Epidemiology and Population Health Strategies for Cardiac Amyloidosis

Sandesh Dev, MD

Overview

- How common is it? Incidence, prevalence
  - hATTR , wtATTR, AL
- What is population health?Who should be screened? Screening strategies
  - What is the ideal risk group?
    - LVH
    - Biomarkers
  - Operationalizing ‘clinical red flag’s
    - E.g. bilateral carpal tunnel
    - Spinal stenosis
    - Orthopedic
    - ECG
    - hATTR
- Screening tools/strategies
- Tissue carpal tunnel, spinal stenosis
  - Predictive scores, mayo
  - AI, Huda, UCLA
    - imaging
    - EMR
    - ECG
- Benefits, Risks, Costs
  - HE clinical

Why population health?

- ‘However, reliance on the appropriate and timely diagnosis by individual clinicians may continue to underperform.’
- Patients identified 39 months after cardiac symptoms develop (Lane)
- Most patients identified at stage II or III

Martyn T, et al. Opportunities for Earlier Diagnosis and Treatment of Cardiac Amyloidosis. Methodist DeBakey Cardiovasc J. 2022;18(5):27-39. doi: 10.14797/mdcvj.1163

Patients

Cardiac Amyloidosis HF Hospitalizations Are Increasing with Geographic Variation

- Medicare, 2002 to 2012
- Increase in prevalence rate (8 to 17 per 100,000 person-yr)
- Increase in incidence rate (18 to 55 per 100,000 person-yr)
- Increase most in men, those >=75 years old, Black populations

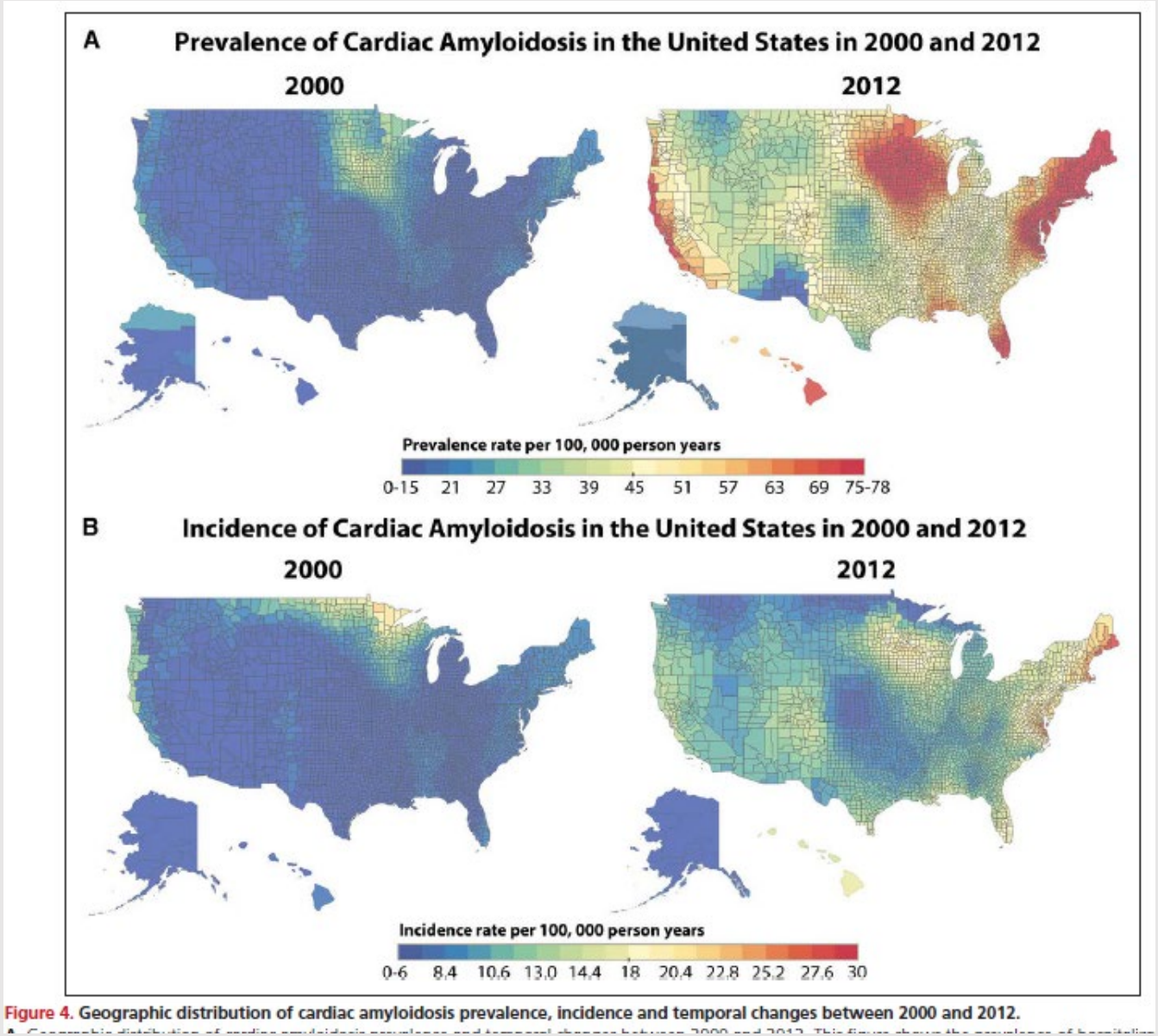


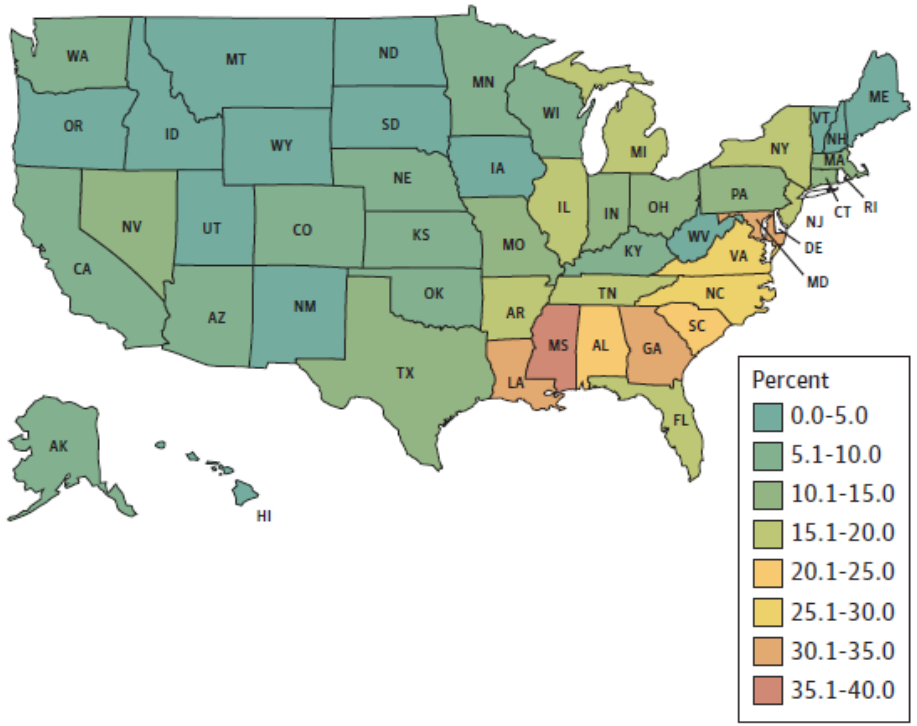
Figure 4. Geographic distribution of cardiac amyloidosis prevalence, incidence and temporal changes between 2000 and 2012.

Circ Heart Fail. 2019;12:e005407. DOI: 10.1161/CIRCHEARTFAILURE.118.005407

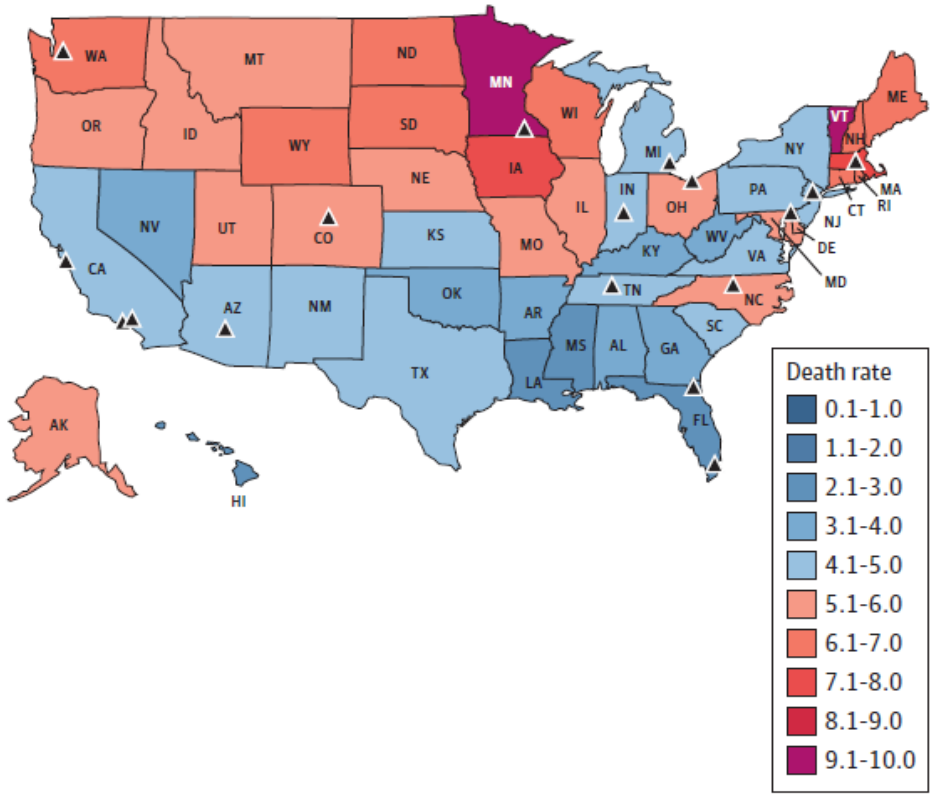
Geographic Disparities In Death Rates: Mirrors referral centers and Southern U.S. lags

Figure 2. Geographic Disparities in Reported Age-Adjusted Death Rates for Amyloidosis in the United States

A Proportion of black residents per state in 2014



B Amyloidosis death rates by state from 1979 to 2015

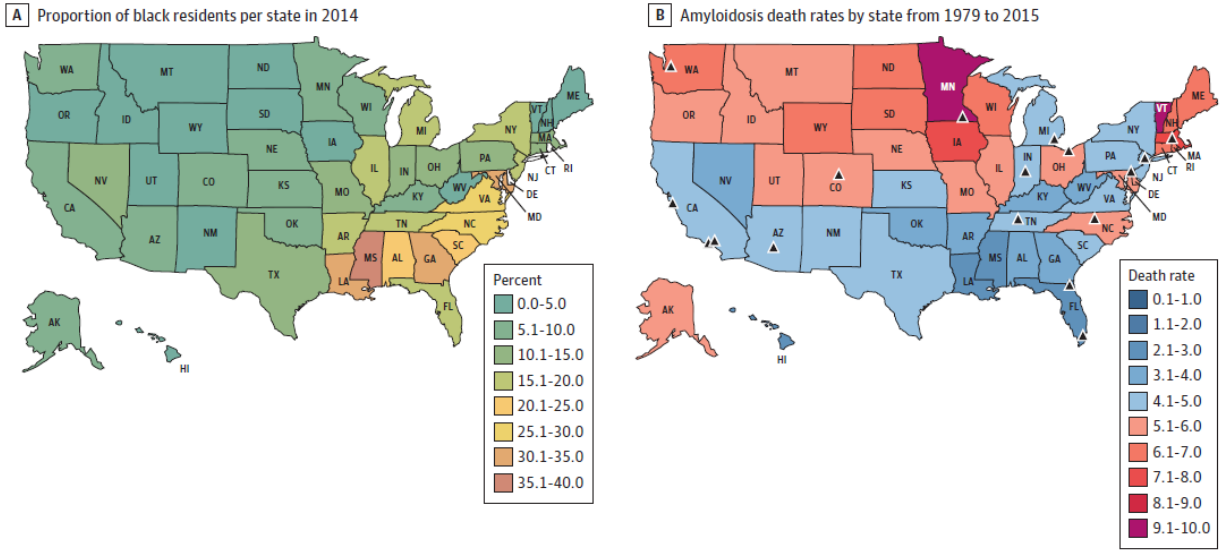


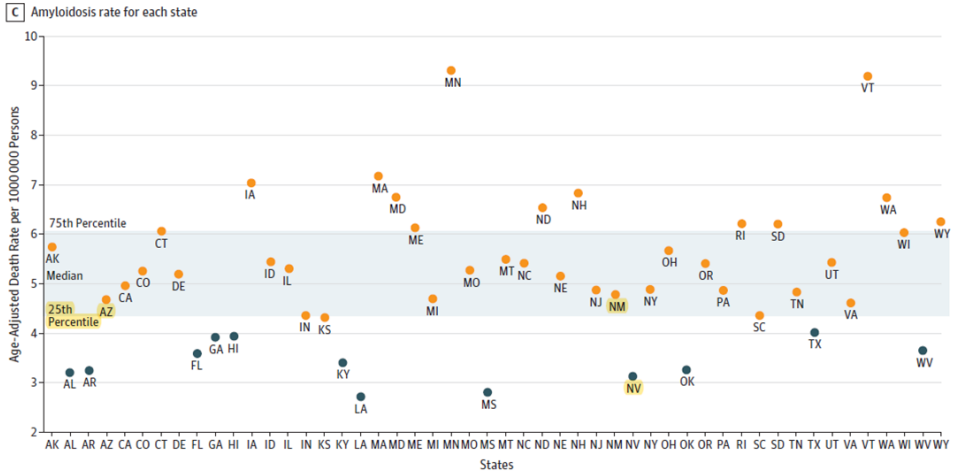
C Amyloidosis rate for each state

10.1001/jamacardio.2018.2093

Deep South and Southwest USA are underperforming

Figure 2. Geographic Disparities in Reported Age-Adjusted Death Rates for Amyloidosis in the United States





