Optimizing Heart Failure Management

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June 5th, 2026

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Disclosures

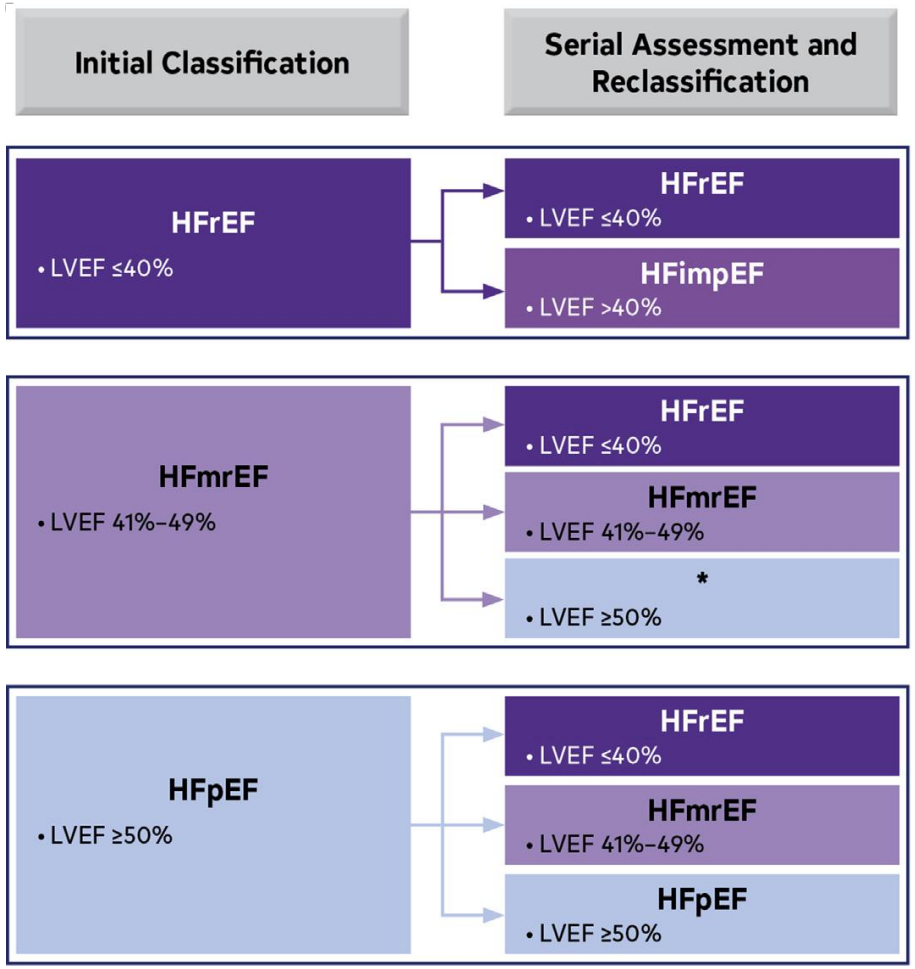
- Speaking honoraria and advisory board: Novo Nordisk, Bayer, Merck, Astra Zeneca, Kestra, Kiniksa, MannKind, CVRx, Bridgebio

- I will not discuss off-label use and/or investigational use of any drugs or devices

What is Heart Failure?

The heart can't pump enough blood and oxygen to meet the body's demands.

This can happen when the heart is too weak or stiff to fill up with enough blood or pump properly, respectively.



Heidenreich PA, *et al. J Card Fail* 2022

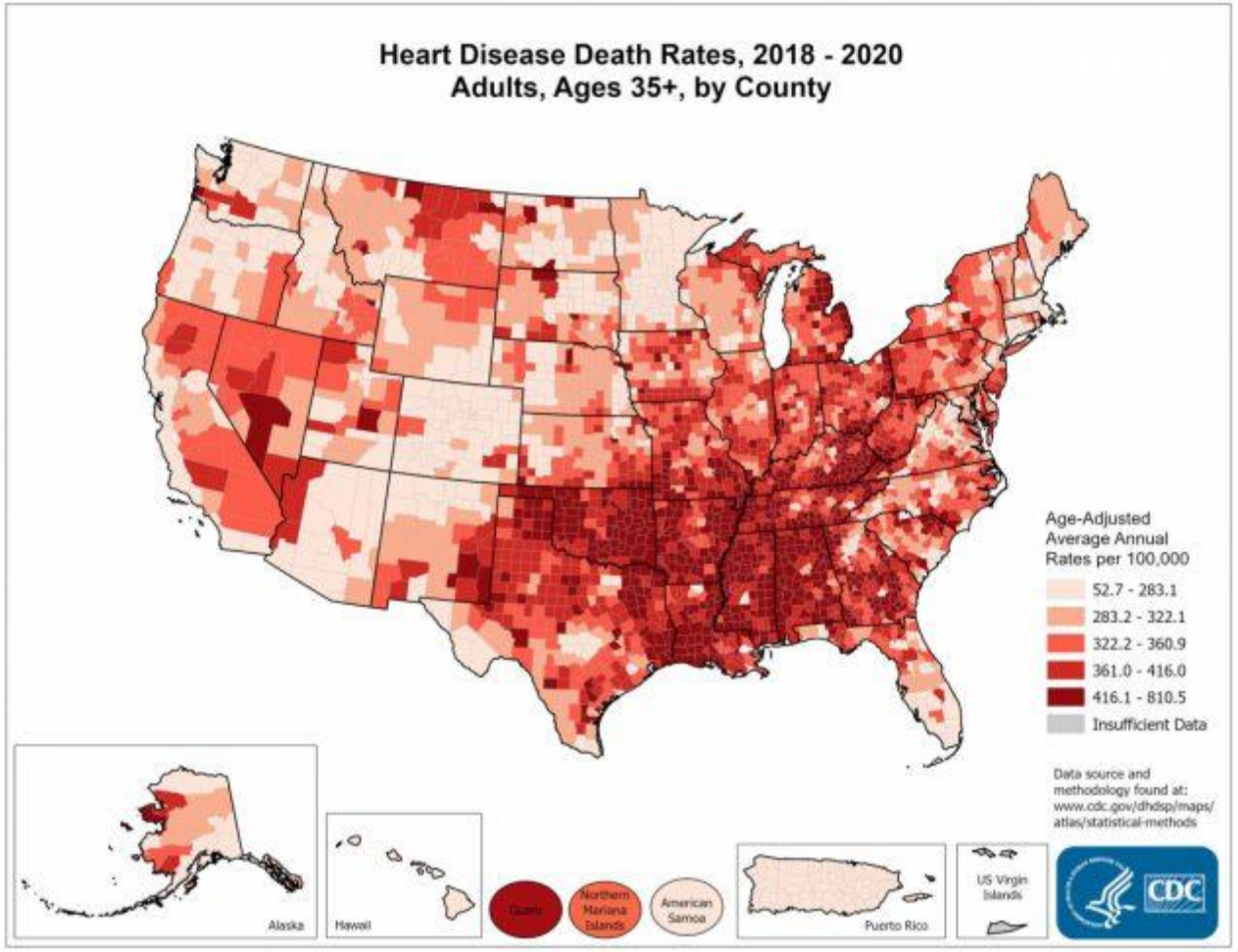
Heart Failure: Nationwide

~6.8 million adults (2.4%) in the US have heart failure. By 2030, > 8 million adults (3.0%) will have heart failure

1,297,000 hospitalizations annually

#1 diagnosis associated with 30 days readmissions

HF was a contributing cause in approximately 425,147 deaths and accounted for 45% of cardiovascular deaths in the U.S. in 2021



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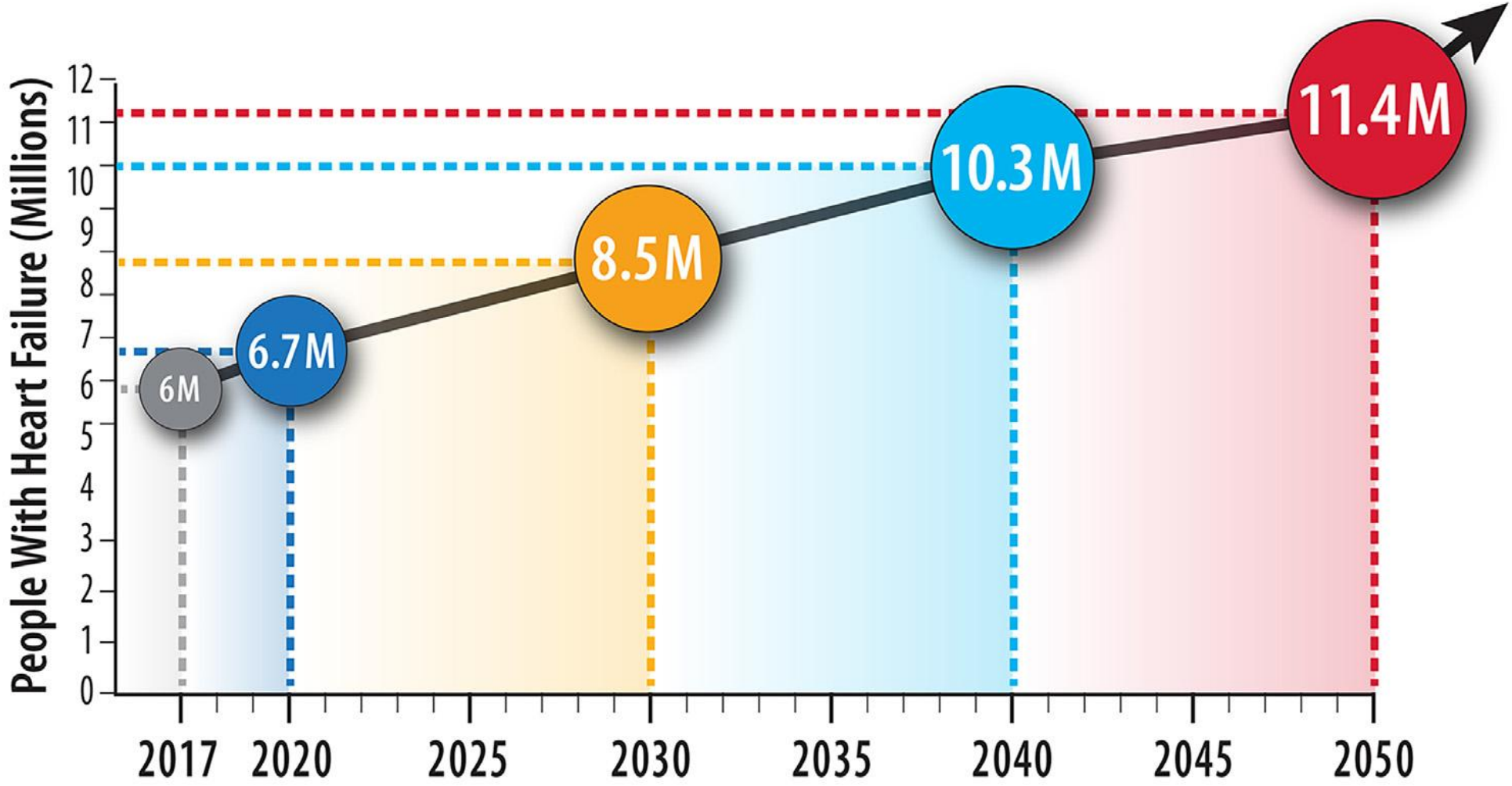
Bozkurt B, et al. J Card Fail. 2025 Aug 29:S1071-9164(25)00326-4

