What to do When the Big 4 Are Not Enough

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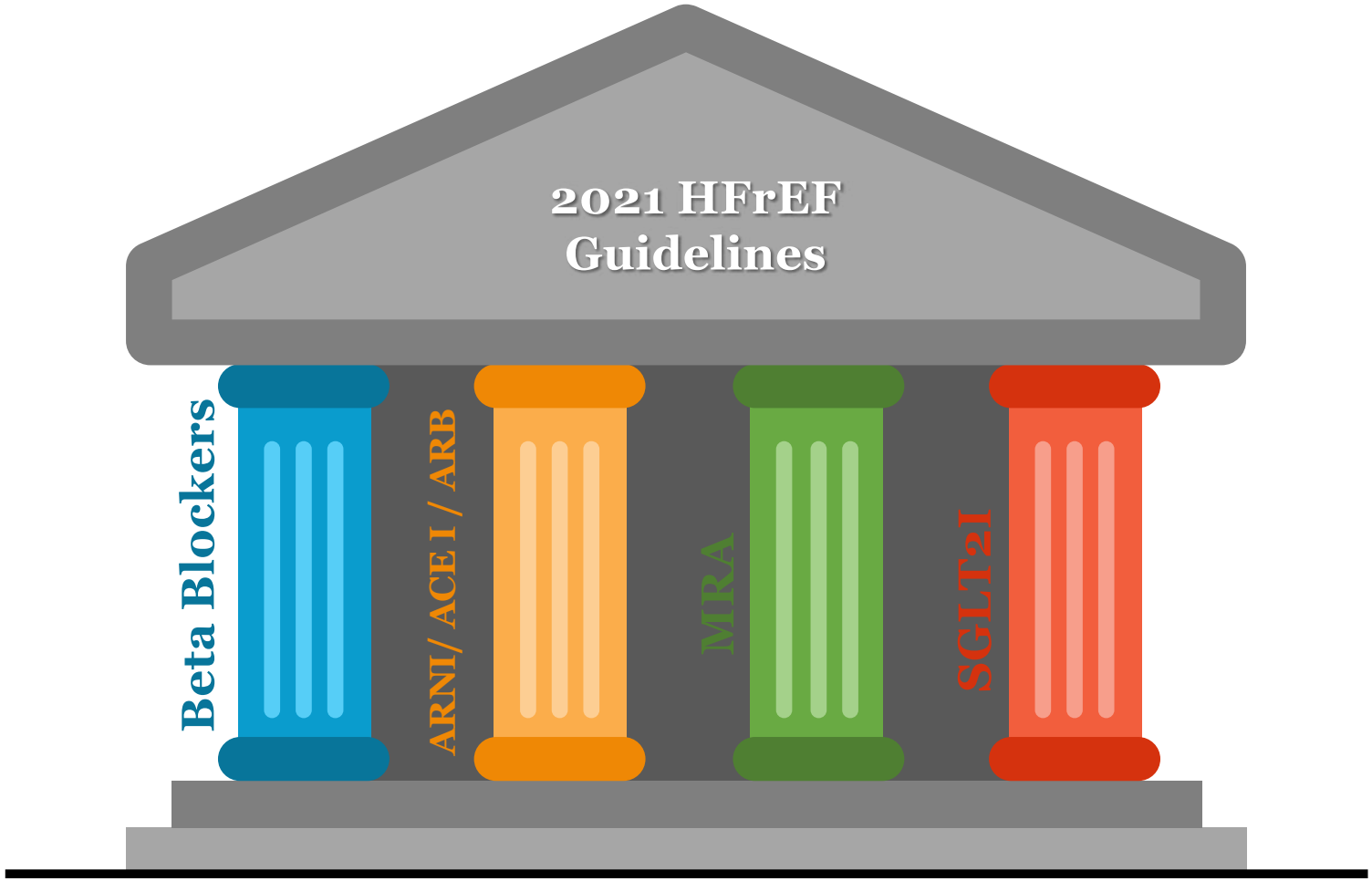
Conflict of Interest Disclosures

- **Grants/research support**: Astra Zeneca, BI, Bayer

- **Consulting fees/ Speaker fees**: Astra Zeneca, Bayer, Janssen, Novartis, Servier, BI

The 4 Foundational Therapies in HFrEF Management



Cumulative impact of evidence-based HFrEF medical therapies on all-cause mortality

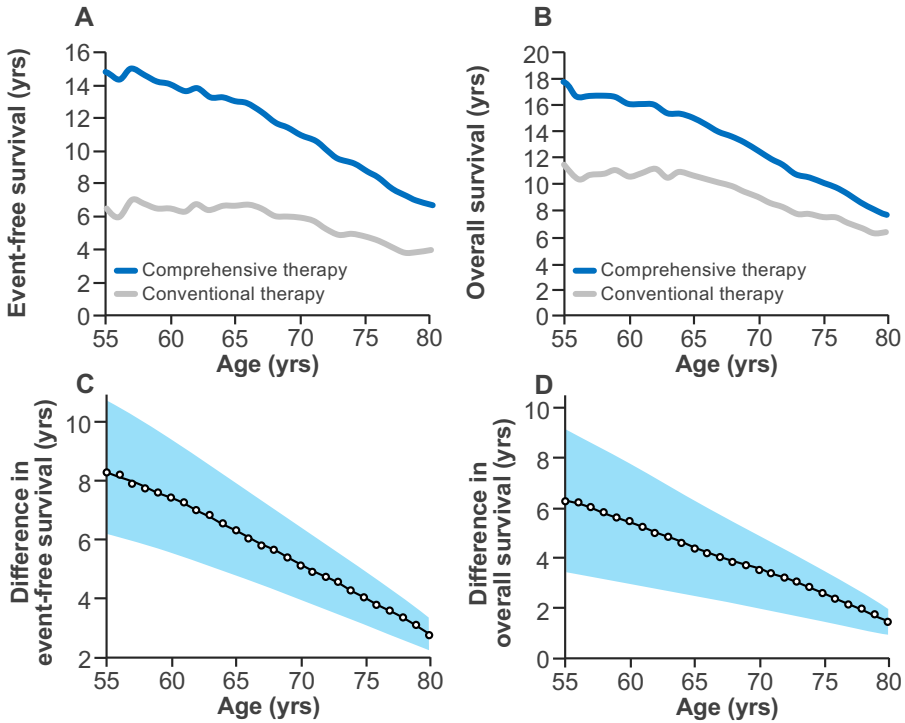
	Relative Risk	Two-year Mortality
None	---	35.0%
ARNI (vs. imputed placebo)	↓ 28%	25.2%
BB	↓ 35%	16.4%
MRA	↓ 30%	11.5%
SGLT2i	↓ 17%	9.5%

Cumulative risk reduction in mortality if all evidence-based medical therapies are used:
RRR 72.9%, ARR: 25.5%, NNT=3.9

ARNI, angiotensin-receptor-neprilysin inhibitor; ARR, absolute risk reduction, BB, beta-blocker; EF, ejection fraction; MRA, mineralocorticoid receptor antagonist; NNT, number needed to be treated to prevent prespecified outcomes within 1 year; RRR, relative risk reduction; SGLT2i, sodium-glucose cotransporter 2 inhibitor
Updated from Fonarow GC et al. Am Heart J 2011;161(6):1024-1030 and Fonarow GC et al. Lancet 2008;372(9645):1195-1196.

COMPREHENSIVE THERAPY WITH NEWER AGENTS IMPROVES SURVIVAL AND EVENT-FREE SURVIVAL IN HFrEF

- In HFrEF, treatment effects of comprehensive therapy (**ARNI, beta- blocker, MRA, SGLT2i**) was compared to conventional therapy (ACEI/ARB, beta-blocker) in cross trial analyses
- This showed **significant improvement** with comprehensive therapy in both overall survival and event-free survival across all age groups
- In 55-year-old men, comprehensive therapy improved **event-free survival by 8.3 years and overall survival by 6.3 years**



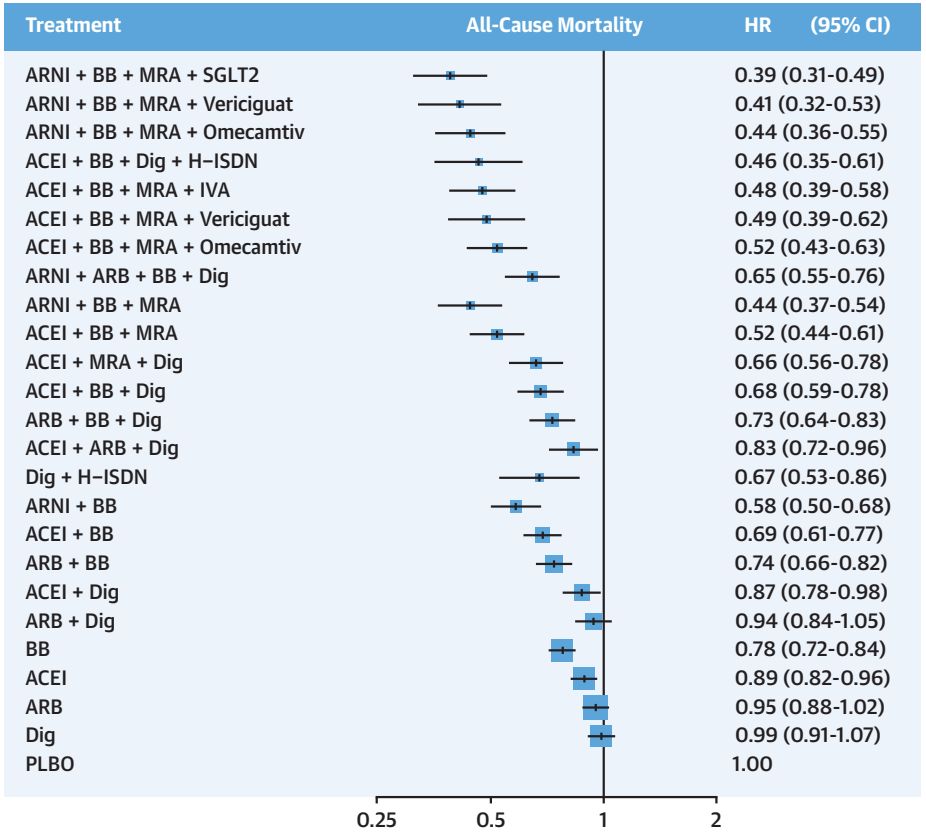
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin-receptor-neprilysin inhibitor; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor

Vaduganathan M et al. Lancet 2020;S0140-6736(20)30748-0.

Impact of Goal Directed Medical Therapy for Heart Failure

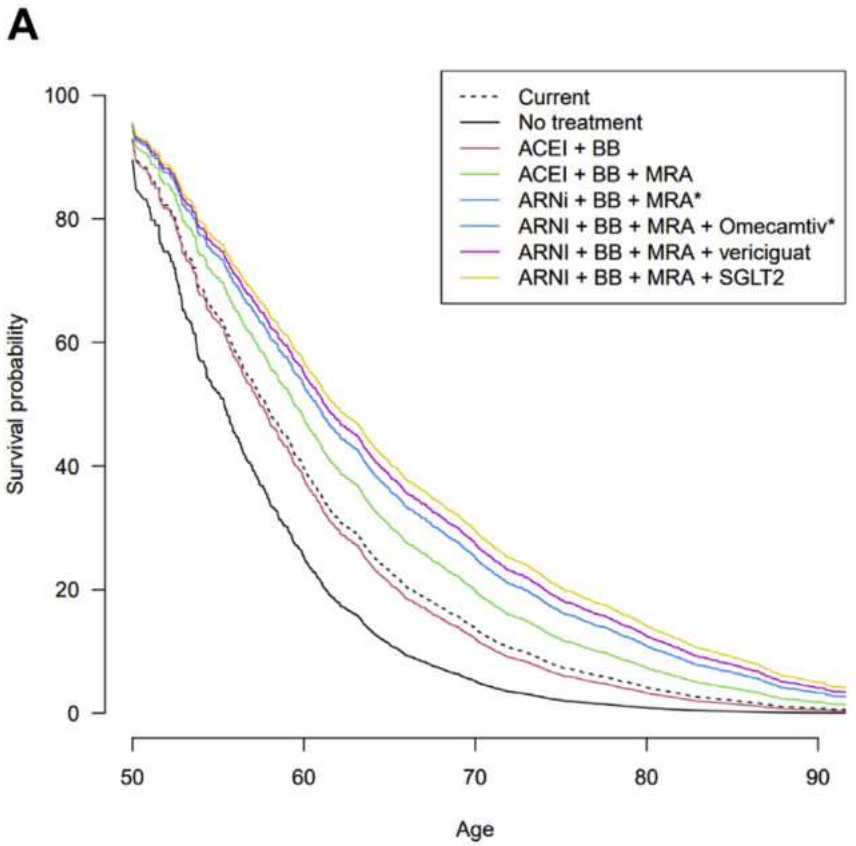
CENTRAL ILLUSTRATION Relative Risk Reduction of Different Pharmacological Treatment Combinations for Heart Failure

A



Tromp, J. et al. J Am Coll Cardiol HF. 2022;10(2):73–84.

FIGURE 3 Estimated Average Lifetime Graphs




Sometimes good
isn't good enough.
SUITS
SEASON FINALE
usa

THERAPEUTIC INERTIA: MISSED OPPORTUNITY TO INITIATE AND OPTIMIZE MEDICAL THERAPY

CHAMP-HF Registry of 3518 HFrEF patients in 150 US primary care and cardiology practices

	Patients Without Contraindications but Not Treated	Patients Treated at <100% of Target Dose
ACEI/ARB	39.1%	82.5%
ARNI	86.1%	86.0%
ACEI/ARB/ARNI	26.2%	83.2%
Beta-blocker	32.9%	72.5%
MRA	65.9%	23.4%

<1% of patients eligible for all medications were simultaneously receiving target doses of ACEI/ARB/ARNI, beta-blocker and MRA

ARB, angiotensin-receptor blocker

Greene SJ et al. J Am Coll Cardiol 2018;72(4):351-366.

