Heart Failure with Preserved Ejection Fraction

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CONTINUING EDUCATION COMPANY

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Disclosure

Consultant: Alnylam; Boehringer Ingelheim; BridgeBio

Speakers' Bureau: Alnylam; Boehringer Ingelheim; BridgeBio

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Objectives

- To gain a better understanding of the challenges associated with finding substantial treatments for HFpEF
- To be able to explain the pathophysiology of HFpEF
- To apply the limited therapies that improve QOL, exercise tolerance, and heart failure hospitalizations to their patients with HFpEF

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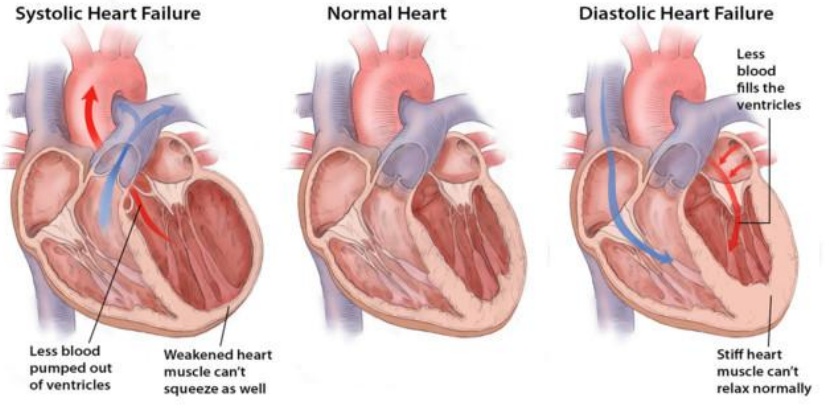
Previous Description of Heart Failure



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Circulation
Volume 145, Issue 18, 3 May 2022; Pages e895-e1032
https://doi.org/10.1161/CIR.0000000000001063

AHA/ACC/HFSA CLINICAL PRACTICE GUIDELINE

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

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New Heart Failure Categories

HF with reduced EF (HFrEF)

- LVEF ≤ 40%

HF with mildly reduced EF (HFmrEF)

- LVEF 41- 49%

HF with preserved EF (HFpEF)

- LVEF ≥ 50

HF with improved EF (HFimpEF)

- Baseline LVEF ≤ 40%, a ≥ 10 pt increase in baseline LVEF, and a 2nd measurement of LVEF > 40%

Bozkurt B, Coats AJ, Tsutsui H, et al. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure [published online ahead of print, 2021 Mar 1]. *J Card Fail*. 2021;S1071-9164(21)00050-6. doi:10.1016/j.cardfail.2021.01.022

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Early Description of HFpEF

Congestive Heart Failure with Normal Systolic Function

ANNE HAMILTON DOUGHERTY, MD, GERALD V. NACCARELLI, MD,
ELAYNE L. GRAY, BSN, CHARLES H. HICKS, MD, and RICHARD A. GOLDSTEIN, MD

Although there have been isolated reports of congestive heart failure (CHF) with normal systolic function, the prevalence and characteristics of this condition have not previously been described. Accordingly, 188 patients with CHF undergoing radionuclide ventriculography were prospectively evaluated. Sixty-seven (36%) had a normal ejection fraction (EF) of 0.45 or greater, and 121, an abnormal EF of less than 0.45. Of these, 72 (55 with an abnormal EF [group I] and 17 with a normal EF [group II]) were also reviewed for clinical characteristics. There was no demographic difference between groups, except that systemic hypertension appeared to be a contributing factor in 65% of the patients in group II, compared with 23% of the patients in group I ($p < 0.002$). Echocardiographic left atrial emptying index, reflecting left ventricular compliance, was determined in 72 patients and 14 normal subjects. Left atrial emptying index in normal control subjects was 0.93 ± 0.11 (± standard deviation), compared with 0.41 ± 0.18 in group I and 0.44 ± 0.19 in group II patients ($p < 0.001$ vs control in both groups). Thus, normal systolic function is common among patients with CHF. Diastolic dysfunction, consistent with a noncompliant left ventricle, was found in both CHF groups.

(Am J Cardiol 1984;54:778–782)

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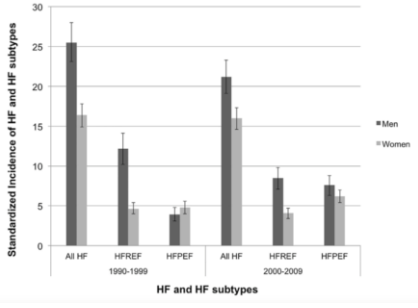
Incidence of HFpEF Is Increasing

Tsao et al. *JACC: HF 2018*
N=15,217 (FHS, CHS); 60% women; 2,524 incident HF cases; 115,703 person-years of follow-up



- Higher rates of Diabetes, HTN, CKD, Obesity
- Greater number of Elderly population
- Increased awareness by providers

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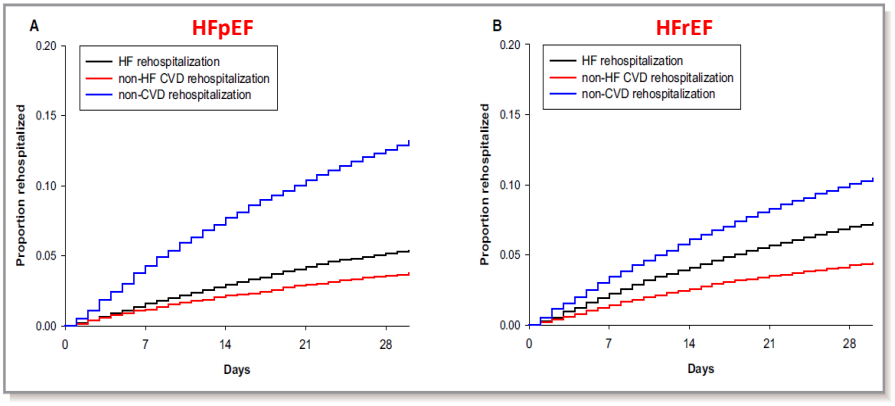
Causes and Temporal Patterns of 30-Day Readmission Among Older Adults Hospitalized With Heart Failure With Preserved or Reduced Ejection Fraction



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Causes and Temporal Patterns of 30-Day Readmission Among Older Adults Hospitalized With Heart Failure With Preserved or Reduced Ejection Fraction

Cause	HFpEF Readmissions (n=3075) n (%)	HFrEF Readmissions (n=3367) n (%)
HF	743 (24.2)	1105 (32.8)
Non-HF cardiovascular-related	517 (16.8)	673 (20.0)
Dysrhythmia	139 (4.5)	142 (4.2)
Acute myocardial infarction	54 (1.8)	108 (3.2)
Coronary atherosclerosis	60 (2.0)	97 (2.9)
Hypertension with complications	77 (2.5)	89 (2.6)
Non–cardiovascular-related	1815 (59.0)	1589 (47.2)
Acute renal failure	168 (5.5)	167 (5.0)
Septicemia	160 (5.2)	155 (4.6)
Pneumonia	150 (4.9)	106 (3.1)
Adult respiratory failure	141 (4.6)	104 (3.1)
COPD	99 (3.2)	84 (2.5)
Fluid/electrolyte diagnosis	82 (2.7)	81 (2.4)
Urinary tract infection	73 (2.4)	60 (1.8)

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What Is HFpEF?

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Pathophysiology of HFpEF

- LV diastolic *and* systolic dysfunction
- Vascular stiffening and abnormal ventricular-arterial coupling
  - Cardiac Output reduction during exercise
  - Markedly elevated filling pressures during exercise
- Chronotropic incompetence

Borlaug and Paulus Eur Ht J 2011

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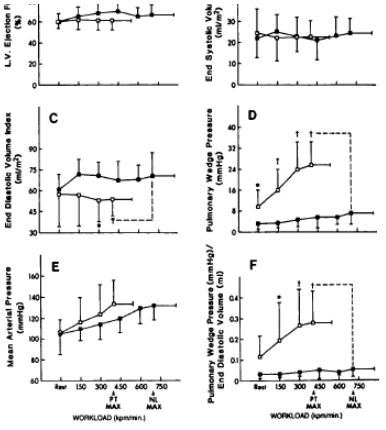
Exercise Intolerance in Patients With Heart Failure and Preserved Left Ventricular Systolic Function: Failure of the Frank-Starling Mechanism

DALANE W. KITZMAN, MD, MICHAEL B. HIGGINBOTHAM, MB, FREDERICK R. COBB, MD, KHALID H. SHEIKH, MD, MARTIN J. SULLIVAN, MD
Durham, North Carolina

The abnormalities in left ventricular diastolic function **limited patients' ability to augment stroke volume** by means of the Frank-Starling mechanism, resulting in **severe exercise intolerance**



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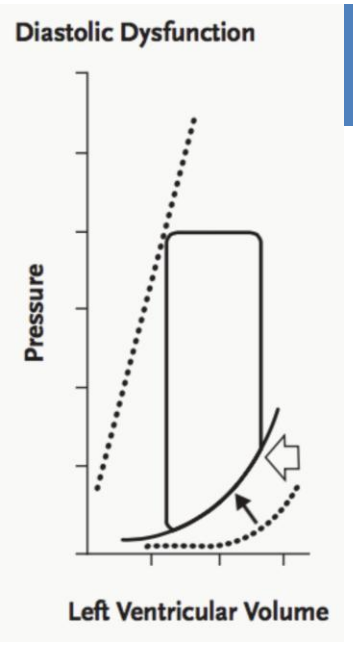

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HFpEF & CoMorbidities

- Advanced age, hypertension, obesity, female gender, anemia, diabetes, renal dysfunction, and impaired LV compliance have been either associated with the prevalence of HFpEF or the ventricular-vascular dysfunction seen in patients with HFpEF
- These comorbidities do not fully account for the poor outcomes seen in the HFpEF population

Ather S, Chan W, Bozkurt B, et al. **Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction.** *J Am Coll Cardiol* 2012;59:998–1005.

