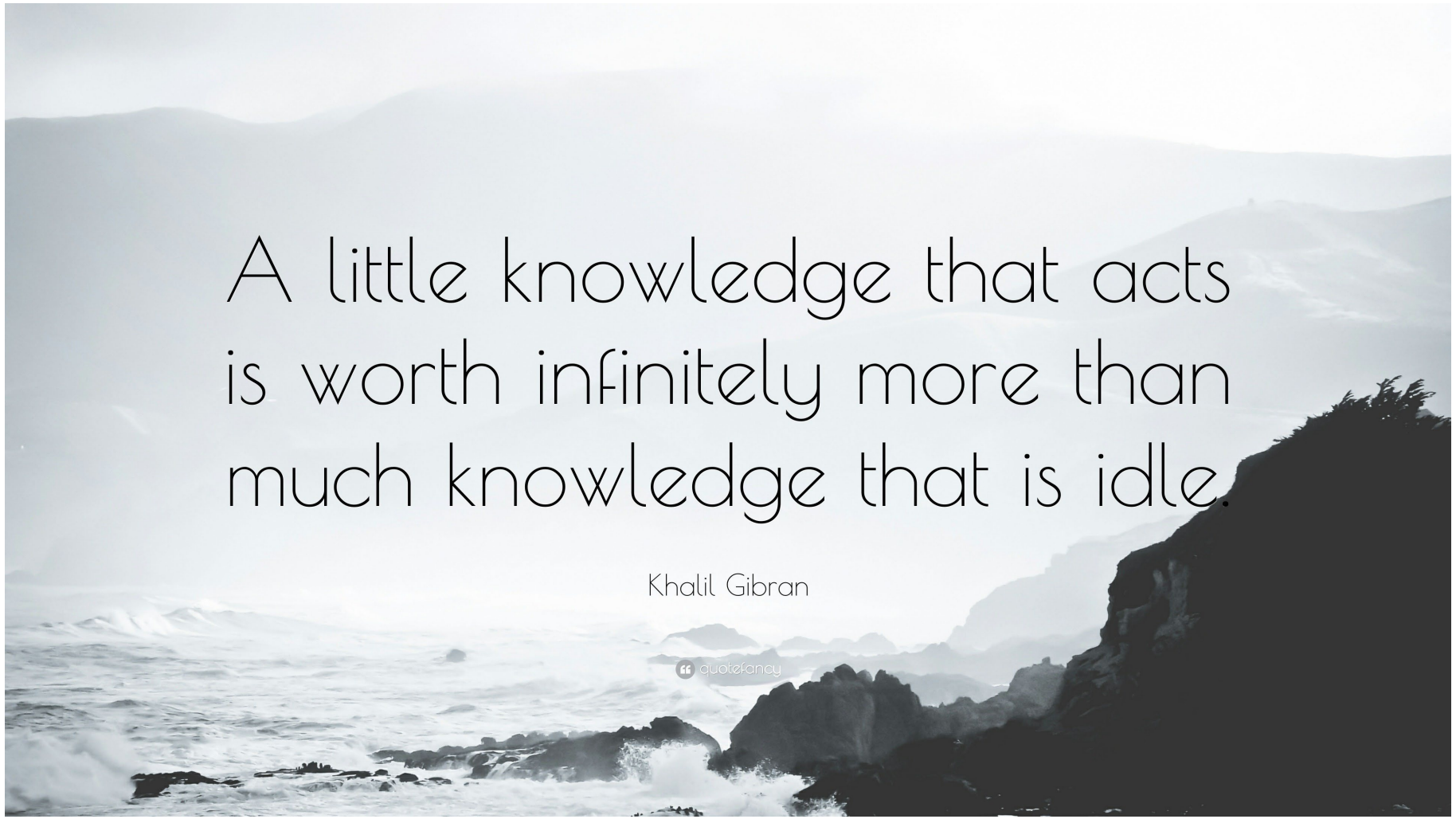
Heart Failure with Preserved EF Clinical Pearls

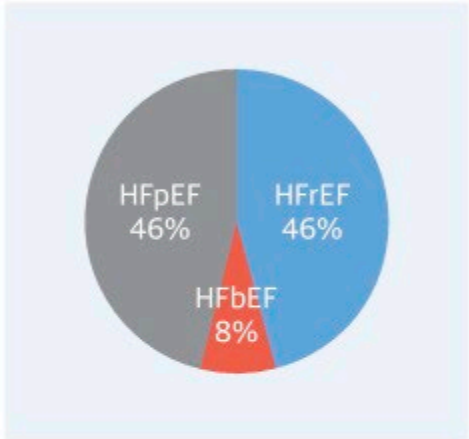
Kariann Abbate, MD

April 17, 2026

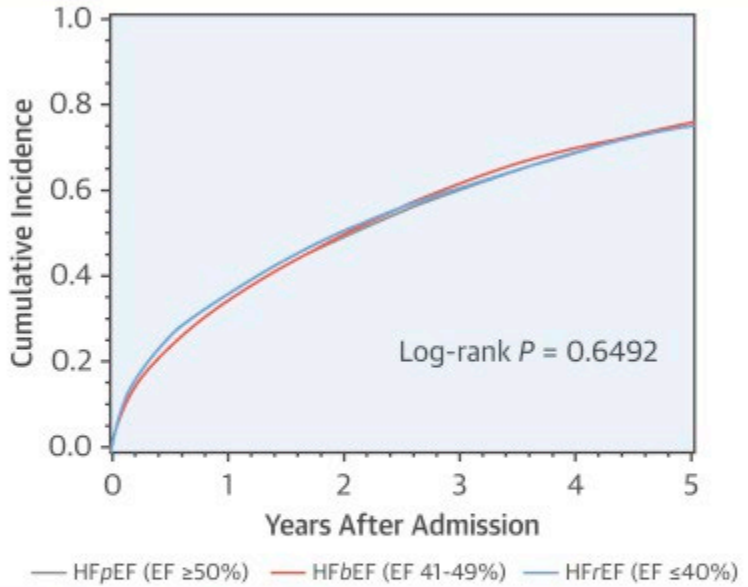

A little knowledge that acts is worth infinitely more than much knowledge that is idle.
Khalil Gibran
quotefancy

CENTRAL ILLUSTRATION: 5-Year Outcomes in Patients Hospitalized With HF With Preserved, Borderline, and Reduced EF

Heart Failure



5-Year Mortality



Outcomes – 5-Year Event Rates (%)					
	Mortality	Readmission	CV Readmission	HF Readmission	Mortality/Readmission
HFrEF	75.3	82.2	63.9	48.5	96.4
HFbEF	75.7	85.7	63.3	45.2	97.2
HFpEF	75.7	84.0	58.9	40.5	97.3

Shah, K.S. et al. J Am Coll Cardiol. 2017;70(20):2476-86.

Hypertension

Renal disease

Aging

Valvular disease

Diabetes

Metabolic syndrome/obesity

Infiltrative cardiomyopathies

- Amyloid
- Sarcoid
- Fabry
- HCM

3 Pillars of Therapy for Heart Failure with EF > 40%

SGLT-2i

nsMRA

GLP1 or GLP1/GIP RA (if obese)

SGLT2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials

Muthiah Vaduganathan, Kieran F Docherty*, Brian L Claggett, Pardeep S Jhund, Rudolf A de Boer, Adrian F Hernandez, Silvio E Inzucchi, Mikhail N Kosiborod, Carolyn S P Lam, Felipe Martinez, Sanjiv J Shah, Akshay S Desai, John J V McMurray†, Scott D Solomon†*

Lancet 2022; 400: 757-67

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This online publication has been corrected. The corrected version first appeared at thelancet.com on January 12, 2023

See Comment page 711

*Joint first authors

Summary

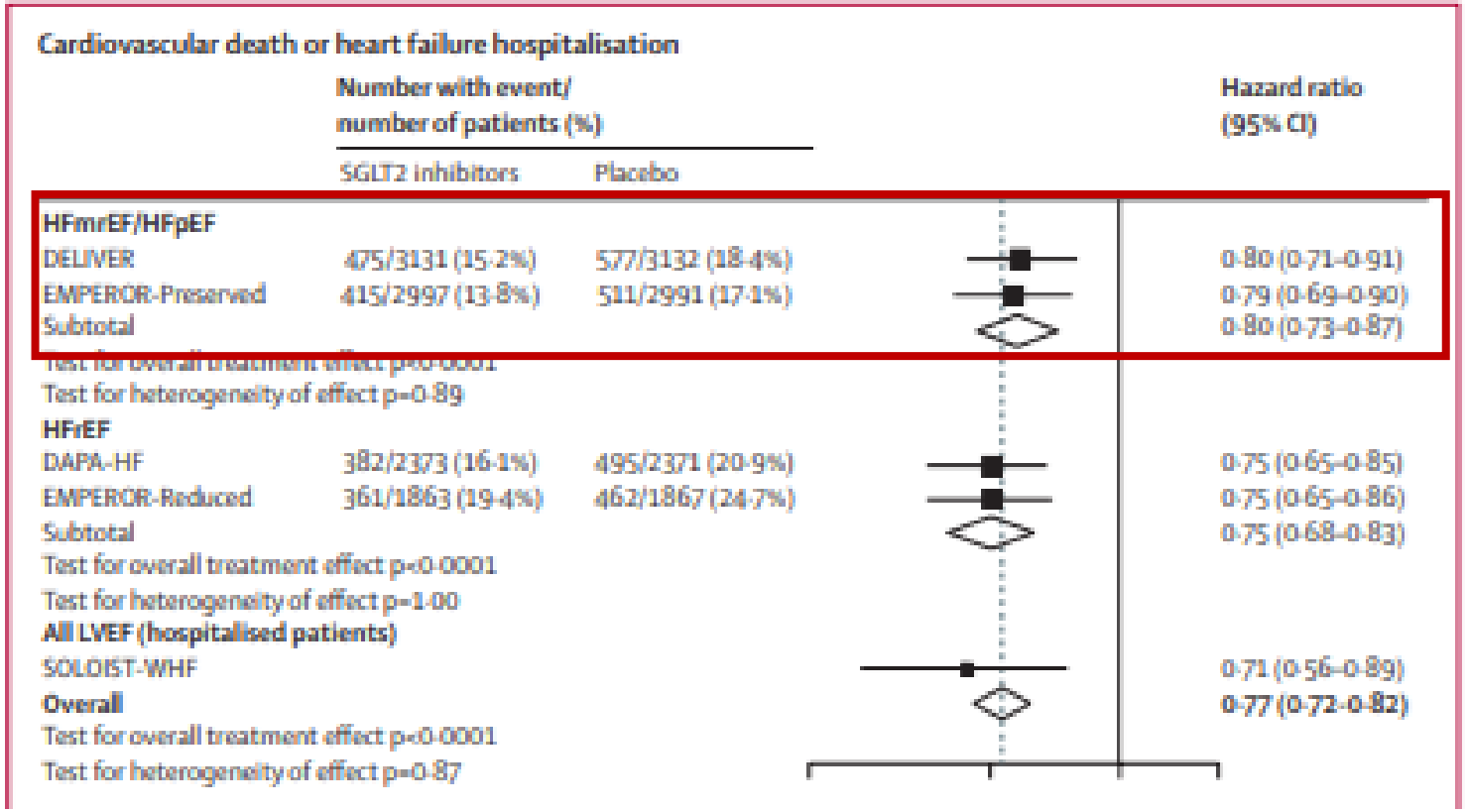
Background SGLT2 inhibitors are strongly recommended in guidelines to treat patients with heart failure with reduced ejection fraction, but their clinical benefits at higher ejection fractions are less well established. Two large-scale trials, DELIVER and EMPEROR-Preserved, in heart failure with mildly reduced or preserved ejection fraction have been done, providing power to examine therapeutic effects on cardiovascular mortality and in patient subgroups when combined with the earlier trials in reduced ejection fraction.

Methods We did a prespecified meta-analysis of DELIVER and EMPEROR-Preserved, and subsequently included trials that enrolled patients with reduced ejection fraction (DAPA-HF and EMPEROR-Reduced) and those admitted to hospital with worsening heart failure, irrespective of ejection fraction (SOLOIST-WHF). Using trial-level data with harmonised endpoint definitions, we did a fixed-effects meta-analysis to estimate the effect of SGLT2 inhibitors on various clinical endpoints in heart failure The primary endpoint for this meta-analysis was time from randomisation to the c of the composite of cardiovascular death or hospitalisation for heart failure. We assessed heterogeneity in effects for the primary endpoint across subgroups of interest. This study is registered with PROSPERO, CRD420

Findings Among 12 251 participants from DELIVER and EMPEROR-Preserved, SGLT2 inhibitors reduced cardiovascular death or first hospitalisation for heart failure (hazard ratio 0·80 [95% CI 0·73–0·87]) with reductions in both components: cardiovascular death (0·88 [0·77–1·00]) and first hospitalisation for he (0·74 [0·67–0·83]). In the broader context of the five trials of 21 947 participants, SGLT2 inhibitors reduced composite cardiovascular death or hospitalisation for heart failure (0·77 [0·72–0·82]), cardiovascular d [0·79–0·95]), first hospitalisation for heart failure (0·72 [0·67–0·78]), and all-cause mortality (0·92 [0· These treatment effects for each of the studied endpoints were consistently observed in both the trials of he with mildly reduced or preserved ejection fraction and across all five trials. Treatment effects on the primary were generally consistent across the 14 subgroups examined, including ejection fraction.

Interpretation SGLT2 inhibitors reduced the risk of cardiovascular death and hospitalisations for heart f broad range of patients with heart failure, supporting their role as foundational therapy for heart failure, i of ejection fraction or care setting.

Funding None.

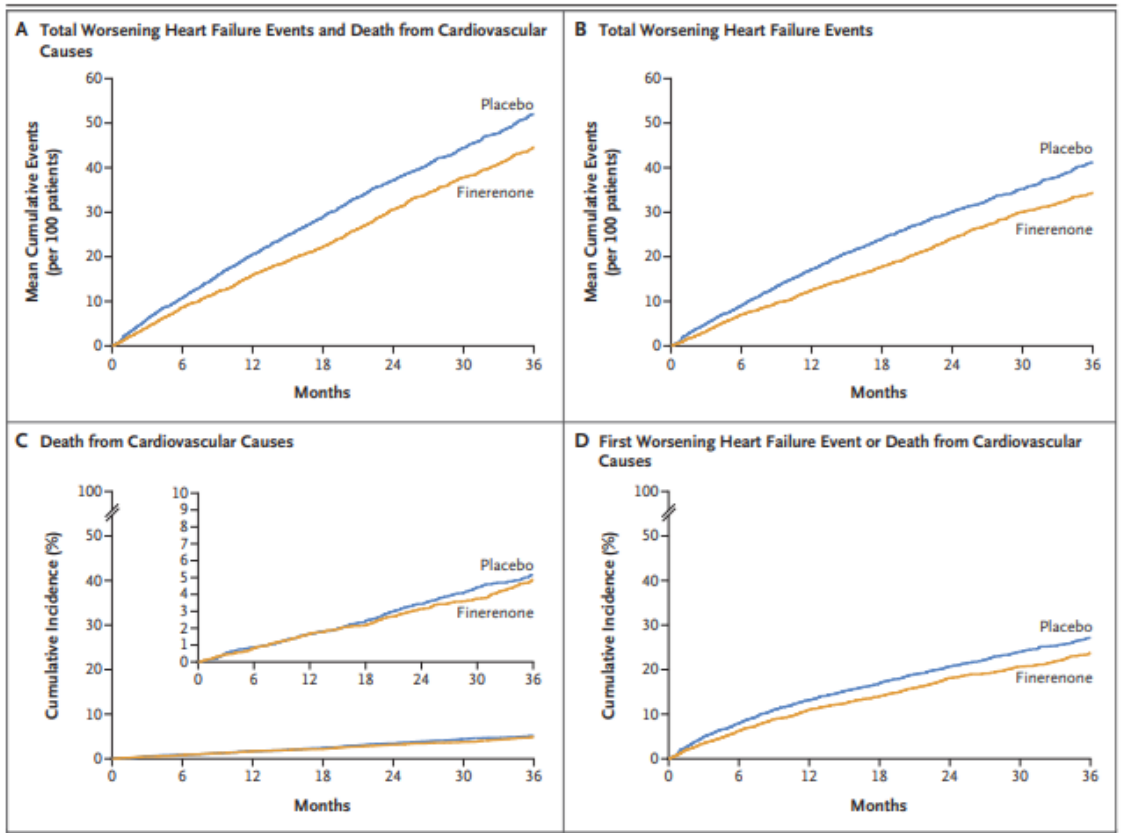


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 24, 2024 VOL. 391 NO. 16

Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, M. Vaduganathan, B. Claggett, P.S. Jhund, A.S. Desai, A.D. Henderson, C.S.P. Lam, B. Pitt, M. Senni, S.J. Shah, A.A. Voors, F. Zannad, I.Z. Abidin, M.A. Alcocer-Gamba, J.J. Atherton, J. Bauersachs, M. Chang-Sheng, C.-E. Chiang, O. Chioncel, V. Chopra, J. Comin-Colet, G. Filippatos, C. Fonseca, G. Gajos, S. Goland, E. Goncalvesova, S. Kang,

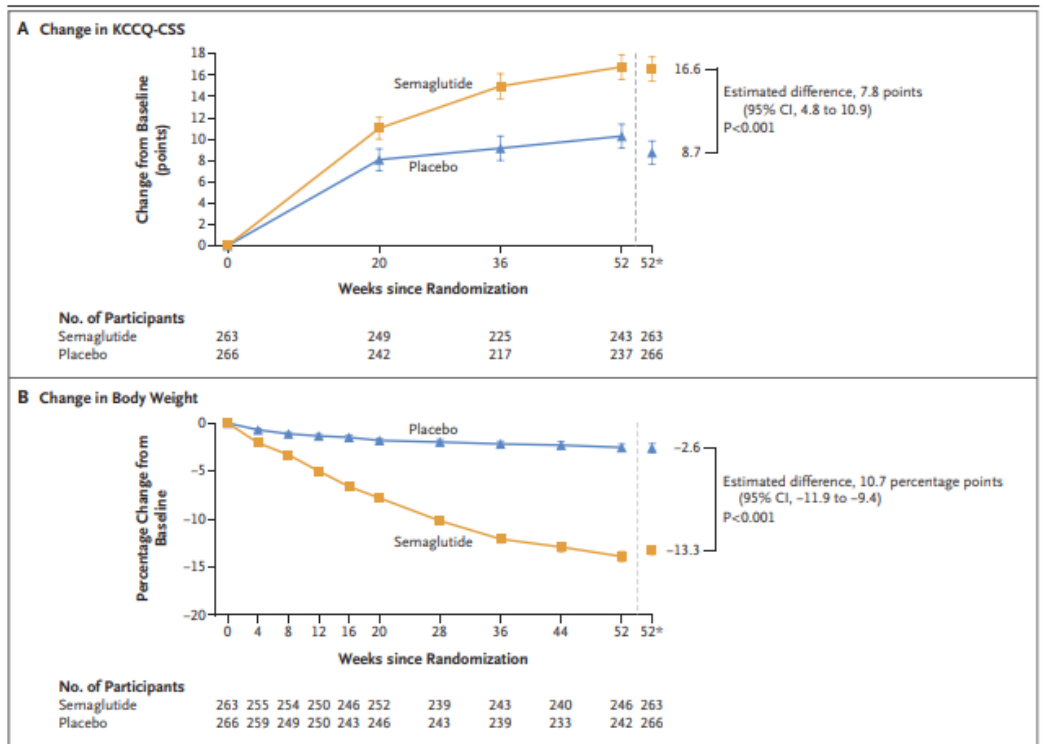


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 21, 2023 VOL. 389 NO. 12

Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

M.N. Kosiborod, S.Z. Abildstrøm, B.A. Borlaug, J. Butler, S. Rasmussen, M. Davies, G.K. Hovingh, D.W. Kitzman, M.L. Lindegaard, D.V. Møller, S.J. Shah, M.B. Treppendahl, S. Verma, W. Abhayaratna, F.Z. Ahmed, V. Chopra, J. Ezekowitz, M. Fu, H. Ito, M. Lelonek, V. Melenovsky, B. Merkely, J. Núñez, E. Perna, M. Schou, M. Senni, K. Sharma, P. Van der Meer, D. von Lewinski, D. Wolf, and M.C Petrie, for the STEP-HFpEF Trial Committees and Investigators*



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 30, 2025 VOL. 392 NO. 5

Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity

Milton Packer, M.D., Michael R. Zile, M.D., Christopher M. Kramer, M.D., Seth J. Baum, M.D., Sheldon E. Litwin, M.D., Venu Menon, M.D., Junbo Ge, M.D., Govinda J. Weerakkody, Ph.D., Yang Ou, Ph.D., Mathijs C. Bunck, M.D., Karla C. Hurt, B.S.N., Masahiro Murakami, M.D., and Barry A. Borlaug, M.D., for the SUMMIT Trial Study Group*

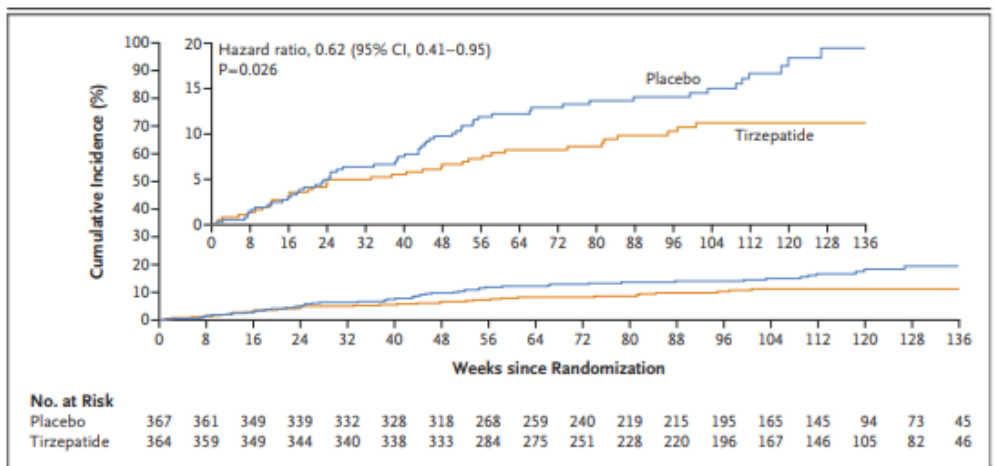
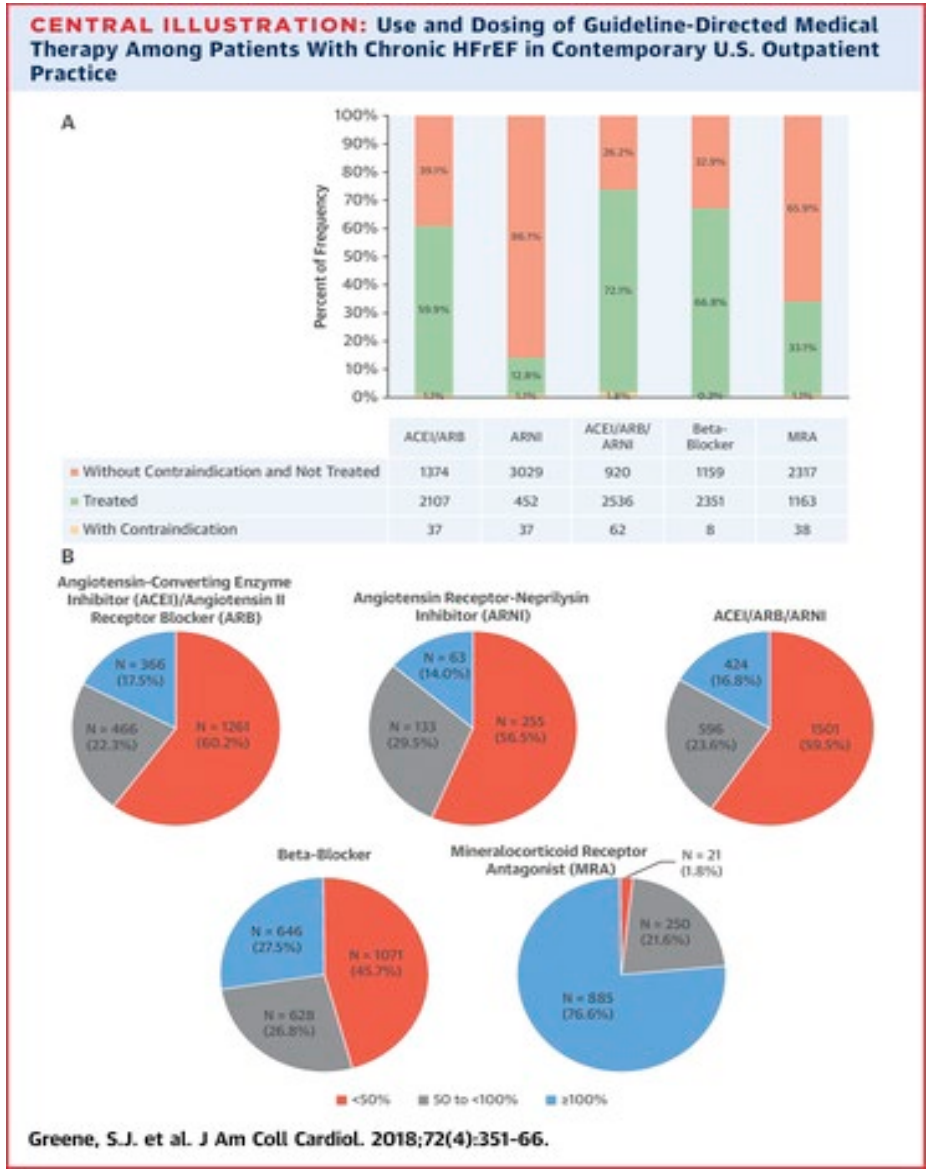


Figure 1. Composite of Death from Cardiovascular Causes or a Worsening Heart-Failure Event.

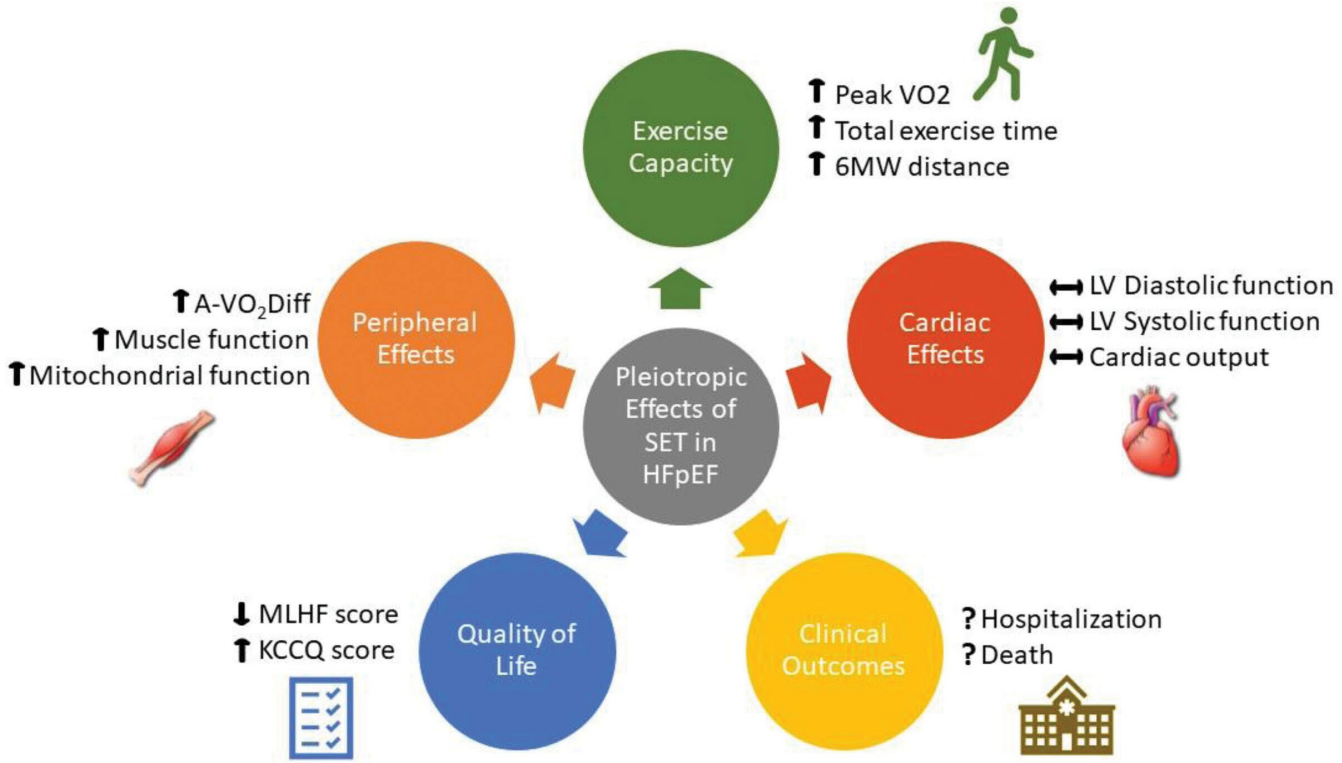
Shown is the cumulative incidence of death from cardiovascular causes or a worsening heart-failure event (the composite primary end point), assessed in a time-to-first-event analysis, among 364 patients who received tirzepatide and 367 patients who received placebo. The inset shows the same data on an expanded y axis.



Stephen J. Greene et al. *JACC* 2018; 72:351-366.