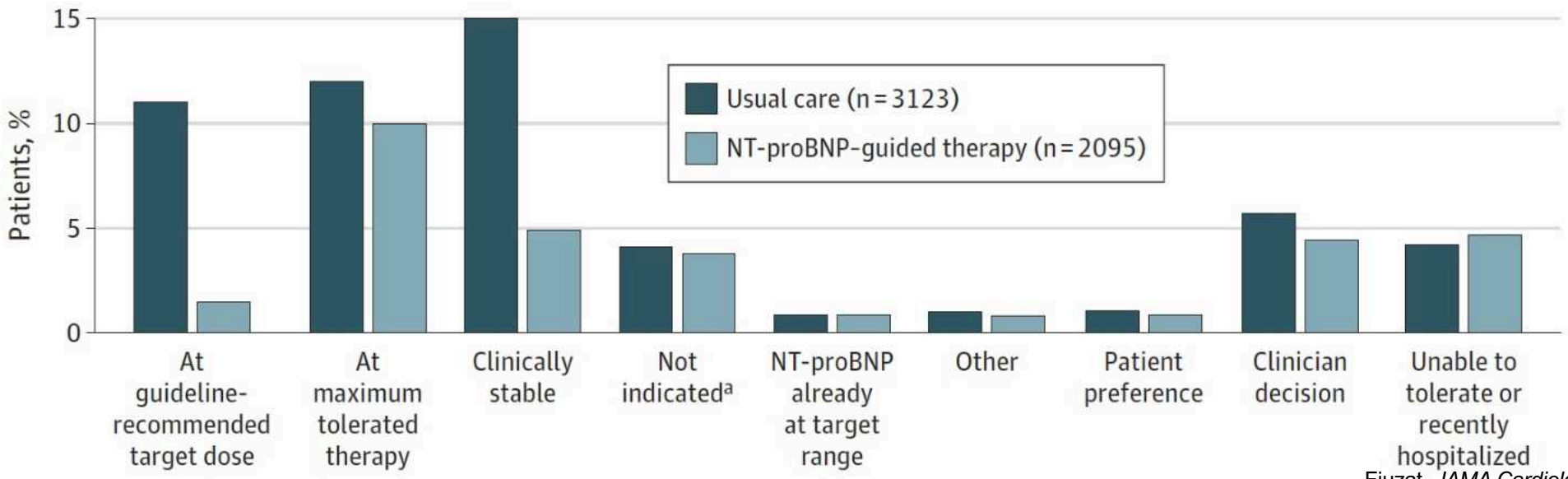
JAMA Cardiology | Original Investigation

Assessment of Limitations to Optimization of Guideline-Directed Medical Therapy in Heart Failure From the GUIDE-IT Trial

A Secondary Analysis of a Randomized Clinical Trial

Mona Fiuzat, PharmD; Justin Ezekowitz, MB BCh, MSc; Wendimagegn Alemayehu, PhD; Cynthia M. Westerhout, PhD; Marco Sbolli, MD; Dario Cani, MD; David J. Whellan, MD, MHS; Tariq Ahmad, MD; Kirkwood Adams, MD; Ileana L. Piña, MD; Chetan B. Patel, MD; Kevin J. Anstrom, PhD; Lawton S. Cooper, MD, MPH; Daniel Mark, MD, MPH; Eric S. Leifer, PhD; G. Michael Felker, MD, MHS; James L. Januzzi, MD; Christopher M. O'Connor, MD

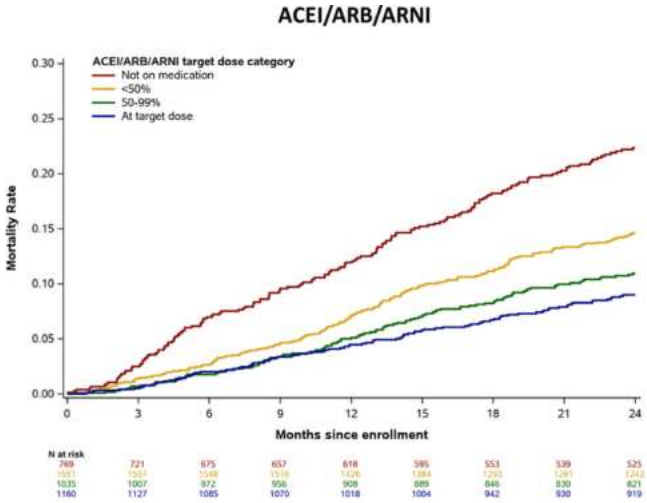
Figure 2. Reasons for Not Titrating Medications by Treatment Arm



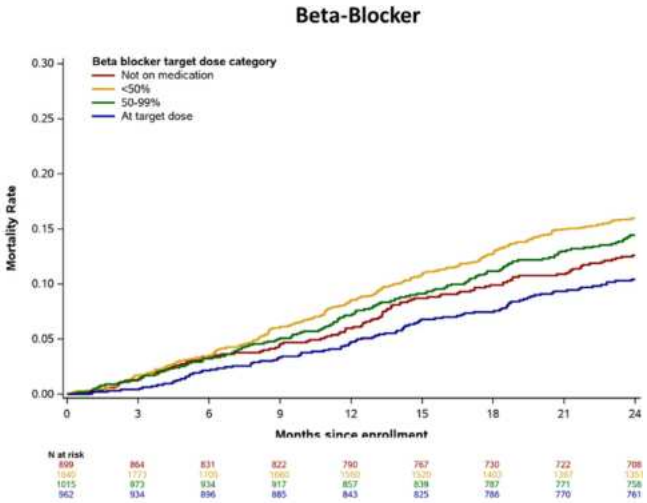
Fiuzat, *JAMA Cardiology*, 2020

Use of Goal Directed Medical Therapy: Dose Matters

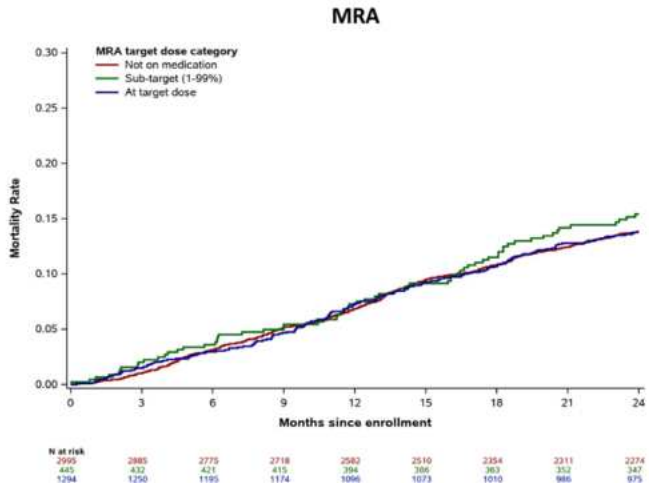
ACEI/ARB/ARNI



BETA BLOCKER

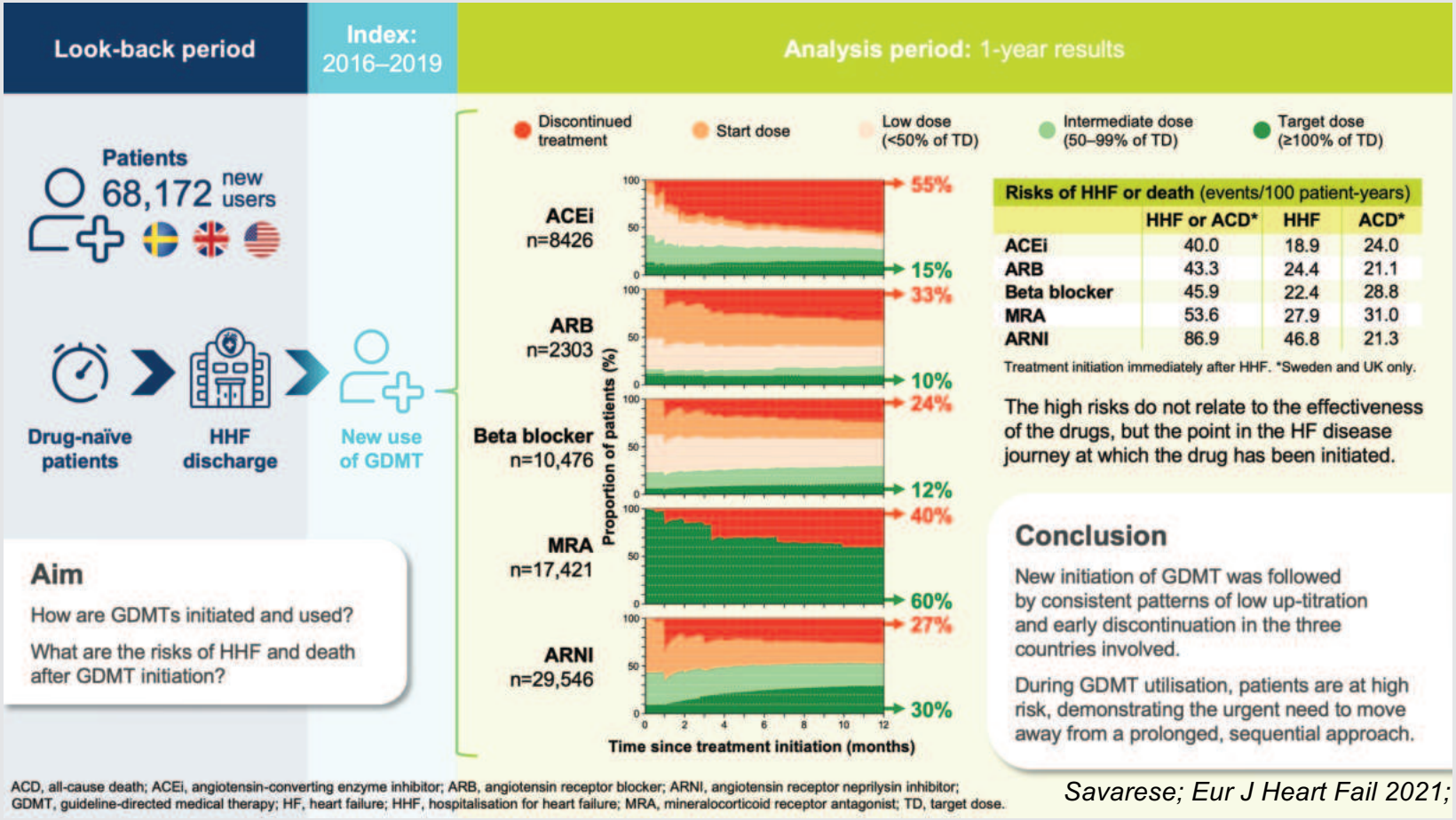


MRA



Greene; J Card Fail 2022; 28:370-84

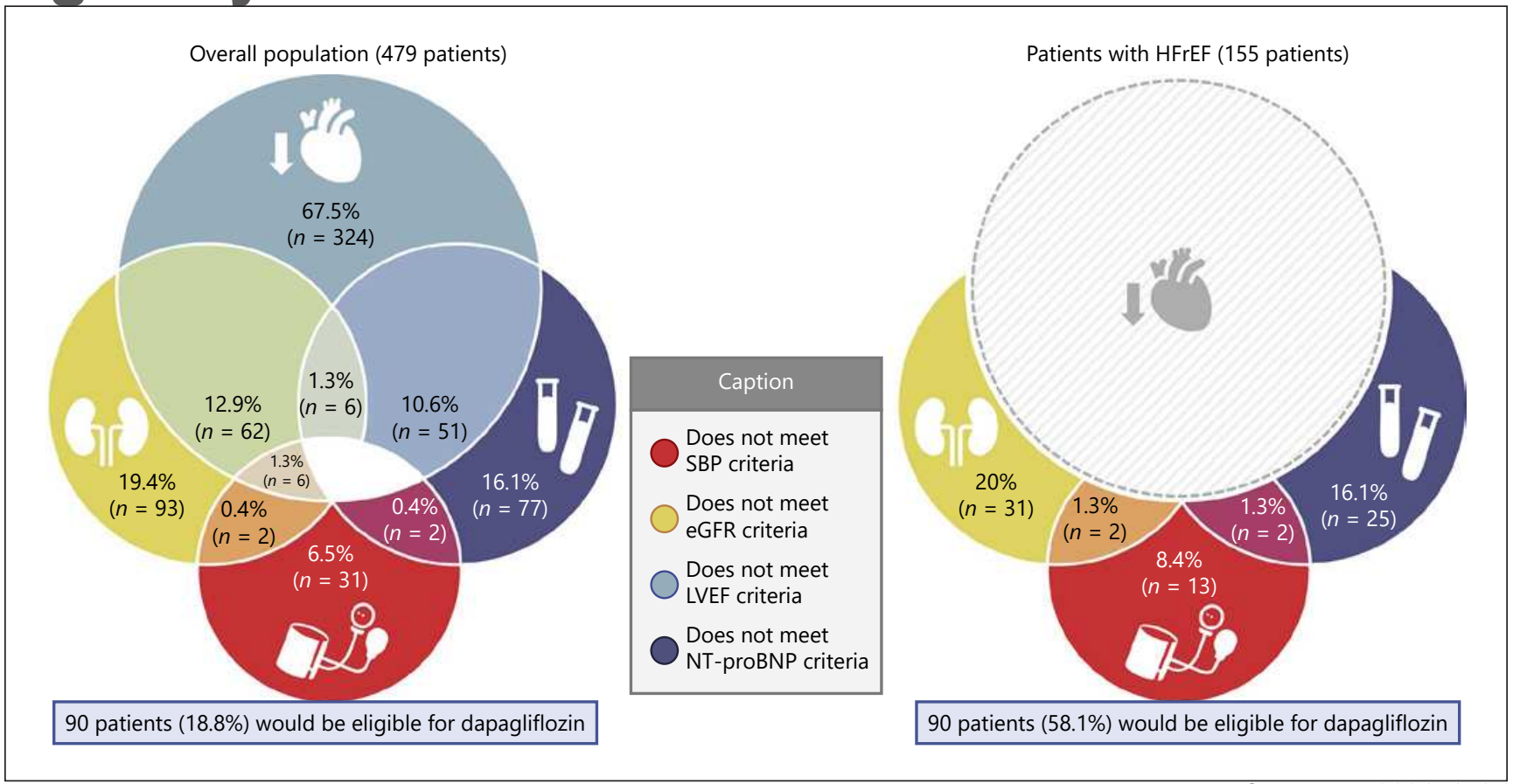
Use of Goal Directed Medical Therapy in Clinical Practice



ACD, all-cause death; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; GDMT, guideline-directed medical therapy; HF, heart failure; HHF, hospitalisation for heart failure; MRA, mineralocorticoid receptor antagonist; TD, target dose.

Savarese; Eur J Heart Fail 2021; 23: 1499

Goal Directed Medical Therapy: Real World Eligibility



Maltes; Cardiology 2021: 146:201

Foundational Therapy: Real World Eligibility

HFrEF (N= 1295)

PARADIGM-HF / DAPA-HF eligible
N=805 (62.2% among patients with HFrEF)

ACEi/ ARB
N= 599 (74.4%)

Beta-blocker
- On treatment N= 701 (87.1%)
- ≥ 50% of recommended dose N= 233 (28.9%)
- Full of recommended dose N= 58 (7.2%)

MRA
N= 384 (47.8%)

- ACEi + BB : N= 548 (68.1%)
- ACEi + BB + MRA: N= 273 (33.9%)

