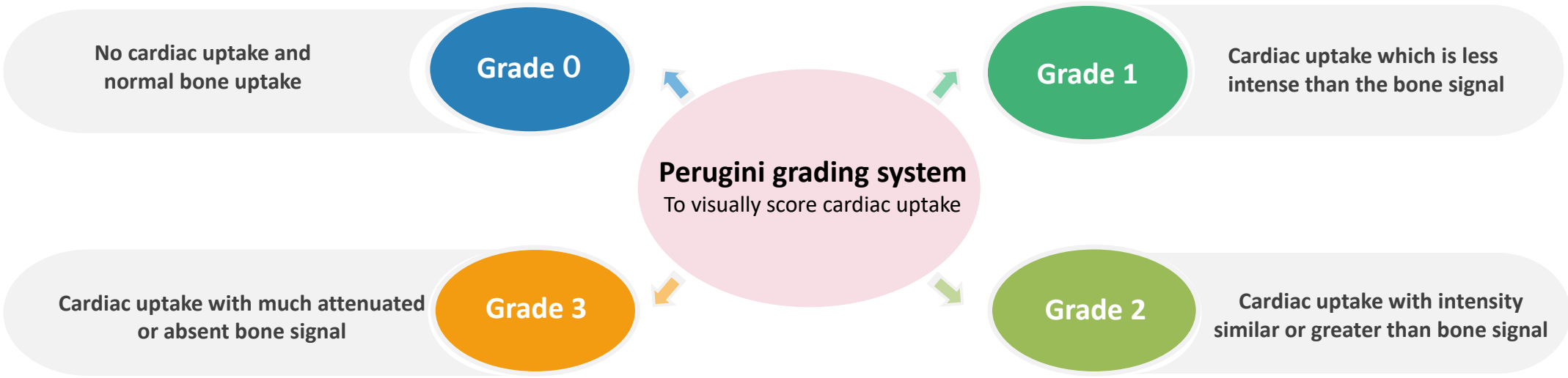
Criteria for diagnosis

- For **Grade 1:** non-invasive diagnosis is not possible and histological confirmation (cardiac or extracardiac) is required
- **Grade 2 and above** is considered significant
- Grade 2 and Grade 3: scans are reported to have 100% positive predictive value for detecting ATTR with 87% specificity and 97% sensitivity
- **To rule out AL amyloidosis**: hematological tests such as serum free light chain (FLC) assay, serum (SPIE) and urine (UPIE) protein electrophoresis with immunofixation in combination with nuclear scintigraphy
- The combination of serum and urine immunofixation and quantification of serum free light chains has 99% sensitivity for AL amyloidosis



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Criteria for diagnosis

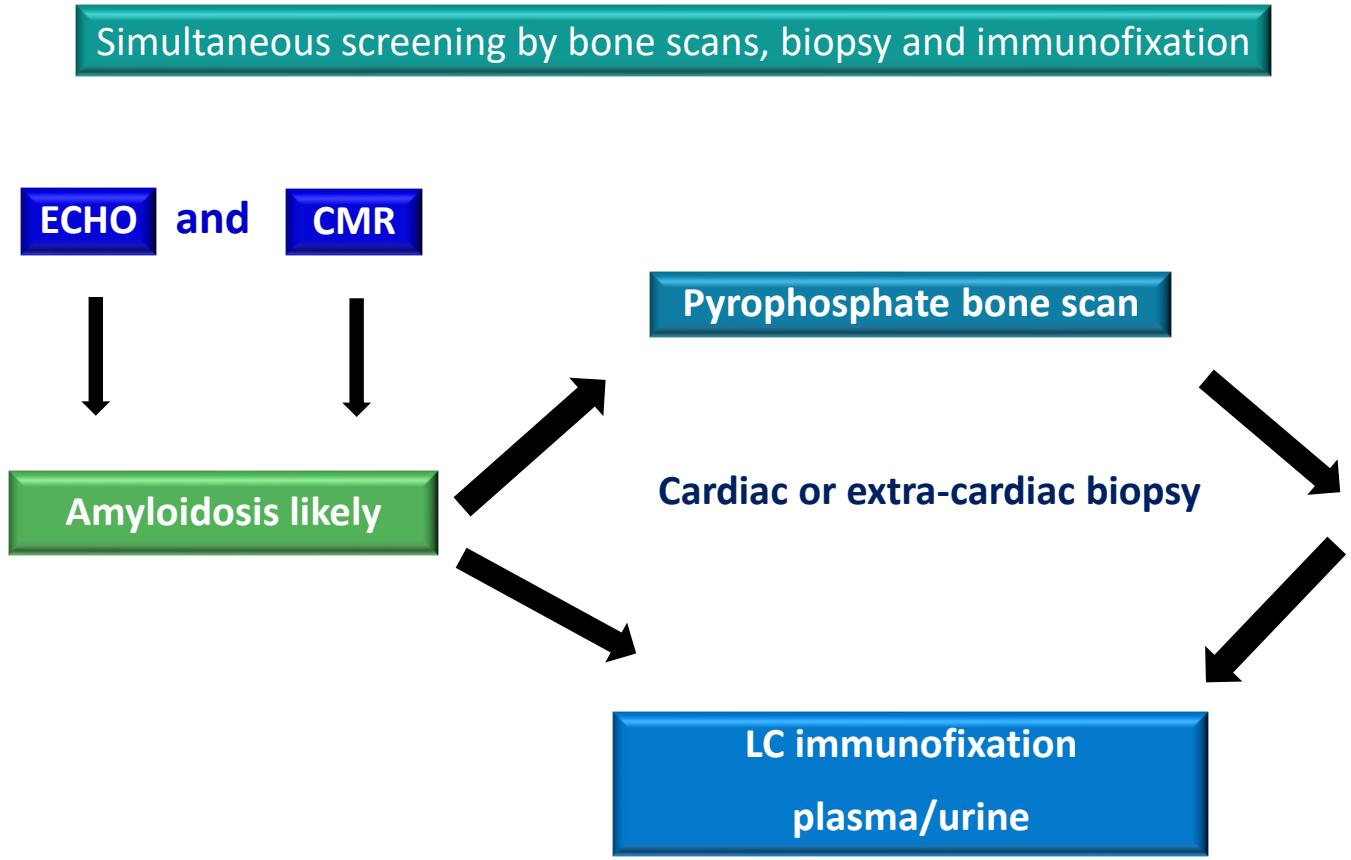
Invasive diagnosis of ATTR-CM:

- **Extracardiac biopsy**: abdominal fat pad, rectal and tongue biopsies but have low diagnostic accuracy
- **Cardiac biopsy**: gives confirmatory diagnosis but should be done when diagnosis could not be made using non-invasive methods or when clinical suspicion is high despite negative non-invasive diagnostic criteria

Histologic confirmation is still needed when both bone scintigraphy and tests for monoclonal protein (suggestive of possible AL amyloidosis) are abnormal/inconclusive.

Genetic testing: for younger people with high suspicion of HF and in conditions of peripheral neuropathy.

Biopsy should be reserved only in case of ambiguity and not to be included in the diagnostic protocol.



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Tools and its characteristics to raise the suspicion of ATTR-CM

1. Electrocardiogram (ECG)

Pseudo infarct pattern: **ECG showing old infarct pattern with low voltage**. Commonly seen in ATTRwt (63-65%) and ATTRv (18-69%)

Diagnostic yield of 60-65%

LVF without any infarction

HF with conduction disorders; left BBB, right BBB and first-degree atrioventricular (AV) blocks and other AV blocks

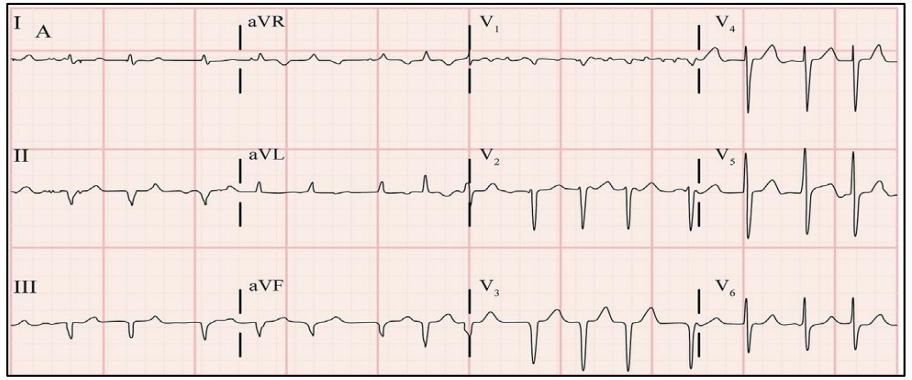
Goldberger triad (Low QRS voltage in limb leads, normal voltage in precordial leads, poor R wave progression (V1-V3)

RV dysfunction (R wave in aVR, positive T wave in aVR)