JACC®

Benefits of Exercise in HFpEF



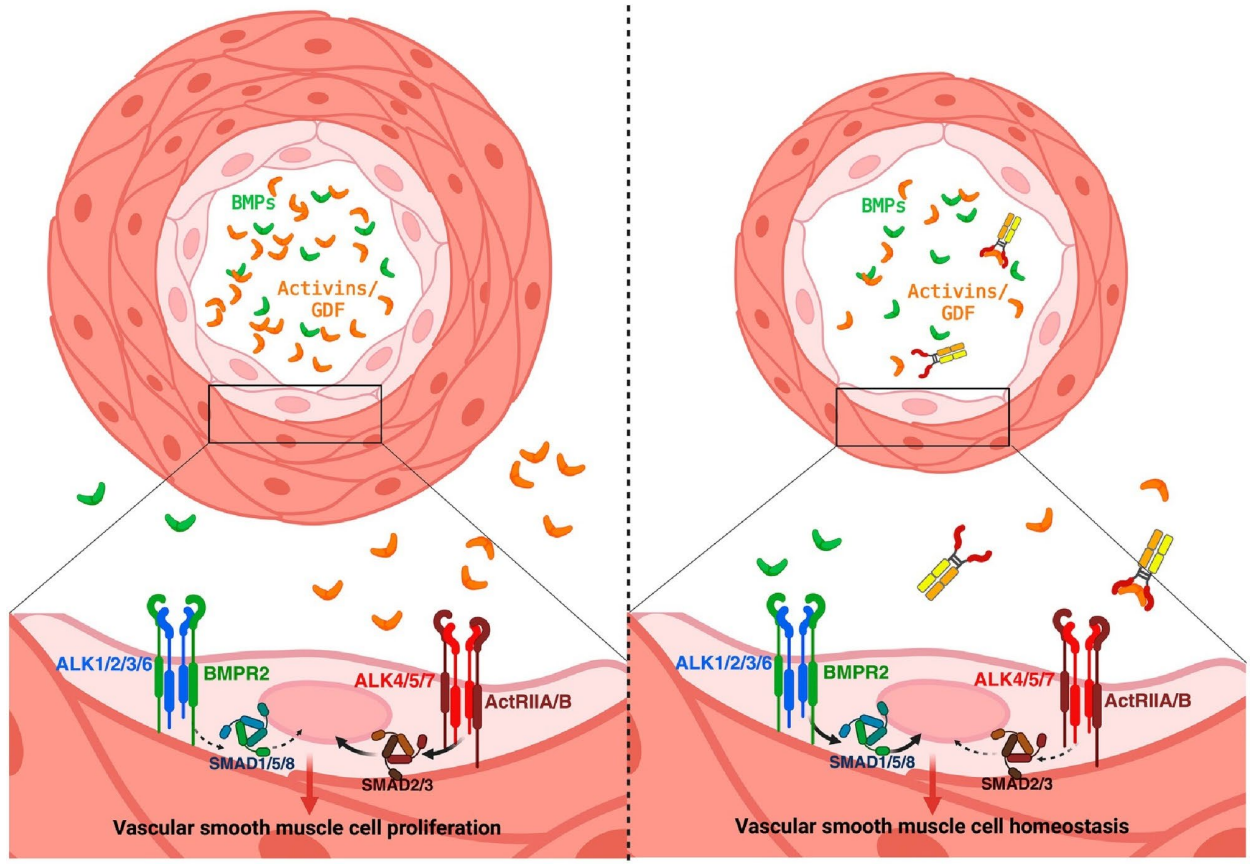
Vandana Sachdev. Circulation. Supervised Exercise Training for Chronic Heart Failure With Preserved Ejection Fraction: A Scientific Statement From the American Heart Association and American College of Cardiology, Volume: 147, Issue: 16, Pages: e699-e715, DOI: (10.1161/CIR.0000000000001122)

RESEARCH ARTICLE | Originally Published 29 March 2026 |

Sotatercept for Combined Post- and Pre-capillary Pulmonary Hypertension Associated With Heart Failure: Results from the Phase 2, Randomized, Placebo-Controlled CADENCE Study

Mardi Gomberg-Maitland, Ryan J. Tedford, David Langleben, Stephan Rosenkranz, Barry Miller, Aaron D. Jones, Alessia Urbinati, Ciaran J. McMullan, Alexandra G. Cornell, and Jean-Luc Vachiery | AUTHOR INFO & AFFILIATIONS

Circulation • New online • https://doi.org/10.1161/CIRCULATIONAHA.126.079918



The imbalance of anti-proliferative (BMPR-II-mediated) and pro-proliferative (ActRIIA-mediated) signalling leads to vascular cell hyperproliferation and pulmonary arteries remodelling in **pulmonary arterial hypertension**

Sotatercept improves the balance between the growth-promoting activin/GDF pathway and the BMP pathway and attenuates pulmonary vessels medial hypertrophy

Trends in Pharmacological Sciences

Don’t be asleep at the wheel…

HFrEF Unlocked: Practical Pearls that Change Outcomes

Samit Shah, MD

Advanced Heart Failure/Transplant

Medical Director of Mechanical Circulatory Support

Valley Health System

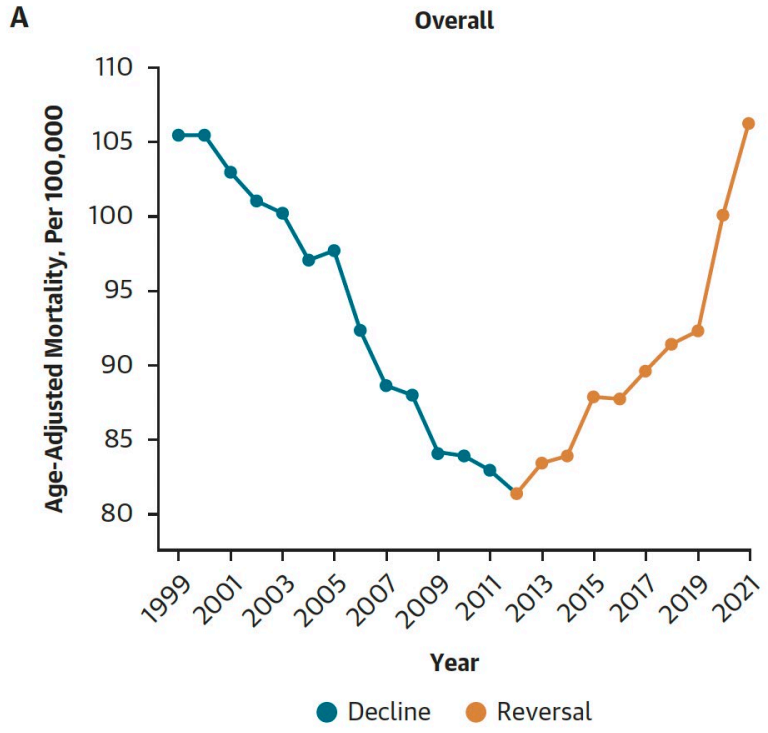
The Heart Failure Paradox

Heart Failure Deaths Are Increasing. New Treatments Could Help.

New drugs and a growing awareness of the common condition offer hope for patients.

CNN Health | Life, But Better | Fitness | Food | Sleep | Mindfulness | Relationships | Watch

Heart failure deaths on the rise in younger US adults, researchers say



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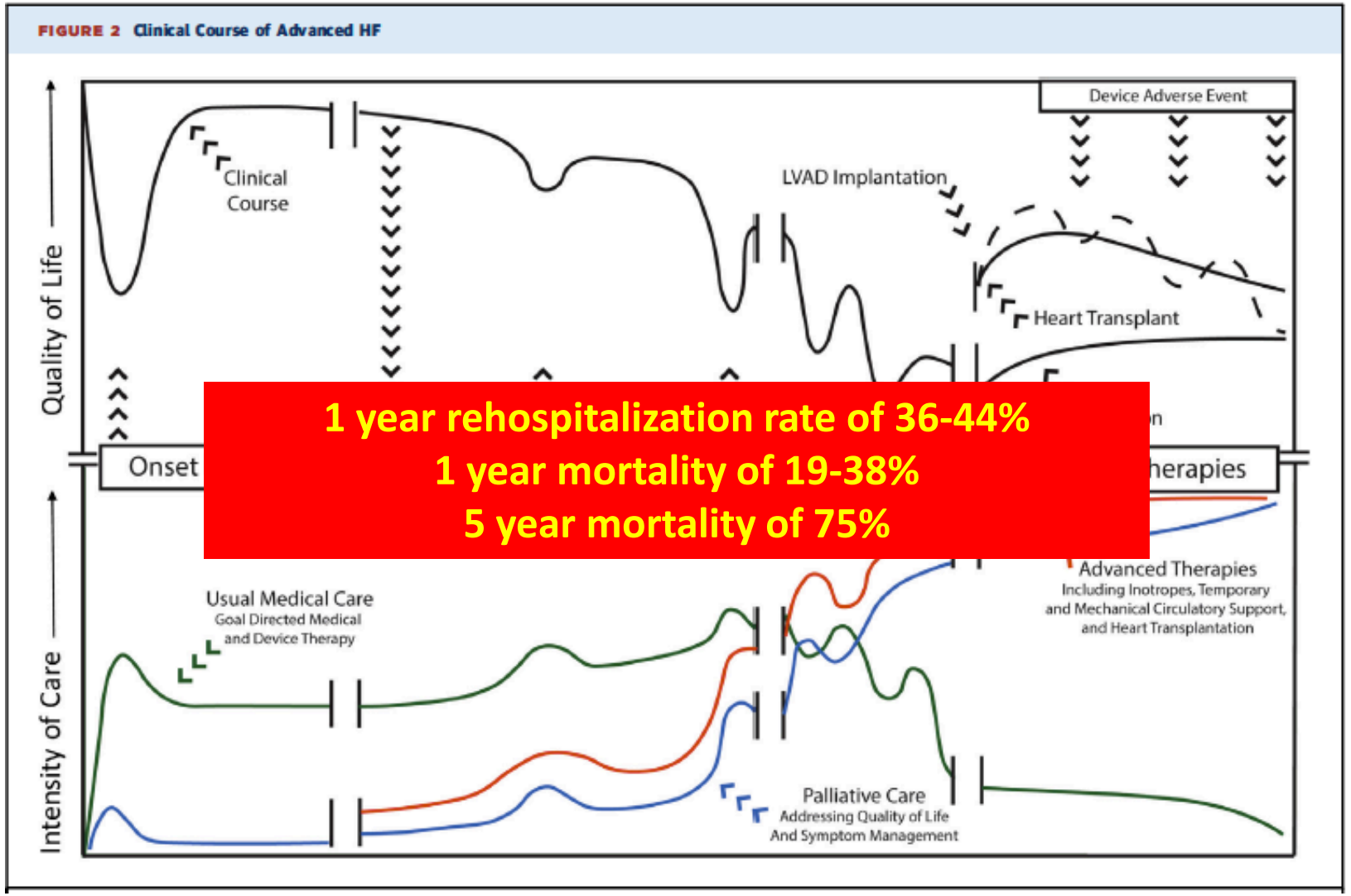
HF Hospitalization = Sentinel Event



J Am Coll Cardiol HF 2020; 8: 523-36

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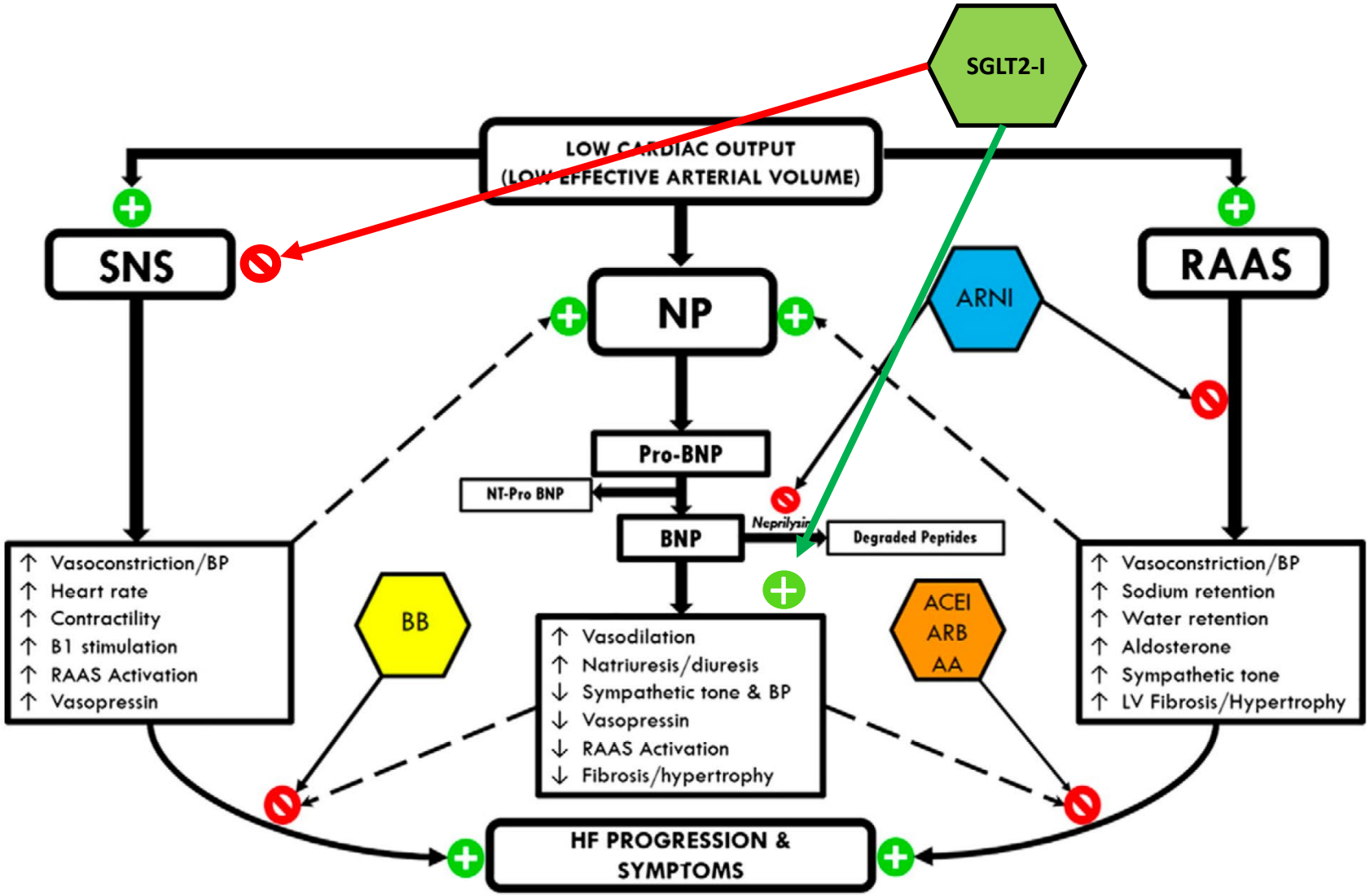
Pathophysiology and Targets of HF



Adapted from Biglane et al. *Prog Cardiovasc Disease* (60) 2017: 187-197

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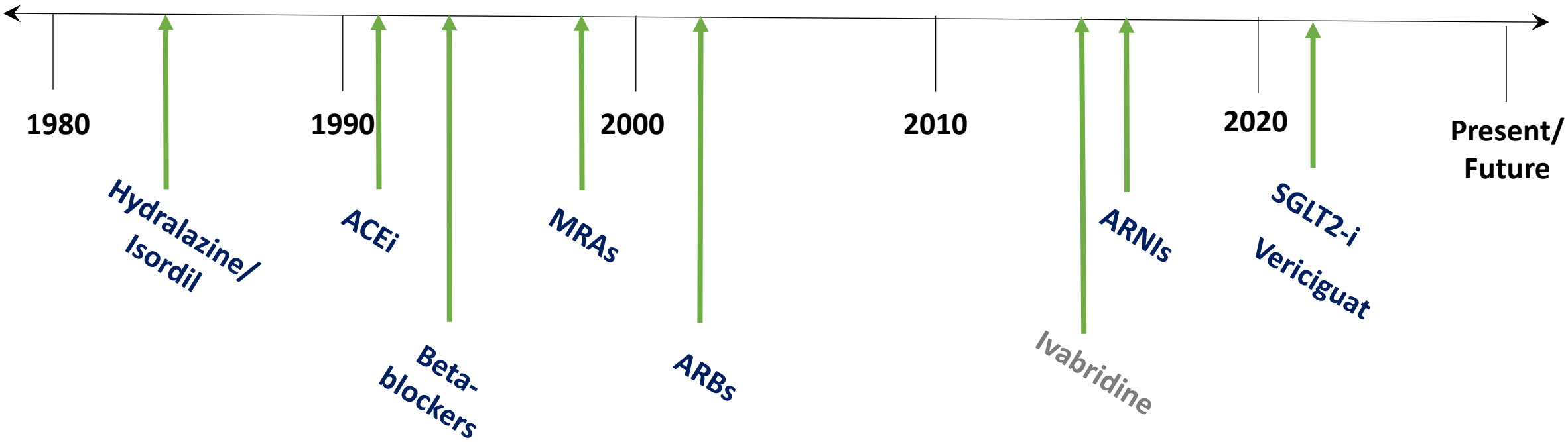
Pharmacologic Advancements



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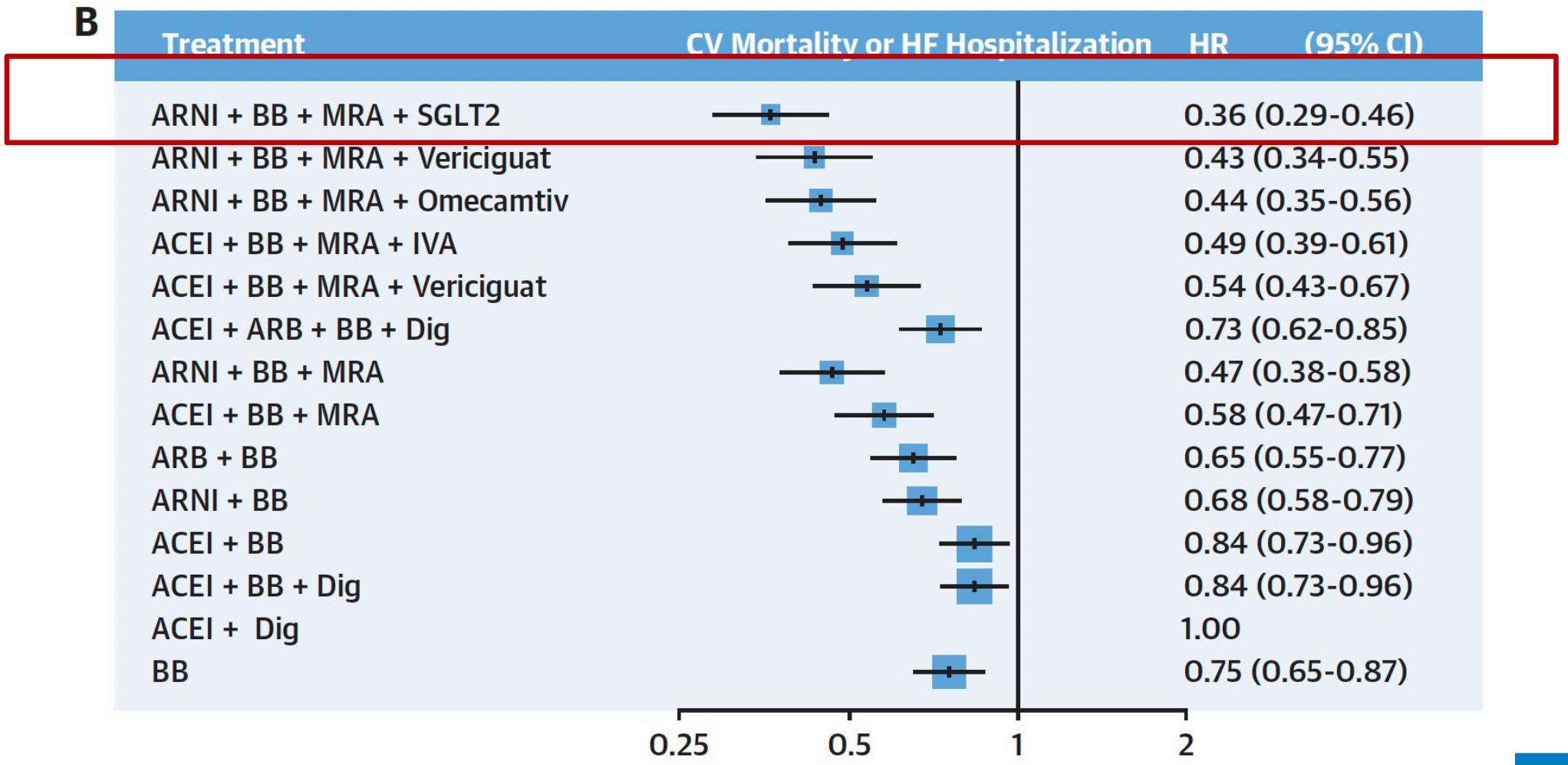
Quadruple Therapy



Tromp et al. J Am Coll Cardiol HF 2022; 10: 73-84

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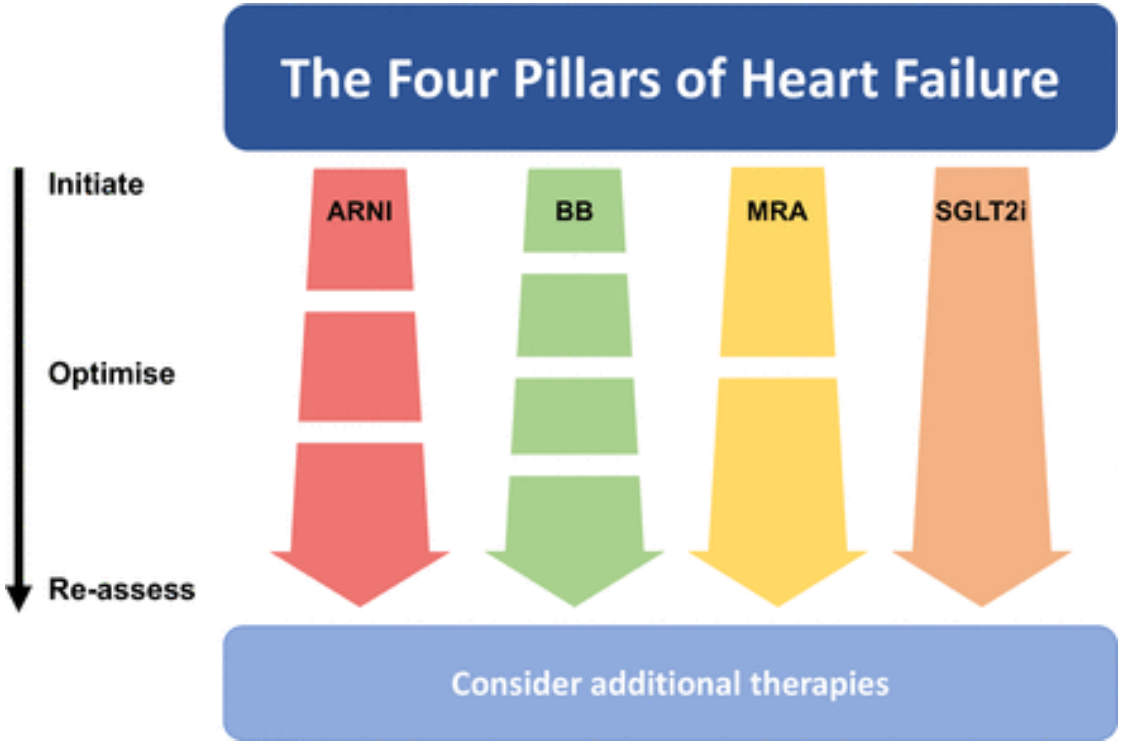
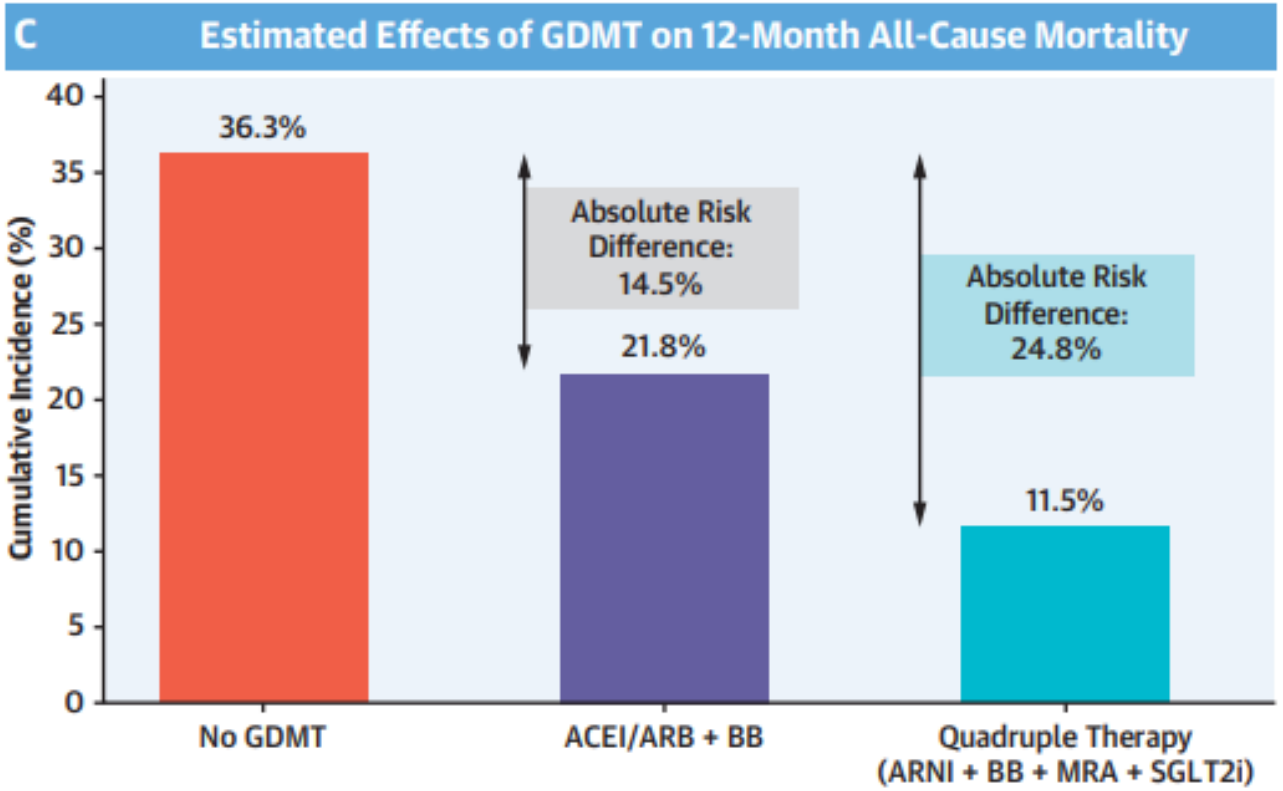
Quadruple Therapy for HFrEF





Start Low Dose in Parallel and Uptitrate

Greene et al. JACC Heart Failure 2024; 12: 1365-1377

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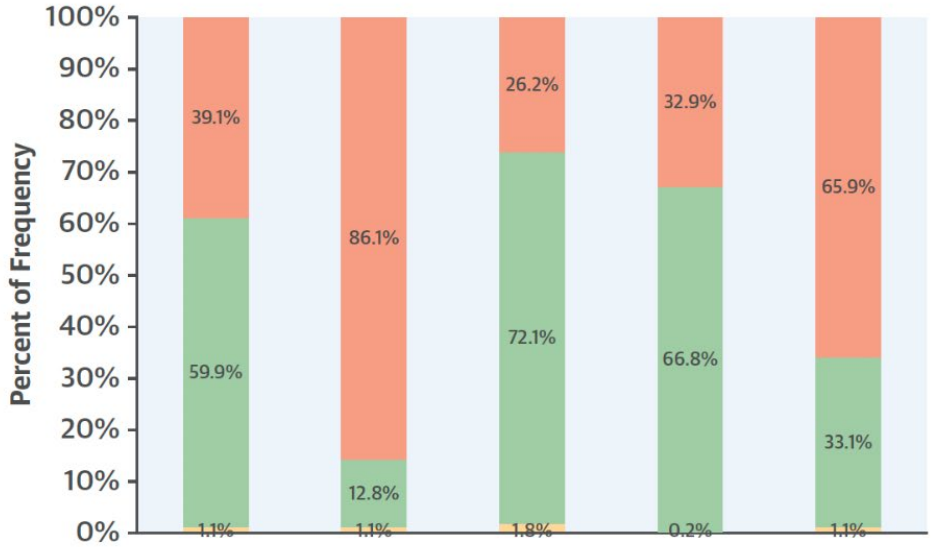
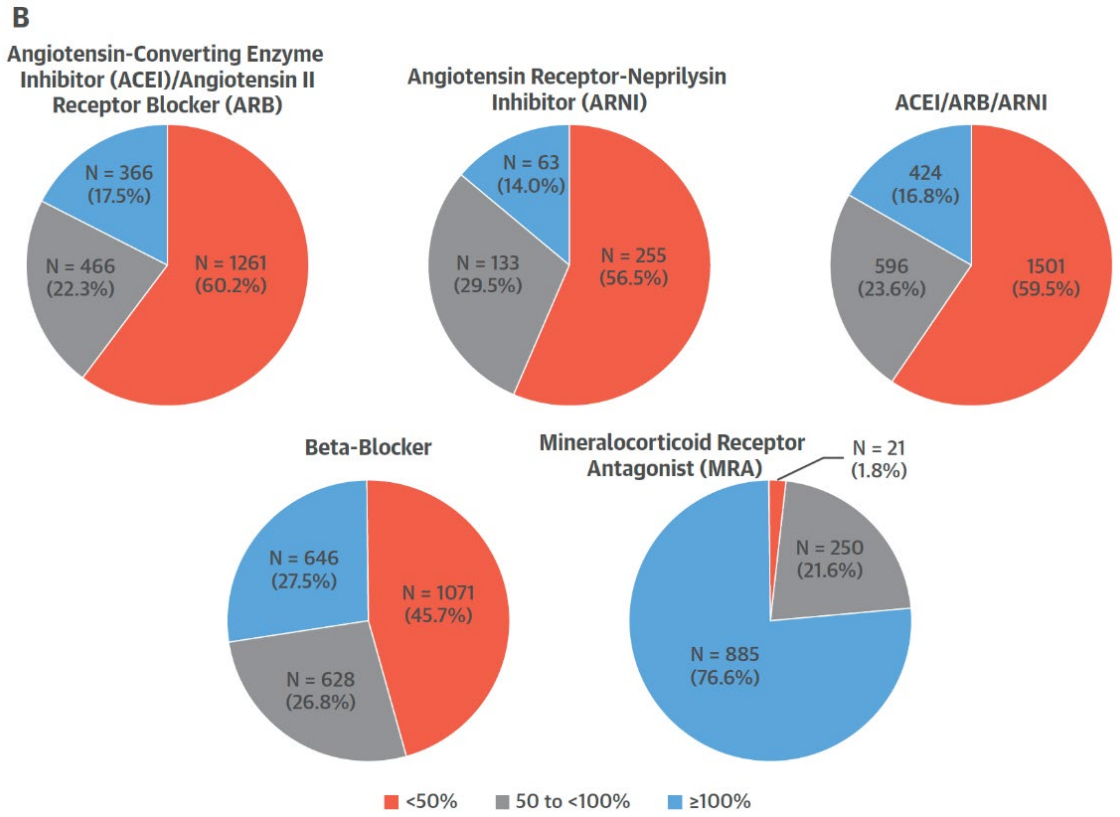
Underutilization of GDMT

A



	ACEI/ARB	ARNI	ACEI/ARB/ ARNI	Beta-Blocker	MRA
Without Contraindication and Not Treated	1374	3029	920	1159	2317
Treated	2107	452	2536	2351	1163
With Contraindication	37	37	62	8	38

B



J Am Coll Cardiol. 2018;72(4):351–66.