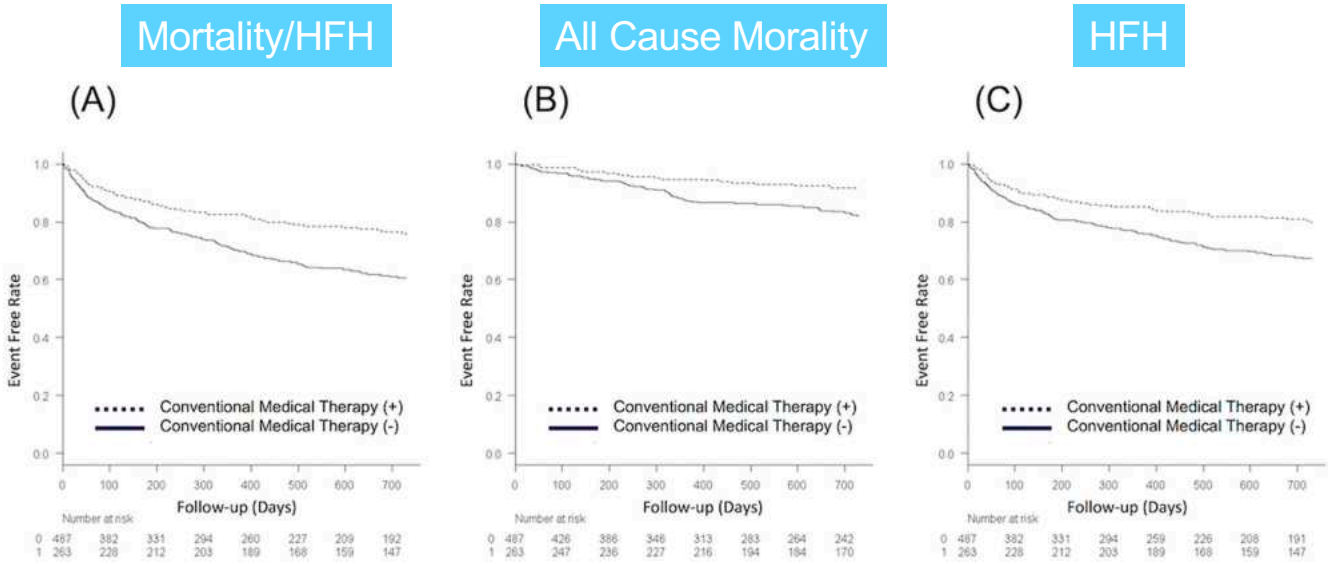
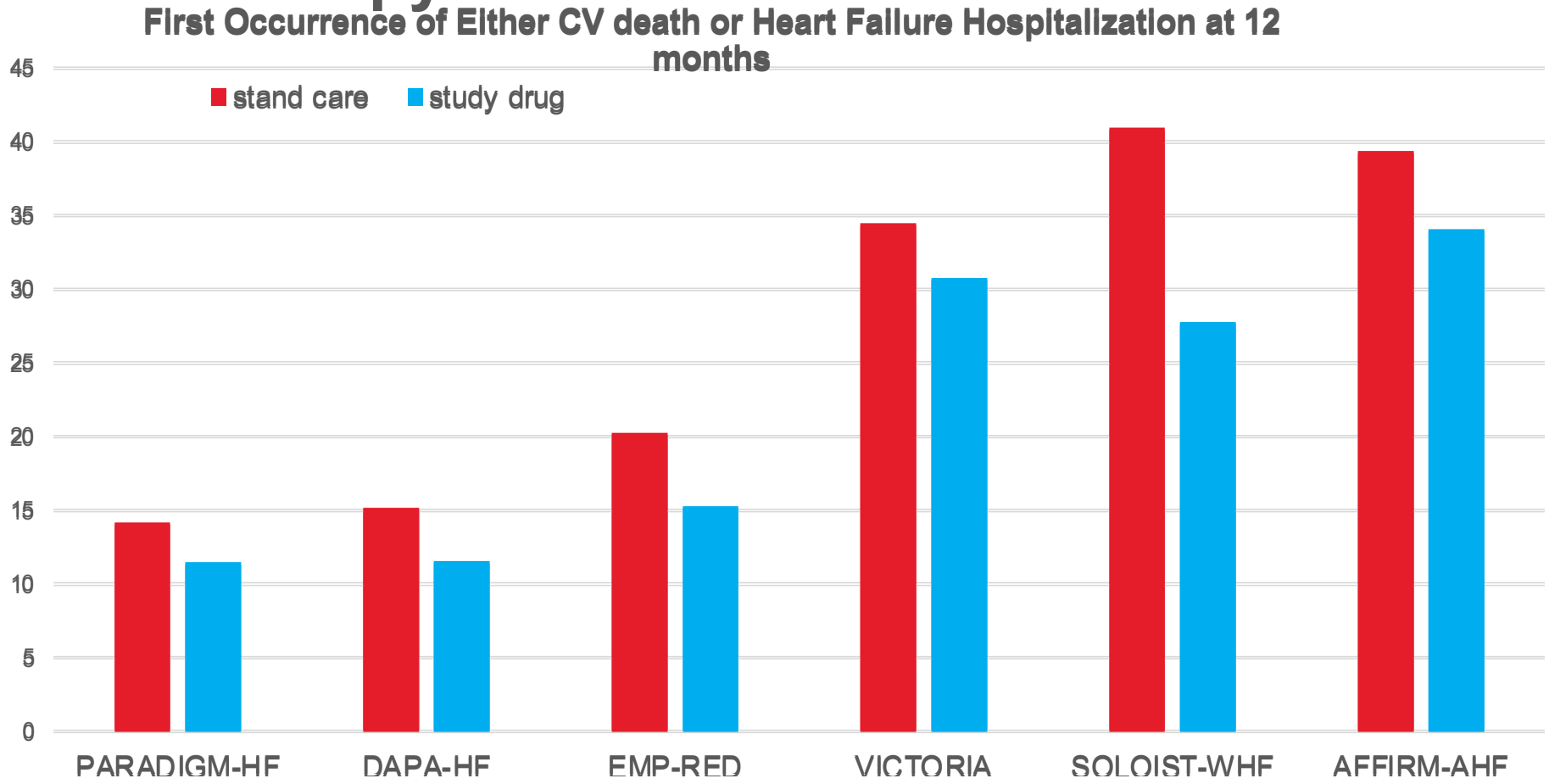


Fig. 2. Association between the use of conventional medical therapy and long-term outcomes [(A) the composite outcome of all-cause death and heart failure readmission, (B) all-cause death, and (C) heart failure readmission within 2 years] within patients meeting the PARADIGM-HF/ DAPA-HF enrollment criteria.

Shoji, International Journal of Cardiol 2022

Residual Risk Despite Optimized Goal Directed Medical Therapy

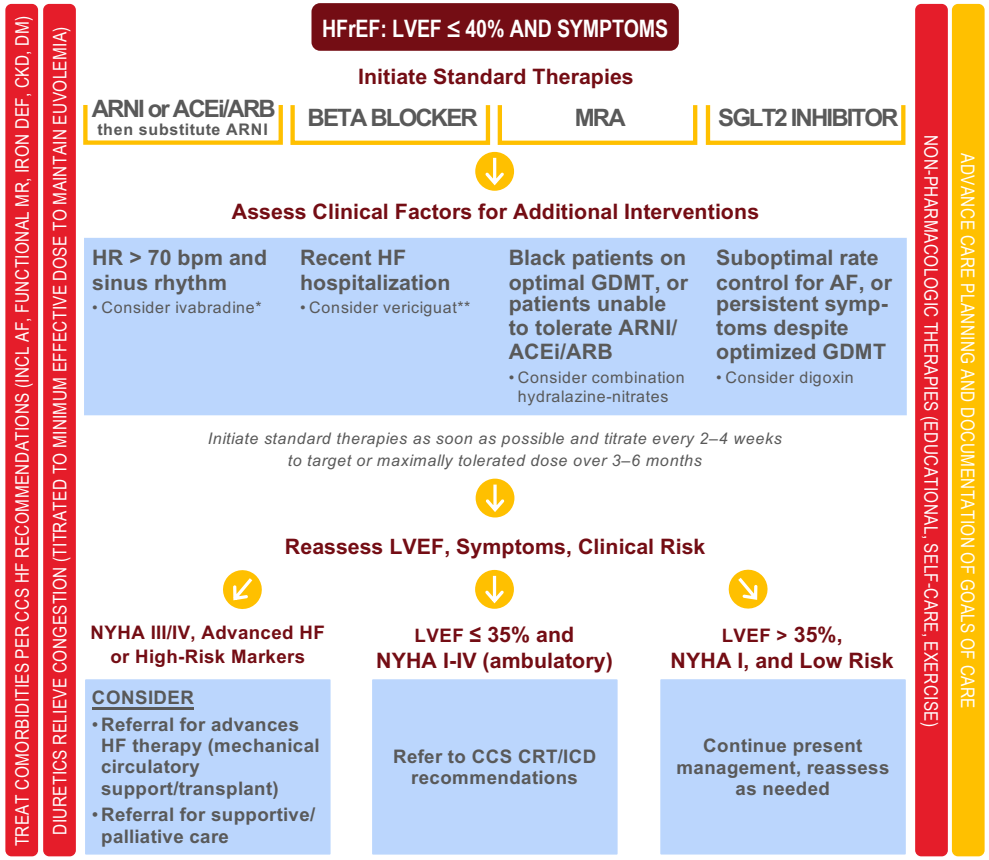


2021 CCS/CHFS Heart Failure Guidelines Update

Laying the Foundation

Personalization

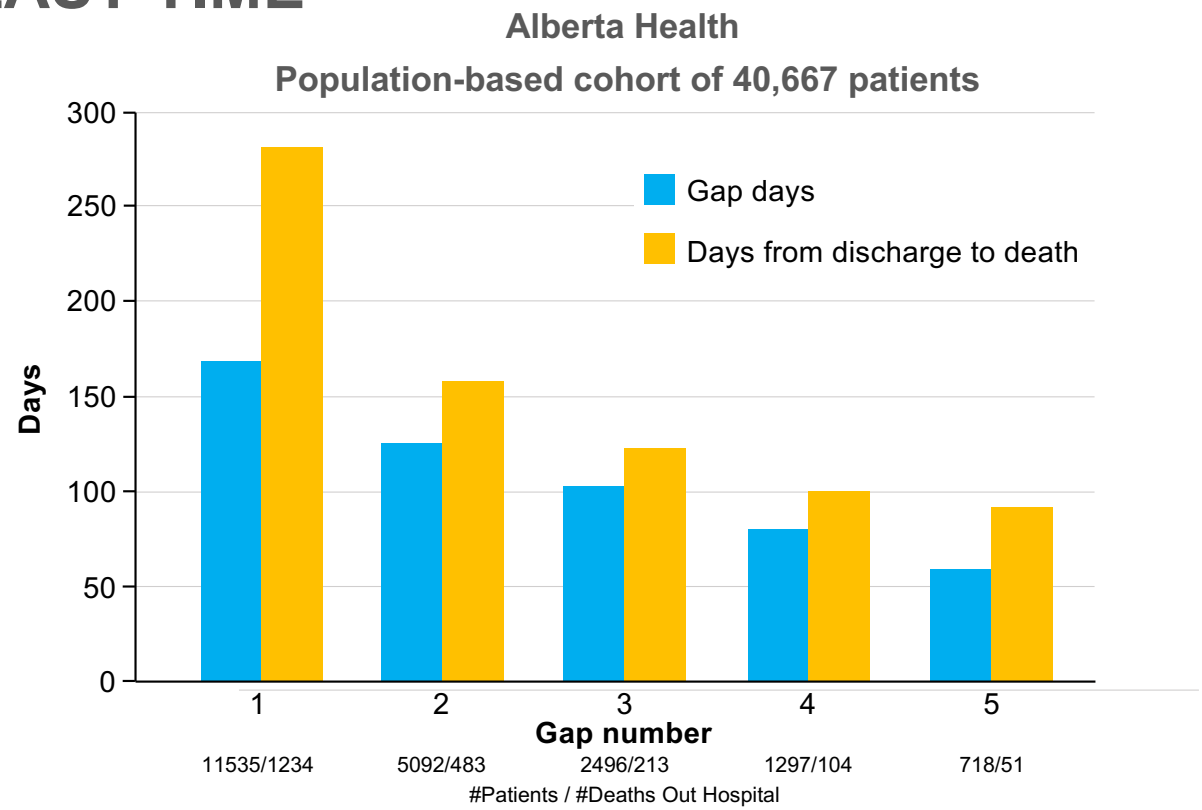
Recalibration



ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CCS, Canadian Cardiovascular Society; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; GDMT, guideline-directed medical therapy; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SGLT, sodium glucose transport. * Health Canada has approved ivabradine for patients with HFrEF and heart rate (HR) 77 bpm in sinus rhythm. ** Vericiguat is not yet approved for use in Canada.

Canadian Journal of Cardiology 2021 37531-546DOI: (10.1016/j.cjca.2021.01.017)

EACH TIME PATIENTS ARE HOSPITALIZED FOR HF, THEY ARE BACK IN HOSPITAL 28 DAYS FASTER THAN THE LAST TIME



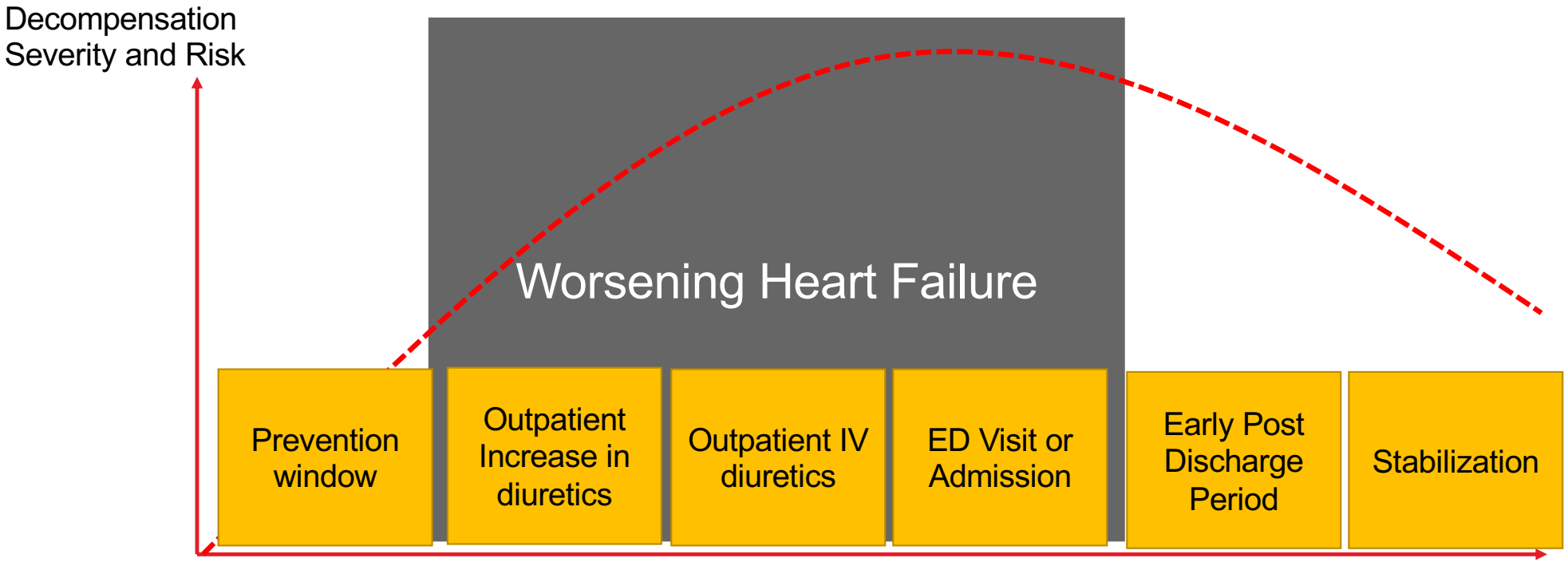
168
Median gap days between first and second hospitalizations

Average reduction of 28 gap days for each rehospitalization

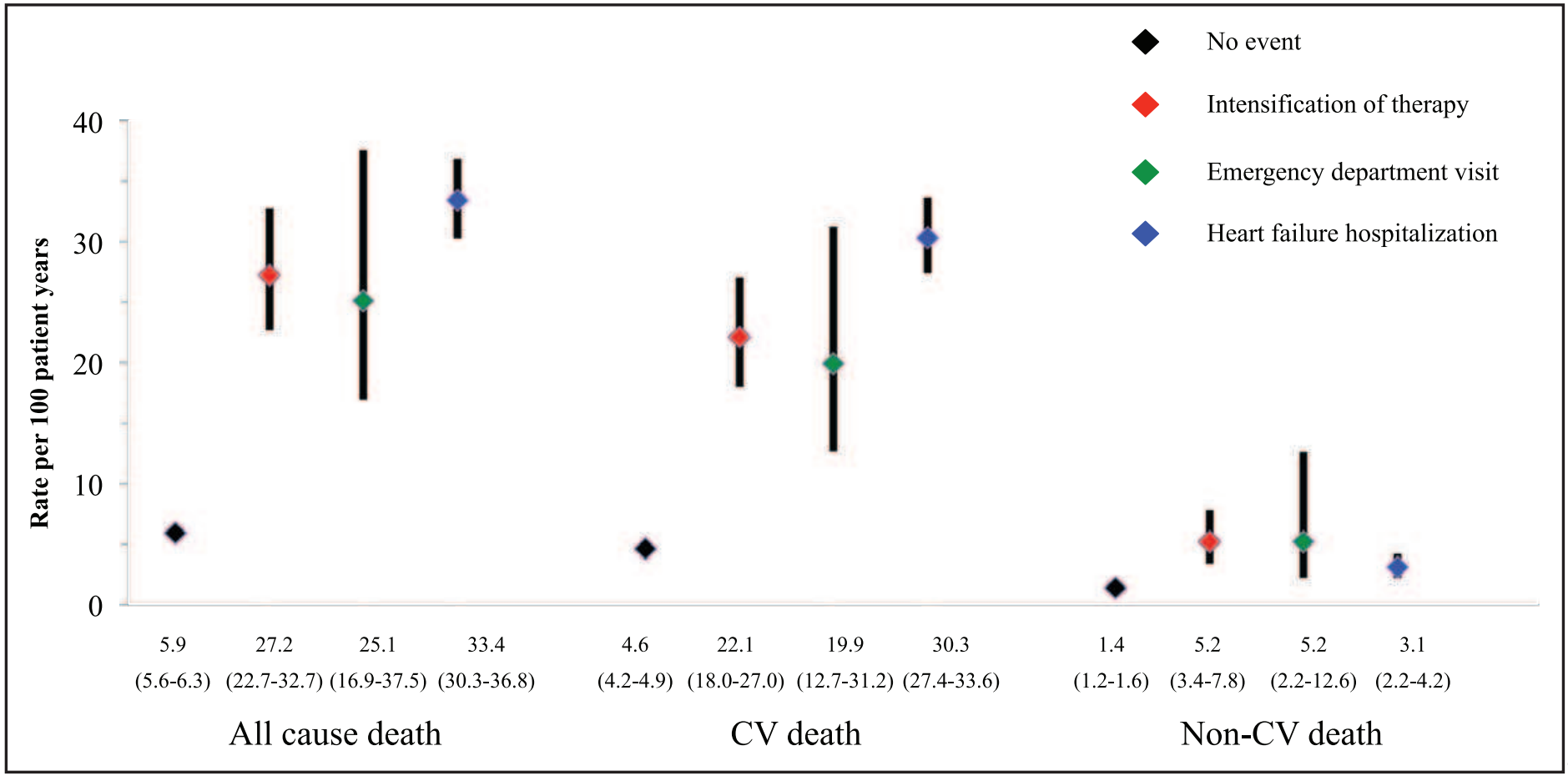
60
Median gap days between fourth and fifth hospitalizations

Bakal JA et al. PLoS One 2014;9(9)e106494.