Proportion of black residents per state (A) in 2014 compared with the geographic distribution of reported age-adjusted death rates per 1 000 000 persons for amyloidosis as a contributing cause of death during 1999 to 2015 (B). Amyloidosis referral centers are marked with an arrowhead. Age-adjusted death rates per 1 000 000 persons for each state (1999-2015) is listed in alphabetical order (C). Most states, except for 1, below the 25th percentile ranking for reporting of amyloidosis mortality did not have an amyloidosis referral center (B). US territories and Washington, DC, are not included in these maps. Interactive online Tableau figures are available at https://goo.gl/RCdBV8.

Distribution of cardiac amyloidosis hospitalization: highest in Black men, women

	Incidence (95% CI)	Prevalence (95% CI)
N (No. of patients in each cohort in 2012)	4746	15 737
Overall patients (per 100 000 person-years)	16.6	55.2
Sex		
Men	18.3	69.6
Women	15.4	43.8
Race and sex		
White women	14.2	36.2
Black women	29.5	128.9
White men	17.2	62.6
Black men	35.6	174.0
Other race women	12.6	33.8
Other race men	13.1	44.5
Geography		
Midwest	16.2	54.4
Northeast	24.0	87.4
South	13.5	40.5
West	14.5	44.2

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    - E.g. bilateral carpal tunnel
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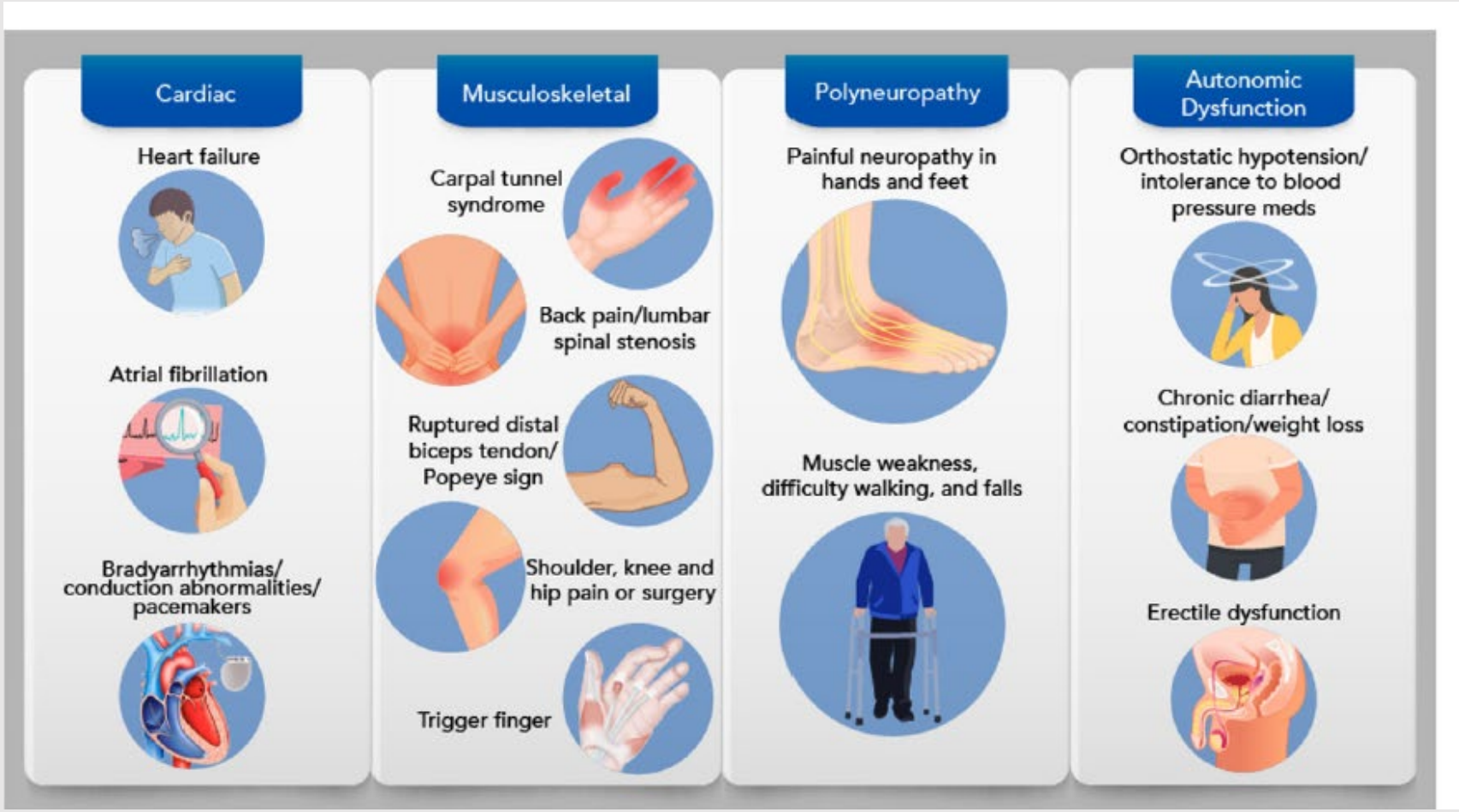
    - ECG
- Benefits, Risks, Costs
  - HF clinical
  - Genotype, phenotype

Diagnosis: Clinical Clues Across Organ Systems But Not Specific for Amyloid



Clinicians and health system need predictive tools to identify patients at risk

Nativi-Nicolau, Karam, Khella, Maurer, Heart Failure Reviews 2021; Feb 20.

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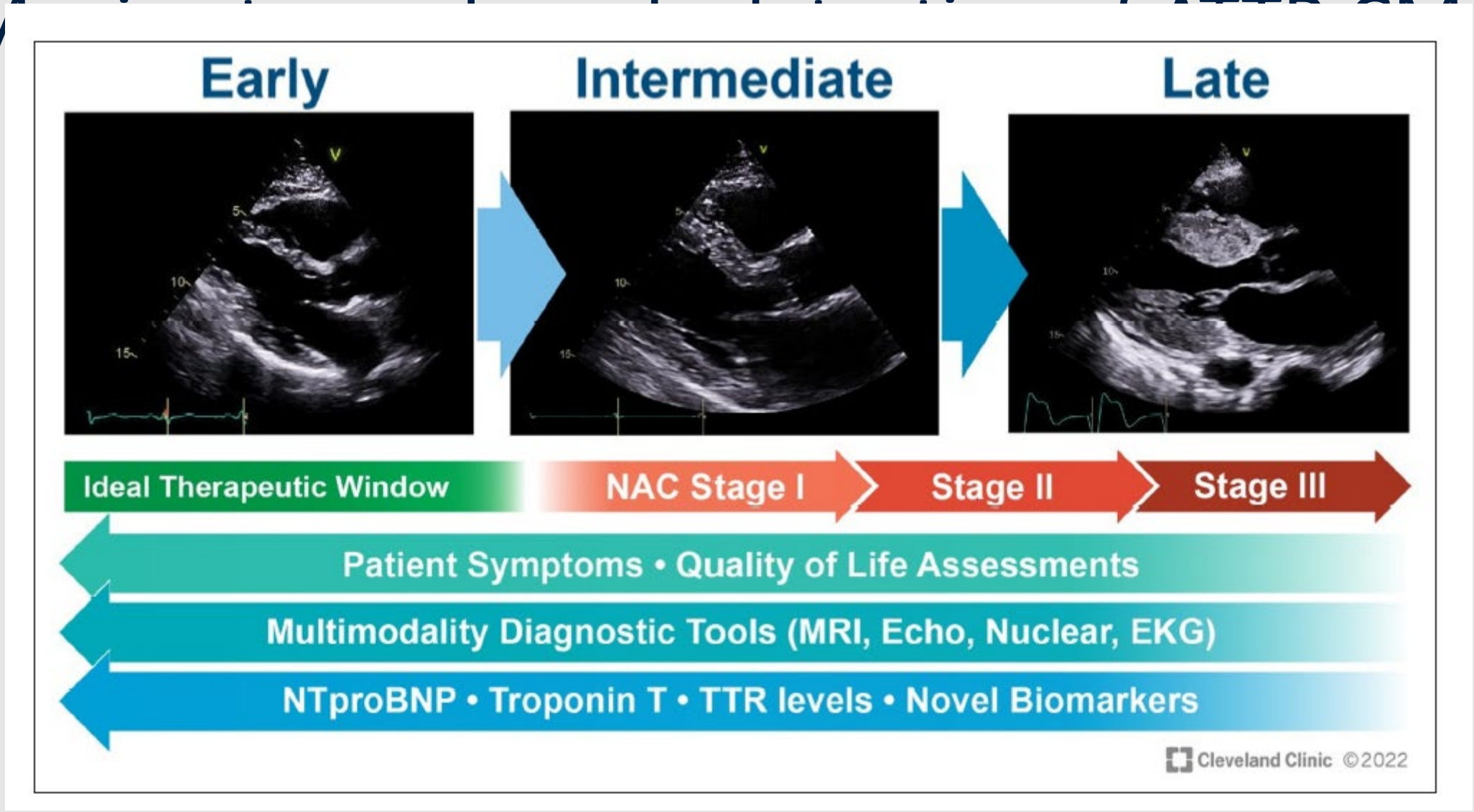

Early
Intermediate
Late
Ideal Therapeutic Window
NAC Stage I
Stage II
Stage III
Patient Symptoms • Quality of Life Assessments
Multimodality Diagnostic Tools (MRI, Echo, Nuclear, EKG)
NTproBNP • Troponin T • TTR levels • Novel Biomarkers
Cleveland Clinic ©2022

Pertinent History for Cardiac Amyloid

Orthopedic

- Carpal tunnel syndrome
- Spinal stenosis
- Biceps tendon rupture
- Trigger finger
- Rotator cuff tear
- Hip/knee/shoulder replacement