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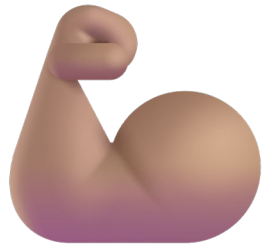
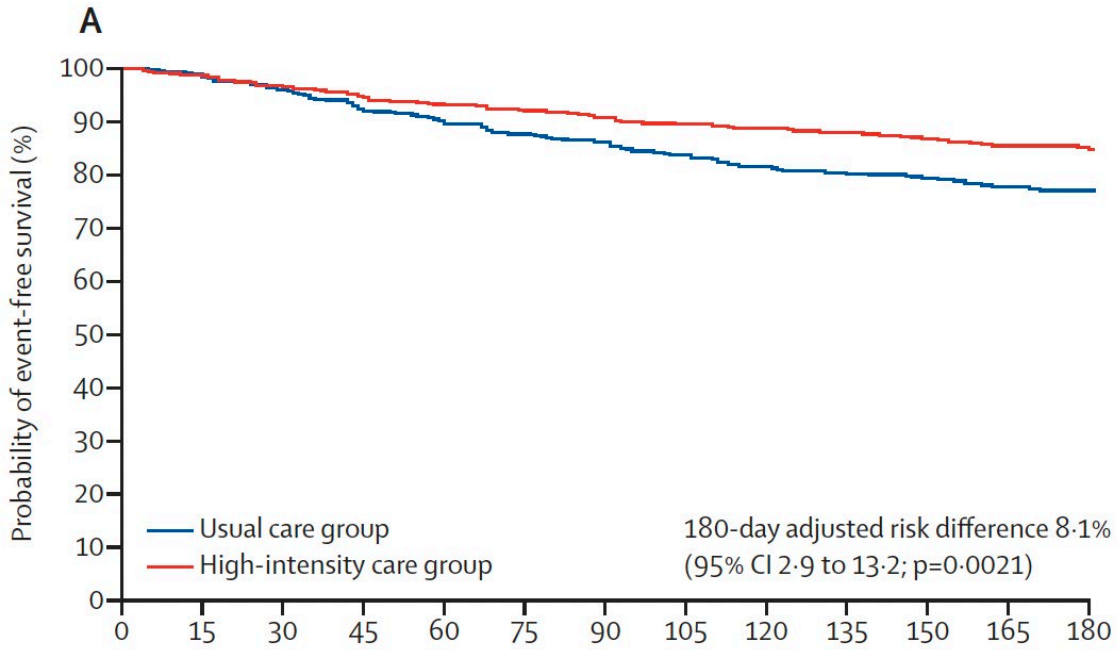
STRONG-HF Trial

Safety, tolerability, and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial



- Prospective multinational RCT of hospitalized patients admitted with acute HF
- Randomized to usual care vs. high-intensity care (uptitration to max doses within 2 weeks of discharge)
- Primary endpoint 180-day readmission d/t HF or all-cause death
- First dose adjustment was within 2 days prior to anticipated discharge
- Primary endpoint occurred 15.2% (high-intensity) vs. 23.3% (usual care)



Lancet 2022; 400: 1938-52

Health System

Temptation to Reduce GDMT

- Benefits of GDMT are higher than the perceived risks of SBP >90 in otherwise asymptomatic patients
- If peeling back GDMT due to low BP, worsening kidney function, lightheadedness/fatigue, likely identifies a **high-risk cohort**
- Referral to HF specialist is important for consideration of other therapies

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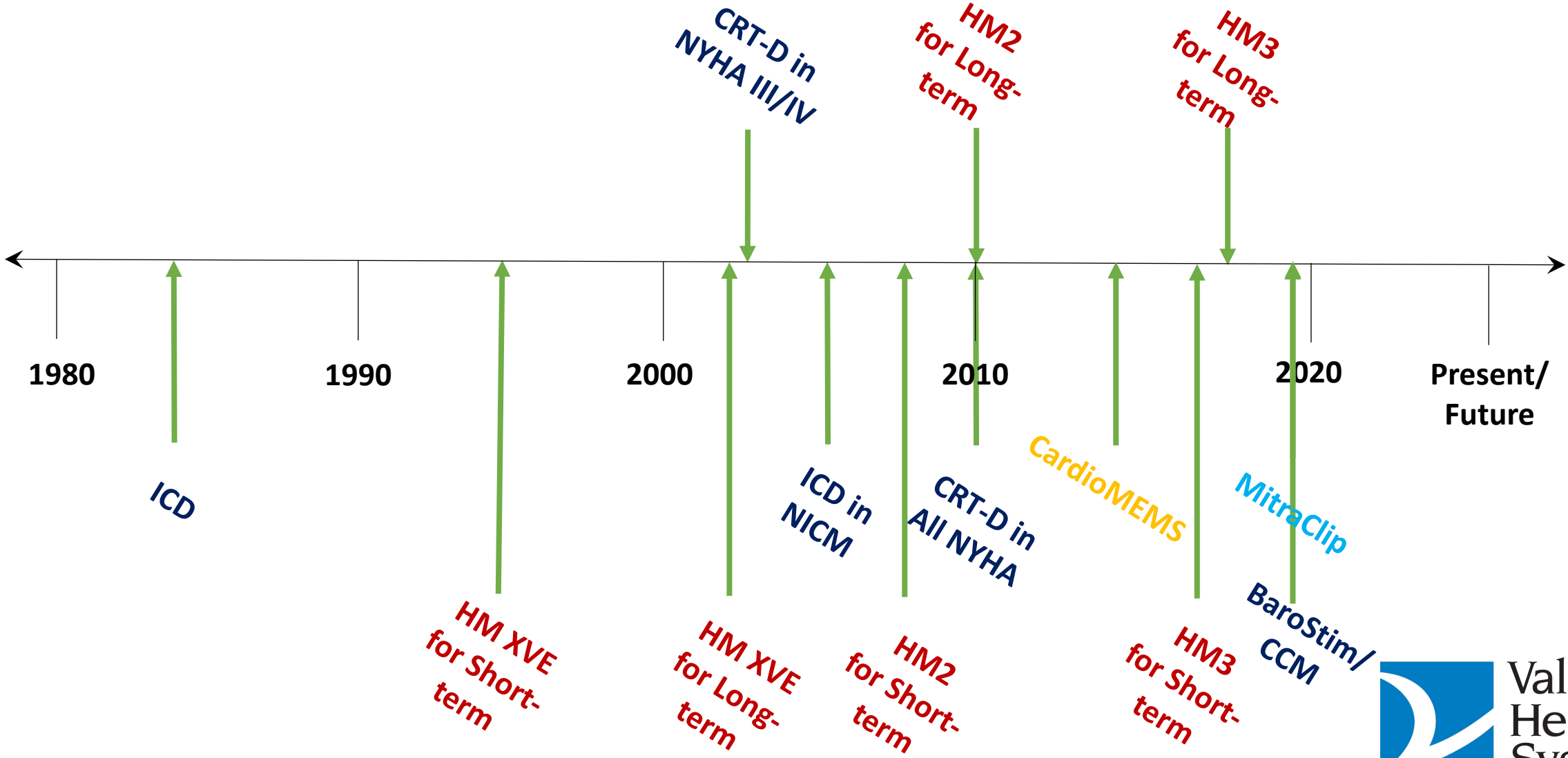
Device Advancements



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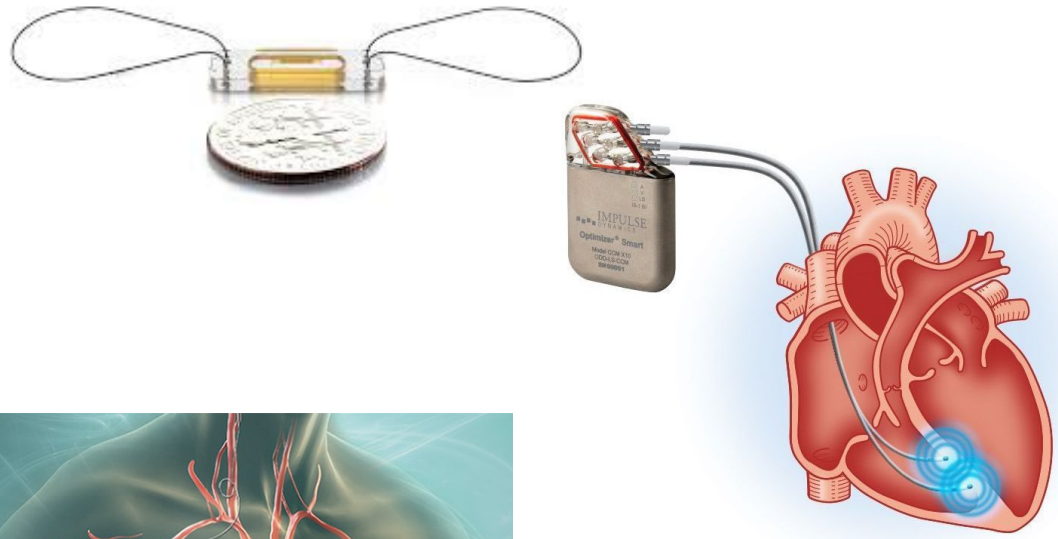
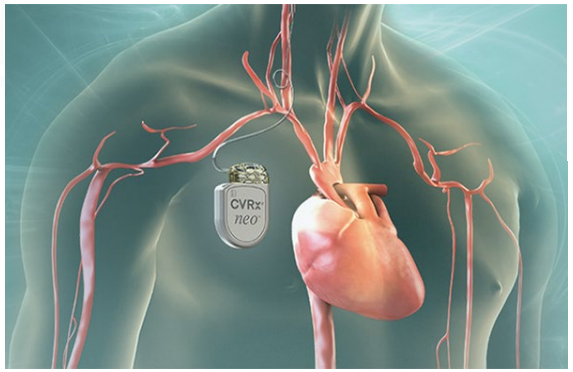
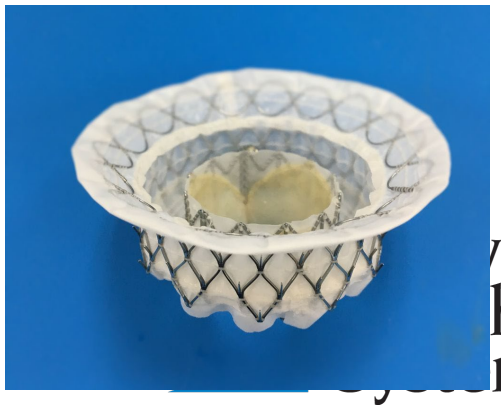
Devices


RESONATE X4
CRT-D
Boston Scientific


IMPULSE
Optimizer Smart


CVRx
neo



CRT-D – Are We Delaying Too Long?

4. For patients who have LVEF ≤35%, sinus rhythm, left bundle branch block (LBBB) with a QRS duration ≥150 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT, CRT is indicated to reduce total mortality, reduce hospitalizations, and improve symptoms and QOL (16-21).

- Prior RCTs mandated optimizing GDMT for 3 months prior to implanting CRT-D given the benefits in improving EF
- Recent appreciation that early CRT might more rapidly improve LV function than with GDMT
- Risk/benefit ratio balancing appropriateness of device implantation and complications

J Am Coll Cardiol 2022 AHA/ACC/HFSA Heart Failure Guideline

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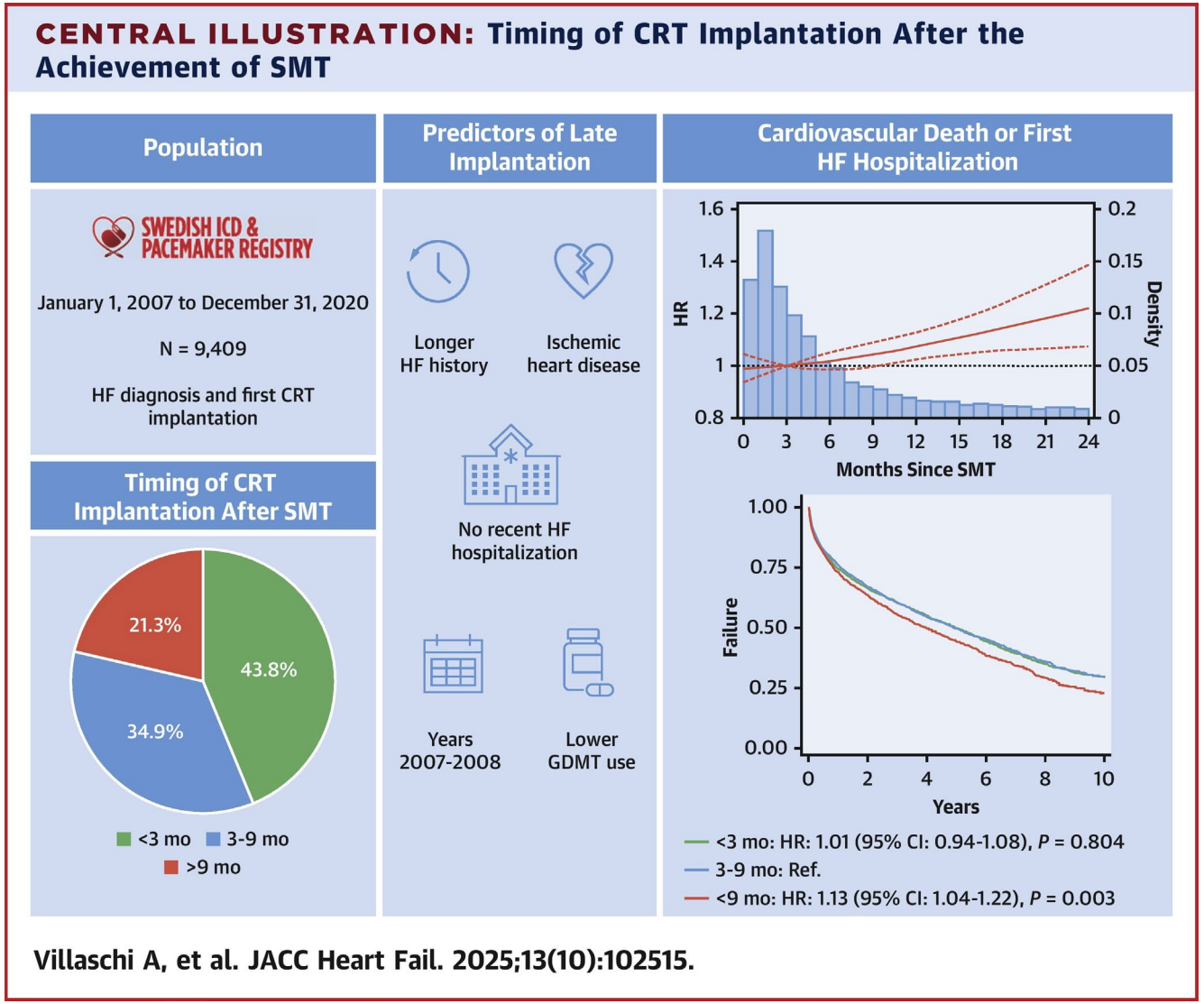
CRT-D – Don’t Delay!



Villaschi A, et al. JACC Heart Fail. 2025;13(10):102515.

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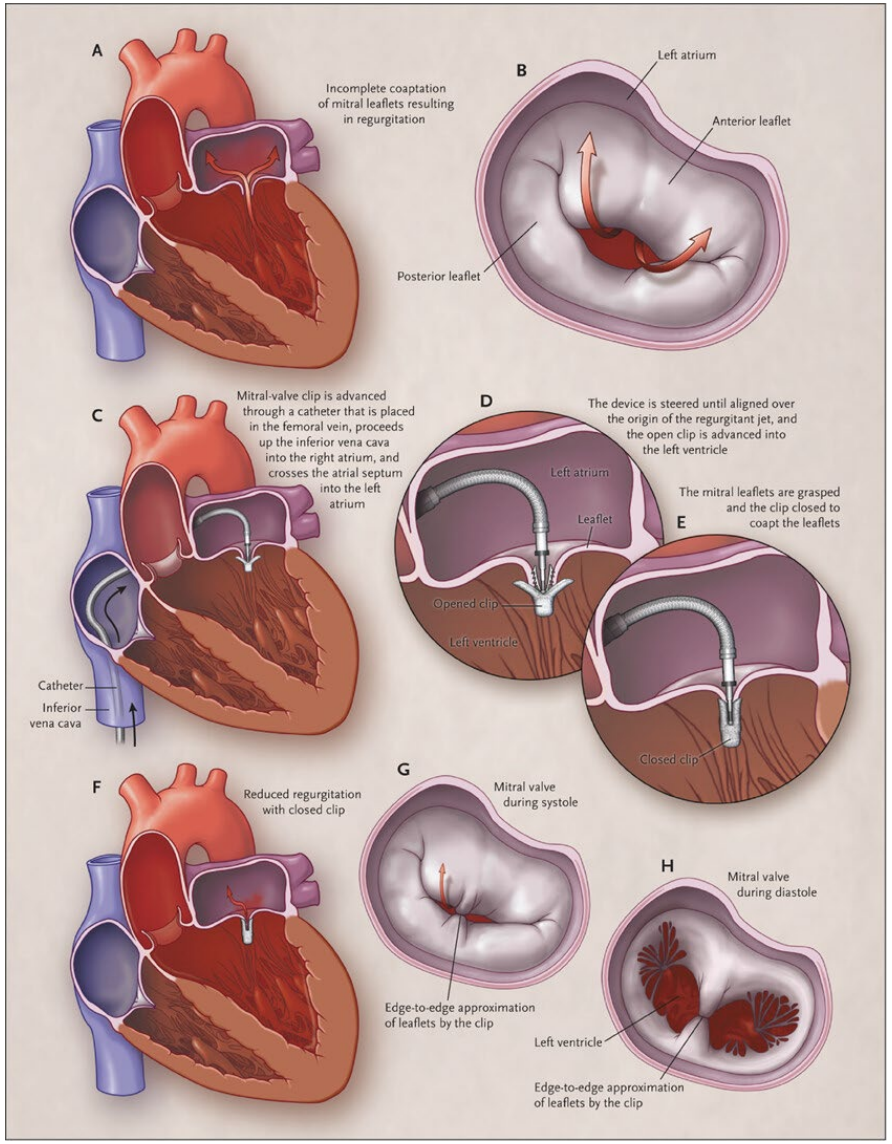
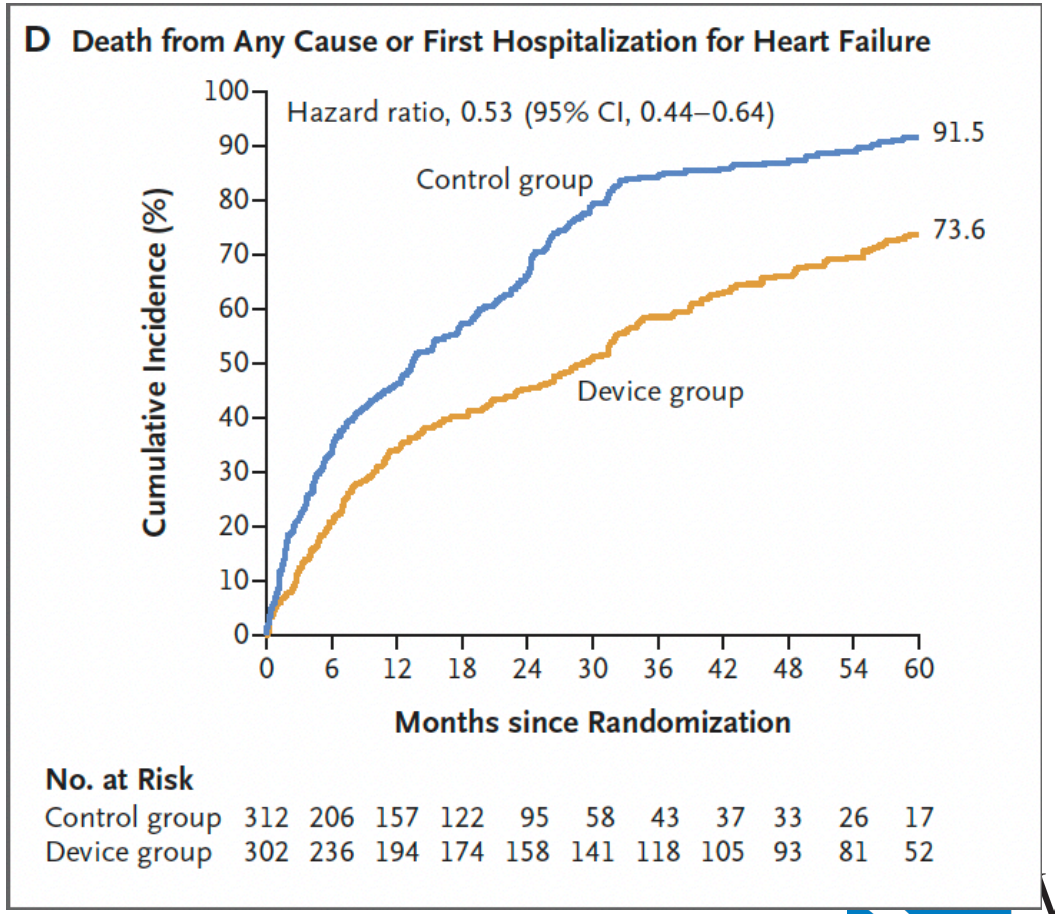
Functional Mitral Regurgitation





N Engl J Med 2023; 388: 2037-48

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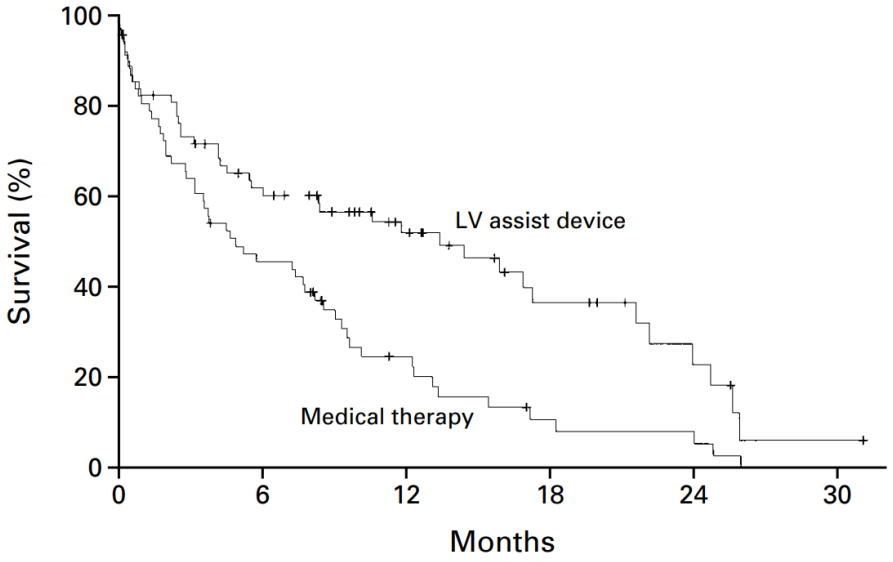
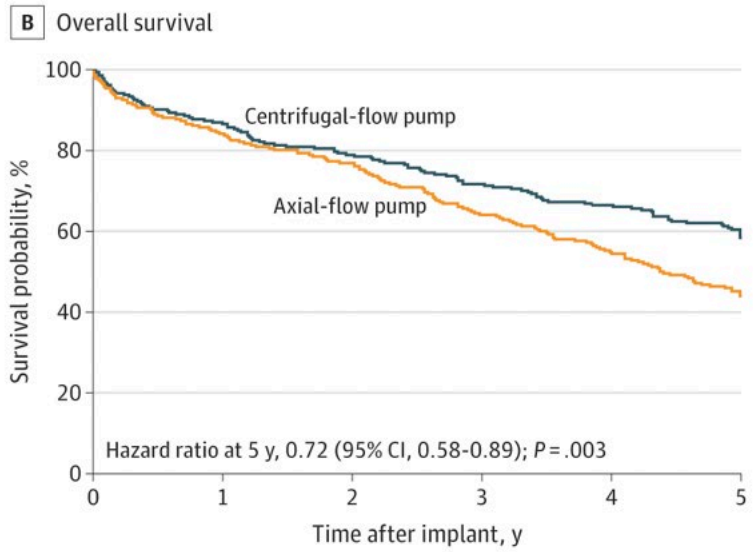
Stage D Heart Failure





I	**I**notropes	Previous or ongoing requirement for dobutamine, milrinone, dopamine or levosimendan
N	**N**YHA class/**N**atriuretic peptides	Persisting NYHA Class III or IV and/or persistently high BNP or NT-pro-BNP
E	**E**nd-Organ Dysfunction	Worsening renal or liver dysfunction in the setting of heart failure
E	**E**jection Fraction	Very low ejection fraction $<20\%$
D	**D**efibrillator shocks	Recurrent appropriate defibrillator shocks
H	**H**ospitalizations	More than 1 hospitalization with heart failure in the last 12 months
E	**E**dema/**E**scalating diuretics	Persisting fluid overload and/or Increasing diuretic requirement
L	**L**ow blood pressure	Consistently low BP with systolic <90 to 100 mm Hg
P	**P**rognostic medication	Inability to up-titrate (or need to decrease/cease) ACEI, B-blockers, ARNIs or MRAs

N Engl J Med 2001;345:1435-43
JAMA. 2022 Sep 8;328(12):1233–1242

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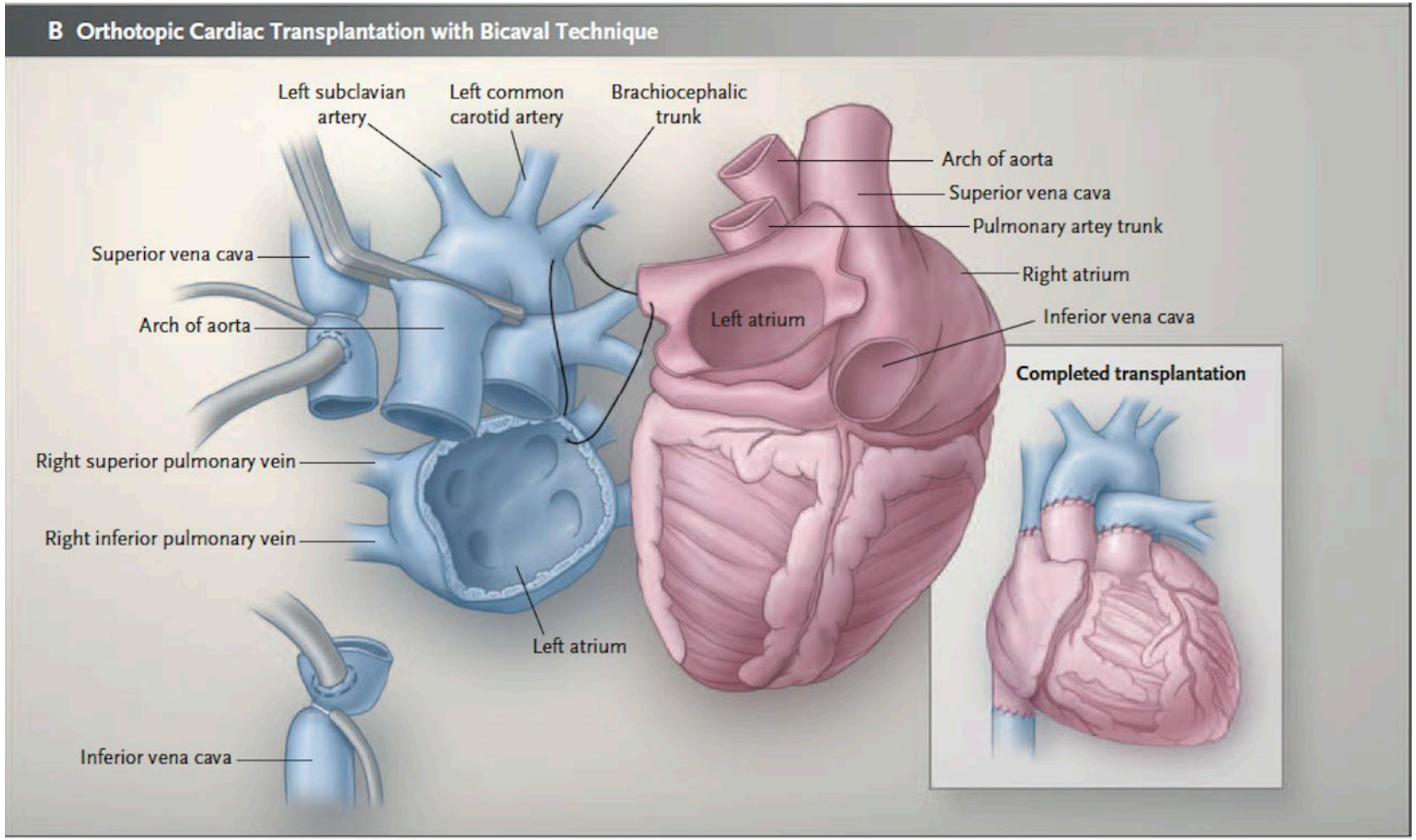
Orthotopic Heart Transplantation



Hunt SA. *N Engl J Med* 2006;355:231-5.

