



3

Challenges and Shifting Paradigms

AMYLOID: HIDING IN PLAIN SIGHT

Welcome



Please note this session
is being recorded



We encourage open communication
and collaboration amongst the group.
Please submit your questions by
visiting the Q&A button on the menu
bar or unmute your microphone to
ask your question live.



Polling questions have been
prepared and will be presented
throughout the session.

Your Host Today

Dr. Joe Ricci



Dr. Joe Ricci

Regional Cardiac Care Program
CELHIN Cardiologist
Scarborough Rouge Hospital
Lakeridge Health

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- Cardiology University of Toronto
- Past President, CRNO
- Medical Director, Regional Cardiac Care Program 2000-2017
- Manager, Cardiac Rehabilitation Services
- Vascular Lead, Central East LHIN 2014-2017
- Member SRH Foundation Board of Directors

Financial disclosure

Dr. Joe Ricci

Direct financial relationships including grants and honoraria	<ul style="list-style-type: none">• Amgen• Bayer• Boehringer-Ingelheim• Novartis• Servier• Pfizer• Sanofi• Servier• HLS Therapeutics
Membership on advisory boards or speakers' bureaus	Medical Education: <ul style="list-style-type: none">• Amgen• Bayer• Boehringer-Ingelheim• Janssen• Novartis• Pfizer• Servier• HLS Therapeutics
Other	Corcare Quality and Education Director

What is the 'Corcare Quality and Education Platform'

The Corcare Quality and Education Platform(CQEP),
is a Canadian not-for-profit corporation
Providing quality of care research and medical education
for community care providers
to advance the secondary prevention of cardiovascular disease.

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Accredited Program



This one-credit-per-hour Group Learning program has been certified by the College of Family Physicians of Canada and the Ontario Chapter for up to 1.50 Mainpro+ credits.

Program Disclosure of Financial Support

Excellence in Education
is a
Partnership.

- CorCare Inc.
- Pfizer

We are grateful for the
educational support.

Disclosure of Financial Support

- This program was developed by Corcare Quality and Education Platform, a not-for-profit medical education Canadian Corporation
- Corcare Quality and Education Platform has received financial support from industry in the form of educational grants from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Janssen, HLS Therapeutics Inc., Pfizer, Sanofi, Servier and Novartis
- This program has received no in-kind support from outside sources
- Potential for conflict(s) of interest are noted in the disclosure data

Mitigating Potential Bias

- Our scientific planning committee (SPC) members, speakers, moderators, facilitators, and authors have completed their *Declaration of Conflict of Interest* forms, prior to this program.
- Our SPC have reviewed each speakers, moderators conflict of Interest forms and determine no action was required to manage potential or real conflicts of interests.
- All members of the SPC, speakers, moderators, facilitators, and authors, will disclose to participants their relationships with a for-profit or not-for-profit entity, verbally and in writing, prior to beginning their presentation.

Learning Objective

During this session, participants will analyze and interpret the:

- What “Amyloid Protein” is
- How “Amyloid” Impacts your patients Health
- ‘Red Flags’ that signal an increased risk of ATTR amyloid
- Practical, Low Cost and Rapid Screening for Cardiac ATTR amyloidosis

ASCVD

Secondary Prevention

The Standard of Care

Poll Question

What is Secondary Prevention?

Treatments that improve outcomes in patients who:

- a) Have been admitted to hospital with a heart attack
- b) Have had a prior heart attack, stroke, or any other vascular event
- c) Have established atherosclerotic cardiovascular disease or heart failure

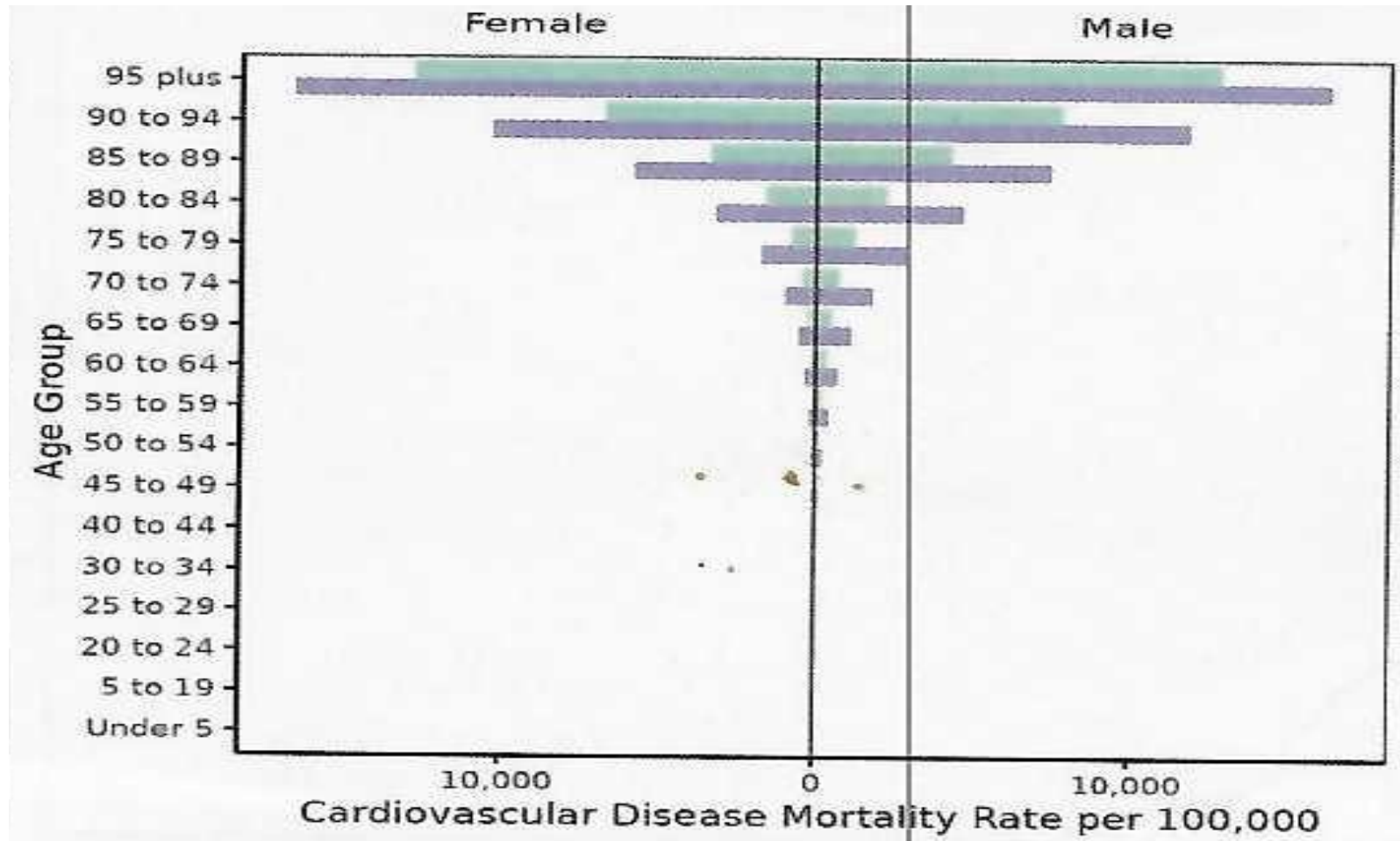
Global Cardiovascular Risk

In one Generation

- Global CVD mortality has fallen >50%
- Myocardial Infarction Mortality declined from 30% to 4%
- > 80% decline in cardiovascular risk factors

55% of the outcome improvement
Due to medical secondary prevention therapies

Cardiovascular Risk is Falling



● 2001
● 1991

Impact of Secondary Prevention

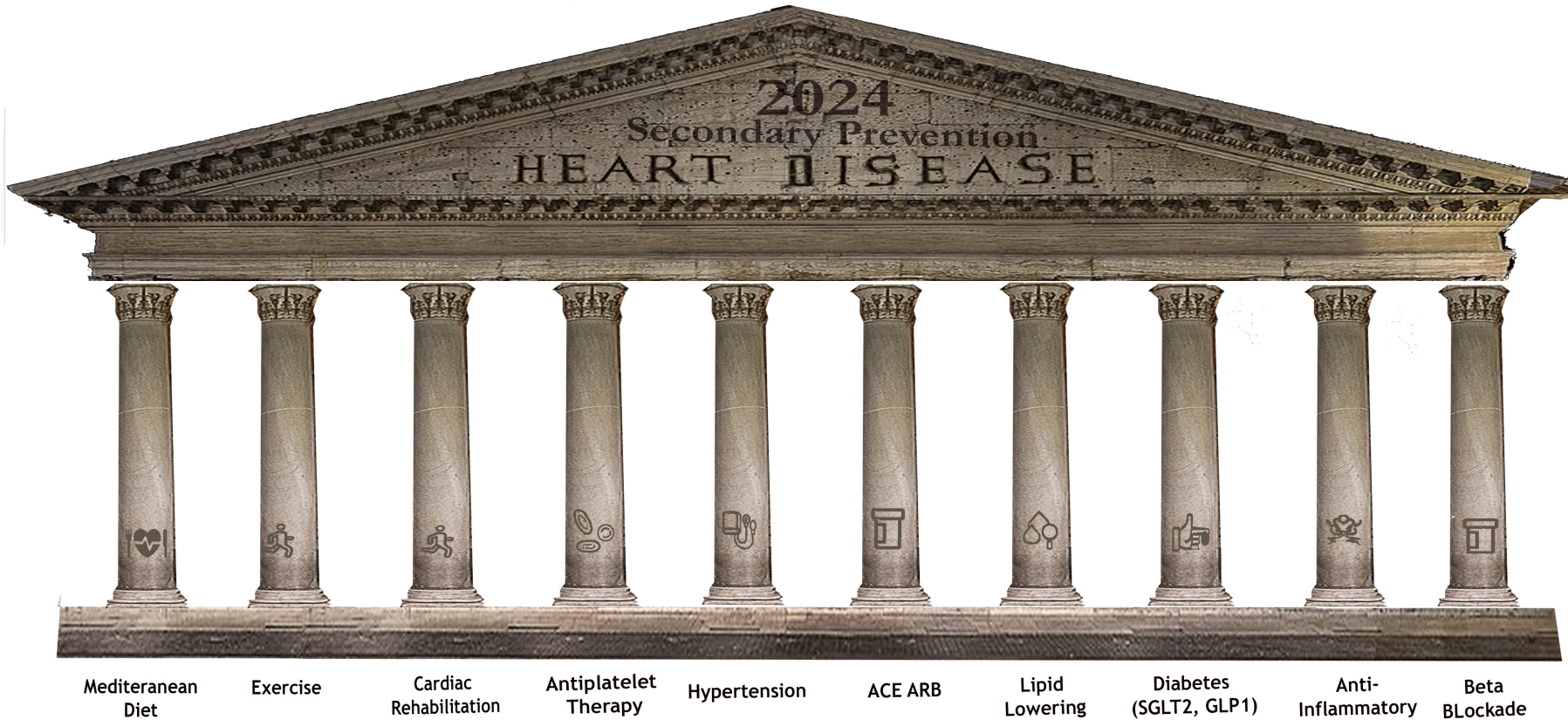
- Vascular Event
- Symptoms
- Imaging evidence
- High Risk Score

Complications and Events

Cardiac	MI, CHF,
Neurologic	Stroke, TIA
Renal	CKD
Vascular	Claudication, gangrene