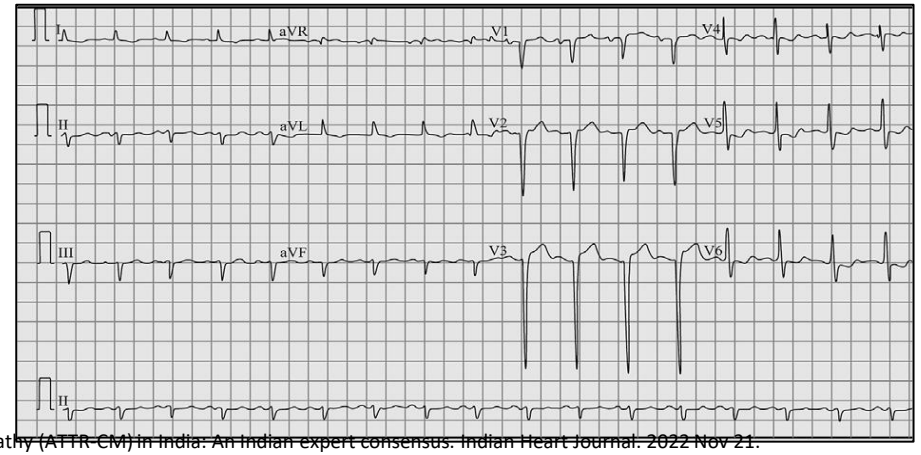
Isolated atrial fibrillation

Presentation

(a): ECG pattern showing old infarct



(b): Goldberger triad and RV dysfunction



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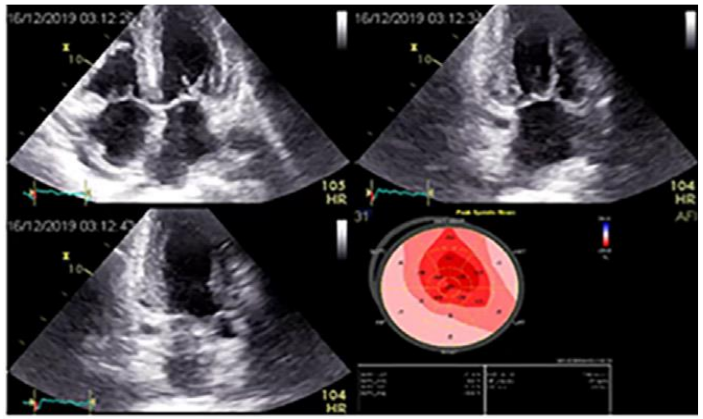
Tools and its characteristics to raise the suspicion of ATTR-CM

2. Echocardiography (ECHO)

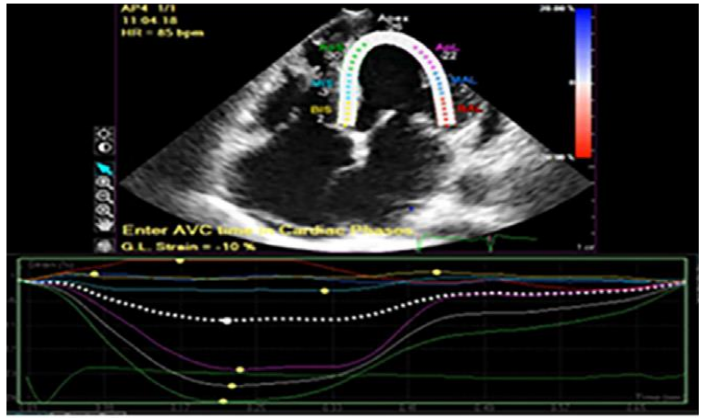
- Thick-walled LV, RV, RA
- RCM or hypokinetic nondilated CM
- Markedly reduced GLS
- LVEF/Longitudinal strain >4
- ‘Bulls eye pattern’ due to apical sparing
- Apical strain/mid basal strain >3:1
- Tissue doppler 5-5-5 sign

Presentation

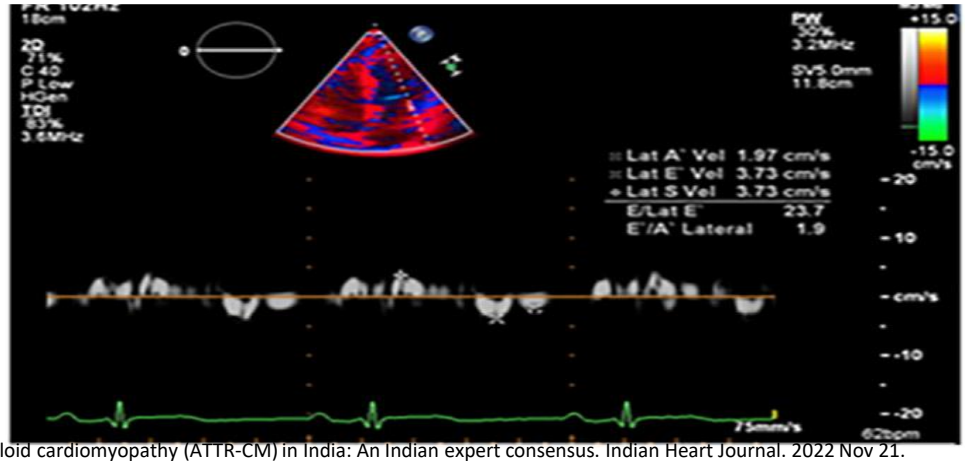
A. Thick-walled LV: LVEF/longitudinal strain >4 Apical sparing