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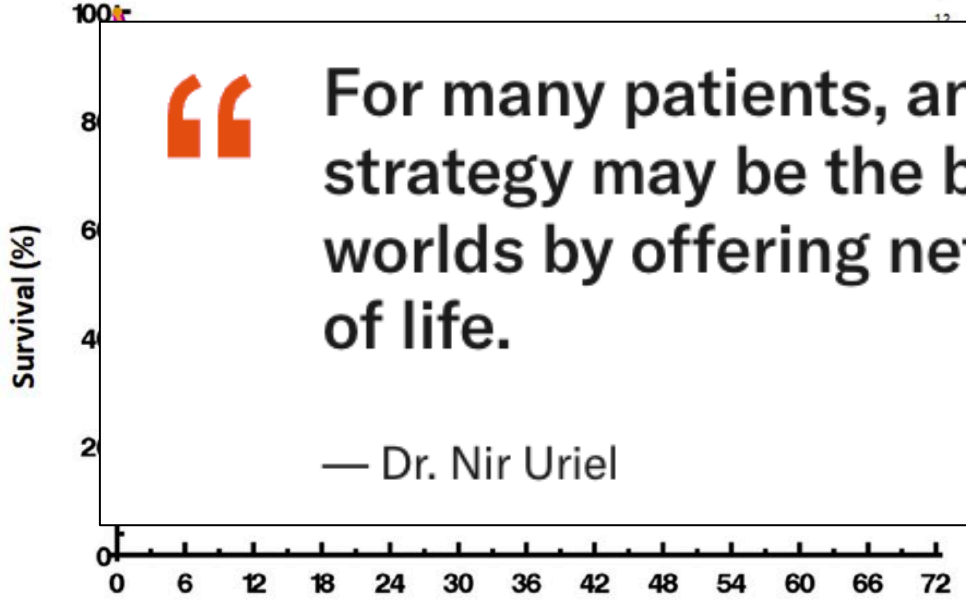
VAD vs. Transplant

Post-implant (months)	Axial (n=6938)	CF-HL (n=4786)	CF-FML (n=1292)	ISHLT (n=30824)
1	95%	95%	94%	93%
3	91%	90%	91%	89%
6	87%	87%	89%	87%
12	83%	81%	87%	85%



> For many patients, an LVAD-first strategy may be the best of both worlds by offering net prolongation of life.
>
> — Dr. Nir Uriel

N at risk:									
	Axial	6938	5722	4771	3268	1920	929	252	
	CF-HL	4786	3592	2539	1065	517	242	55	
	CF-FML	1292	1064	551	20	6	-----	-----	
	TXPL/ISHLT	30824	25338	23631	19210	15002	11392	8067	5134

Ann Thorac Surg 2020; 109: 649-60

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Summary

- Therapies are designed to target sympathetic nervous system, renin-angiotensin-aldosterone system and augment natriuretic pathway
- Most medications are underutilized despite strong evidence of their benefits
- Guideline-directed medical therapy works best when used at optimal doses and in combination
- Novel adjunctive therapies available prior to stage D HF
- Refer for advanced therapies early if persistent symptoms or inability to tolerate NHA

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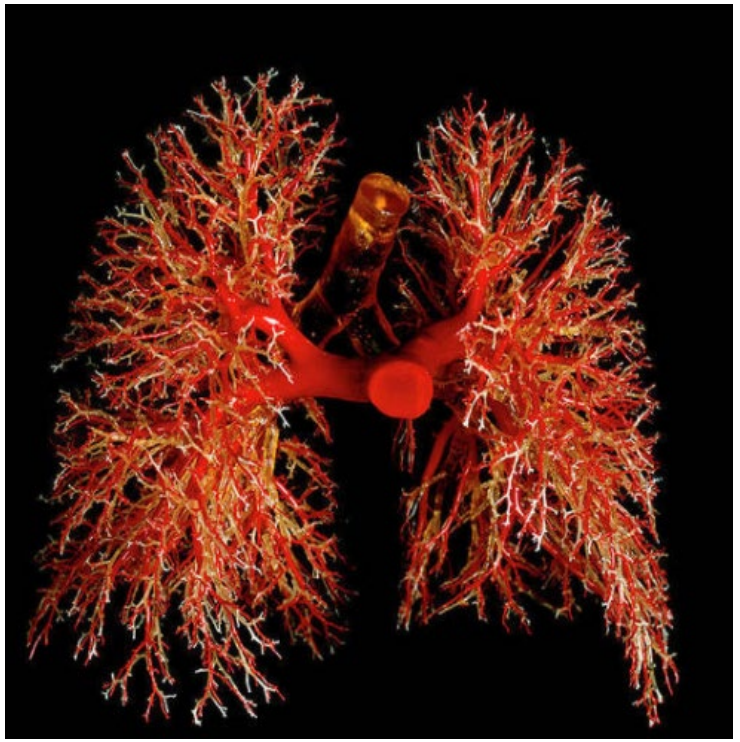
Pulmonary Hypertension Update: Role of Prostacyclin's and early detection



Ashish Rai, MD

Pulmonary Hypertension Specialist

Cardiac Intensivist

Valley Medical Group

Valley Health System

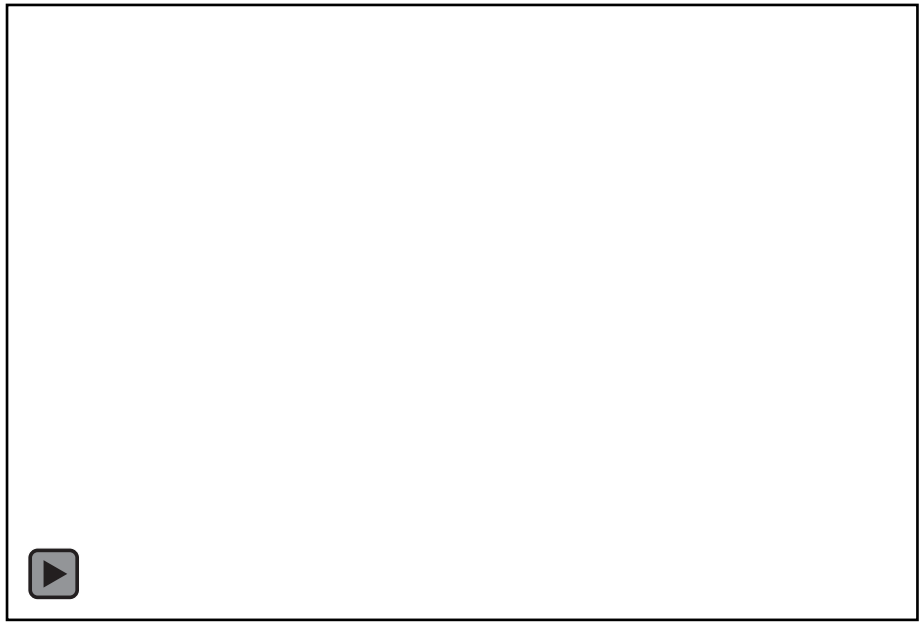
Case discussions

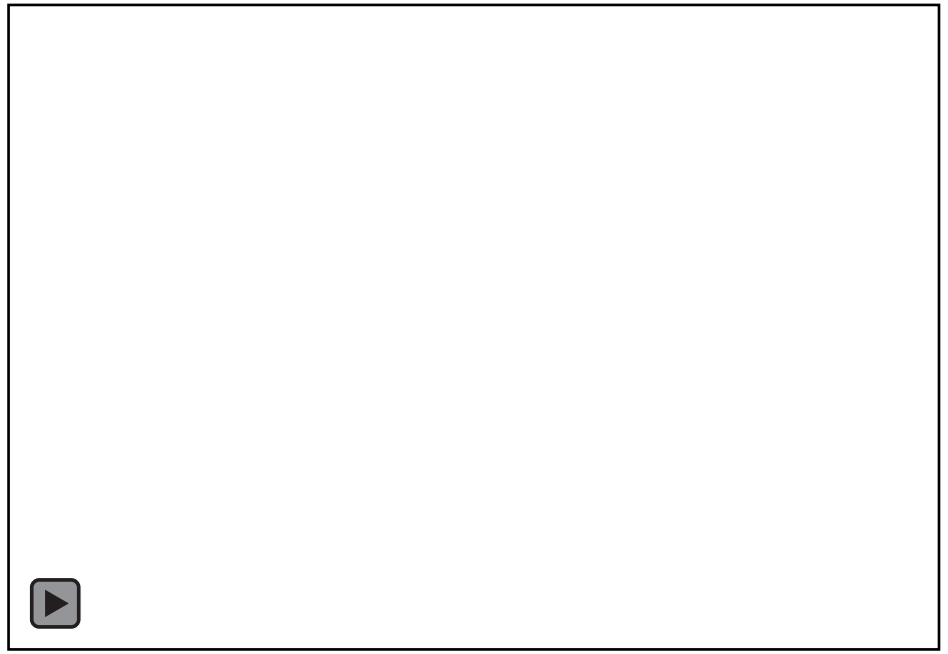
Valley Health System

Case-1:Elenor

• 62 yr old female with PMH of hypertension and anxiety, presents from OSH for evaluation for underlying shortness of breath on exertion

• PAH clinic at Valley:150 meters with desaturation to 85%, on chronic O2 at 5-6L





CT chest and VQ scan: no evidence of ILD or CTEPD

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Case-1:RHC and risk for mortality in one year

PA: 70/30 (36)
PW: 10
Thermal CO: 2.46/thermal CI 1.41
PVR 11.38

Pre-capillary PH (PAH)	mPAP>20mmhg PAWP≤15 mmhg PVR>2WU

Fluid Challenge:
PW 10
Thermal CO 2.8/thermal CI 1.6

REVEAL Score	Risk Group	One year survival
≤6	Low	≥94%
7-8	Intermediate	70 to 90%
≥9	High	<70%

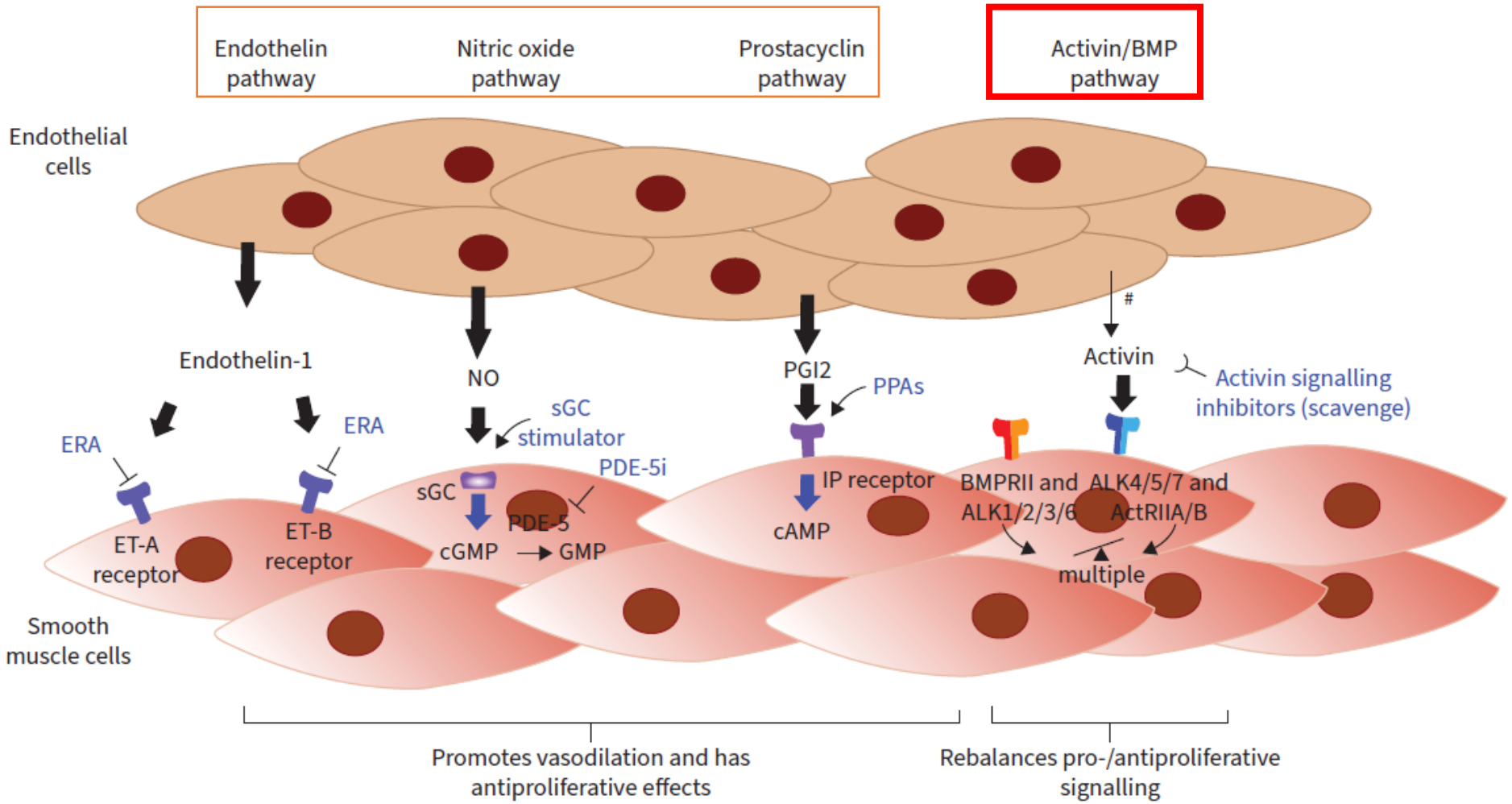
Nitric:
PA 70/21 (42)
PW 10

Severe precapillary PAH

Health System

PH treatment pathways

Fourth line agent: Sotarocept



The new 2022 pulmonary hypertension guidelines: some small steps and some giant leaps forward for evidence-based care. Price LC et al

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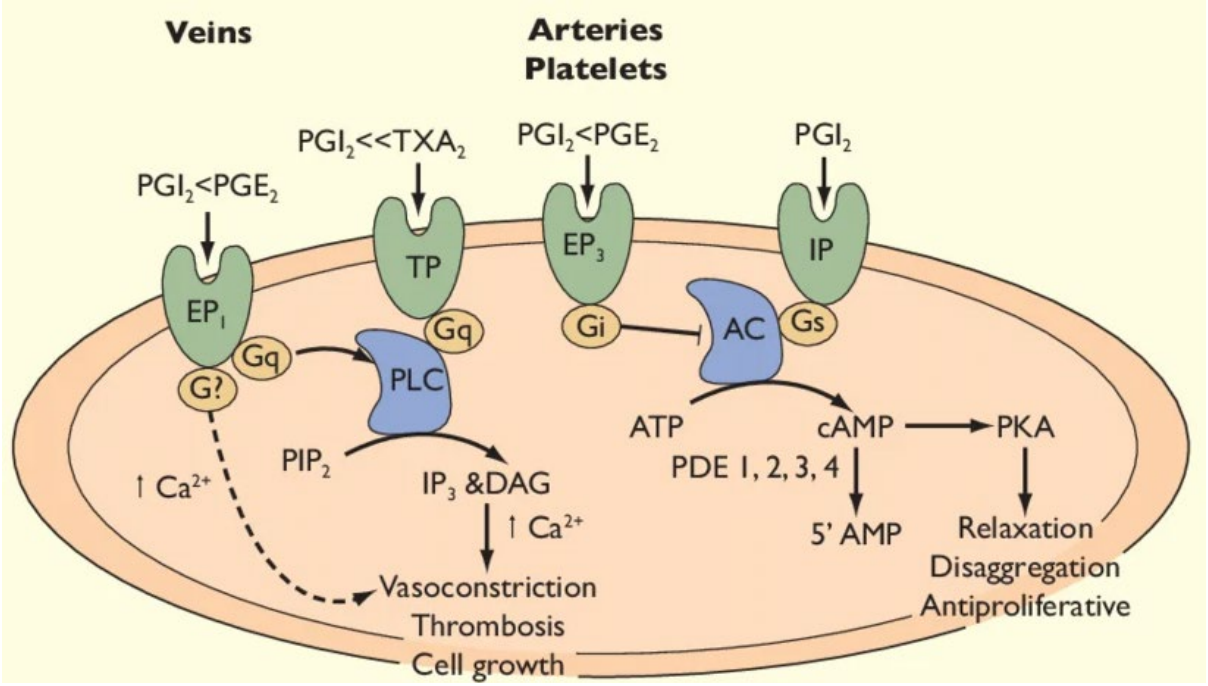
Role of prostacyclin's:

- Pulmonary arterial hypertension patients are characterized by reduced prostacyclin synthase expression and decreased endogenous prostacyclin levels in pulmonary vascular tissue, contributing to vasoconstriction, platelet activation, and vascular remodeling



Tuder RM et al. Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. Am J Respir Crit Care Med. PMID: 10351941.

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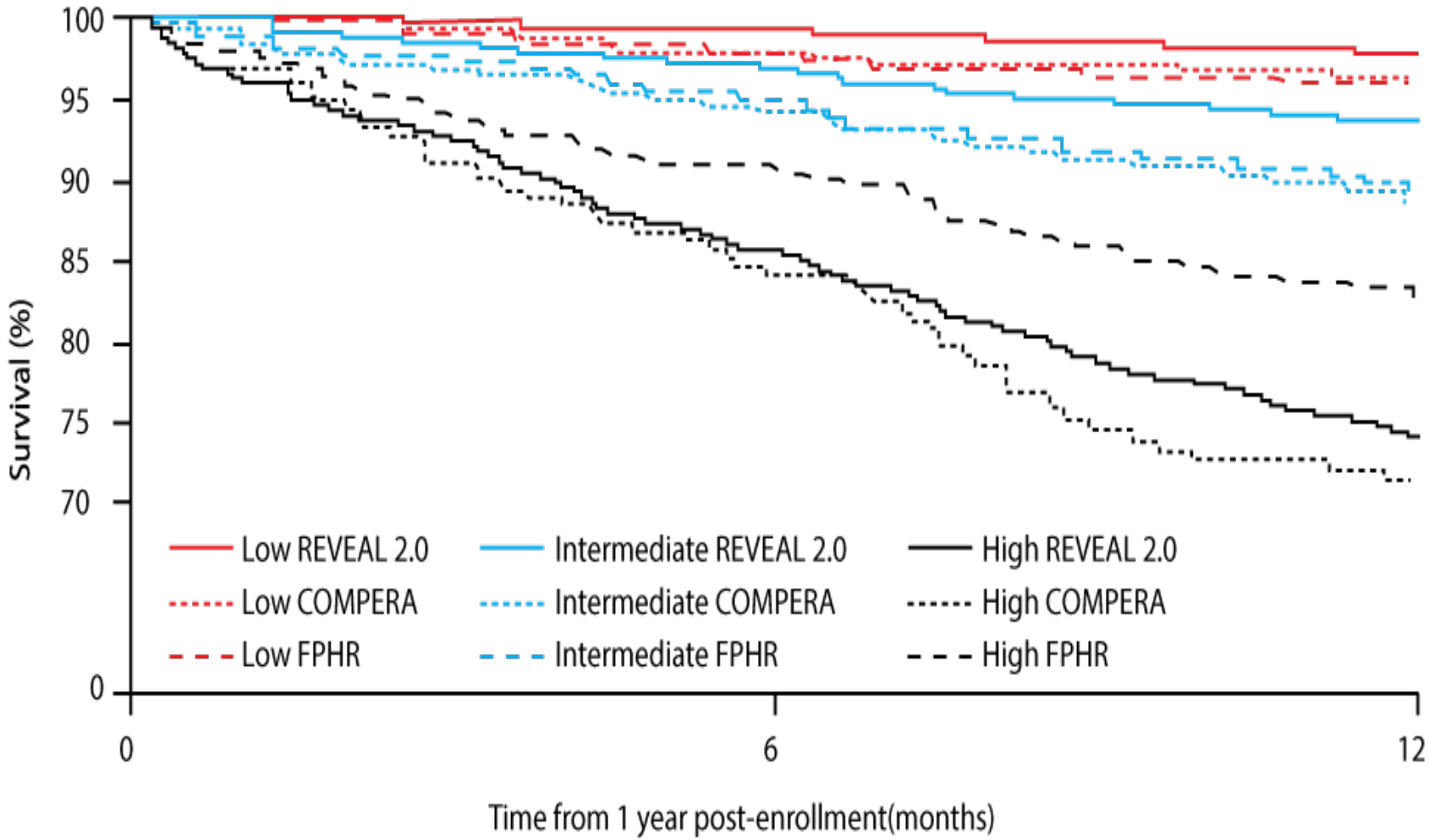
Role of prostacyclin's: RV rescue-> low risk



- **25% reduction in mortality within one year when moved from high to low risk**

A comprehensive risk stratification at early follow-up determines prognosis in PAH."*Eur Heart J. 2018*

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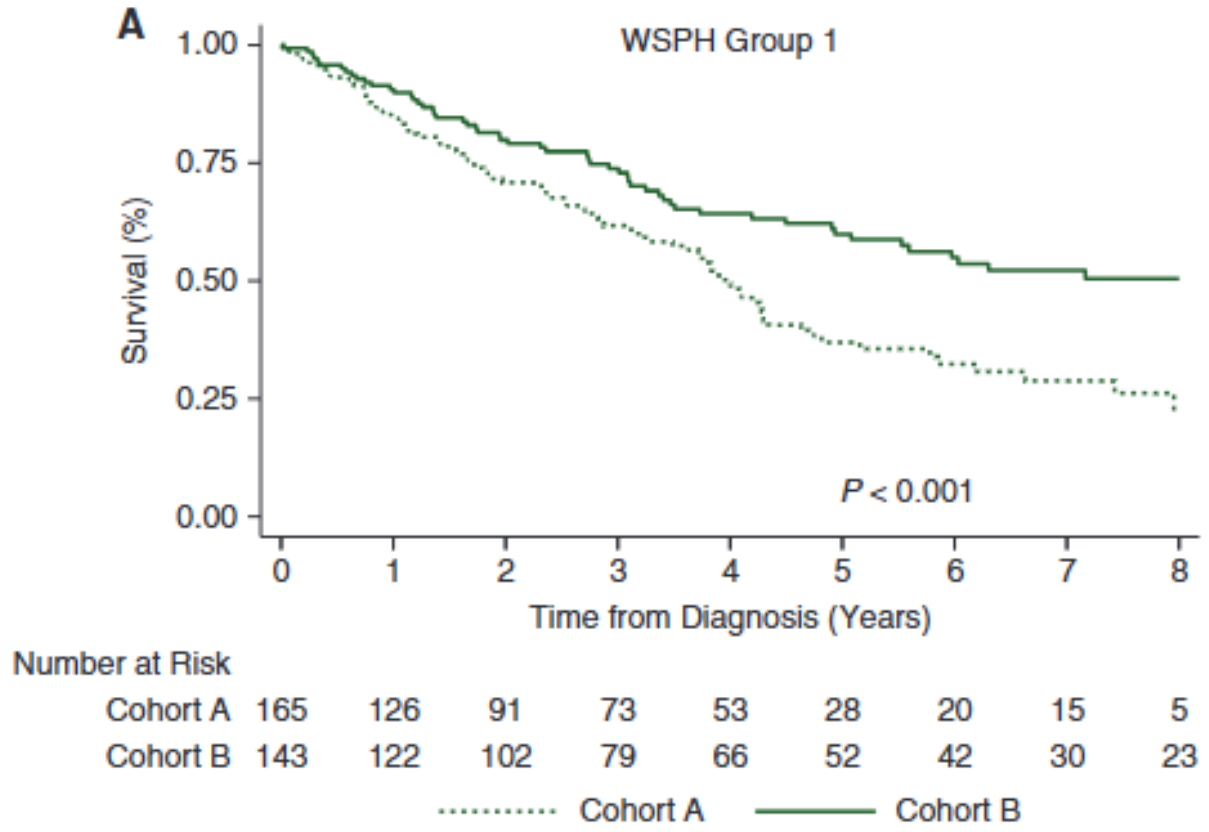
Survival:

American Journal of Respiratory and Critical Care Medicine
Volume 207, Issue 3
February 1, 2023

Improved Survival for Patients with Systemic Sclerosis–associated Pulmonary Arterial Hypertension
The Johns Hopkins Registry

Hussein J. Hassan[1], Mario Naranjo[1], Nour Ayoub[1], Traci Housten[1], Steven Hsu[2], Aparna Balasubramanian[1], Catherine E. Simpson[1], Rachel L. Damico[1], Stephen C. Mathai[1], Todd M. Kolb[1], and Paul M. Hassoun[1]

[1]Division of Pulmonary and Critical Care Medicine and [2]Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland



- Cohort B(Triple therapy with PCs+ERA andPDE5) had significantly better transplant-free survival than cohort A(dual:ERA+PDE5).

- 8-year transplant free survival rates: 51% vs 27%, with median survival, 8.8 yr vs. 4.0 yr.

- Upfront triple therapy versus dual therapy

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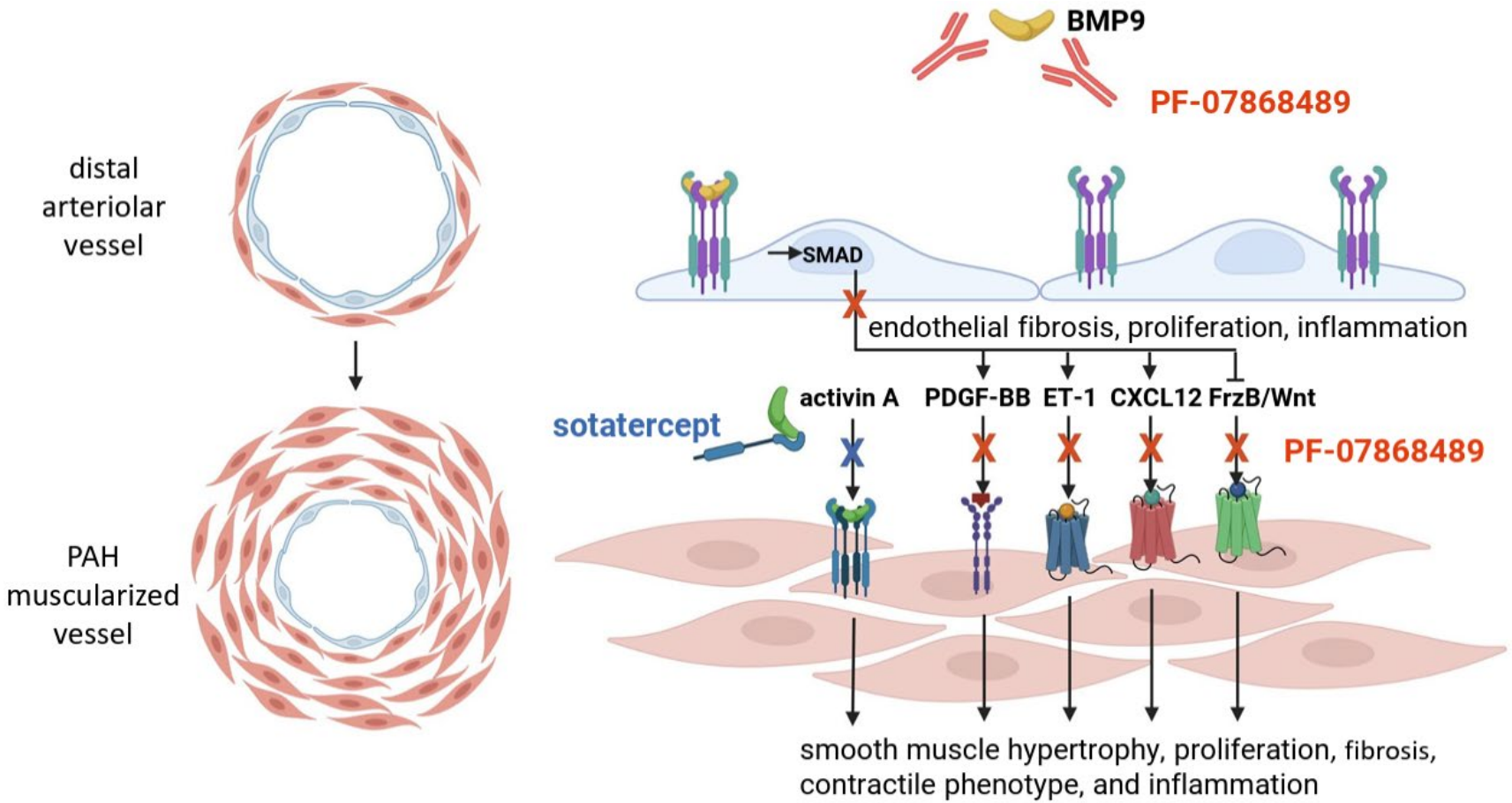
Biologic agent: Activin inhibitors: Sotatercept : new generation of medication



- 30% reduction for either death or clinical worsening among sotatercept group when added to background therapy.

