CHANGING THE FACE OF WORSENING HEART FAILURE

FRIDAY MAY 13, 2022
8:30 – 9:30 a.m. EDT

Welcome and Introductions

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Cardiologist, St. Boniface Hospital
Professor, University of Manitoba
Immediate Past President, Canadian Heart Failure Society
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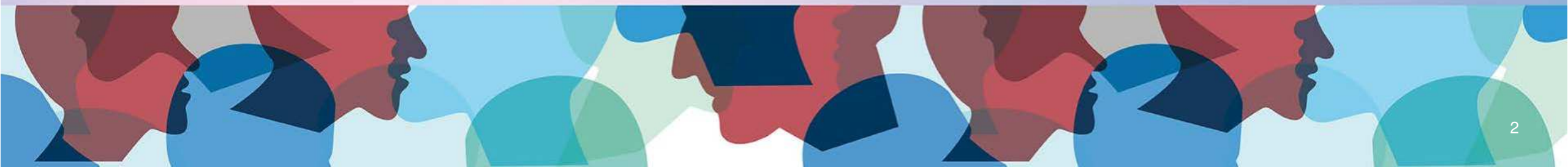

Planning Committee & Faculty

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Immediate Past President, Canadian Heart Failure Society
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Disclosure / Conflict of Interest

Shelley Zieroth, MD, FCCS, FHFSA (hon), FESC, FACC, FHFA, FRCPC

Relationships with for profit and/or non-profit organization:

- **Consulting Fees/Honoraria:** Abbott Vascular, Akcea, Alnylam, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Eli Lilly, HLS Therapeutics, Janssen, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Servier, Vifor, CCS, CHFS, EOCI, Hypertension Canada, Liv, Medscape, Mededgs, Ology, PHRI, Radcliffe, Translational Medicine Academy, Vigour

- **Clinical Trials:** AstraZeneca, Boehringer Ingelheim, Eidos, Novartis, Merck, Servier

Disclosure / Conflict of Interest

Justin Ezekowitz, MBBCH MSc

Relationships with for profit and/or non-profit organization:

- **Consulting Fees/Honoraria:** American Regent, Amgen, Astra Zeneca, Bayer, Bristol Myers Squibb/Pfizer, Merck, Novartis, Sanofi, Servier, Ortho-Biotech/Johnson & Johnson
- **Clinical Trials:** American Regent, Amgen, Bayer, Merck, Novartis, Ortho-Biotech/Johnson & Johnson
- **Speaker Fees:** Bristol Myers Squibb/Pfizer, Servier
- **Research Grants:** American Regent, Amgen, Bayer, Bristol-Myers Squibb, eko.ai, Merck, Novartis, Sanofi
- **Educational Grants:** Servier
  - VICTORIA: Executive Committee
  - The VICTORIAL trial was funded by Bayer and Merck/MSD
  - Full breakdown of disclosures available at thecvc.ca

Disclosure / Conflict of Interest

Lisa Mielniczuk, MD, FRCPC

Relationships with for profit and/or non-profit organization:

- **Clinical Trial:** Amgen, Bayer
- **Speakers Bureau/Honoraria/Advisory Board:** Janssen, Novartis, Bayer, Canadian Heart Failure Society, Pulmonary Hypertension Society of Canada, Canadian Cardiovascular Society CPD Committee

Disclosure/ Conflict of Interest

Javed Butler, MD, MPH, MBA
Consulting fees from:

- Abbott
- Adrenomed
- Amgen
- Applied Therapeutics
- Array
- AstraZeneca
- Bayer
- Boehringer Ingelheim
- CVRx
- G3 Pharma
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- Janssen
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- Luitpold
- Medtronic
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- Novartis
- Novo Nordisk
- Relypsa
- Sequana Medical
- and Vifor Pharma

Disclosure of Commercial Support

This program was made possible through an educational grant from Bayer to the Canadian Heart Failure Society.

