BEYOND AWARENESS
How to Diagnose and Treat Hereditary ATTR Amyloidosis in your Practice

FRIDAY, APRIL 17, 2020 / 5:20 p.m. - 6:05 p.m.

CHFS SCIC
Canadian Heart Failure Society
Société canadienne d'insuffisance cardiaque

Welcome and Introductions

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Past President, Quebec Heart Failure Society
Sherbrooke, QC

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Disclosures: Dr. Diego Delgado

- **Consultancy/speaking fees**: Pfizer, Akcea, Alnylam

- **Clinical trial participation**: ATTRACT extension (Tafamidis), HELIOS-B (Alnylam), Cardio TTRANSFORM (Ionis-Akcea) ATRIBUTE-CM (AG10)

Disclosures: Dr. Vera Bril

- **Consultancy/speaking fees**: Akcea, Alnylam, Ionis

- **Clinical trial participation**: CSL, Takeda, RVT, Momenta, UCB, Alexion, Akcea, Talecris, Octapharma

Disclosures: Dr. Margot Davis

- **Consultancy/speaking fees**: Janssen, Novartis, Boehringer-Ingelheim, Takeda, Pfizer, Akcea, Alnylam, Amgen, Ferring

- **Grant funding**: Pfizer, Takeda, Boehringer-Ingelheim, Servier, Akcea

Disclosures: Dr. Anil Gupta

- **Consultancy/speaking fees**: Amgen, Astrazeneca, Bayer, Boehringer Ingelheim, BMS/Pfizer Alliance, Novartis, Pfizer, Sanofi, Servier

- **Clinical trial participation**: None

Disclosures: Dr. Serge Lepage

- **Consultancy/speaking fees**: Amgen, AstraZeneca, Boehringer Ingelheim, Novartis, Servier

- **Clinical trial participation**: Amgen, Novartis

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- This program has received in-kind support from Canadian Heart Failure Society in the form of logistical support

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- Alnylam is the manufacturer of a product that will be discussed in this program

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Potential biases are acknowledged and are mitigated by presenting data supported by national and international guidelines, and as follows:

- Information presented is evidence-based
- Material has been developed and reviewed by a Planning Committee

Off-label uses of drugs may be discussed and will be identified as such by the speaker

Accreditation

This event is an accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification Program of the Royal College of Physicians & Surgeons of Canada and approved by the Canadian Cardiovascular Society. You may claim a maximum of 0.75 hours.

Learning Objectives

- Distinguish between hereditary and wild-type ATTR amyloidosis in terms of presentation and diagnosis
- Establish a care pathway for patients following genetic testing
- Assess the treatment options and the benefit of a multidisciplinary team approach to treating hATTR
- Understand the importance of tailoring the treatment approach based on the disease phenotype

Agenda

Topic	Facilitator
Welcome and Introductions	Dr. Serge Lepage
Hereditary and Wild-Type ATTR Amyloidosis: Different Diseases, Different Presentations	Dr. Diego Delgado Dr. Vera Bril Dr. Anil Gupta
Neuropathy in a Systemic Disease	Dr. Vera Bril Dr. Anil Gupta
Diagnosis of hATTR: The Key to a Hopeful Outcome	Dr. Margot Davis Dr. Anil Gupta
Treatment Plan and Treatment Goals	Dr. Diego Delgado Dr. Vera Bril
Treating Patients with hATTR Amyloidosis in the Community	Dr. Diego Delgado Dr. Anil Gupta Dr. Serge Lepage
Closing Remarks	Dr. Diego Delgado

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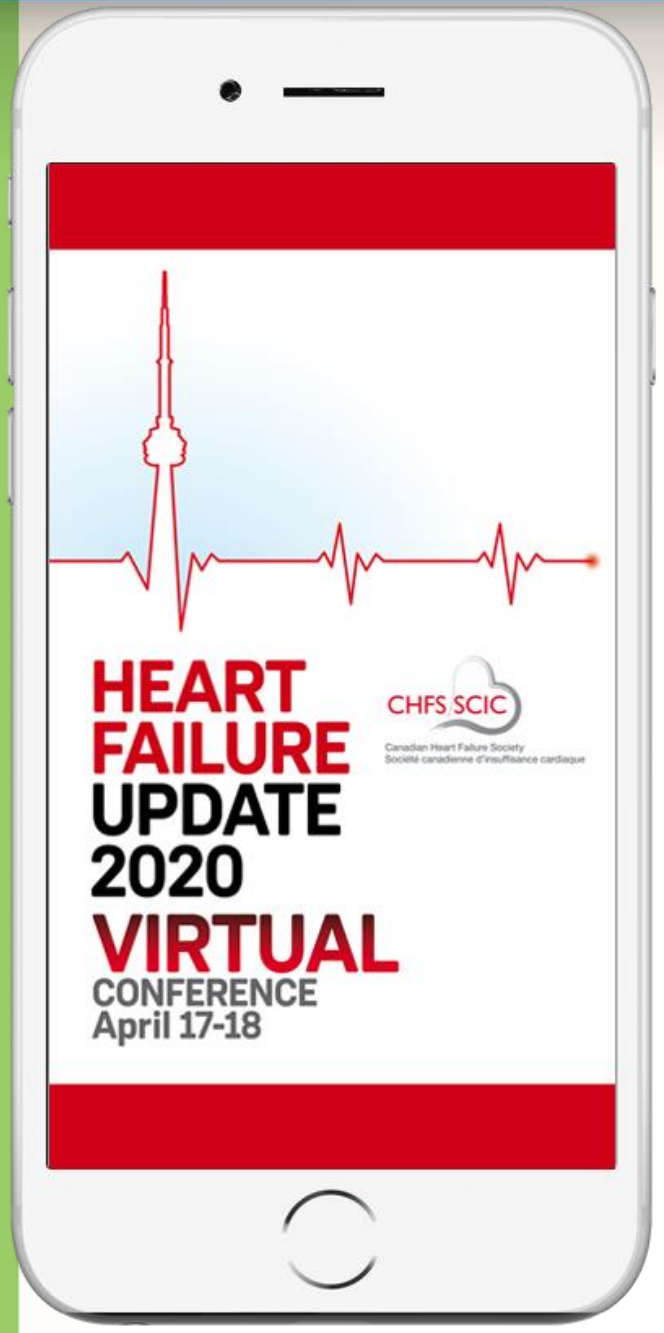

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Hereditary and Wild-Type ATTR Amyloidosis: Different Diseases, Different Presentations

Vera Bril
BSc, MD, FRCPC

Diego Delgado
MD, MSc, FCCS, FACC

Anil Gupta
MD, FRCPC

Key Questions

- What's the **difference** between wtATTR and hATTR?