Takeda Y, Sakata Y, Mano T, et al. **Competing risks of heart failure with preserved ejection fraction in diabetic patients.** Euro J Heart Fail 2011 Jun;13(6):664-9.

Mohammed SF, Borlaug BA, Roger VL, et al. **Comorbidity and ventricular and vascular structure and function in heart failure with preserved ejection fraction: a community-based study.** *Circ Heart Fail* 2012;5:710–9.

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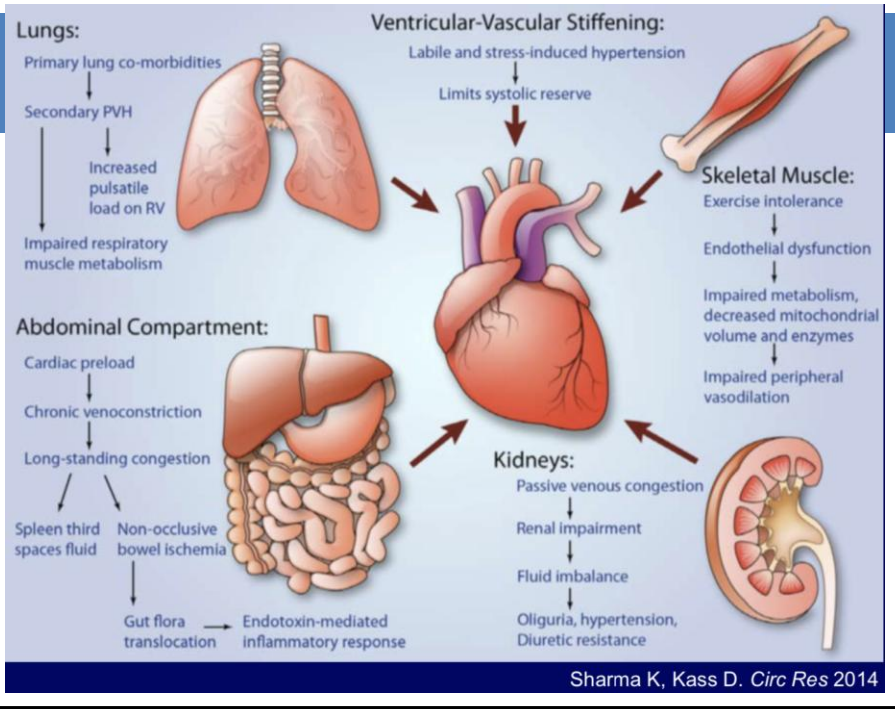

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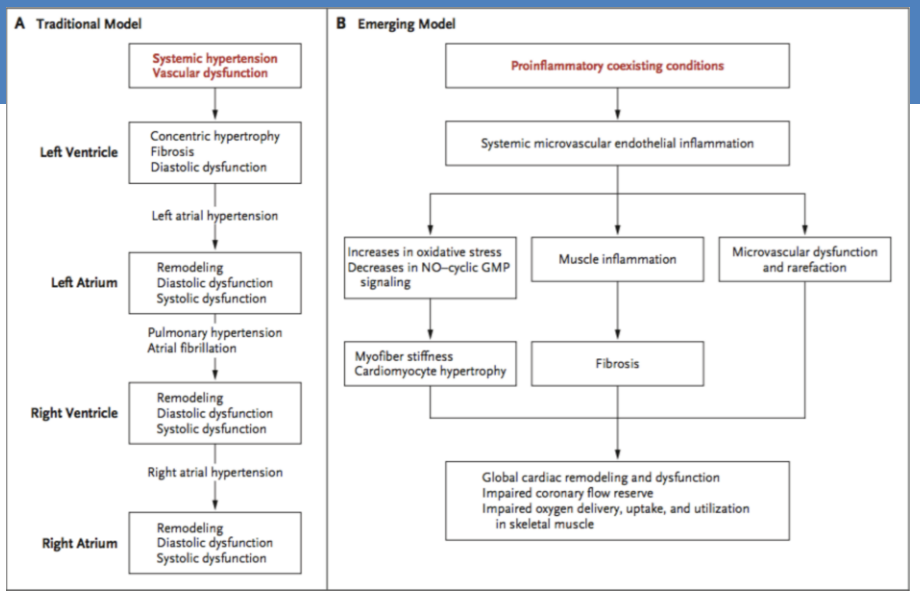

Redfield M *NEJM* 2018

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Phosphokinase G (PKG) & HFpEF

- PKG is found in cardiac myocytes, vascular smooth muscle cells, renal cells, zona glomerulosa, adrenal cortex, intestinal mucosa, fibroblast, leukocytes

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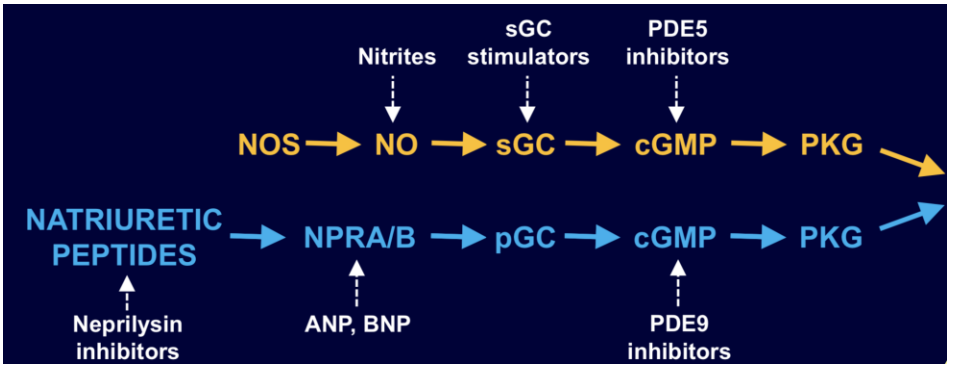
PKG Pathway As Treatment Targets for HFpEF



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Benefits of Phosphokinase G (PKG)

- Promotes Smooth muscle relaxation
- ↓ Cardiac Hypertrophy
- ↓ Cardiac fibrosis
- ↓ Cardiac dysfunction
- ↓ Endothelial dysfunction
- ↑ Lipolysis
- ↑ Metabolism
- ↑ Skeletal muscle performance
- ↑ Renal function

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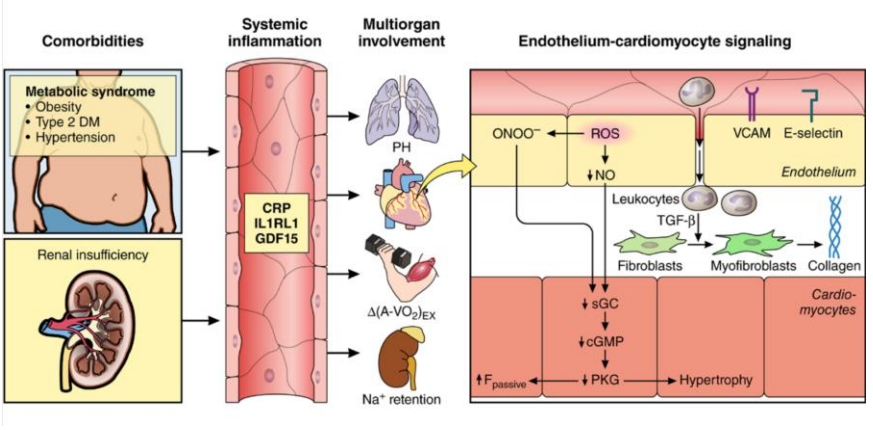
HFpEF Remodeling Pathway



Shah S…Paulus W *Circulation* 2016

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Medical Therapy for HFpEF

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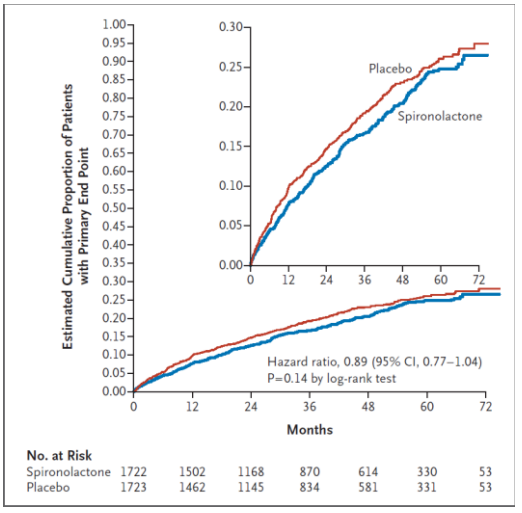
TOPCAT

Spironolactone vs. Placebo
1º Endpoint: Composite of CV Death, Aborted Cardiac Arrest, or HF Hospitalization



Pitt et al. NEJM 2014

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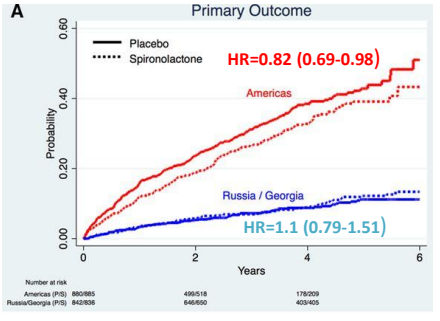
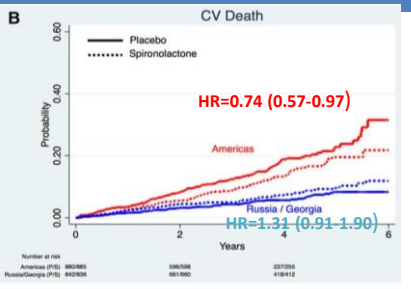
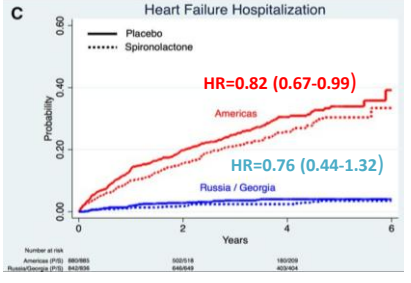
Regional Variation in Outcomes in TOPCAT







American Heart Association.