Mitigating Potential Bias

- Bias in this program has been mitigated using independent content validation as follows:
  - All content has been reviewed by a cardiovascular expert steering committee and expert reviewers
  - All data has been sourced from evidence that is clinically accepted
  - All support used in justification of patient care recommendations conform to generally accepted standards, clinical practice guidelines and consensus statements

Accreditation

- This symposium is being presented as part of the Heart Failure Update 2022 Congress as an Accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada and approved by the Canadian Cardiovascular Society. You may claim a maximum of 1.0 hours (credits are automatically calculated).

Learning Objectives

- Recognize the unmet need and apply evidence-based strategies to close the gap on worsening heart failure
- Describe the epidemiology and risk factors that contribute to worsening heart failure
- Define and diagnose worsening heart failure across a spectrum of patient presentations
- Evaluate when to initiate therapy to improve outcomes in patients with worsening heart failure

Agenda

TIME (EDT)	TOPIC	SPEAKER
8:30 am	**Welcome and Introductions**	Shelley Zieroth, MD
8:35 am	**Worsening Heart Failure Through the Lens of Epidemiology**	Justin Ezekowitz, MD
8:45 am	**NT-proBNP as a Biomarker-Guided Strategy for Better HF Management**	Lisa Mielniczuk, MD
9:00 am	**Patient Management Strategies and Treatment Options: What, When, How?**	Javed Butler, MBBS
9:15 am	**Panel Discussion and Q&A**	Moderated by Shelley Zieroth, MD
9:30 am	**Closing Remarks**	Shelley Zieroth, MD

Worsening Heart Failure Through the Lens of Epidemiology

Justin A. Ezekowitz, MBBCH, MSc
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Co-Director, Canadian VIGOUR Centre
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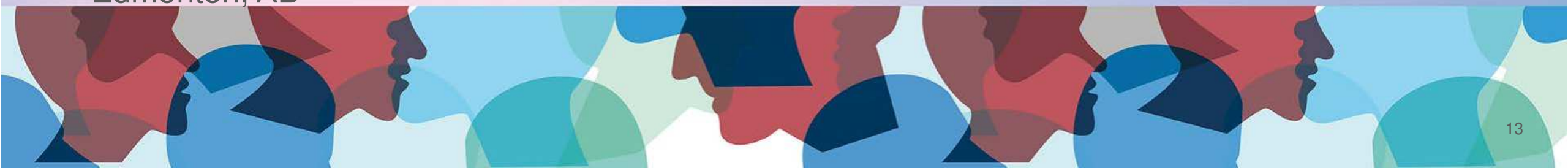


HF: Epidemiology and Impact

Highly prevalent

>60 million people worldwide have HF[1]

This is more than 5× the number of cancer patients globally[2]

1 in 5

lifetime risk of developing HF for people at 40 years old[3]

High rates of morbidity and mortality

50% of HFrEF patients will **die within 5 years** of diagnosis[4]

Despite advances in management, HF remains as **malignant as some common cancer** (prostate, bladder, and breast)[5]

Significant strain on healthcare system

HF is the **#1 reason for hospitalisation** in patients aged >65 years globally[6]