Prevalence of Heart Failure



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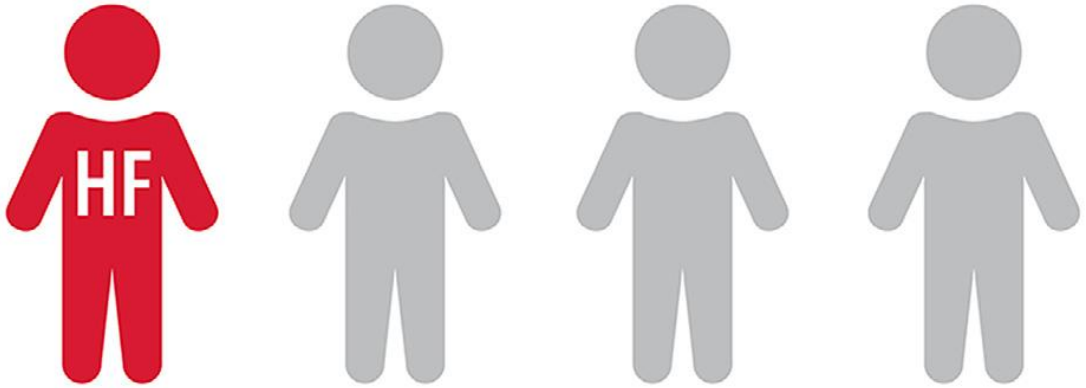
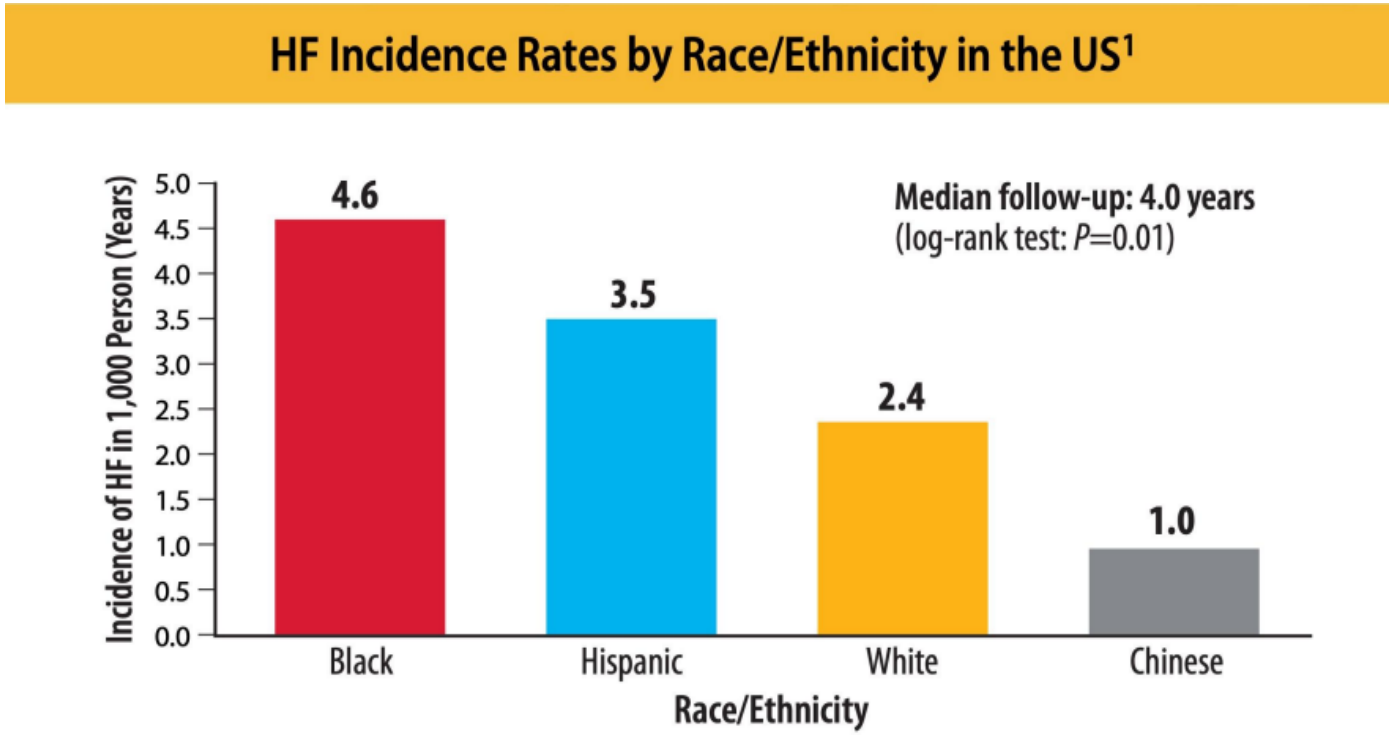
Bozkurt B, et al. J Card Fail. 2025 Aug 29:S1071-9164(25)00326-4

Lifetime Risk of Heart Failure Percentage Distribution of HF



The lifetime risk of heart failure is 1 in 4 people.



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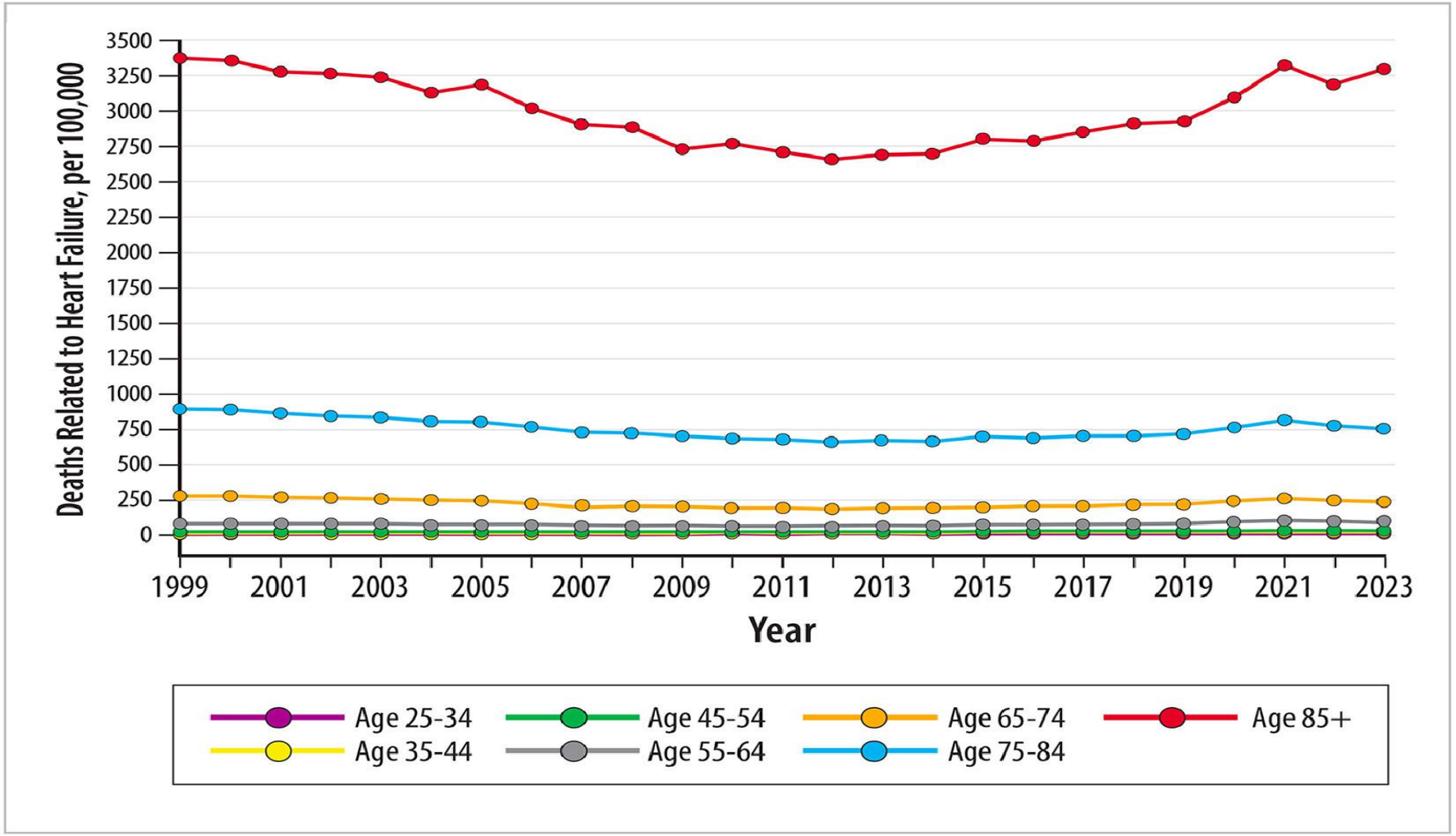


Data from the Centers for Disease Control and Prevention Wide-Ranging ONline Data for Epidemiological Research (CDC WONDER). Accessed April 6, 2025. https://wonder.cdc.gov.

Bozkurt B, et al. J Card Fail. 2025 Aug 29:S1071-9164(25)00326-4

CENTRAL ILLUSTRATION: National Trends and Disparities in Heart Failure Hospitalizations

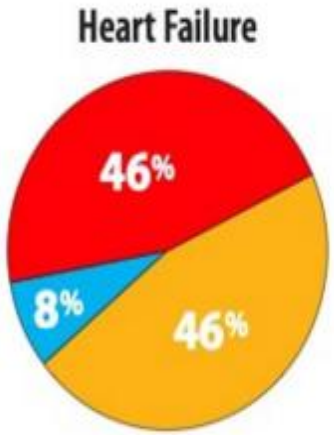
Age-Standardized HF Hospitalization Rates (per 100,000 U.S. Adults) for Older Age Groups (Primary Y-Axis) and Younger Age Groups (Secondary Y-Axis)

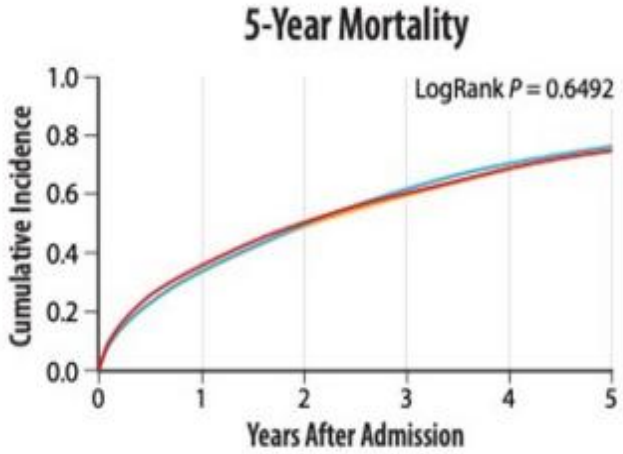
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Age Group >64 Years	1,775	1,806	1,695	1,660	1,649	1,700	1,688	1,813	1,842	1,853	1,501	1,578	1,525
Age Group 18 to 64 Years	124	121	116	117	123	131	137	150	159	165	151	162	161

- NH-Black adults had the highest HF hospitalization rates each year from 2010 to 2022 with an overall declining trend.
- Uptrend in hospitalization rates for Medicare and Medicaid insurers. Medicaid beneficiaries experienced significant increase compared to private insurers.
- Lower hospitalization rates in rural hospitals compared to urban centers with an overall decrease in rural HF hospitalizations.
- Age-standardized in-hospital mortality had an increase in 2020 disrupting prior year trends, coinciding with the onset of the COVID-19 pandemic.

Agarwal MA, et al. JACC Heart Fail. 2025;10.1016/j.jchf.2025.102777

5-year Outcomes in Patients Hospitalized with HF with Preserved, Borderline, and Reduced EF[1]

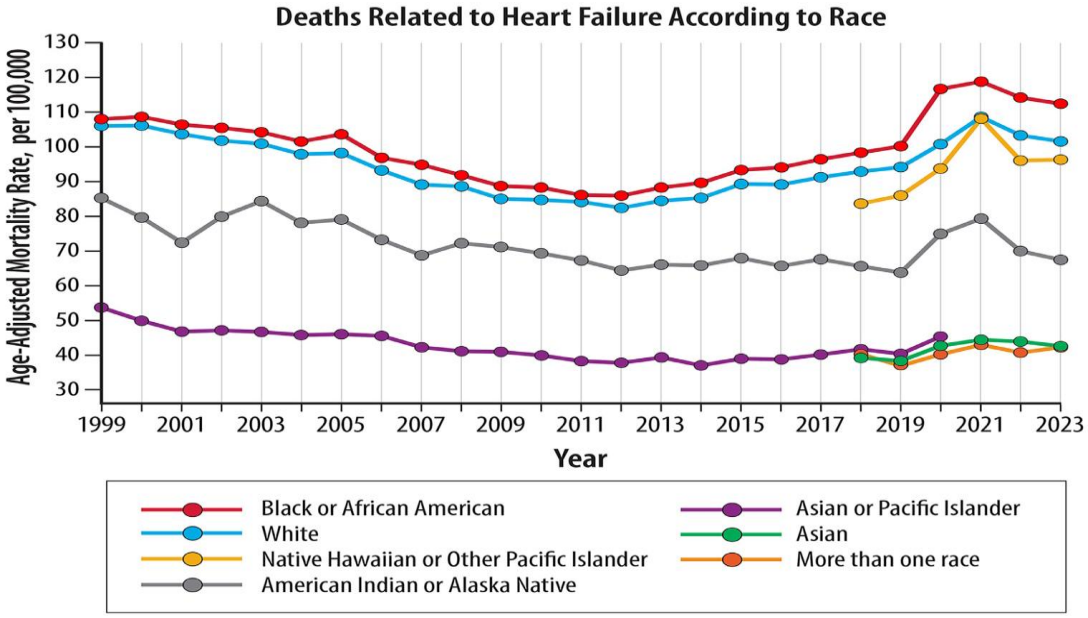




HFpEF (EF ≥50%) HFbEF (EF 41-49%) HFrEF (EF ≤40%)