Phase 3 trial of Sotatercept for treatment of pulmonary arterial hypertension. Marius M. Hoeper et al, N Engl J Med 2023;388:1478-1490

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Case-1: Elenor

February 2025: Diagnosed with PAH
Started on Prostacyclin(PC)
REVEAL score:14(<70% Survival in one year),BNP:1300, on 6L O2
RHC: PVR of 11WU, CO:2.4L
6 min walk:158 meters

May 2025:
Other PH meds added: ERA and PDE5
PC increased to 64 ng/kg/min
BNP:200, on 2L O2 with exercise
VO2 on CPET(oxygen uptake):30%

October 2025:
Sotatercept added every 3 weeks
PC increased to 94 ng/kg/min
BNP:75, O2 only with exertion

March 2026:
PC at 128 ng/kg/min
Sotatercept+ Macitentan+Tadalafil
RHC: PVR of 5WU,CO:4.4L
6 min walk:400 meters without O2
VO2:65%

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Case-1 take away:

- **Low risk-**> reduction in mortality: “feel better is not the goal”
- **Early introduction with prostacyclin and disease modifying biologic agent: team** based approach: Valley PAH clinic

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Case-2: John: unexplained dyspnea

- 71 yr old male with PMH of hyperlipidemia, BMI of 30, who was refereed for evaluation for **unexplained shortness of breath**.
- Ct chest: no evidence of ILD, no emphysema, normal lung parenchyma
- PFT: normal spirometry, **DLCO mildly reduced (65%)**
- Echo with normal LV function, RV normal with RVSP of 20 mmhg at rest, BNP:70, stress test negative for ischemia and no evidence of CAD on CT coronary
- Exam: well, appearing, normal S1 S2, O2 sat at rest:98%, with **6-minute walk: 380 meters**(intermediate to low for age) with **no desaturation**.
- Negative autoimmune panel, Hb:15 mg/dl, with normal renal and liver function
- Over past 6 months: unable to supervise his construction crew due to SOB

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Case-2: John: unexplained dyspnea

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Case-2 John: Unexplained dyspnea

September 2025:
1st visit to pulmonary and cardiology : normal test results with mildly reduced **DLCO(65%)** with normal echo

November 2025:
2 month follow up with pulmonary:
CT chest: mild ground glass change in base
Echo :RVSP of 20-25 mm hg with normal RV function]
PFT: DLCO:55%

December 2025
Lung biopsy: dendriform changes , calcifications and **nonspecific findings,? Early ILD**
Spirometry values preserved with FVC of 80%, does not qualify for antifibrotics

February 2026:
CPET: low VO2 at 45% with signs of early PVD
Resting(Supine) RHC and exercise on table:
PAP:25/13,**mPAP:17**,**CO:4.3**,**PVR:1.6**
PAP:27/15,**mPAP:18**,**CO:4.1**,**PVR:1.7**
On oxygen with exertion at 3-4L
Unable to go to work

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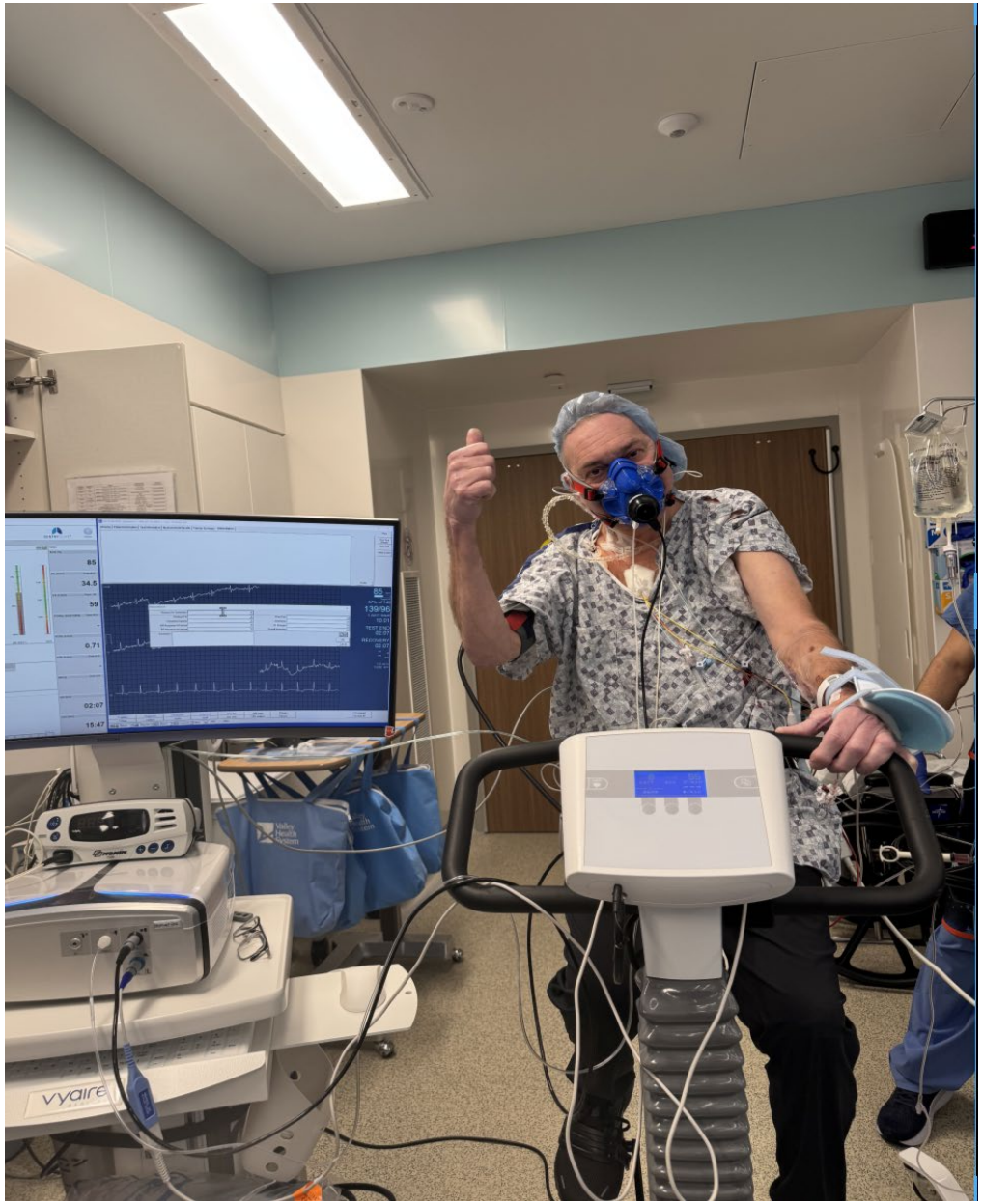
John: Unexplained SOB: Invasive cardiopulmonary exercise testing(iCPET)



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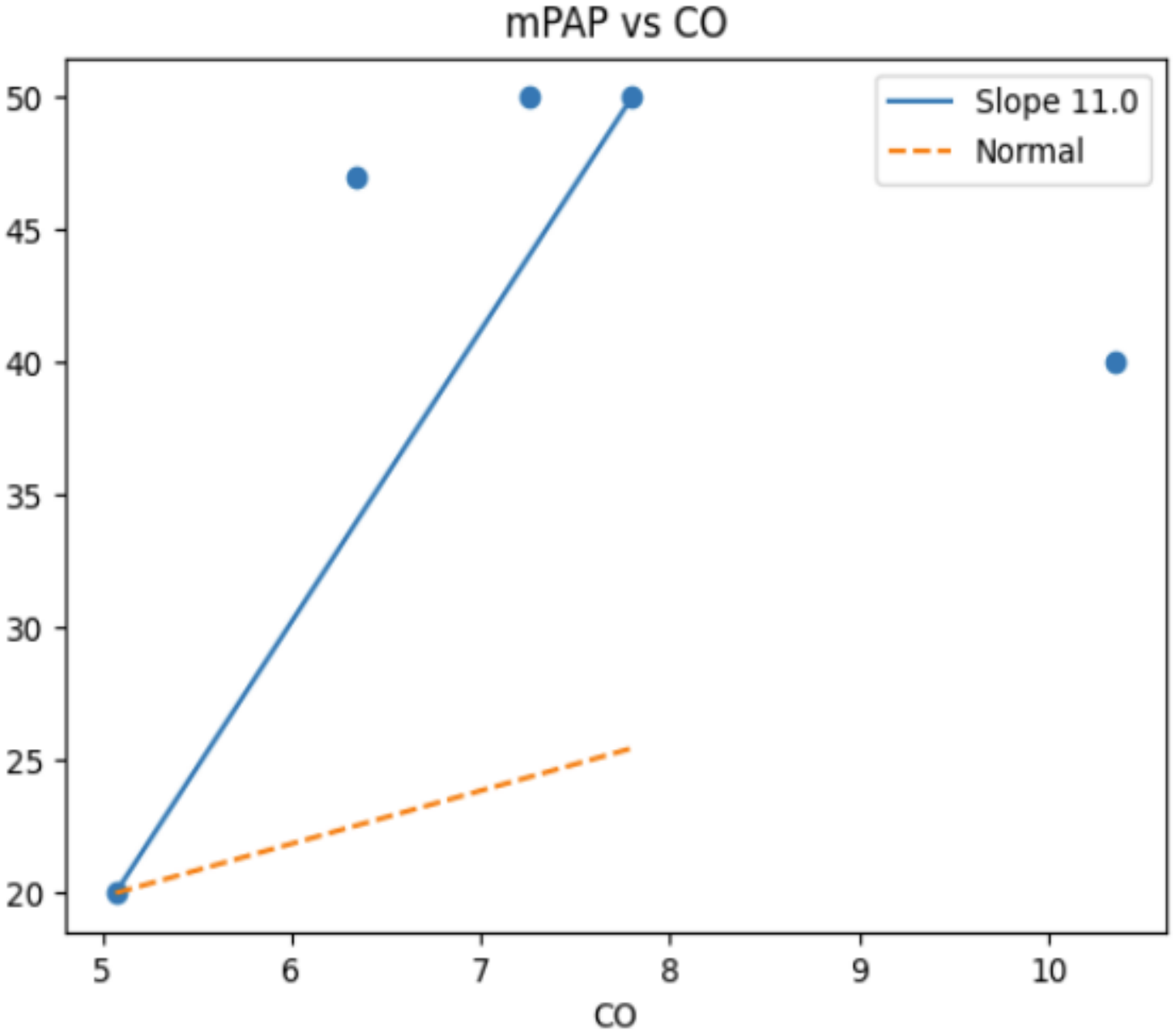
Consent obtained from patient to share picture; name changed



Exercise PH	mPAP/CO slope between rest and exercise>3 mmhg/l/min

- **At rest, upright: mPAP:20 mm hg, Direct cardiac output(measured VO2):5L/min**
- **mPAP at peak exercise: 53 mmhg**

Direct cardiac output(measured VO2):8L/min

- **mPAP/CO slope:11 (33/3), PVR at peak:6**
- **Exercise induced pulmonary hypertension**

Less than one month ago:

- mPAP supine at rest:17,CO:4.3,PVR:1.6
- mPAP supine with submax exercise on table:18,CO:4.1,PVR:1.7

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Case-2 John: Unexplained dyspnea: Latent PH

September 2025:
1st visit to pulmonary and cardiology : normal test results with **mildly reduced DLCO(65%)** with normal echo, stress echo and coronary CT

February 2026: ?Early ILD with low DLCO:55%

Normal resting supine PA pressure

Early March 2026: Exercise induced pulmonary hypertension
Inhaled prostacyclin initiated with goal to increase to 128 mcg and add Sotatercept. Repeat iCPET in 6 months

Latent PH:
Lost opportunity to treat PH
15% of patients develops PH in approximately 8-10 months among interstitial lung disease patients after diagnosis and 80% by time for transplant

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Nathan SD et al. Shining a spotlight on pulmonary hypertension associated with interstitial lung disease care: The latest advances in diagnosis and treatment. J Manag Care Spec Pharm. 2025 Jan;31(1-a Suppl):S2-S17 PMID: 39749862; PMCID: PMC11695281.

Case 2 take away

- Echo are highly unreliable, 40% accuracy for detecting pulmonary hypertension

- Resting right heart catheterization in supine position, does not reproduce the physiological state a person is living in, good for overt PH.

- Invasive cardiopulmonary exercise testing should be considered to replicate the real-world scenario, and early detection of PH, left sided diastolic dysfunction, oxygen extraction problems(Post viral (long COVID) syndrome, autonomic dysfunction), Post PE syndrome: Dyspnea on exertion with unclear etiology.

Farber HW, et al. *Congest Heart Fail.* 2011;17:56-63.

Valley Health System

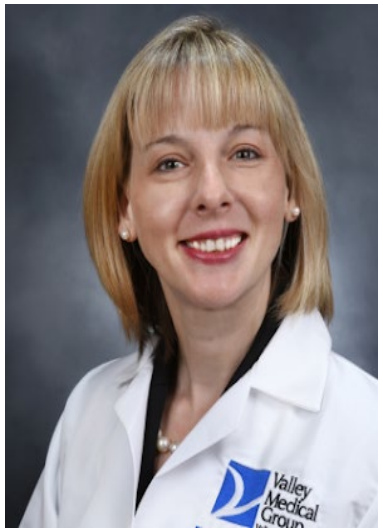
Valley PH team

Ashish Rai, MD
Pulmonary, PH Specialist

Emma Goebel, APN,
PH Center Coordinator

Jaclyn Hoti, LPN
Heart failure clinical coordinator

Samit Shah, MD
Heart failure specialist



Karian Abbate, MD
Heart failure specialist

Thank You

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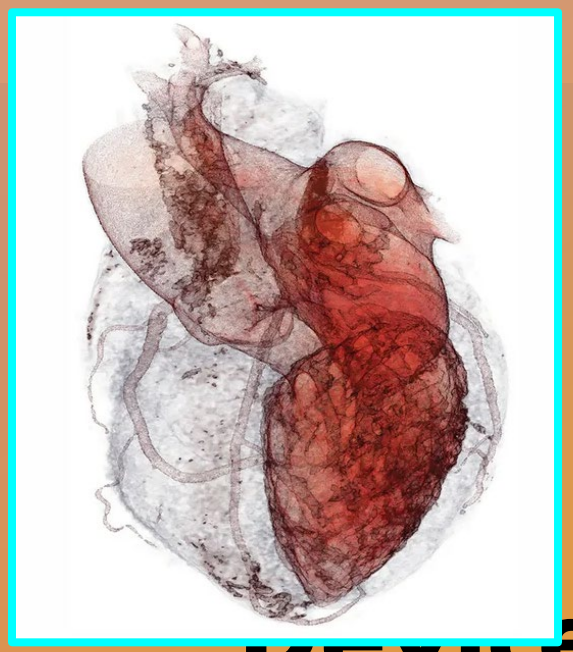

Device Therapy in Patients with Heart Failure

Tina Sichrovsky, MD, FACC, FHRS

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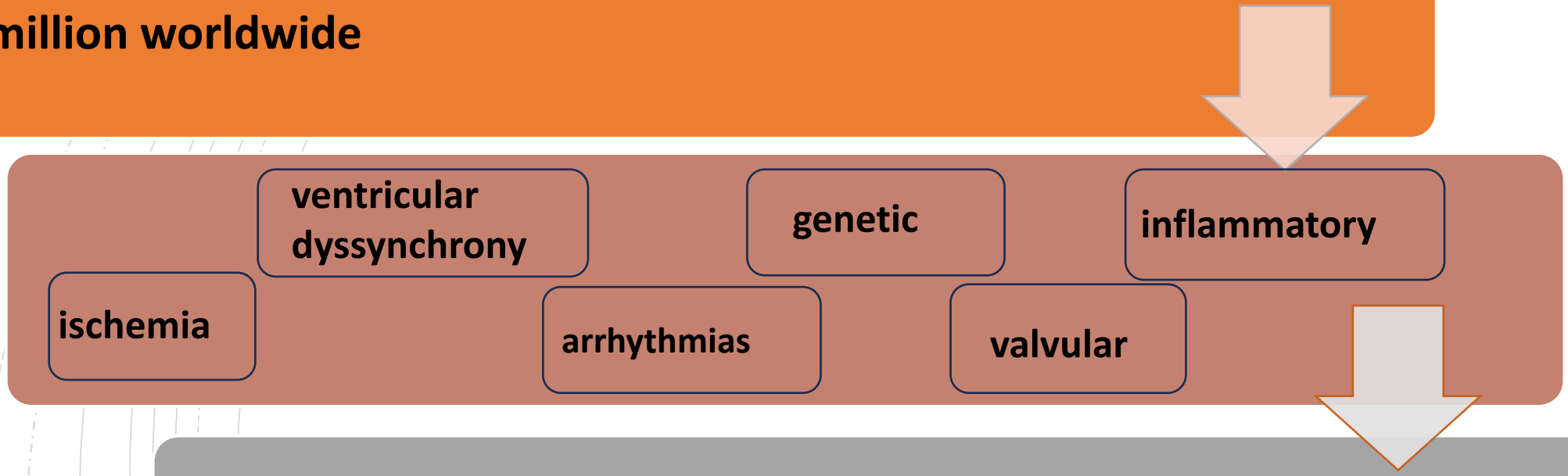
Background

Poor prognosis and QOL similar to cancer

>64 million worldwide



Low activities of sarcoplasmic reticulum calcium-ATPase (SERCA) and reduced Ca2+ transients.

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Background

Guideline directed medical therapy (GDMT)

Primary prevention ICD implant if LV dysfunction persists

CRT for ventricular dyssynchrony

If ***in***eligible for CRT: **Cardiac contractility modulation (CCM)**

This talk will therefore focus on ***CRT*** and ***CCM*** devices.

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Mechanical Dyssynchrony in Heart Failure:

Synchronous contraction:

Intact conduction system

Viable and well-perfused myocardium

Conduction abnormalities, particularly **LBBB**, result in inter- and intraventricular dyssynchrony

complete proximal conduction block

distal conduction defects

LBBB CMP

Significant HF risk in patients with LBBB if QRS >/=**150** ms.

The septum is contracting early, prior to the aortic valve opening → elongating during systole → resulting in **wasted work with no contribution to stroke-volume**

Hypoperfusion of the septum LV remodeling → Dilatation and asymmetric LVH → HF with reduced EF

Impaired Ca cycling reducing SR Ca uptake (SERCA2a dysfunction).

CRT

CS lead placement can face anatomical challenges and is not feasible in every patient.

Left bundle branch area pacing (LBBAP) has been utilized as a bailout technique.

Several studies have been conducted/in progress to assess this approach.

LBBAP: significant reduction of all-cause mortality or HF hospitalizations compared to BiVP.

Limitations: **Distal** LBBB or **atypical** LBBB.

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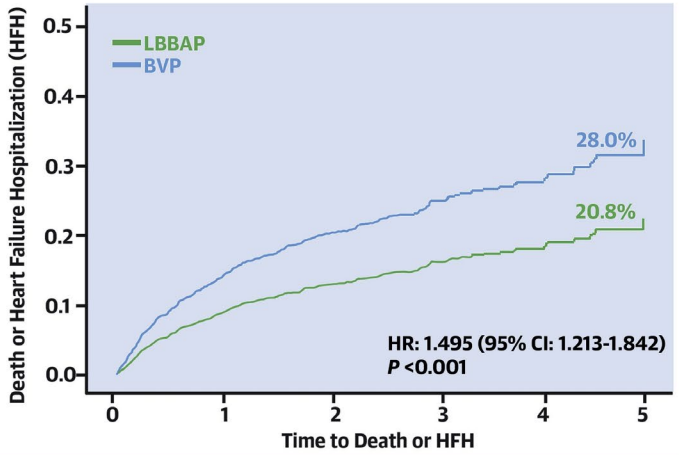
CENTRAL ILLUSTRATION: Death or Heart Failure Hospitalization

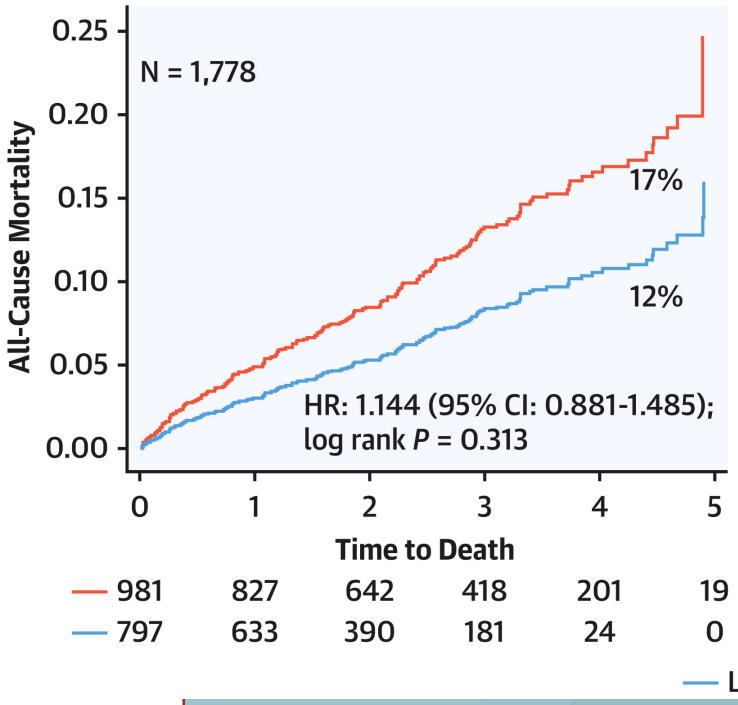
Time to Death or Heart Failure Hospitalization
All Patients (n = 1,778)



BVP	981	728	546	352	166	18
LBBAP	797	574	342	152	18	0

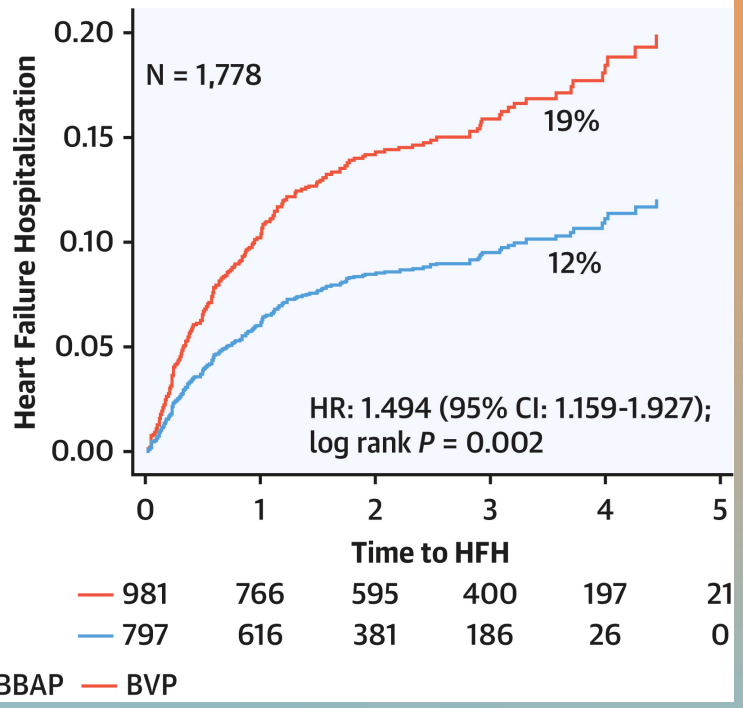
Secondary Endpoints

Mortality



981	827	642	418	201	19
797	633	390	181	24	0

Heart Failure Hospitalization

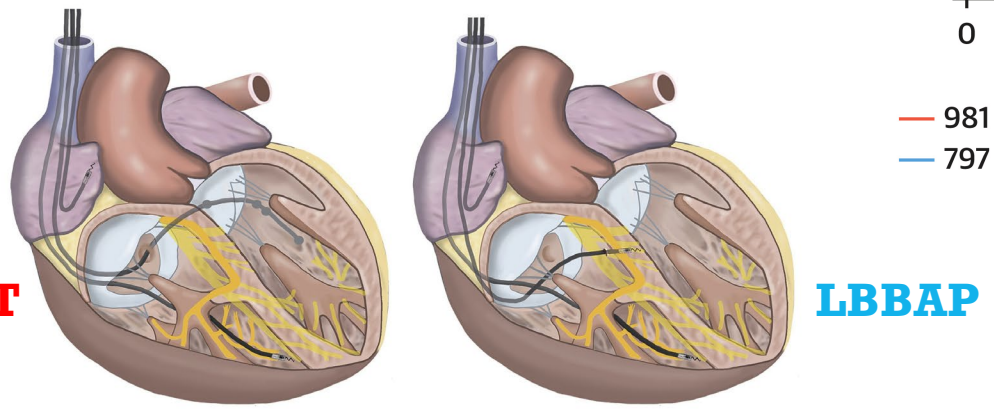


981	766	595	400	197	21
797	616	381	186	26	0

LBBAP BVP

Biventricular Pacing (BVP)

Left Bundle Branch Area Pacing (LBBAP)



Vijayaraman P, et al. J Am Coll Cardiol. 2023;82(3):228-241.

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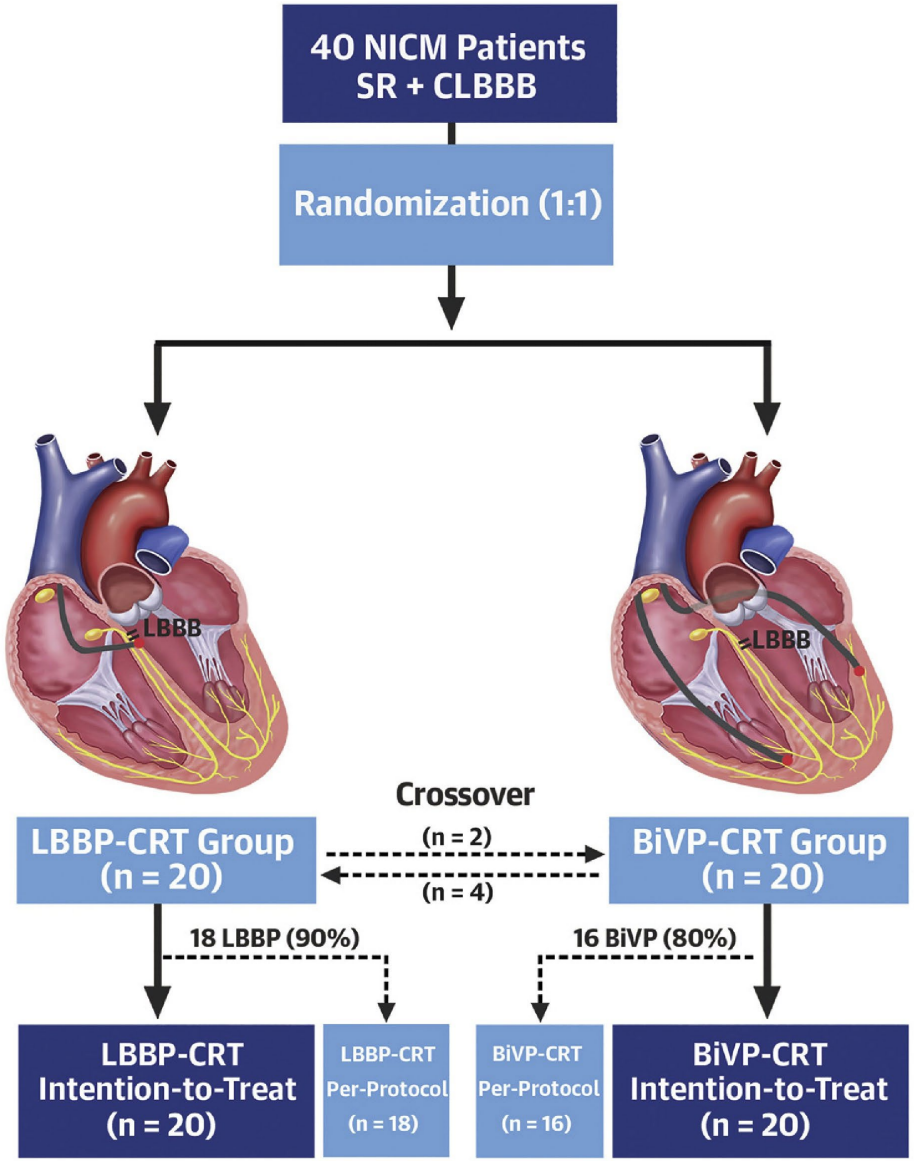
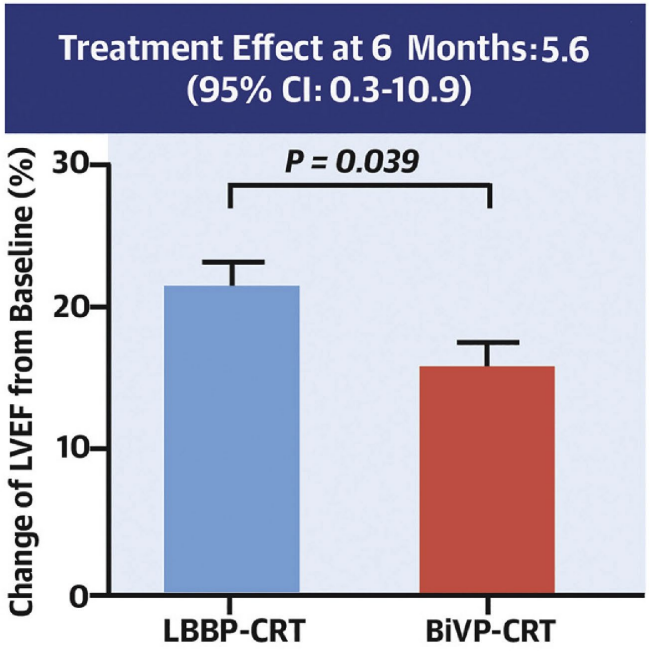
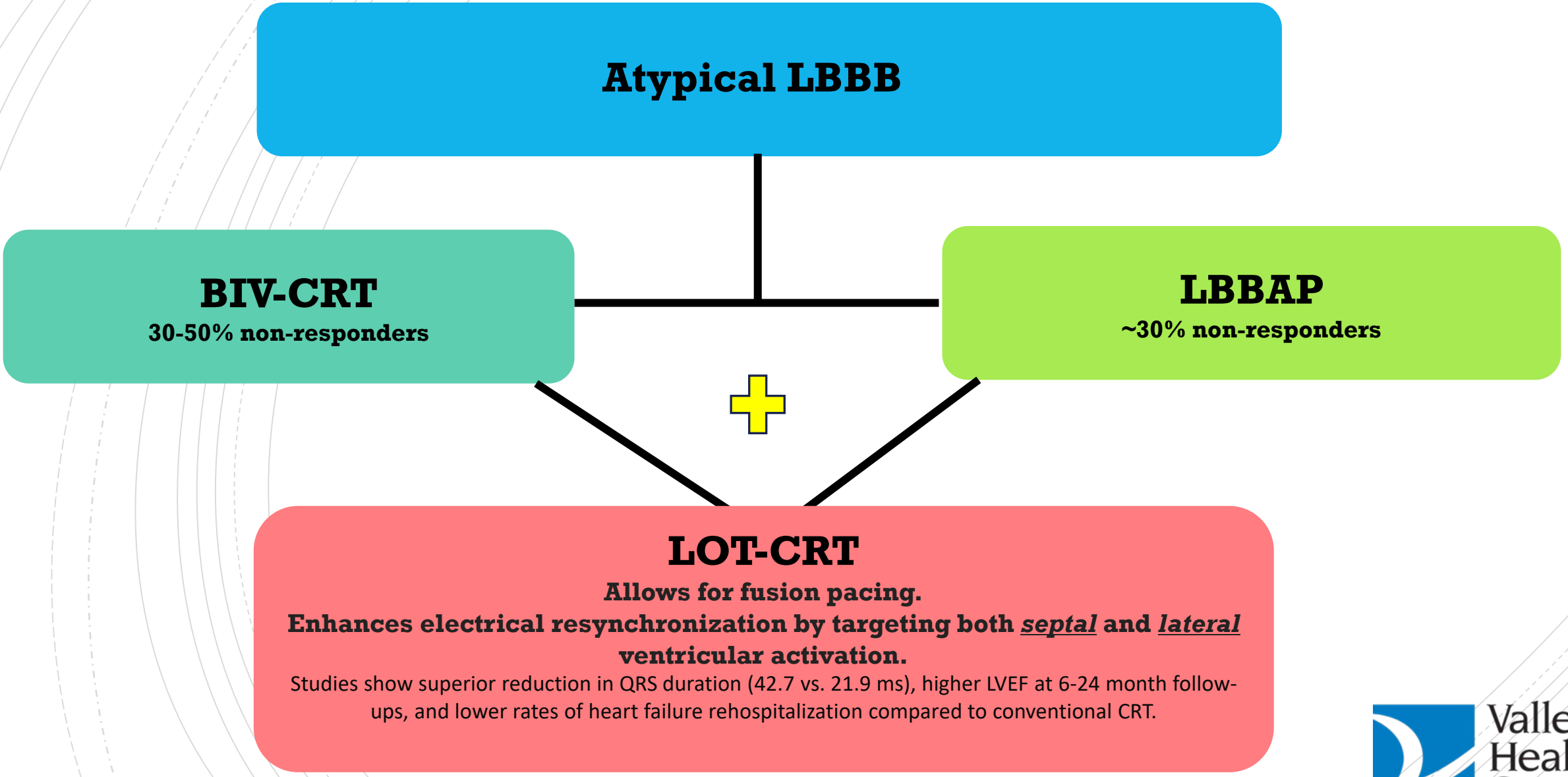
CENTRAL ILLUSTRATION: Left Bundle Branch Pacing vs Biventricular Pacing for cardiac Resynchronization Therapy





Wang Y, et al. J Am Coll Cardiol. 2022;80(13):1205-1216.