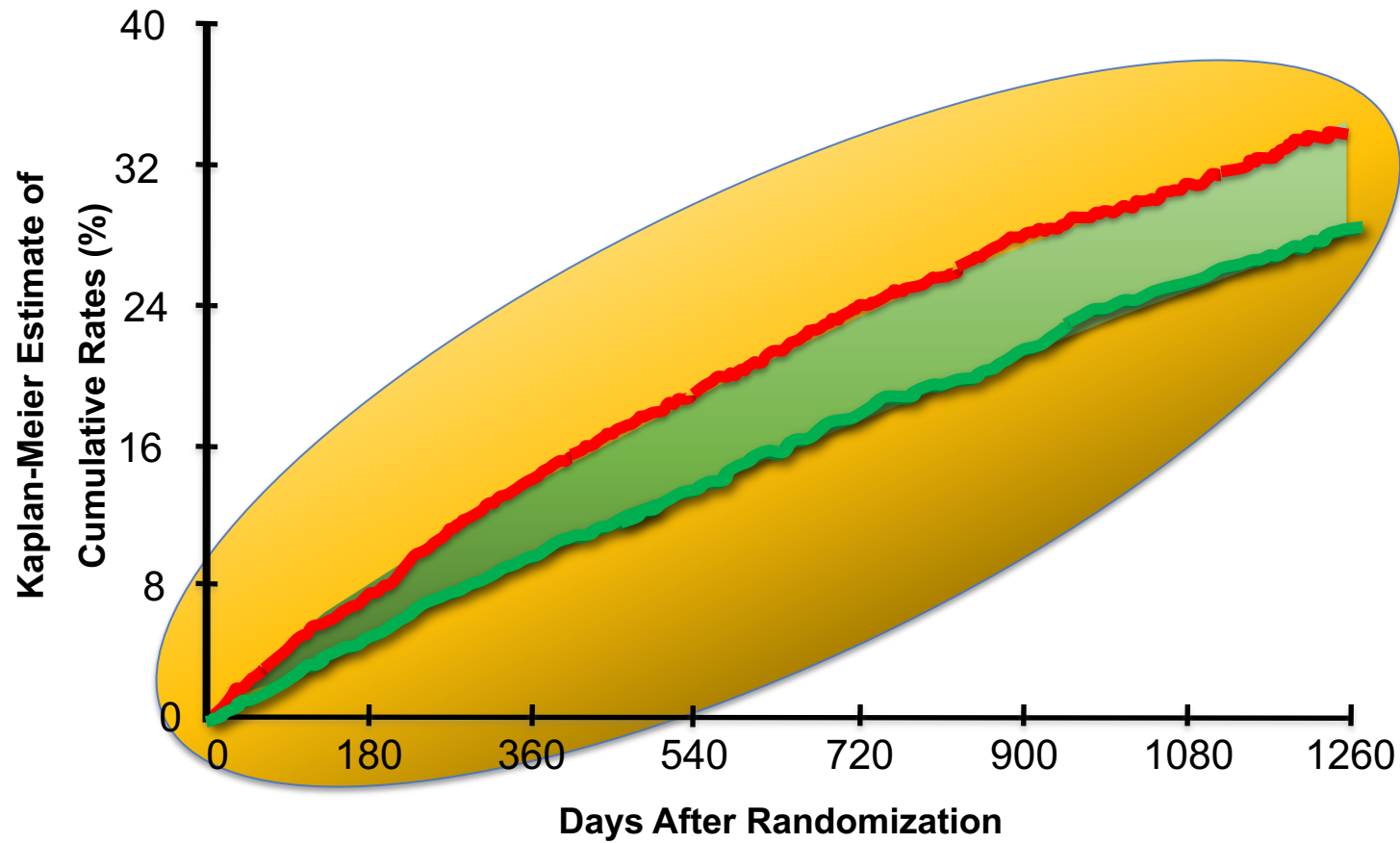
↓ Quality of Life
↓ Survival

The Pillars Of Prevention



	Risk Reduction
Exercise	25%
Diet	25%
Hypertension	25%
Anti-Platelet	25%
Lipid Management	>30%
ACE	25%
SGLT2	25%
GLP1	20%
Anti-Inflammatory	25%
Beta Blockers	15%
Overall Benefit	+80%