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



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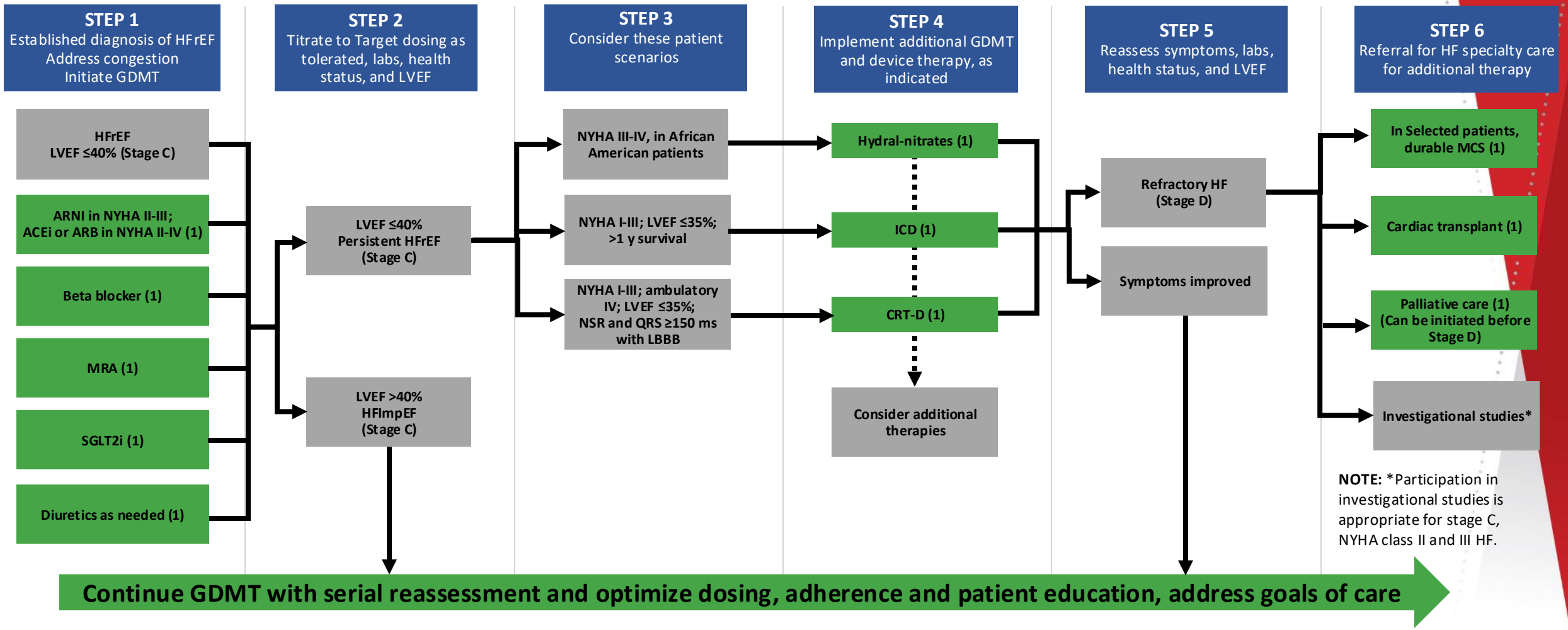
Bozkurt B, et al. J Card Fail. 2025 Aug 29:S1071-9164(25)00326-4

Treatment of HFrEF Stages C and D

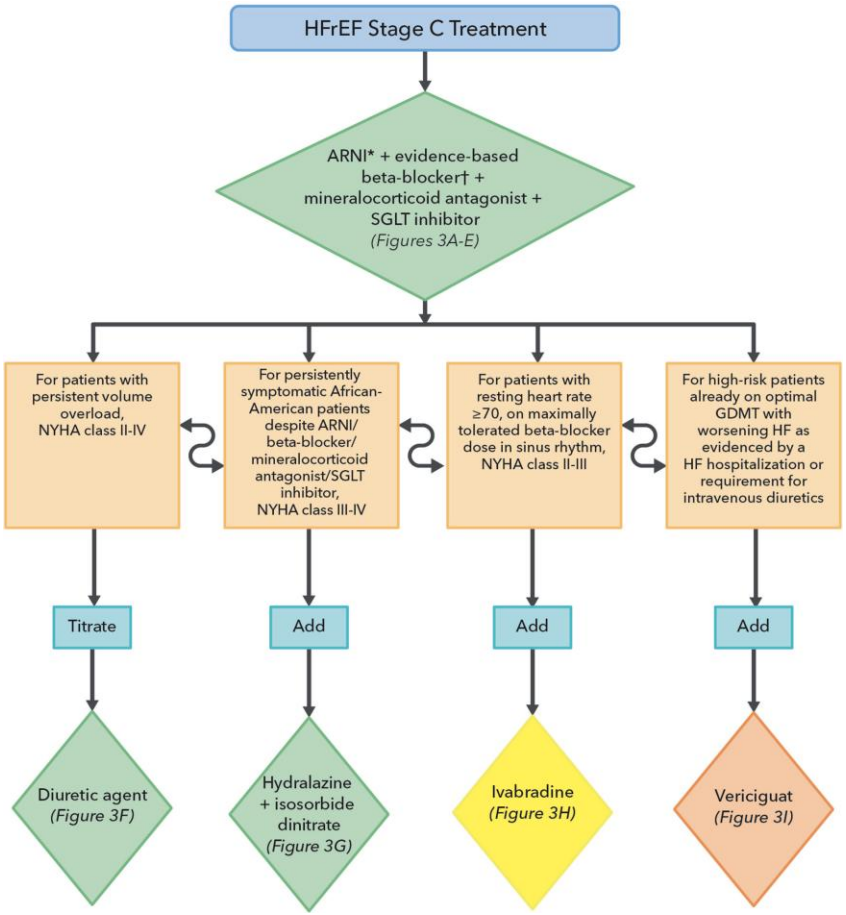


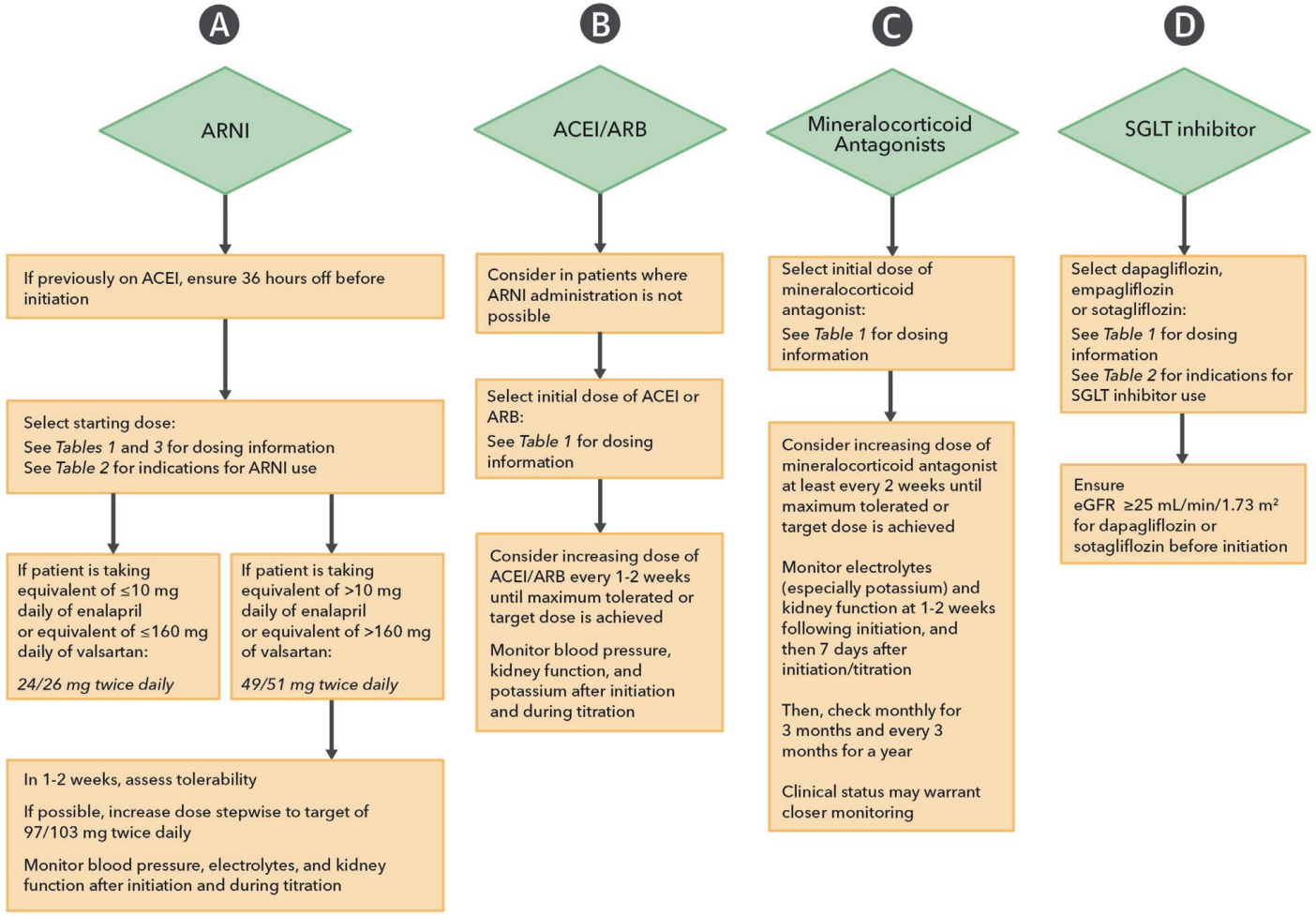
Abbreviations: ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; hydral-nitrates, hydralazine and isosorbide dinitrate; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; NSR, normal sinus rhythm; NYHA, New York Heart Association; SCD, sudden cardiac death; and SGLT2i, sodium-glucose cotra

Heidenreich, P. A. et al. (2022). 2022 AHA/ACC/HFSA Guideline for Heart Failure. *Circulation*.

American Heart Association.

Macon & Joan Brock Virginia Health Sciences at Old Dominion University





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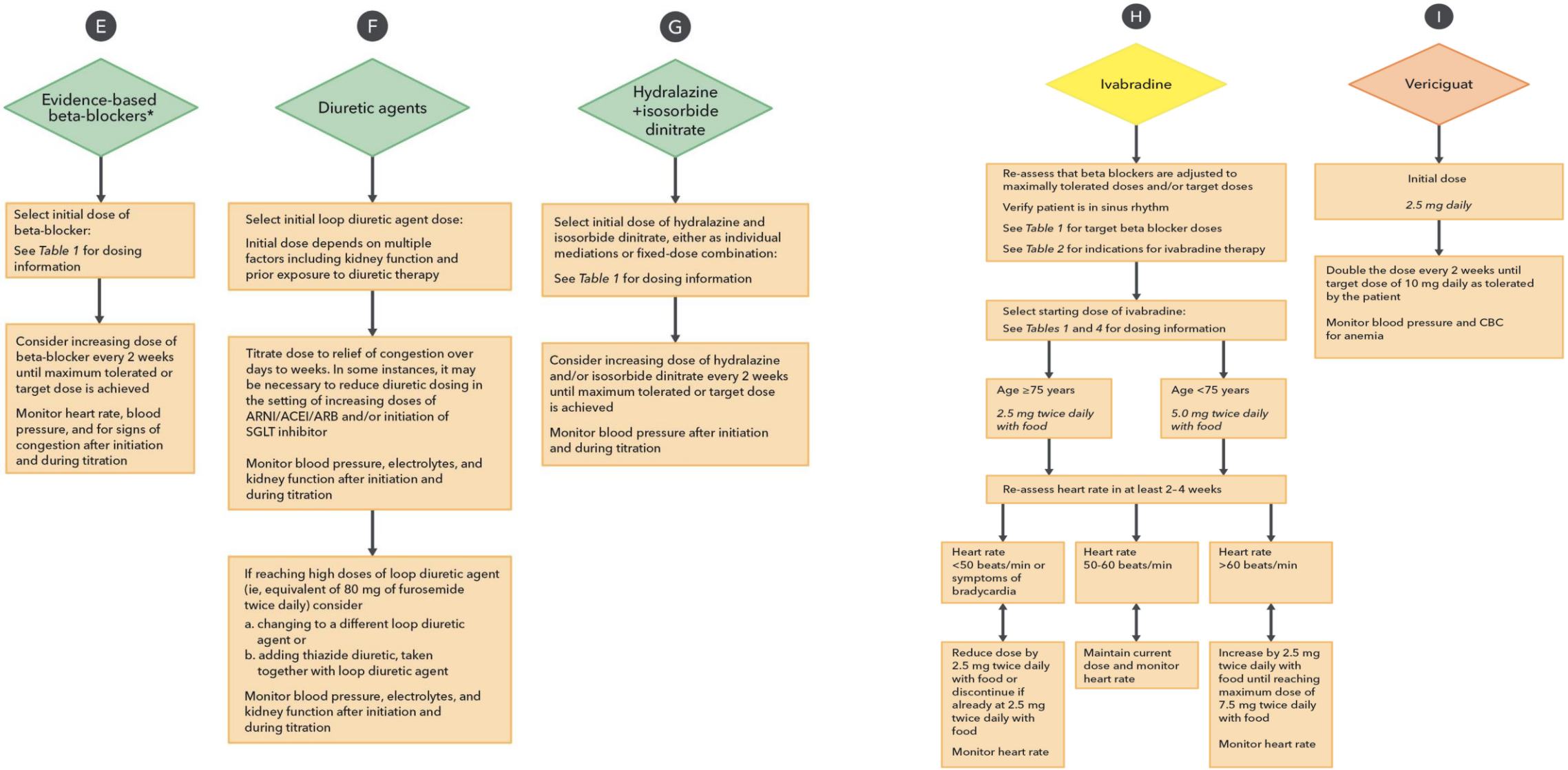
Maddox et al. JACC. 2024 Apr, 83 (15) 1444–1488