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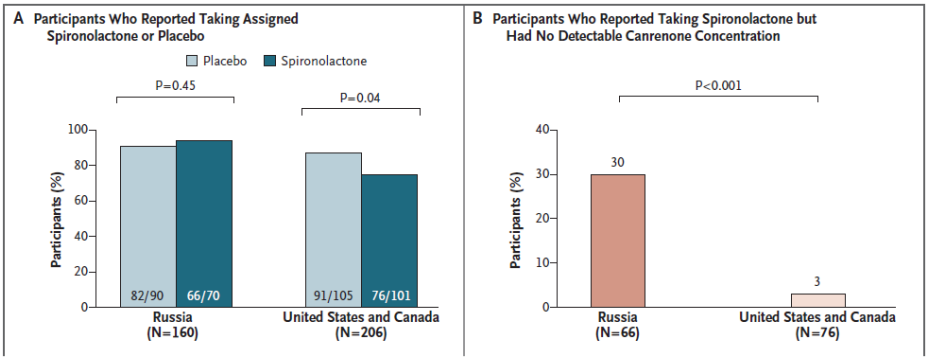
Regional Variation in Outcomes in TOPCAT



American Heart Association.

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ORIGINAL ARTICLE

Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, I.S. Anand, J. Ge, C.S.P. Lam, A.P. Maggioni, F. Martinez, M. Packer, M.A. Pfeffer, B. Pieske, M.M. Redfield, J.L. Rouleau, D.J. van Veldhuisen, F. Zannad, M.R. Zile, A.S. Desai, B. Claggett, P.S. Jhund, S.A. Boytsov, J. Comin-Colet, J. Cleland, H.-D. Düngen, E. Goncalvesova, T. Katova, J.F. Kerr Saraiva, M. Lelonek, B. Merkely, M. Senni, S.J. Shah, J. Zhou, A.R. Rizkala, J. Gong, V.C. Shi, and M.P. Lefkowitz, for the PARAGON-HF Investigators and Committees

N=4822
NYHA II-IV
EF ≥45%
Evidence of structural heart disease
Elevated levels of natriuretic peptides
Requiring chronic treatment with diuretics

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PARAGON
Sacubitril-Valsartan VS Valsartan in HFpEF

Methods

- 4822 pts Randomized
- NYHA Class II –IV
- LVEF ≥ 45%
- ↑ BNP
- 1° Endpoint
  - Total HHF + Death from CV Causes
- 2 Endpoints
  - Death from CV causes
  - Worsening Renal Function
  - Change in KCCQ
  - Safety

Results

- Valsartan-Sacubitril did not significantly reduce:
  - 1° endpoint of Total HHF+Death from CV causes (RR 0.87, CI 0.75 -1.01, p 0.06)
  - 2° endpoint of Death from CV causes compared to Valsartan (8.5% VS 8.9%)
- Subgroup Analysis Sacubitril-Valsartan demonstrated improvement in 1 Endpoint compared to Valsartan in the following groups
  - Lower EF (<57%)
  - Women

Solomon S et al. NEJM 2019

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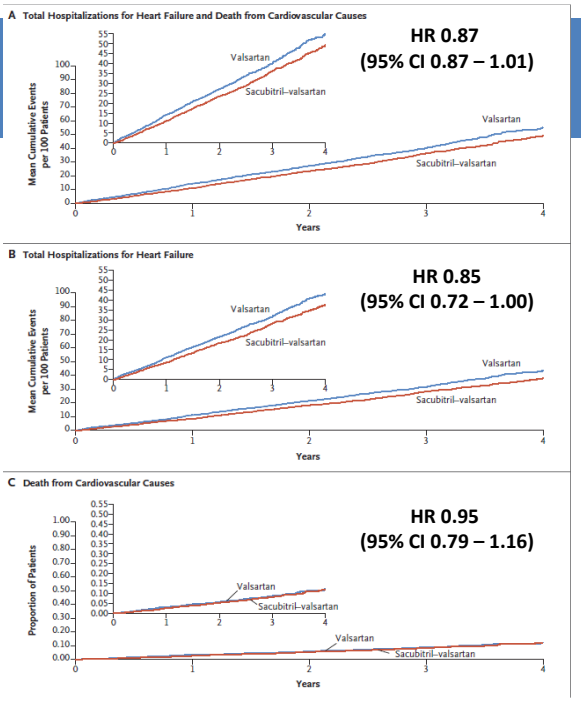

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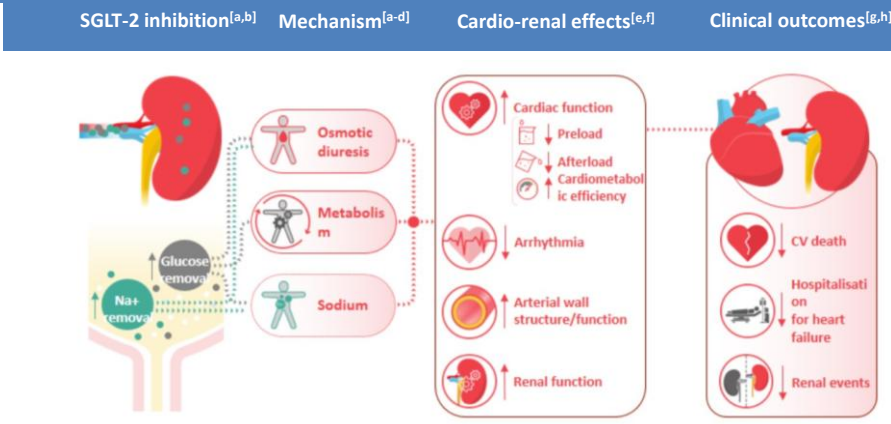
Mechanisms of Preservation of CV and Renal Function in SGLT2-inhibition that May Benefit HFpEF



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SGLT-2 Inhibitors and CVD

EMPA-REG

- Empagliflozin lowered composite outcome and all-cause death
- Reduction in HF hospitalization
- BP reduced ≈4/2 mmHg; weight loss ≈2 kg

CANVAS

- In two trials involving patients with T2DM and CVD risk, canagliflozin reduced risk for CV events
- Reduction in HF hospitalization

CVD-REAL

- A real-world comparative effectiveness study of SGLT-2i compared to other glucose lowering drugs
- 39% lower risk of HF hospitalization, 51% lower risk of death, and 46% lower risk of composite (HF hospitalization and death)

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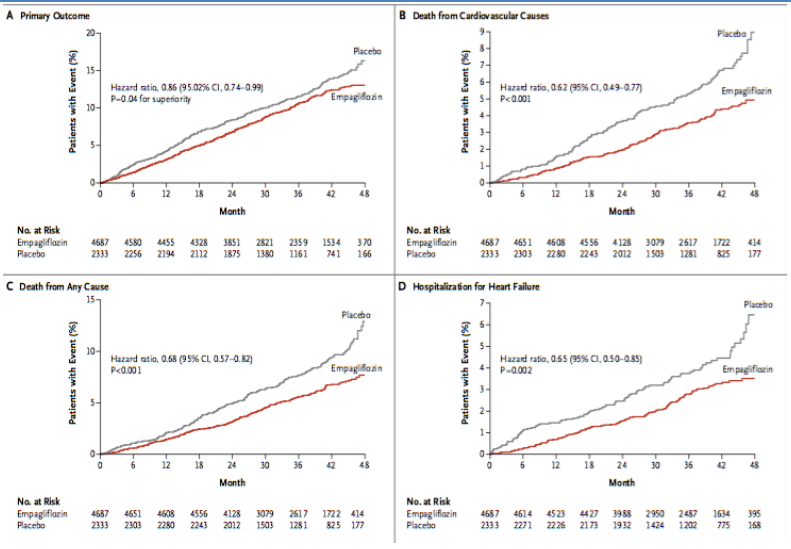
EMPA-REG



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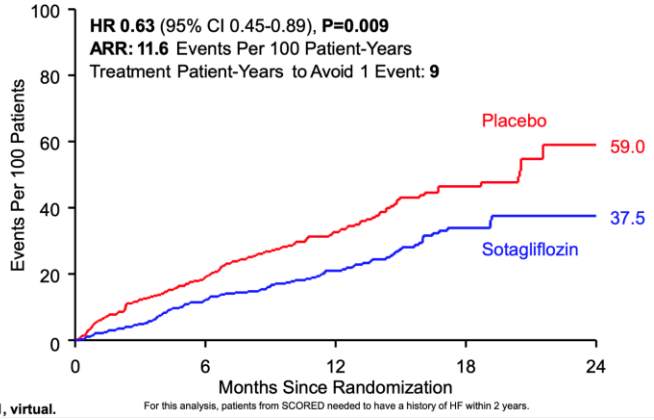
Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 739 Patients with HFpEF (≥50%)

SOLOIST
SCORED



Bhatt DL. ACC 2021, virtual.

For this analysis, patients from SCORED needed to have a history of HF within 2 years.