Neuropathic

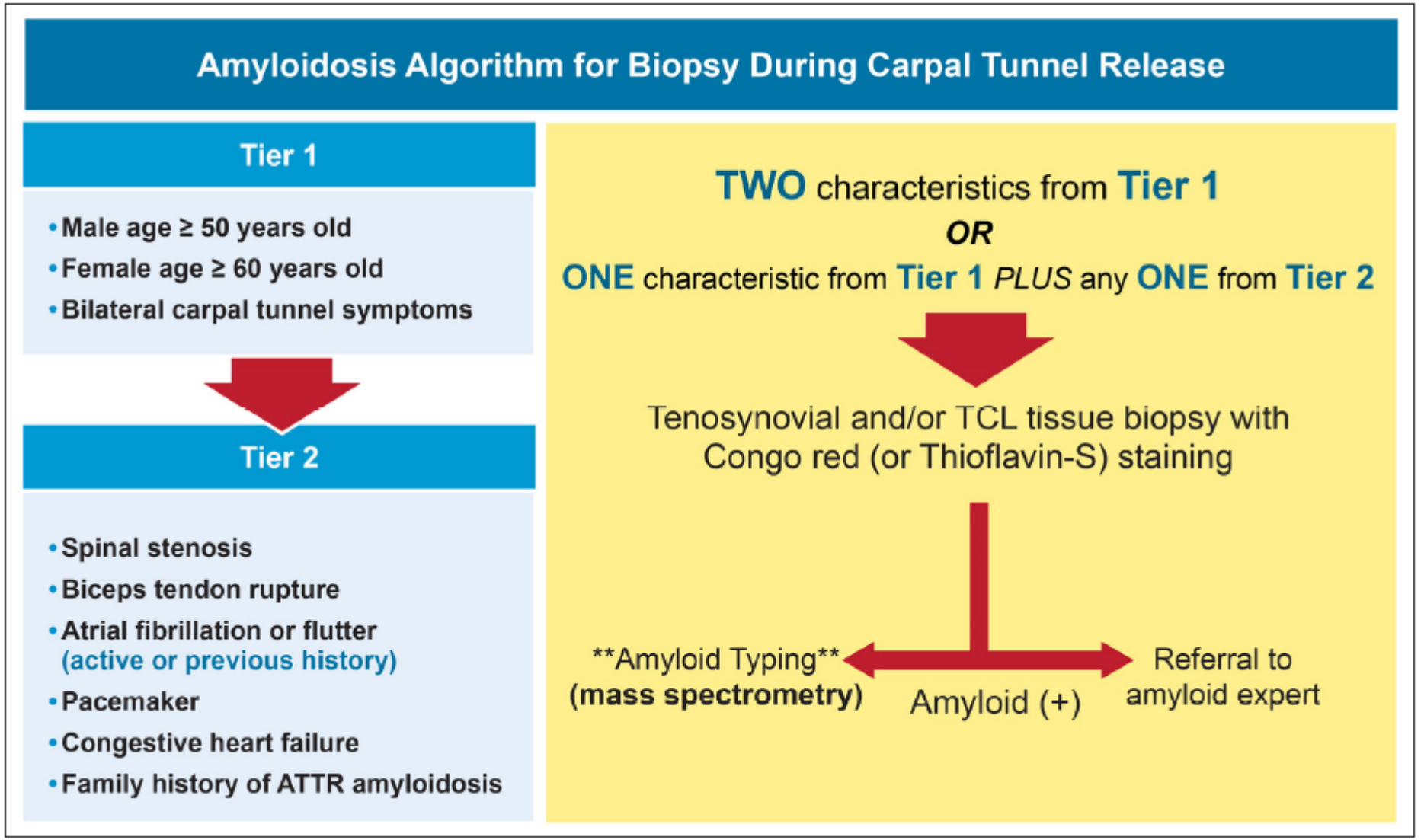
- Numbness in lower extremities
- Orthostatic symptoms
- Erectile dysfunction
- Diarrhea

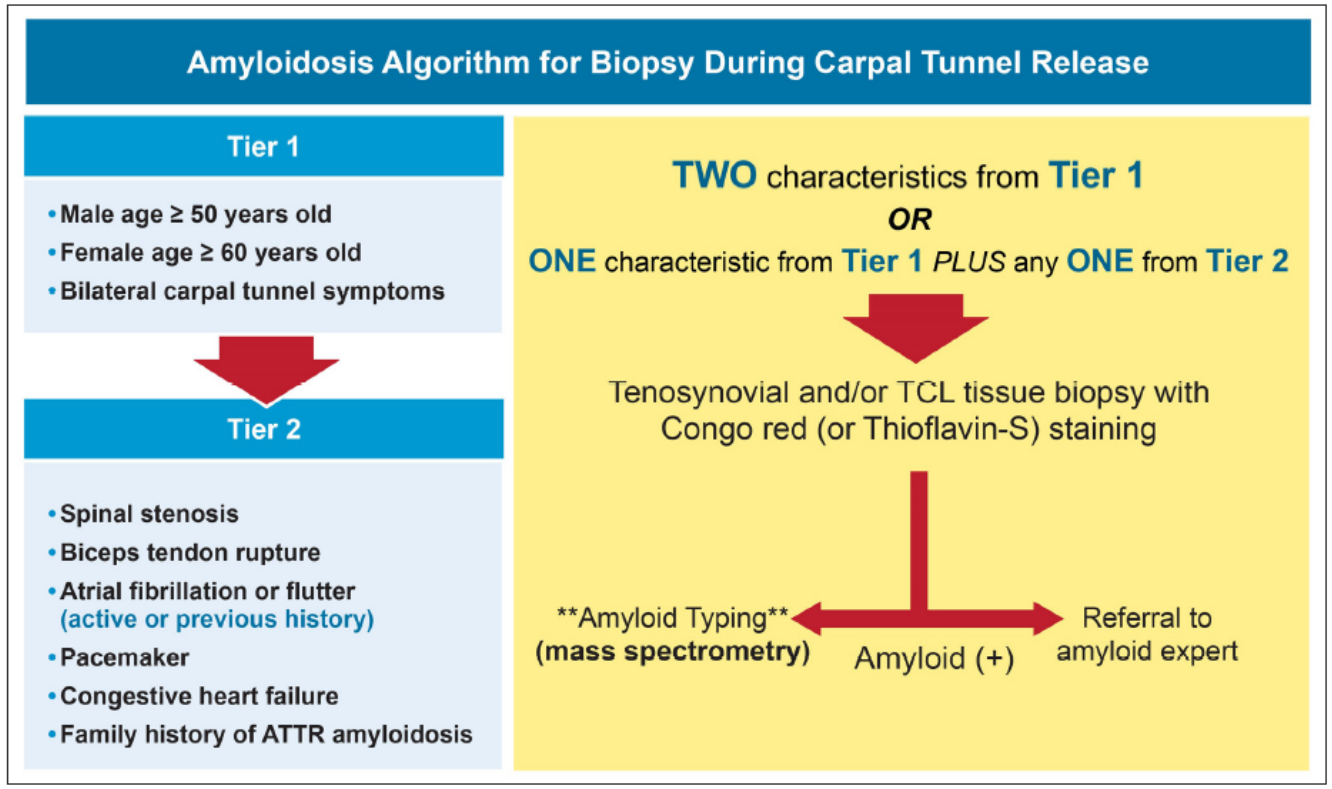
Eye

- Periorbital purpura
- Vitreous opacities/vitrectomy

Cardiac

- History of pacemaker
- History of atrial fibrillation/ ablation


Amyloidosis Algorithm for Biopsy During Carpal Tunnel Release
Tier 1
• Male age ≥ 50 years old
• Female age ≥ 60 years old
• Bilateral carpal tunnel symptoms
Tier 2
• Spinal stenosis
• Biceps tendon rupture
• Atrial fibrillation or flutter (active or previous history)
• Pacemaker
• Congestive heart failure
• Family history of ATTR amyloidosis
TWO characteristics from Tier 1
OR
ONE characteristic from Tier 1 PLUS any ONE from Tier 2
Tenosynovial and/or TCL tissue biopsy with Congo red (or Thioflavin-S) staining
Amyloid Typing
(mass spectrometry)
Amyloid (+)
Referral to amyloid expert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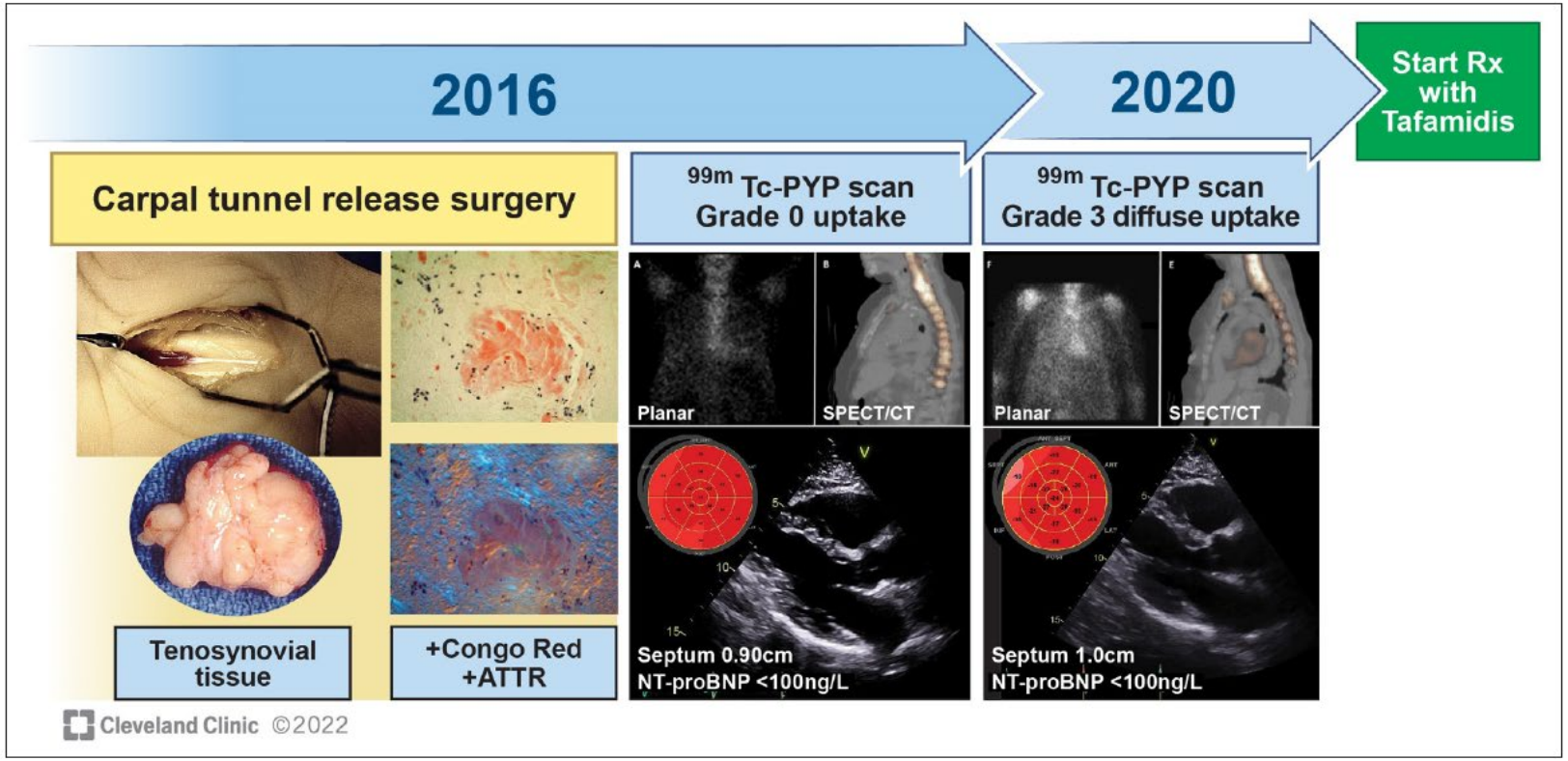

2016
2020
Start Rx with Tafamidis
Carpal tunnel release surgery
99m Tc-PYP scan Grade 0 uptake
99m Tc-PYP scan Grade 3 diffuse uptake
Planar
SPECT/CT
Planar
SPECT/CT
Tenosynovial tissue
+Congo Red +ATTR
Septum 0.90cm
NT-proBNP <100ng/L
Septum 1.0cm
NT-proBNP <100ng/L
Cleveland Clinic ©2022

Orthopedic manfestations

- Tufts
- 13% SS,

High risk populations TAVR

- 11.8%
- Clinical risk score:

High risk populations TAVR

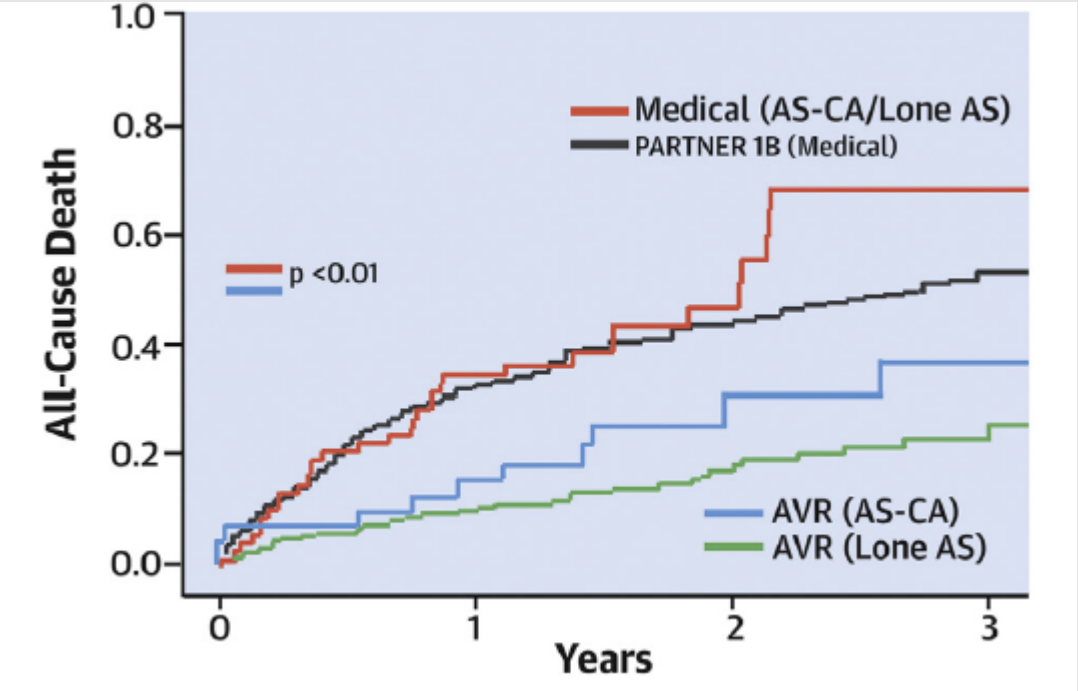
- 11.8%
- Clinical risk score:
- Population: 407 patients with AS patients, at 3 sites, referred for TAVR evaluation, underwent DPD scintigraphy
- Outcome: death, predictors of CA

1. Nitsche C, Scully PR, Patel KP, et al. Prevalence and Outcomes of Concomitant Aortic Stenosis and Cardiac Amyloidosis. *Journal of the American College of Cardiology*. 2021;77(2):128-139.