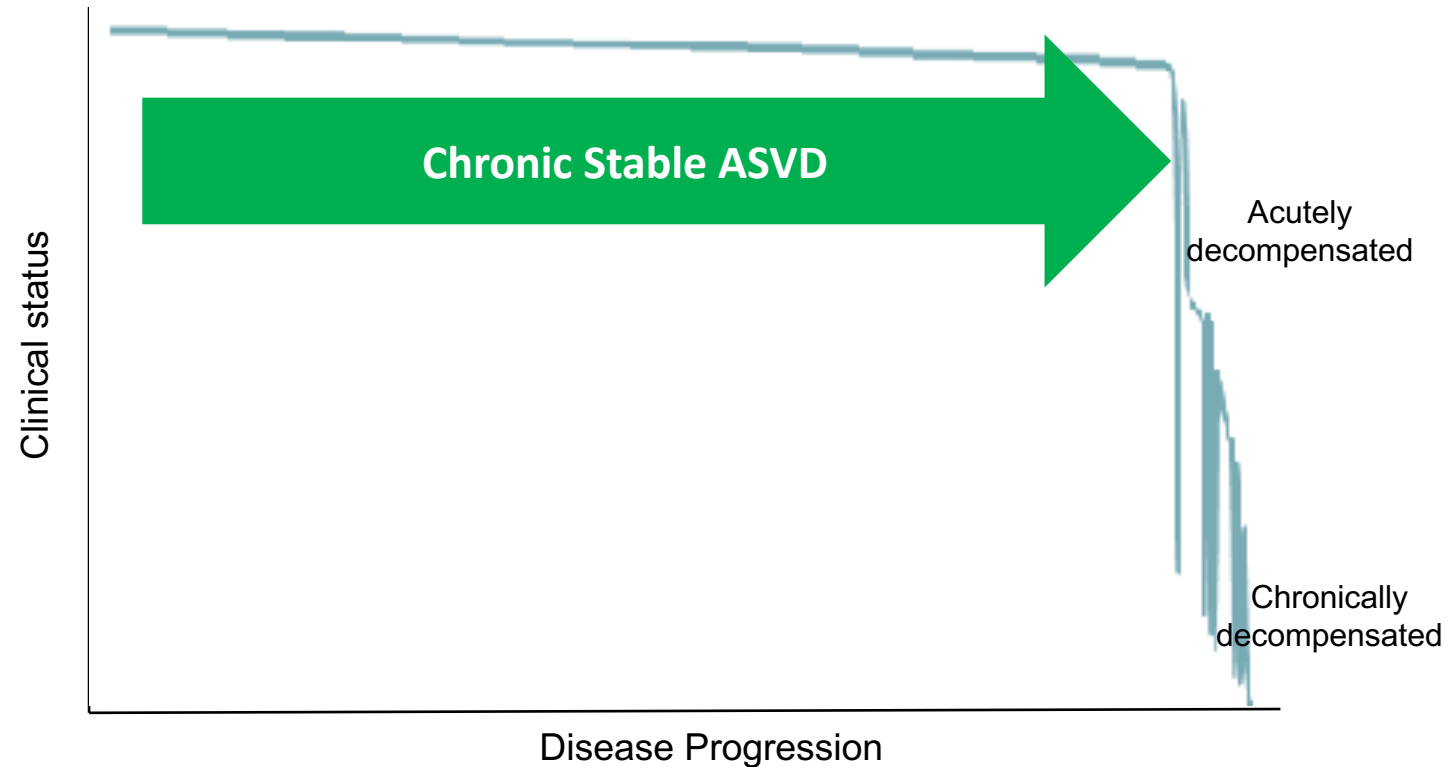
Time Under Treatment Matters



Benefits start early

& increase over time

Reframing the Perspective



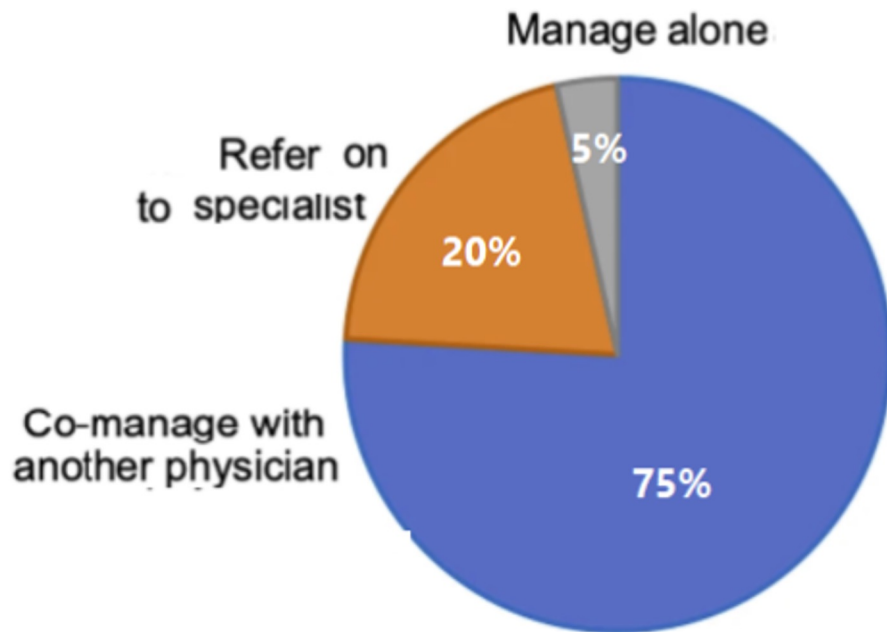
ASCVD and HF as Chronic Conditions

Secondary Prevention

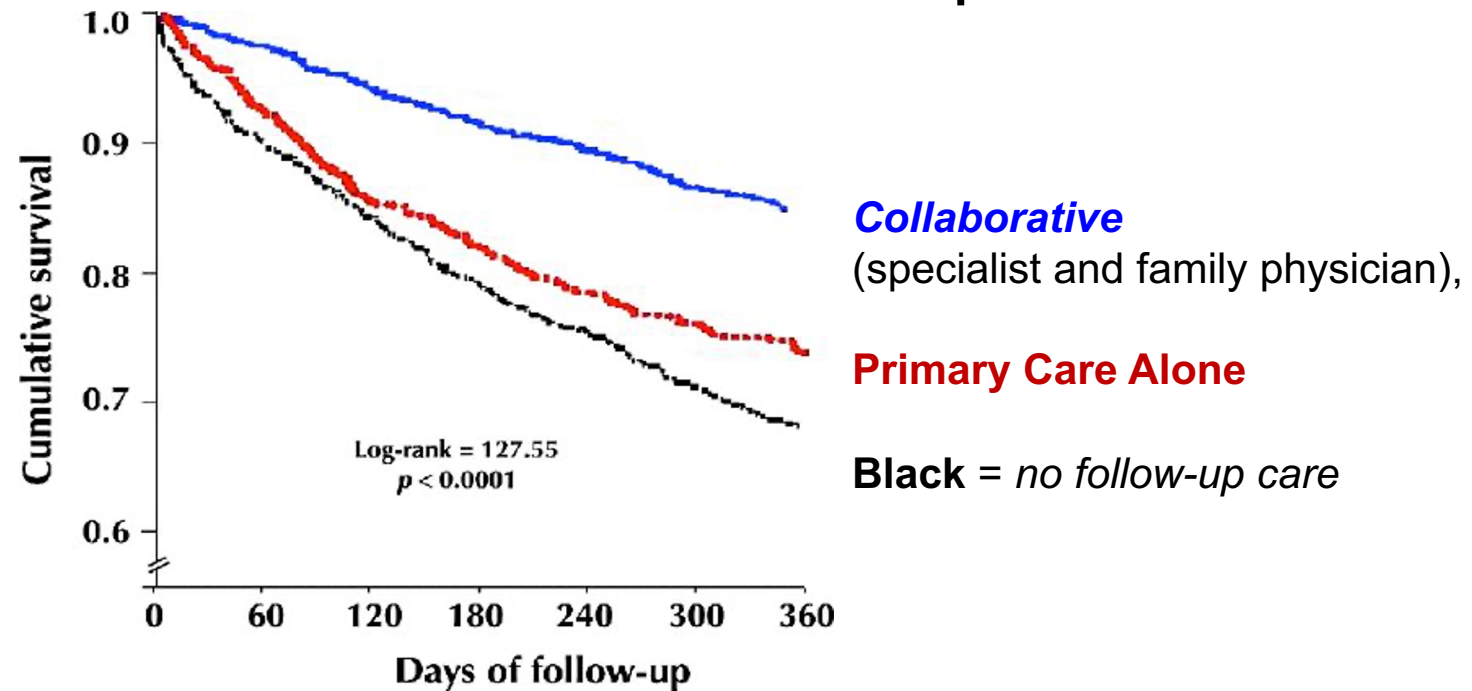


Expect Primary Care & Specialist Alignment

Co-Management

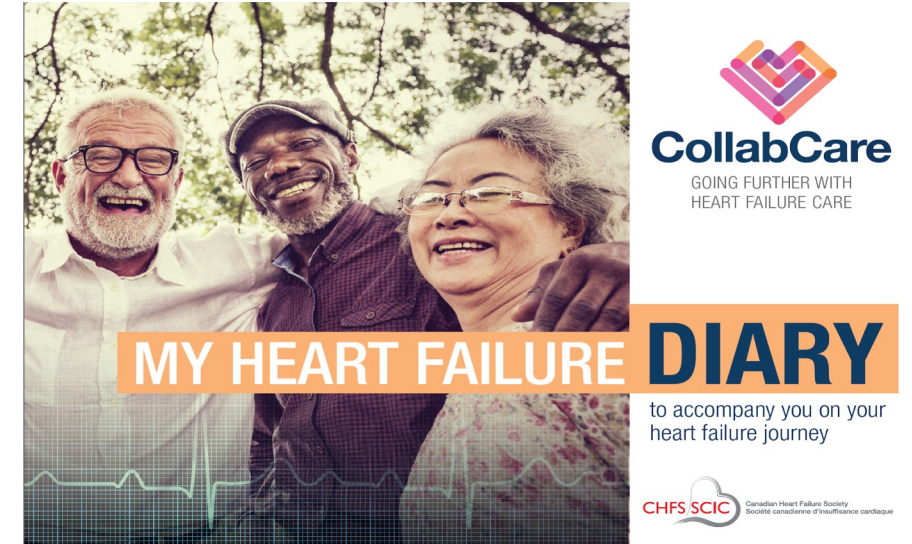


- Provide Collaboration Improves



Make Patients 'OWN' their Playbook

- EXPECT a REGULAR Personal Diary
 - BP
 - Heart Rate
 - Weight
 - Medication
 - Exercise Diary
- Teach Self Management
 - Recognize changes in Weight, BP, HR
 - Evaluate their significance
 - Take appropriate action
 - Evaluate effects of action

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Managing The Challenges with a Focus on Outcomes

Disparities

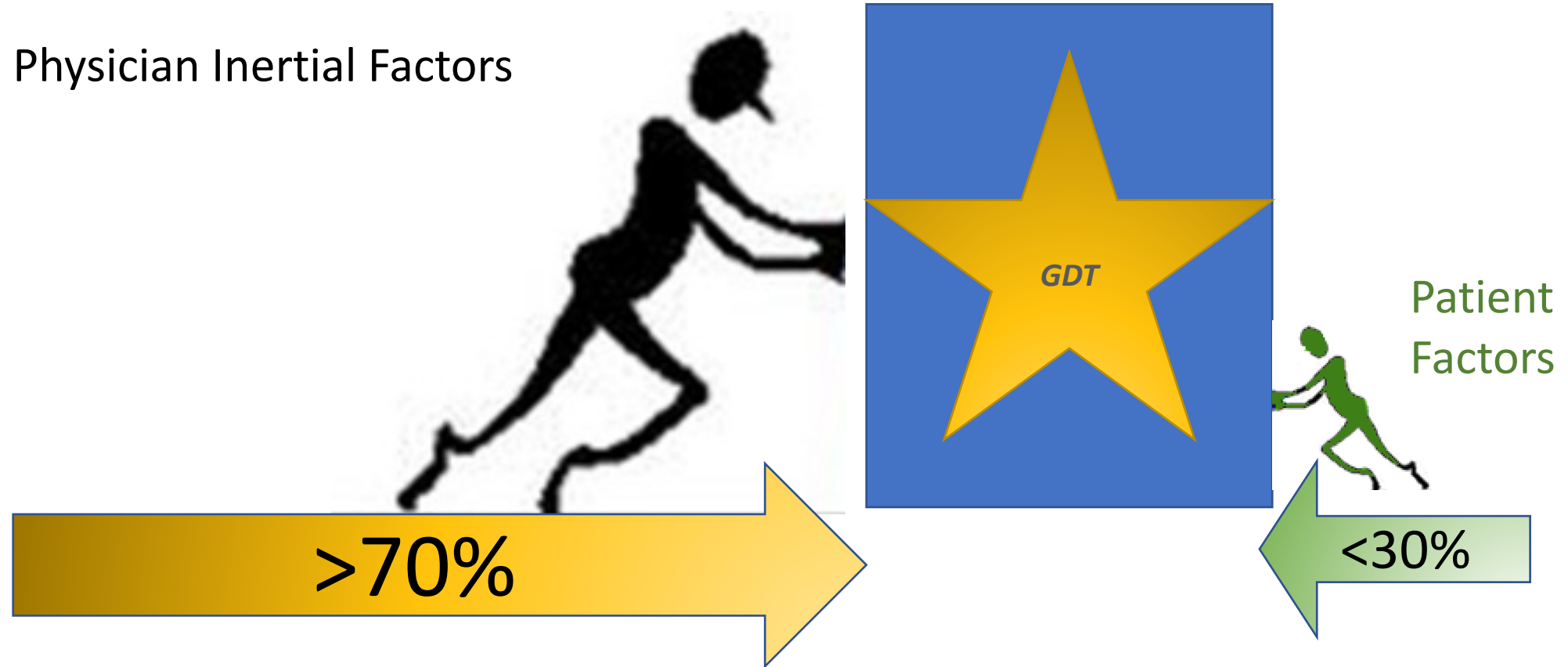
Primary Care Physician access
Specialist Access
Social Economic Status

Barriers

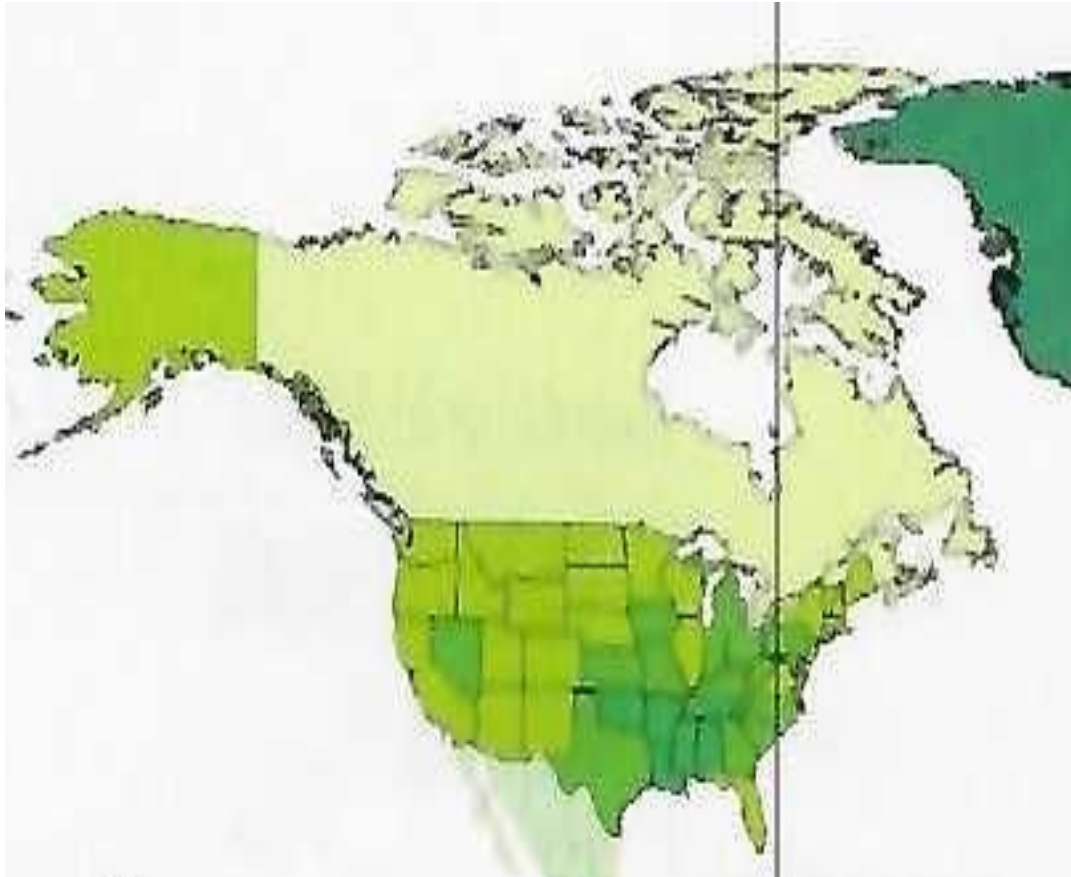
Economic
Personal Loss
Knowledge gaps

Physicians Drive Patient Outcome

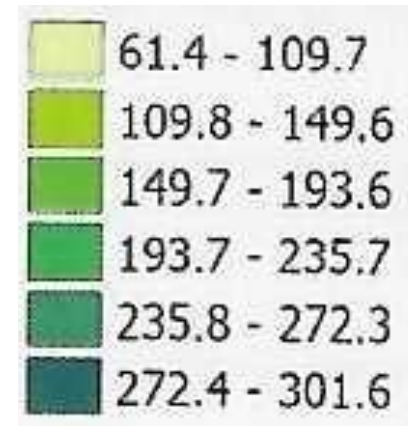
Physician Inertial Factors



Canada As A Leader



Age Standardized Cardiovascular Mortality
Per 100,000 population > 40 years of age



Every Day Counts

INITIATE Secondary Prevention Strategies

From the **FIRST DAY** the Diagnosis of ASCVD is made

at the **EARLIEST OPPORTUNITY**

and at **EVERY VISIT**

For the **REST OF YOUR PATIENTS' LIFE**

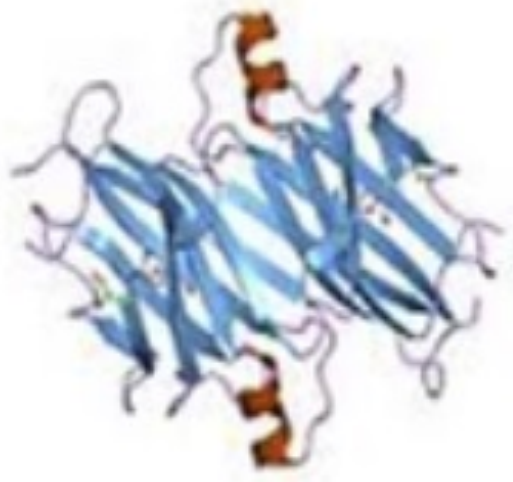
Why Amyloid is Important to Patients Today!