B. Apical strain/mid basal strain index >3:1



C. Tissue doppler 5-5-5 sign



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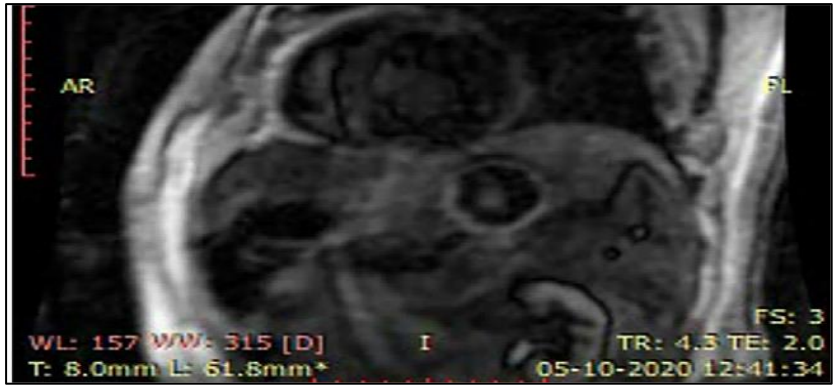
Tools and its characteristics to raise the suspicion of ATTR-CM

3. Cardiac magnetic resonance (CMR)

- T-1> 1400msec
- ECV >42%
- Positive global subendocardial LGE
- Thick-walled ventricle and atrium
- Pleural effusion

Presentation

A. Amyloidotic HF (male, 65 years)

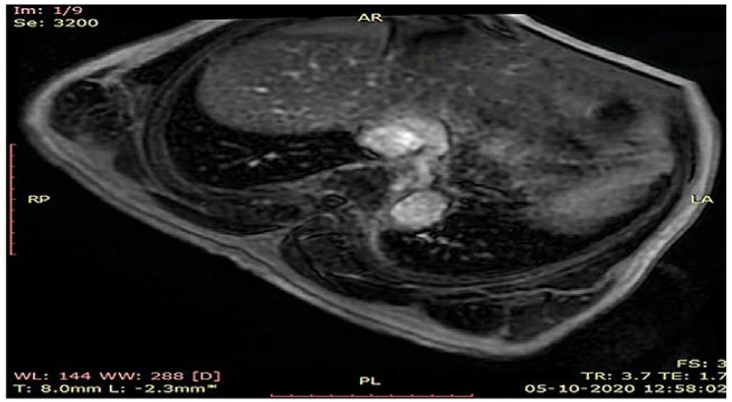


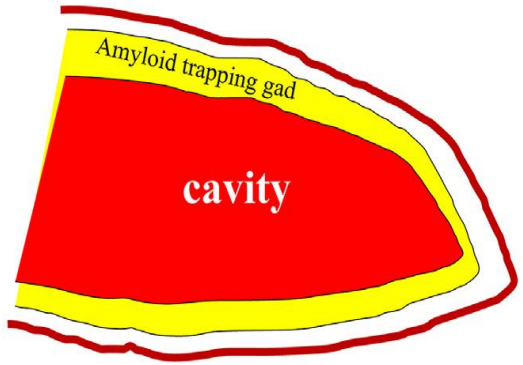
Inability to null the myocardium because blood and myocardial T-1 times are very similar (T-1 1480 msec)

4. Double inversion recovery (DIR) a type of "black blood"

- Technique useful for visualizing the walls of the cardiac chambers
- and blood vessels (including the coronary arteries)
- Abnormal gadolinium kinetics typical for amyloidosis, myocardial nulling prior to blood pool nulling

B. Phase-sensitive myocardial delayed enhancement at 20 min after gad injection in 4CV





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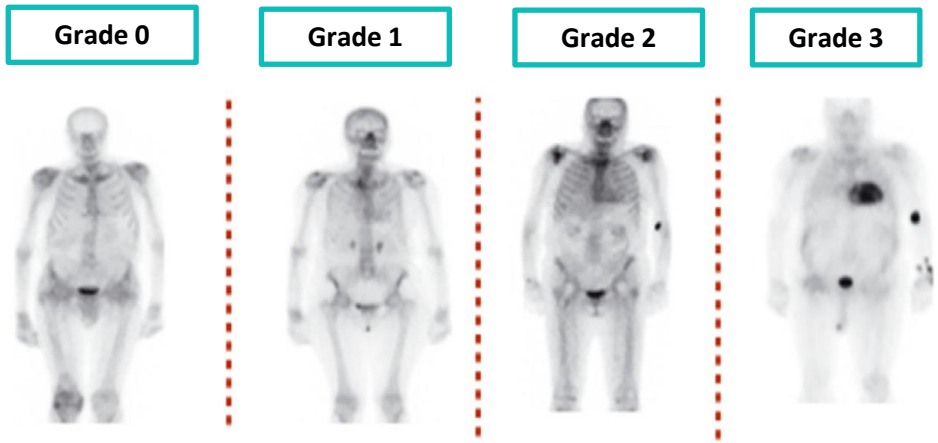
Tools and its characteristics to raise the suspicion of ATTR-CM

5. Bone scintigraphy

Semi-quantitative visual Grade of 2 or 3, target to background (LV myocardium to blood pool) ratio >1.5 and retention index >0.030/min

If cardiac uptake is Grade 1, histological confirmation of amyloid deposits (could be extracardiac) is required as non-invasive diagnosis is not possible.