What is Worsening Heart Failure?



Worsening HF in PARADIGM-HF



Okumura N, Circulation 2016;133:2254

Victoria Trial Patient Population

"Chronic HF" ***after*** **_"Worsening event"_**

- NYHA class II–IV
- **LVEF < 45%**
- Guideline based HF therapies

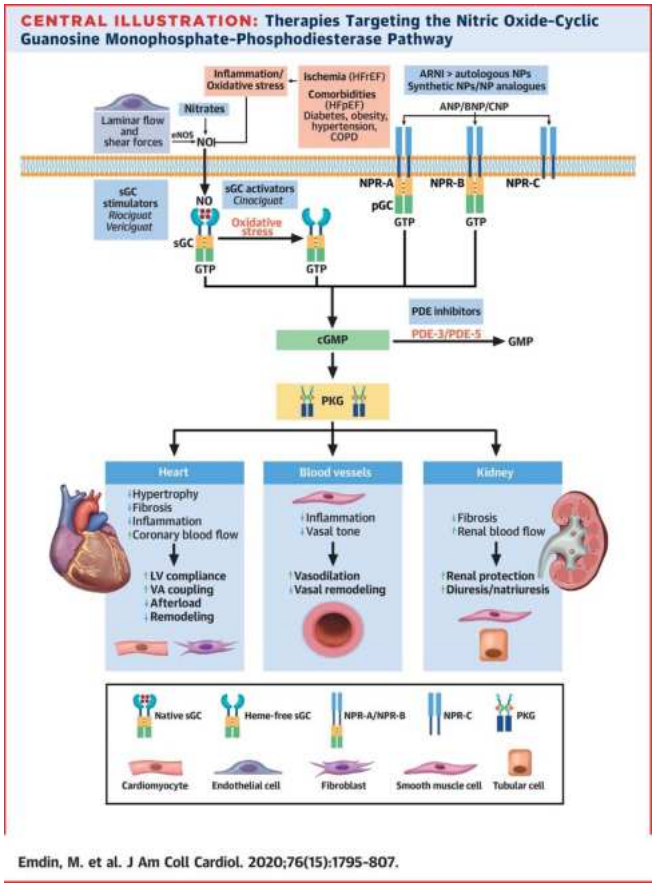
- Recent HFH or IV diuretic use
- With very elevated natriuretic peptides (BNP or NT-proBNP)

  BNP ≥ 300 & pro-BNP ≥ 1000 pg/ml NSR
  BNP ≥ 500 & pro-BNP ≥ 1600pg/ml AF

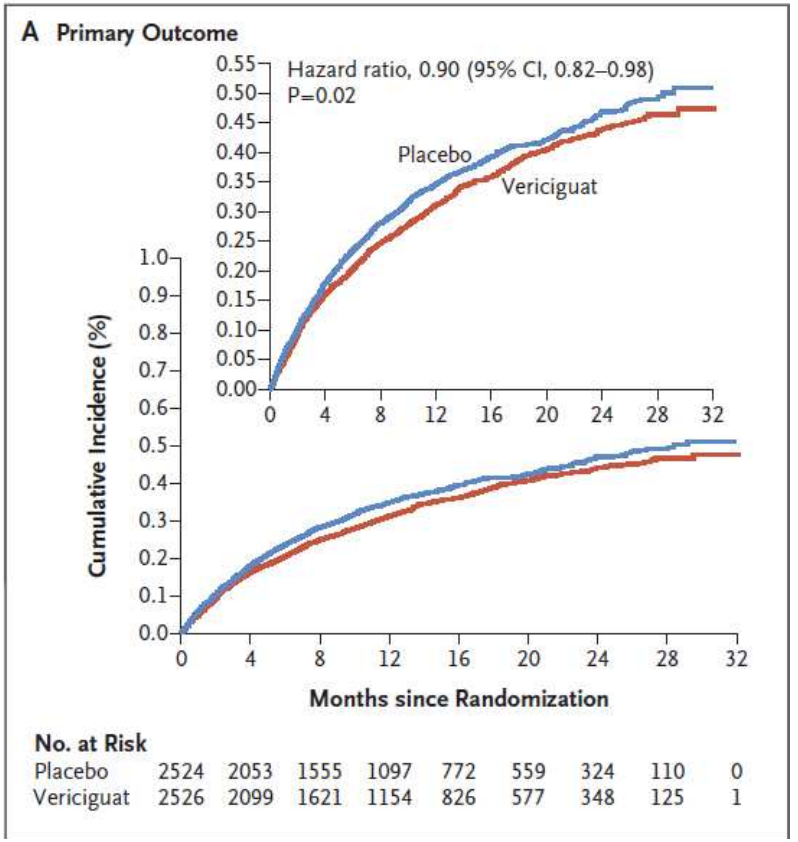
Patients may have been randomized as an inpatient or outpatient but must have met criteria for clinical stability (e.g., SBP ≥ 100 mmHg, off IV treatments ≥ 24 hours)

Armstrong et al. JACC Heart Fail. 2018 Feb;6(2):96-104. doi: 10.1016/j.jchf.2017.08.013.

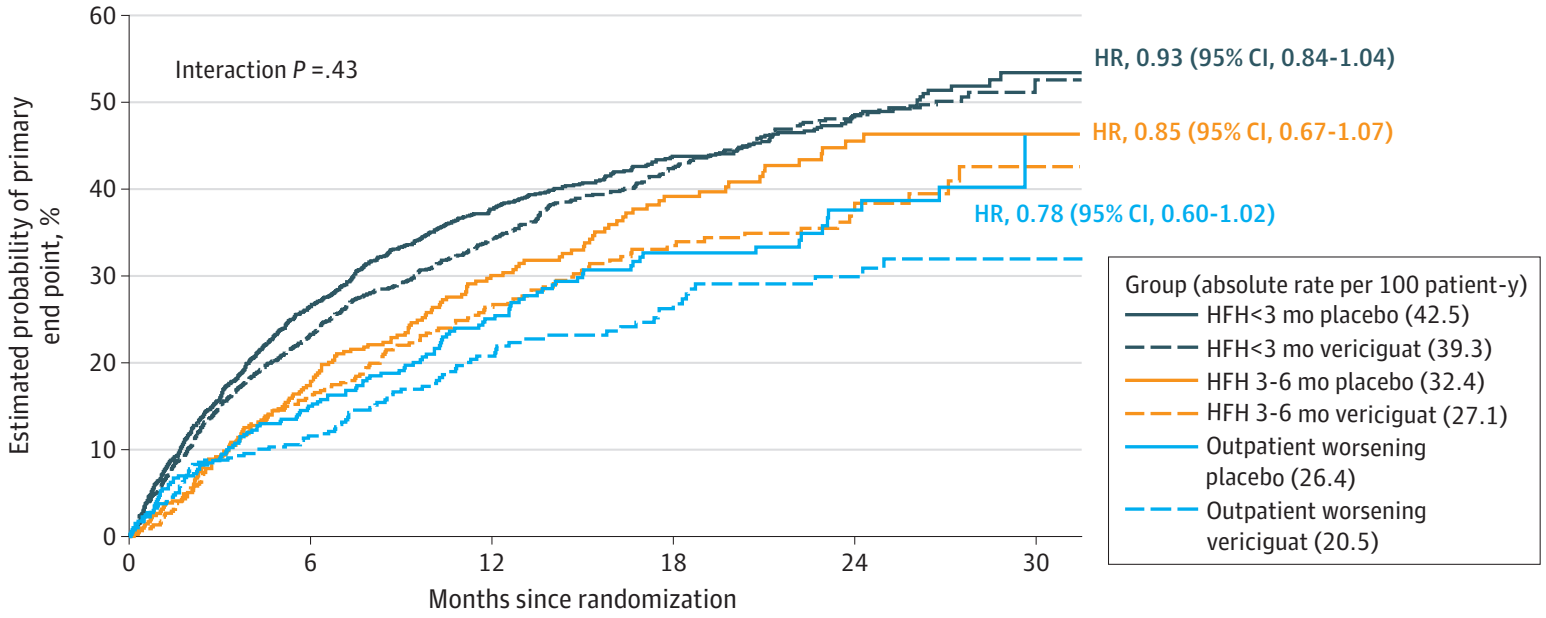
Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction



Emdin, M. et al. J Am Coll Cardiol. 2020;76(15):1795-807.



Worsening HF Events in VICTORIA

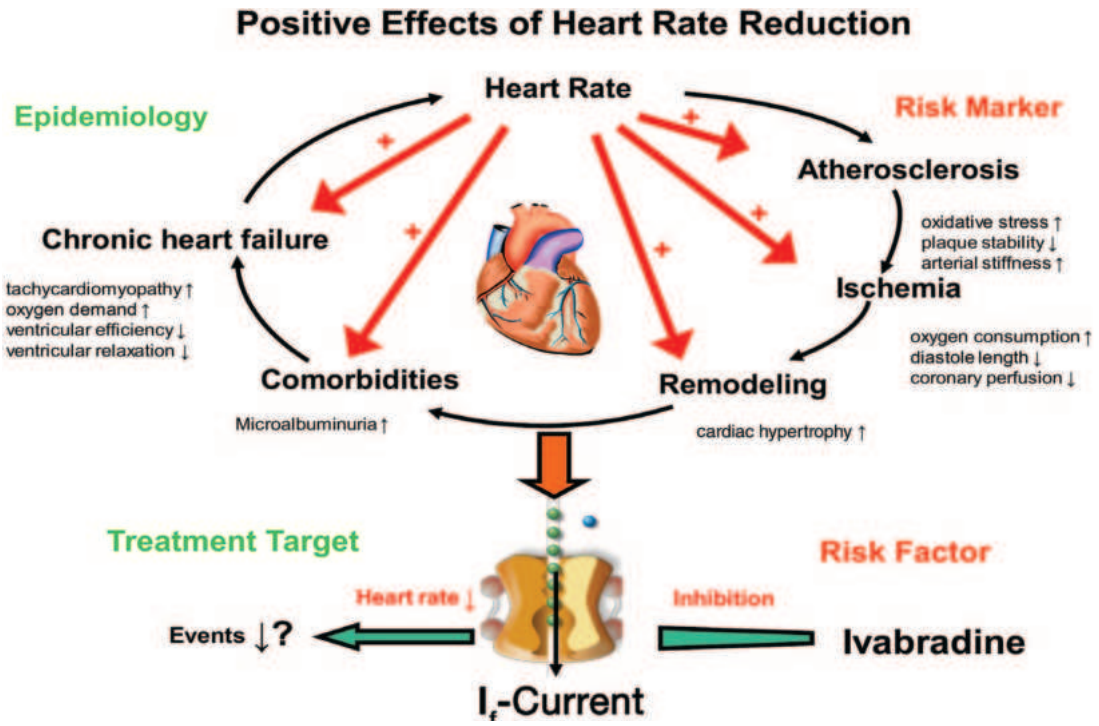


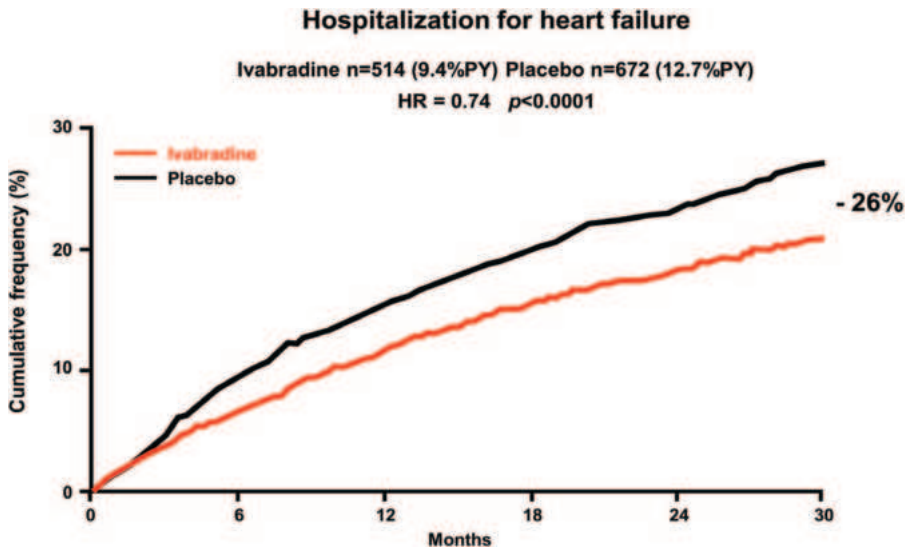
No. at risk

HFH<3 mo placebo (42.5)	1705	1233	701	419	221	27
HFH<3 mo vericiguat (39.3)	1673	1264	741	436	217	33
HFH 3-6 mo placebo (32.4)	417	341	215	122	71	9
HFH 3-6 mo vericiguat (27.1)	454	373	235	151	86	9
Outpatient worsening placebo (26.4)	402	338	205	131	61	6
Outpatient worsening vericiguat (20.5)	399	349	205	133	73	14

Lam C, JAMA Cardiol 2021;6:706

Heart Rate and its Reduction in Chronic Heart Failure





Vukadinovic; Eur J Heart Fail, 2017; 19:1230-41

Effects of Ivabradine in Patients with HR>77 bpm

Quality of Life and Patient Reported Outcomes

Table 2 Change between baseline and last visit for New York Heart Association class and global assessment in patients with a heart rate ≥ 77 b.p.m. at rest

	Ivabradine group (*N* = 1657)	Placebo group (*N* = 1700)	*P*
NYHA functional class, % (*n*)	Nobs = 1643	Nobs = 1680	0.0003
Improved	28.0% (*n* = 460)	22.7% (*n* = 382)	
Stable or worsening	72.0% (*n* = 1183)	77.0% (*n* = 1298)	
Change in global self-assessment, % (*n*)	Nobs = 1497	Nobs = 1515	0.0006
Improved	72.3% (*n* = 1082)	66.6% (*n* = 1009)	
Stable or worsening	27.7% (*n* = 415)	33.4% (*n* = 506)	
Change in global assessment, physician perspective, % (*n*)	Nobs = 1573	Nobs = 1596	<0.0001
Improved	61.0% (*n* = 960)	54. 5% (*n* = 869)	
Stable or worsening	39.0% (*n* = 613)	45.5% (*n* = 727)	

Nobs, number of observations; NYHA, New York Heart Association.