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Maddox et al. JACC. 2024 Apr, 83 (15) 1444–1488

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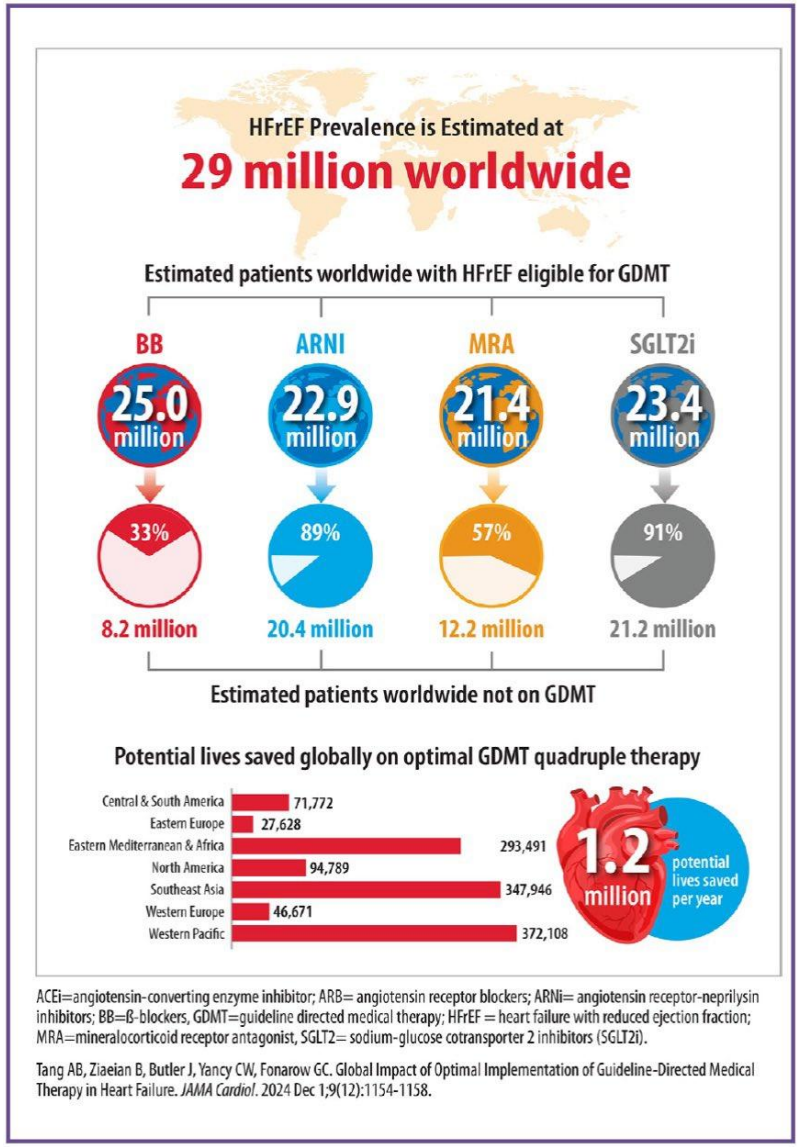
Quadruple GDMT for HFrEF — Mortality Evidence & COR Class I in Guidelines

Drug Class	Example Agents	Landmark Trial(s)	Year Mortality Benefit Demonstrated	Year First Class I in Guideline (ACC/AHA/HFSA)
Beta-Blocker (BB)	Carvedilol Metoprolol succinate Bisoprolol	US Carvedilol (1996) COPERNICUS (2001) MERIT-HF (1999) CIBIS-II (1999)	1996	2001
ARNI (Sacubitril / Valsartan)	Sacubitril / Valsartan	PARADIGM-HF (2014)	2014	2016
MRA (Mineralocorticoid Receptor Antagonist)	Spironolactone Eplerenone	RALES (1999) EPHESUS (2003)	1999	2005
SGLT2i (Sodium-Glucose Cotransporter-2 Inhibitor)	Dapagliflozin Empagliflozin	DAPA-HF (2019) EMPEROR-Reduced (2020)	2019	2022

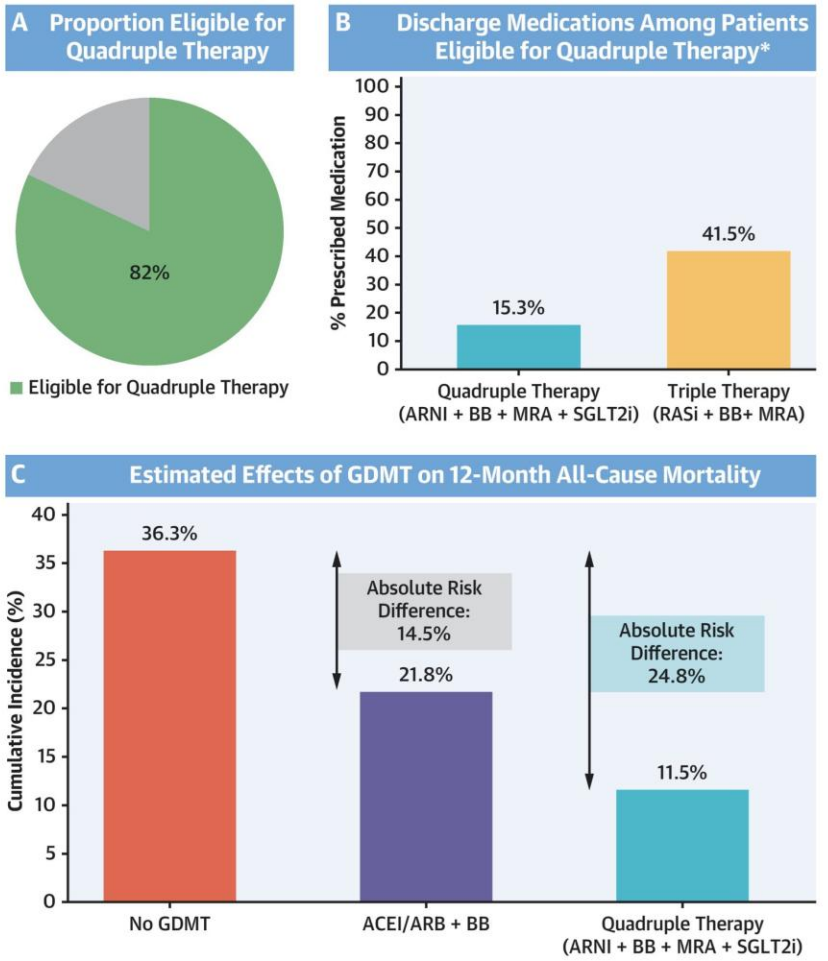
BB = Beta-Blocker · ARNI = Angiotensin Receptor –Neprilysin Inhibitor · MRA = Mineralocorticoid Receptor Antagonist · SGLT2 i = Sodium-Glucose Cotransporter-2 Inhibitor · HFrEF = Heart Failure with Reduced Ejection Fraction



ACEi=angiotensin-converting enzyme inhibitor; ARB= angiotensin receptor blockers; ARNi= angiotensin receptor-neprilysin inhibitors; BB=ß-blockers, GDMT=guideline directed medical therapy; HFrEF = heart failure with reduced ejection fraction; MRA=mineralocorticoid receptor antagonist, SGLT2= sodium-glucose cotransporter 2 inhibitors (SGLT2i).

Tang AB, Ziaeian B, Butler J, Yancy CW, Fonarow GC. Global Impact of Optimal Implementation of Guideline-Directed Medical Therapy in Heart Failure. *JAMA Cardiol*. 2024 Dec 1;9(12):1154-1158.

CENTRAL ILLUSTRATION: Treatment Gap and Projected Clinical Benefits of Rapid Implementation of Quadruple Medical Therapy for Newly Diagnosed HFrEF



Greene SJ, et al. J Am Coll Cardiol HF. 2024;12(8):1365-1377.

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Cumulative Impact of Evidence-Based HFrEF Medical Therapies on Clinical Outcomes

Benefits of Quadruple Therapy (GDMT)

Therapy	Relative Risk	2 Yr Mortality
None	- -	35.0%
ARNI (vs imputed placebo)	↓ 28%	25.2%
Beta Blocker	↓ 35%	16.4%
Aldosterone Ant	↓ 30%	11.5%
SGLT2 inhibitor	↓ 17%	9.5%
Cumulative with all 4 therapies: RRR 72.9% | ARR 25.5% | NNT = 4		

SURVIVAL

7–11 Years

Extension in median survival

vs. no therapy

HF HOSPITALIZATIONS

85%	33%	3
Relative Risk Reduction	Absolute Risk Reduction	NNT (24 mo) to prevent HF hosp

Over 24 months with quadruple therapy

Updated from Fonarow GC, et al. Am Heart J 2011;161:1024-1030 and Lancet 2008;372:1195-1196.