2010 Recognition that ATTR Amyloidosis is prevalent

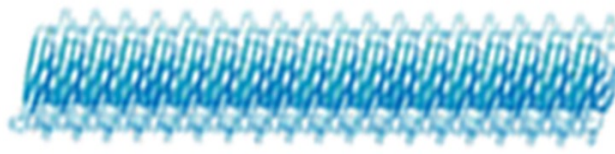
2018 Widely available and 95+% Sensitive TC⁹⁹ Screening

2020 Effective Treatment of ATTR Amyloid And Light Chain Disease

What is Cardiac Amyloid?



An Abnormal Protein
Circulates in the
blood



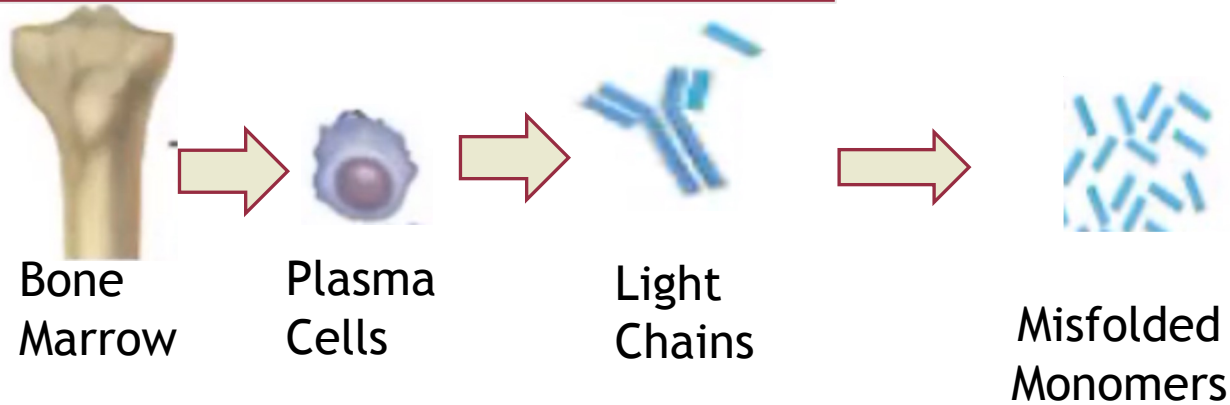
The Abnormal Proteins
Clump (aggregate)
Into fibrils



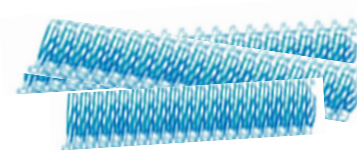
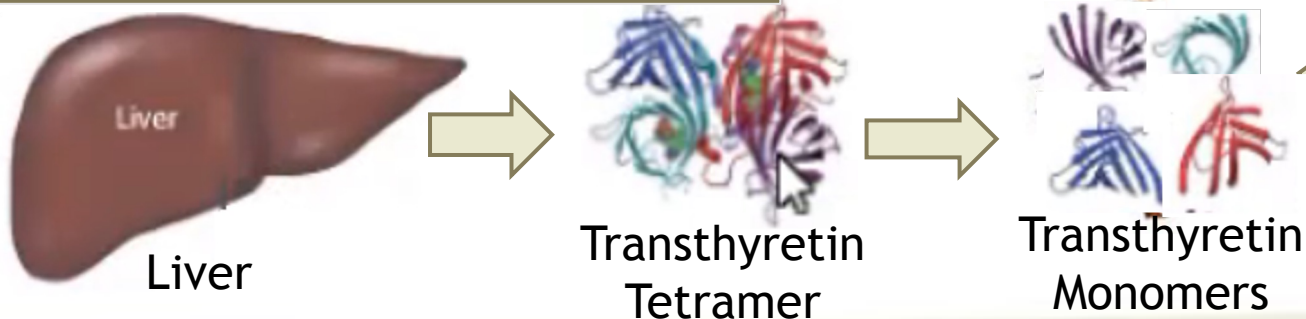
End Organ
Deposition

2 Sources of Cardiac Amyloidosis

AL Amyloidosis



ATTR Amyloidosis

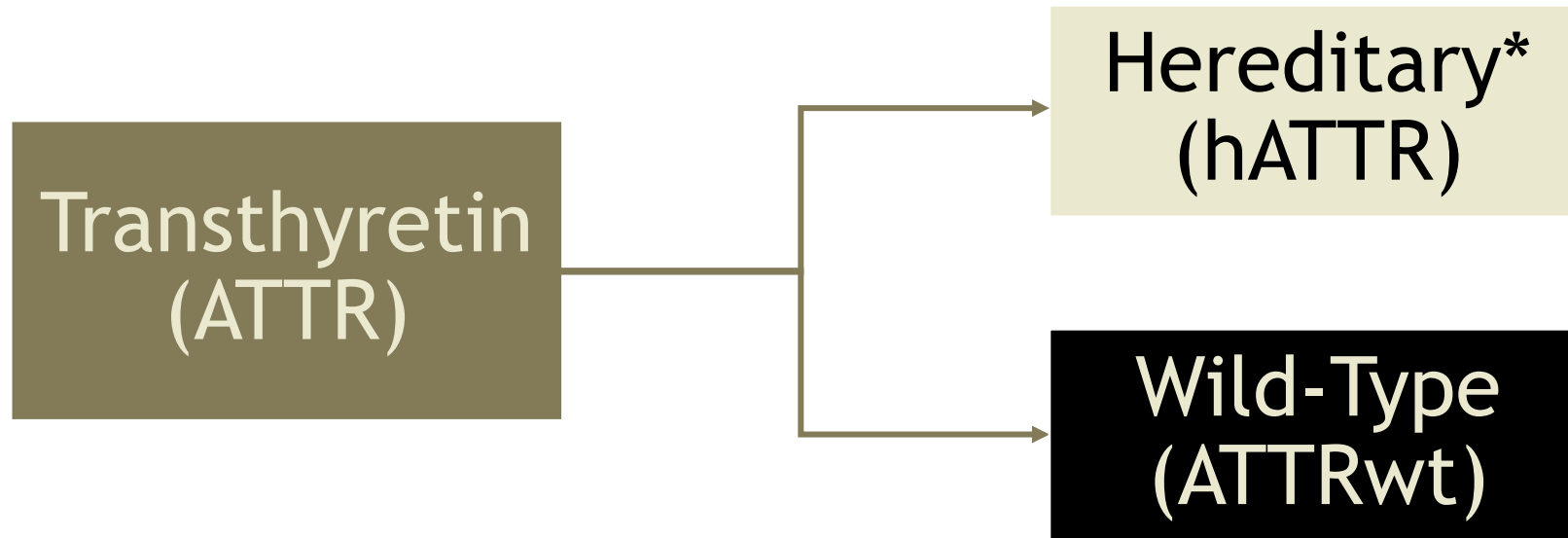


Misfolded
Amyloid
fibrils



End Organ
Deposition

Two Types of aTTR Amyloidosis

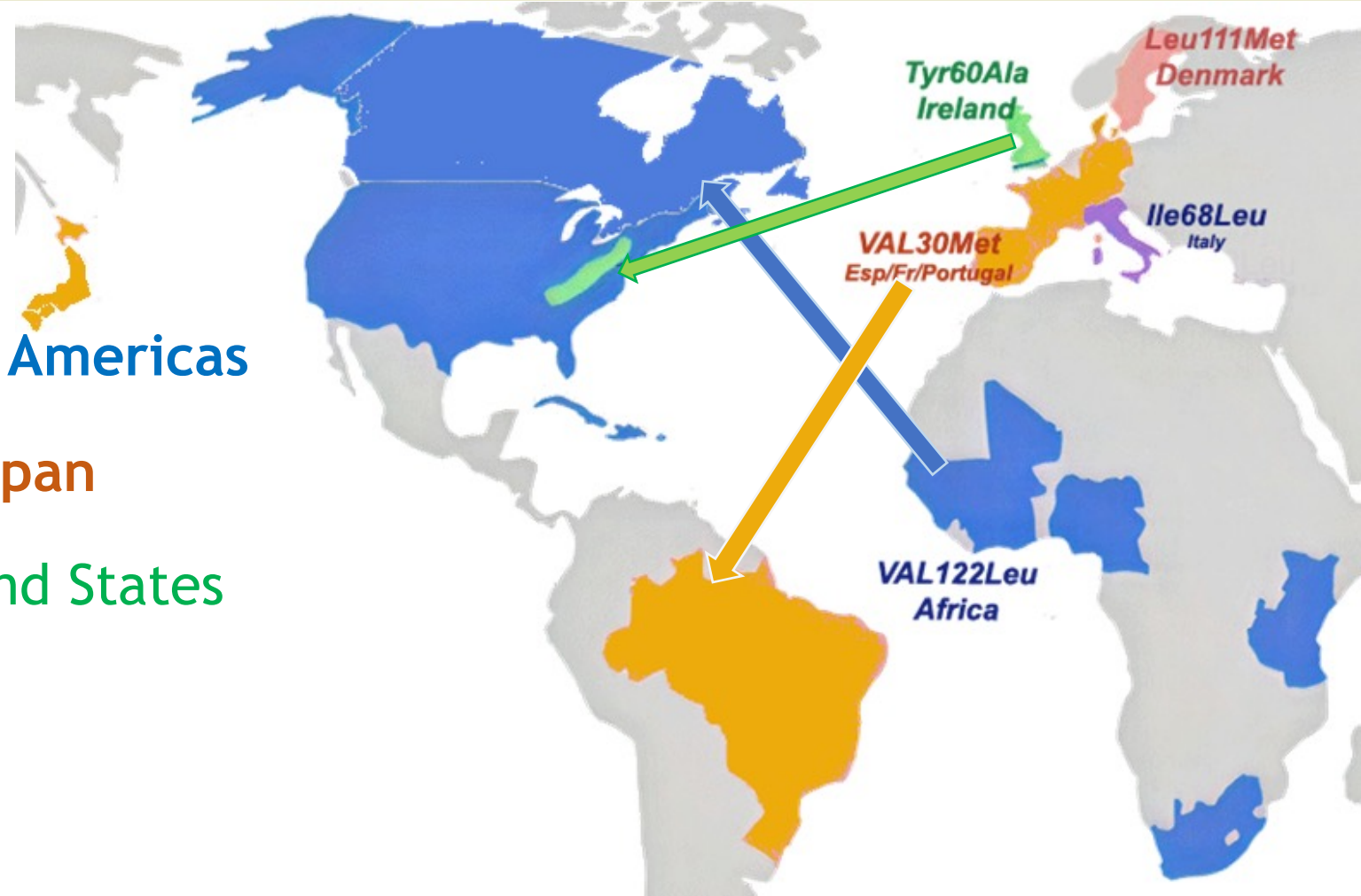


The Wild Type and Hereditary presentation are similar,
But hereditary forms may have a worse prognosis

One hATTR Type is Common in Our Community

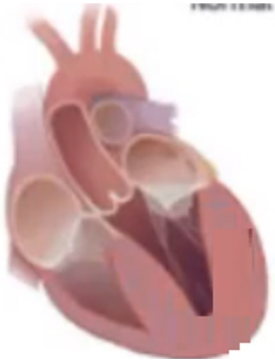
Val122Leu is common in Caribbean/African Blacks