Table 3 Quality of life, subgroup of patients with a heart rate ≥ 77 b.p.m. at rest

KCCQ scores	Ivabradine group (*N* = 510)	Placebo group (*N* = 512)	Treatment effect (change in QoL at 1 year)	
			Estimate (95% CI)	*P*
CSS, at baseline mean (±SD)	66.58 (±20.74)	66.38 (±20.04)	—	—
CSS, changes at last post-baseline value mean (±SD)	3.66 (±18.51)	1.24 (±18.67)	2.37 (0.25–4.48)	0.028
OSS, at baseline mean (±SD)	63.27 (±20.67)	63.13 (±19.31)	—	—
OSS, changes at last post-baseline value mean (±SD)	5.30 (±18.54)	2.19 (±18.86)	3.00 (0.89–5.10)	0.005

CSS, clinical summary score; KCCQ, Kansas City Cardiomyopathy Questionnaire; OSS, overall summary score; QoL, quality of life.

Bouabdallaoui, ESC Heart Fail 2019; 6:1199

Figure 2 Kaplan–Meier curves for cardiovascular mortality alone in patients with a heart rate ≥ 77 b.p.m. at rest.

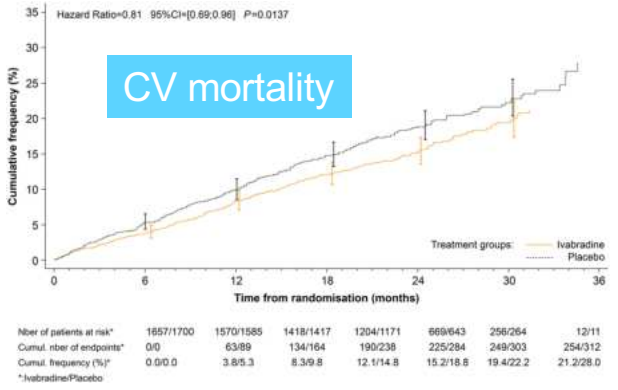
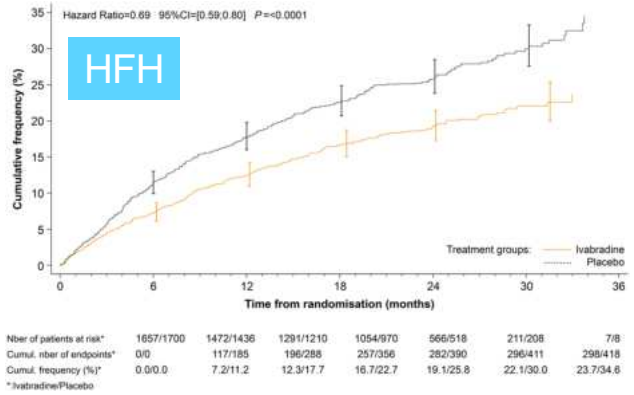


Figure 3 Kaplan–Meier curves for hospitalization for worsening heart failure alone in patients with a heart rate ≥ 77 b.p.m. at rest.



Ivabradine: Pooled Outcome Estimates

Patient or population: patients with heart failure
Setting: any setting
Intervention: Ivabradine
Comparison: placebo/no intervention/usual care

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo/no intervention/usual care	Risk difference with Ivabradine
All-cause mortality	19257 (22 RCTs)	⨁⨁⨁⨁ High [a,b,c]	**RR 0.94** (0.88 to 1.01)	134 per 1.000	**8 fewer per 1.000** (16 fewer to 1 more)
Serious adverse events	20144 (31 RCTs)	⨁⨁◯◯ Low [b,c,d]	**RR 0.90** (0.87 to 0.94)	374 per 1.000	**37 fewer per 1.000** (49 fewer to 22 fewer)
Quality of life (KCCQ)	1781 (2 RCTs)	⨁⨁◯◯ Low [b,e,f]	-		MD **2.92 higher** (1.34 higher to 4.5 higher)
Quality of life (MLWHFQ)	221 (4 RCTs)	⨁◯◯◯ Very low [b,g,h]	-		MD **5.28 lower** (6.6 lower to 3.96 lower)
Cardiovascular mortality	18738 (15 RCTs)	⨁⨁⨁⨁ High [a,b,c]	**RR 0.98** (0.90 to 1.06)	103 per 1.000	**2 fewer per 1.000** (10 fewer to 6 more)
Myocardial infarction	18190 (9 RCTs)	⨁⨁◯◯ Low [a,c,i]	**RR 1.00** (0.80 to 1.24)	17 per 1.000	**0 fewer per 1.000** (3 fewer to 4 more)
Non-serious adverse events	21598 (49 RCTs)	⨁⨁⨁⨁ High [a,b,c]	**RR 1.10** (1.07 to 1.12)	471 per 1.000	**47 more per 1.000** (33 more to 57 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence

Maagaard; BMJ Evidence Based Med 2021

Ivabradine: Pooled Outcome Estimates

Heart Rate Reduction

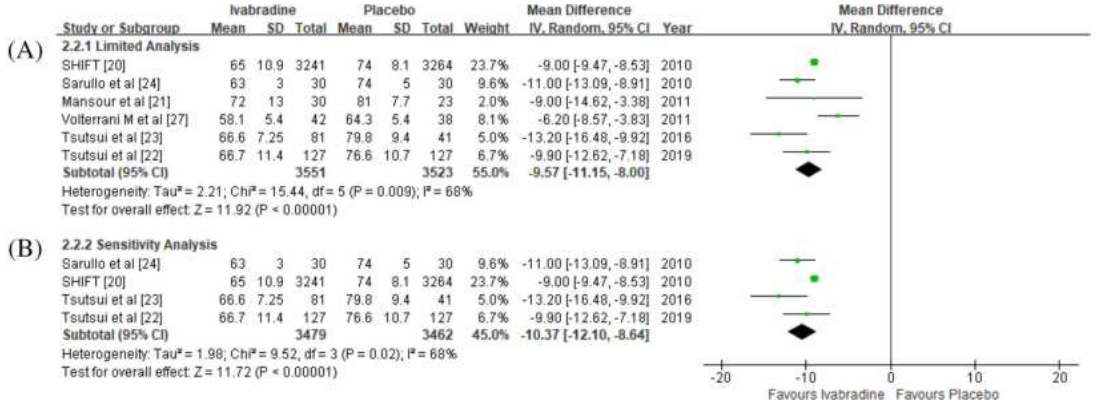
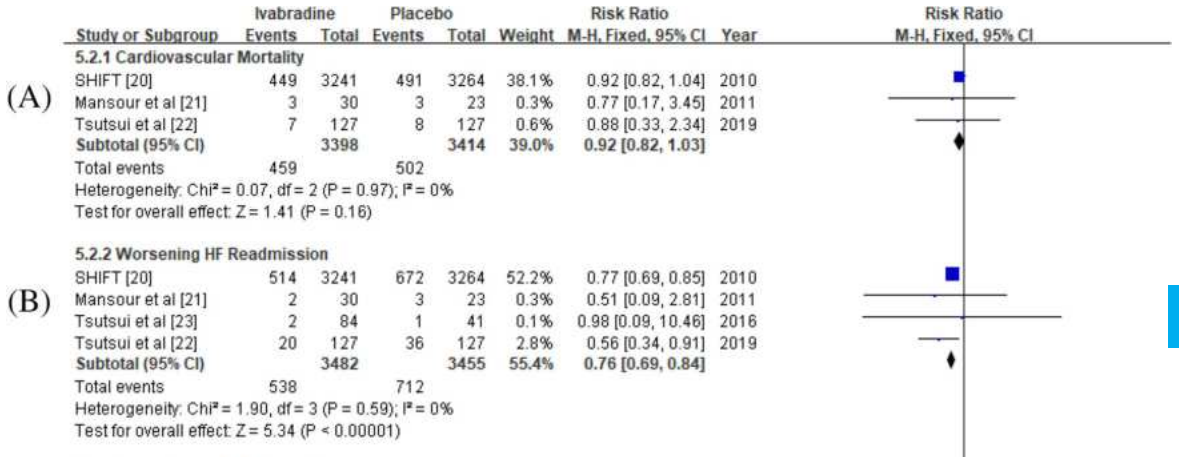


FIGURE 2 Effect of Ivabradine versus placebo on heart rate reduction. (A) limited analysis; (B) sensitivity analysis



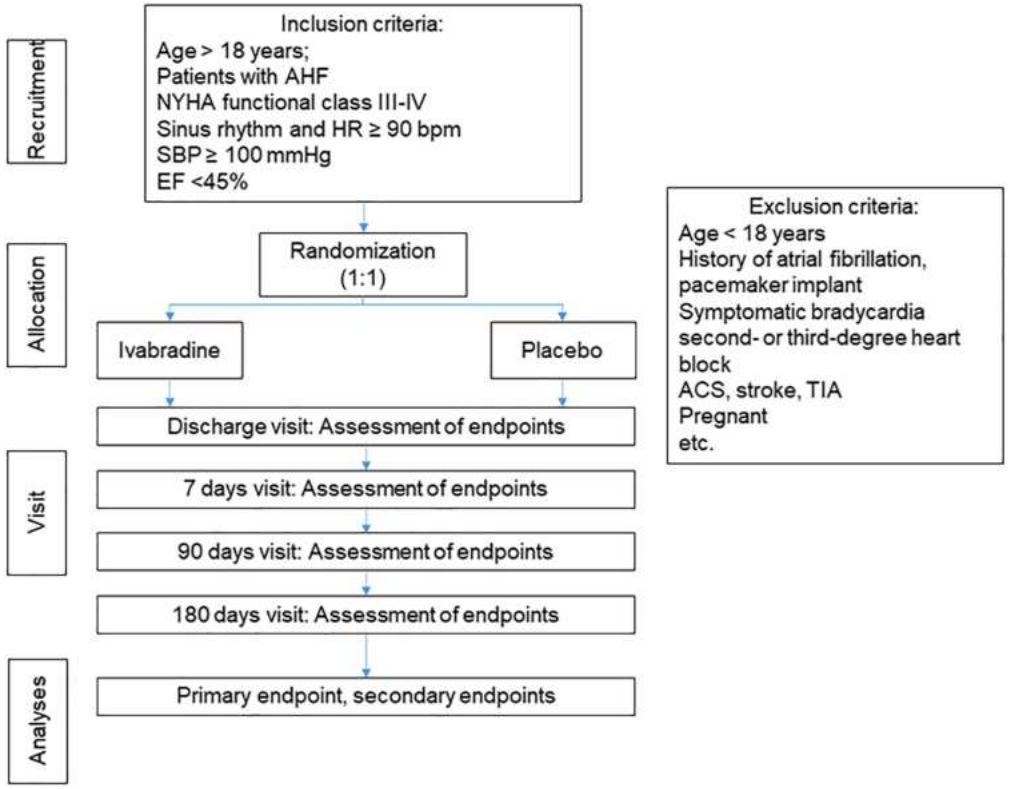
CV Mortality

HF Hospitalization

Richard, Clini Cardiol: 2021: 44:463

Use of Ivabradine in Acute Heart Failure

FIGURE 1 Flow chart of SHIFT-AHF trial. ACS, acute coronary syndrome; TIA, transient ischaemic attack.



Primary Endpoint:
- Composite of all cause-mortality or HF readmission

Secondary Endpoints:
- All cause death
- CV death
- HFH
- Cardiac remodelling
- Change in FC
- QOL

Su; ESC Heart Fail; 2020; 7:4465

Real World Eligibility of Ivabradine

Table 2 SHIFT study-like characteristics potential Ivabradine patients

Characteristic, *n* (%)	**AI *n* = 491**	**CH *n* = 605**	***p* value AH/CH**
LVEF ≤ 35%	172/491 (35.0)	184/605 (30.4)	0.1045
Sinus rhythm	279/491 (56.8)	366/605 (60.5)	0.2191
HR ≥ 70 bpm	205/491 (41.8)	317/605 (52.4)	0.0004*
"SHIFT study-like" characteristics	41 (8.4)	71 (11.7)	0.0658

AH Academic hospital, *CH* community hospital, *HR* heart rate, *LVEF* left ventricular ejection fraction, *%* percentage
* Significant *p* value

Roth, Moe, Adva Therp 2017; 34:1340-48

Real World Eligibility of Ivabradine

HFrEF (N= 1295)

SHIFT eligible
N= 457 (35.3% among patients with HFrEF)

ACEi/ ARB
N= 315 (68.9%)

Beta-blocker
- On treatment N= 385 (84.2%)
- ≥ 50% of recommended dose N= 105 (23.0%)
- Full-of recommended dose N= 20 (4.4%)

MRA
N= 209 (45.7%)

- ACEi + BB : N= 283 (61.9%)
- ACEi + BB + MRA: N= 146 (31.9%)

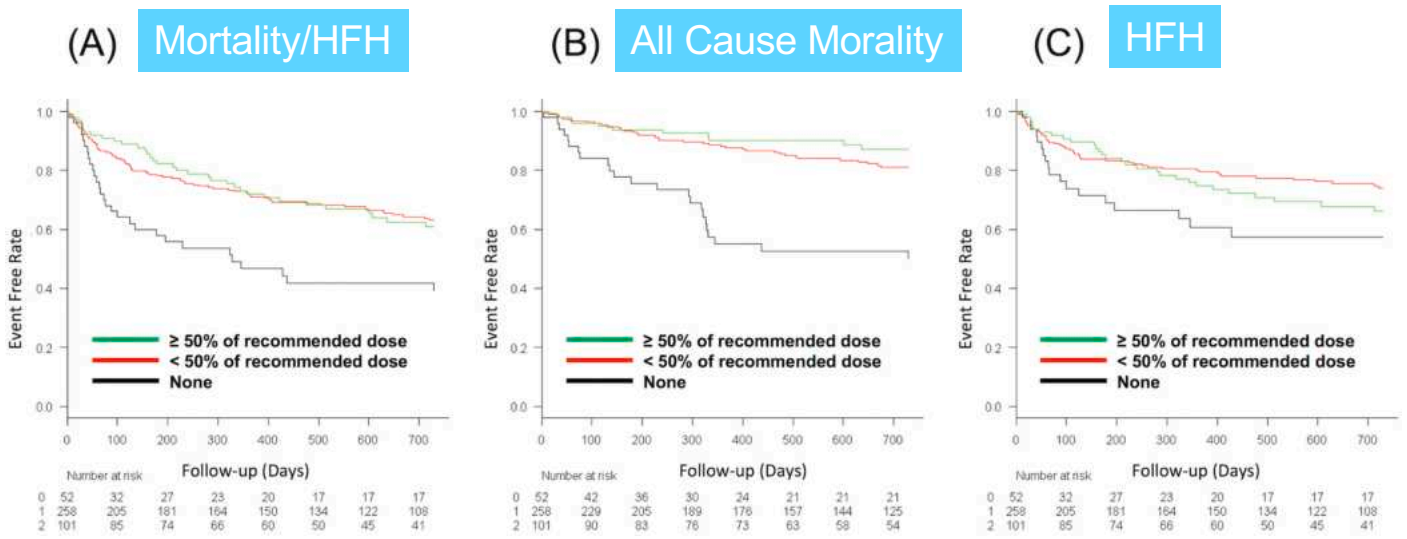
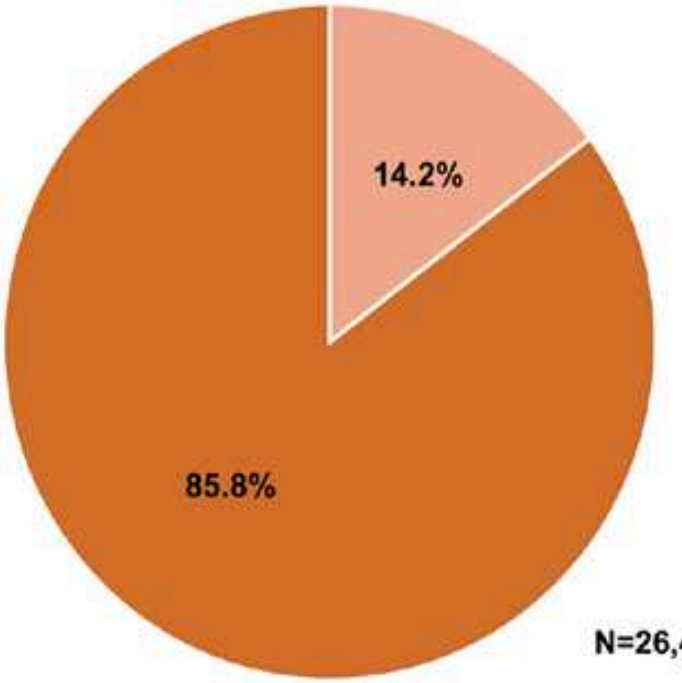


Fig. 3. Association between the dose of beta-blockers and long-term outcomes [(A) the composite outcome of all-cause death and heart failure readmission, (B) all-cause death, and (C) heart failure readmission within 2 years] within patients meeting the SHIFT enrollment criteria.