Bone scintigraphy grades



6. Hematology

Serum free kappa: lambda light chain ratio >3 and free light chain >18 mg/dL is suggestive to go for hematological testing; immunofixation electrophoresis of urine and serum

7. Biochemical marker

Persistent increase in the levels of Troponin T > 0.05 ng/mL, NT-proBNP >3000 pg/mL

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Key recommendations by panel on tools for diagnosis

1. Red flags, ECG and ECHO should be used to raise the suspicion of ATTR-CM and nuclear scintigraphy should be considered to confirm the diagnosis
2. Hematological tests should be done simultaneously with ATTR-CM to rule out AL amyloidosis
3. Nuclear scintigraphy must be performed on suspicion by patient history and ECHO/ECG and should be preferred over CMR, considering the sensitivity, availability and cost
4. No need of performing biopsy in all patients and should not be part of diagnostic algorithm
5. CMR and biopsy should be utilized to confirm the diagnosis in case of ambiguity

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ATTR-CM, Transthyretin amyloid cardiomyopathy, ECG, electrocardiogram; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LGE, late gadolinium enhancement; LV, left ventricular; NTproBNP, N-terminal pro b-type natriuretic peptide; ECHO, echocardiography; CMR, cardiac magnetic resonance

Discussion and recommendations

- **Global and regional recommendations for diagnosis and management of ATTR-CM**

Global and regional recommendations for diagnosis and management of ATTR-CM

Expert opinions available in the United states (American Heart Association) and Europe (European Society of Cardiology) for diagnosis of ATTR-CM were discussed by the panel members, in the meeting

The guidelines were analyzed to adapt them to Indian population for raising early suspicion and diagnosing the patients

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Comparison of global guidelines with panel recommendations

Key Points	AHA	ESC	Indian panel recommendations
Aim of position papers	To help practicing cardiologists focus on diagnosis and management of ATTR-CM	To help cardiologists and other physicians in suspecting, diagnosing, and treating patients with CA • **Suspicion**: LV wall thickness>12 mm along with presence of at least one red signal • **Diagnosis**: non-invasive (for ATTR-CM) and invasive (all types) • **Treatment**: managing cardiac complications and disease modifying agent	**To develop India specific diagnostic approach protocol to help cardiologists in India to raise the suspicion and diagnosis of ATTR-CM**
When to suspect	Presence of moderate to severe **left ventricular (LV) thickening (wall thickness ≥14 mm)** triggers consideration of ATTR-CM especially if there is discordance between wall thickness on ECG and QRS voltage on ECG	Presence of **LV wall thickness >12 mm** along with either heart failure, aortic stenosis, or red flag signs/symptoms, particularly if older than 65 years	• **Age limit should be lower (40 years) considering propensity of Indians to develop heart conditions at an earlier age** • **Important red flag: Thick-walled non-dilated hypokinetic ventricle** • **HFpEF, LV thickness ≥11 mm), GLS, aortic stenosis, arrythmias, cardiac conduction abnormalities are some of the other common red flags**

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Comparison of global guidelines with panel recommendations

Key Points	AHA	ESC	Indian panel recommendations
Non-invasive diagnostic tests: **1) ECG**	• Recommends ECG • Also important in patients with advanced diseases as <40% of such patients show low voltage on ECG • Absence of low voltage does not rule out ATTR-CM	Recommends ECG at the time of first suspicion and every 6 months	• **Primary and mandatory screening test: ECG, chest x-ray and ECHO** • **The tests should also be used for follow up periodically**
2) ECHO	• Not recommend it for diagnosis of ATTR-CM since - it cannot distinguish between ATTRv and ATTRwt • However, can identify non-amyloid causes of LV thickening (HCM, aortic stenosis, and Fabry disease)	Recommends ECHO under following conditions: Unexplained LV thickness (≥12 mm) plus 1 or 2: 1**) Characteristic echocardiography findings (≥2 of a, b, and c have to be present)** a) Grade 2 or worse diastolic dysfunction b) reduced tissue Doppler s', e', and a' waves velocities (<5cm/s) c) decreased global longitudinal LV strain (absolute value<-15%) **2) Multiparametric echocardiographic score ≥8 points:** d) relative LV wall thickness (IVS+PWT)/LVEDD >0.6: 3 points e) doppler E wave/e0 wave velocities >11: 1 point f) TAPSE ≤19 mm: 2 points g) LV global longitudinal strain absolute value ≤ -13%: 1 point h) systolic longitudinal strain apex to base ratio >2.9: 3 points	• **Recommends ECHO for raising suspicion of ATTR-CM** • **Helps in early diagnosis of all types of cardiac amyloidosis** • **Including: increased LV thickness, myocardium granular sparkling, and pericardial effusion** • **Important ECHO features: Left ventricular wall thickness (>11 mm), right ventricular wall thickness, free valves of the right atrium, LV longitudinal**