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 14, 2021 VOL. 385 NO. 16

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

S.D. Anker, J. Butler, G. Filippatos, J.P. Ferreira, E. Bocchi, M. Böhm, H.-P. Brunner–La Rocca, D.-J. Choi, V. Chopra, E. Chuquiure-Valenzuela, N. Giannetti, J.E. Gomez-Mesa, S. Janssens, J.L. Januzzi, J.R. Gonzalez-Juanatey, B. Merkely, S.J. Nicholls, S.V. Perrone, I.L. Piña, P. Ponikowski, M. Senni, D. Sim, J. Spinar, I. Squire, S. Taddei, H. Tsutsui, S. Verma, D. Vinereanu, J. Zhang, P. Carson, C.S.P. Lam, N. Marx, C. Zeller, N. Sattar, W. Jamal, S. Schnaidt, J.M. Schnee, M. Brueckmann, S.J. Pocock, F. Zannad, and M. Packer, for the EMPEROR-Preserved Trial Investigators*

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EMPEROR Preserved

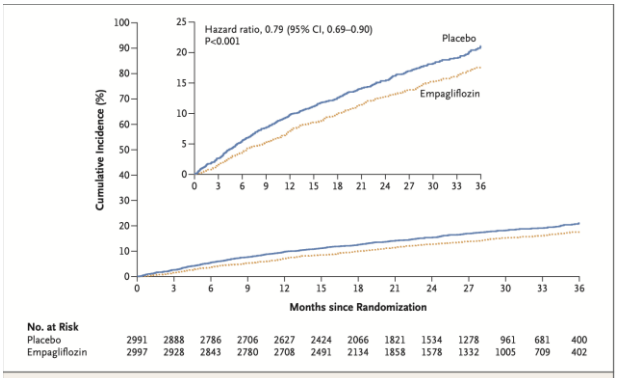

Figure 1. Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.
The estimated cumulative incidence of the primary outcome in the two groups is shown. The inset shows the same data on an expanded y axis.

- 1st HFpEF medication to reach it's 1º Endpoint
- CV Death or Hospitalization for HF
  - Empagliflozin Group 415 of 2997 pts (13.8%)
  - Placebo Group 511 of 2991 patients (17.1%) HR 0.79 (0.69 to 0.90); P<0.001
- NNT 31 pts for 36 months

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EMPEROR Preserved

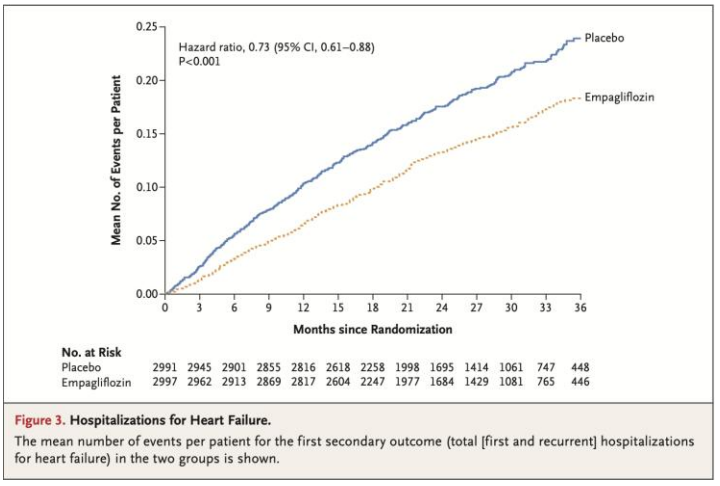

Figure 3. Hospitalizations for Heart Failure.
The mean number of events per patient for the first secondary outcome (total [first and recurrent] hospitalizations for heart failure) in the two groups is shown.

RRR = 27%

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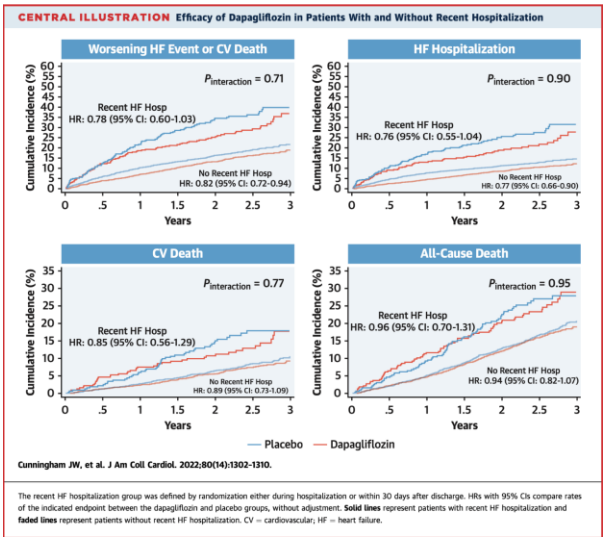
DELIVER- HF



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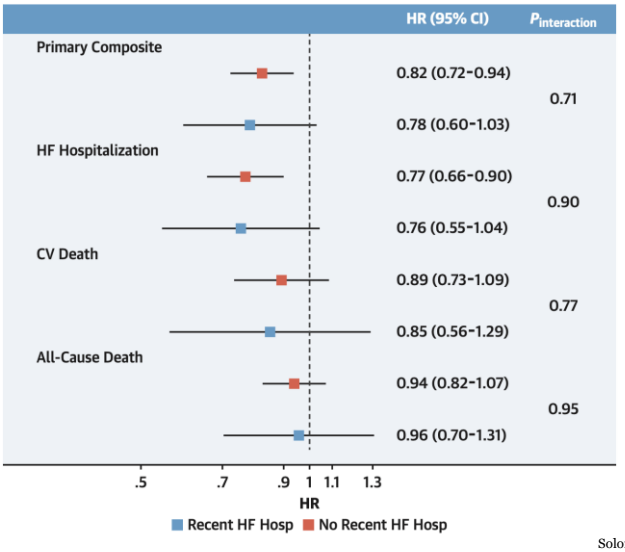
DELIVER-HF



Solomon et al, NEJM 2022

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Semaglutide: STEP-HF

- 529 pts with HFpEF and Obesity (BMI >30)
- Placebo VS Semaglutide 2.4 mg weekly for 52 wks
- 1 Endpoint: Change in KCCQ-CSS
- 2 Endpoints:
  - 6-min walk distance
  - Composite of death, HF events, KCCQ-CSS diff, 6-min walk
  - C-Reactive Protein levels

Kosiborod et al NEJM 2023

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Semaglutide: STEP-HF

Semaglutide Group VS Placebo Changes from Baseline

- KCCQ-CCS: 16.6 pts VS 8.7 pts
- Body Weight: -13.3% VS -2.6%
- 6 Min Walk: 21.5 m VS 1.2 m
- CRP Level: -43.5% VS -7.3%
- Serious Adverse Events: 13.3% VS 26.7%
- Composite: More wins with Semaglutide group (win ratio 1.72)

Kosiborod et al NEJM 2023

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2022 ACC/AHA/HFSA HF Guidelines

COR	LOE	Recommendations
1	C-LD	1. Patients with HFpEF and hypertension should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity.[1–3]
2a	B-R	2. In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.[4]
2a	C-EO	3. In patients with HFpEF, management of AF can be useful to improve symptoms.
2b	B-R	4. In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[5–7]
2b	B-R	5. In selected patients with HFpEF, the use of ARB may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[8,9]
2b	B-R	6. In selected patients with HFpEF, ARNi may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[10,11]
3: No-Benefit	B-R	7. In patients with HFpEF, routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QOL is ineffective.[12,13]

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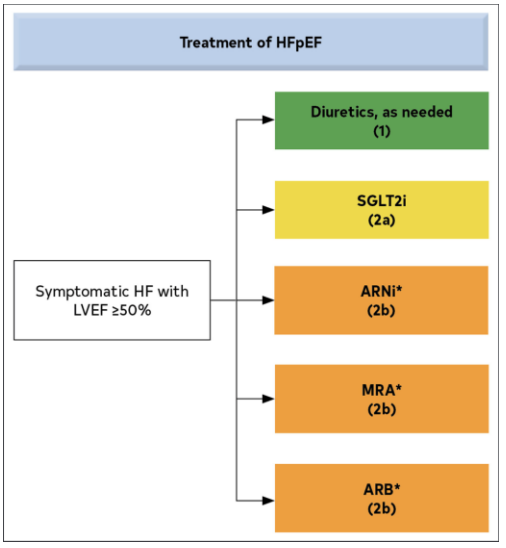
2022 ACC/AHA/HFSA HF Guidelines



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ACC/AHA 2017 Guidelines for Treatment of HFpEF

Recommendations	COR	LOE
Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines	I	B
Diuretics should be used for relief of symptoms due to volume overload	I	C
Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT	IIa	C
Management of AF according to published clinical practice guidelines for HFpEF to improve symptomatic HF	IIa	C
Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF	IIa	C
ARBs might be considered to decrease hospitalizations in HFpEF	IIb	B
In appropriately selected patients with HFpEF, aldosterone receptor antagonists might be considered to decrease hospitalizations	**IIb**	**B-R**

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Device Therapy

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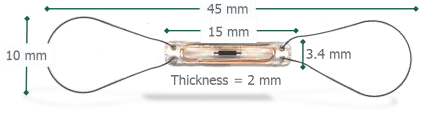
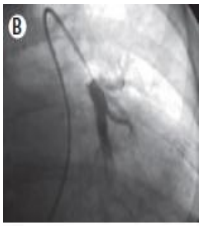
CHAMPION TRIAL CardioMEMS