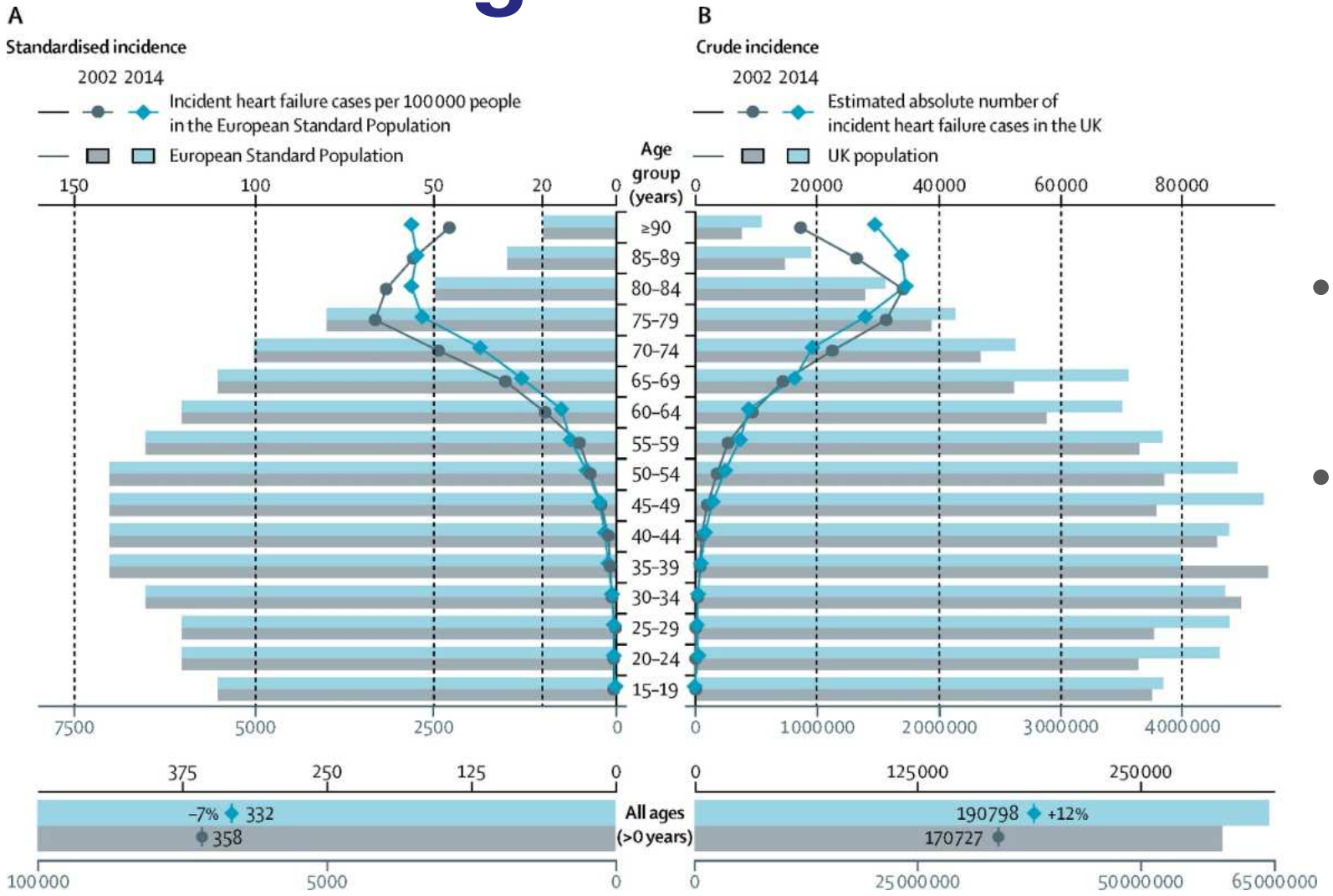
24% median 30-day HF readmission rate[7]

60% of HF patients rehospitalised for HF within 1 year[8]

HCP, healthcare practitioner; HF, heart failure; HFrEF, HF with reduced ejection fraction; SoC, standard of care.

1. Vos D et al. *Lancet.* 2017;390:1211–1259; 2. Globocan 2018. Available at http://gco.iarc.fr. Accessed April 2020; 3. Mozaffarian D et al. *Circulation.* 2016;133:e38–e360; 4. Benjamin EJ et al. *Circulation.* 2019;139:e56–e528; 5. Mamas MA et al. *Eur J Heart Fail.* 2017;19:1095–1104; 6. Maggioni AP et al. *Eur J Heart Fail.* 2016;18:402–410; 7. Krumholz HM et al. *Circ Cardiovasc Qual Outcomes.* 2009;2:407–413; 8. Chun S et al. *Circ Heart Fail.* 2022;5:414–421.