Greene, Butler, Fonarow, Circulation 2024 https://doi.org/10.1161/CIRCULATIONAHA.124.070228

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HF with EF ≤40%

Lack of Initiation, Titration, or Persistence of:

Beta-Blocker

- ↑ *34%-35% relative risk of all-cause mortality*
- ↑ *19%-24% relative risk of all-cause mortality or hospitalization*

MRA

- ↑ *24%-35% relative risk of all-cause mortality*
- ↑ *35%-42% relative risk of HF hospitalization*

ARNI

- ↑ *~25% relative risk of all-cause mortality vs putative placebo*
- ↑ *~30% relative risk of CV mortality or HF hospitalization vs putative placebo*

SGLT2i

- ↑ *13% relative risk of all-cause mortality*
- ↑ *31% relative risk of HF hospitalization*

HF with EF >40%

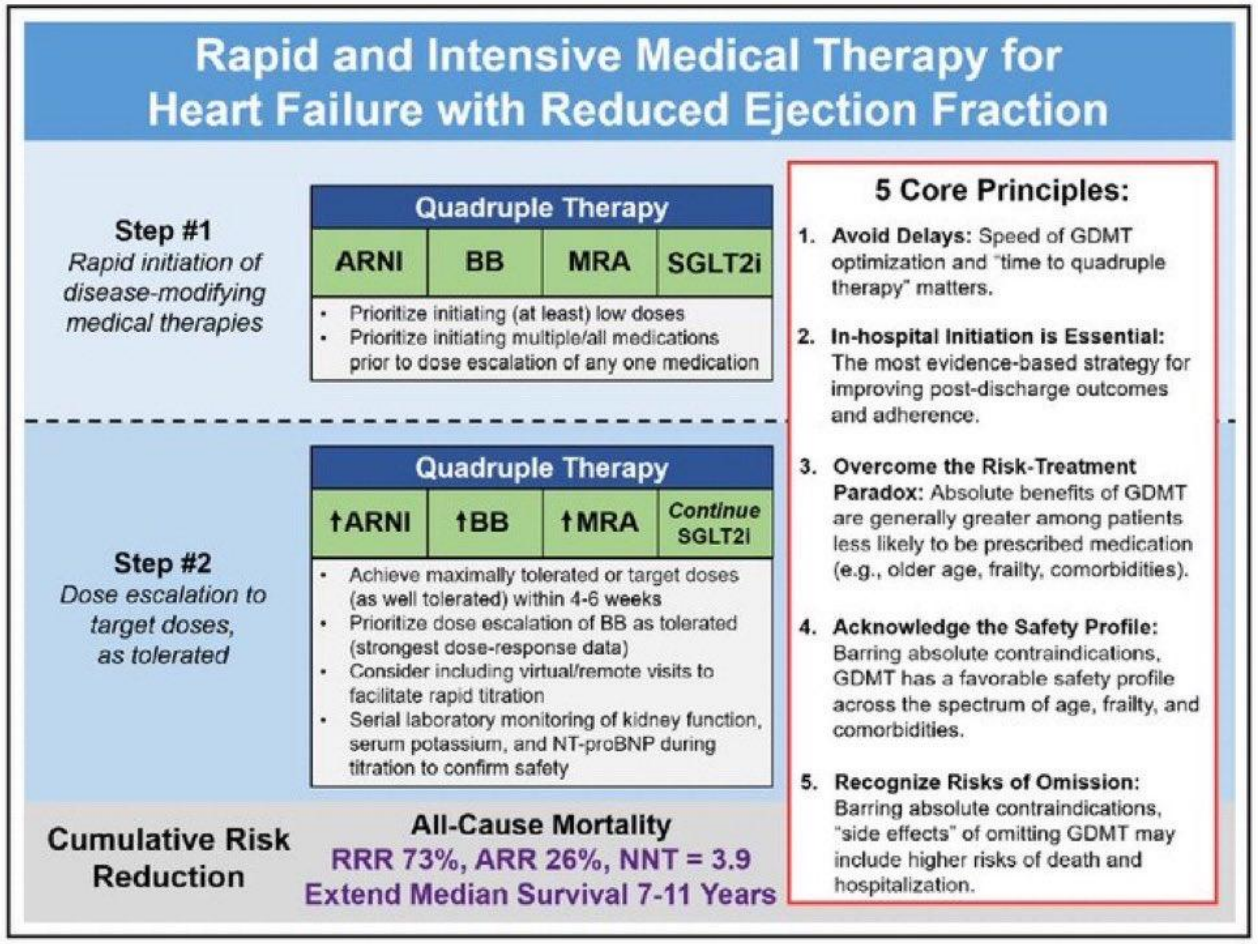
Lack of Initiation or Persistence of:

SGLT2i

- ↑ *20% relative risk of CV mortality or HF hospitalization*
- ↑ *26% relative risk of HF hospitalization*

Delaying or Omitting GDMT in Eligible Patients With Heart Failure Associated With:

- Patient never being initiated on GDMT, or substantial delay
- Worse quality of life and health status
- Excess risk of disease progression
- Preventable deaths and hospitalizations



VIEWPOINT

Simultaneous or Rapid Sequence Initiation of Quadruple Medical Therapy for Heart Failure—Optimizing Therapy With the Need for Speed

GDMT	*Day 1*	Days 7-14	Days 14-28	Days 21-42
ARNI	Initiate, low dose	Continue	Titrate, as tolerated	Titrate, as tolerated
Beta-blocker	Initiate, low dose	Titrate, as tolerated	Titrate, as tolerated	Titrate, as tolerated
MRA	Initiate, low dose	Continue	Titrate, as tolerated	Continue
SGLT2i	Initiate	Continue	Continue	Continue

Start all 4 mortality reducing drugs without delay, or in rapid sequence

Greene SJ, Butler J, Fonarow GC. *JAMA Cardiol* 2021

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Reasons for Not Utilizing GDMT in HFrEF

Common Clinician Barriers to Initiating and Optimizing HFrEF Therapy

ARNI | BB | MRA | SGLT2i

Clinical Inertia
"Their stable, I'll optimize next visit"

Lab Monitoring Concern
"K^+ or creatinine may rise"

Hemodynamic Concern
"BP is too low to start or uptitrate"

Polypharmacy Worry
"They're already on too many pills"

Cost / Access
"They can't afford the SGLT2i or ARNI"

Frailty / Age Bias
"They're too old or too frail for this"

Specialist Deferral
"I'll let someone else handle the titration"

Side Effects Fear
"How will I know which medication caused the side effect if I start more than one medication?"

Misperception of Risk
"Their symptoms are mild and they are stable, the event risk must be low"

Discharge Rush
"Not the right time — I'll do it outpatient"

Guideline Doubt
"Evidence doesn't apply to my patient"

Incomplete Dosing
"Low dose is fine, no need to uptitrate"

GDMT = Guideline-Directed Medical Therapy | HFrEF = Heart Failure with Reduced Ejection Fraction | ARNI · Beta -Blocker · MRA · SGLT2i

Greene, Butler, Fonarow. *JAMA Cardiology* 2021 doi:10.1001/jamacardio.2021.0496.

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New Era in Quadruple GDMT

Generic Priced Options

Cost Plus Drug (online, self pay, cash price, 30-day supply)

ARNI (sacubitril/valsartan)	$14.40
BB (carvedilol)	$6.32
MRA (spironolactone)	$5.89
SGLT2i (dapagliflozin)	$8.36
Total	$34.97

$420 per year

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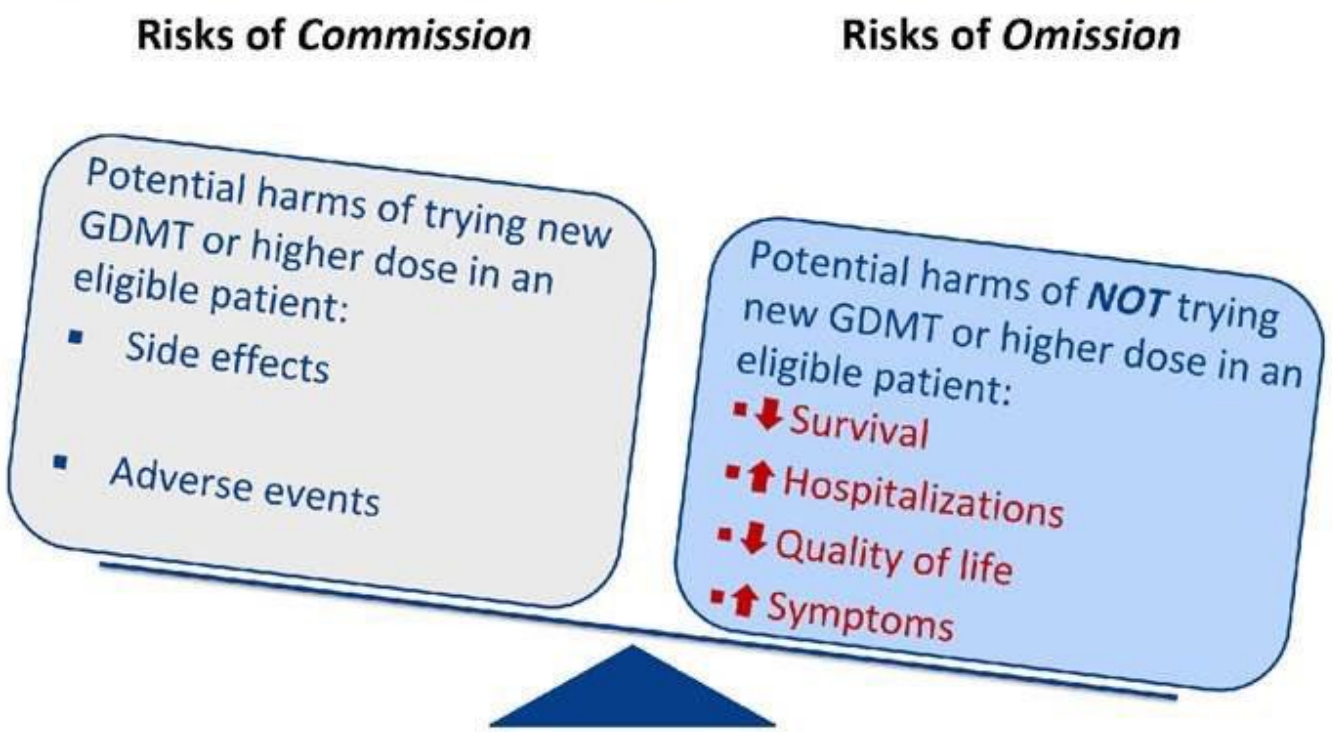
The Risks of Guideline-Directed Medication Changes in HFrEF



Every visit/every setting is an opportunity to initiate and escalate GDMTs, as tolerated

- New-onset heart failure ≠ "low risk"
- "Stable" outpatient heart failure ≠ "low risk"
- Hospitalized heart failure ≠ "low risk"