LOT-CRT:



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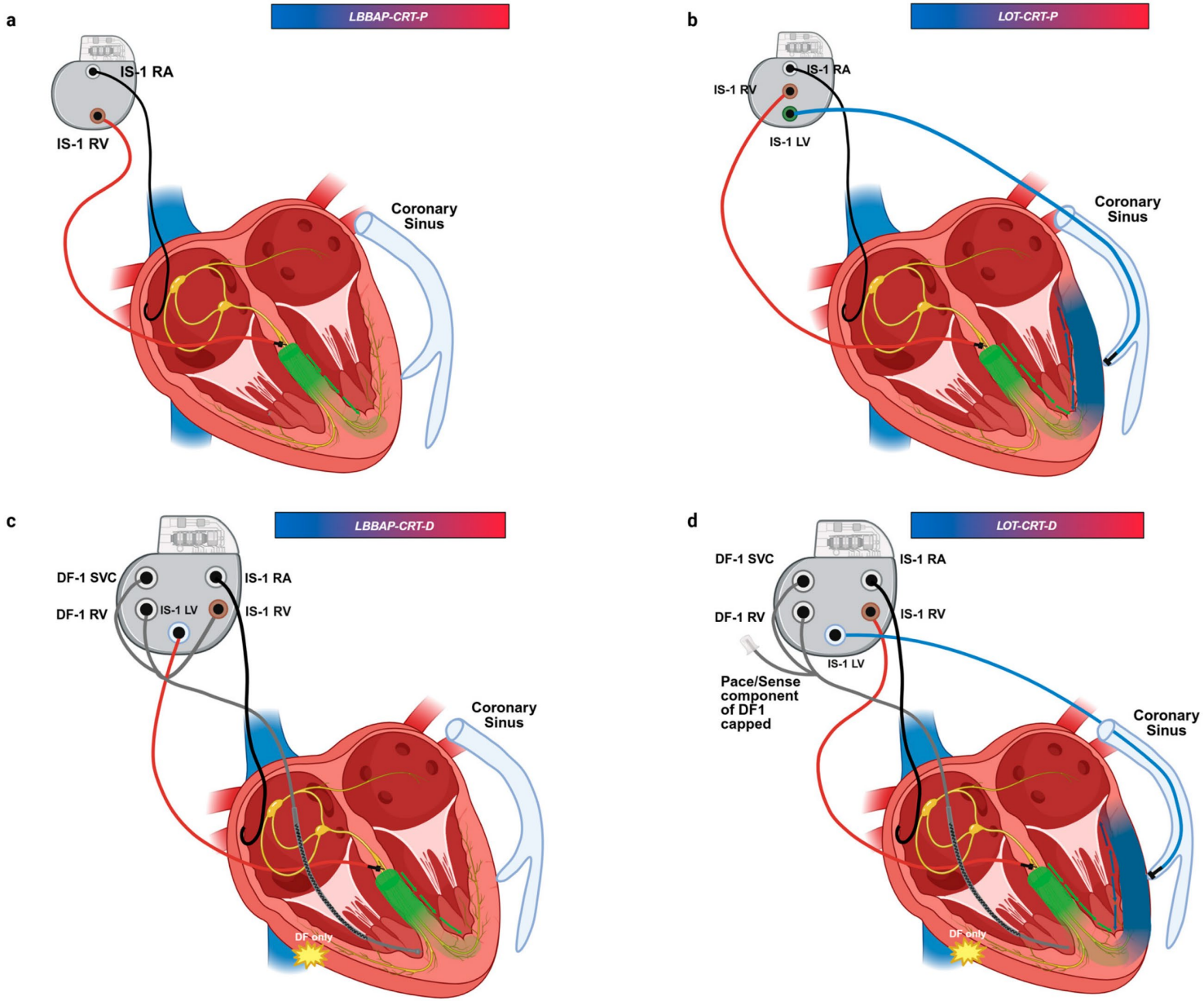
Interventricular conduction pathways during LBBAP- CRT (P/D) and LOT-CRT (P/D)

PPM

ICD



LV-RV offset is programmed at 80 ms, rendering the amount of myocardial tissue depolarized by the defibrillator (DF) lead practically negligible.

J. Clin. Med. **2025**, *14*(9), 3025; https://doi.org/10.3390/jcm14093025

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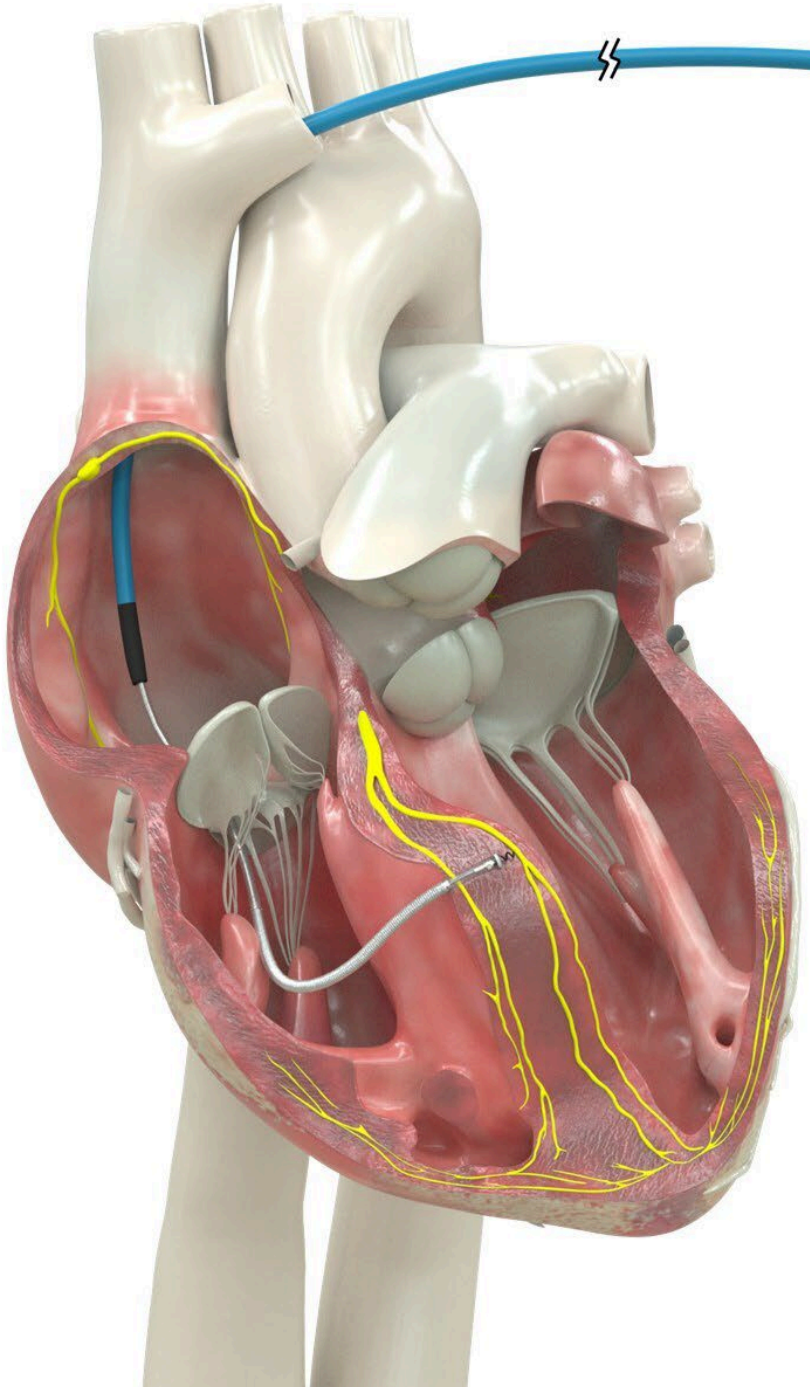

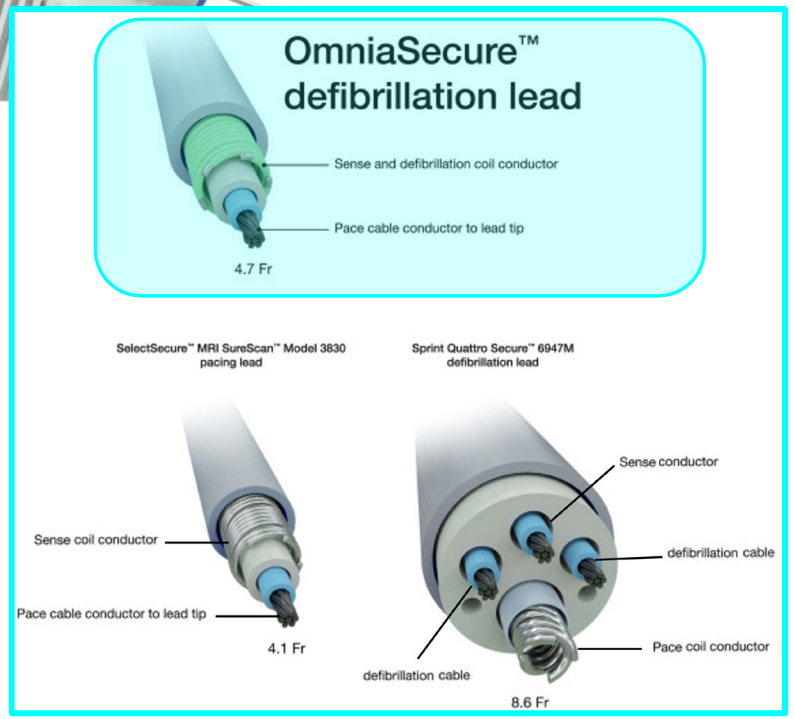

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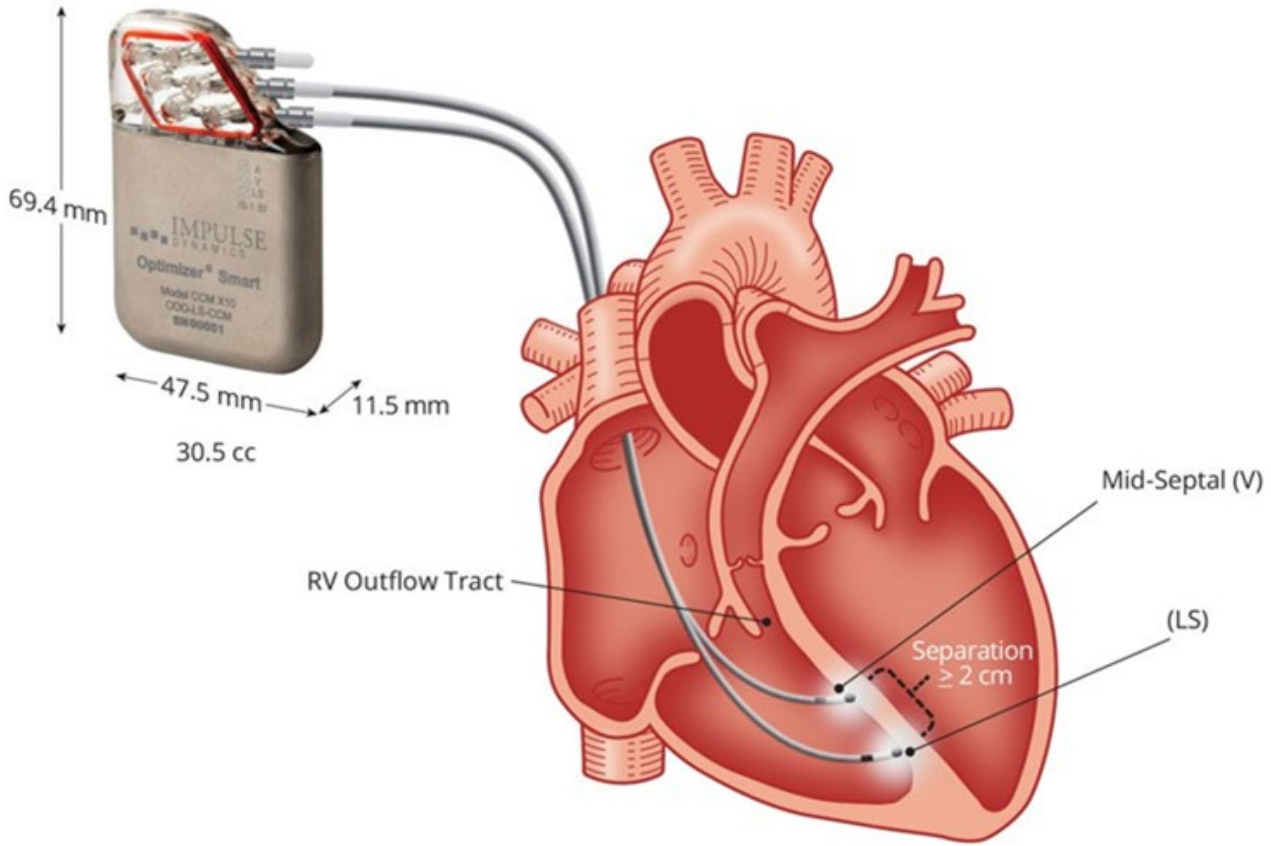
CCM



Biphasic high-voltage bipolar signals to the RV septum **during the absolute refractory period.**

Improves **calcium** handling

Reverses **fetal myocyte gene** program, reactivated in HF

Facilitates **reverse remodeling**

Effect first near the electrodes and within **~3 months**, affect all regions of the heart.

Does **NOT** increase myocardial oxygen consumption **(MVO2)**

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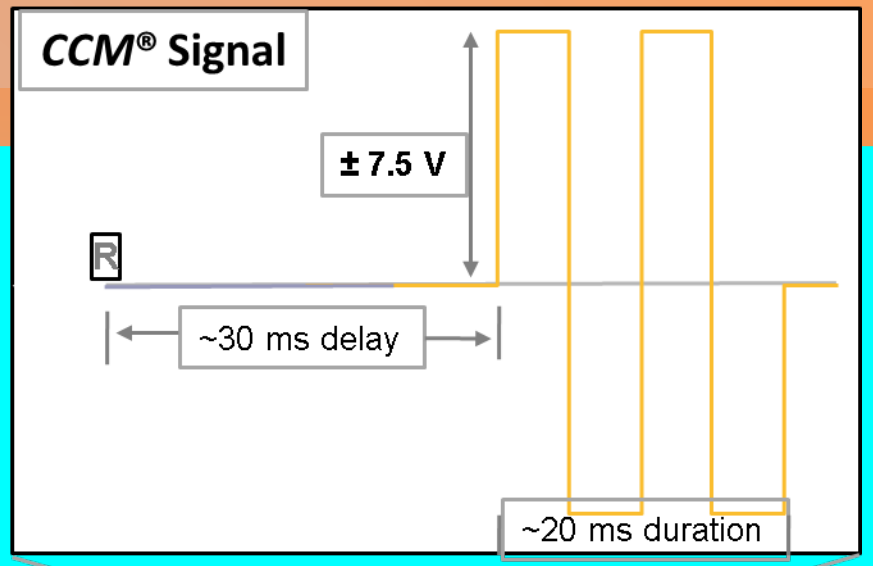
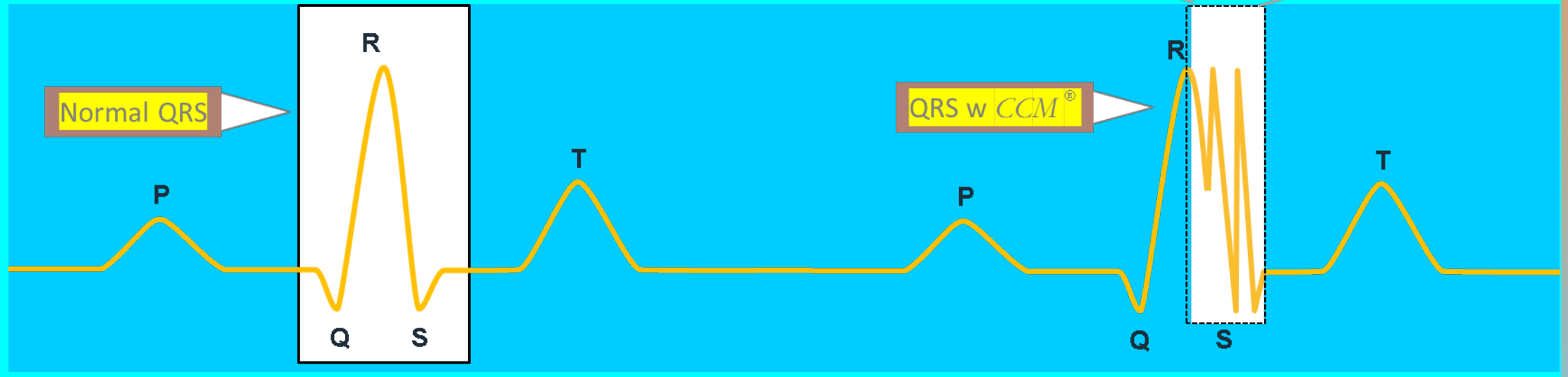
- Non-excitatory, applied during absolute refractory period
- Biphasic
- Duration of ~20msec
- Amplitude ~7.5V
- Never on T wave





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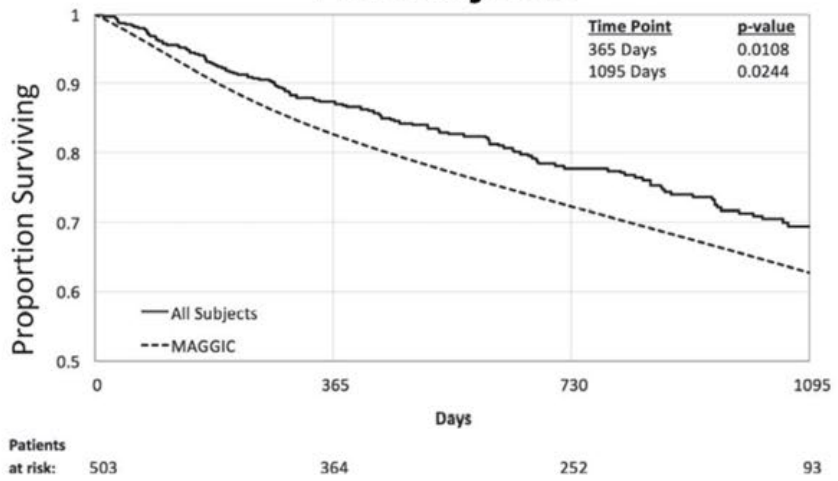
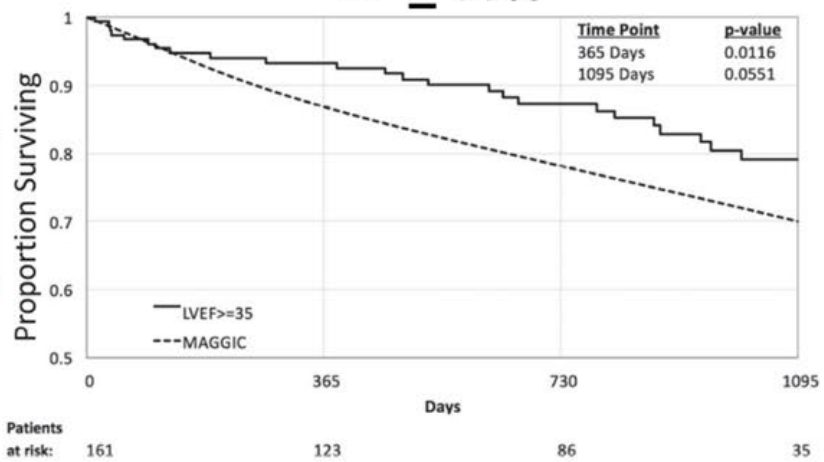
CCM-REG (prospective registry study: n=503)

Kuschyk et al, Eur J Heart Failure 2021 doi:10.1002/ ejhf.2202

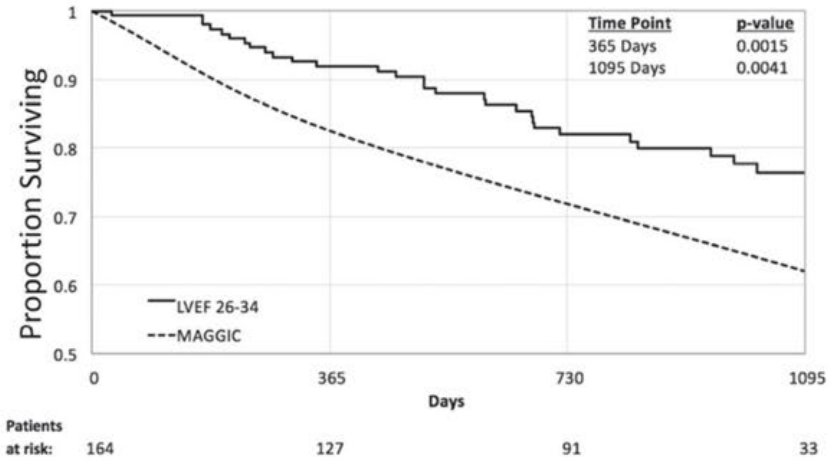
All subjects



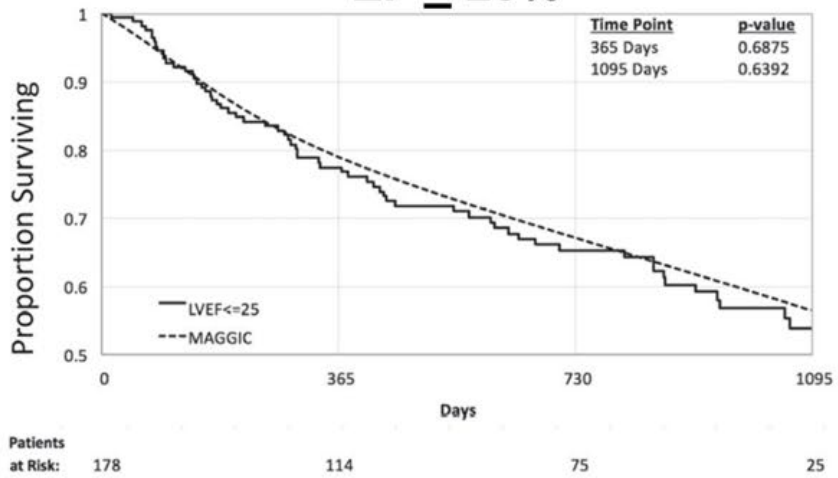
EF ≥ 35%



EF 26-34%



EF ≤ 25%



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CCM® is FDA INDICATED TO

Improve **functional status**

Improve **6-minute hall walk distance**

Improve **quality of life**

For NYHA Class III heart failure patients who...

Have a LVEF (left ventricular ejection fraction) **from 25% to 45%**

AND

Remain **symptomatic despite GDMT** (guideline directed medical therapy)

AND

Are **not receiving CRT** (Cardiac Resynchronization Therapy)

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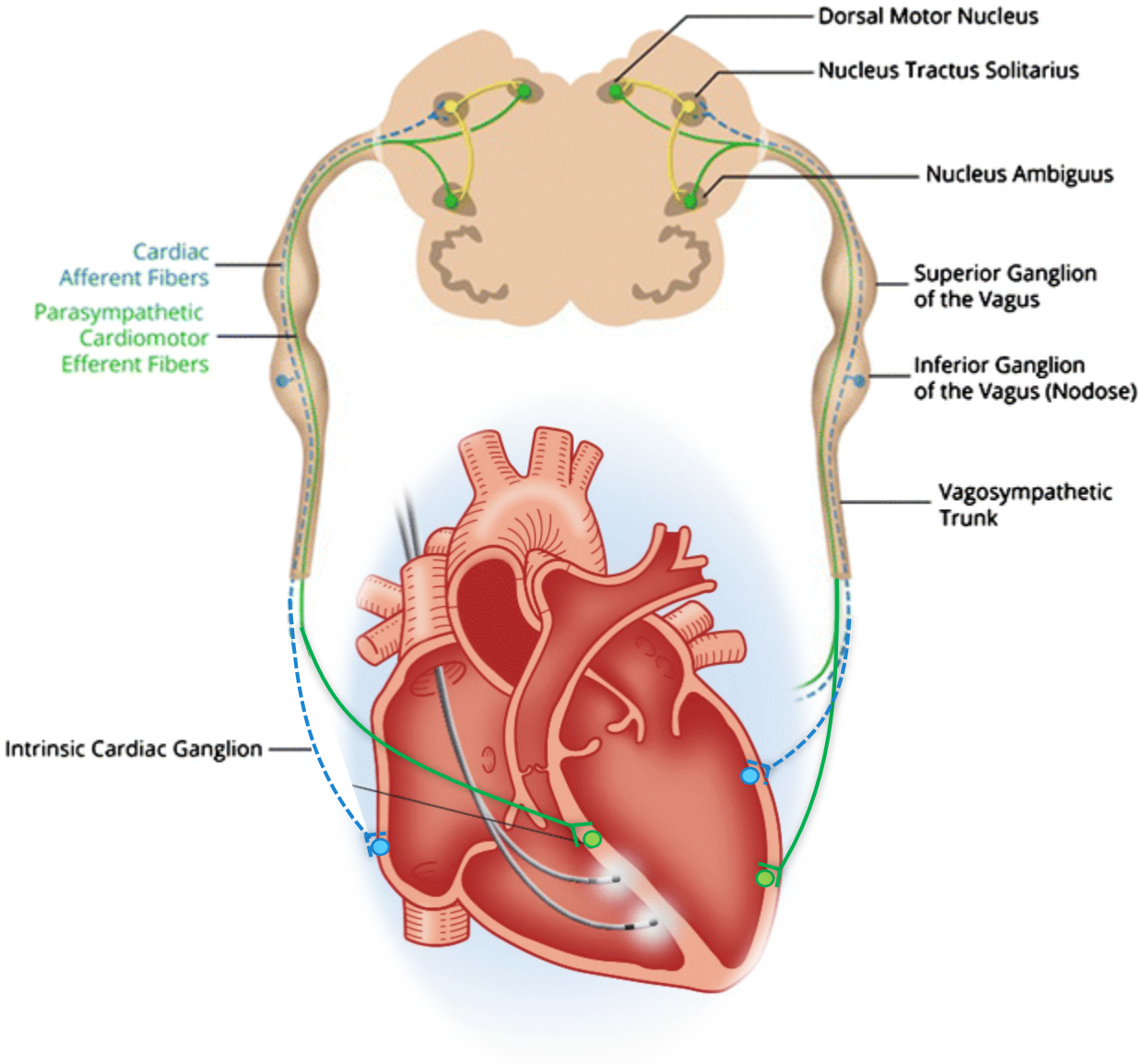
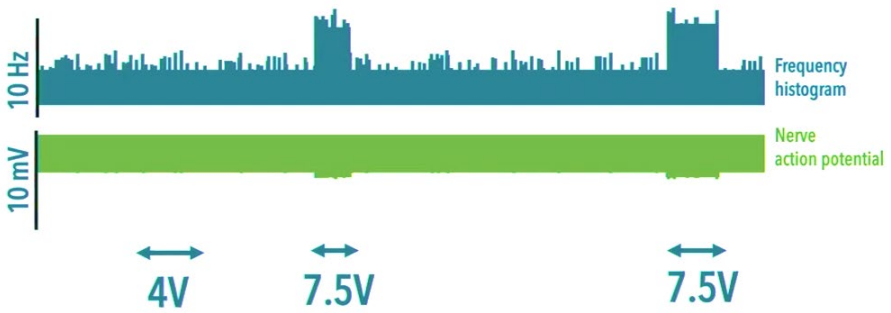
Evidence of *CCM*® Influence on Sympathetic Activity



A. CCM increases septal contraction
B. Mechanoreceptors activate vagal afferents
C. Sympathetic activity decreases (central /peripheral)
D. Improvement in autonomic balance



In vagal nerve fibers CCM produced an intensity dependent increase (p<0.05) in firing frequency

Sengupta et al. FASEBJ, https://www.fasebj.org/doi/abs/10.1096/fasebj.29.1_supplement.65

Adapted from:
Tschöpe et al. Eur J of Heart Fail 2019;21:14–22.
Shivkumar et al. Current treatment in CV med 17 (2015): 1-17.