High risk populations TAVR

- Results:
- mean age 83, 50% men
- 1 in 8 patients had AS-CA
  - +DPD in 11.8% (n=48) (2/3 were grade 2/3) all ATTR except 1 AL
- Intervention: 84% underwent TAVR/SVR and 16% medical management (odds of receiving TAVR =2 for lone AS vs. AS-CA)
- Outcomes:
  - 1-year Mortality (irrespective of treatment): 24.5% vs 13.9% (p=0.05) AS-CA vs lone AS
  - For those undergoing TAVR, no diff. in survival from lone AS

Outcomes after AVR vs. Medical Therapy

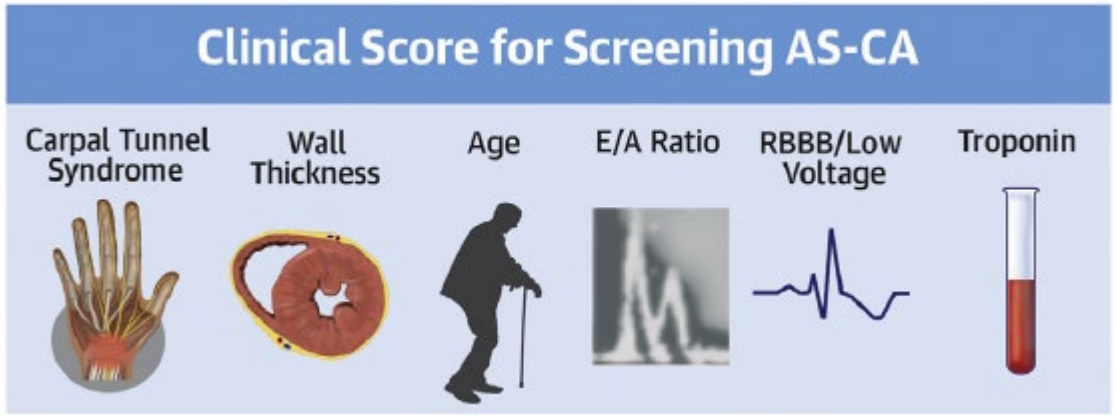


AS-CA patients have distinct profile compared to lone AS patients

- Older age, more men, history of carpal tunnel syndrome, lower prevalence of PAD/CAD, functional status (6 min walk), higher NTproBNP and hsTnT, lower voltage, voltage/mass ratio, low-flow/low-gradient AS more prevalent, worse remodeling (LV mass index), impaired contractility (SV)

Score >=2 Specificity 52% and Sensitivity 94%

RAISE Score of >=2 Suggested to Prompt CA screening in TAVR Referrals



Parameter	Points
CTS	3
RBBB	2
Age ≥85 years	1
Hs-TnT >20 ng/l	1
IVS ≥18 mm	1
If in SR*: E/A ratio >1.4	1
If no BBB or PM: Sokolow index <1.9 mV	1

Remodeling
Age
Injury
Systemic
Electrical

Score >=2 Specificity 52% and Sensitivity 94%

RAISE Score of 2 As Screening Tool in TAVR Referrals

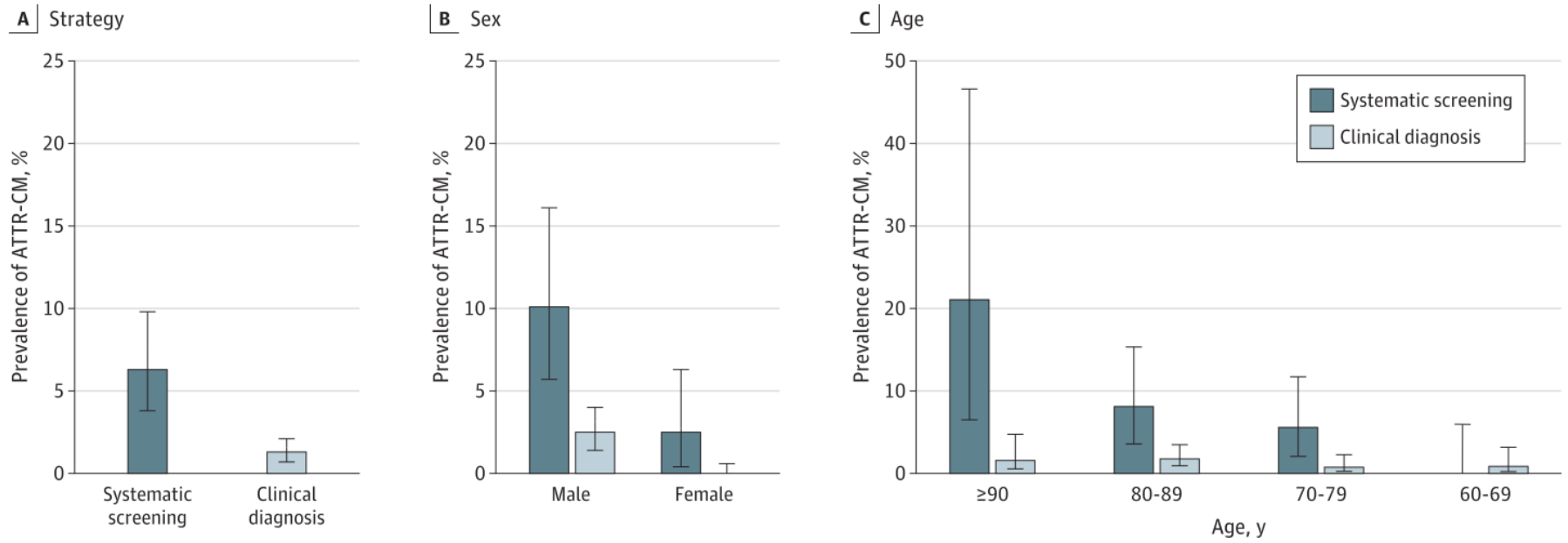
Score	Specificity	Sensitivity
≥6 points	100%	14.9%
≥5 points	98.9%	23.4%
≥4 points	95.0%	42.6%
≥3 points	83.6%	72.3%
≥2 points	52.1%	93.6%
≥1 point	16.7%	97.9%

High risk populations – HF, TAVR

- 13% of HFpEF, LVH
- Sharma

Systematic Screening for Amyloidosis in HFpEF Increases Disease Detection

Figure 2. Prevalence of Transthyretin Amyloid Cardiomyopathy (ATTR-CM) in Heart Failure With Preserved Ejection Fraction



Error bars indicate 95% CIs.

Black patients higher risk

- **Coniglio AC, Segar MW, Loungani RS,** et al. Transthyretin
- V142I Genetic Variant and Cardiac Remodeling, Injury, and
- Heart Failure Risk in Black Adults. JACC Heart Fail. 2022
- Feb;10(2):129-138. doi: 10.1016/j.jchf.2021.09.006

Spinal Stenosis Surgery: ATTR common in Ligamentum Flavum but ATTR CA is rare

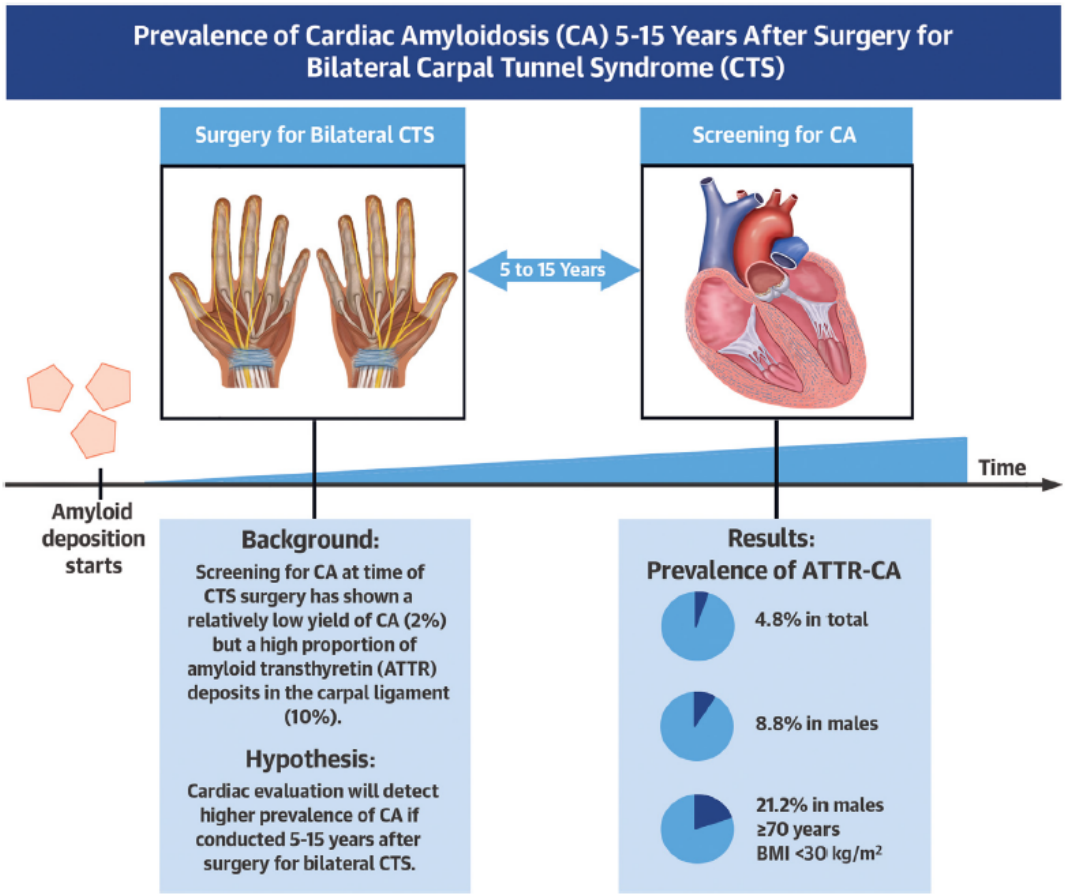
- 13% (43/324) in US study, any site SS, had ATTR in ligamentum flavum (mass spec)
  - Of 43, 4 had ATTR (11%) and 78% were equivocal scans (grade 1 PYP), 11% grade
  - Age > 65, 21% ATTR
  - Patients with ATTR were older, had CTS, and non-cervical SS

- 37% (93/250) in Swedish study, lumbar SS, had ATTR (immunohistochemistry) and no ATTR CA (MRI)

ATTR DEPOSITION MAY BE EARLY SYSTEMIC DISEASE, LONG TERM DEVELOPMENT OF ATTR CA UNKNOWN

Godara A, et al. Amyloid. 2021;28(4):226-233. Eldhagen P, et al, Journal of Internal Medicine. 2021;289(6):895-905.

CENTRAL ILLUSTRATION Overview of Study Background, Hypothesis, and Results



Westin O, et al. J Am Coll Cardiol. 2022;80(10):967-977.

Screening for cardiac amyloidosis (CA) was performed 5 to 15 years after surgery for bilateral carpal tunnel syndrome (CTS). The prevalence of early stage wild-type transthyretin amyloidosis (ATTR) was 4.8% in total and 8.8% in males. Subgroup analysis of nonobese men aged ≥70 years showed a 21.2% prevalence, suggesting potential for systematic screening. BMI = body mass index.