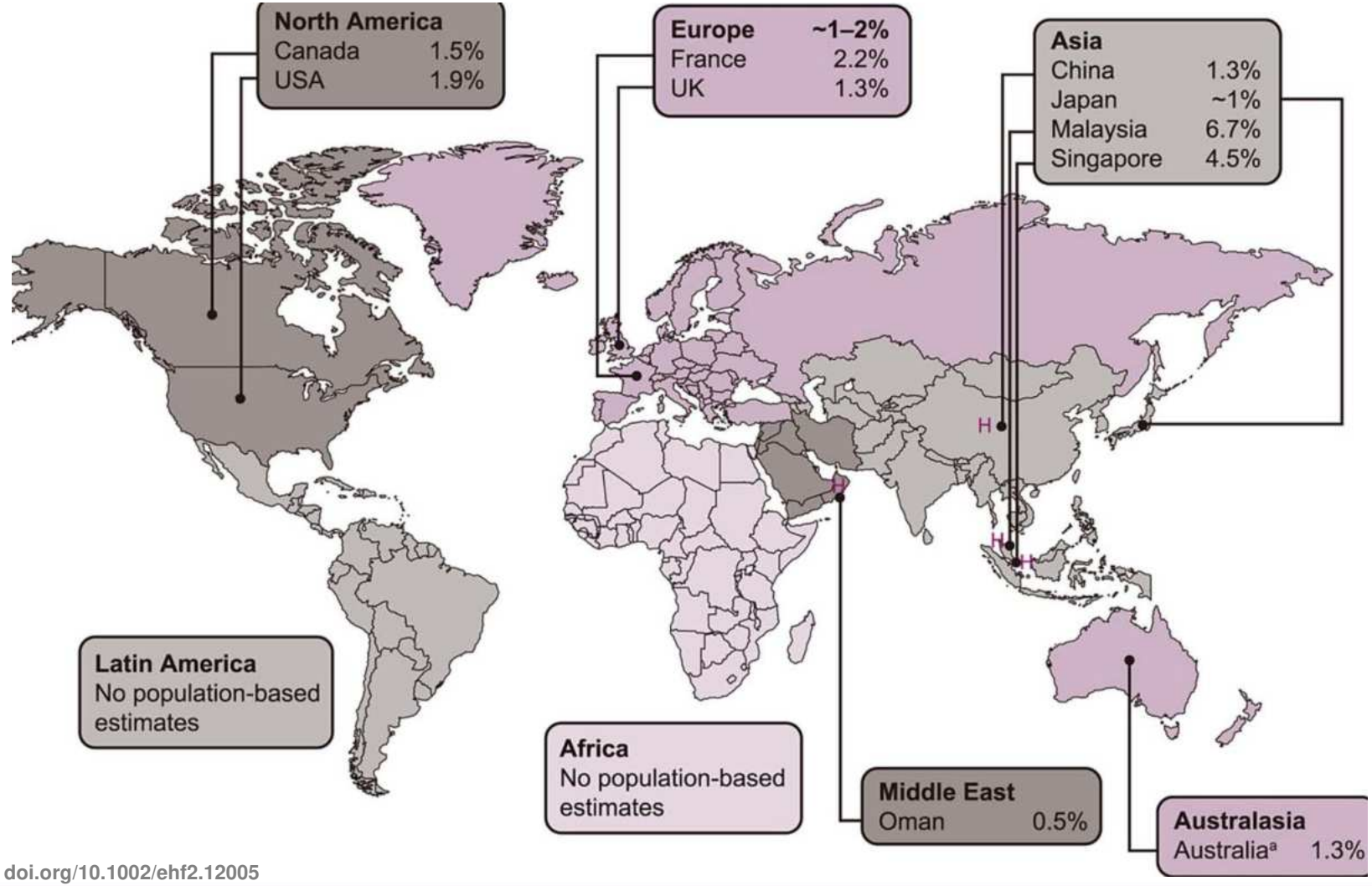
Increasing Prevalence



- Prevalence ~1.5% of adult population
- 23% increase in absolute # of people living with HF over a decade