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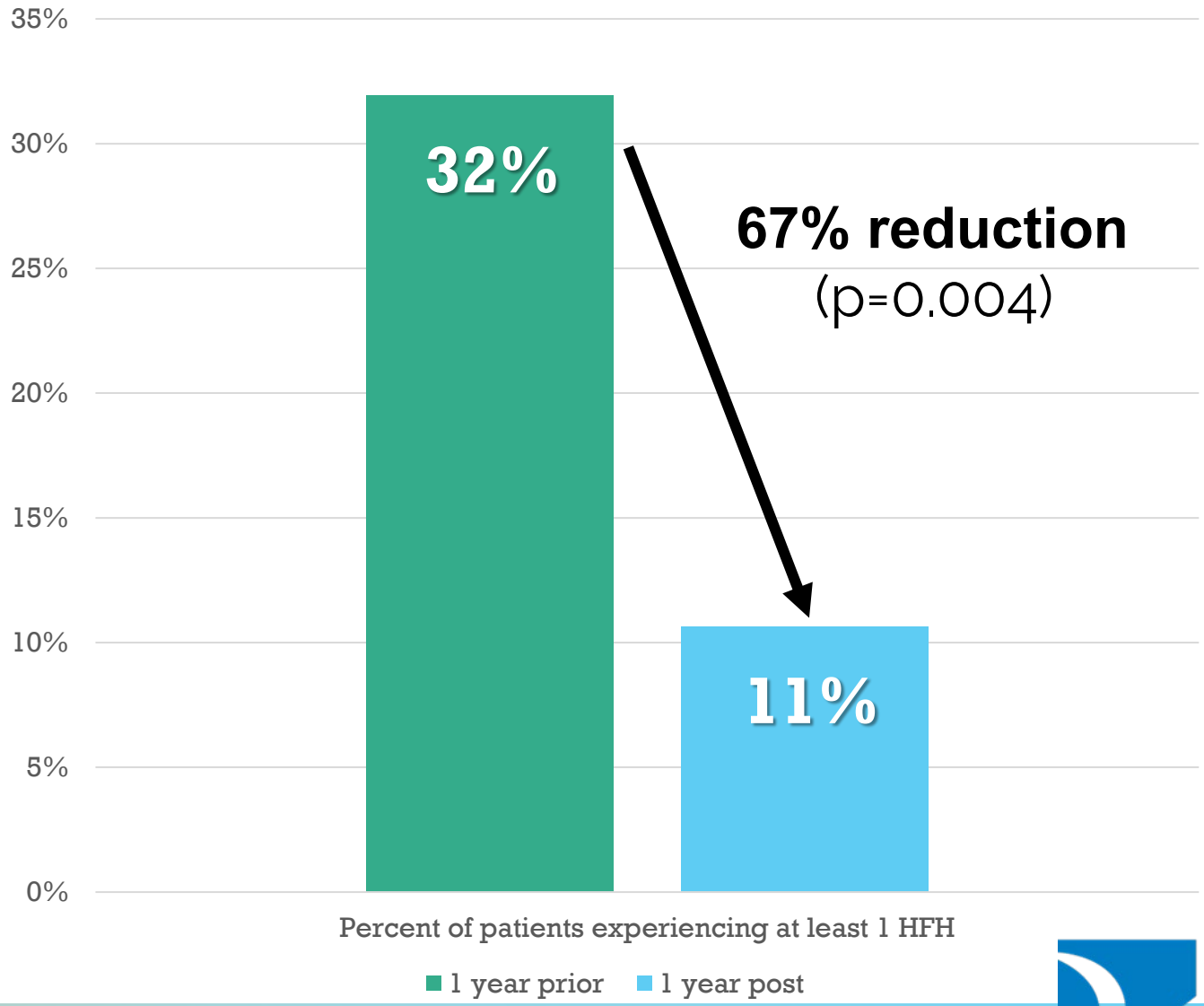
- **68-year-old gentleman with HTN, COPD, PVD,CKD stage IV, CAD, prior MI, CABG and PCI.**
- **EF of 30 to 35% despite GDMT, and severe MR with severely dilated LA.**
- **EKG: SR with narrow QRS.**
- **Single chamber ICD.**
- **In follow-up GDMT had to be discontinued due to worsening renal failure and hypotension.**
- **CCM implanted.**

- **Symptomatic improvement within first week**
- **Now can walk 300 feet without dyspnea, climbing stairs without dyspnea;**
- **no edema or orthopnea.**
- **Blood pressure now typically in the 120s, allowing for reinitiation of GDMT.**
- **Repeat echo 4 months later: EF nearly 50%.**
- **Only small apical wall motion abnormality.**
- **Mitral insufficiency is <moderate.**

Fewer Hospitalizations for HFpEF Pts with CCM

"Fewer patients required HF hospitalization in the 1-year period after CCM therapy device implant compared to the 1-year period prior."

- 15 of 47 patients (**32%**) required at least one HFH in the year prior to device implantation.
- 5 of 47 patients (**11%**) required at least one HFH in the year after device implantation
- represents a **67% reduction** in the number of patients experiencing a HFH (**p=0.004**)



Linde, C., Grabowski, M., Ponikowski, P., Rao, I., Stagg, A., & Tschöpe, C. (2022). Cardiac contractility modulation therapy improves health status in patients with heart failure with preserved ejection fraction: a pilot study (CCM-HFpEF). *European Journal of Heart Failure*.

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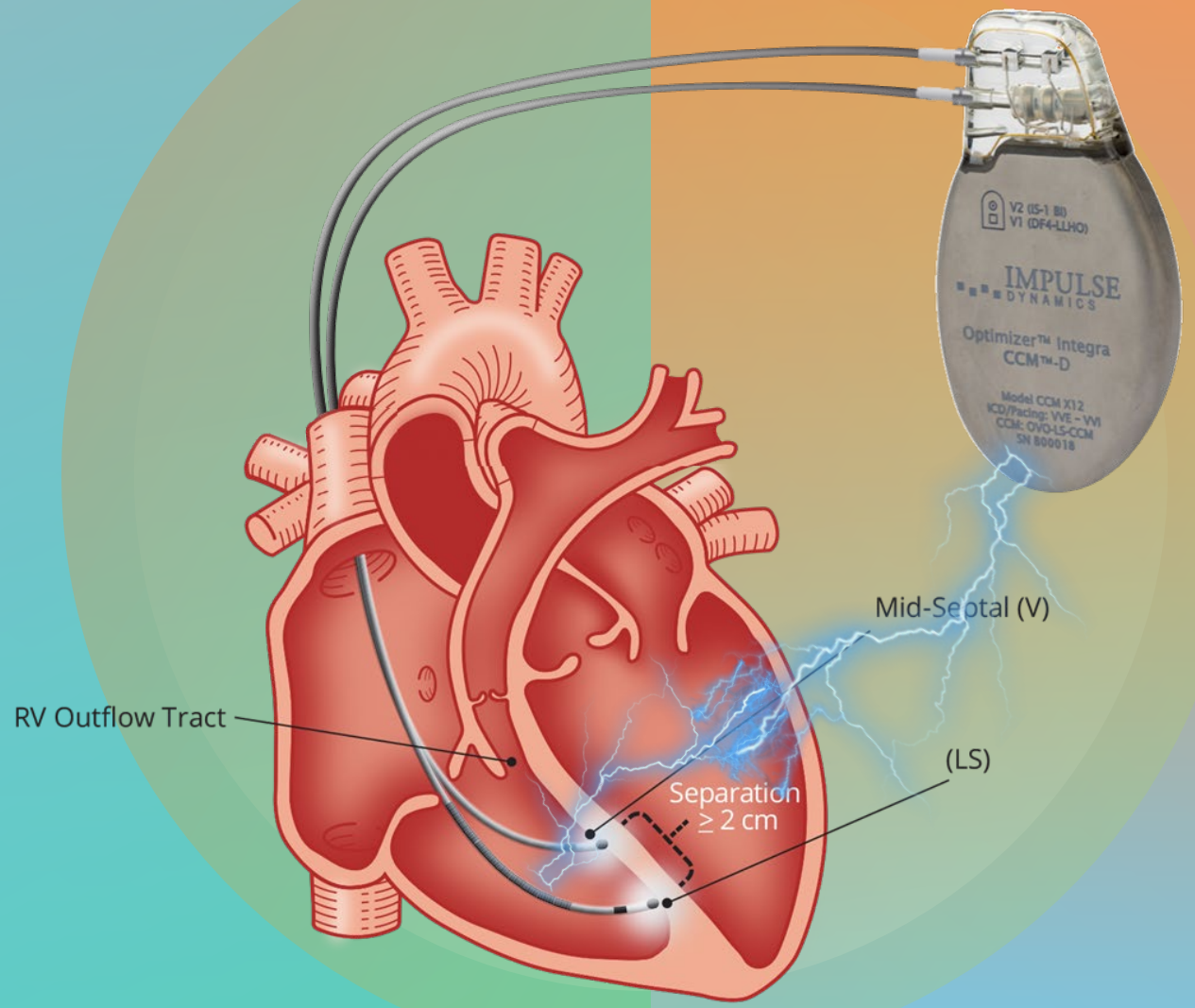
*INVESTIGATONAL DEVICE – INTEGRA-D Trial

INTEGRA-D



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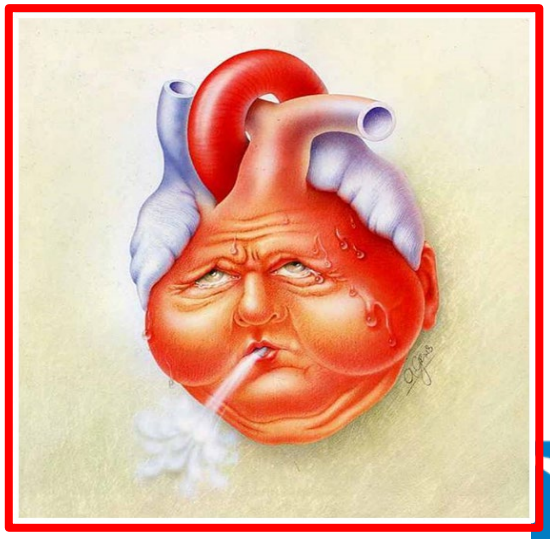
Conclusion

HF remains a challenging to treat chronic condition.

Both CRT and CCM are effective therapies in HF and need to be tailored to individual needs, in addition to GDMT.

Thank You!



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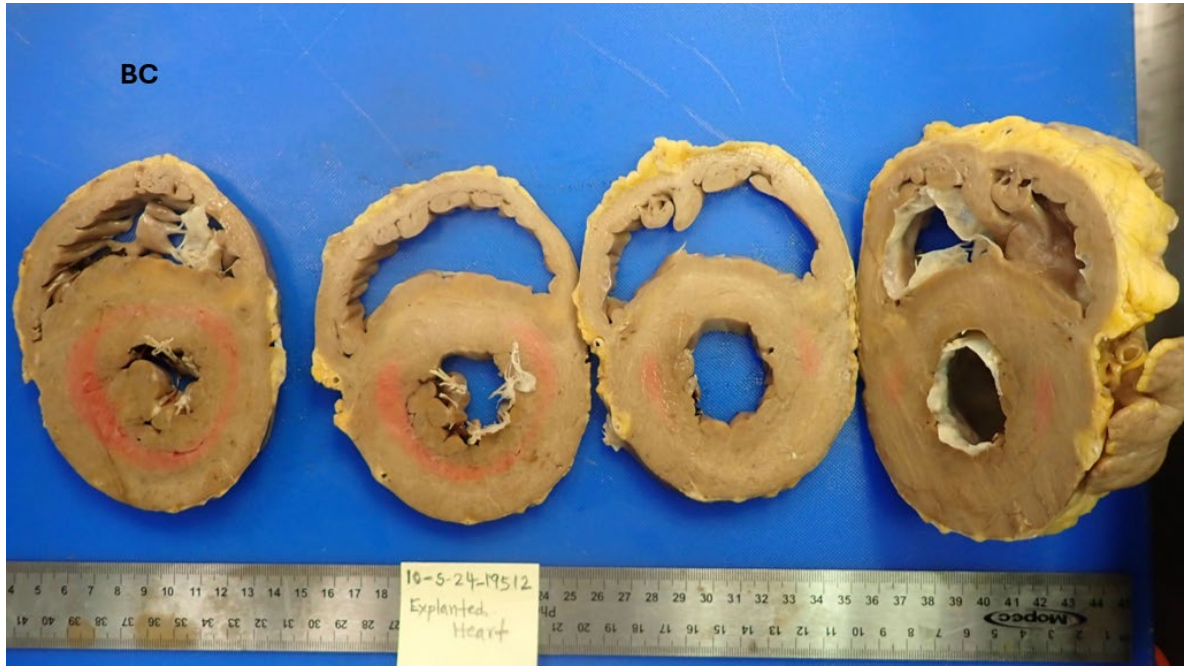
Bridging the Gap: Timely Diagnosis and Precision Management of Amyloidosis



Samit Shah, MD

Advanced Heart Failure/Transplant

Medical Director of Mechanical Circulatory Support

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What is Amyloidosis?

- Amyloidosis – extracellular tissue deposition of fibrillatory material from **precursor proteins** that assemble into cross β-sheet conformation

- Manifestations are dependent on type, location and amount

TABLE 1 Overview of the Common Forms of Amyloidosis That May Affect the Heart

Amyloid Nomenclature	Precursor Protein	Age Range, yrs	Sex	Clinical Clues	Laboratory Abnormalities
AL	Light chains	50+	Either	Multiorgan involvement. Periorbital bruising or macroglossia are almost pathognomonic of AL in setting of typical MRI or echocardiogram. Severe hypotension with ACE inhibitors.	Elevated serum free lambda or kappa, with abnormal ratio. Monoclonal spike in serum and/or urine. Suppressed immunoglobulins. Proteinuria.
ATTRwt	Wild-type (normal) transthyretin	65+	Marked male predominance, >15:1	History of carpal tunnel syndrome 5-10 yrs earlier, with no other organ involvement.	No specific abnormalities. (Normal free light chain values, no proteinuria)
ATTRm	Mutant transthyretin	40+ (mutation dependent). In V122I, the common African-American variant, usual age of clinical onset is 60-65 yrs.	Either, slight male predominance.	African-American/Caribbean origin (for V122I TTR variant).	No specific abnormalities on routine testing. Genetic testing reveals mutation in TTR molecule
AA (Secondary)	Serum amyloid A (an acute phase protein)	May occur in 20s–30s upward with severe inflammatory disease.	Either	Underlying chronic inflammatory disease. Hepatomegaly, splenomegaly. Usually no cardiac involvement, but in rare cases may be severe	High ESR/CRP. Proteinuria.

Falk et al.J Am Coll Cardiol 2016; 68: 1323-41

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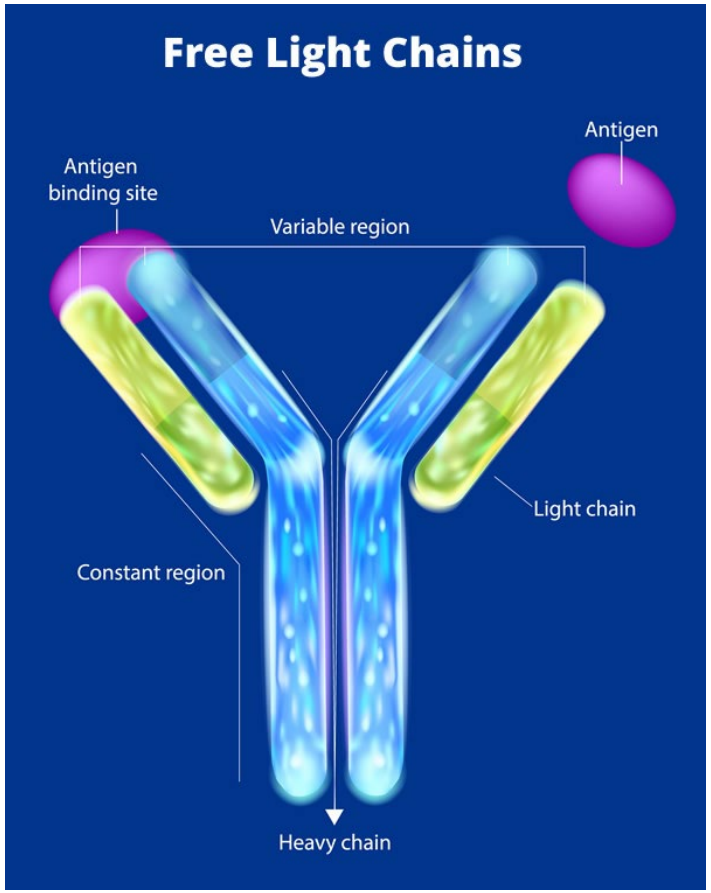
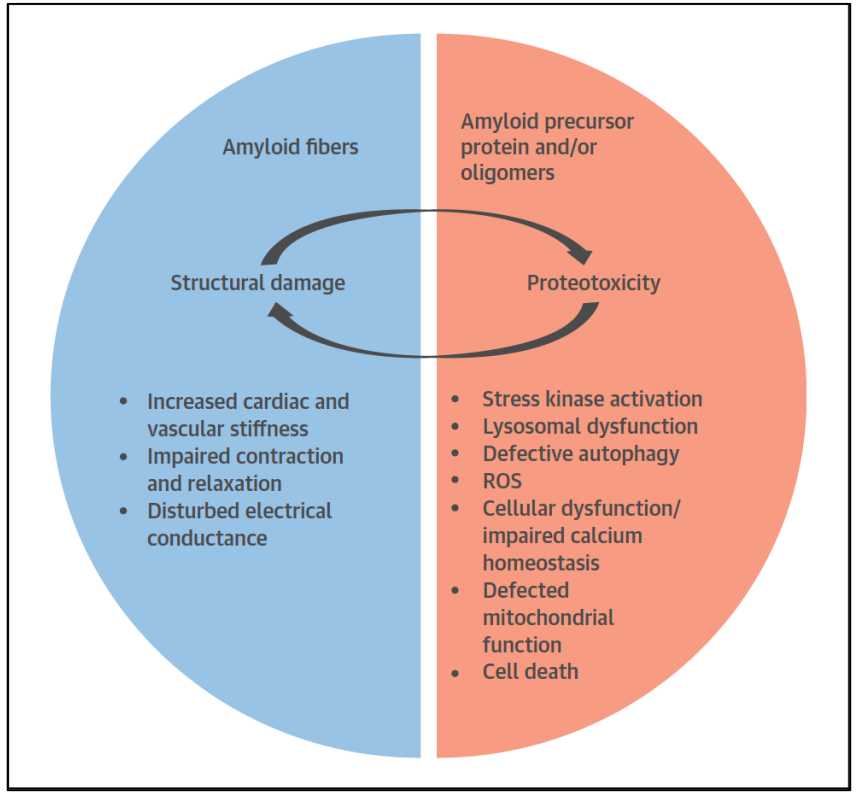
AL Amyloidosis

- Hematologic d/o of plasma cells → overproduction of lambda or kappa light chains
- Related to myeloma but distinct from it
- Toxic infiltrative cardiomyopathy





Falk et al.J Am Coll Cardiol 2016; 68: 1323-41

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AL Amyloidosis

TABLE 2 Spectrum of Clonal Plasma Cell Disorders

	MGUS	Asymptomatic Myeloma	Symptomatic Myeloma	AL Amyloidosis
How common is it?*	+++++++	+++++	+++	+
Typical clonal plasma cell percentage	<10%	10%-60%	>10%	Any
Typical concentration of paraprotein on SPIE/UPIE/serum FLC	Low	Moderate	High	Any
Treatment required?	No	No	Yes	Yes

*More + refers to being more common.

MGUS = monoclonal gammopathy of undetermined significance; other abbreviations as in Table 1.

Witteles et al. J Am Coll Cardiol 2019; 1: 117-30

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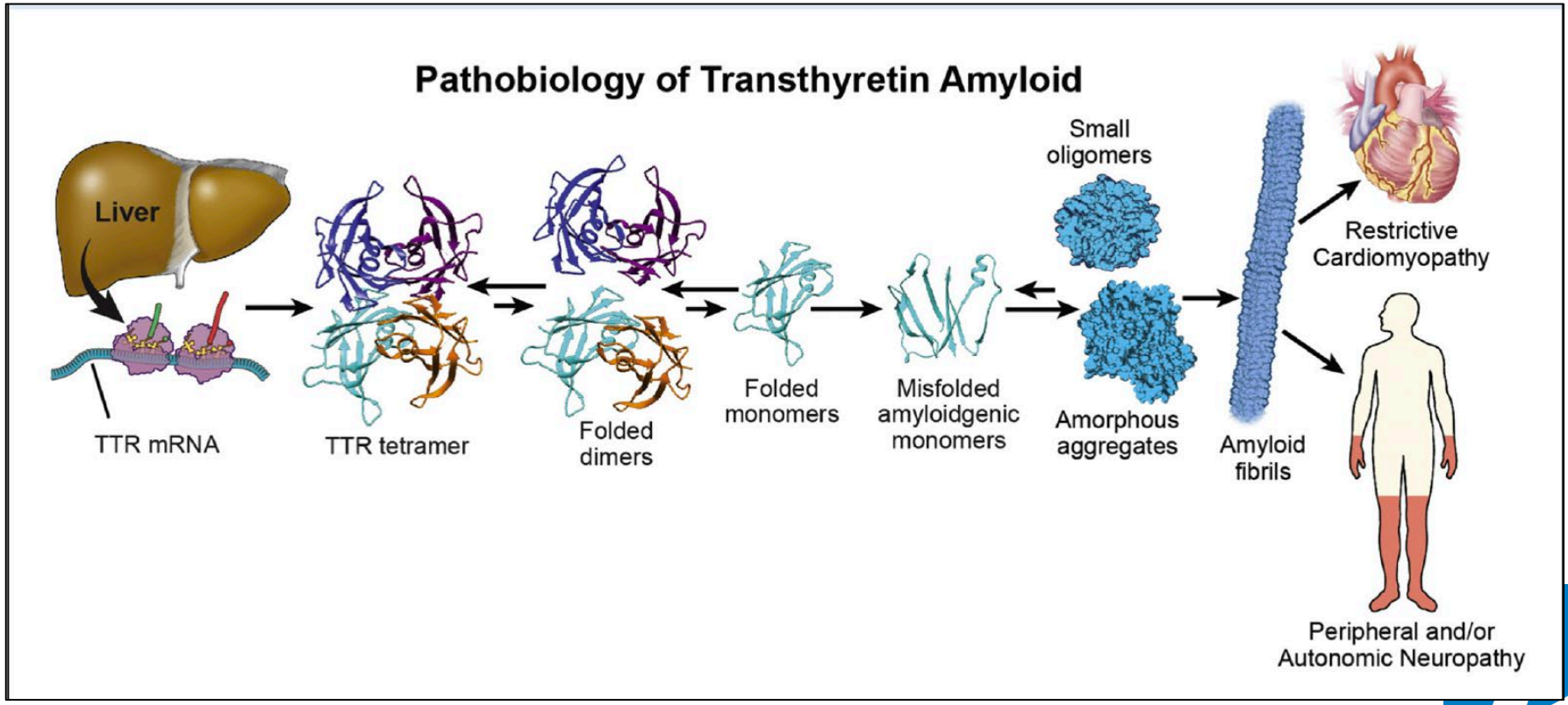
TTR Amyloidosis

- ***trans***ports ***thy***roxine and ***retin***ol = ***transthyretin***
- Synthesized primarily in liver
- Wild-type (wtATTR) or mutation/hereditary (hATTR)



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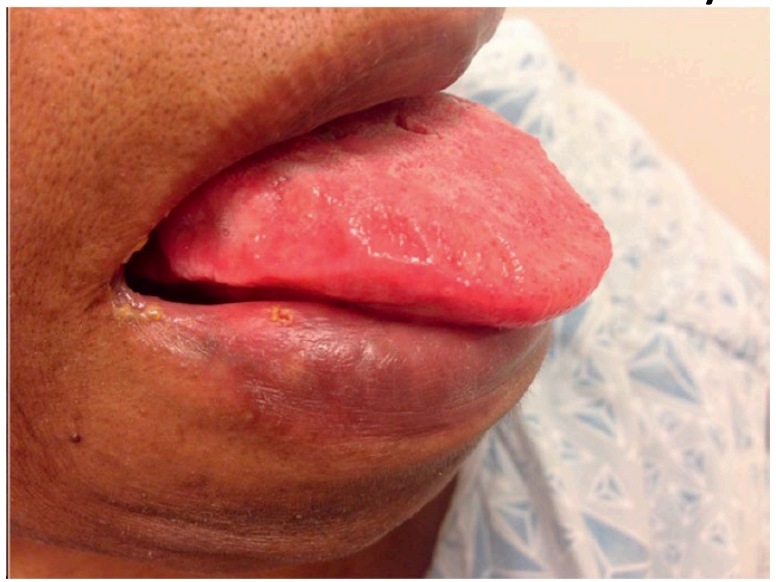
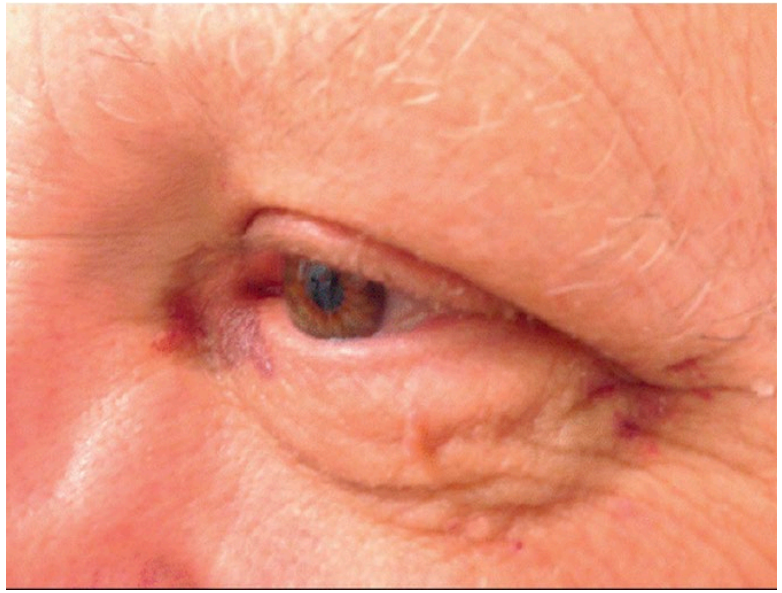
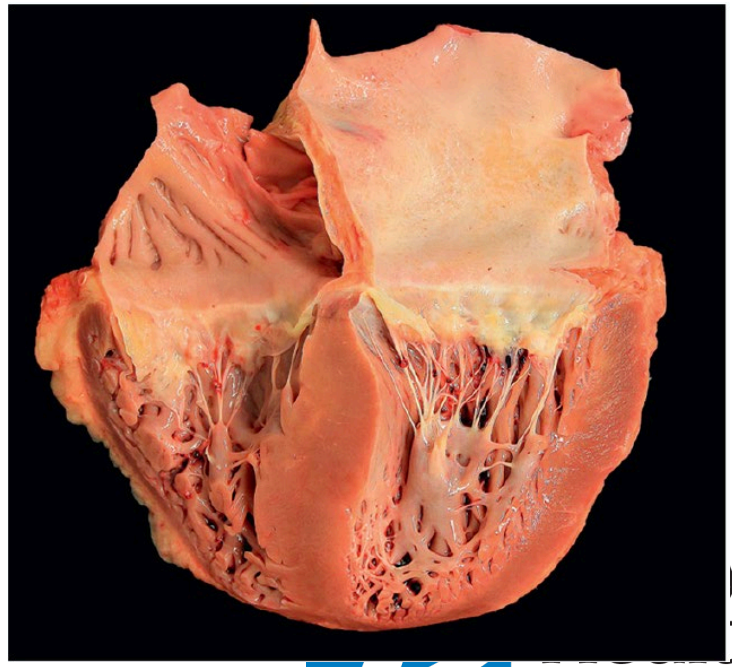
Clinical Manifestations of Amyloidosis

- Restrictive CM and late stages systolic dysfunction
- Heart block, arrhythmias
- Aortic stenosis
- Peripheral neuropathy (usually sensory) - spinal stenosis, carpal tunnel
- Biceps tendon rupture
- Autonomic dysfunction – postural hypotension
- Proteinuria – AL amyloidosis

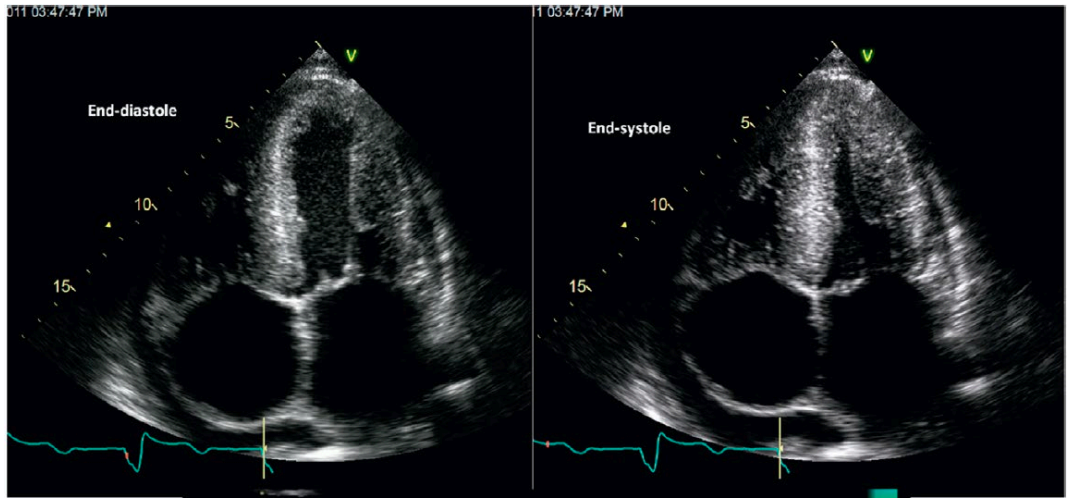


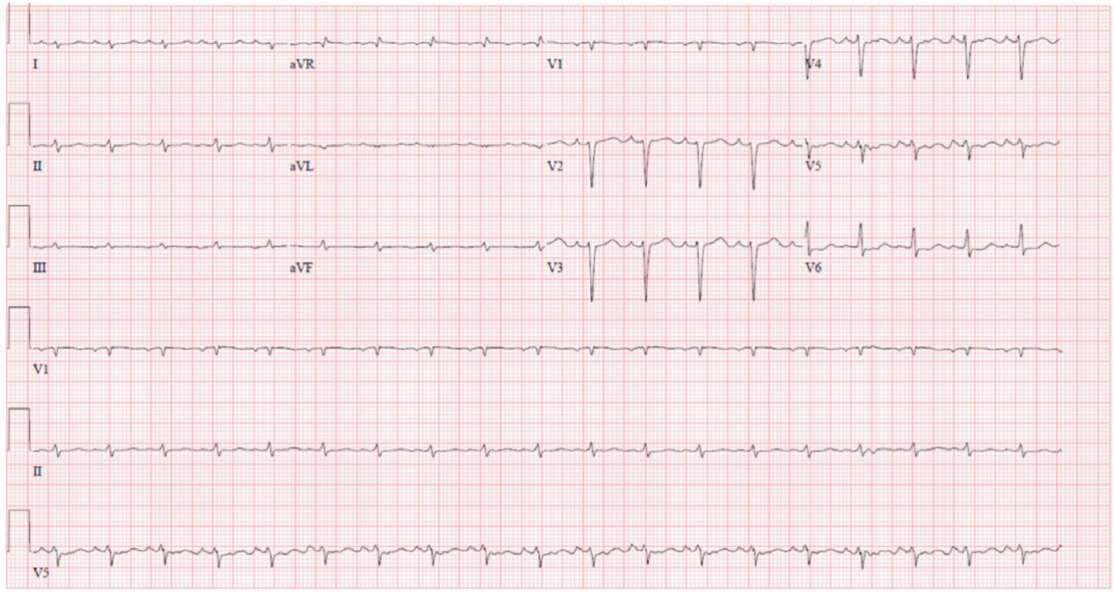




Screening for Amyloidosis

- History consistent with multisystemic infiltrative disease
- Hypertrophy (>14mm) and discordant normal or low ECG voltage