Prior Bilateral Carpal Tunnel Surgery Is a High-Yield Target for ATTR CA screening

- What is prevalence of undiagnosed, early-stage CA 5-15 yrs after bilateral CTS?
  - Denmark, 250 subjects, M:F 1:1 by design, age 60-85 yrs, prior CTS, invited to undergo complete CA screening including PYP, excluding: known amyloidosis, secondary CTS [wrist fracture, ganglion, pregnancy, childbirth within 1 year of CTS]
  - Results: 36% participated, median age 70 yrs, 50% female, median time between CTS surgery and baseline 9.0 yrs
  - CA in 4.8% (n=12), all wtATTR, 1 female
    - One patient with suspected AL was PYP negative but biopsy positive for ATTR
  - Subgroups:
    - Men: 8.8%
    - Men >=70 yrs, BMI <30 kg/m2: 21.2%
    - Most patients had lowest disease severity score

Prior Bilateral Carpal Tunnel Surgery Is a High-Yield Target for ATTR CA screening

- Limitations: real world population, prevalence lower as more women have CTS
- Only 1/3 patients agreed with CA screening
- Subgroup analysis was not prespecified, must be interpreted with caution

Most patients had early stage ATTR CA

False negatives can occur with PYP scintigraphy in very mild disease (i.e., screening population), hence multimodal approach

Maximizing Diagnostic Yield in Late Screening of CTS Surgical Patients

TABLE 3 Prevalence of Cardiac Amyloidosis in Different Subgroups

	N	Cardiac Amyloidosis, n	Diagnostic Yield, % Mean (95% CI)
Males	125	11	8.8 (4.5-15.2)
Age ≥70 y	74	11	14.9 (7.7-25.0)
Age ≥70 y and BMI <30 kg/m^2	52	11	21.2 (11.1-34.7)
Age ≥70 y and BMI <30 kg/m^2 No occupational risk factors for CTS	35	9	25.7 (12.5-43.3)
Females	125	1	0.8 (0.02-4.4)
Age ≥70 y	54	1	1.9 (0.04-9.9)
Age ≥70 y and BMI <30 kg/m^2	40	1	2.5 (0.06-13.1)
Age ≥70 y and BMI <30 kg/m^2 No occupational risk factors for CTS	38	1	2.6 (0.07-13.8)

BMI = body mass index; CTS = carpal tunnel syndrome.

Higher Age, male sex, normal BMI are highly predictive of CA in this population

Progression from Tenosynovial Amyloid to CA?

- Prevalence of ATTR wt in men resembles tenosynovial deposits in carpal ligament in men at time of CTS surgery (8.8% vs 9.8%)
- Requires prospective study
- If true, need trials of therapy at time of amyloid diagnosis in the wrist would prevent development of CA

Autopsy data shows higher likelihood of wtATTR in HFpEF patients vs. non-HF controls

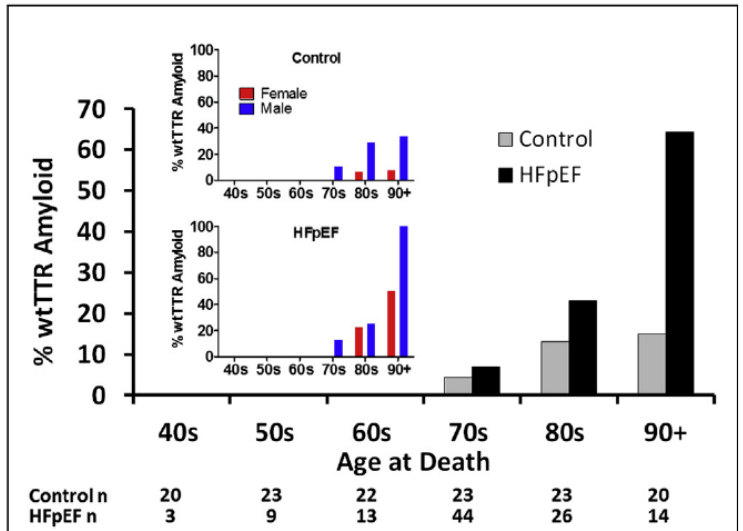


Figure 1 **Prevalence of LV wtTTR Amyloid in Control (n = 131) and HFpEF (n = 109) Patients by Age**

Inset shows the prevalence of left ventricular (LV) wild-type transthyretin (wtTTR) amyloid in men and women by age in control **(top inset)** and heart failure with preserved ejection fraction (HFpEF) **(bottom inset)** groups.

5% of HFpEF patients had moderate-severe interstital wtATTR deposition whereas 12% had mild or intramural coronary deposition

Mohammed et al, *JACC Heart Fail.* 2014;2:113–122. doi: 10.1016/j.jchf.2013.11.004

Epidemiology: Cardiac Amyloid Increasingly Recognized Condition due to New Drugs and Imaging

- 13% of hospitalized heart failure (HF) with preserved ejection fraction patients
- 15% of patients > age 80 undergoing transcatheter aortic valve replacement

However, disease burden in entire U.S. or VA population is not known

Gonzalez-Lopez E, et al Eur Heart J 2015; Hahn V et al JACC Heart Failure 2020; Castano A et al Eur Heart J 2017

Epidemiology – increasingly recognized condition

- ATTR-CM common in older HFpEF patients
- 13% of hospitalized HFpEF pts > age 60 with LVH > 1.2 cm
- 15% of patients > age 80 undergoing transcatheter aortic valve replacement

Gonzalez-Lopez E, et al Eur Heart J 2015; Hahn V et al JACC Heart Failure 2020; Castano A et al Eur Heart J 2017

Diagnosis and Recognition: Past and Current Trends

- Historically considered rare
  - Frequently underrecognized
  - Need for biopsy
  - Attribution to aging, hypertension, hypertrophic cardiomyopathy, HFpEF, lack of approved treatment
- Current, ‘no longer a zebra’:
  - Noninvasive detection available without need for biopsy
  - Studies indicating significant proportion of HF patients have transthyretin amyloid cardiomyopathy (ATTR-CM)
  - Therapies approved for ATTR-CM

Circulation. 2020;142:e7–e22. DOI: 10.1161/CIR.0000000000000792

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- Benefits
- Risks
  - Costs
  - HF clinical

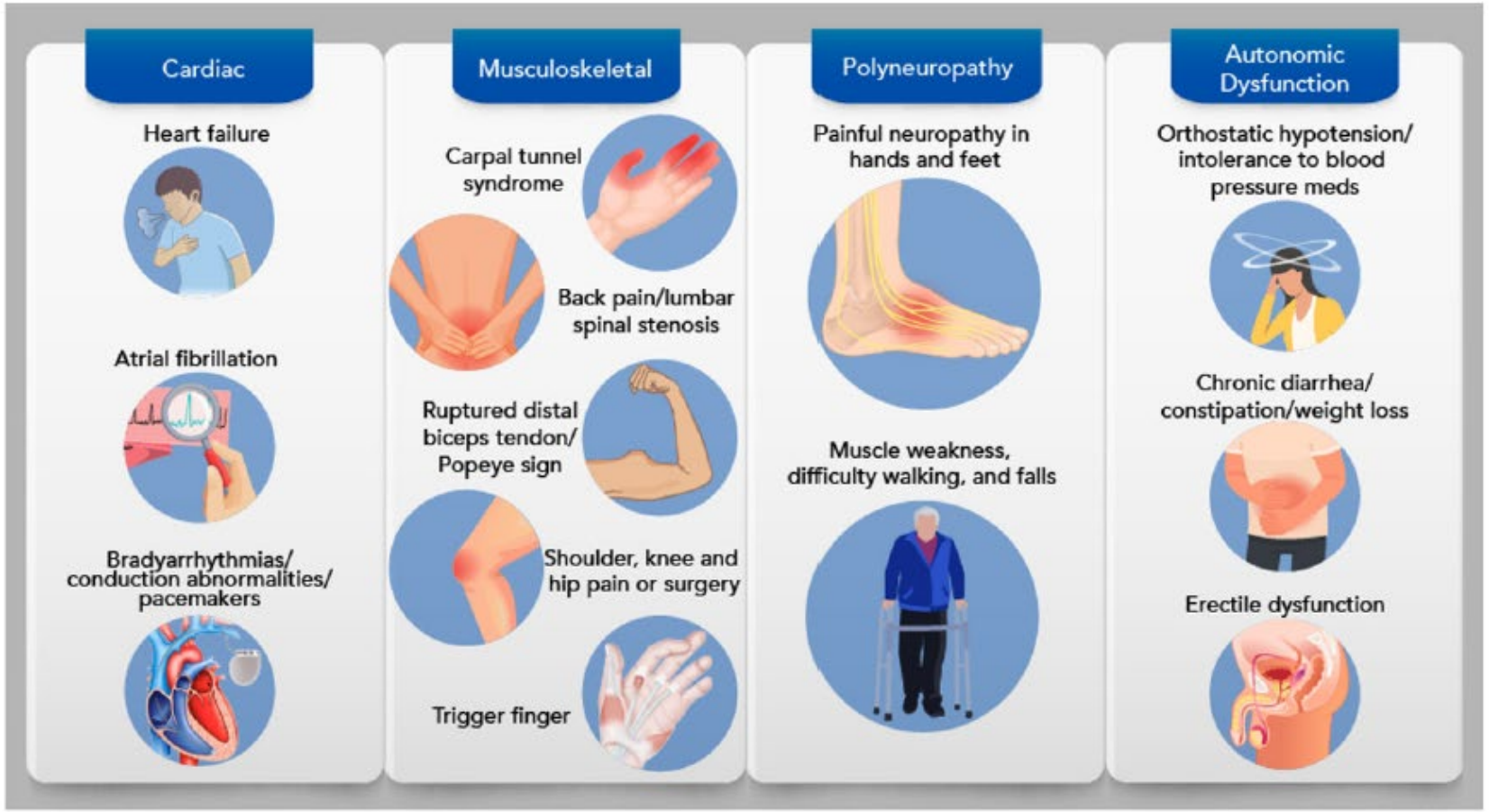
Epidemiology : wild-type TTR most common followed by hereditary (30%)

	Age at Onset, y	Sex Distribution	National/Ethnic Predominance	Cardiac Involvement	Other Organ Involvement
Val30Met (V30M) or pV50M	<30 in early onset >60 in late onset	Slight F>M	Portuguese, Swedish, and Japanese	Conduction disease more common than heart failure	Peripheral neuropathy Autonomic neuropathy
Val122Ile (V122I) or pV142I	60–65 (older age at onset in women)	Slight M>F	Afro-American Afro-Caribbean	Common	Peripheral neuropathy likely Bilateral carpal tunnel syndrome
Thr60Ala (T60A) or pT80A	>60	Unknown	Irish	Common	Autonomic and peripheral neuropathy
TTRwt	70–75	80%–90% male	None	Common	Bilateral carpal tunnel syndrome, spinal stenosis, biceps tendon rupture

Val122Ile is the most important mutation in United States, in 3-5 % of African-Americans

Circulation. 2020;142:e7–e22. DOI: 10.1161/CIR.0000000000000792

Diagnosis: Clinical Clues Across Organ Systems



Nativi-Nicolau, Karam, Khella, Maurer. Heart Failure Reviews, 2021;Feb 20.