Val122Leu	Africa, Caribbean, Americas
Val30Met	Europe , Brazil, Japan
Tyr60Ala	Ireland, New England States
Le68Leu	Italy
Leu111Met	Denmark



How Amyloid Cause Disease

An Infiltrative Tissue Disorder



Hypertrophic
Cardiomyopathy



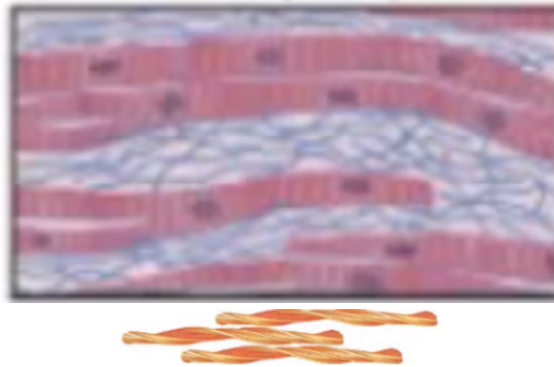
Normal muscle



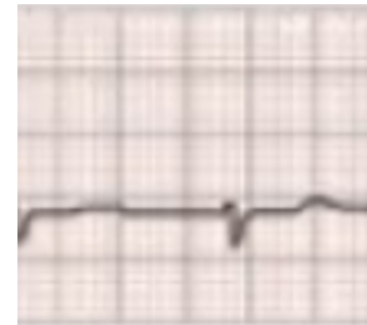
LVH EKG voltages



Infiltrative
Cardiomyopathy



Amyloid fibrils
Expand intercellular
spaces



Low EKG voltages

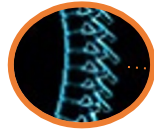
Red Flags for Amyloid Accumulation

Hiding in Plain Sight

Amyloid is Detected Based on Where Fibrils Accumulate

Nerves and Surrounding Tissues

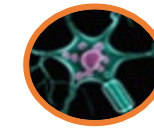
LUMBAR SPINAL STENOSIS^{4,5}



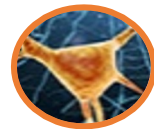
BILATERAL CARPEL TUNNEL



SENSORIMOTOR NEUROPATHY



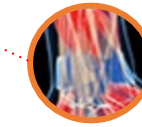
AUTONOMIC NEUROPATHY^{1,3}



Myocardium¹⁻³

Heart failure

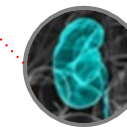
Hypertrophy



Tendons

Biceps tendon rupture

Rotator cuff disease



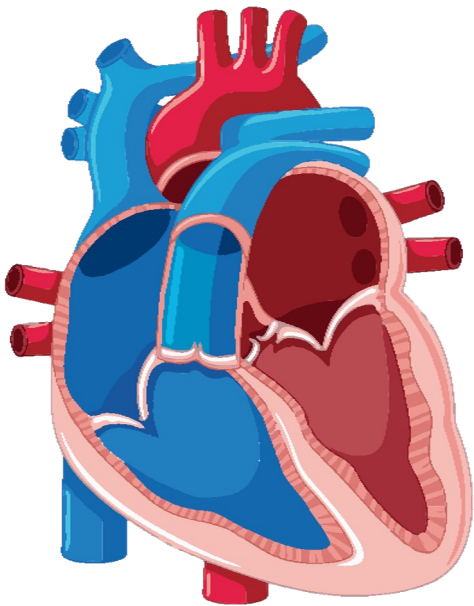
NEPHROPATHY¹

Proteinuria

Renal failure

Cardiac 'Red Flags' for Amyloid

Deposition of Amyloids in the Heart Causes Infiltrative Cardiomyopathies



Heart Failure

HF preserved EF	20-30%
HF Reduced EF	2-5%

Idiopathic LV hypertrophy	5-6%
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Aortic Stenosis

Open AVR biopsy	6%
TAVR Aortic Stenosis	16%

Common but Non-Specific

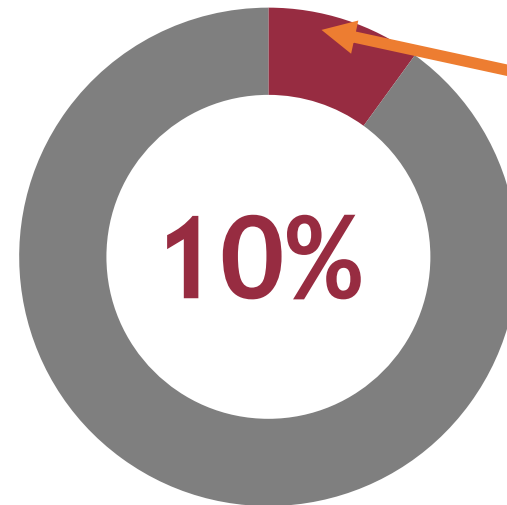
Atrial Fibrillation	69%
Asymptomatic LVH	25%
Atrial dilation	60%

Neurologic ‘Red Flags’ for Amyloid

Amyloid Deposition in Connective Tissue Causes Nerve Entrapment Syndromes



- Carpal Tunnel Syndrome
- CTS diagnosis up to *10 years* before ATTR diagnosis
- Typically bilateral
- Patients often have a history of CTS release surgery

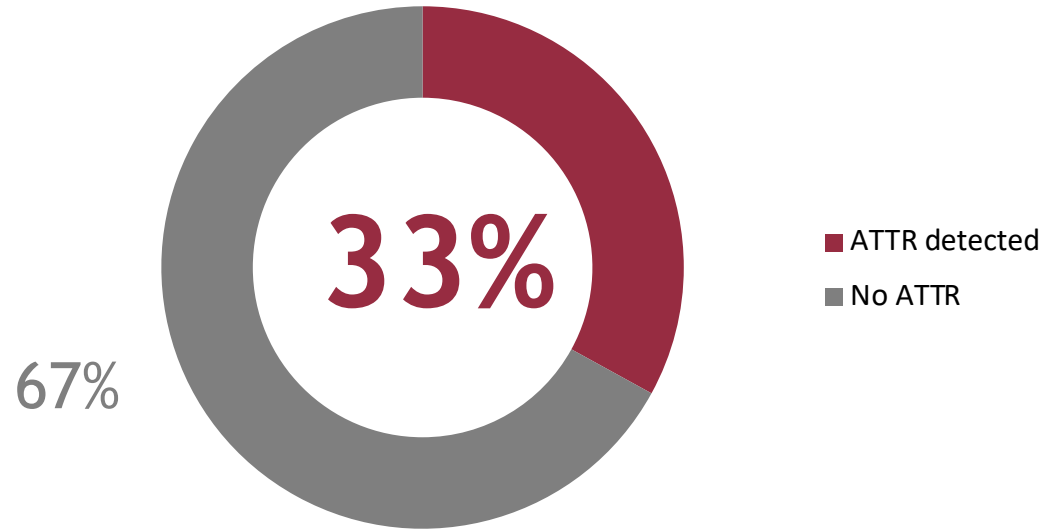


10% have positive
amyloid biopsy
(n= 10/98)

The Neurologic RED FLAGS

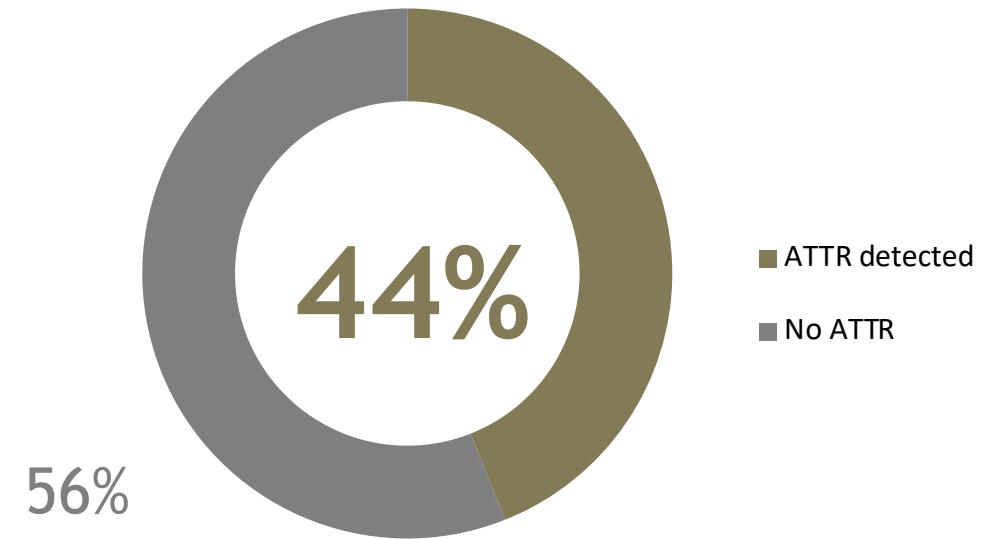
Lumbar Spinal Stenosis

Lumbar spinal stenosis



United Kingdom
(Westermarck 2014, n = 15)

Lumbar spinal stenosis



Kumamoto University Hospital, Japan
(Sueyoshi 2011, n = 36)

Diagnosis was Difficult in the Past

....And Took a LONG time.

- Patients often visit > 5 physicians before diagnosis
- Time to diagnosis typically more than 2-4 years
- In one study, diagnosis took >6 years after the onset of symptoms for 1 in 10 patients



Poll Question

The Screening for ATTR Amyloidosis is best made by:

1. Cardiac Magnetic Resonance imaging
2. Cardiac and liver CT scan
3. Echocardiography with Global longitudinal strain mapping
4. Nuclear Tc99 cardiac Scan
5. Salivary Gland Biopsy
6. Cardiac biopsy (EMB)
7. Measuring circulating amyloid protein in blood

The Gold Standard: CARDIAC Tc99 Scan



Technetium Pyrophosphate Cardiac Amyloid Scan

Patient Information

Name:

Date of Birth:

Health Number:

Referral Information

Indication for Study

Cardiomyopathy

Clinical History

Family history of ATTR amyloidosis

Risk Factors

No cardiovascular risk factors.

Symptoms

Symptoms: no cardiac symptoms.

Medications

Apixaban, Entresto, Spironolactone, Carvedilol, Furosemide.

Imaging Protocol

Protocol

Amyloid protocol

Radionuclide

Dosage: 25 mCi intravenously

Imaging and Quantification

Quality

Image quality good.

Imaging

Tc99 imaging reviewed with autoquant commercial software.

Cardiac:Bone Score

Cardiac:contralateral thoracic activity ratio:1.67.

Summary and Recommendations

Abnormal study

Semi-quantitative visual index 3 (cardiac uptake > ribs).

Planar heart/contralateral thoracic ratio abnormal ≥ 1.5 .

Genetic testing for familial ATTR variant should be considered.