The Lancet 2018 391572-580DOI: (10.1016/S0140-6736(17)32520-5)

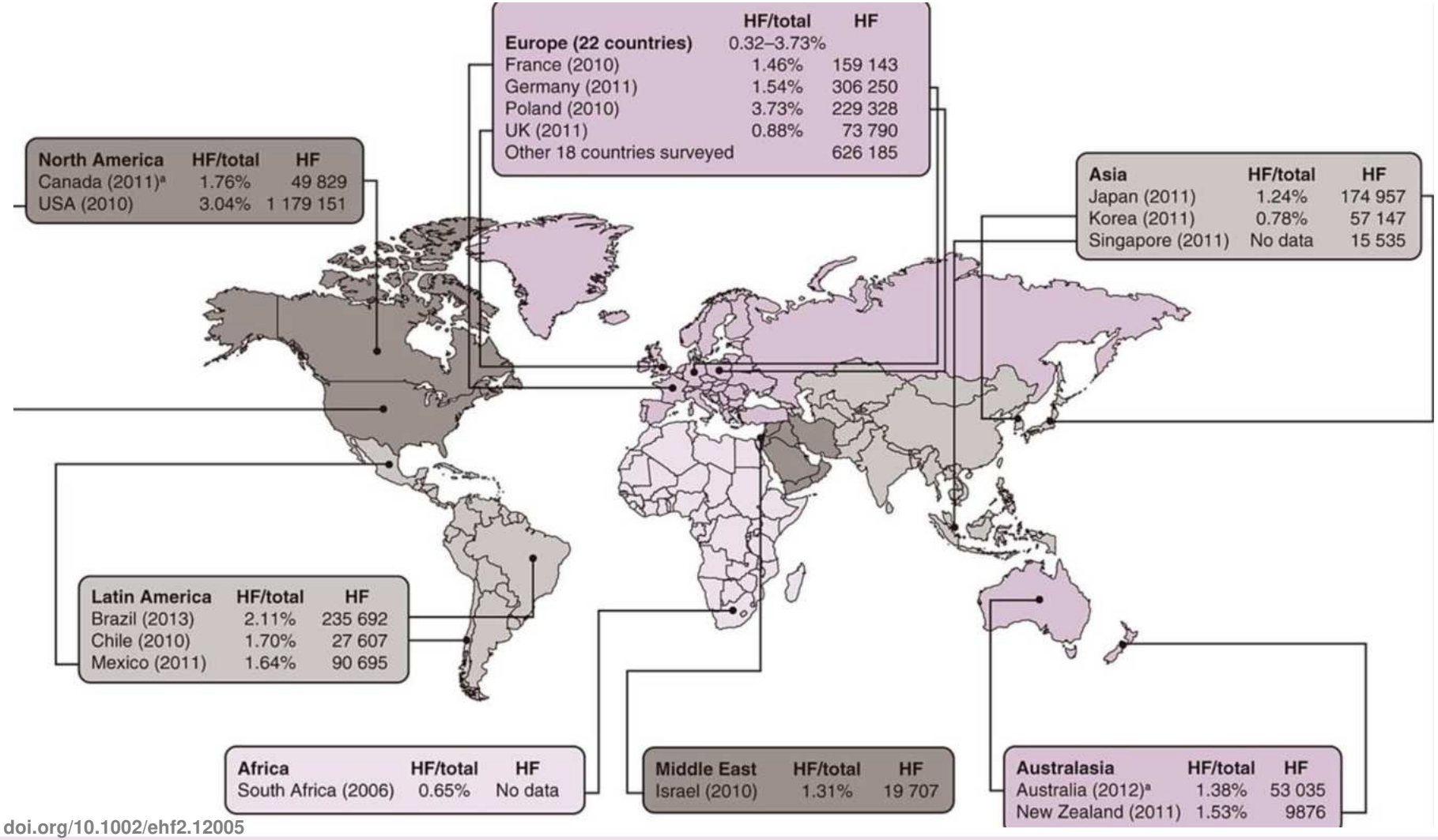
…global disease by prevalence…