Frailty common in wild-type TTR

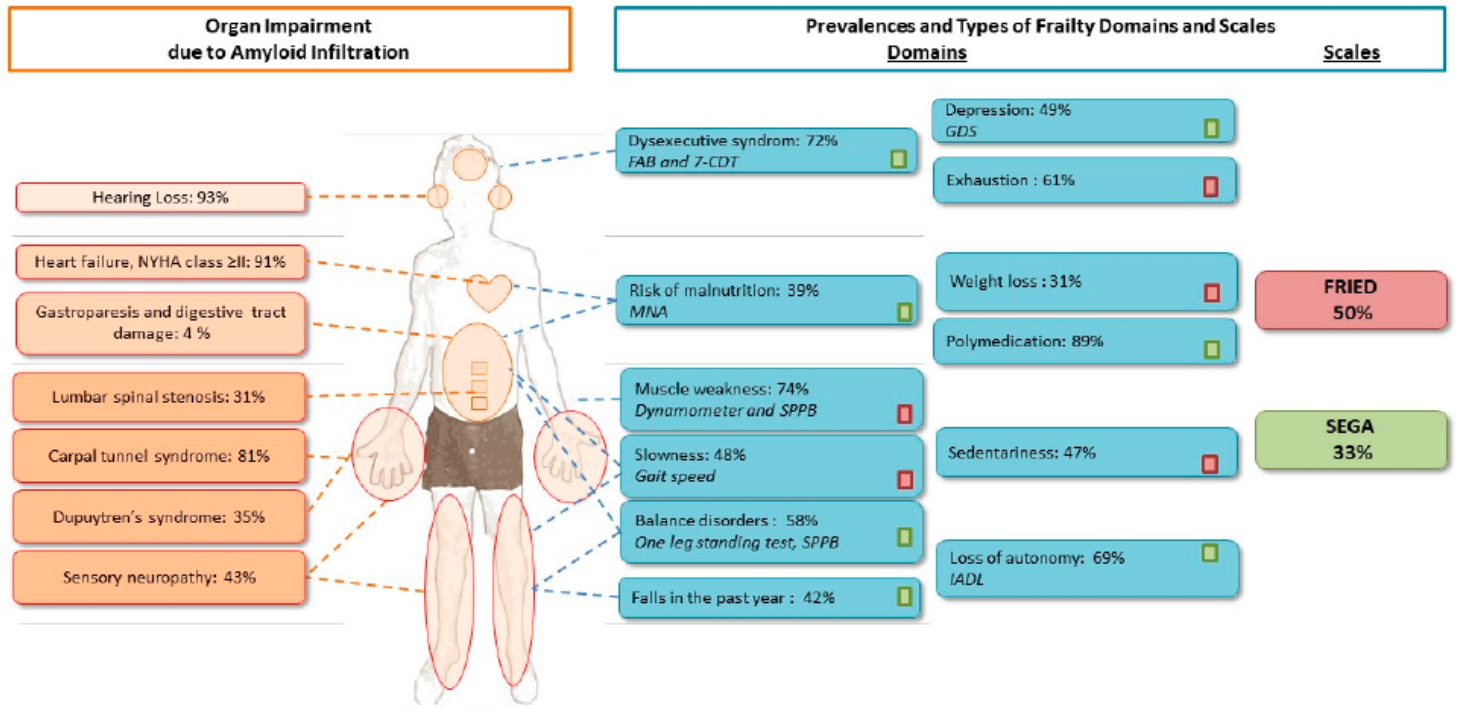
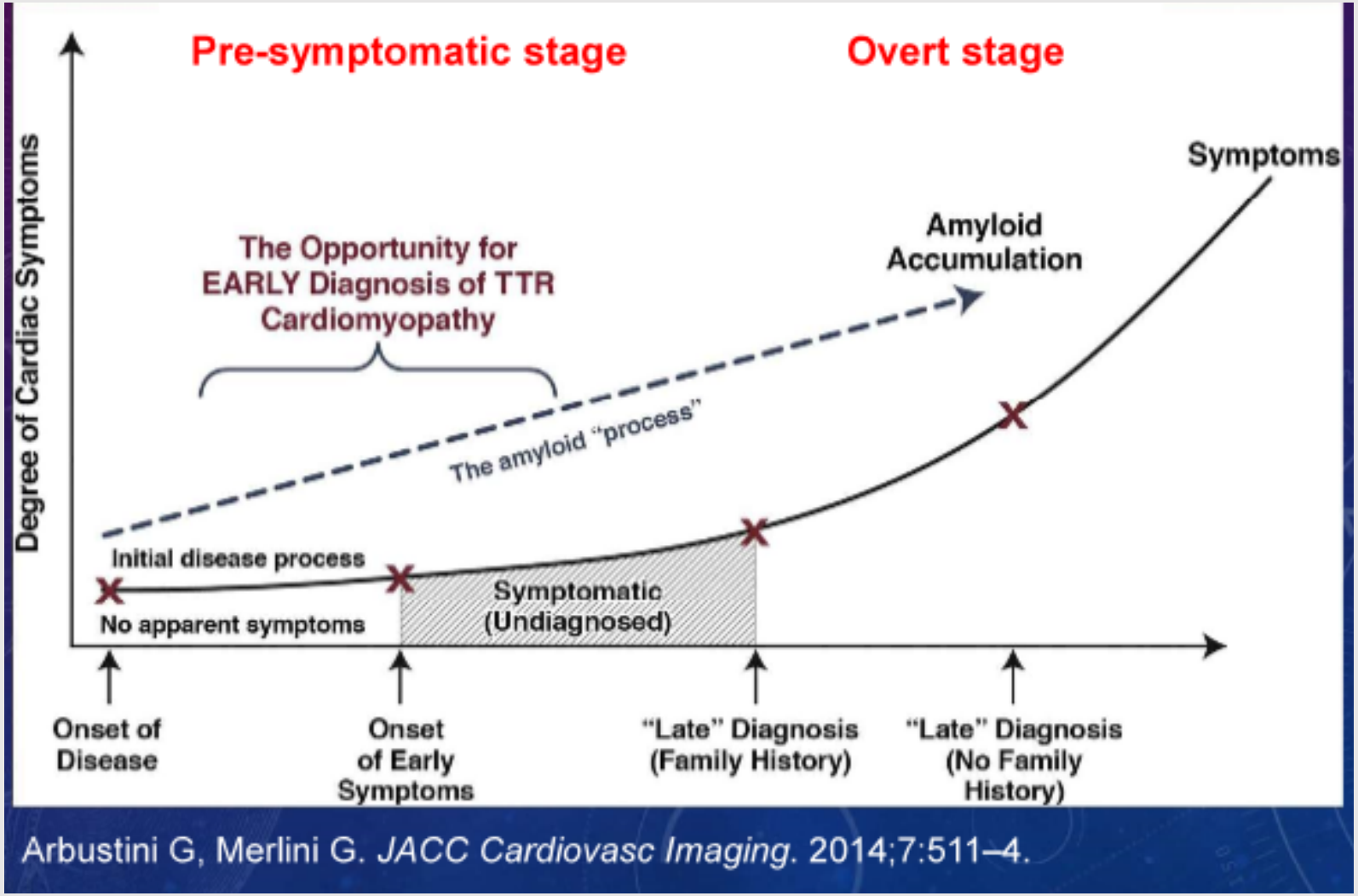


Figure 2. Frequency of frailty, and the relationships between frailty and organ impairment in patients with A-TTRwt-CA. The prevalence of frailty among patients with ATTRwt-CA can be explained by the amyloid fibril infiltration of various organs and tissues, particularly the heart, integumentary system, and nerves. FAB: frontal assessment battery, GDS: geriatric depression scale, IADL: instrumental activity of daily living, MNA: mini nutritional assessment, NYHA: New York heart association, SEGA: short emergency geriatric assessment SPPB: short physical performance battery, 7-CDT: 7-clock drawing test.

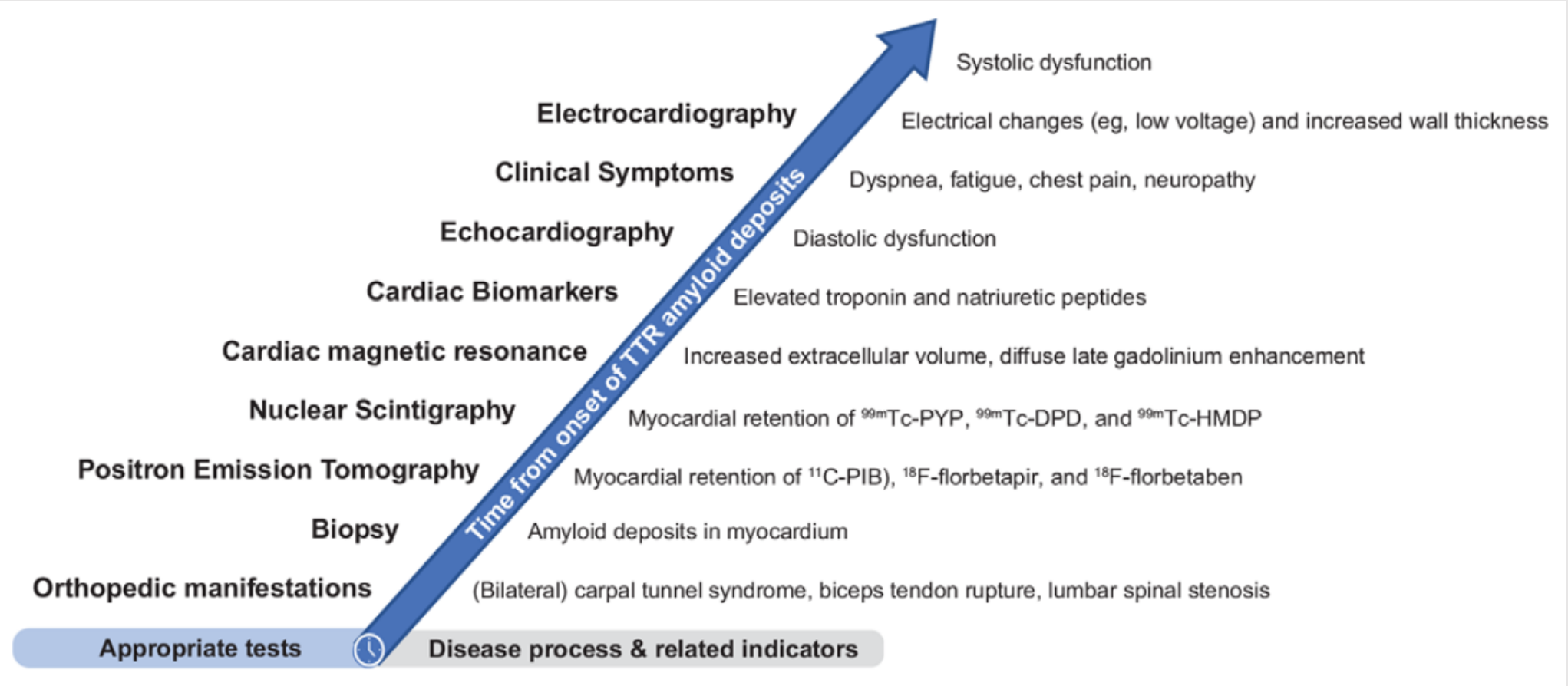
doi.org/10.3390/jcm10153415

Early diagnosis is critical in amyloid:

Red flags often predate diagnosis by years



Proposed timeline of disease process



11C-PIB indicates Pittsburgh compound B; 99mTc-DPD, 99mtechnetium-3,3-diphosphono-1,2-propanodicarboxylic acid; 99mTc-HMDP, hydroxymethylene diphosphonate; 99mTc-PYP, technetium pyrophosphate; ATTR-CM, transthyretin amyloidosis with predominant cardiomyopathy (either wild-type or hereditary); CA, cardiac amyloidosis;ECG, electrocardiography; LVST, left ventricular septal thickness; and TTR, transthyretin.