- What are the key red-flag symptoms of **hATTR amyloidosis** (sensory-motor neuropathy, autonomic neuropathy, and cardiac manifestations)?

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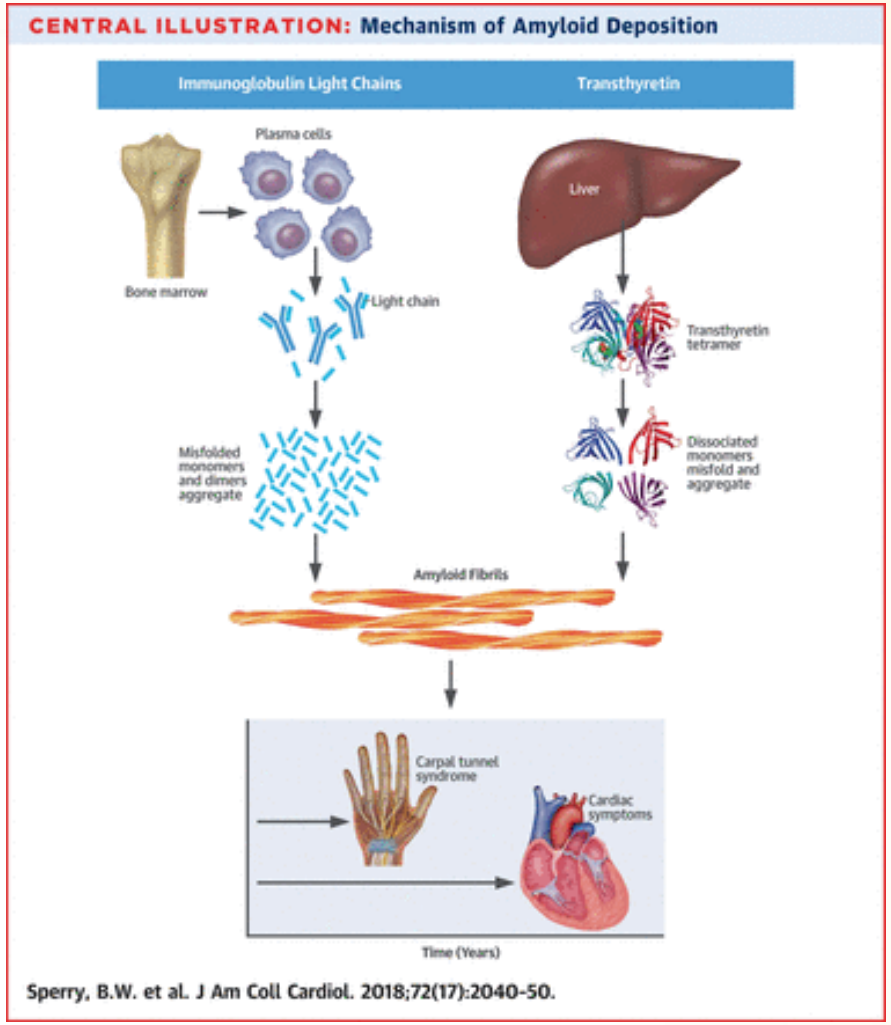
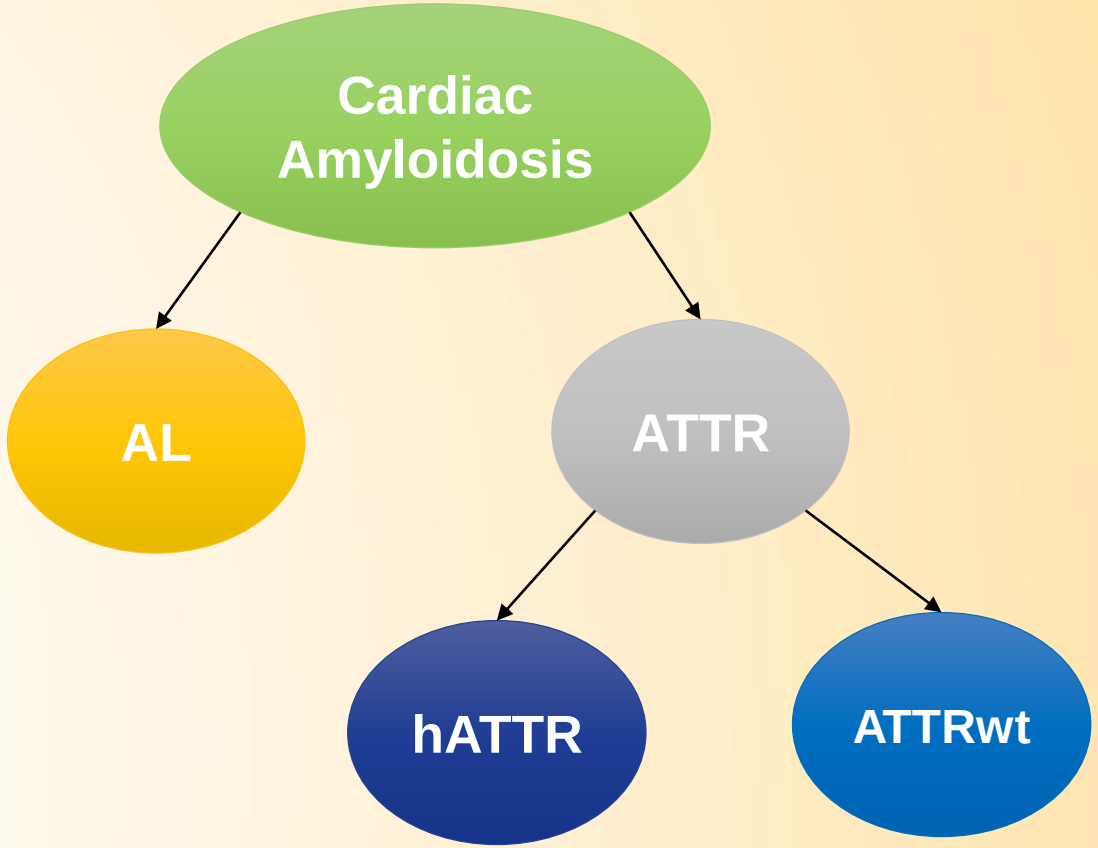
Cardiac Amyloidosis





AL, light-chain amyloidosis; ATTR, transthyretin amyloidosis; m, mutated; wt , wild-type. ; h: hereditary

Maleszewski JJ. Cardiovascular Pathology 2015;24(6):343-350; Rapezzi C et al. Circulation 2009;120:1203-1212; Maurer MS et al. J Am Coll Cardiol 2016;68(2):161-172.