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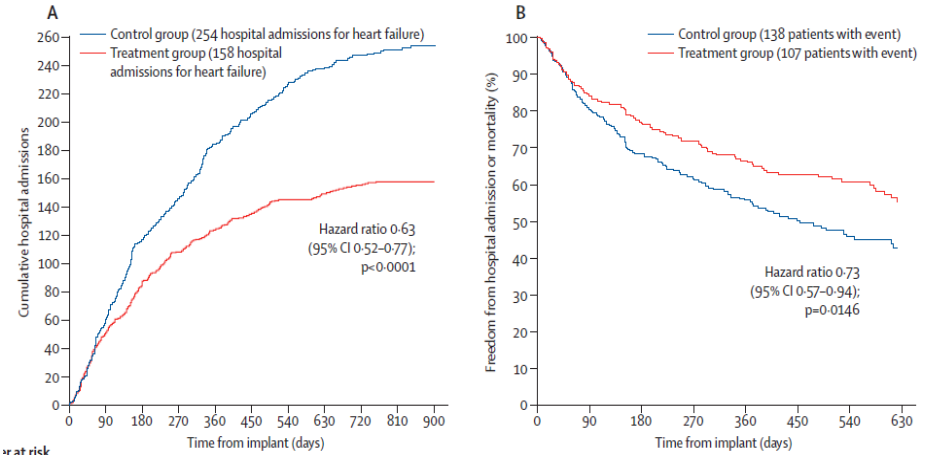
CHAMPION Trial
HF Hospitalization

N=550 NYHA III, 22% HFpEF



Abraham et al. Lancet 2011;377:658-66

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CHAMPION – Results

	Not enrolled (n=25)	Treatment group (n=270)	Control group (n=280)	All patients (n=575)	Risk (95% CI)	p value	NNT
Primary efficacy endpoints*							
Heart-failure-related hospitalisations up to 6 months (number; events per patient per 6 months)	NA	84 (0·32)	120 (0·44)	NA	0·72† (0·60–0·85)	0·0002	8
Primary safety endpoints‡							
Device-related or system-related complications	2 (8%)	3 (1%)	3 (1%)	8 (1%)	§	<0·0001	NA
Pressure-sensor failures	0	0	0	0	§	<0·0001	NA
Prespecified supplementary efficacy endpoints¶							
Heart-failure-related hospitalisations during entire randomised follow-up	NA	158	254	NA	0·63† (0·52–0·77)	<0·0001	4
Secondary efficacy endpoints							
Change from baseline in pulmonary artery mean pressure at 6 months (mm Hg×days; mean area under the curve)	NA	-156	33	NA	NA	0·008	NA
Patients admitted to hospital for heart failure at 6 months	NA	55 (20%)	80 (29%)	NA	0·71‖ (0·53–0·96)	0·03	NA
Days alive outside hospital at 6 months (mean, SD)	NA	174·4 (31·1)	172·1 (37·8)	NA	NA	0·02	NA
Minnesota Living with Heart Failure Questionnaire at 6 months (mean, SD)	NA	45 (26)	51 (25)	NA	NA	0·02	NA

Abraham et al. Lancet 2011;377:658-66

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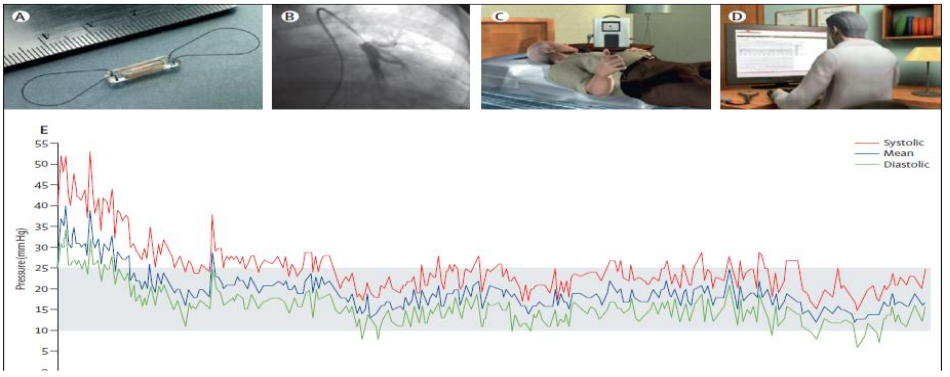
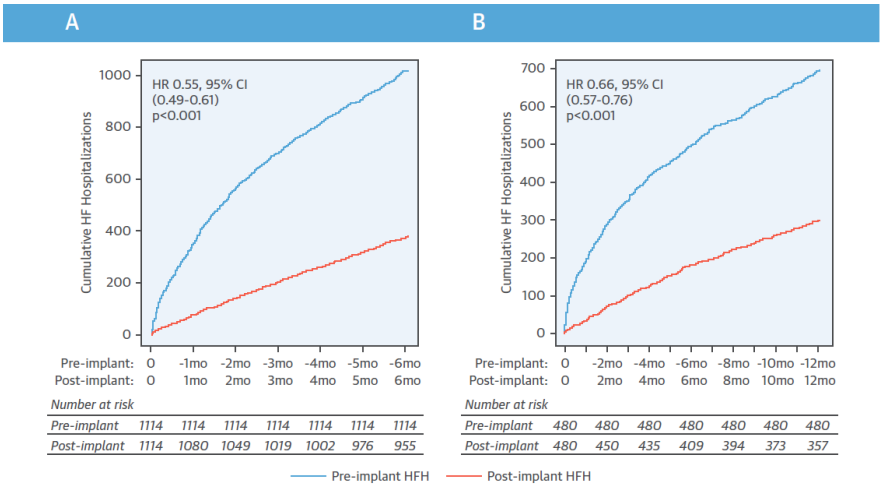
Remote PA Monitoring Waveforms

Indication



47

Wireless PA Monitoring: Real World Experience



Desai, A.S. et al. J Am Coll Cardiol. 2017;69(19):2357-65.

48

Guide HF

- 3/15/2018- 12/20/2019,
- 1022 patients were enrolled
- 1000 patients implanted successfully
- Follow-up completed on Jan 8, 2021
- Hemodynamic Arm
  - 253 out of 497 pts (0·563 per pt-yr)
- Control Group
  - 289 out of 503 pts (0·640 per patient-year) HR 0·88, 95% CI 0·74–1·05; p=0·16

Lindenfeld J, Zile MR, Desai AS, Bhatt K, Ducharme A, Horstmanshof D, Krim SR, Maisel A, Mehra MR, Paul S, Sears SF, Sauer AJ, Smart F, Zughaib M, Castaneda P, Kelly J, Johnson N, Sood P, Ginn G, Henderson J, Adamson PB, Costanzo MR. Hemodynamic-guided management of heart failure (GUIDE-HF): a randomised controlled trial. Lancet. 2021 Sep 11;398(10304):991-1001. doi: 10.1016/S0140-6736(21)01754-2. Epub 2021 Aug 27. PMID: 34461042.

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Guide HF

Full Study Results

Pre-COVID

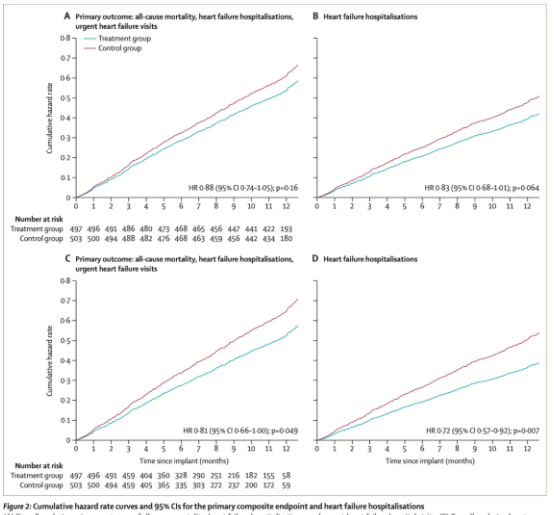
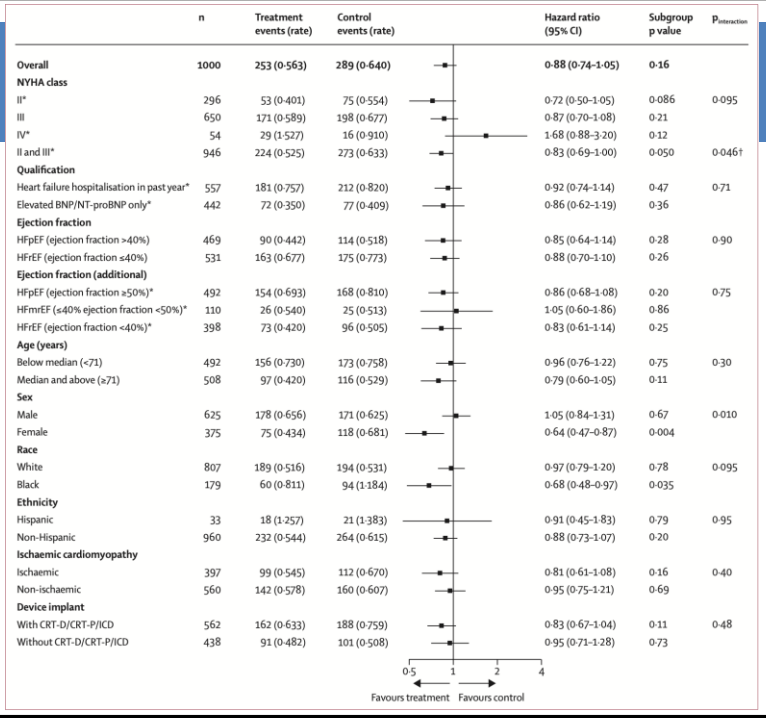


Figure 2: Cumulative hazard rate curves and 95% CIs for the primary composite endpoint and heart failure hospitalisations
(A) Overall analysis—primary outcome of all-cause mortality, heart failure hospitalisations, and urgent heart failure hospital visits. (B) Overall analysis—heart failure hospitalisations. (C) Pre-COVID-19 impact analysis—primary outcome of all-cause mortality, heart failure hospitalisations, and urgent heart failure visits. (D) Pre-COVID-19 impact analysis—heart failure hospitalisations. HR=hazard ratio.