doi: 10.1161/circheartfailure.119.006075

Frailty common in wild-type TTR and prognostic of poor outcomes

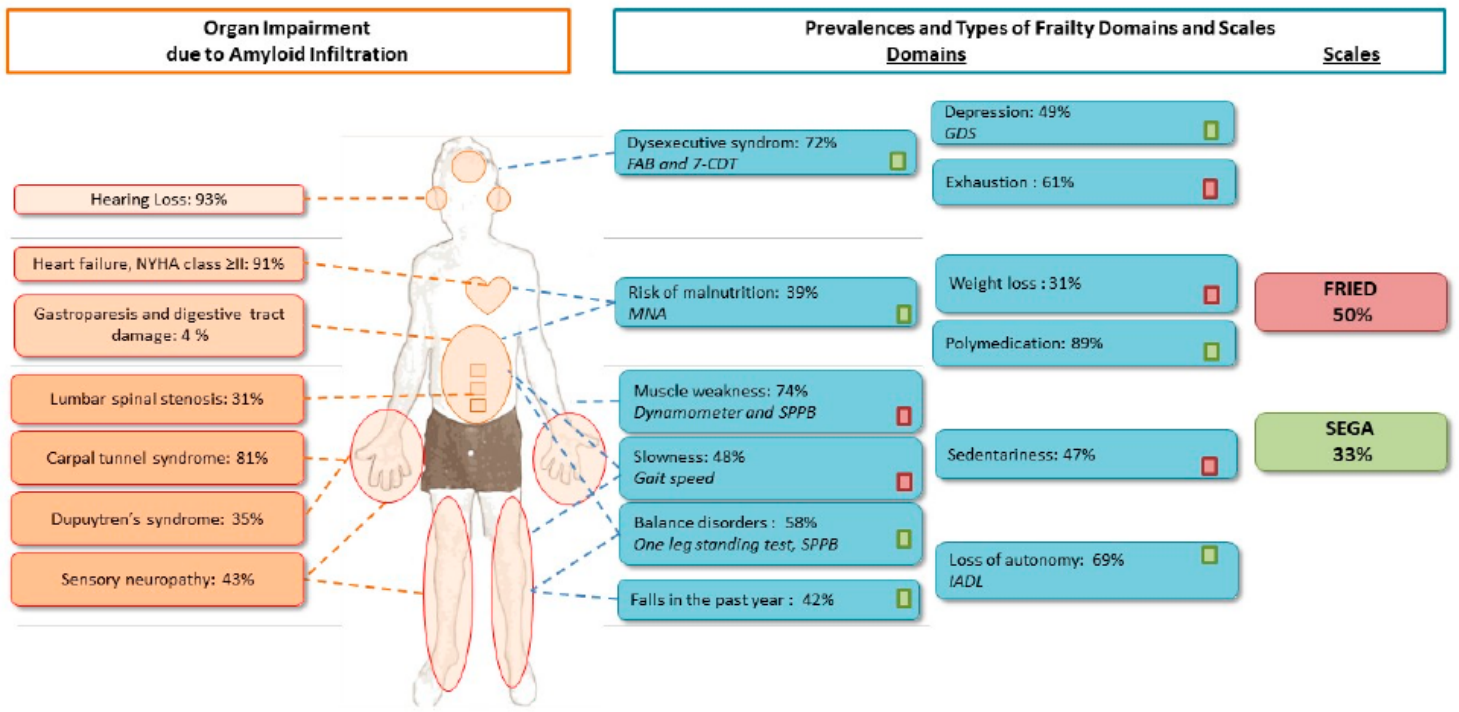
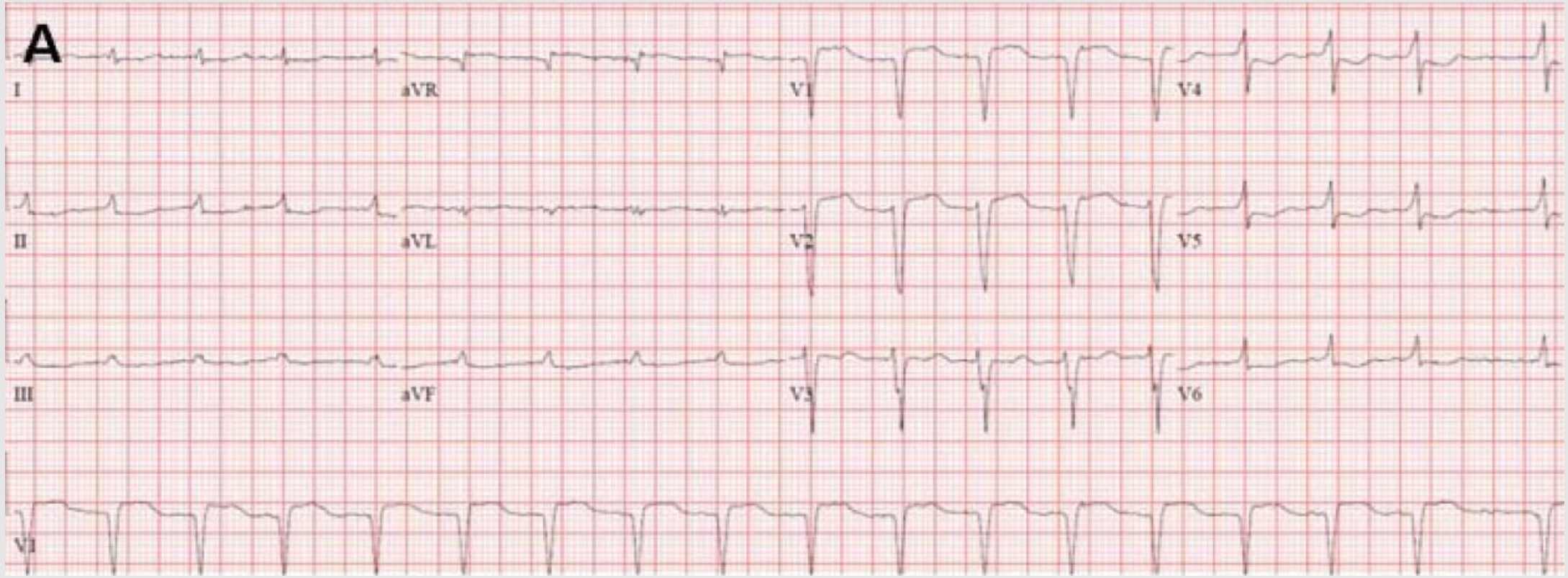


Figure 2. Frequency of frailty, and the relationships between frailty and organ impairment in patients with A-TTRwt-CA. The prevalence of frailty among patients with ATTRwt-CA can be explained by the amyloid fibril infiltration of various organs and tissues, particularly the heart, integumentary system, and nerves. FAB: frontal assessment battery, GDS: geriatric depression scale, IADL: instrumental activity of daily living, MNA: mini nutritional assessment, NYHA: New York heart association, SEGA: short emergency geriatric assessment SPPB: short physical performance battery, 7-CDT: 7-clock drawing test.

doi.org/10.3390/jcm10153415

doi:10.1161/CIRCHEARTFAILURE.120.008105

ECG findings have low predictive value in isolation



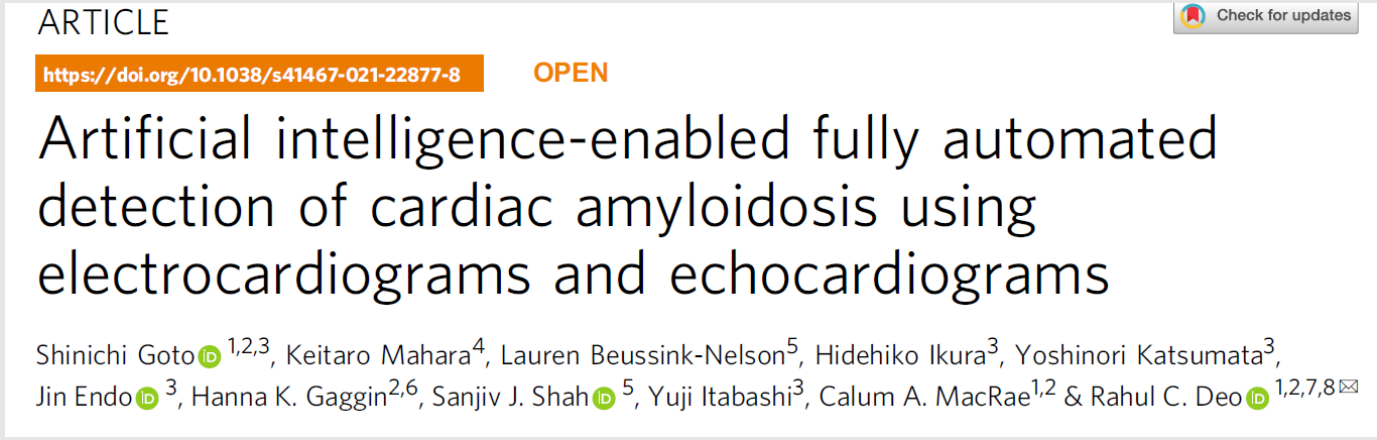
atrial fibrillation, low voltage in the limb leads, and a pseudoinfarct pattern with Q waves in leads V1-V2.

doi:10.3949/ccjm.84.s3.02

Overview

- How common is it? Incidence, prevalence
  - hATTR , wtATTR, AL
- What is population health?Who should be screened? Screening strategies
  - What is the ideal risk group?
    - LVH
    - Biomarkers
  - Operationalizing ‘clinical red flag’s
    - E.g. bilateral carpal tunnel
    - Spinal stenosis
    - Orthopedic
    - ECG
    - hATTR
- Screening tools
  - Predictive scores, mayo
  - AI, Huda, UCLA
    - imaging
    - EMR
    - ECG
- Benefits, Risks, Costs
  - HF clinical
  - Genotype, phenotype

AI for ECG and Echocardiogram is Promising to Aid Detection



ARTICLE

Check for updates

https://doi.org/10.1038/s41467-021-22877-8 OPEN

Artificial intelligence-enabled fully automated detection of cardiac amyloidosis using electrocardiograms and echocardiograms

Shinichi Goto[1,2,3], Keitaro Mahara[4], Lauren Beussink-Nelson[5], Hidehiko Ikura[3], Yoshinori Katsumata[3], Jin Endo[3], Hanna K. Gaggin[2,6], Sanjiv J. Shah[5], Yuji Itabashi[3], Calum A. MacRae[1,2] & Rahul C. Deo[1,2,7,8]✉

JAMA Cardiology | Original Investigation

High-Throughput Precision Phenotyping of Left Ventricular Hypertrophy With Cardiovascular Deep Learning

Grant Duffy, BS; Paul P. Cheng, MD, PhD; Neal Yuan, MD; Bryan He, BS; Alan C. Kwan, MD; Matthew J. Shun-Shin, PhD; Kevin M. Alexander, MD; Joseph Ebinger, MD; Matthew P. Lungren, MD; Florian Rader, MD, MSc; David H. Liang, MD, PhD; Ingela Schnittger, MD; Euan A. Ashley, MBChB, DPhil; James Y. Zou, PhD; Jignesh Patel, MD, PhD; Ronald Witteles, MD; Susan Cheng, MD, MPH; David Ouyang, MD

10.1038/s41467-021-22876-9

10.1038/s41467-021-22877-8

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Simple score

Figure 1. Description of the Transthyretin Amyloid Cardiomyopathy (ATTR-CM) Score

Clinical variable	Value	Points[a]
Age, y	If 60-69	+2
	If 70-79	+3
	If ≥80	+4
Sex	Male	+2
Hypertension diagnosis	Present	−1
Ejection fraction	<60%	+1
Posterior wall thickness	≥12 mm	+1
Relative wall thickness[b]	>0.57	+2

High-risk score ≥6

Description of the ATTR-CM score components and point allocations for each component.

[a] If variable is absent, points = 0.

[b] Sum of septal and posterior wall thickness divided by left ventricular end diastolic diameter.

A machine learning model for identifying patients at risk for wild-type transthyretin amyloid cardiomyopathy

Ahsan Huda[1], Adam Castaño[1], Anindita Niyogi[1], Jennifer Schumacher[1], Michelle Stewart[1], Marianna Bruno[1], Mo Hu[2], Faraz S. Ahmad[2], Rahul C. Deo[3] & Sanjiv J. Shah[2]✉

- Random forest machine learning model to identify transthyretin cardiomyopathy using medical claims
- Derivation: 1071 cases, 1071 non-amyloid controls
- Validation: 3 national cohorts (9412 cases, 9421 controls), EMR cohort (261 cases, 39393 controls)

ML Model Outperformed Clinical Model though PPV was Low

Table 3 Prediction of cardiac amyloidosis in the Northwestern Medicine Enterprise Data Warehouse Heart Failure Cohort using the wild-type ATTR-CM Random Forest prediction model.

Metric	Probability cutoff for the diagnosis of ATTR-CM					
	>0.50	>0.55	>0.60	>0.65	>0.70	>0.75
Sensitivity, %	69.7	64.0	52.5	36.8	22.2	11.1
Specificity, %	75.6	84.5	91.0	95.5	98.0	99.3
PPV, %	1.9	2.7	3.7	5.2	6.8	9.6
NPV, %	99.7	99.7	99.7	99.6	99.5	99.4
Accuracy, %	75.5	84.4	90.8	95.2	97.5	98.7
LR+	2.86	4.12	5.85	8.24	11.07	15.97
LR−	0.40	0.43	0.52	0.66	0.79	0.90

ATTR-CM amyloidogenic transthyretin cardiomyopathy, *LR+* positive likelihood ratio, *LR−* negative likelihood ratio, *NPV* negative predictive value, *PPV* positive predictive value.

Table 4 Areas under the receiver operating characteristic curve for various prediction models in the Northwestern Medicine Enterprise Data Warehouse Heart Failure Cohort.

Model	*N*	AUROC
ATTRwt-CM RF model	39,654	0.80
ATTRwt-CM RF model, age > 70 years	23,570	0.82
Age only	39,624	0.54
Age + sex	39,618	0.62
Age + sex + ethnicity[a]	39,203	0.70
Age + sex + ethnicity + logBNP[b]	20,419	0.73
Age + sex + ethnicity + logBNP + abnormal troponin-I[c]	15,046	0.73
ATTRwt-CM RF model + age + sex + ethnicity	39,203	0.83
ATTRwt-CM RF model + age + sex + ethnicity + total number of encounters	38,337	0.83

ATTRwt-CM amyloidogenic transthyretin (wild-type), *AUROC* area under the receiver operating characteristic curve, *RF* Random Forest, *BNP* B-type natriuretic peptide.
[a]Ethnicity categories: non-Hispanic White, non-Hispanic Black, Hispanic, Asian, others.
[b]Highest BNP value in the electronic health record, log-transformed.
[c]Based on the highest troponin-I in the electronic health record (abnormal defined as >0.04 ng/ml).