Candidate for medical therapy

High probability of ATTR amyloid

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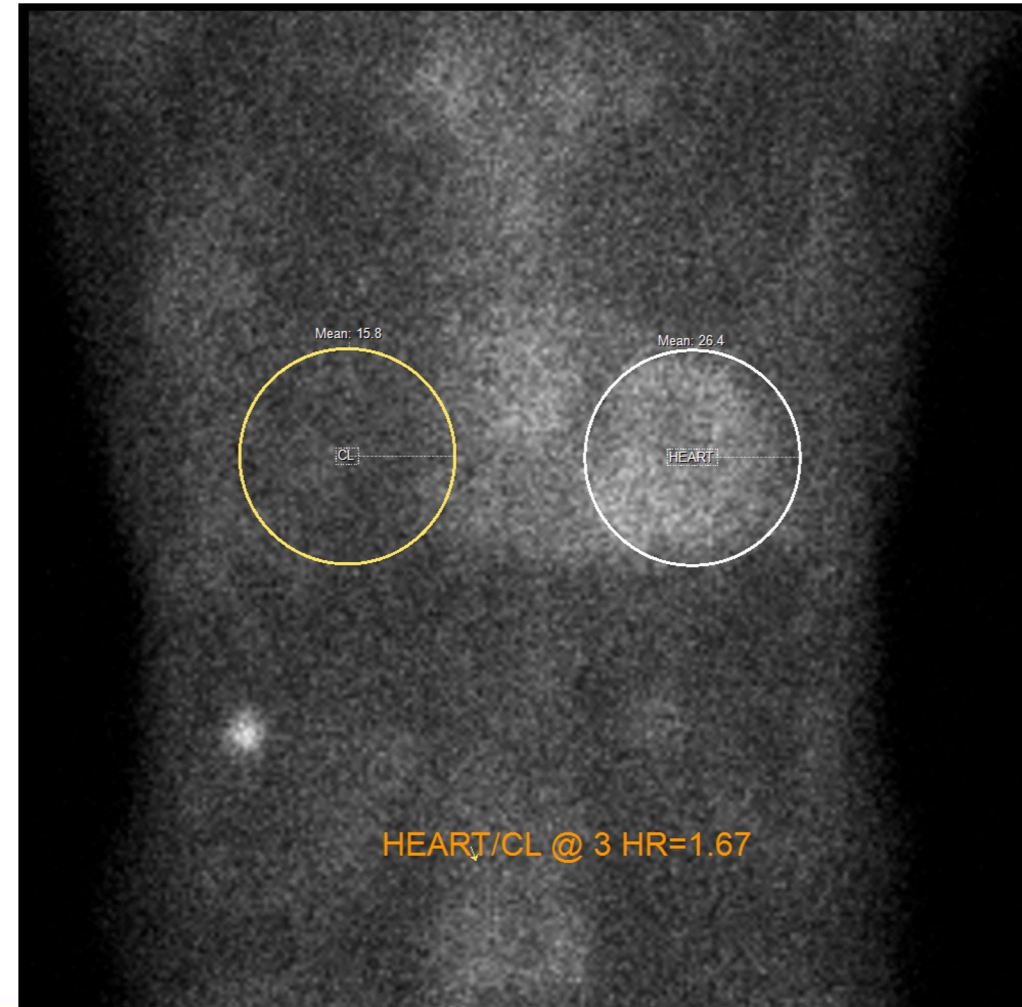
Pickering, ON L1V 1B5

Tel: 416.284.4744

Fax: 416.284.0141

Email: info@corcare.net

www.corcare.net



How Cardia ATTR Scan is Done

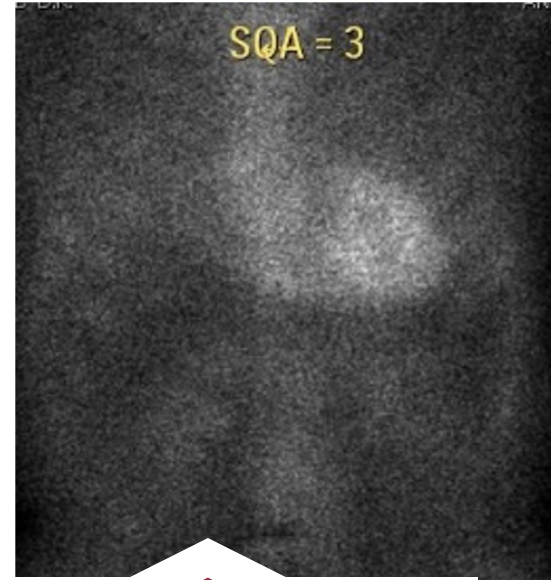
A Gamma Detector Is Used to Identify Uptake of a Nuclear Radiotracer in the Body



Radiotracer



Camera



SPECT Scan¹

Cardiac ATTR Scanning

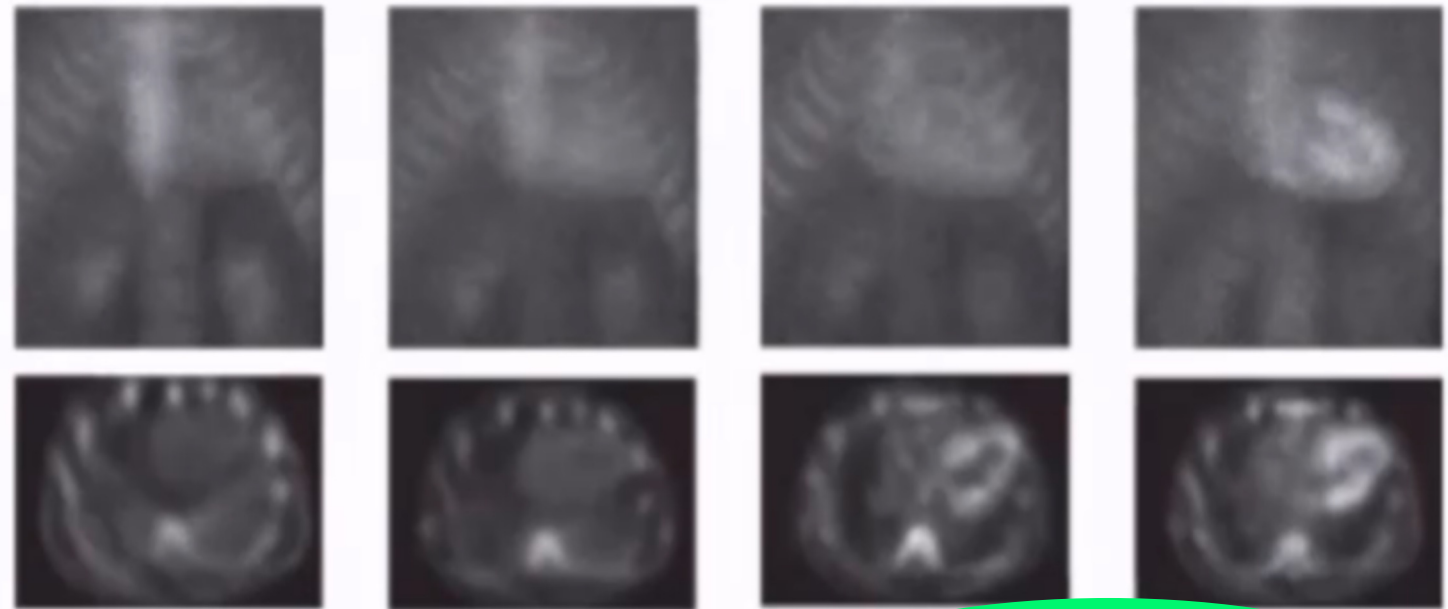
Inexpensive, Safe and Reliable

Sensitivity: 95+%

Specificity: 90%

Grade 2+ tracer uptake
without monoclonal protein

- Specificity 99.9%
- Positive predictive value 99.9%



Grade 0	Grade 1	Grade 2	Grade 3
No uptake and normal bone uptake	Uptake less than rib uptake	Uptake equal to rib uptake	Uptake greater than rib uptake with mild/absent rib uptake

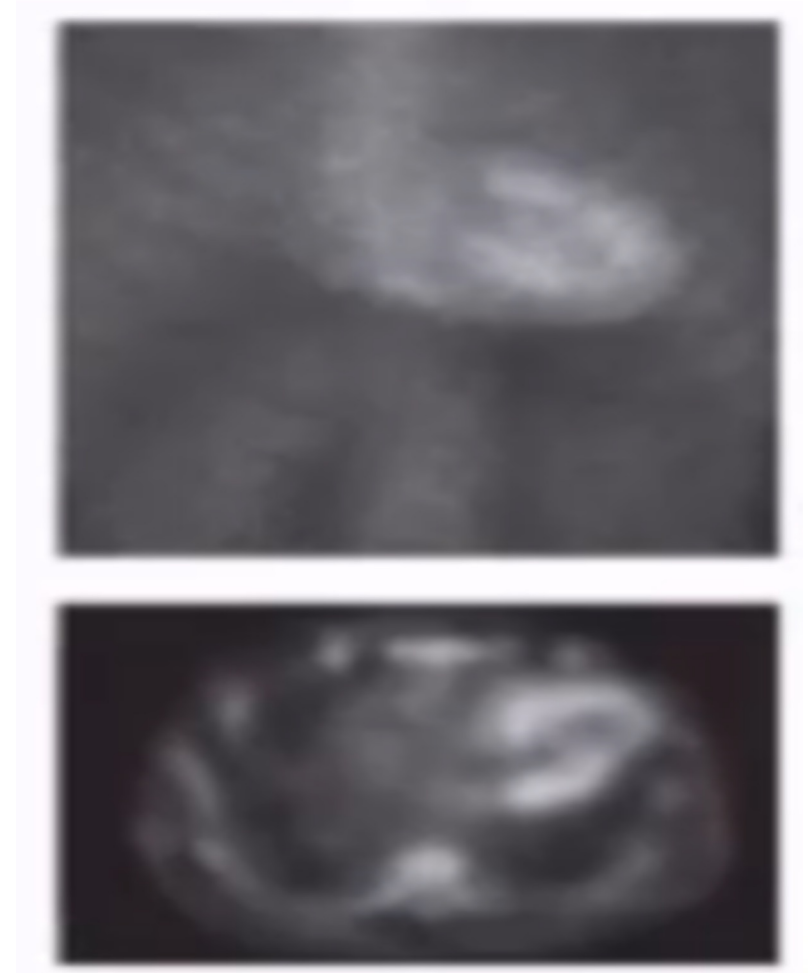
Cardiac TC99 ATTR Scan is Low Risk

No contraindications for:

- Renal failure
- Atrial fibrillation
- Devices
- Obesity

Single Rest image only at 3 hours

Low radiation at 15mCi 3.2 mSV



Amyloid is More Common than We Realized

Prevalence of Transthyretin Cardiac Amyloidosis in Elderly Subjects From the General Population: The Catch Study

The prevalence of ATTR in a higher risk population is approximately 1/500



Simplified screening with sensitive TC99 scans identifies a higher prevalence of wild type disease populations with red flags than we realized

Amyloid: Time To Diagnosis Improving Dramatically

A Real World Evaluation with Chart review of 239 physicians in Europe and North America