Shoji, International Journal of Cardiol 2022

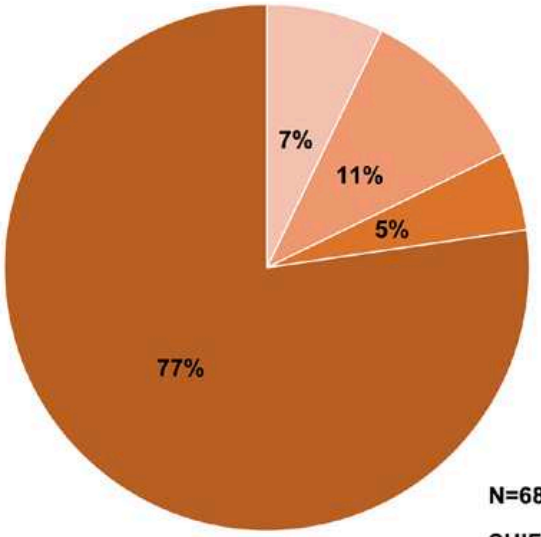
Real World Eligibility of Ivabradine



N=26,404

Baseline SHIFT eligibility

SHIFT-type Non-SHIFT-type



N=6840

SHIFT eligibility at 12-months

Remained Eligible Eligible to Ineligible Ineligible to Eligible Remained Ineligible

12 months

Das; Circ Heart Fail 2017;

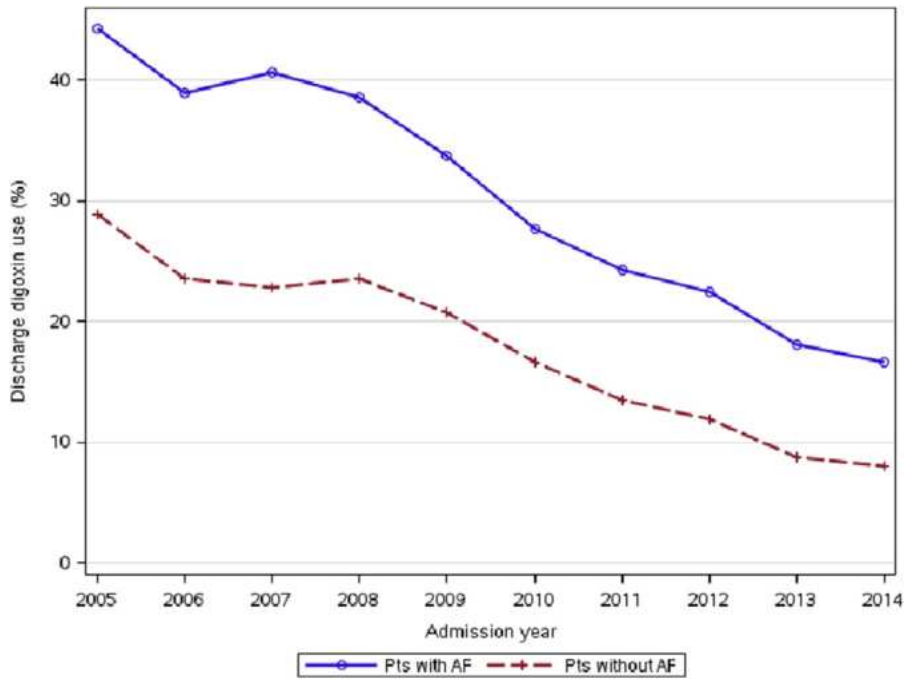
Digoxin: The Great Divide

Study Design				Outcomes
Meta-analyses and other study designs	**Meta-analyses of RCTs**	**RCTs**		
		DIG [6] *Ahmed et al. [7, 8] *Gheorghiade et al. [10] RADIANCE [11] PROVED [12] RATE-AF [24]	**Positive**	
Lopes et al. [17] Allen et al. [18] Gheorghiade et al. [19]	Ziff et al. [20]		**Neutral**	
Mate at el. [13, 16] Wang et al. [14] Ouyang et al. [15]			**Negative**	

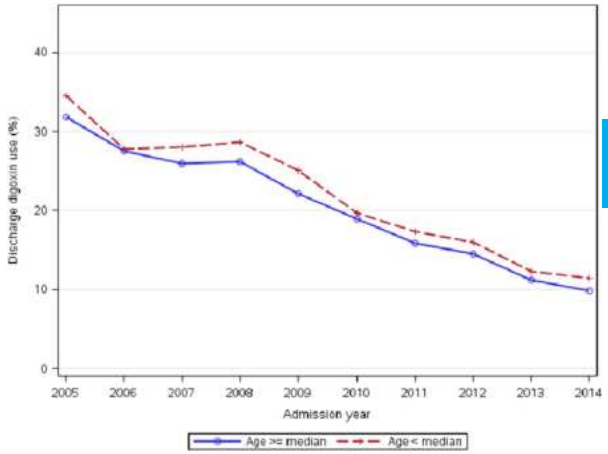
Triska; Card Drugs Ther 2021

Temporal Trends in Digoxin Use Over Time

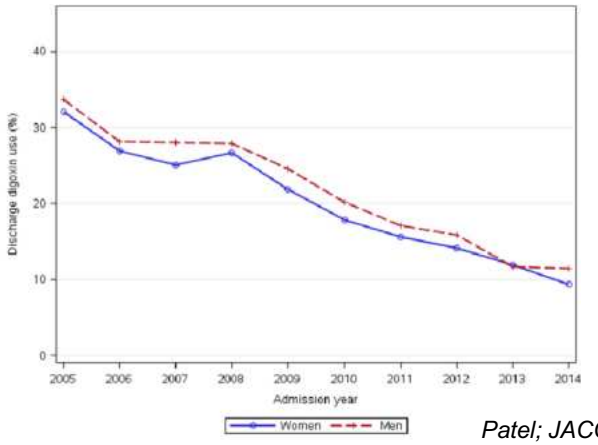
FIGURE 3 **Trends of Digoxin Use Among Patients With or Without Atrial Fibrillation in the HFrEF Patient Population**



AF = atrial fibrillation; HFrEF = heart failure with reduced ejection fraction.



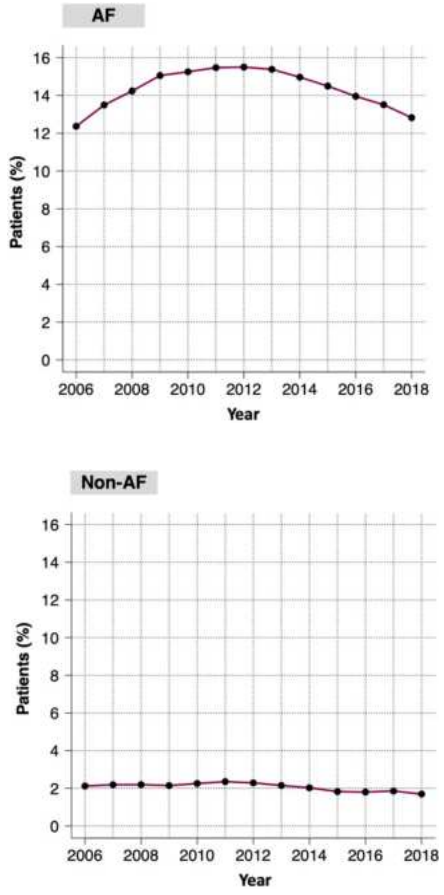
Age above or below 68 years



Sex

Patel; JACC HF; 2016; 4:348

Digoxin Use in HFrEF: Swedish Heart Failure Registry



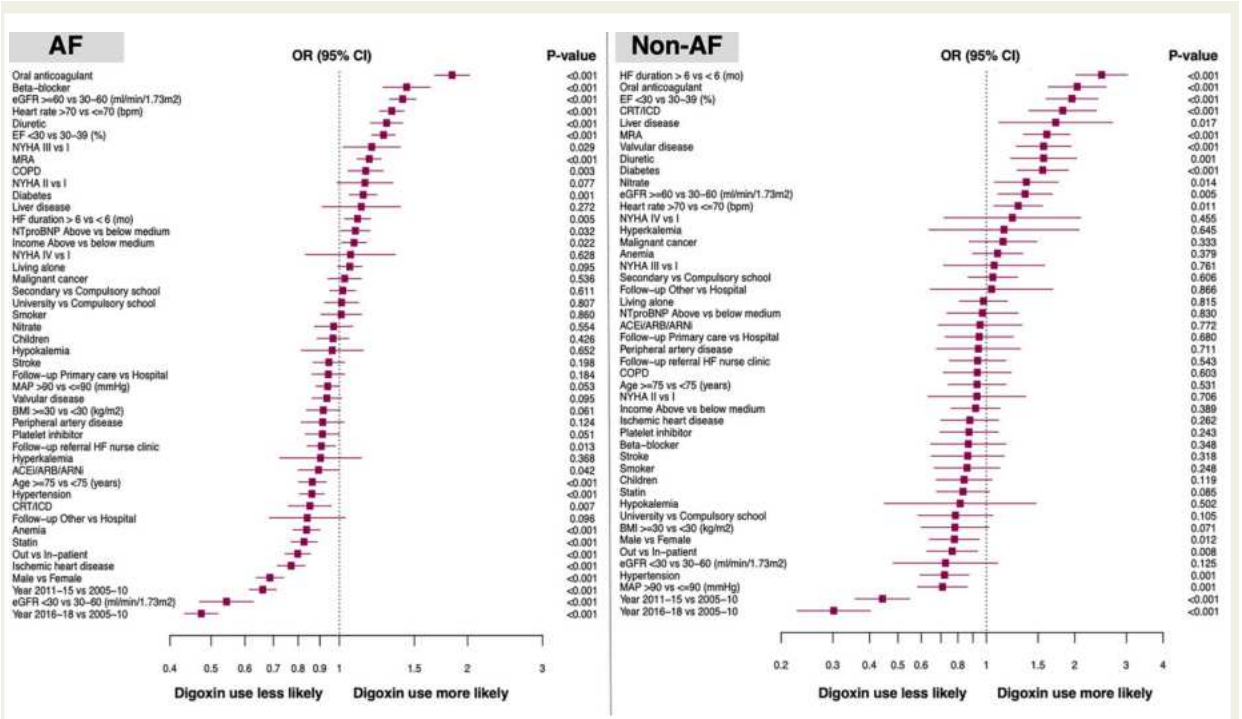
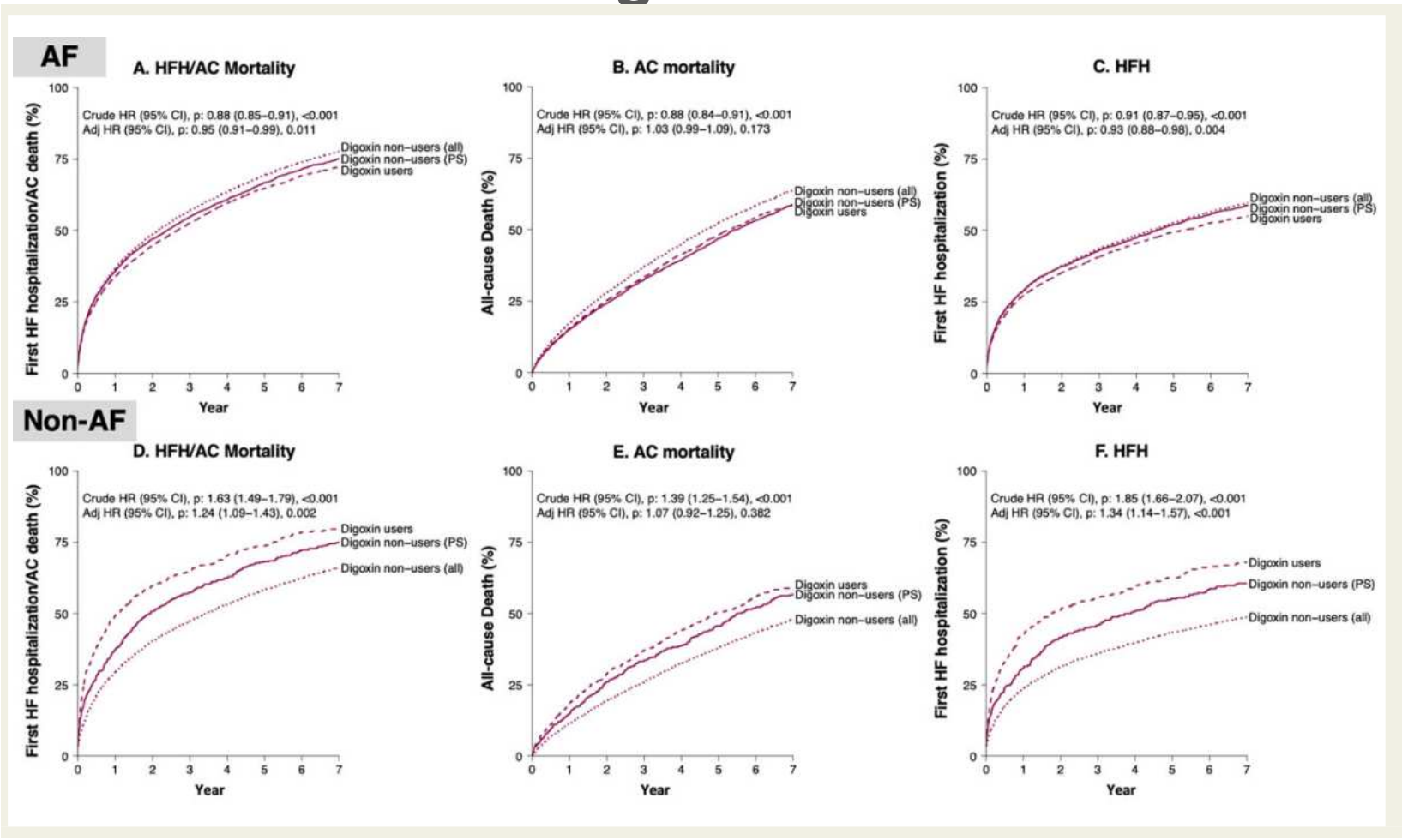


Figure 3 Independent predictors of digoxin use in patients with (left panel) and without atrial fibrillation (right panel). The forest plots report the odds ratios and 95% confidence intervals derived from multivariable logistic regression analyses using digoxin use as the dependent variable. Abbreviations as in *Table 1*.