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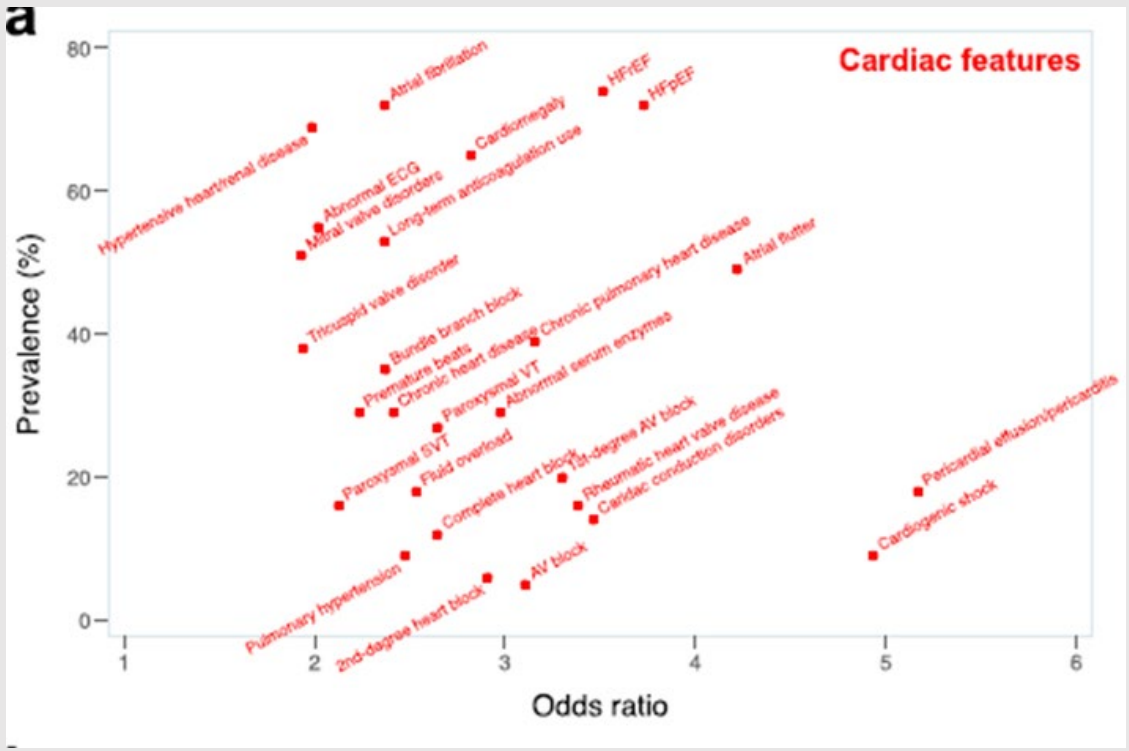
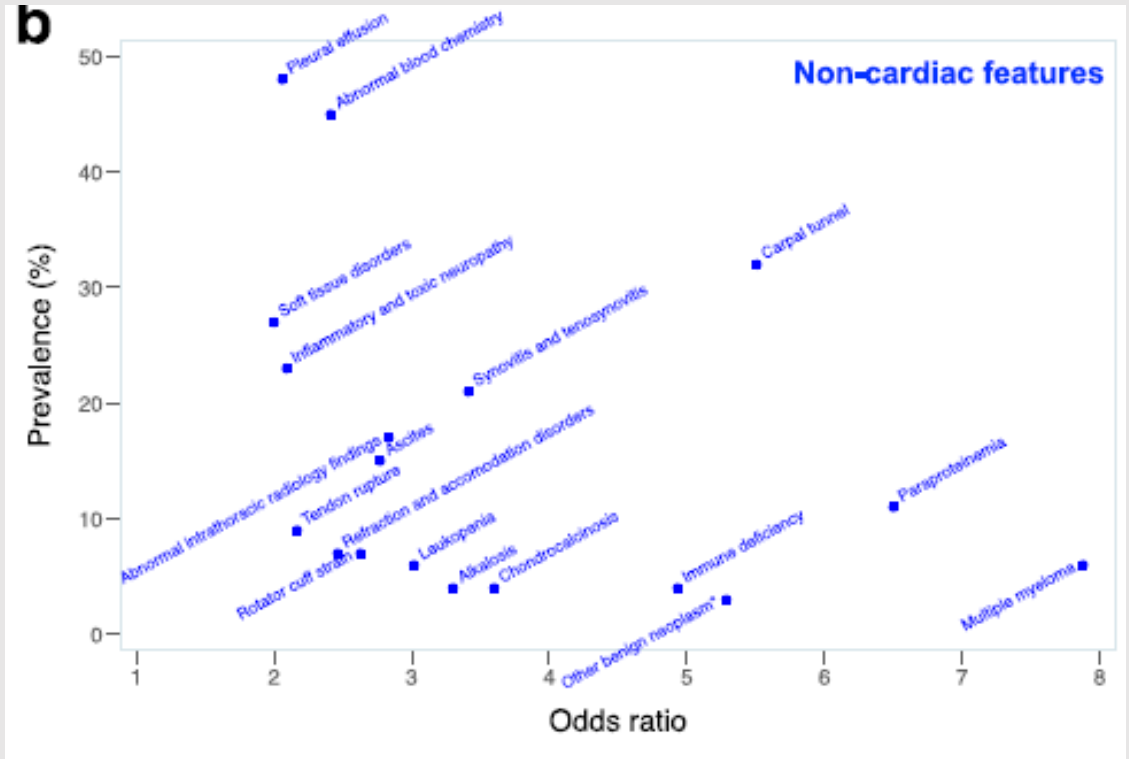
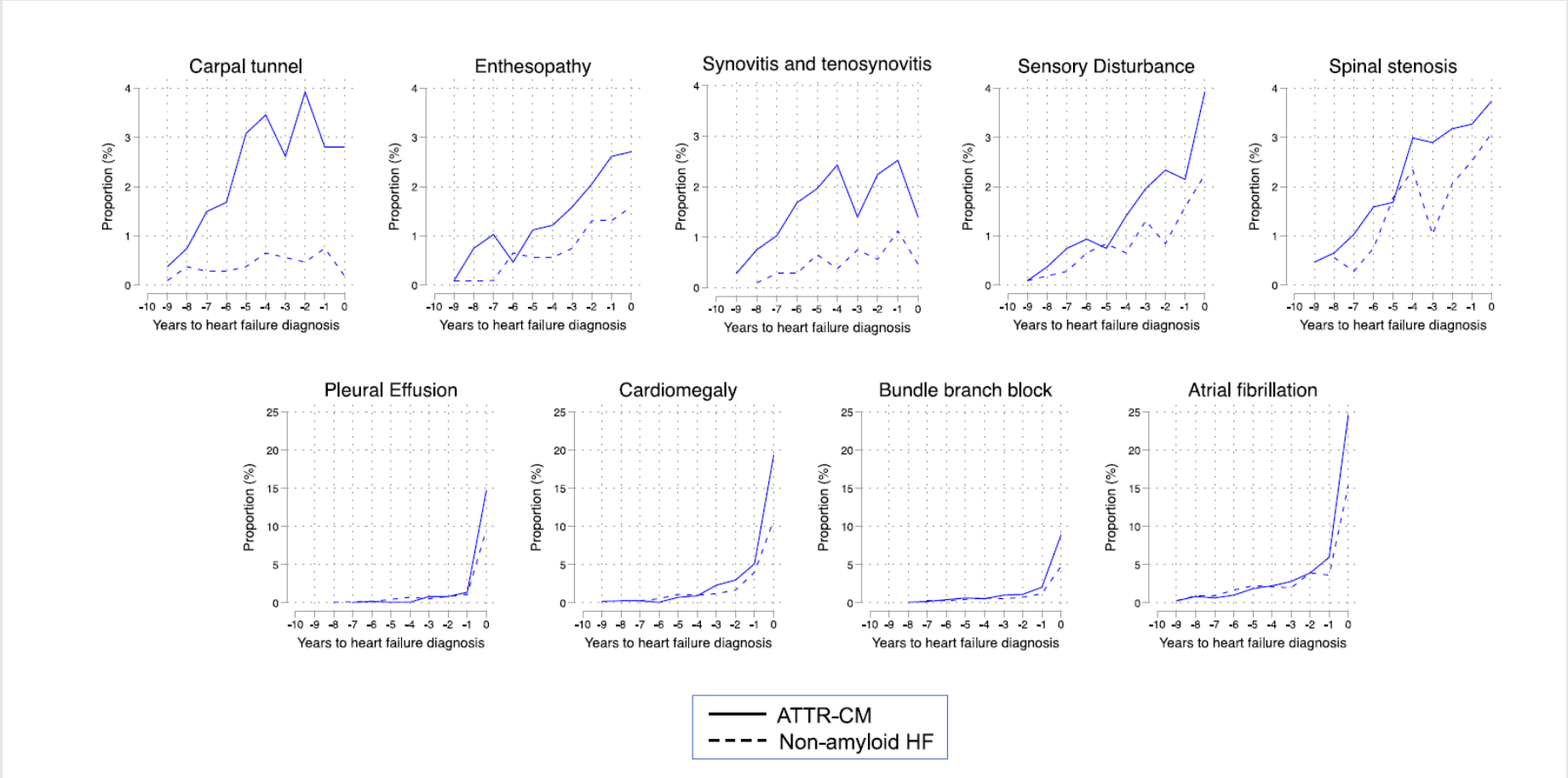




Time course of non-cardiac and cardiac phenotypes prior to HF diagnosis



Potential Projects

1. Epidemiology
   - Incidence, prevalence, predictors
   - Disparities, Geographic and facility level variation
2. AI/ML Prediction Tool Using EHR data, Implementation of Clinical Decision Support
3. Prognostic staging, phenotyping
4. Comparative effectiveness, pharmacoepidemiology

<u>Other:</u>

Quality of life

Health economics, cost effectiveness, extremes of age

Quality of care, diagnosis

High Medicare Part D out-of-pocket costs

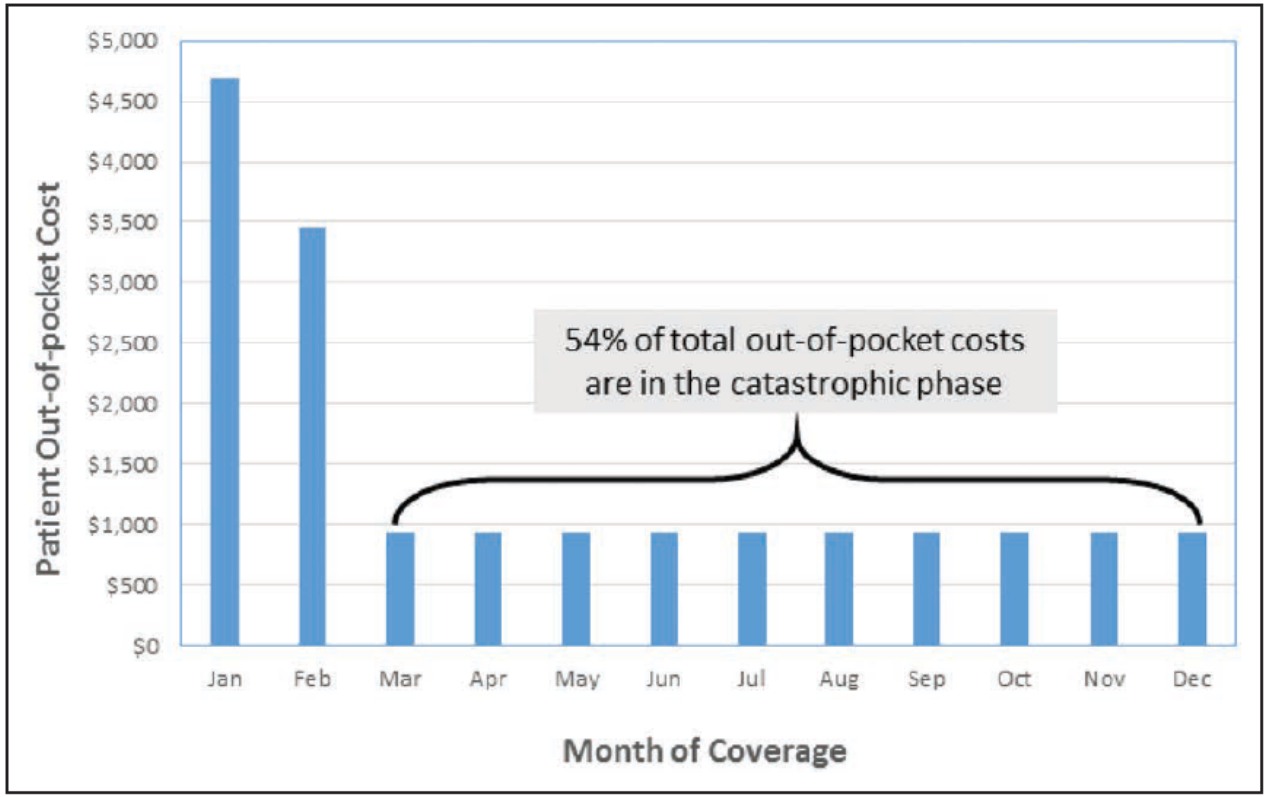


Figure 5. Projected Medicare Part D beneficiary monthly out-of-pocket costs for tafamidis.
Projected annual out-of-pocket expenses were calculated using the standard 2019 Medicare Part D plan including: (1) an initial $415 deductible; (2) an initial coverage period until drug costs reach $3810; (3) a coverage gap ("donut hole") with 25% cost sharing until out-of-pocket costs reach $5100; and (4) catastrophic coverage with 5% cost sharing without an upper limit. Monthly insurance premiums and the costs of other medications were not included in this projection.

10.1161/cir.0000000000000792