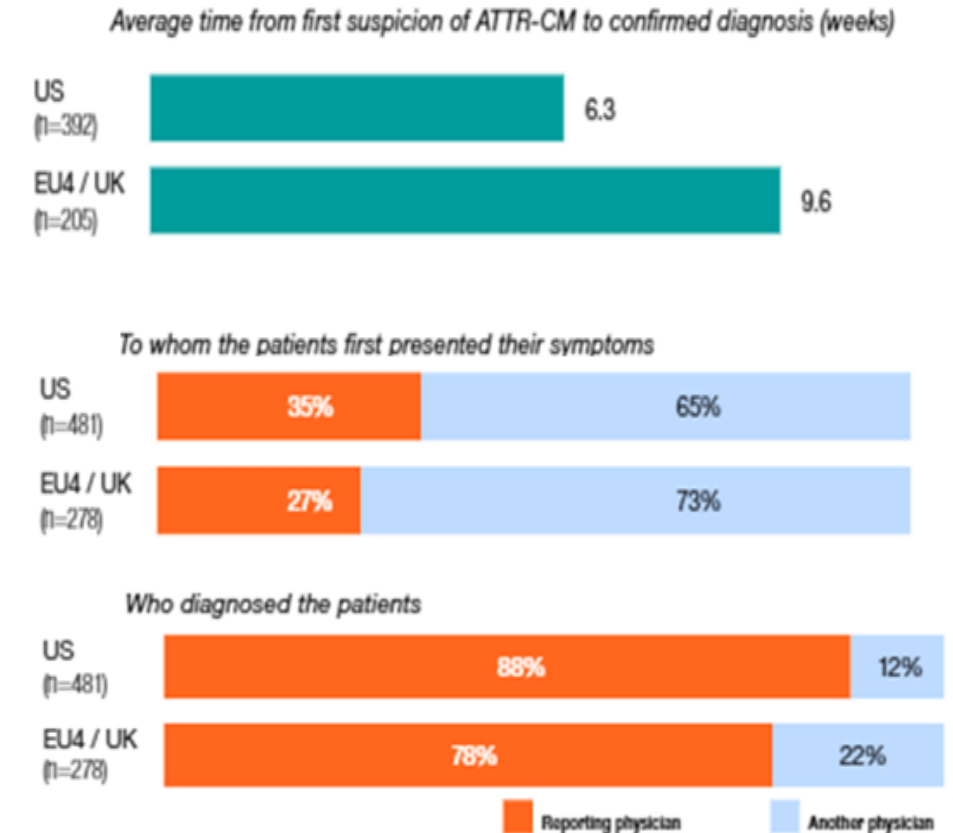
Average time to diagnosis 6-9 weeks

Primary physician made the diagnosis 35% of patients

Tc99 ATTR scan + IEP routinely used for screening and diagnosis

Implications:

1. Tc99 screening is widely used world wide
2. Tc99 screening has dramatically reduced time to DX.
3. Access to timely effective therapies will improve



Tc99 Amyloid Scan: First year experience

86 PYP reported scans

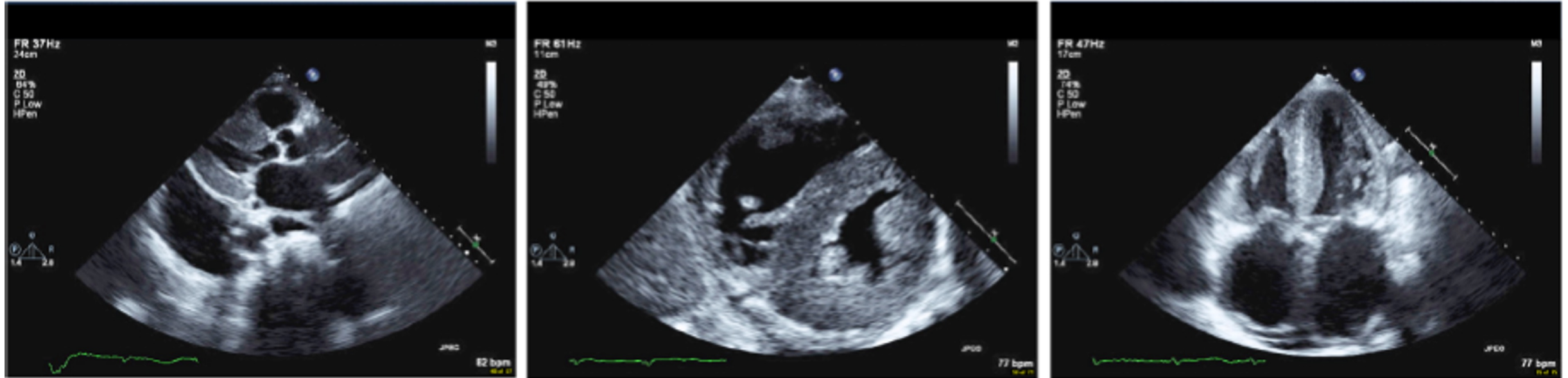
15 (1 in 6 =16%) diagnostic ATTR cardiac scan

8 on therapy for ATTR (7), hATTR(1)

Echocardiography

ECHOCARDIOGRAPHY

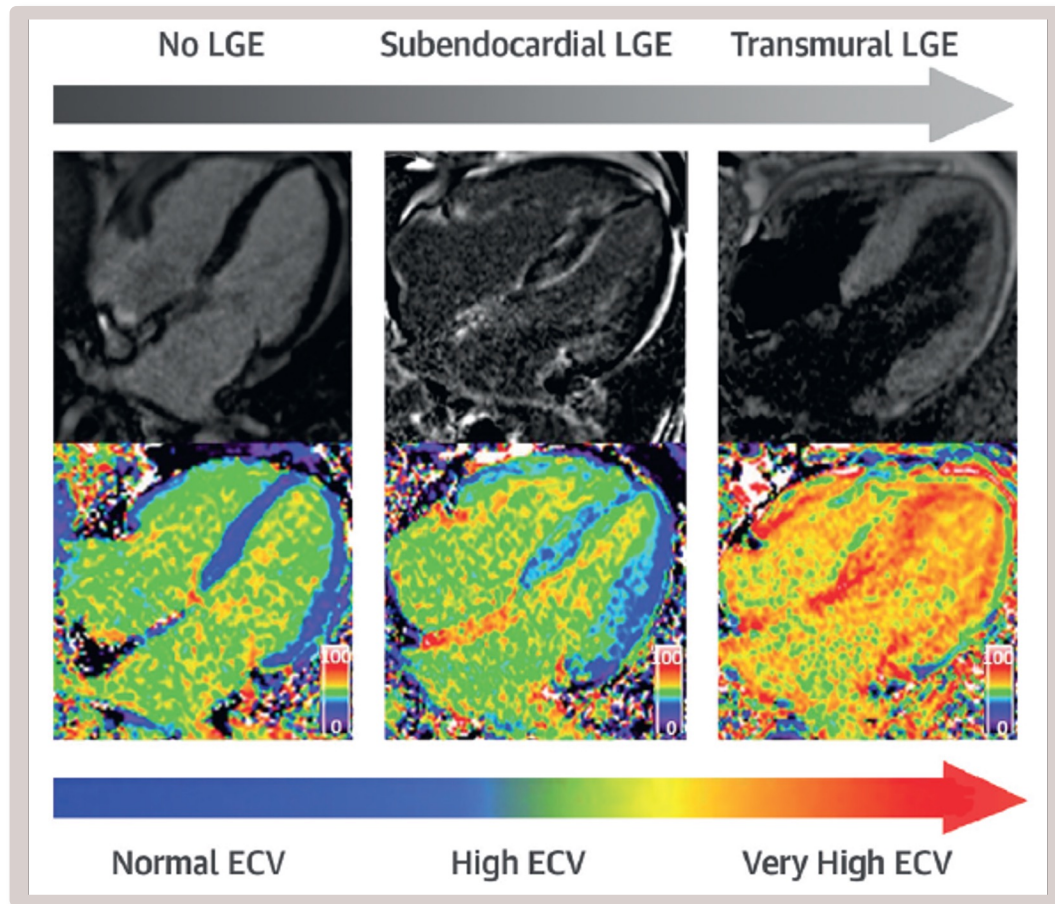
Clinical value but NOT a sensitive screening test



- Biventricular wall thickening (>12 mm) with granular, speckling appearance of the myocardium
 - Thickening of valves, interatrial septum, and papillary muscles
 - Pericardial effusion
 - Left atrial enlargement

MRI

Gadolinium enhancement and extracellular volume expansion Valuable Confirmatory evidence in selected situations



- Extracellular volume expansion
- Diffuse atrial and LV late gadolinium enhancement
- Prolonged T1 times

Poll Question

64 Male Canadian, Black born in Caribbean

PMH: Referred for progressive SOBE
No cardiac risk factors

Echo: LVEF 50%
Severe LVH with septum 1.6 cm
Mild global hypo-kinesis
grade diastolic 3 dysfunction

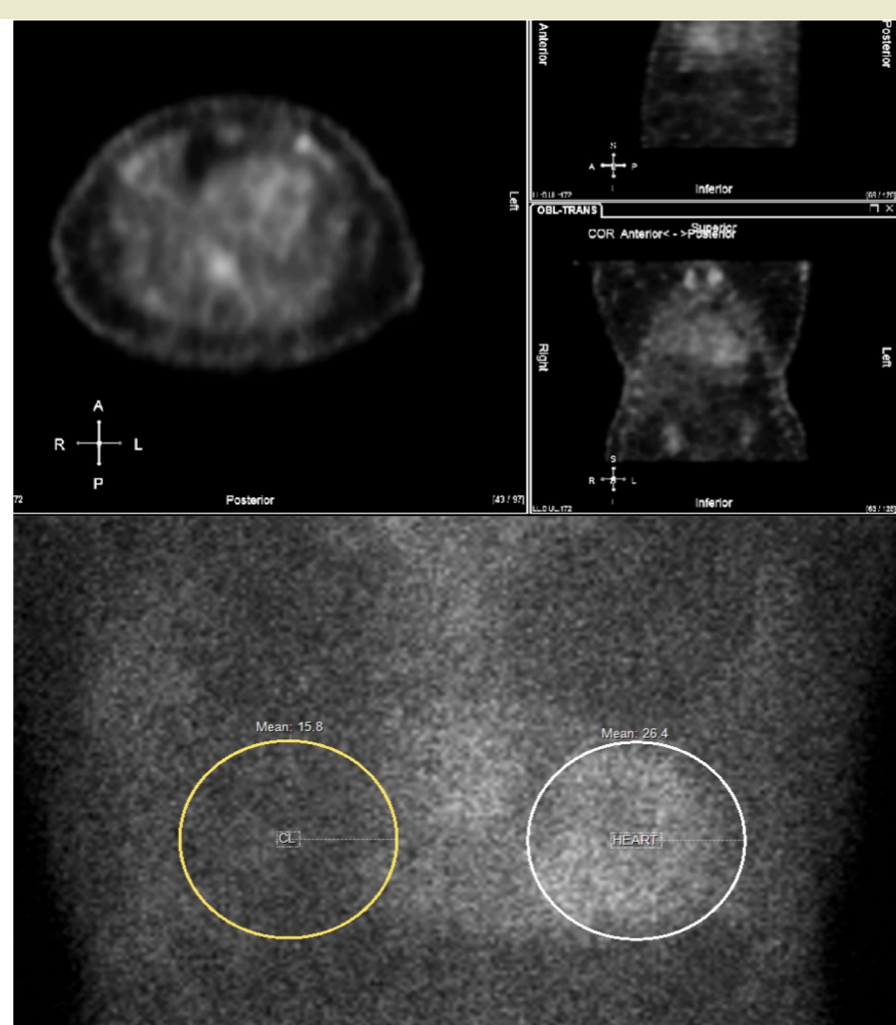
Treatment Perindopril 8 mg
Atorvastatin 40 mg
Lasix 40 mg po od
Spironolactone

Feels better on treatment with CCS 2 dyspnea
A Cardiologist appointment in 4 weeks

What would you do next?