Clinical Presentations

Table 1. Demographic profiles of common subtypes of cardiac amyloidosis

Characteristic	AL	hATTR	wtATTR
Age of onset (years)	Median age > 60	Variable, depends on genotype	Median age > 70
Sex	Slight male predominance	No clear predominance	Male predominance
Ethnic/geographic background	None	Most common gene mutations in North American: Val122Ile (West African descent), Thr60Ala (Northern Ireland descent), Val30Met (Swedish, Portuguese, Japanese descent)	None
Prevalence/incidence	Annual incidence 10 per million, increases with age	Variable, depends on genotype	Unknown, increases with age

AL, light chain amyloidosis; hATTR, hereditary transthyretin amyloidosis; wtATTR, wild type transthyretin amyloidosis.

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Cardiac Manifestations

- Heart failure - frequently biventricular, typically preserved LVEF
- Atrial fibrillation
- Conduction system disease
- Ventricular arrhythmia - may be asymptomatic
- Aortic stenosis - low-flow low-gradient for wtATTR, typically with preserved LVEF

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Extracardiac Manifestations

- Renal
- Autonomic
- **Neurologic peripheral sensorimotor neuropathy *(might be predominant feature of hATTR)***
  - **Carpal tunnel syndrome**
- Musculoskeletal
- Gastrointestinal
- Hematologic
- Ocular manifestations

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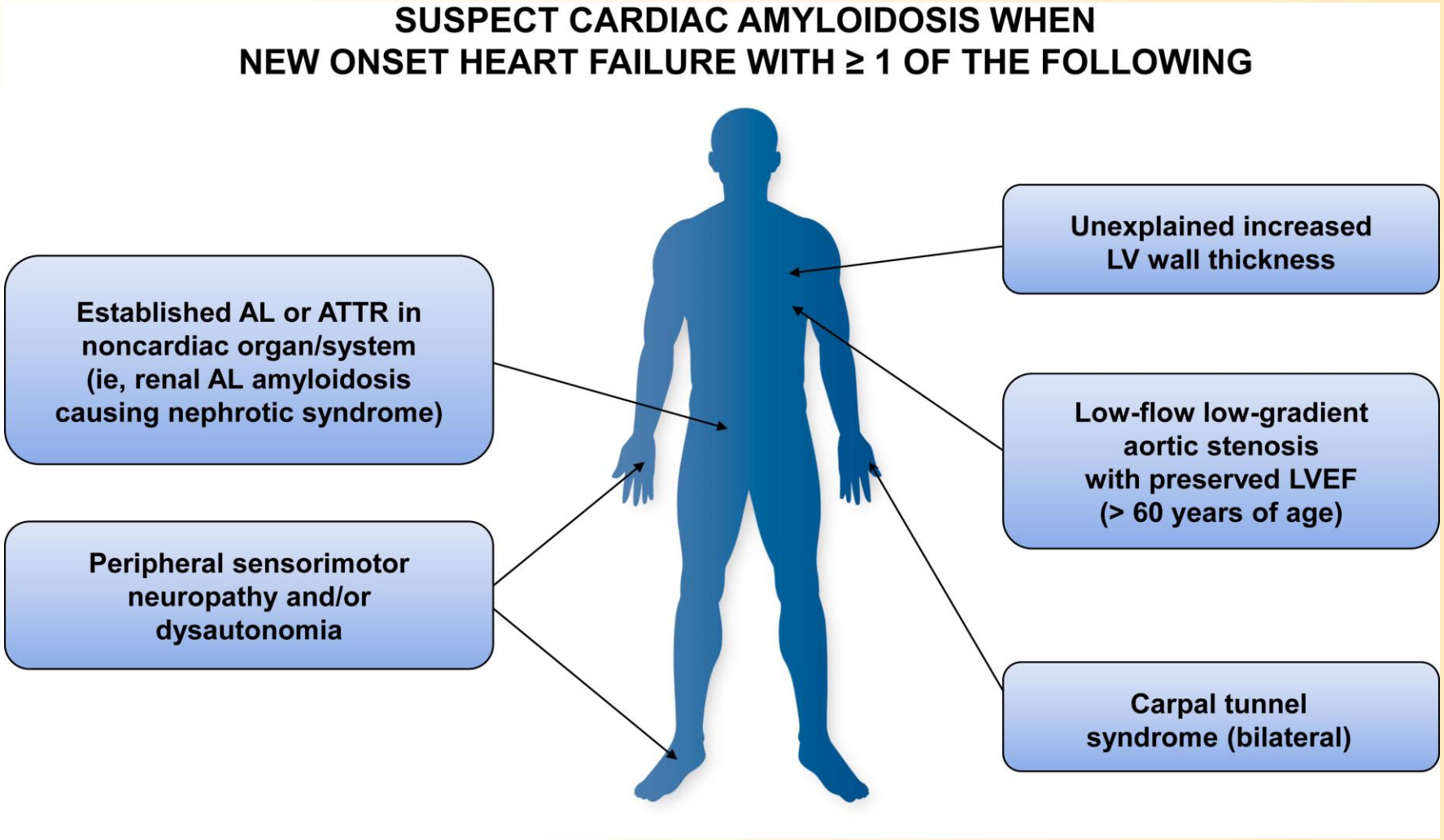
Extracardiac Manifestations

Table 2. Extracardiac manifestations of common subtypes of cardiac amyloidosis

Manifestation	AL	hATTR	wtATTR
Renal	• Renal insufficiency • Nephrotic syndrome	• Milder renal insufficiency (mainly due to heart failure)	
Autonomic		• Orthostatic hypotension • Gastroparesis • Sexual dysfunction • Sweating abnormalities	
Neurologic	• Peripheral sensorimotor neuropathy (might be predominant feature of hATTR, and relatively mild or absent for wtATTR)	• Carpal tunnel syndrome (bilateral)	
			• Spinal stenosis (predominantly lumbar)
Musculoskeletal		• Muscle weakness • Arthropathy • Fatigue • Cachexia/weight loss	
	• Pseudohypertrophy (ie, macroglossia)		• Biceps tendon rupture
Gastrointestinal	• Nausea, constipation, early satiety, abdominal bloating (gastroparesis might be secondary to dysautonomia and/or gastrointestinal involvement)	• Elevated liver enzymes	
Hematologic	• Bleeding and easy bruising (ie, periorbital)		
Ocular manifestations		• Vitreous opacities	

AL, light chain amyloidosis; hATTR, hereditary transthyretin amyloidosis; wtATTR, wild type transthyretin amyloidosis.