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Comparison of global guidelines with panel recommendations

Key Points	AHA	ESC	Indian panel recommendations
Non-invasive diagnostic tests: **3) Nuclear scintigraphy**	• Scans may be positive even in AL amyloidosis • Bone scintigraphy scan without testing for light chains: not valid for distinguishing ATTR-CM from AL-CM • Assessment of ATTR-CM with bone scintigraphy is accomplished by quantitative approaches comparing heart to rib uptake **Grade 0: no cardiac and normal rib uptake** **Grade 1: cardiac less than rib uptake** **Grade 2: cardiac equal to rib uptake** **Grade 3: cardiac greater than rib uptake with mild/absent rib uptake** • If no light chain abnormality - 99mTc-PYP scintigraphy is diagnostic of ATTR-CM if there is Grade 2 to 3 cardiac uptake or a heart/contralateral chest ratio >1.5	While recommending scintigraphy, SPIE, UPIE and serum FLC, **four scenarios** should be considered **a)** No cardiac uptake in scintigraphy and test negative for monoclonal proteins are - **amyloidosis unlikely** **b)** Scintigraphy shows cardiac uptake and monoclonal proteins are negative – if **Grade 2/3** uptake - **ATTR-CM**; **Grade 1** - confirmation by **biopsy** **c)** Scintigraphy does not show cardiac uptake and at least one of the monoclonal protein tests is abnormal - CMR to see cardiac involvement followed by biopsy if CMR inconclusive **d)** Scintigraphy shows cardiac uptake and at least one of the monoclonal protein tests is abnormal. TTR amyloidosis with concomitant MGUS, AL amyloidosis, or coexistence of both AL and ATTR amyloidosis are possible	• **Considered as a gold standard for confirming ATTR-CM** • **It is accurate, cheap, easy interpretation and has high sensitivity and specificity** • **Pyrophosphate scans are recommended**

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Comparison of global guidelines with panel recommendations

Key Points	AHA	ESC	Indian panel recommendations
Non-invasive diagnostic tests: **4) CMR Imaging**	CMR appropriate test when an infiltrative cardiomyopathy is suspected but ATTR-CM is less likely, as in younger patients or those with findings suggestive of other infiltrative/inflammatory or restrictive cardiomyopathies	Characteristic CMR findings (a and b must be present): • diffuse subendocardial or transmural LGE • abnormal gadolinium kinetics • ECV >0.40% (strongly supportive, but not essential/diagnostic)	• **CMR is useful if ECHO findings are inconclusive or ambiguous** • **Recommended as optional (depending on the cost availability and need)**
5) Hematologic consideration	• Based on history, ECHO and ECG findings suggestive of amyloidosis • Scintigraphy along with serum FLC and serum and urine IFE (Measurement of serum IFE, urine IFE, and serum FLC is >99% sensitive for AL amyloidosis)	• Based on clinical, laboratory and ECG suspicion • Scintigraphy coupled to assessment for monoclonal proteins by SPIE, UPIE, and quantification of serum FLC is recommended	• **Based on clinical findings: Combination of SPIE, UPIE and serum FLC to rule out AL amyloidosis** • **It has 99% sensitivity for abnormal pro-amyloidotic precursor in AL amyloidosis**

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Comparison of global guidelines with panel recommendations

Key Points	AHA	ESC	Indian panel recommendations
6) Genetic testing	Recommends genetic testing to **distinguish ATTRv and ATTRwt** after confirmation of ATTR-CM from bone scintigraphy or EMB	• Strongly recommends genetic testing once ATTR-CM is confirmed in order to **differentiate between ATTRwt and ATTRv** • Genetic testing should be performed even in elderly patients, as a significant number of patients can have TTR mutations	• **Once diagnosis of ATTR-CM is confirmed the first-degree relatives should be offered genetic testing** • **Should not be a rate limiting step in the initiation of treatment** • **Not recommended as a mandatory test**
Invasive diagnostic tests **Endomyocardial biopsy (EMB)**	It is mandatory in other **3 scenarios**: **1)** a positive 99mTc-PYP scan and evidence of a plasma cell dyscrasia by serum/urine IFE or serum free light Chain analysis to exclude AL-CM **2)** a negative or equivocal 99mTc-PYP scan despite a high clinical suspicion to confirm ATTR-CM **3)** unavailability of 99mTc-PYP scanning. Given its low sensitivity, a fat-pad biopsy is not sufficient to exclude ATTR-CM	• It is recommended to confirm ATTR-CM in case of any discrepancy • Demonstrates amyloid deposits after Congo red staining irrespective of the degree of LV wall thickness • Diagnosis of CA in case of MGUS (or any hematological disorder that produces FLC), AL amyloidosis, or coexistence of both • AL and ATTR amyloidosis require histology with amyloid typing, usually via EMB	• **Biopsy may not be needed to confirm diagnosis of amyloidosis** • **Fat aspiration biopsy may be positive in 80% of cases of AL and 40% cases of ATTR**