50



	n	Treatment events (rate)	Control events (rate)	Hazard ratio (95% CI)	Subgroup p value	$p_{interaction}$
Overall	**1000**	**253 (0·563)**	**289 (0·640)**	**0·88 (0·74–1·05)**	**0·16**	
NYHA class						
II*	296	53 (0·401)	75 (0·554)	0·72 (0·50–1·05)	0·086	0·095
III	650	171 (0·589)	198 (0·677)	0·87 (0·70–1·08)	0·21	
IV*	54	29 (1·527)	16 (0·910)	1·68 (0·88–3·20)	0·12	
II and III*	946	224 (0·525)	273 (0·633)	0·83 (0·69–1·00)	0·050	0·046†
Qualification						
Heart failure hospitalisation in past year*	557	181 (0·757)	212 (0·820)	0·92 (0·74–1·14)	0·47	0·71
Elevated BNP/NT-proBNP only*	442	72 (0·350)	77 (0·409)	0·86 (0·62–1·19)	0·36	
Ejection fraction						
HFpEF (ejection fraction >40%)	469	90 (0·442)	114 (0·518)	0·85 (0·64–1·14)	0·28	0·90
HFrEF (ejection fraction ≤40%)	531	163 (0·677)	175 (0·773)	0·88 (0·70–1·10)	0·26	
Ejection fraction (additional)						
HFpEF (ejection fraction ≥50%)*	492	154 (0·693)	168 (0·810)	0·86 (0·68–1·08)	0·20	0·75
HFmrEF (≤40% ejection fraction <50%)*	110	26 (0·540)	25 (0·513)	1·05 (0·60–1·86)	0·86	
HFrEF (ejection fraction <40%)*	398	73 (0·420)	96 (0·505)	0·83 (0·61–1·14)	0·25	
Age (years)						
Below median (<71)	492	156 (0·730)	173 (0·758)	0·96 (0·76–1·22)	0·75	0·30
Median and above (≥71)	508	97 (0·420)	116 (0·529)	0·79 (0·60–1·05)	0·11	
Sex						
Male	625	178 (0·656)	171 (0·625)	1·05 (0·84–1·31)	0·67	0·010
Female	375	75 (0·434)	118 (0·681)	0·64 (0·47–0·87)	0·004	
Race						
White	807	189 (0·516)	194 (0·531)	0·97 (0·79–1·20)	0·78	0·095
Black	179	60 (0·811)	94 (1·184)	0·68 (0·48–0·97)	0·035	
Ethnicity						
Hispanic	33	18 (1·257)	21 (1·383)	0·91 (0·45–1·83)	0·79	0·95
Non-Hispanic	960	232 (0·544)	264 (0·615)	0·88 (0·73–1·07)	0·20	
Ischaemic cardiomyopathy						
Ischaemic	397	99 (0·545)	112 (0·670)	0·81 (0·61–1·08)	0·16	0·40
Non-ischaemic	560	142 (0·578)	160 (0·607)	0·95 (0·75–1·21)	0·69	
Device implant						
With CRT-D/CRT-P/ICD	562	162 (0·633)	188 (0·759)	0·83 (0·67–1·04)	0·11	0·48
Without CRT-D/CRT-P/ICD	438	91 (0·482)	101 (0·508)	0·95 (0·71–1·28)	0·73	

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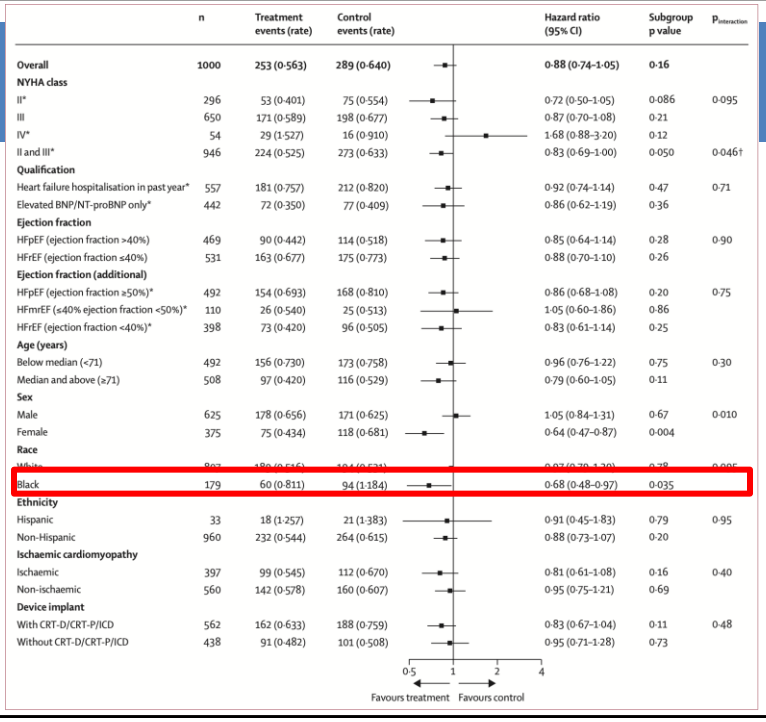

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Guide HF-Pandemic Influence

Overall results found no significant reduction in the cumulative incidence of primary endpoint events

When adjusted for the COVID-19 pandemic, a significant decrease was observed in the pre-COVID-19 impact analysis

Primary Event Pre-Covid

- Hemodynamic Group: 177 primary events
- Control Group 224 events

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Exercise Training

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HFpEF Exercise Training Trials Summary

Name	N	Mo	Diast Fx	ET Type	Results
Kitzman et al 2010	53	4	N/A	Aerobic	Improved exercise capacity (VO2peak, workload, exercise time) and submaximal exercise performance (VAT, 6MWT). Increased HR peak, HRR, O2 pulse. Improved physical score of MLHFQ
Edelman et al 2011	64	3	Grade ≥1	Both	Improved exercise capacity (VO2peak, workload, exercise time) and submaximal exercise performance (VAT, 6MWT). Improved E/e'. Decreased LAVI. Improved SF-36 and MLHFQ scores. Reduced procollagen type 1 blood levels
Smart et al 2012	30	4	Delayed relax or Psnl	Aerobic	Increased exercise capacity (VO2peak, workload). Increased CO. Improved strain rate, SV, and CO, in patients with >10% increase in VO2peak
Haykowsky et al 2012	40	4	N/A	Aerobic	Improved exercise capacity (VO2peak). Increased HRpeak, HRR. Increased estimated peak and reserve A-VO2 Diff and peak and reserve circulatory power
Fujimoto et al 2012	20	12	N/A	Aerobic	Improved E/A ratio
Kitzman et al 2013	63	4	N/A	Aerobic	Improved exercise capacity (VO2peak, workload, exercise time) and submaximal exercise performance (VAT, 6MWT). increased HRpeak, Improved SF-36 score

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Higher Cardiorespiratory Fitness Predicts Long-term Survival in Patients with Heart Failure & Preserved Ejection Fraction The Henry Ford Exercise Testing (FIT) Project

Results:

- Mean age was 64 ±13 years, with 55% women, and 46% Black
- Over a median follow-up of 9.7 (5.2–18.9) years, there were 103 deaths
- In fully adjusted models, **moderate-high CRF was associated with 63% lower mortality risk (HR = 0.37, 95% CI: 0.18–0.73)** compared to the poor-CRF group
- In the propensity-matched cohort, HFpEF was associated with a HR of 2.3 (95% CI: 1.7–3.2) for mortality compared to non-HFpEF patients, which was attenuated to 1.8 (95% CI: 1.3–2.5) after adjusting for CRF

Orimoloye o, Kambhampati S, **Hicks A** et.al *Arch Med Sci* 2019

56

Higher Cardiorespiratory Fitness Predicts Long-term Survival in Patients with Heart Failure & Preserved Ejection Fraction The Henry Ford Exercise Testing (FIT) Project

Mortality Rates of the Study Population with HFpEF Stratified by METs Category

Death	Total, *n*, %	1–4 METs, *n*, %	5–6 METs, *n*, %	≥ 7 METs, *n*, %	*P*-value
At 1 year	10, 6.0	7, 7.8	3, 9.1	0, 0	0.14
At 2 years	17, 10.2	13, 14.4	4, 12.1	0, 0	0.03
At 3 years	26, 15.6	20, 22.22	5, 15.2	1, 2.3	0.01
At 4 years	31, 18.6	25, 27.8	5, 15.2	1, 2.3	0.001
At 5 years	40, 24.0	32, 35.6	6, 18.2	2, 4.6	< 0.001
At 7 years	59, 35.3	41, 45.6	13, 39.4	5, 11.4	< 0.001
At 10 years	78, 46.7	50, 55.6	16, 48.5	12, 27.3	0.008

Orimoloye o, Kambhampati S, **Hicks A** et.al *Arch Med Sci* 2019

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Amyloid Cardiomyopathy

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Amyloid the Great Confounder

- Many HFpEF studies may be neutral due to high number of unknown patients with cardiac amyloid confounding the outcomes
- Patients with amyloid traditionally do not tolerate GDMT for HF

Oghina S. et al. J Am Coll Cardiol HF. 2021;9(3):169-78.