1. MRI
2. Cardiac Amyloid Scan
3. Genetic testing for Hattr
4. Immunoelectrophoresis of serum and
urine with Light chain assay
5. Nothing for now

Case



Investigations:

PYP Scan Visual grade 3, strongly suggestive of ATTR amyloid
Serum/Urine IEP, IF, LC: Negative
Genetic testing: negative

Cardiac investigation

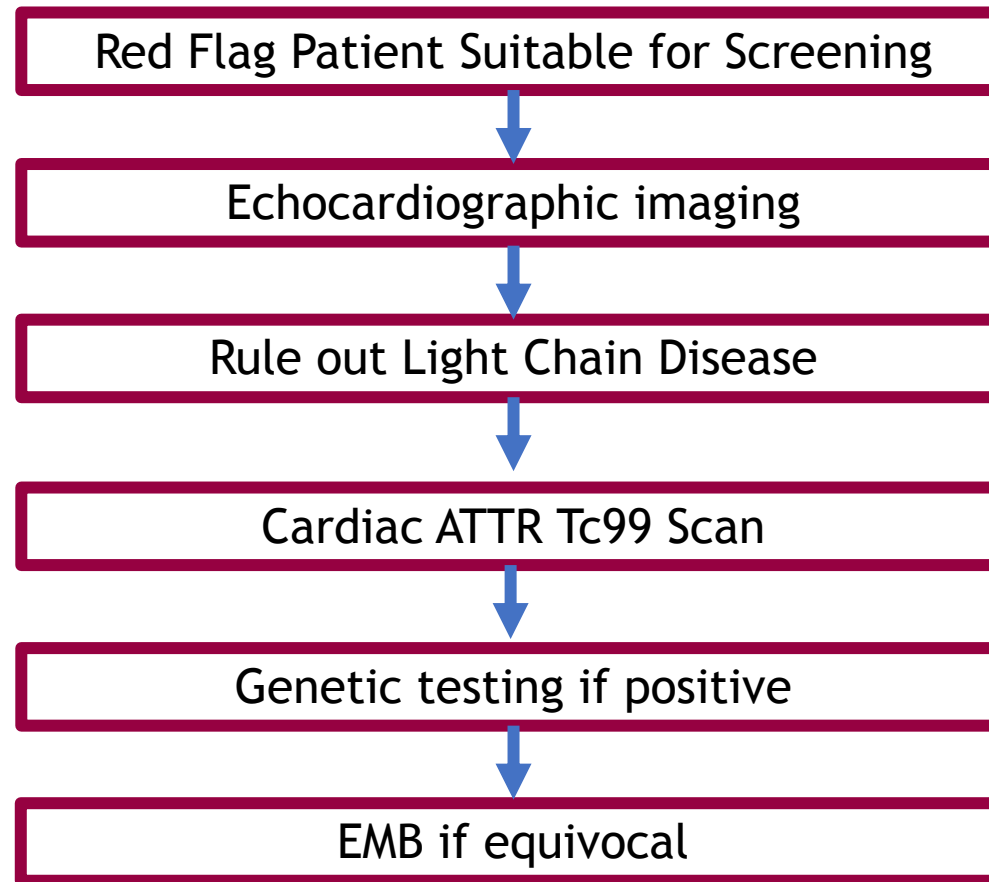
EMB biopsies 6/6 strongly positive for ATTR amyloid

Therapy

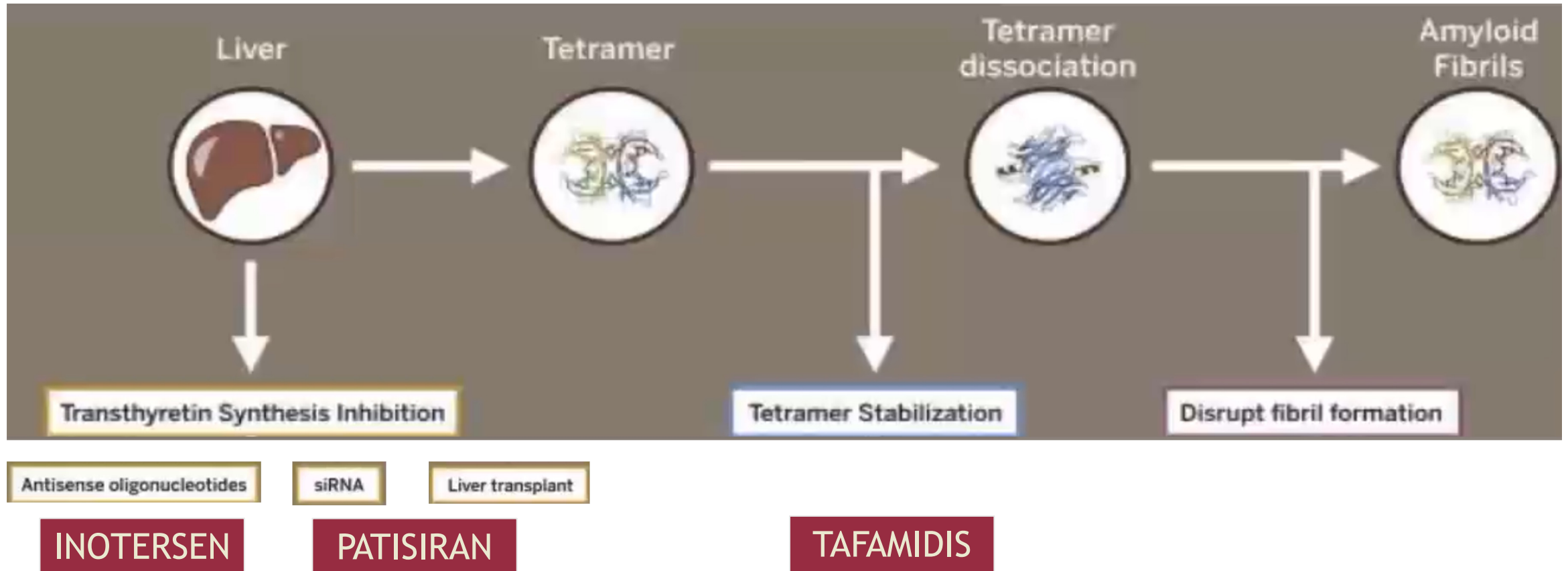
EAP approval for tafamidis

Canadian Cardiovascular Society Guidelines

Diagnostic Algorithm



Screening is the Gateway to Therapy and Improved Prognosis



Prognosis Without Therapy is Poor

Median survival:

Wild Type	3.5 years
Hereditary > Wild Type	2.5 years

By Presentation

Polyneuropathy	8-10 years
Heart Failure	2.5-3.5 years

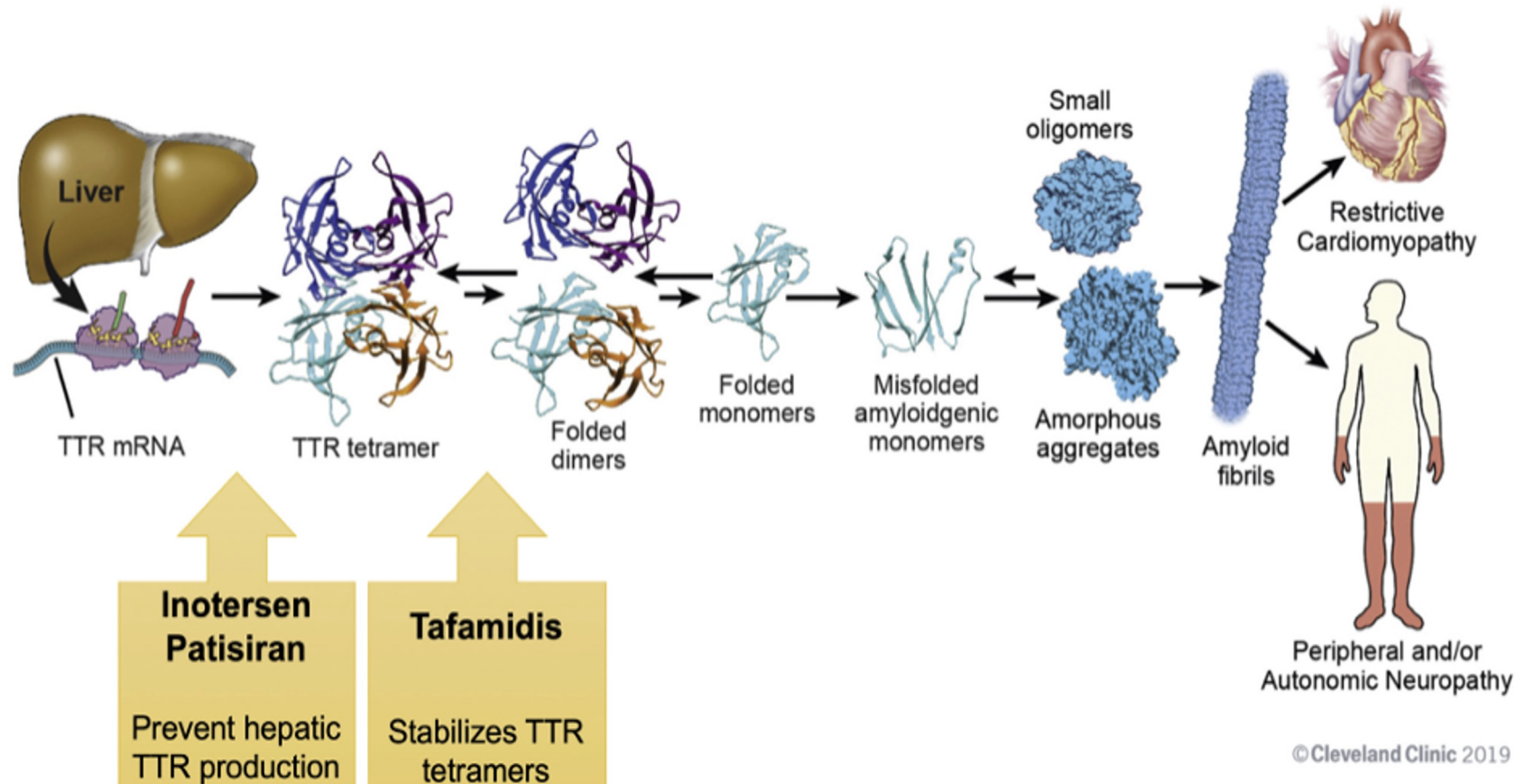
Non Predictors:

LVH
Diastology
LVMass
Atrial fibrillation

Management of Amyloidosis

AL Amyloidosis:	Chemotherapy +/- stem cell transplant
wtATTR Amyloidosis:	Tafamidis
hATTR polyneuropathy:	Inotersen or patisiran

Canadian Cardiovascular Society Guidelines



Strong recommendation

- Tafamidis

Strong recommendation

- Inotersen
- Patisiran

Key Messages

1. Amyloid is underdiagnosed but common in specific 'Red Flag' presentations
2. Primary care physicians have important role in identifying "Red flags"
3. Diagnosis: Cardiac TC99 imaging is sensitive, specific and inexpensive
4. Diagnosis is the gateway to approved provincially funded & effective therapy

Thought Question

Will you Screen for Amyloid With ATTR Tc99 Scan
Where There are 'Red Flags' such as

Heart Failure

Spinal Stenosis

Biceps Tendon Rupture

Unexplained LVH

Bilateral Carpal
Tunnel

Sensory Motor
Polyneuropathy



SUPPORT AVAILABLE 24/7



Have a patient question?
Reach out to our
Corcare Cardiologist directly

416-COR-CARE



WWW.CORCAREEDUCATION.COM



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Through your registration, you will automatically become a CQEP member. As a member, you will receive access to our web portal, where you will find:

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3. **Access to downloadable resources** such as certificates of attendance, referral forms, and fact sheets
4. **Direct connection** and mentorship from our faculty all year-round
5. **Accessible on any device:** desktop, tablet, and mobile device

THANK YOU