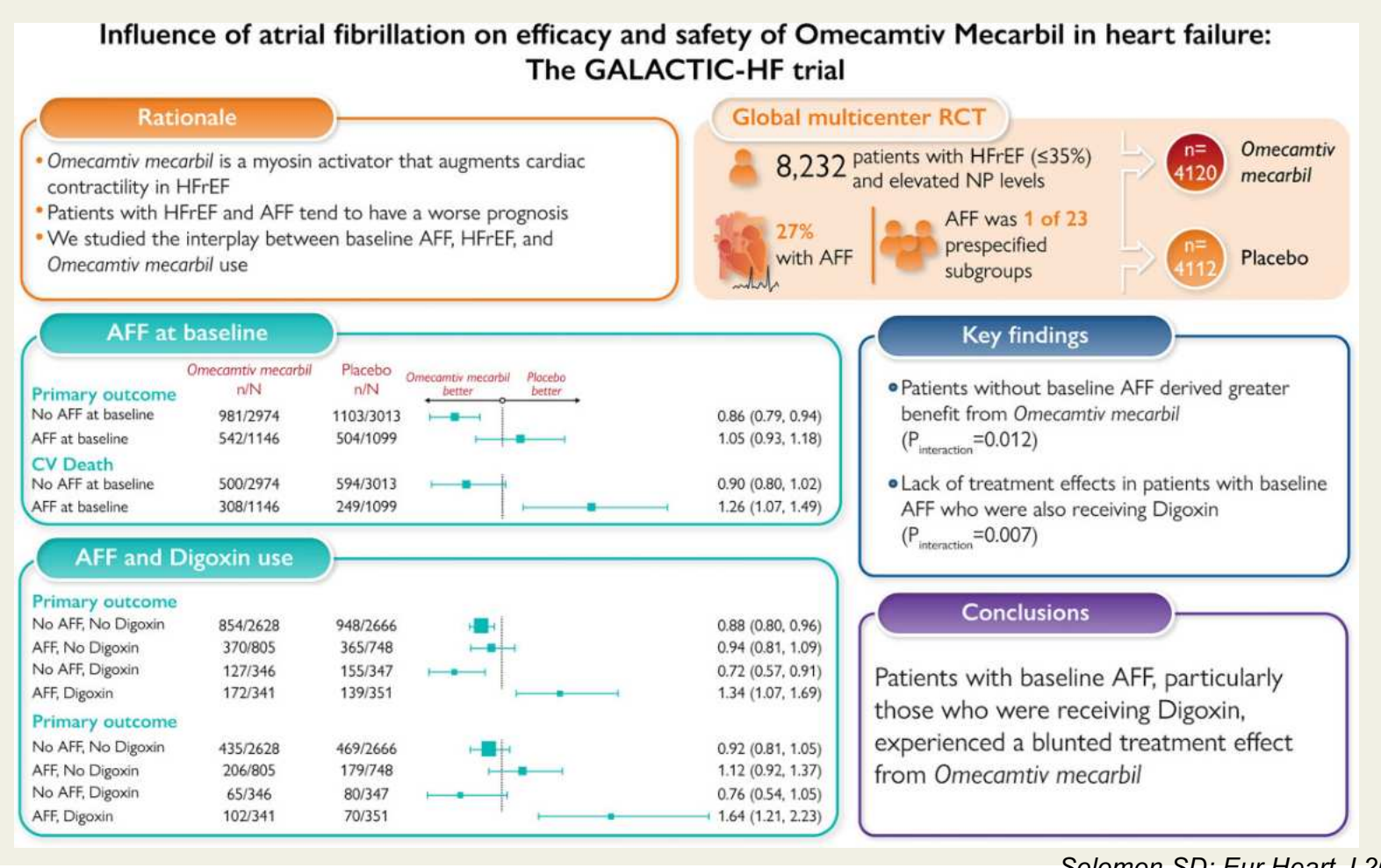
Kapelios; Eur Heart J 2021

Outcomes Based on Digoxin Use



Kapelios; Eur Heart J 2021

Caution: Potential Risks of Combination Therapy



Solomon SD; Eur Heart J 2022

Digoxin and SGLT2 Inhibitors Compared..

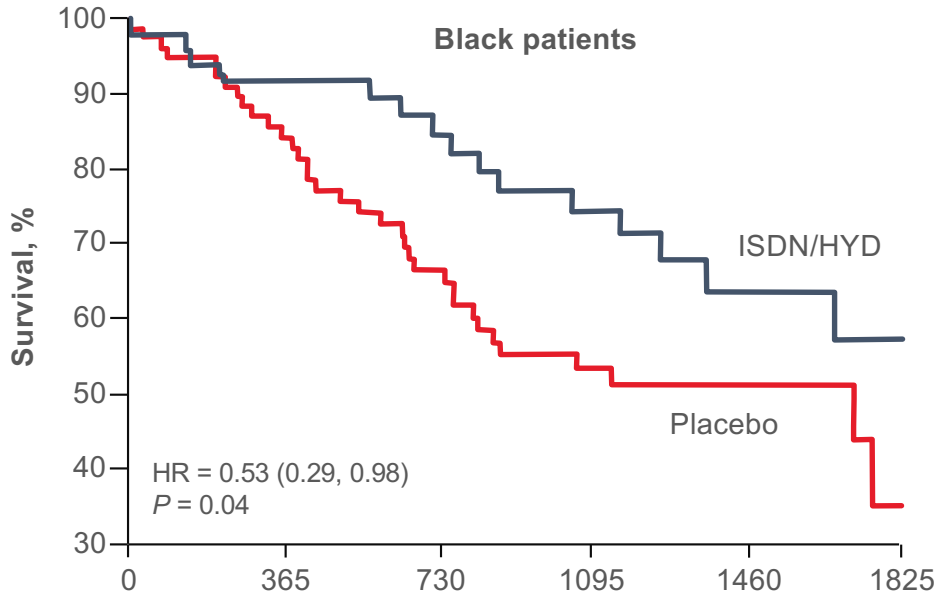
Table 1. Outcomes in Large-Scale Trials of SGLT2 Inhibitors and Digoxin in Patients With Heart Failure and a Reduced Ejection Fraction

	DIG	DAPA-HF	EMPEROR-Reduced
No. of randomized patients	7372	4744	3730
Median duration of double-blind therapy	37 months	18 months	16 months
Effect on all-cause mortality	0.99 (0.91–1.07)	0.83 (0.71–0.97)	0.92 (0.77–1.10)
Effect on cardiovascular deaths	1.01 (0.93–1.10)	0.82 (0.69–0.98)	0.92 (0.72–1.12)
Effect on heart failure deaths	0.88 (0.77–1.01)	Not reported	Not reported
Effect on all-cause hospitalizations	0.92 (0.87–0.98)	Not reported	0.82 (0.74–0.90)
Effect on cardiovascular hospitalizations	0.87 (0.81–0.93)	Not reported	0.75 (0.67–0.85)
Effect on heart failure hospitalizations	0.72 (0.66–0.79)	0.70 (0.59–0.83)	0.69 (0.59–0.81)

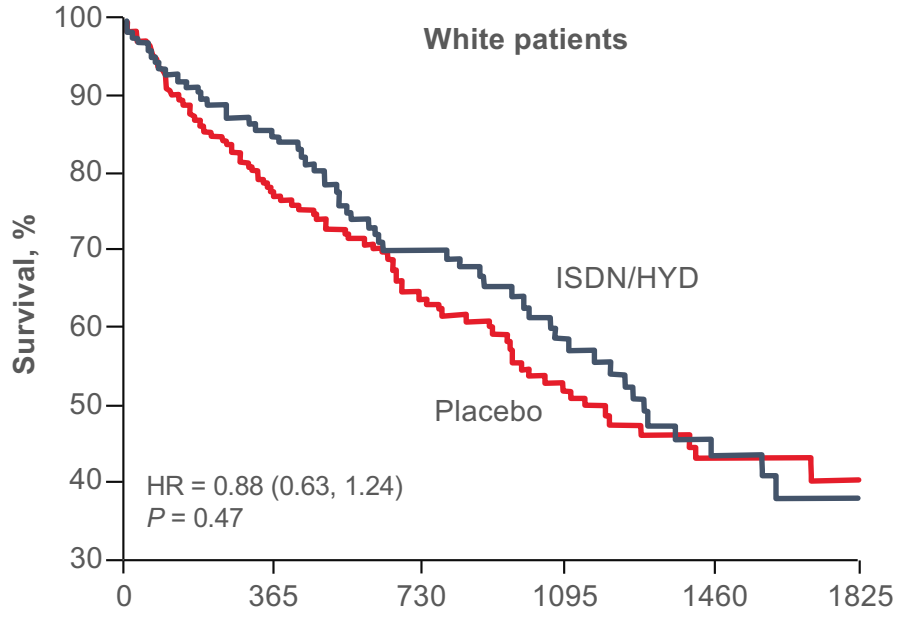
Packer M, JCF 2022

Considering Hydralazine-Nitrates Combinations

Survival in Black patients and White patients in the V-HeFT 1 trial (from Cohn *et al.*[7])



No. at Risk						
ISDN/HYD	49	43	36	28	16	8
Placebo	79	61	44	29	14	3

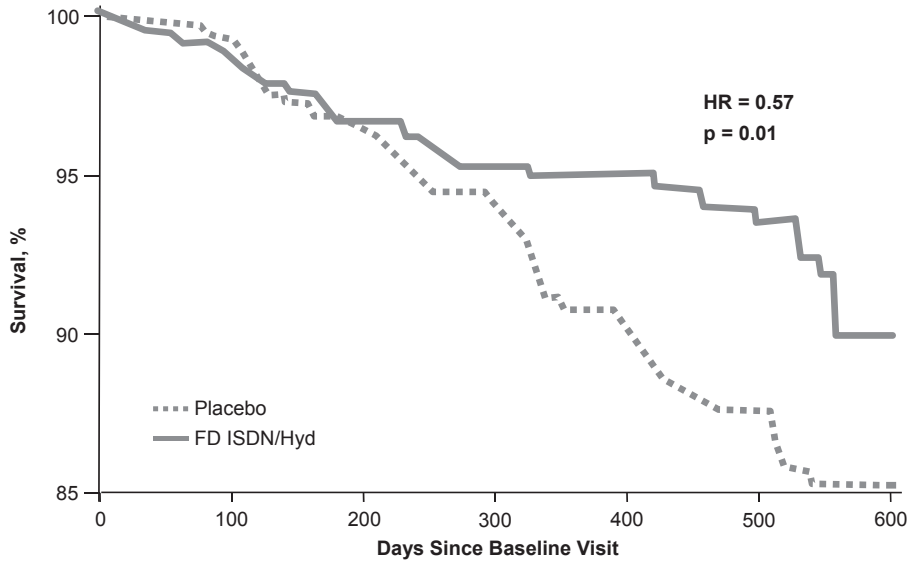


No. at Risk						
ISDN/HYD	132	102	71	42	22	9
Placebo	192	140	91	55	27	8

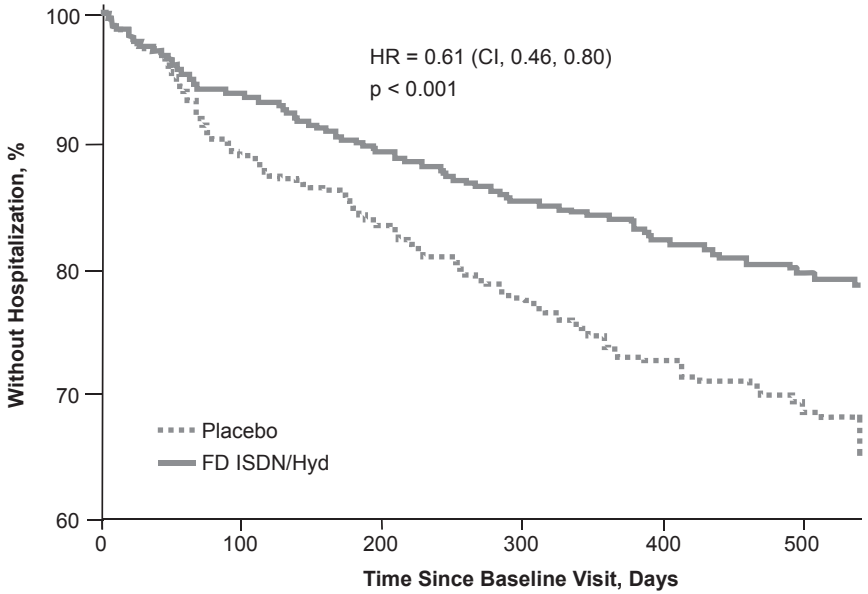
HR, hazard ratio; ISDN/HYD, isosorbide dinitrate/hydralazine

Al-Mohammad A. Hydralazine and nitrates in the treatment of heart failure with reduced ejection fraction. *ESC Heart Fail*. 2019;6(4):878-883. doi:10.1002/ehf2.12459

Considering Hydralazine-Nitrates Combinations



Placebo	532	466	401	340	285	232	24
FD ISDN/Hyd	518	463	407	359	313	251	13



Placebo	532	407	329	264	203	160
FD ISDN/Hyd	518	430	357	305	253	197

Taylor AI; New Engl J Med 2004; 351:2049

Use of Hydralazine-Nitrates in Contemporary Heart Failure Management

Table 4
Percent of participants reaching target dose of hydralazine/nitrate and sacubitril/valsartan by race

	Black				Nonblack			
	Target dose* achieved (patients on therapy)			Eligible patients on target dose	Target dose* achieved (patients on therapy)			Eligible patients on target dose
	Less than 50%	50% to <100%	100% or more	100% or More	Less than 50%	50% to <100%	100% or more	100% or More
Hydralazine/ Nitrate	56%	33%	10%	2%	65%	28%	7%	0.1%
Sacubitril/ Valsartan	33%	36%	29%	8%	49%	29%	19%	4%

* Target total daily doses were as follows: hydralazine 300 mg, nitrate (isosorbide dinitrate) 120 mg, and sacubitril/valsartan 400 mg.

Giblin, Am J Cardiol 2019; 124: 1900

Use of Hydralazine-Nitrates in Contemporary Heart Failure Management

Total number of African American HF admissions screened.

13,011

Final cohort after exlusion criteria.