Key Clinical Features



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Red Flags for TTR-FAP[1,2]

- Family history
- Carpal tunnel syndrome
- Cardiac involvement
- Small fiber and Autonomic involvement
- (2^{nd} to 4^{th} decade onset)

1. Rapezzi C *et al. Nat Rev Cardiol* 2010;7:398–408.
2. Coutinho P. In: Glenner GG *et al*, eds. *Amyloid and Amyloidosis*. Amsterdam: Excerpta Medica; 1980.

Clinical Presentation: hATTR Amyloidosis with PNP

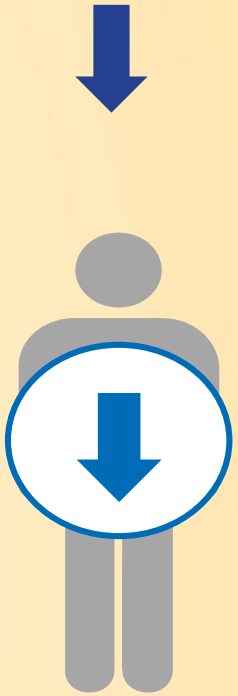
- Characterized by symmetrical length-dependent peripheral neuropathy[1,2]
  - Symptoms initially in lower limbs and progress proximally involving areas above the ankles, legs, thighs, arms and anterior trunk
- Early clinical findings:
  - Numbness and pain in feet with impaired temperature and pinprick sensation; muscle strength and tendon reflexes are preserved
- Sensory loss progressively increases and light touch and deep sensations become impaired

hATTR, hereditary amyloid transthyretin

1. Ando Y, et al. Orphanet J Rare Dis 2013;8:31
2. Coelho T, et al. Amyloidosis Foundation, 2008. https://www.researchgate.net/publication/265490881_A_Physician's_Guide_to_Transthyretin_Amyloidosis_Authored_by Accessed January 3, 2019

Clinical Presentation: hATTR Amyloidosis with PN

- Eventually until walking, balance, and gait are compromised, fine hand movements become difficult, and autonomic dysfunction manifests[1,2]
- Symptoms of autonomic dysfunction:[3,4]
  - Alternating diarrhea and constipation
  - Anhidrosis
  - Nausea
  - Delayed gastric emptying
  - Vomiting
  - Erectile dysfunction
  - Urinary retention and incontinence
- Autonomic dysfunction can occur early in the disease[4]
- Weight loss and muscle wasting are common



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3. Coelho T, et al. Amyloidosis Foundation. http://www.amyloidosis.org/wp-content/uploads/2017/05/2017-ATTR-guide.pdf Accessed April 24, 2019.
4. Ando Y, et al. Muscle Nerve 1992;15:507-12.

Neuropathy in a Systemic Disease

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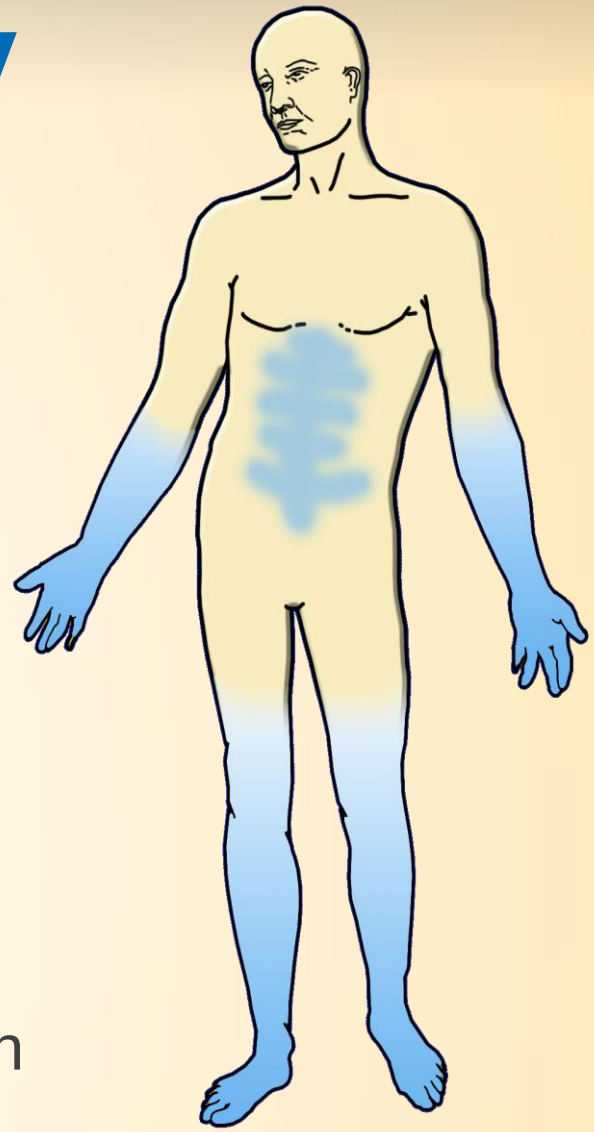
Small Fiber Polyneuropathy

- Distal symmetrical polyneuropathy (PNP)
- Burning pain in the feet
- Worse at night
- Less noticeable during the day
- Difficult to control
- Associated with fear, anxiety, depression
- Reduced quality of life
- Refractory to many treatments
- Loss of pinprick, temperature on examination
- Normal reflexes strength, vibration and proprioception



hATTR Amyloidosis: Broad Spectrum of Presentation with Different TTR Mutations

- Hereditary amyloidosis is caused by many gene variants, but TTR mutations account for the majority[1]
- Transmitted in an autosomal dominant manner with variable penetrance[2,3]
- More than 120 TTR mutations have been discovered[1]
- Although some genotypes are associated predominantly with polyneuropathy or cardiomyopathy, most patients with hATTR have mixed clinical phenotypes[3,4]

hATTR, hereditary amyloid transthyretin; TTR, transthyretin

1. Rowczenio D, et al. Hum Mutat 2014;35:E2403-E2412 2. Ando Y, et al. Orphanet J Rare Dis 2013;8:31; 3. Coelho T, et al. Curr Med Res Opin 2013;29:63-76.
4. Gertz MA, et al. J Am Coll Cardiol 2015;66:2451-66.
Figure sources: Benson MD. Am J Pathol 1996;148: 351–54. Rapezzi C, et al. Eur Heart J 2013;34:520-28. Connors LH, et al. Amyloid 2003;10:160-84.