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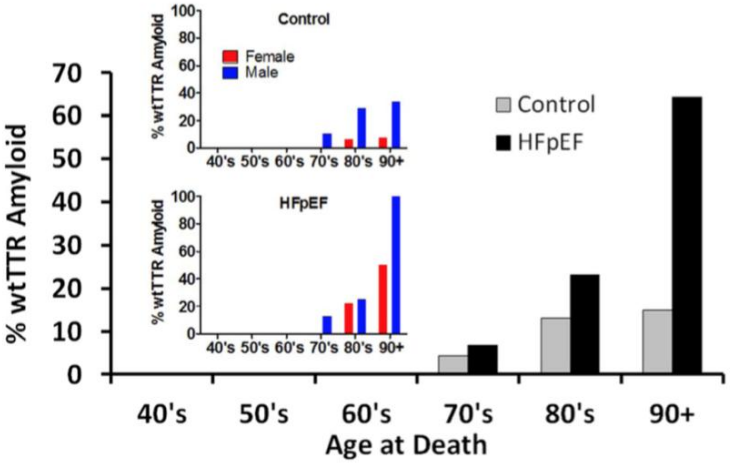
Left Ventricular Amyloid Deposition in Patients with HFpEF



Mohammed et al. JACC HF 2014

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Common Amyloid Types

Protein Class	Precursor Protein	Amyloid Type	Clinical Type
High Density Apolipoproteins	Serum Amyloid A protein	AA	Amyloid complicating chronic infections, inflammatory diseases, and some familial periodic fever syndromes (Mediterranean fever). Serum Amyloid A is an acute phase reactant.
Immunoglobulin (Ig)	Ig Light chain	AL	Myeloma Associated
Transport Protein	Transthyretin (TTR; prealbumin)	ATTRmt ATTRwt	Amyloid involving cardiac, renal, and nervous system caused by normal TTR tissue deposition over time (Wild Type) or from TTR gene point mutation

Adapted from UpToDate 2021

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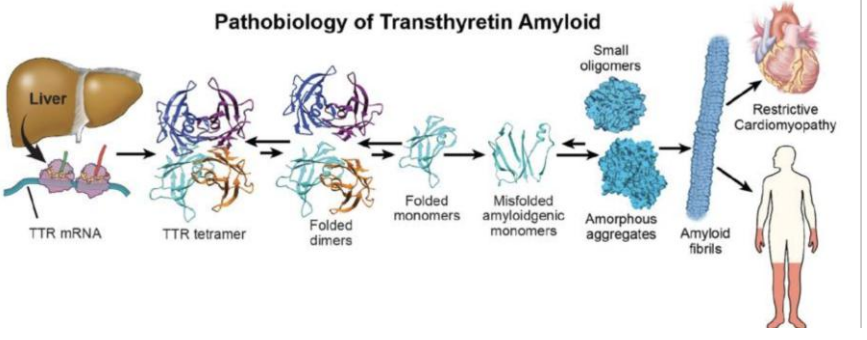
ATTR Pathophysiology



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ATTR Cardiac Amyloidosis

- ATTR Wild Type (ATTRwt) is most common transthyretin amyloidosis, with genetically unaltered deposition of transthyretin in body tissues after the 6th decade of life
- ATTR mutation (ATTRmt) involves a point mutation of the transthyretin gene resulting in a substitution of isoleucine for valine at position 122 (Val122Ile)

Cornwell GG, Murdoch WL, Kyle RA, Westermark P, Pitkänen P. Frequency and distribution of senile cardiovascular amyloid. A clinicopathologic correlation.Am J Med. 1983; 75:618–623.

Shah KB, Mankad AK, Castano A, Akinboboye OO, Duncan PB, Fergus IV, Maurer MS. Transthyretin Cardiac Amyloidosis in Black Americans. Circ Heart Fail. 2016 Jun;9(6):e002558. doi: 10.1161/CIRCHEARTFAILURE.115.002558. PMID: 27188913; PMCID: PMC4874558.

63

ATTRmt-CM Genotype

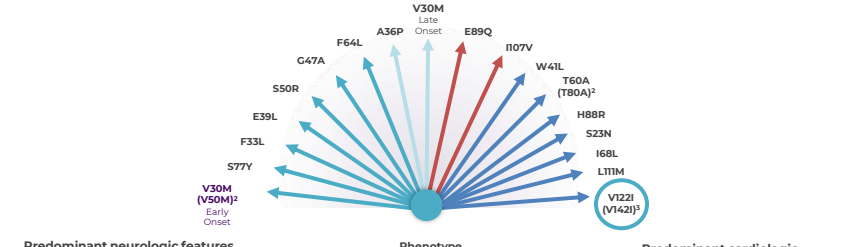
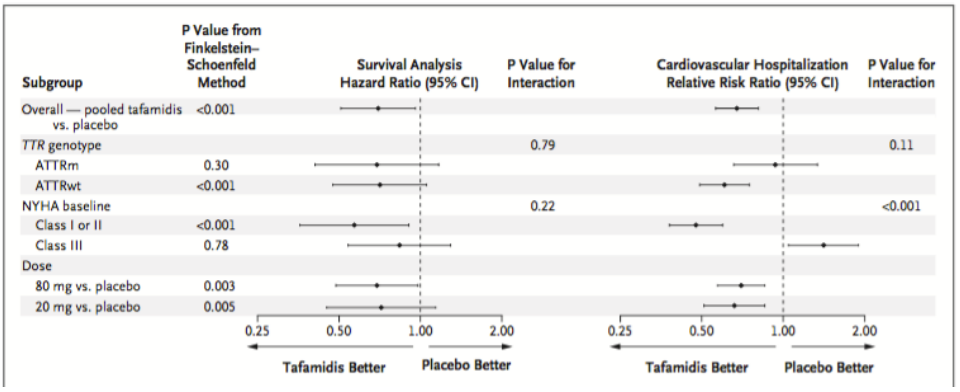


Figure adapted from Poli et al.[1]

Poli L, et al. *Front Neurol*. 2023;14:1242815.2. Griffin JM, et al. *JACC CardioOncol*. 2021;3(4):488-505. 3. Buxbaum JN, Ruberg FL. *Genet Med*. 2017;19(7):733-742.

64

Tafamadis Reduces Mortality TTR in Amyloid Cardiomyopathy



Maurer et al. NEJM 2018

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Prevalence of ATTR-CM in Other Conditions

AORTIC STENOSIS	HFpEF	CARPAL TUNNEL SYNDROME	LVWT	INHERITED VARIANTS
~16% among older adults undergoing TAVR for severe AS[1]	**~10%-13.3%** among hospitalized patients with HFpEF[2,3]	**~10%** among older adults undergoing carpal tunnel release surgery[4]	**~5%** among cases with increased LVWT of 18 mm[6]	**~3%-4%** of African Americans with V122I variant[8]
• ATTR-CM is associated with a severe, low-flow, low-gradient AS phenotype with mildly reduced ejection fraction[1]	• ATTRwt-CM may cause HFpEF[2]	• Carpal tunnel syndrome has a prevalence of 15% to 60% in ATTR-CM[5] • Symptoms may manifest several years before cardiac symptoms appear[5]	• ATTR-CM affects 21% of patients 90 years of age and older with increased LVWT ≥12 mm[7]	• There is an ~38% prevalence of HF among this population[9]

AS, aortic stenosis; LVWT, left ventricular wall thickness; TAVR, transcatheter aortic valve replacement.

1. Castaño A, et al. *Eur Heart J*. 2017;38(38):2879-2887. 2. González-López E, et al. *Eur Heart J*. 2015;36(38):2585-2594. 3. Hahn VS, et al. *JACC Heart Fail*. 2020;8(9):712-724 4. Sperry BW, et al. *J Am Coll Cardiol*. 2018;72(17):2040-2050. 5. Brito D, et al. *Glob Heart*. 2023;18(1):59. 6. Damy T, et al. *Eur Heart J*. 2016;37(23):1826-1834. 7. AbouEzzeddine OF, et al. *JAMA Cardiol*. 2021;6(11):1267-1274.
8. Quarta CC, et al. *N Engl J Med*. 2015;372(1):21-29. 9. Shah KB, et al. *Circ Heart Fail*. 2016;9(6):e002558.

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ATTRmt Cardiac Amyloidosis

ATTRmt Cardiac Amyloid is a great mimicker
- HTN Heart Disease
- Hypertrophic Cardiomyopathy

Approximately 4% of African Americans in the US carry the Val122Ile mutation

Diagnosis tends to occur late in disease course and involve multiple organ systems (Cardiac, Nervous System, Renal)

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Rule Out AL Amyloidosis

- Serum Kappa/Lambda Free Light Chain Assay
  - < 0.26 or > 1.65
  - Abnormality based on renal function
- Serum Immunofixation
  - Detects for monoclonal proteins

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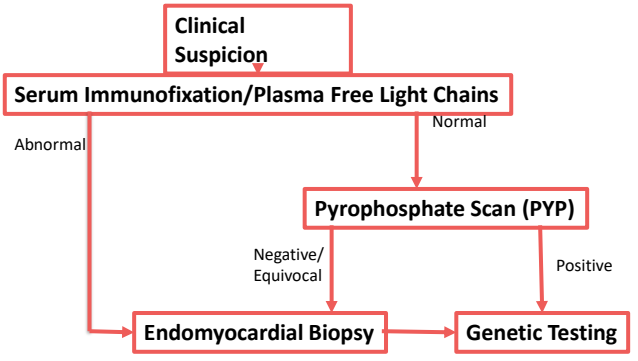
Diagnose Cardiac Amyloidosis



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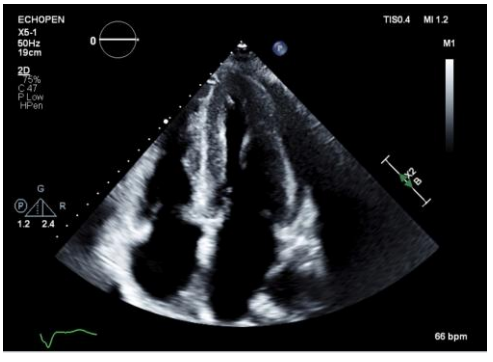
Echocardiogram



- Diastolic Dysfunction
- Increased LV wall thickness >12 mm
- Thickening of valve leaflets and interatrial septum
- Pleural and pericardial effusion(s)
- Biatrial enlargement