5,168

Exclusions:

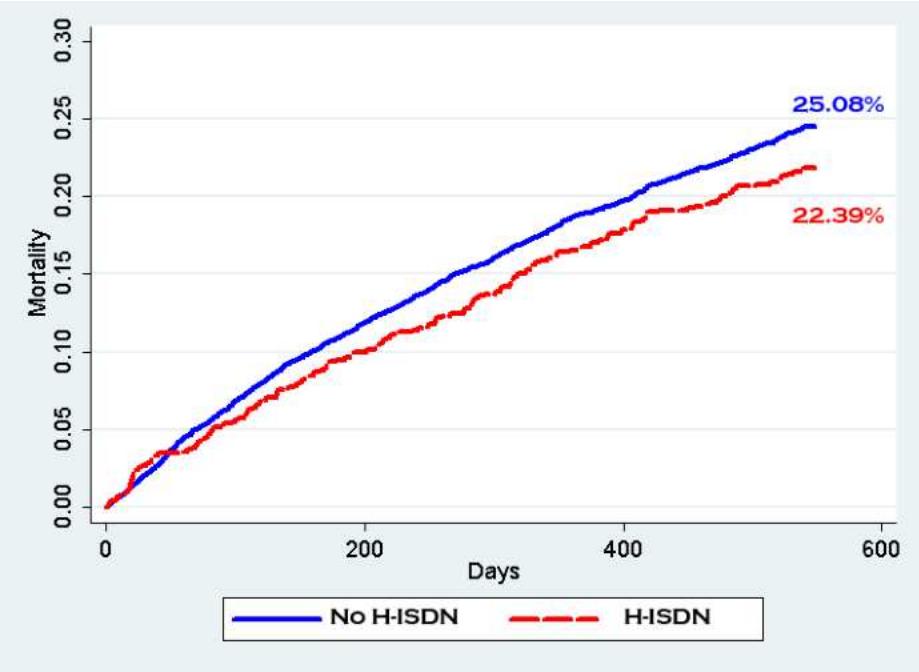
6,116: LVEF ≥ 40

986: Renal failure

522: ACEi and ARB contraindication

109: Comfort care

110: No VA prescriptions in prior 6 months



Ziaeian B. JACC Heart Fail 2017; 5:632

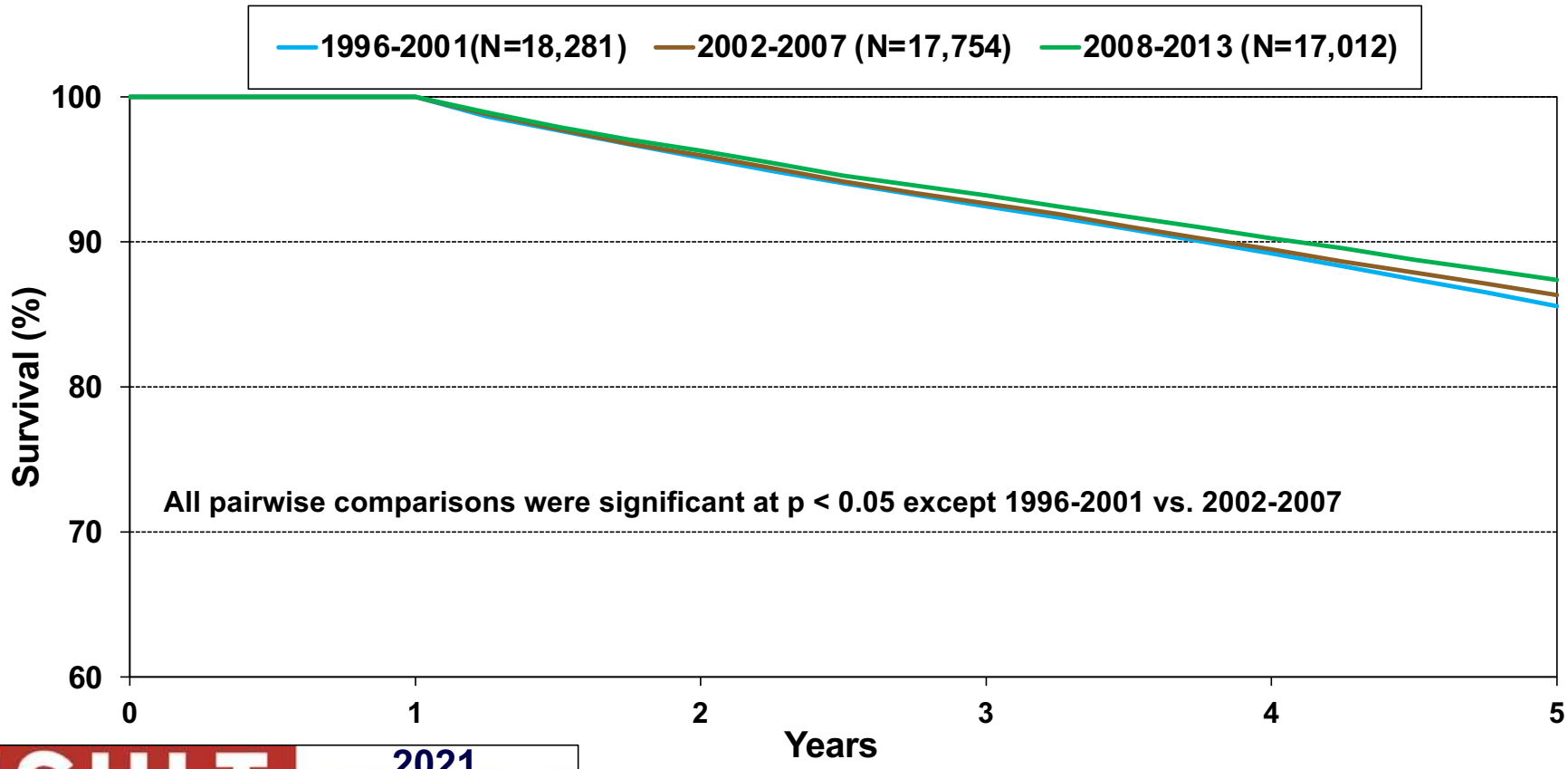
When to Recognize Transition to Advanced Heart Failure " I NEED HELP"

	Factor	Description
I	Inotropes	Previous or ongoing requirement for inotropes
N	NYHA FC OR Natriuretic peptides	Persistently > 3 Persistently elevated>1000
E	End organ dysfunction	Worsening renal or liver dysfunction
E	Ejection fraction	<20%
D	ICD shocks	Recurrent shocks
H	hospitalization	>1 in one year
E	Escalating diuretics	
L	Low BP	Consistently<90 mmHg
P	Prognostic meds	Inability to titrate or initiate

Giblin, J HLT 2019; 124

Adult Heart Transplants

Kaplan-Meier Survival within 5 Years Conditional on Survival to 1 Year By Era (Transplants: Jan 1996 - Jun 2013)



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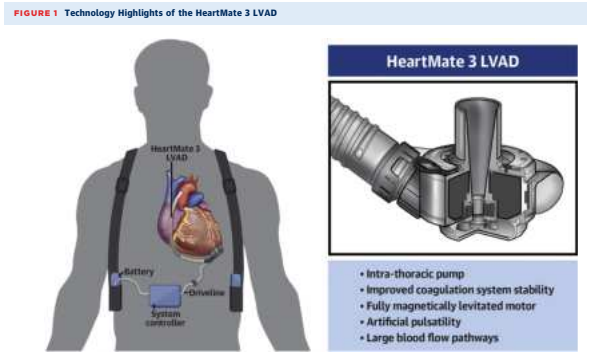
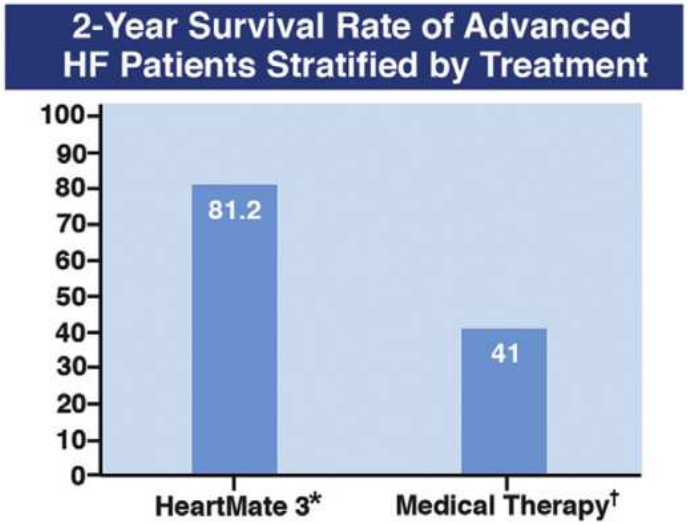
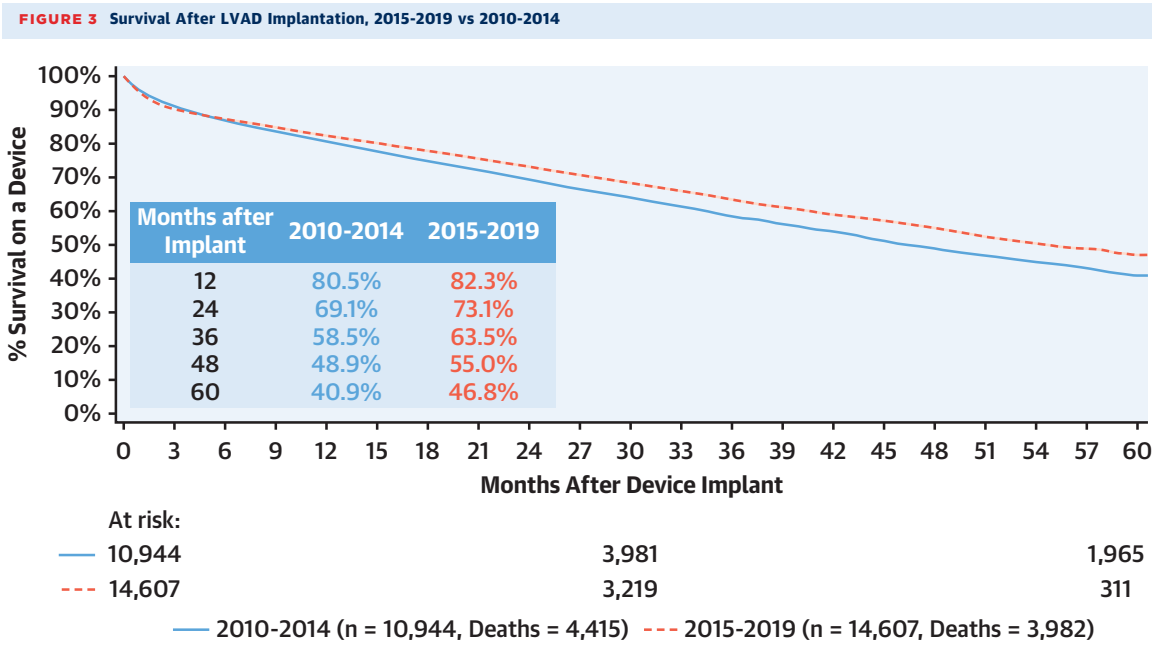
2021
JHLT. 2021 Oct; 40(10): 1023-1072

Note: Y-axis is truncated for clearer presentation

Tends in LVAD Outcomes

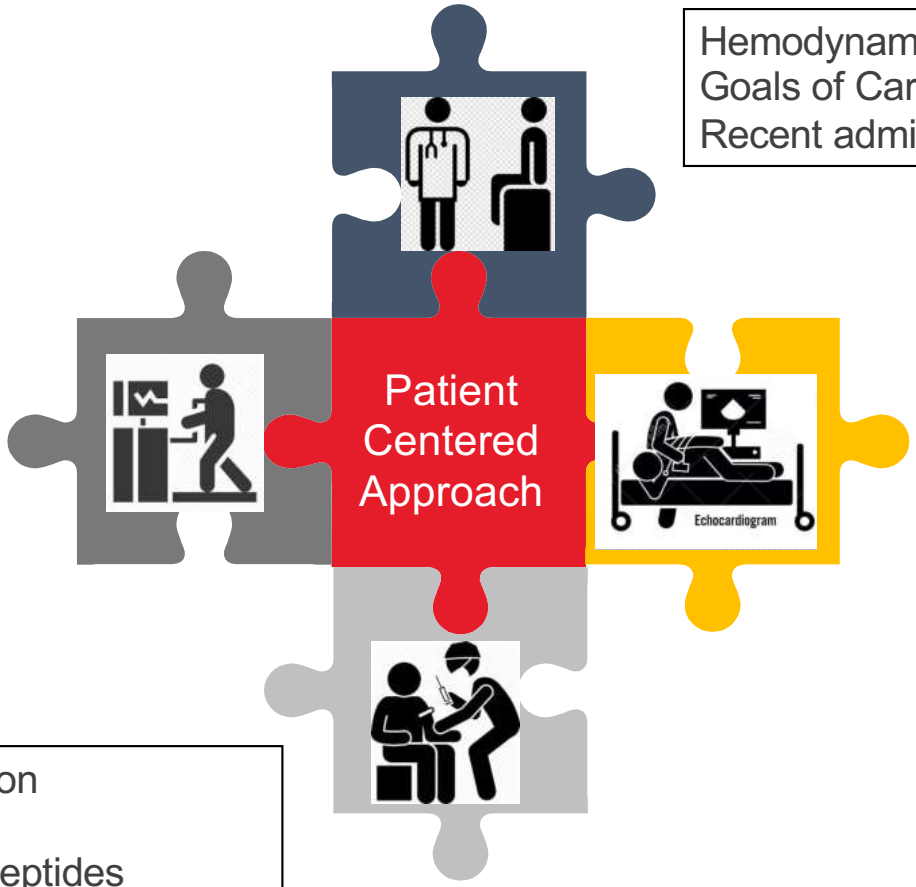






Varshney. JACC 2022;79:1092

Putting it All Together From the Patient's Perspective



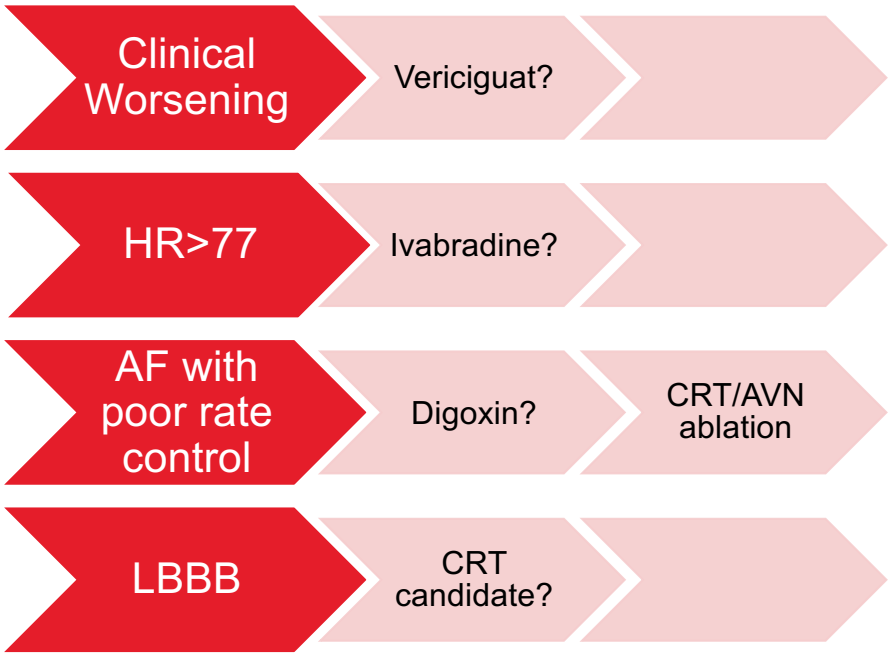
Hemodynamic Profile
Goals of Care
Recent admission/worsening ?

Functional capacity
frailty

QRS duration
Concomitant valve disease
LVEF

Renal function
CBC
Natriuretic peptides

Putting it All Together From the Patient's Perspective



Is there Opportunity to Advance or Initiate 4 Foundational Therapies?

Is the Patient a Candidate for Referral for Advanced Therapies?

Have we sufficiently addressed goals of care and advanced directives?

Summary Points

- Substantial gains evident in the use of four foundational therapies
  - Care gaps exist
    - Have we made every attempt to initiate drug?
    - Have we attempted dose escalation?
    - Underuse continues to exist

- Additional therapies can be personalized to patient goals/unique profile
  - Majority of drugs will provide benefit on reducing HF hospitalization
  - Improvement in quality of live
  - Need to be balanced with potential side effects/risks

- Key to identify patients eligible for interventions that improve mortality
  - Transplant
  - MCS
  - Devices