When to Suspect hATTR Amyloidosis – RED FLAGS

Look for evidence of multisystem involvement, which may include:

- **Progressive, symmetric sensorimotor neuropathy**
- **Bilateral carpal tunnel syndrome***
- **Early autonomic dysfunction** (e.g., erectile dysfunction or postural hypotension)
- **GI complaints** (e.g., chronic diarrhea, constipation or diarrhea, constipation)
- **Unexplained weight loss**
- **Cardiac signs & symptoms** (e.g., cardiac hypertrophy, arrhythmias, ventricular blocks, or cardiomyopathy)
- **Renal abnormalities** (e.g., albuminuria or mild azotemia)
- **Vitreous opacities**
- **Positive family history**

Additional alert signs:

+ Rapid disease progression
+ Failure of response to prior therapies

***Consider particularly in men without predisposing occupation**

GI, gastrointestinal

Adapted from: Conceição I, et al. J Peripher Nerv Syst 2016;21:5-9

Key Questions

- When should the cardiologist refer the patient to a neurologist?
- How can both work together to improve outcomes for the mixed phenotype patient?

Diagnosis of hATTR: The Key to a Hopeful Outcome

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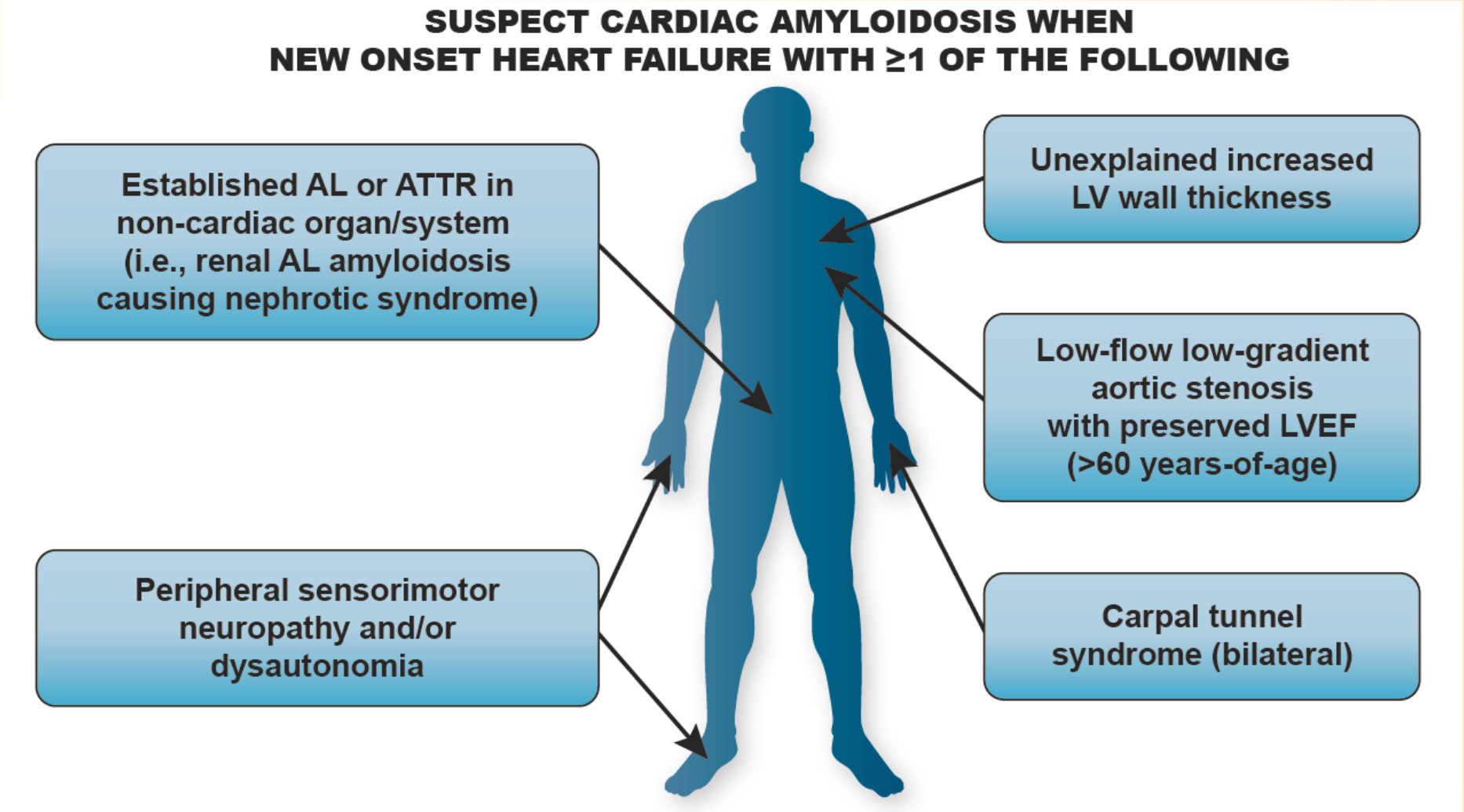
Cardiac Manifestations