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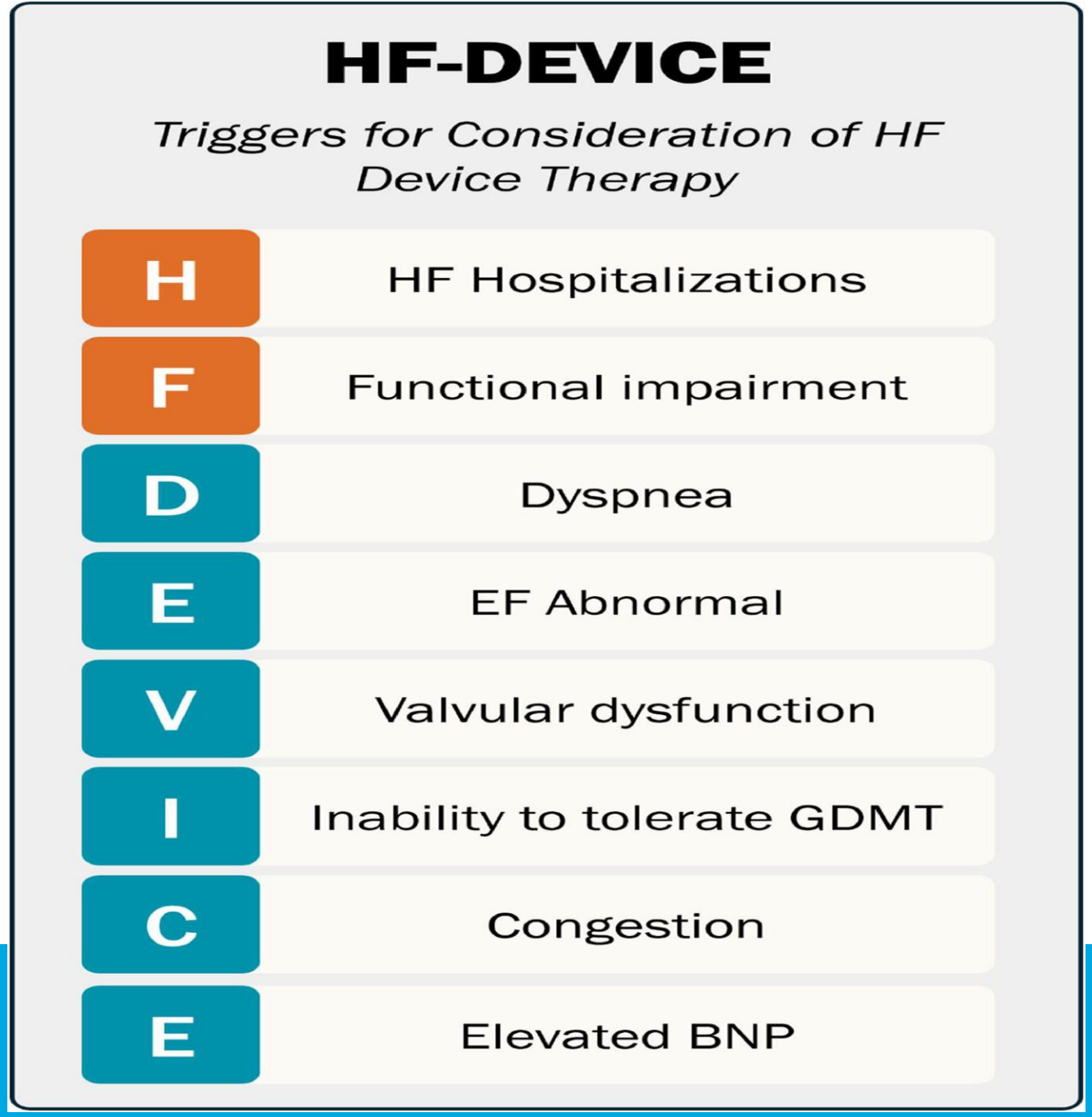
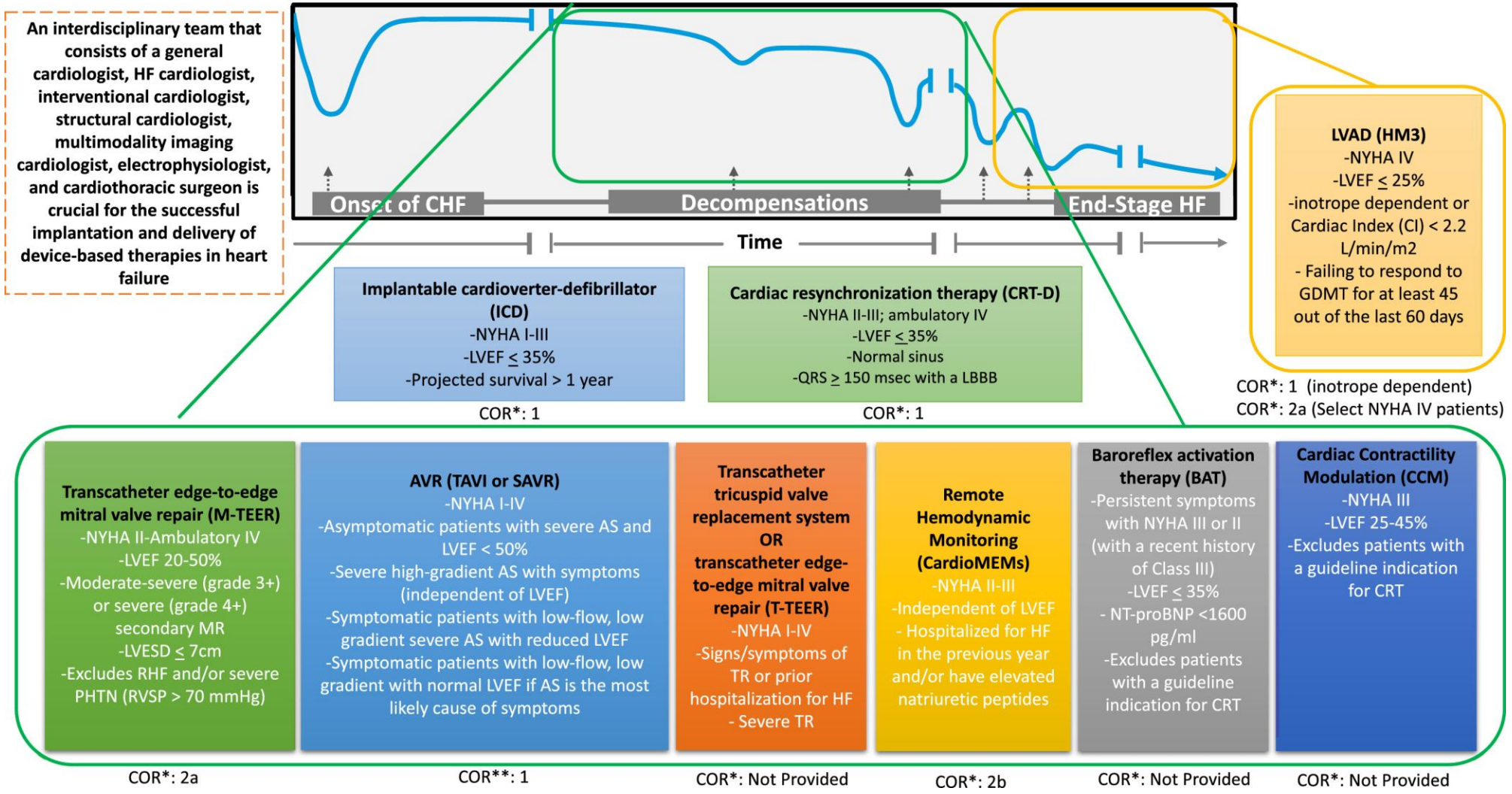
WHEN TO CONSIDER DEVICE THERAPY?

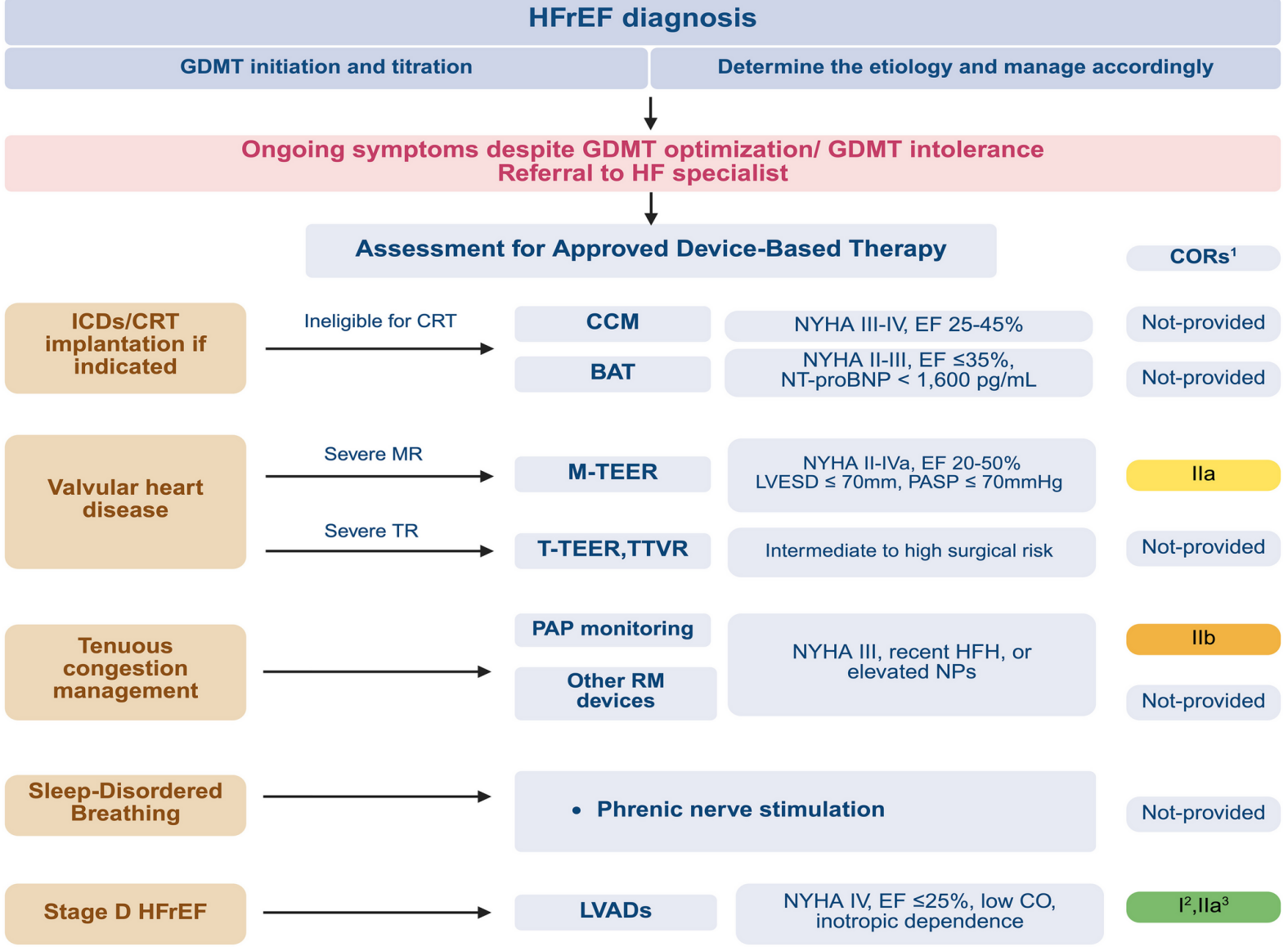


Fudim M, ..., **Yehya A**, et al. J Card Fail. 2025 Sep 26:S1071-9164(25)00429-4.

Approved Devices for Stage C and D Chronic Heart Failure



Estep JD, Fudim M. J Card Fail. 2024 Sep 10:S1071-9164(24)00258-6



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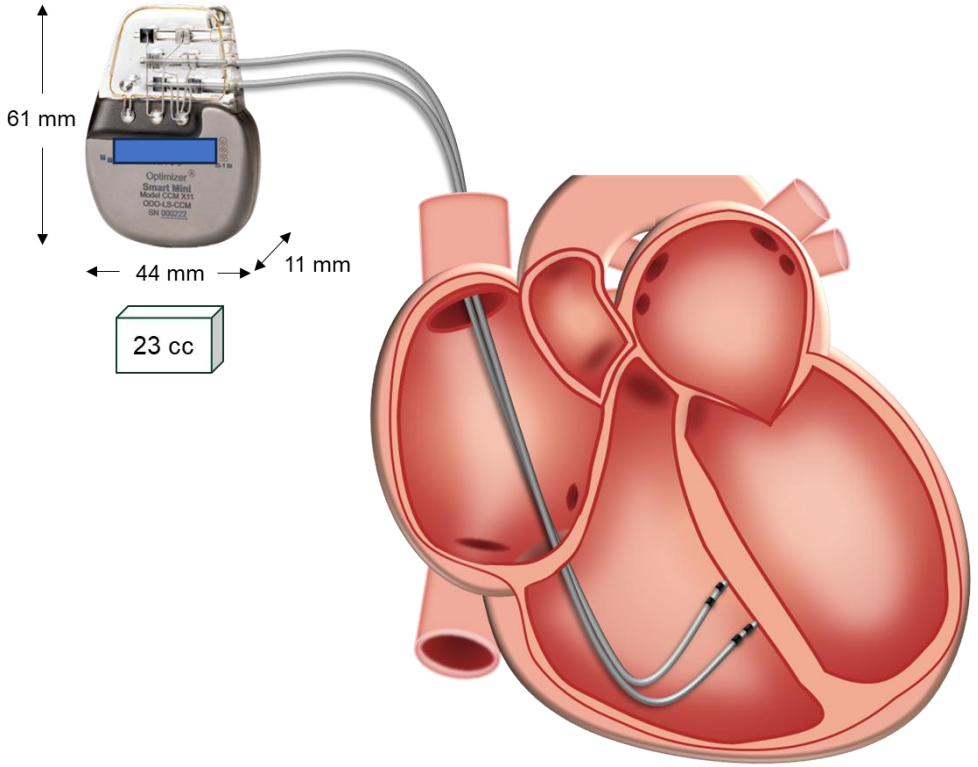
Wattanachayakul P, et al. Heart Fail Rev. 2025 Sep 30.