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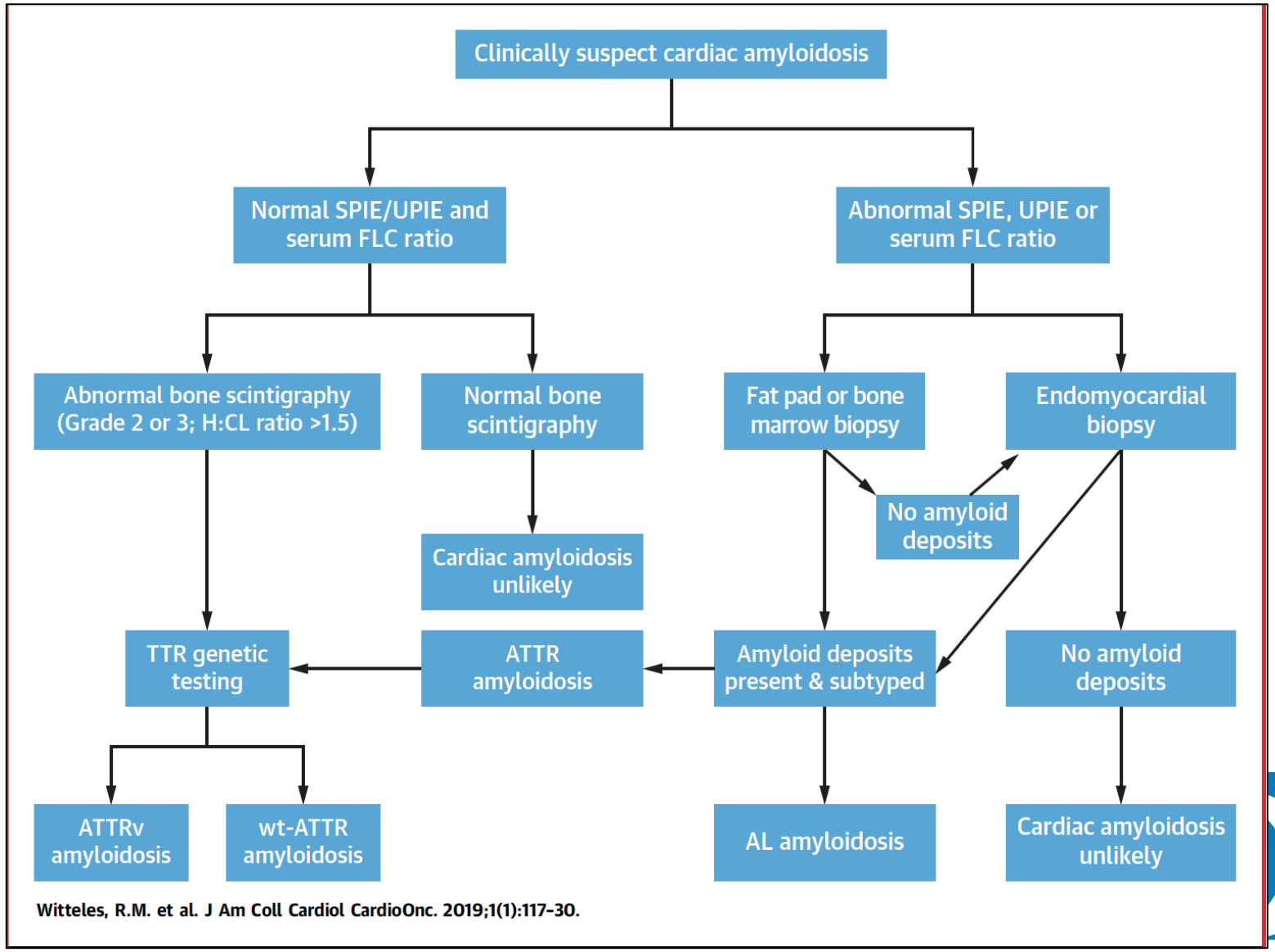
Testing Algorithm



Witteles, R.M. et al. J Am Coll Cardiol CardioOnc. 2019;1(1):117-30.

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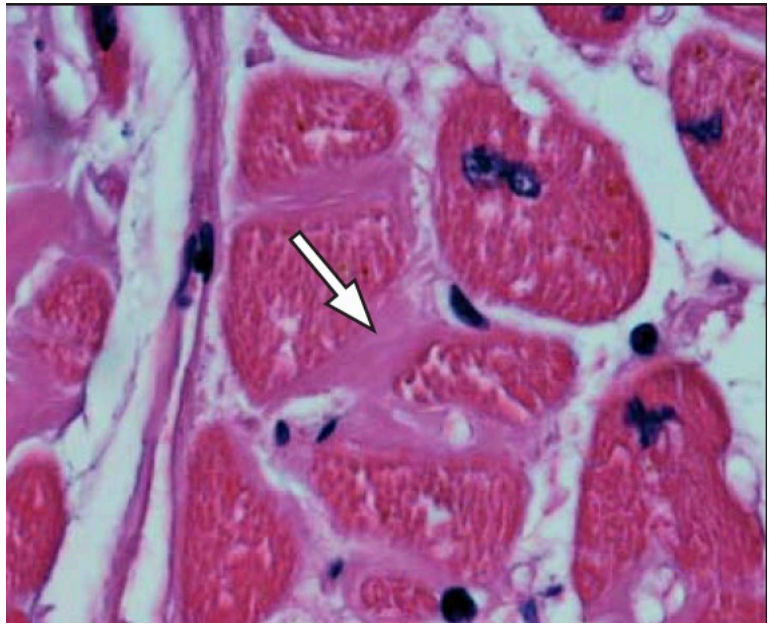
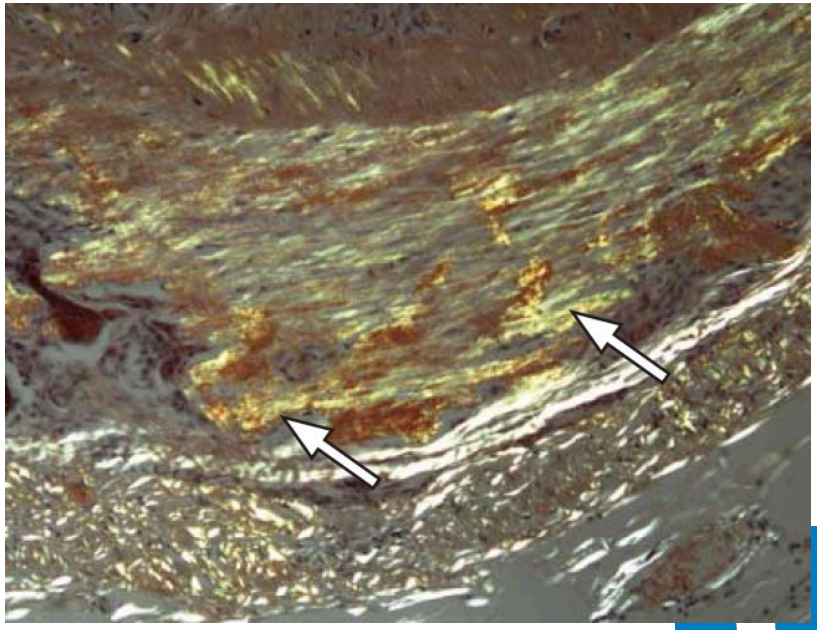
Biopsy

- Consider site of biopsy and diagnostic yield
  - Fat pad biopsy more sensitive/specific for AL
  - Congo red staining identifies amyloid deposits
- Subtyping important to further determine etiology (e.g. AL, TTR, etc.)
  - Mass spectrometry done at specialized centers





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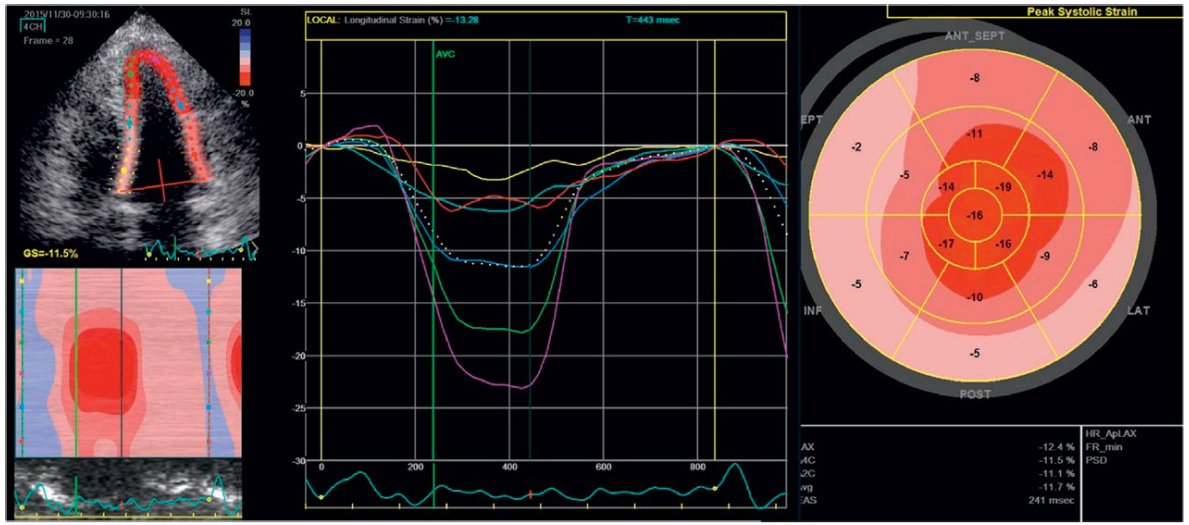
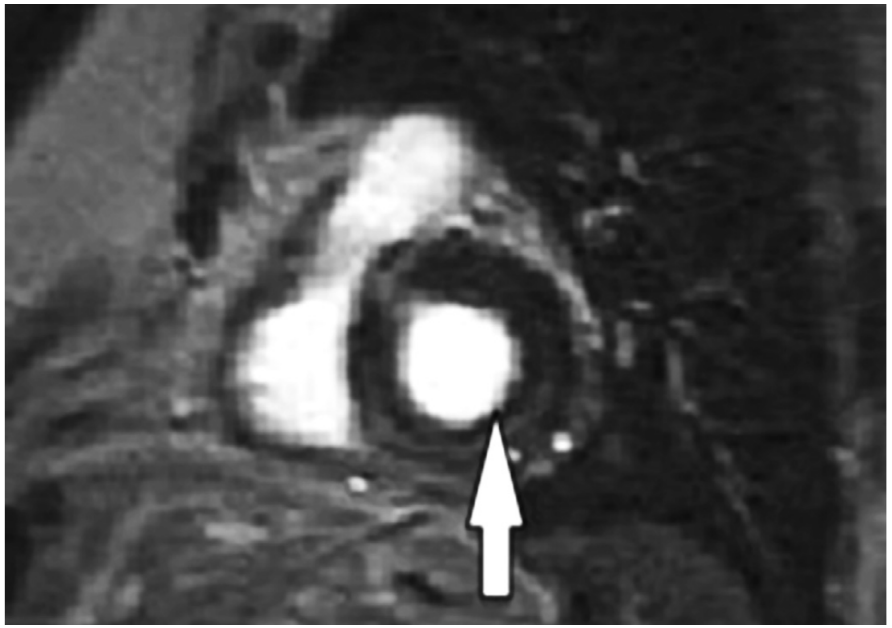
Imaging



Strain Imaging



CMR

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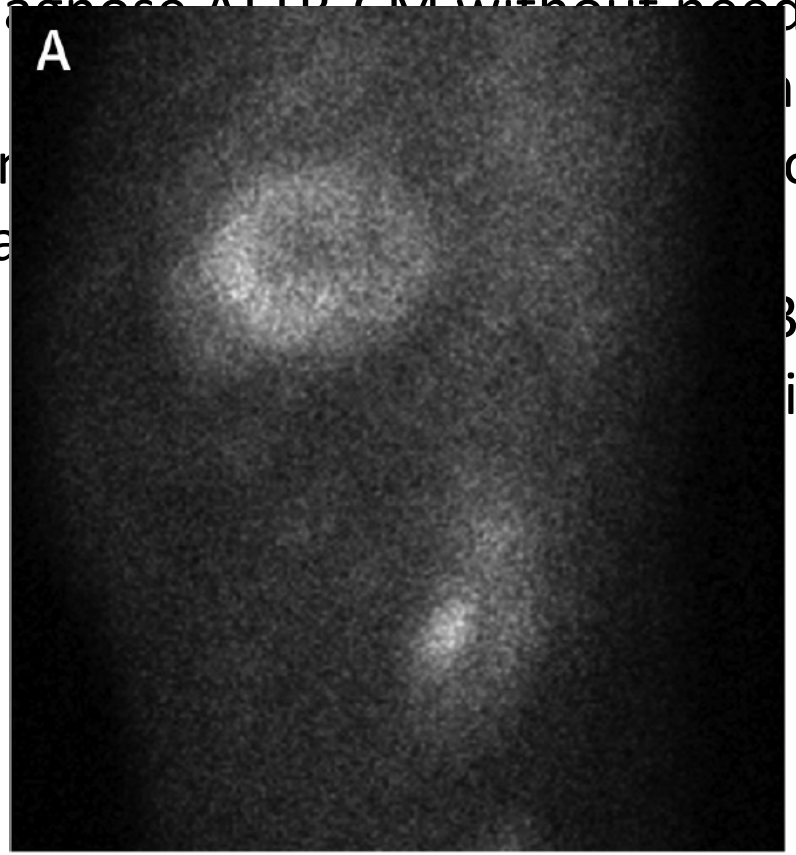
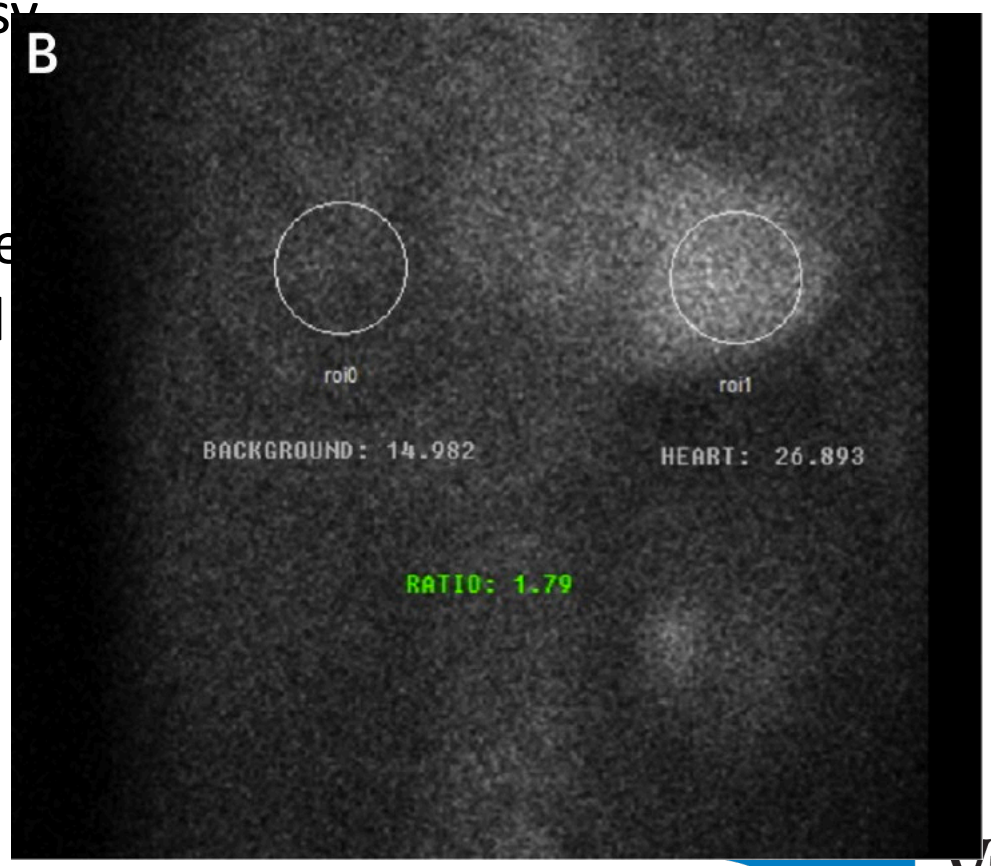
Bone Tracers - Scintigraphy

- Nuclear scintigraphy with bone-avid tracers - only imaging that can accurately di[illegible] for biopsy
  - [illegible] US
- Ur[illegible] amyloid
- Ca[illegible] with bone
  - [illegible] – exceed
  - [illegible] io>1.5





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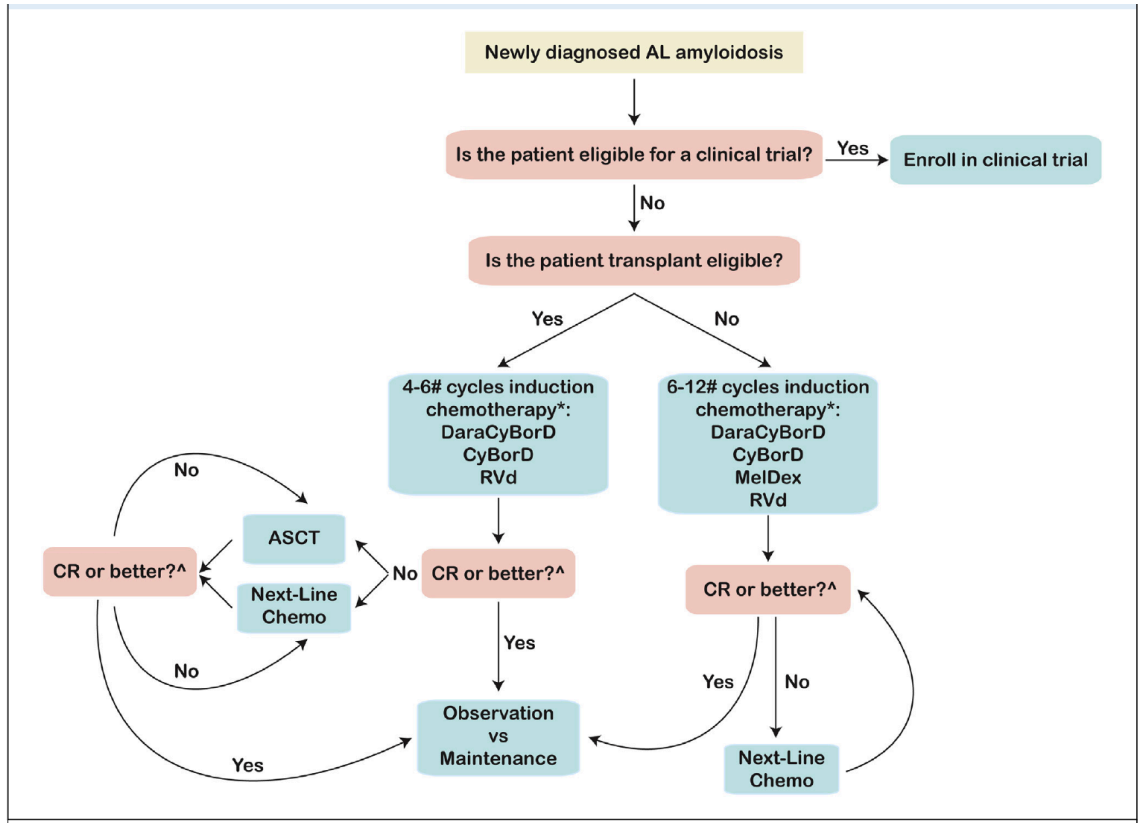
AL Amyloidosis Therapy

- Main goal – hematologic response
  - Follow free light chains as main indicator of degree of response to treatment
- Time to treatment is ***critical!***



Daratumumab-Based Treatment for Immunoglobulin Light-Chain Amyloidosis

E. Kastritis, G. Palladini, M.C. Minnema, A.D. Wechalekar, A. Jaccard, H.C. Lee, V. Sanchorawala, S. Gibbs, P. Mollee, C.P. Venner, J. Lu, S. Schönland, M.E. Gatt, K. Suzuki, K. Kim, M.T. Cibeira, M. Beksac, E. Libby, J. Valent, V. Hungria, S.W. Wong, M. Rosenzweig, N. Bumma, A. Huart, M.A. Dimopoulos, D. Bhutani, A.J. Waxman, S.A. Goodman, J.A. Zonder, S. Lam, K. Song, T. Hansen, S. Manier, W. Roeloffzen, K. Jamroziak, F. Kwok, C. Shimazaki, J.-S. Kim, E. Crusoe, T. Ahmadi, N.P. Tran, X. Qin, S.Y. Vasey, B. Tromp, J.M. Schecter, B.M. Weiss, S.H. Zhuang, J. Vermeulen, G. Merlini, and R.L. Comenzo, for the ANDROMEDA Trial Investigators*

Bianchi G et al. J Am Coll Cardiol Cardioonc 2021; 3 (4): 467-487

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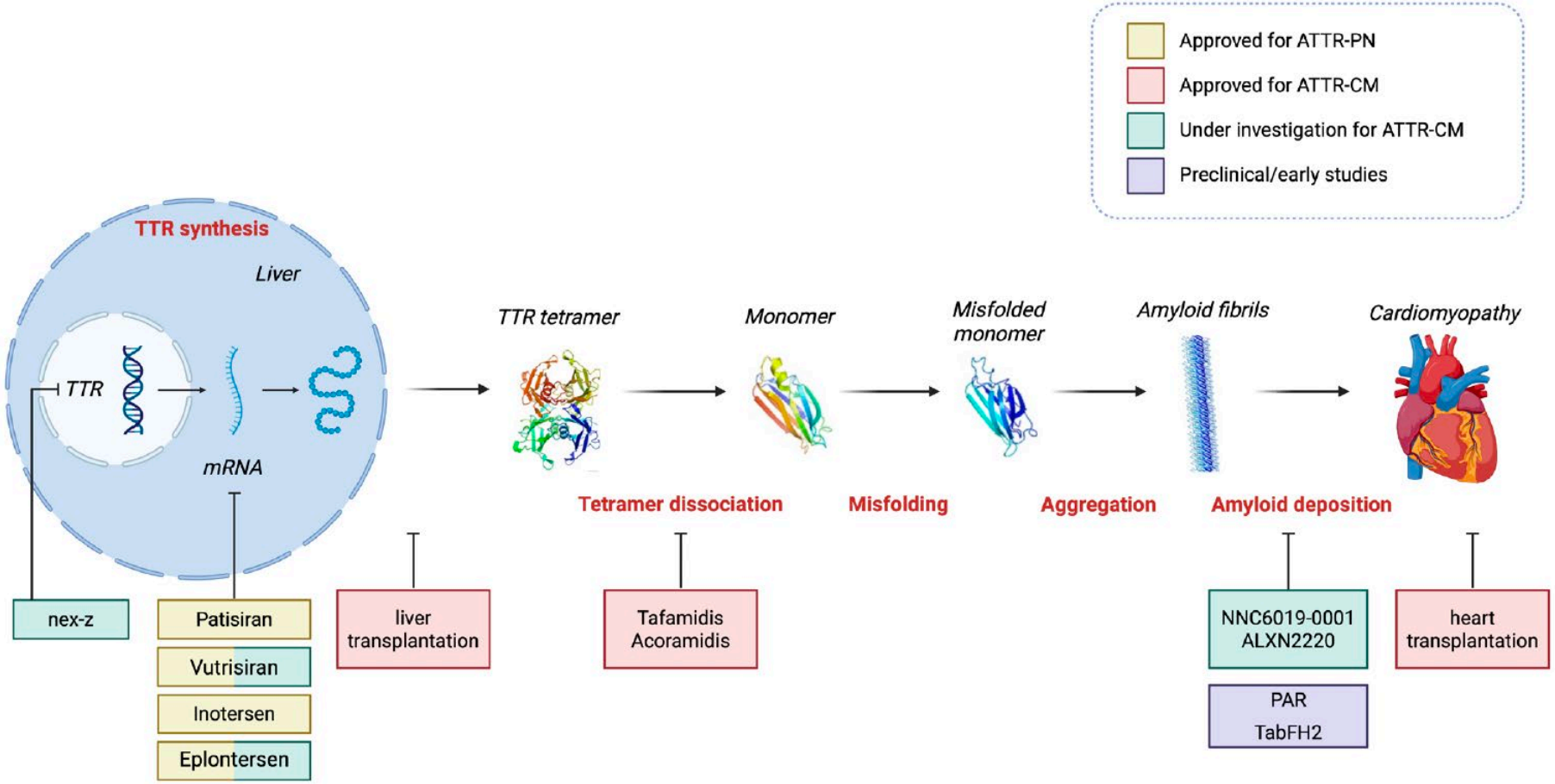
TTR Amyloidosis Therapy



Vergaro G et al. Heart 2025

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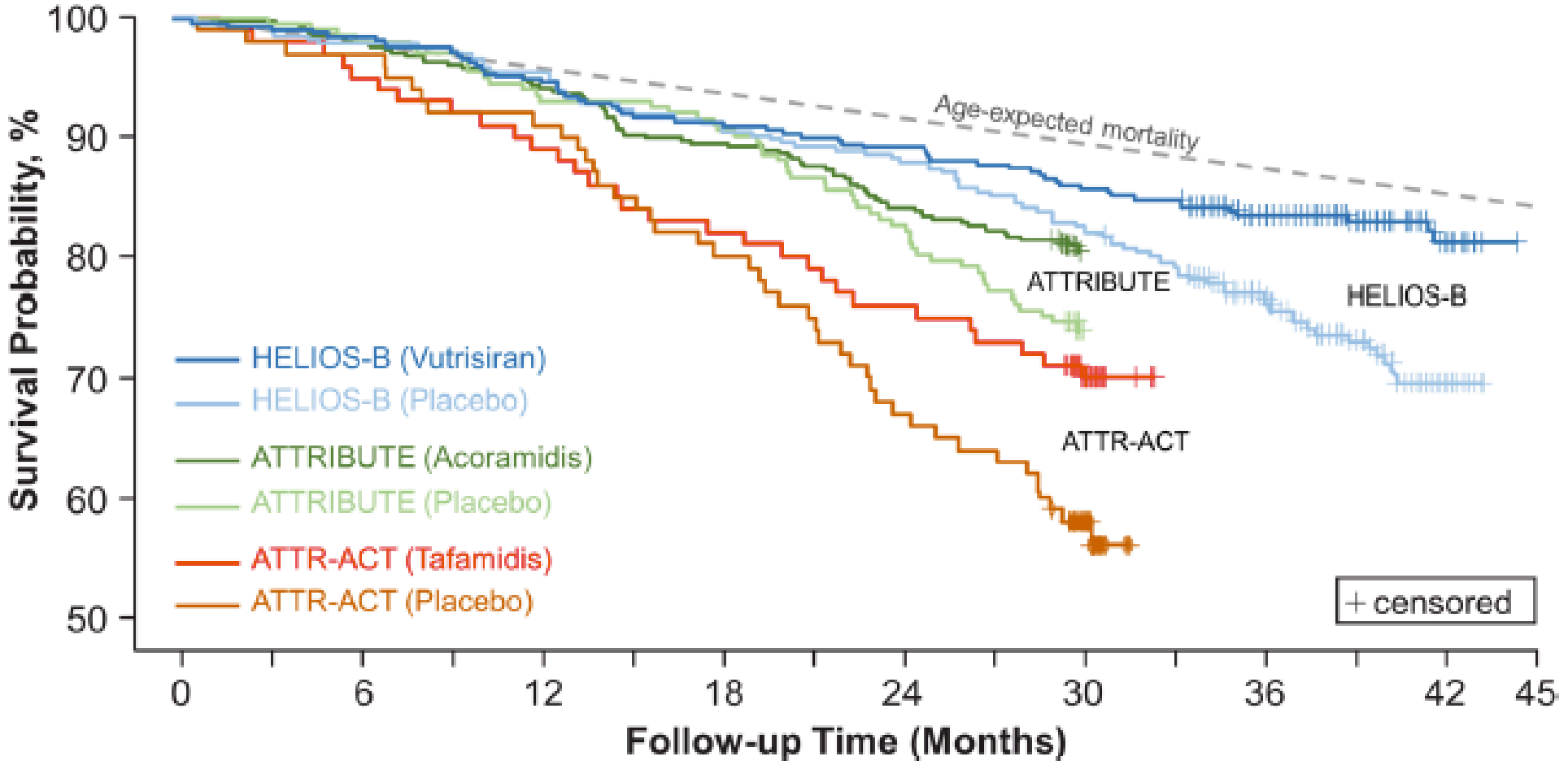
Survival Curves of TTR Therapy Trials



Girard A. Heart Failure Reviews (2025) 30: 69-73

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Unanswered Questions

❓ Which therapy is superior

❓ Benefit to combination therapy

- Secondary analyses of HELIOS-B in cohort of patients that had received tafamadis suggest complementary benefit from stabilizer/silencer

❓ Role of measuring prealbumin levels or other biomarkers to guide therapy and prognosticate

❓ Is there a role for disease-modifying therapies in patients with early amyloid deposits ***before*** TTR-CM is present

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Summary

- Amyloidosis is **more prevalent** than previously thought – have a low index of suspicion
- Important to rule out presence of monoclonal protein **first**
- Diagnosis can be made **without** cardiac biopsy however there is still a role for biopsy in certain situations
- Timing for diagnosis and treatment is **everything** especially for AL amyloidosis!

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