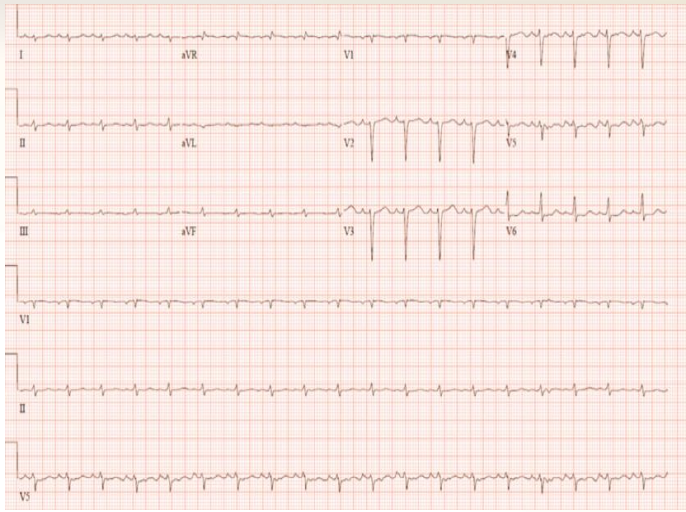
- Heart failure - frequently biventricular, typically preserved LVEF
- Atrial fibrillation
- Conduction system disease
- Ventricular arrhythmia - may be asymptomatic
- Aortic stenosis - low-flow low-gradient for wtATTR, typically with preserved LVEF

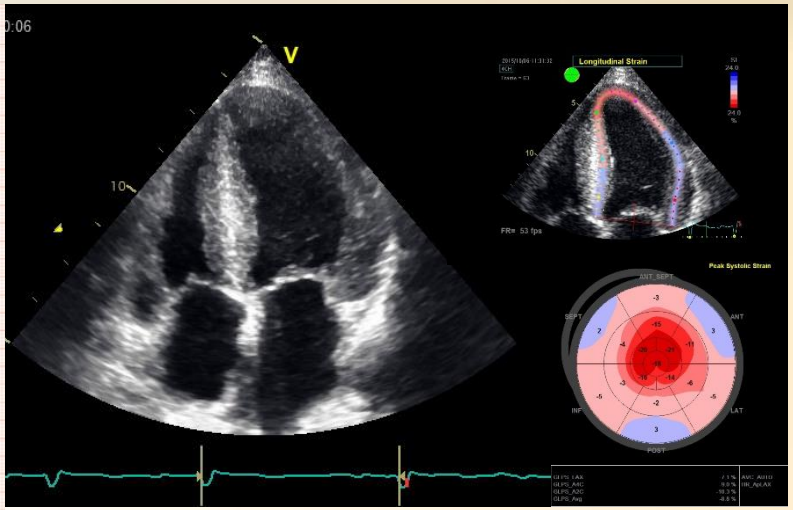
Index of Suspicion – Key Features



ECG

- Low voltage (especially limb leads)
- Pseudo-infarct pattern
- Atrial fibrillation
- Conduction system disease
- Ventricular ectopy



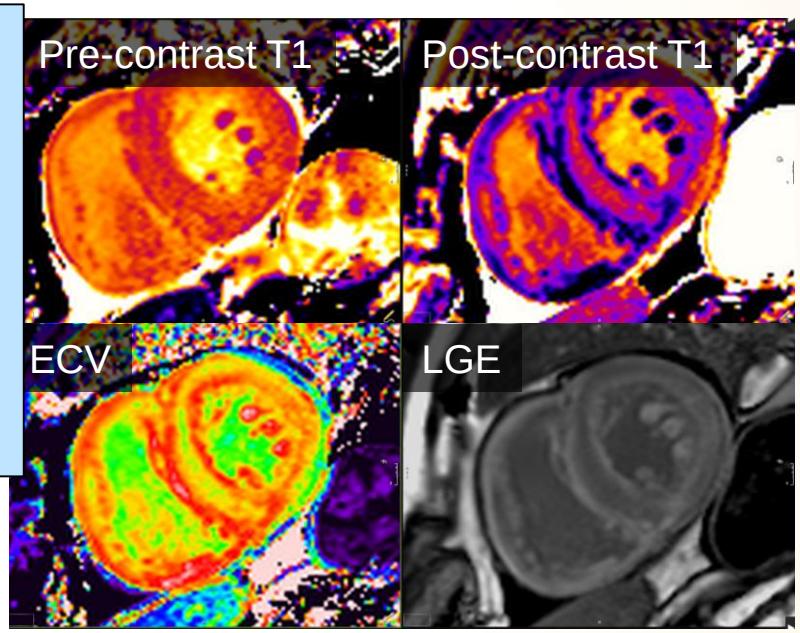


Echo

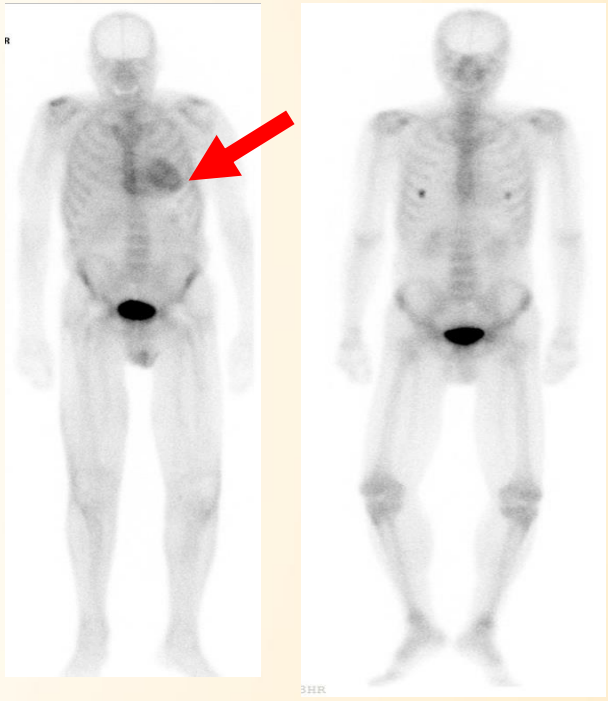
- Increased LV and RV wall thickness
- Preserved ventricular size, biatrial enlargement
- Diastolic dysfunction
- Increased valvular and interatrial septum thickness
- Small pericardial effusion
- Reduced LV GLS, preserved apical strain (basal-apical strain gradient)

- Diffuse transmural or subendocardial pattern LGE
- Left atrial LGE
- Elevated native (non-contrast) T1 mapping time
- Extracellular volume expansion (post-contrast T1 mapping)