Cardiac Contractility Modulator (CCM) Using IMPULSE OPTIMIZER

- HF patients have abnormal intracellular Ca handling affecting the function of the myocyte
- Delivers biphasic long duration ~20 msec, high voltage electrical signal to the RV septum during absolute refractory period
  - It does not result in myocardial contraction
  - ⟹ structural and functional changes in myocardium
  - ⇑ contractility without ⇑ in myocardial O2 requirement
  - ⇓ LV volume
  - Changes are driven by increase in intracellular Ca



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Benarroch Y, Tapaskar N, **Yehya A.** US Cardiol. 2025 Sep 24;19:e19.
Heidenreich PA et al. Circulation. 2022 May 3;145(18)
Estep JD, Fudim M. J Card Fail. 2024 Sep 10:S1071-9164(24)00258-6

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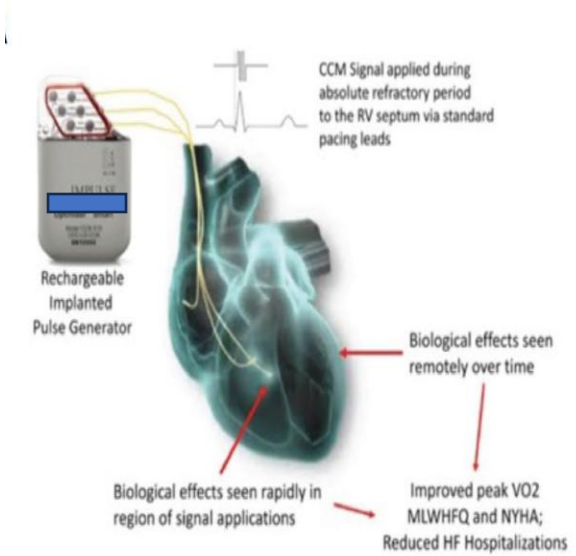
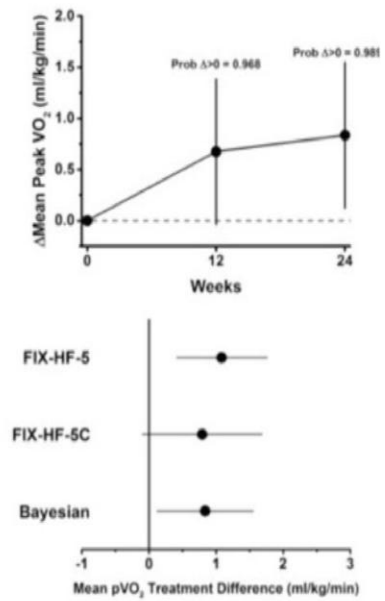
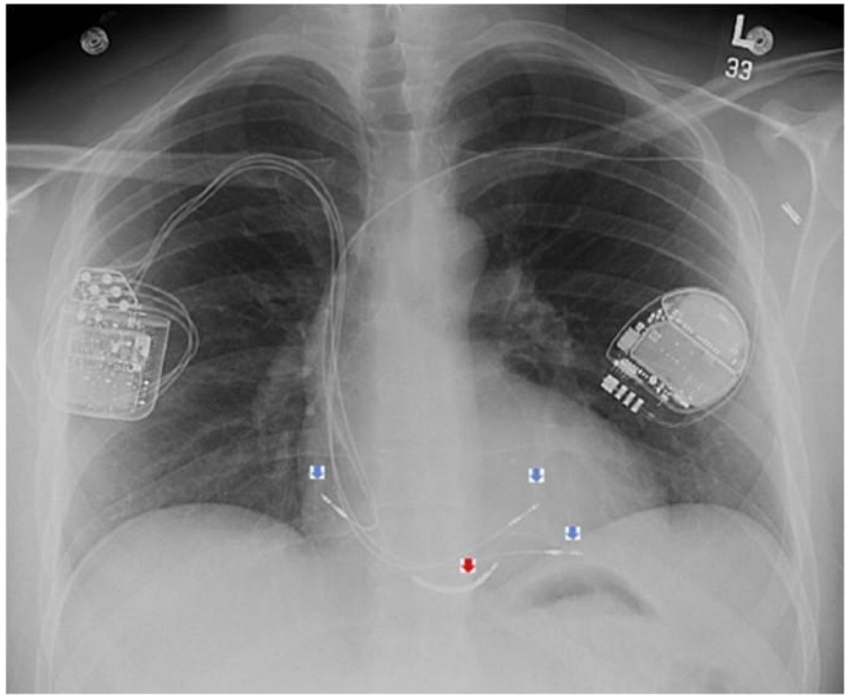
Cardiac Contractility Modulator (CCM) Using IMPULSE OPTIMIZER

- Approved in 2019, FIX-HF-5C trial
  - LVEF 25-45%,
  - NYHA Class III, and
  - Not candidate for, or receiving CRT







Abstract presented at HFSA ASM 2025 showing real world data with 43% reduction in HFH, LVAD or Transplant, or all cause mortality between CCM vs control, p=0.002

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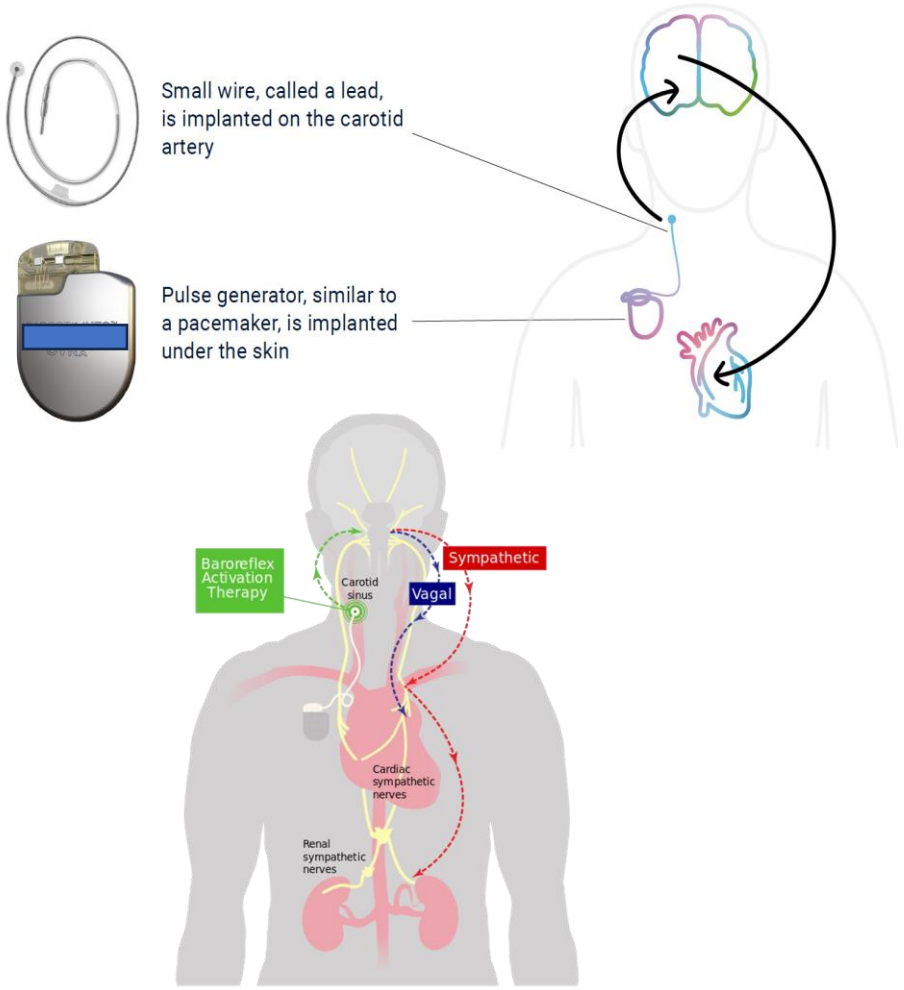
Patel, P.A., Nadarajah, R., Ali, N. et al. Heart Fail Rev **26**, 217–226 (2021).
Heidenreich PA et al. Circulation. 2022 May 3;145(18)
Estep JD, Fudim M. J Card Fail. 2024 Sep 10:S1071-9164(24)00258-6

Autonomic Nervous System Modulation

Autonomic Nervous System Modulation



- Imbalance of the ANS plays a crucial role in pathogenesis of HF as the SNS exceeds the buffer capabilities of PNS
- ANS modulates HR, SVR, arterial BP and cardiac afterload. Constant stimulation results in maladaptive responses and cardiac remodeling

- Devices to modulate the ANS such as Barostim
- Stimulates carotid baroreceptors by electrical impulses from an implanted generator leading to centrally mediated ⇓ in SNS and ⇑ in PNS

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Al Danaf J, Butler J, **Yehya A**. Curr Heart Fail Rep. 2018 Apr;15:53-60

Salah HM, **Yehya A**, Fudim M. J Card Fail. 2024 Sep 26:S1071-9164(24)00415-9

Guzik M et al. J Clin Med. 2022 Jul 25;11(15):4303.

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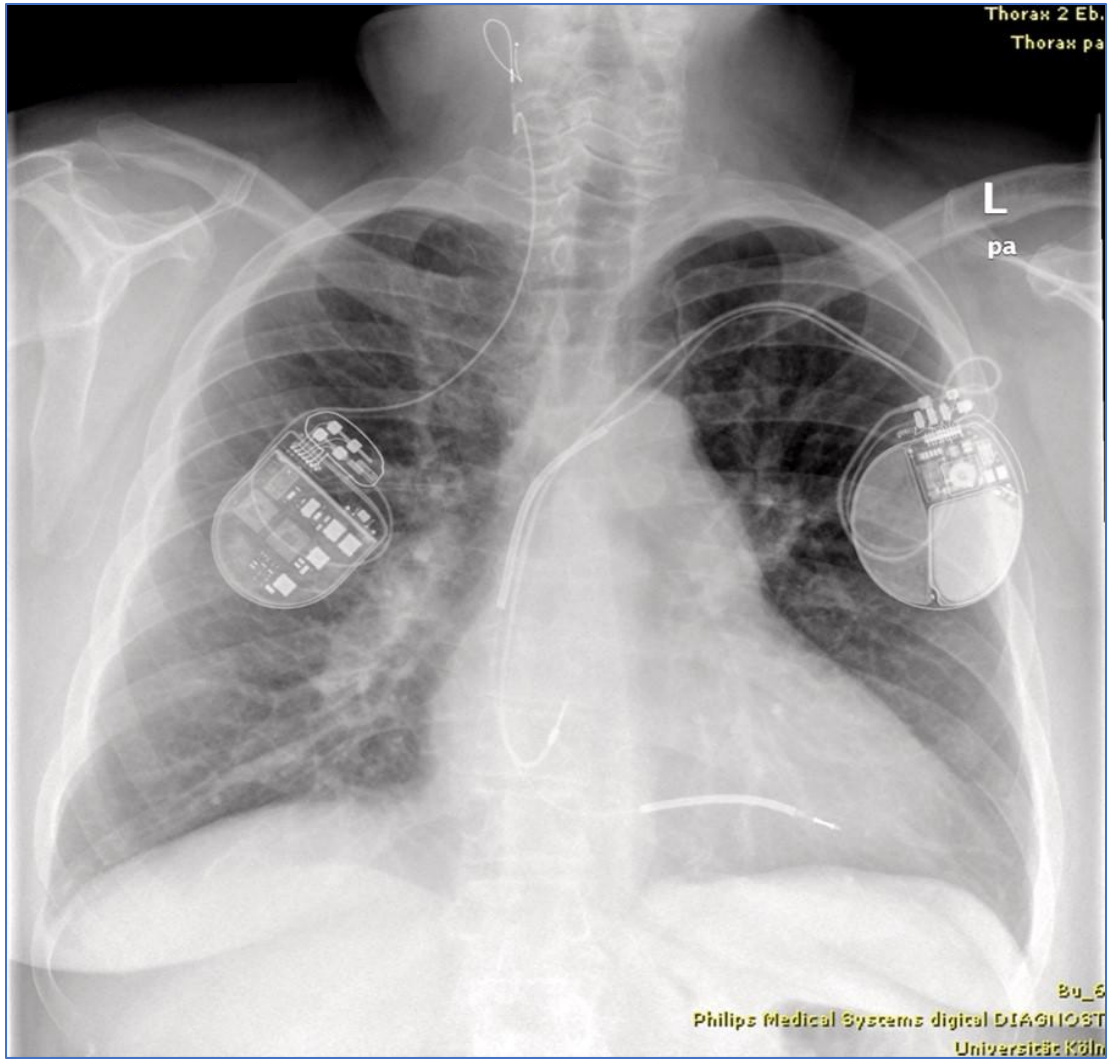
BeAT-HT Trial

BeAT-HF is multicenter randomized trial 408 pts with LVEF <35%, NTproBNP <1600, Class III with no indication of CRT

- Improvement in QoL, Exercise capacity
- Decrease in NT-proBNP
- Trend to decrease in HFH

- Approved In 2019
  - NYHA Class III or Class II with previous Class III,
  - LVEF ≤ 35% with no indication for CRT



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Fudim M, ..., **Yehya A**, et al. J Card Fail. 2025 Sep 26:S1071-9164(25)00429-4.
Salah HM, **Yehya A**, et al. J Card Fail. 2025 Jan;31(1):117-126.
Madershahian N, et al. Europace. 2014 Jun;16(6):861-5.