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Key recommendations by the panel on comparison of global ATTR-CM guidelines

1. Minor differences exist between AHA and ESC guidelines and the Indian panel recommended a personalized diagnostic approach
2. Lower age limit ≥40 years with red flags should be considered as the cut off limit to suspect ATTR-CM
3. Lab tests like troponins and ECG, ECHO in addition to clinical findings should be used for raising suspicion as screening tests
4. Nuclear scintigraphy may be used after suspicion has been raised based on clinical symptoms and investigations
5. CMR should be used in case of ambiguity or when suspicion is high despite negative tests
6. Genetic testing should be offered for the relatives first degree family members of the patients with an inheritable form of CA

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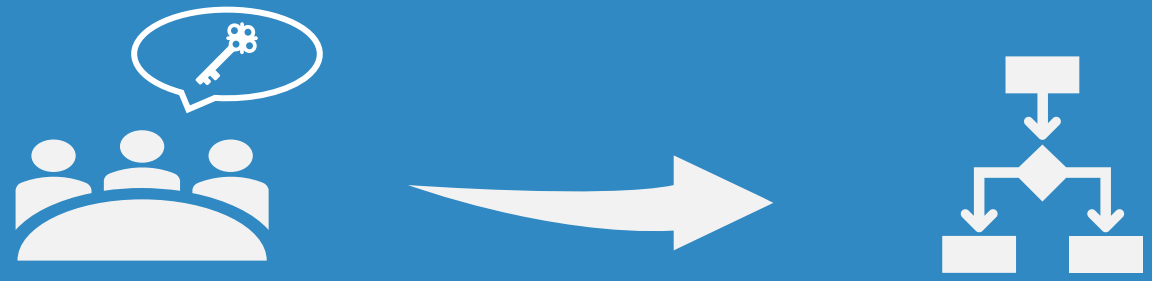
Proposed diagnostic algorithm

India specific diagnostic algorithm

Based on the discussions and key recommendations, a stepwise standardized diagnostic algorithm was proposed which would be used as a guiding tool for diagnosing patients with ATTR-CM across India



This is a first attempt to standardize the suspicion and diagnosis of ATTR-CM in India, however, there are currently no experimental data to support the algorithm

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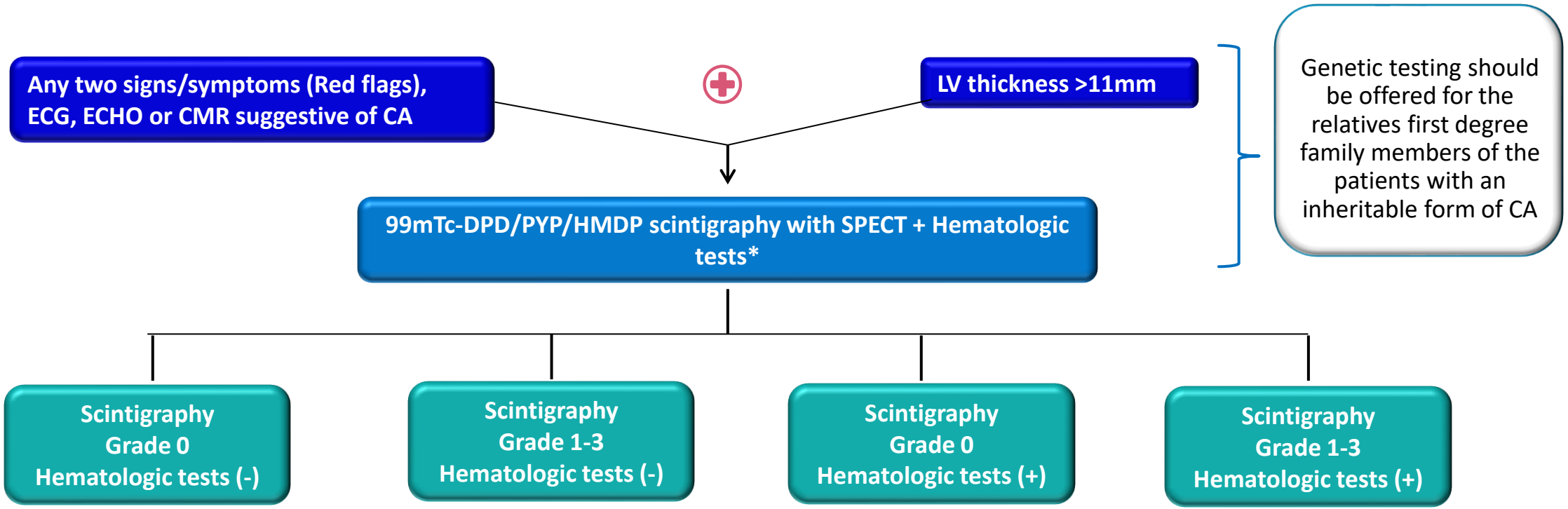
India specific diagnostic algorithm (part 1/2)