CMRI



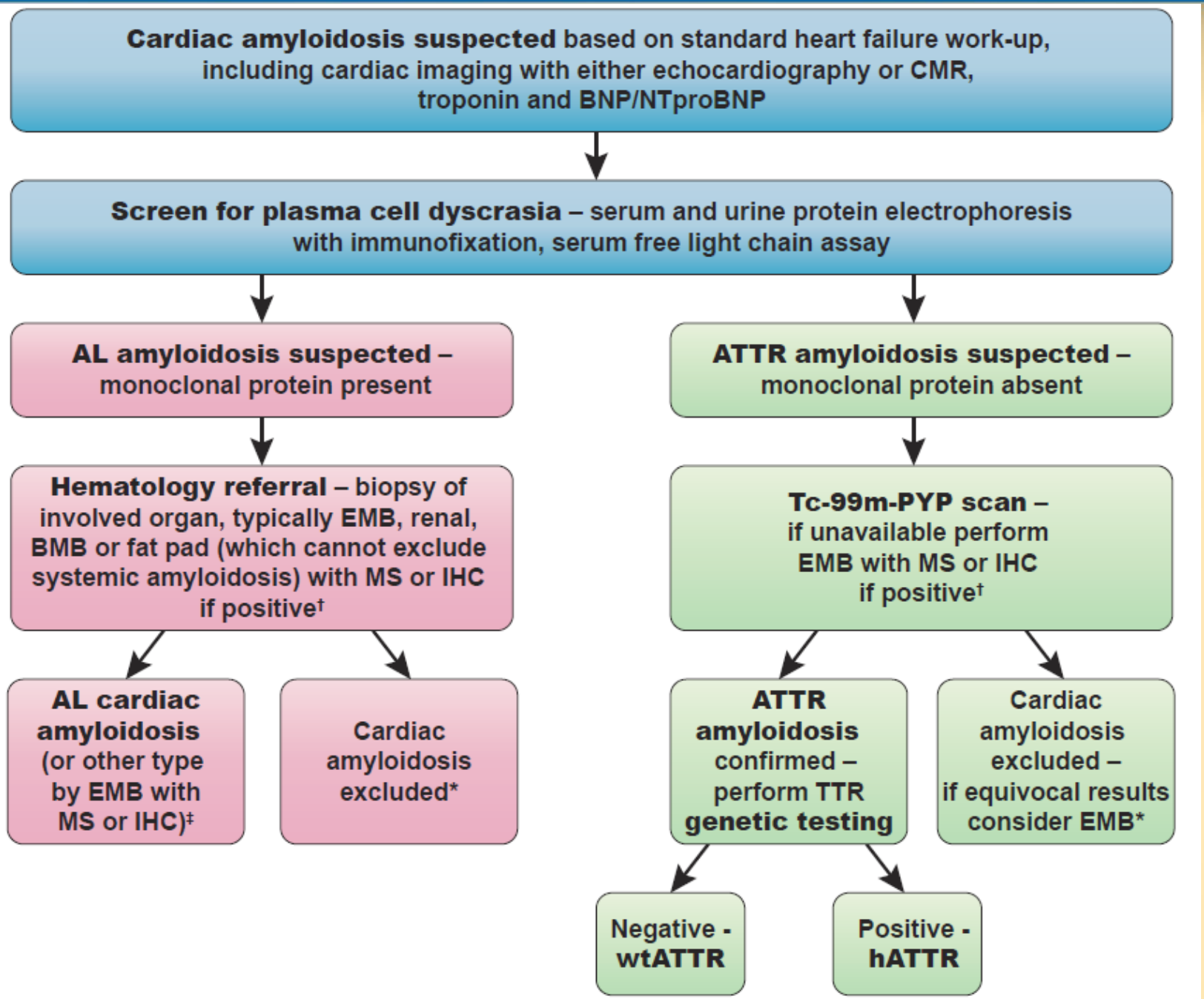
Courtesy Dr. James White, Dr. Denise Chan, University of Calgary



- Increased myocardial radiotracer uptake equal to or greater than bone (≥Grade 2), or in quantitative comparison with the contralateral lung (HCL ratio ≥1.5)

Tc-99m-PYP

CCS/CHFS Joint Position Statement



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Key Question

- How would a community cardiologist go about having a patient undergo all of these tests when the physician doesn’t have the resources of an academic centre?

Availability of Diagnostic Testing

Serum/urine protein studies:

widely available, may need to argue for IFE

PYP scans:

increasingly available (>10 hospitals in BC), but may need QA

Endomyocardial biopsy:

all transplant centres, most centres with cath labs

IHC:

not widely available, depends on local expertise/experience

Mass spectrometry:

not widely available, send out to Mayo or Toronto

Genetic testing:

Publicly funded availability varies by province, industry partners provide testing kits (US-based)

Treatment Plan and Treatment Goals

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Canadian Journal of Cardiology 36 (2020) 322–334