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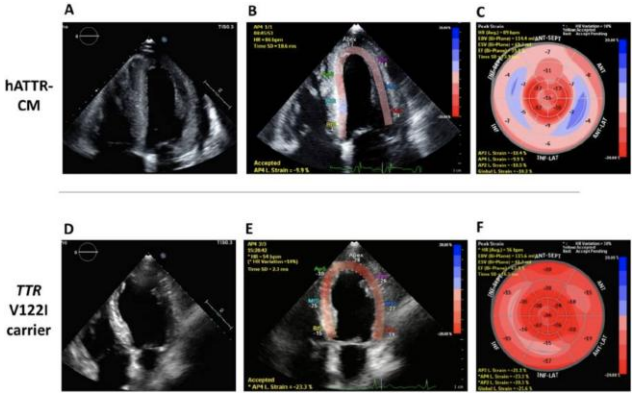
Echocardiogram & Longitudinal Strain Patterns



ATTR CM

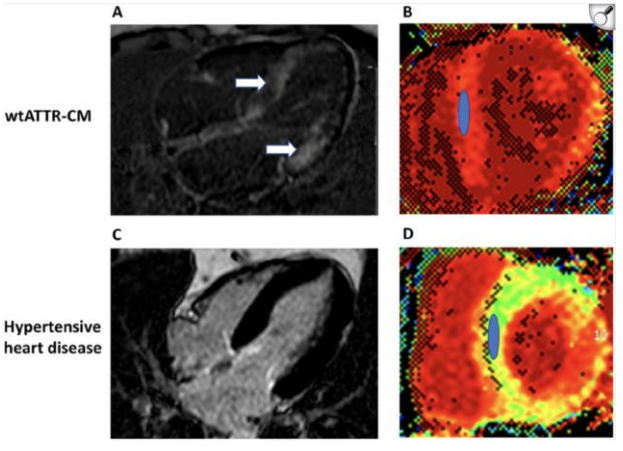
- > 2:1 apical:basal ratio or "cherry on top"
- Abnormal GLS < -15% (-10.3%)

No Amyloid

- Bullseye map shows absence of apical sparing
- Normal GLS < -15% (-21%)

Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin Amyloid Cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019 Jun 11;73(22):2872-2891. doi: 10.1016/j.jacc.2019.04.003. PMID: 31171094; PMCID: PMC6724183.

71



Cardiac MRI

A. **Late Gadolidium Enhancement (LGE)**
- Consistent with ATTR

B. **Extracellular Volume (ECV)**
- High ECV
- Consistent with ATTR (60%)

C. **No LGE**
- Normal

D. **Normal ECV**
- No ATTR (27%)

Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin Amyloid Cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019 Jun 11;73(22):2872-2891. doi: 10.1016/j.jacc.2019.04.003. PMID: 31171094; PMCID: PMC6724183.

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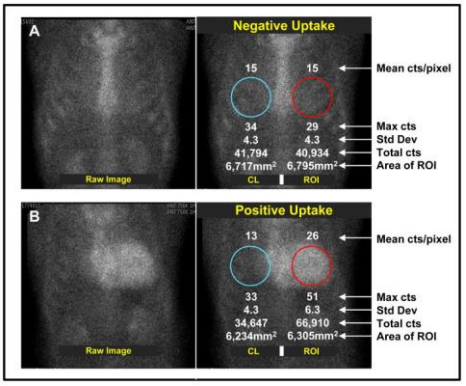
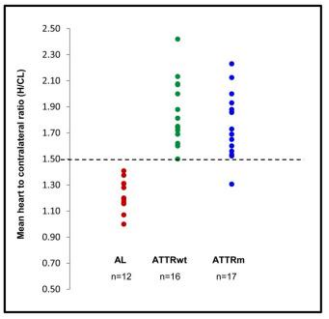
Pyrophosphate Scan for Cardiac ATTR



Positive scan: 97% sensitivity, 100% specificity for identifying ATTR cardiac amyloidosis (p<0.0001)



Bokhari S, Castaño A, Pozniakoff T, Deslisle S, Latif F, Maurer MS. (99m)Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. Circ Cardiovasc Imaging. 2013 Mar 1;6(2):195-201. doi: 10.1161/CIRCIMAGING.112.000132. Epub 2013 Feb 11. PMID: 23400849; PMCID: PMC3727049.

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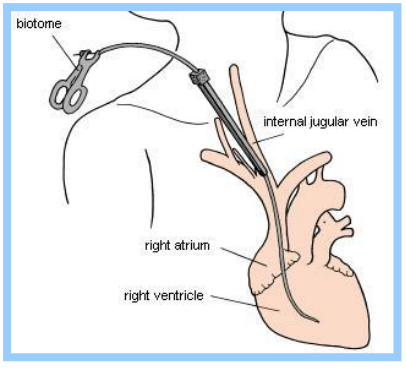
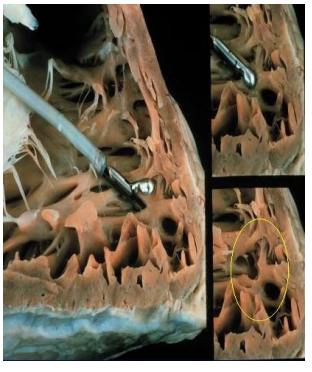
Heart Biopsy





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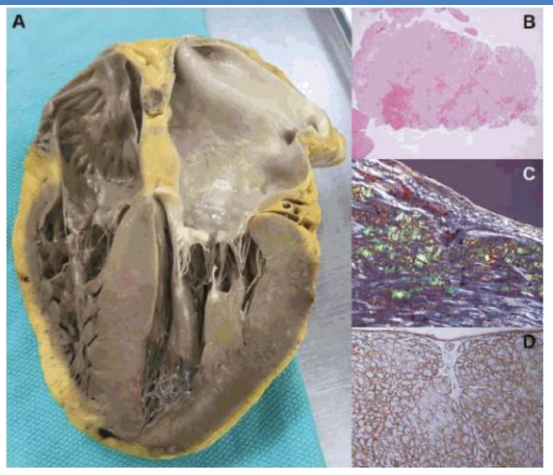

Endomyocardial Biopsy

A. **Autopsy**
- Biventricular Thickening
- Biatrial Dilation
- Thick of Mitral & Tricuspid valves

B. **Congo red staining**
- Hemoxylin & eosin staining

C. **Polarized Light Microscopy**
- Apple-Green birefringence

D. **Immunohistochemistry**
- Typing amyloid (AL VS ATTR)

Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin Amyloid Cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019 Jun 11;73(22):2872-2891. doi: 10.1016/j.jacc.2019.04.003. PMID: 31171094; PMCID: PMC6724183.

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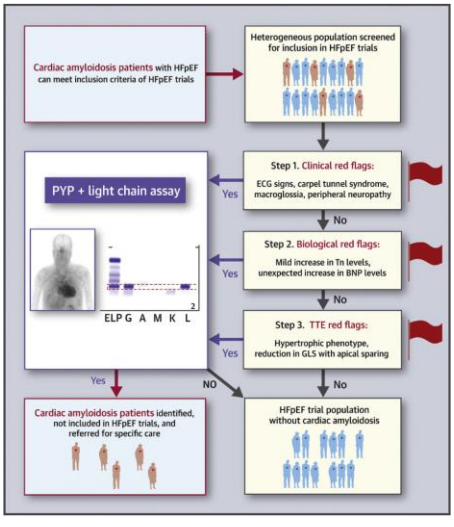
Strategy for Screening Amyloid in Clinical Trials



Oghina S. et al. J Am Coll Cardiol HF. 2021;9(3):169-78.

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2022 ACC/AHA/HFSA Guidelines

COR	LOE	Recommendations
1	B-R	1. In select patients with wild-type or variant transthyretin cardiac amyloidosis and NYHA class I to III HF symptoms, transthyretin tetramer stabilizer therapy (tafamidis) is indicated to reduce cardiovascular morbidity and mortality.[1]
Value Statement: Low Value (B-NR)		2. At 2020 list prices, tafamidis provides low economic value (>$180 000 per QALY gained) in patients with HF with wild-type or variant transthyretin cardiac amyloidosis.[2]
2a	C-LD	3. In patients with cardiac amyloidosis and AF, anticoagulation is reasonable to reduce the risk of stroke regardless of the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack [TIA], vascular disease, age 65 to 74 years, sex category) score.[3,4]

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FDA Approved Therapies for HFpEF

- Empagliflozin (Class 2a)
- Spironolactone (Class 2b)
- Sacubitril-Valsartan (Class 2b)
- CardioMems
- Amyloid Therapy

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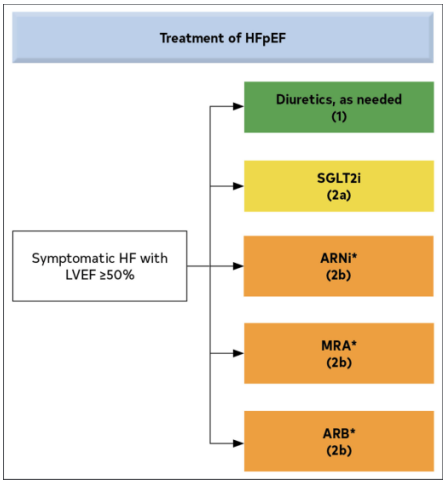
2022 ACC/AHA/HFSA Guidelines



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HFpEF SUMMARY

- SGLT2-I first line therapy for HFpEF
- Exercise Training is beneficial for QOL
- Fitness can predict long-term survival
- Rule out Amyloidosis in HFpEF patients
- Spironolactone in appropriate patients
- Sacubitril-Valsartan in lower EFs
- Consider CardioMems to reduce HHF
- Future Therapies

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