*Serum free-light chain quantification and serum, and urine immunofixation

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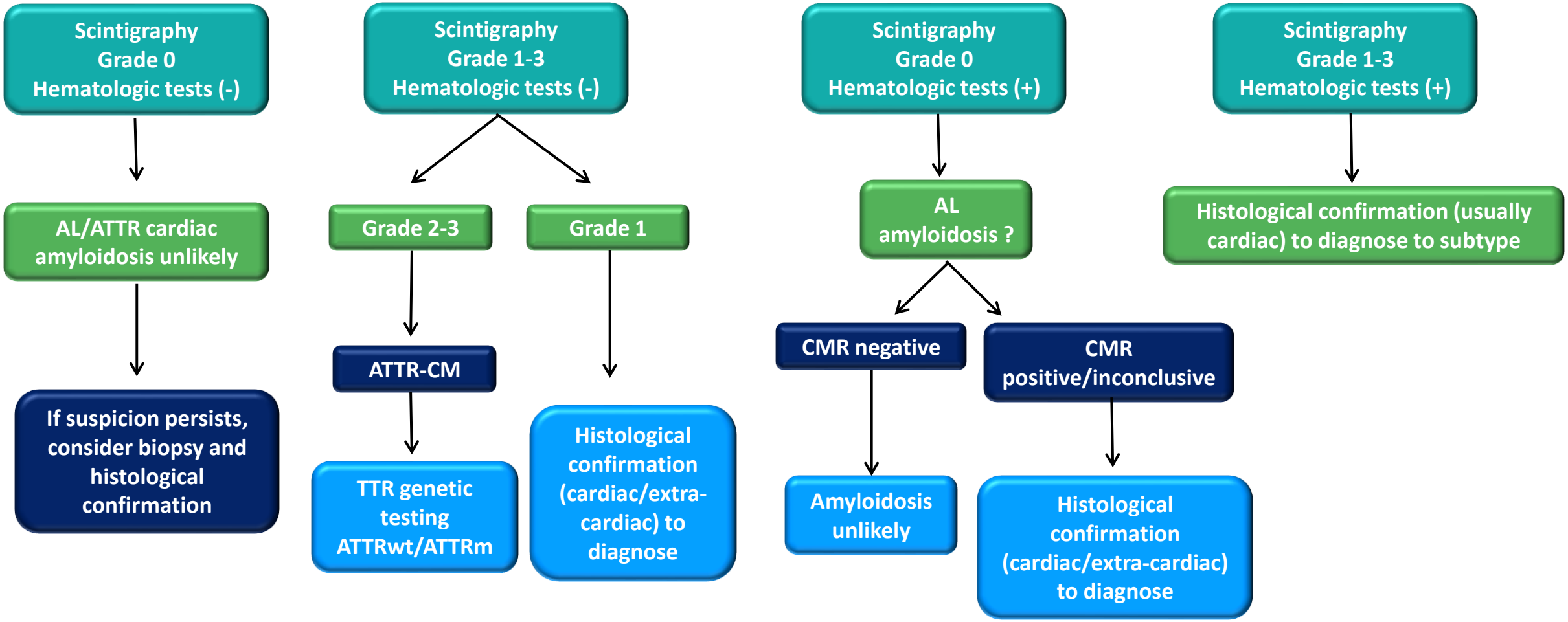
India specific diagnostic algorithm (part 2/2)



EMB is not recommended for ATTR-CM, though it can be helpful to confirm AL amyloidosis

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Conclusion

Conclusion

1. ATTR-CM is a complicated and rare disorder that is often missed or misdiagnosed due to its heterogeneous nature of symptoms mimicking other cardiac conditions such as HF
2. Prevalence of ATTR-CM is reported worldwide, however, in Asia, particularly in India, data was found to be lacking
3. There is a need to raise the awareness of this rare disorder among all patients and health care professionals
4. Guidelines are available in the United states (American Heart Association) and Europe (European Society of Cardiology) for diagnosis of ATTR-CM, however, none from Asia region
5. It is expected that this expert opinion effort would bring standardization in the diagnosis of ATTR-CM which in turn would reduce morbidity and mortality with timely treatment

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Thank You