Society Position Statement

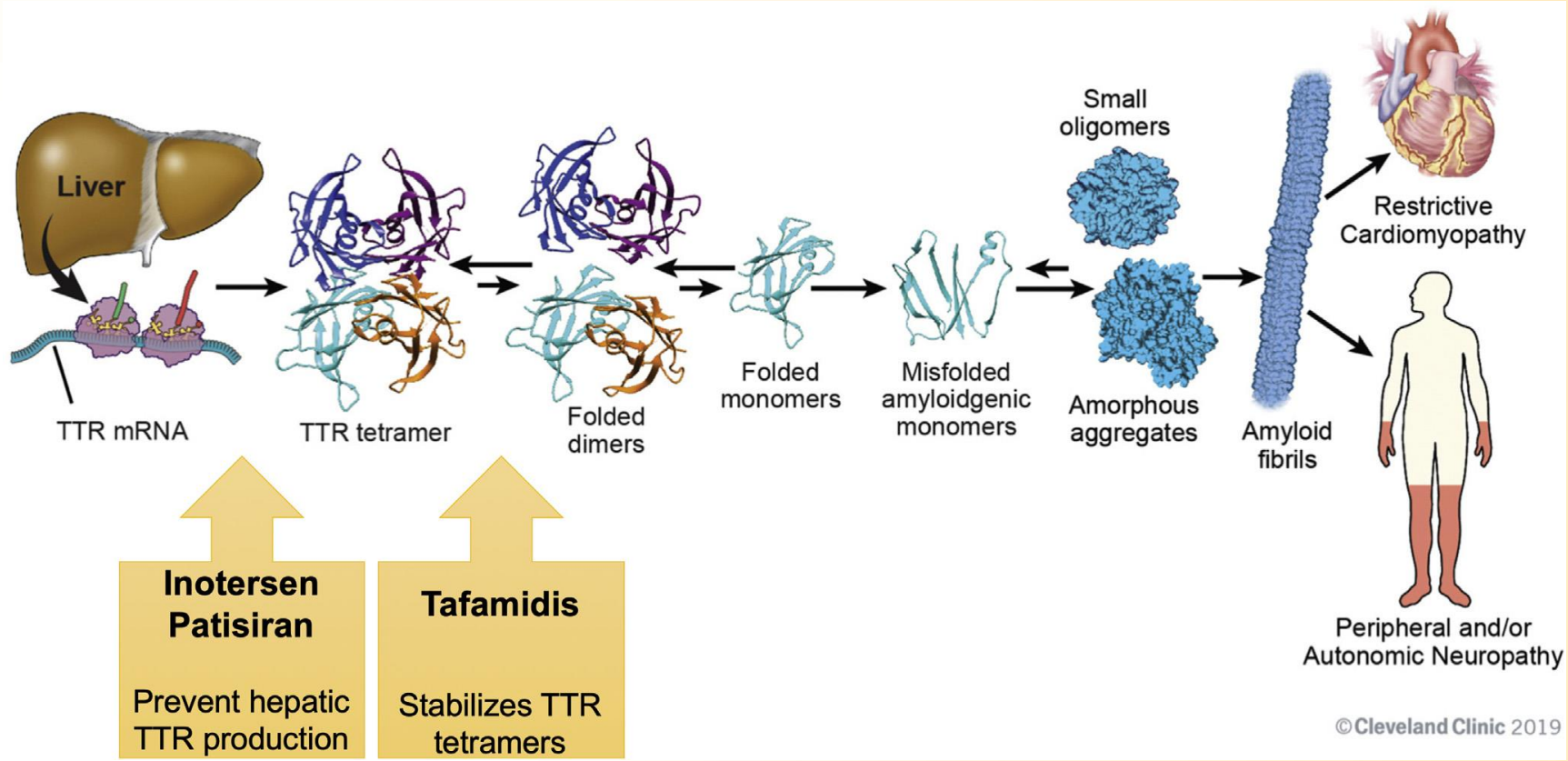
Canadian Cardiovascular Society/Canadian Heart Failure Society Joint Position Statement on the Evaluation and Management of Patients With Cardiac Amyloidosis

Primary Panel: Nowell M. Fine, MD, SM (Co-chair),[a] Margot K. Davis, MD, SM (Co-chair),[b] Kim Anderson, MD,[c] Diego H. Delgado, MD,[d] Genevieve Giraldeau, MD,[e] Abhijat Kitchlu, MD,[d] Rami Massie, MD,[f] Jane Narayan, NP,[b] Elizabeth Swiggum, MD,[g] Christopher P. Venner, MD,[h]

Secondary Panel: Anique Ducharme, MD, MSc,[e] Natalie J. Galant, PhD,[d] Christopher Hahn, MD,[a] Jonathan G. Howlett, MD,[a] Lisa Mielniczuk, MD,[i] Marie-Claude Parent, MD,[e] Donna Reece, MD,[d] Virginie Royal, MD,[j] Mustafa Toma, MD,[b] Sean A. Virani, MD,[b] and Shelley Zieroth, MD[k]

[a] University of Calgary, Calgary, Alberta, Canada; [b] University of British Columbia, Vancouver, British Columbia, Canada; [c] Dalhousie University, Halifax, Nova Scotia, Canada; [d] University of Toronto, Toronto, Ontario, Canada; [e] Montreal Heart Institute, Montreal, Quebec, Canada; [f] McGill University, Montreal, Quebec, Canada; [g] Royal Jubilee Hospital, Victoria, British Columbia, Canada; [h] University of Alberta, Edmonton, Alberta, Canada; [i] Ottawa Heart Institute, Ottawa, Ontario, Canada; [j] University of Montreal, Montreal, Quebec, Canada; [k] University of Manitoba, Winnipeg, Manitoba, Canada

Disease-Modifying Therapy



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Disease-Modifying Therapy: CCS/CHFS Recommendations

- **ATTR Cardiac Amyloidosis and NYHA I-III: Tafamidis**

RECOMMENDATION

10. We recommend tafamidis (if available) for patients with ATTR cardiac amyloidosis and NYHA class I-III symptoms (Strong Recommendation, High-Quality Evidence).

- **hATTR with ambulatory polyneuropathy:** Patisiran or Inotersen

RECOMMENDATION

11. We recommend treatment with a TTR RNA silencing agent (patisiran or inotersen) for patients with hATTR amyloidosis with ambulatory polyneuropathy (Strong Recommendation, High-Quality Evidence).

Values and preferences. To date, randomized placebo-controlled clinical trials of TTR silencers have only included patients with hATTR polyneuropathy and have examined their efficacy with respect to neurologic outcomes. Cardiac outcomes have not been rigourously studied in patients receiving TTR silencers, and cardiac subpopulations in trials of these agents did not undergo testing to confirm cardiac involvement.

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Head, Neuromuscular Section, University of Toronto
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UHN Experience

- Patients started on gene silencers just over 1 year ago
- Variable results: stable, better, worse
- Manage expectations to encourage continued therapy
- Patients do not always separate progression of disease from side-effects of medication

Treating Patients with hATTR Amyloidosis in the Community

Diego Delgado
MD, MSc, FCCS, FACC

Anil Gupta
MD, FRCPC

Serge Lepage
MD, FRCPC, CSPQ

Key Questions

- How can a community cardiologist take all the learnings from this program and apply them into his or her practice?

- How can he/she start diagnosing, testing, and treating patients with hATTR amyloidosis in practice today?

Dr Diego Delgado, MD, MSc, FCCS, FACC

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Collaboration and Interdisciplinary Management

RECOMMENDATION

13. We recommend that comprehensive interdisciplinary management be offered to patients with established cardiac amyloidosis (Strong Recommendation, Very Low-Quality Evidence).

Values and preferences. Care provided by multidisciplinary teams has not been rigourously studied. Centres with access to multidisciplinary care should consider patient referral to appropriate subspecialty services to ensure adequate management of multisystem disease and access to novel therapies and clinical trials, which are more likely to be offered in these settings. This might not be feasible in many centres.

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Key Learnings

- Cardiac amyloidosis is a potentially fatal disease in which early recognition and diagnosis are crucial
- TTR RNA silencing agents are indicated for hATTR patients with polyneuropathy and mixed phenotype
- Comprehensive interdisciplinary management is recommended

Q&A

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Thank you!