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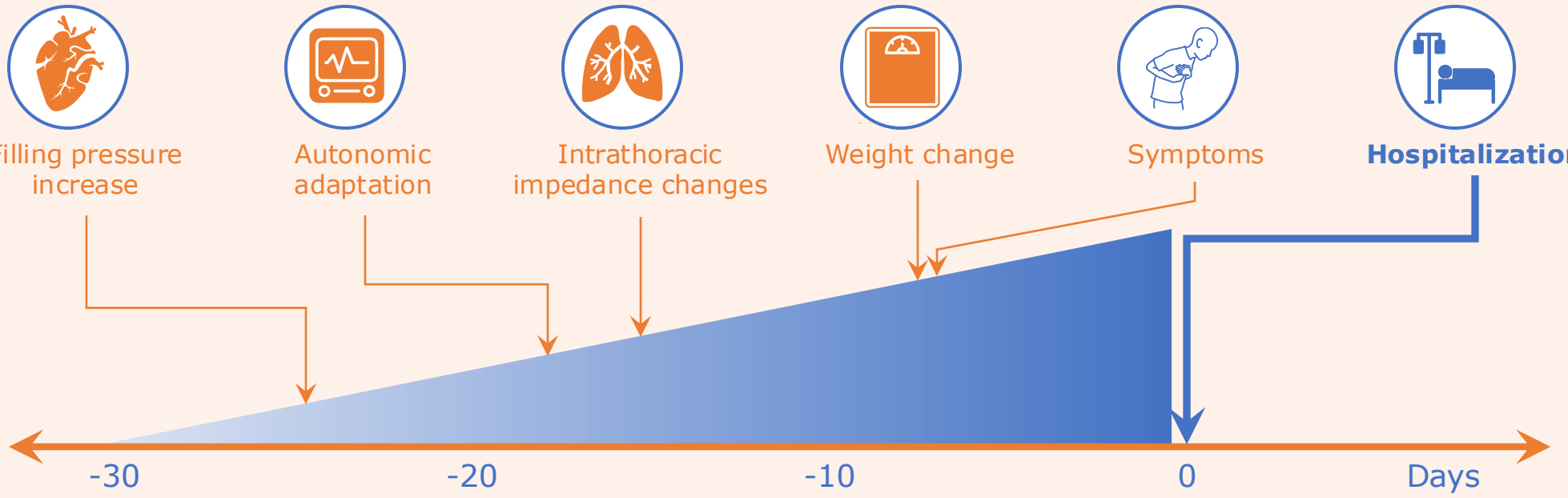
Worsening of Symptoms Occurs Over Days to Weeks

Pathophysiology of Congestion



Earlier identification and treatment of congestion in patients with heart failure is important[3]

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Greene SJ et al. *JAMA Cardiol.* 2018;3(3):252-259.
Adamson PB. *Curr Heart Fail Rep.* 2009;6(4):287-292
Bui AL, Fonarow GC. *J Am Coll Cardiol.* 2012;59(2):97-104.

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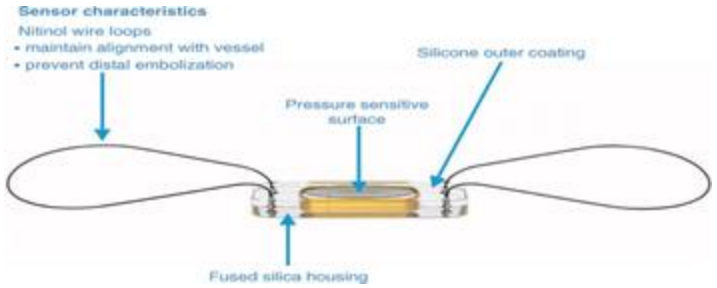
CardioMEMS



- Pulmonary pressure monitoring helps with early detection increases of intravascular volume
- CardioMEMS is approved to decrease risk of HFH
- CHAMPION trial: 28% ⇓ of HFH after 6 months
- MONITOR-HF: Patients managed by CardioMEMS had significant ⇑ in QoL & 44% ⇓ in HFH

Recommendation for Wearables and Remote Monitoring (Including Telemonitoring and Device Monitoring)
Referenced studies that support the recommendation are summarized in the Online Data Supplements.

COR	LOE	Recommendation
2b	B-R	1. In selected adult patients with NYHA class III HF and history of a HF hospitalization in the past year or elevated natriuretic peptide levels, on maximally tolerated stable doses of GDMT with optimal device therapy, the usefulness of wireless monitoring of PA pressure by an implanted hemodynamic monitor to reduce the risk of subsequent HF hospitalizations is uncertain.[1–4]

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Heidenreich PA et al. Circulation. 2022 May 3;145(18)
Brugts JJ et al. Lancet. 2023 May 19:S0140-6736(23)00923-6
Adamson PB et al. Curr Heart Failure Reports. 2009. Abbott

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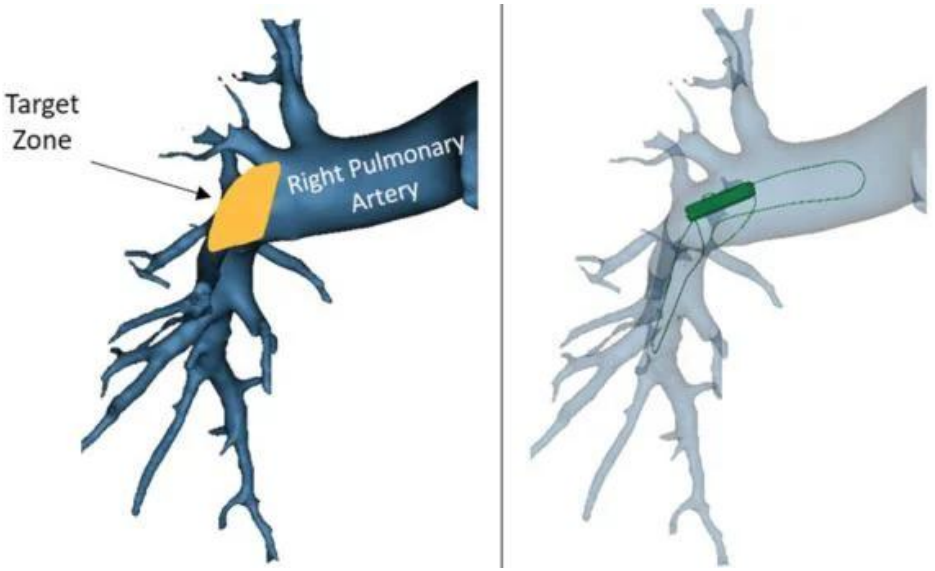
Cordella

- Implanted in the R-PA, approved in 2024
- Similar to CardioMEMS but collects additional data (BP, O2 sat, weight, HR)
- PROACTIVE-HF trial: 456 patients with NYHA Class III, implanted, open label, single arm, evaluating the safety and efficacy
- Remote management of seated mPAP is safe and results in a low rate of HFH



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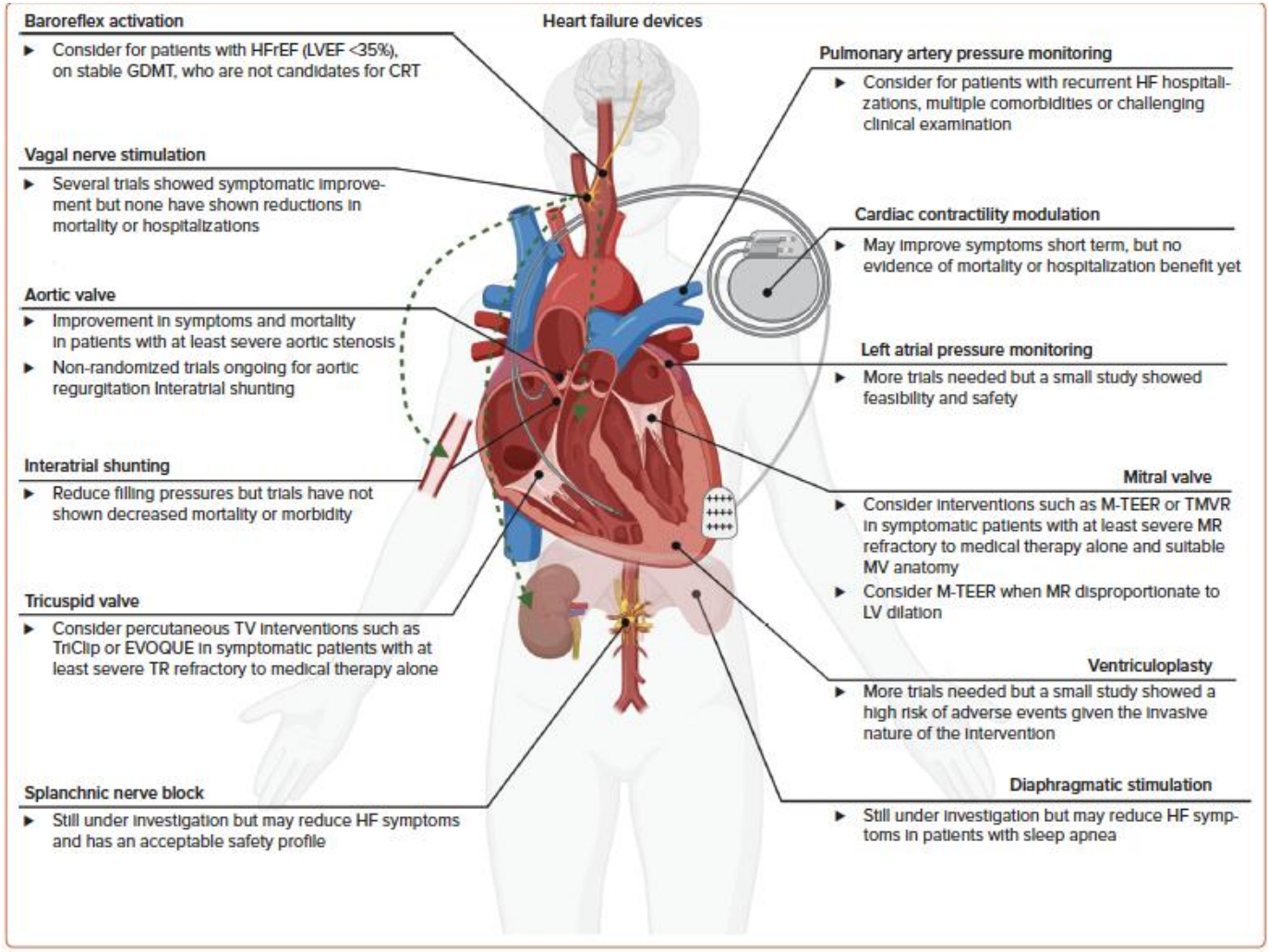
Guichard JL, et al. JACC Heart Fail. 2024 Nov;12(11):1879-1893.

In Conclusion

- The **M** in GDMT should not only include pharmacotherapy but device therapy in appropriately managing patients with HFrEF

- Both are considered synergistic rather than in competition



Don't Be A Scrooge ☺ Thank you!

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Macon & Joan Brock Virginia Health Sciences at Old Dominion University

Cumulative Impact of Evidence-Based HFrEF Medical Therapies on All Cause Mortality

	Relative Risk	2 Year Mortality
None	- -	35.0%
ARNI (vs imputed placebo)	↓ 28%	25.2%
Beta Blocker	↓ 35%	16.4%
Aldosterone Ant	↓ 30%	11.5%
SGLT2 inhibitor	↓ 17%	9.5%

Cumulative risk reduction in mortality if all evidence-based medical therapies are used:
Relative risk reduction 72.9%, Absolute risk reduction: 25.5%, NNT = 4

Updated from Fonarow GC, et al. Am Heart J 2011;161:1024 -1030 and Lancet 2008;372:1195 -1196.

Quadruple GDMT for HFrEF: Substantial Delays in Translating Randomized Clinical Trial Evidence into Routine Clinical Practice

Drug Class	Landmark Trials	Year Mortality Benefit Shown	Relative Risk Reduction in Mortality	Use Rate in EPIC COSMOS (2023–2025)
Beta-Blocker (BB)	*US Carvedilol (1996)* *MERIT-HF (1999)* *CIBIS-II (1999)*	1996	↓ 35%	73%
ARNI (Sacubitril/Valsartan)	*PARADIGM-HF (2014)*	2014	↓ 28%	67%*
MRA	*RALES (1999)* *EPHESUS (2003)*	1999	↓ 30%	36%
SGLT2 Inhibitor	*DAPA-HF (2019)* *EMPEROR-Reduced (2020)*	2019	↓ 17%	34%
Quadruple GDMT (All 4 Therapies)	Cumulative Evidence	All 4 by 2019	↓ 72.9% cumulative RRR	18%

Quadruple GDMT: 2-yr mortality 35% → 9.5% | RRR 72.9% | ARR 25.5% | NNT = 4 |

Yet only 18% of eligible patients with HFrEF received all 4 therapies

EPIC COSMOS N=3,275,176 (July 2023–June 2025, 1,884 hospitals, 42,400 clinics) | * RASi category includes ARNI and ACE-I/ARB

Sources: Greene, Butler, Fonarow. Circulation 2024 https://doi.org/10.1161/CIRCULATIONAHA.124.070228 J Card Fail. 2026 Mar 24:S1071-9164(26)00148-X.