~23 million patients

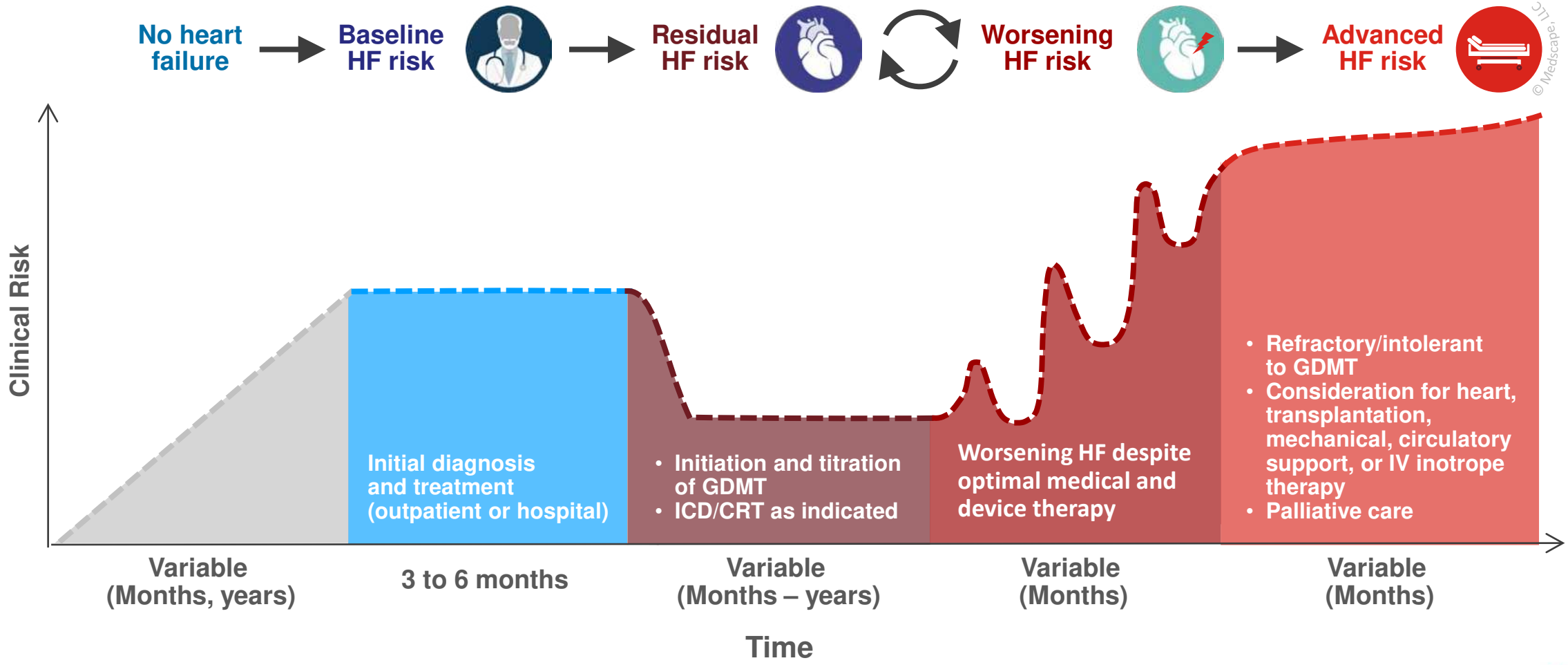
Ponokowski doi.org/10.1002/ehf2.12005

…and by hospitalizations…..



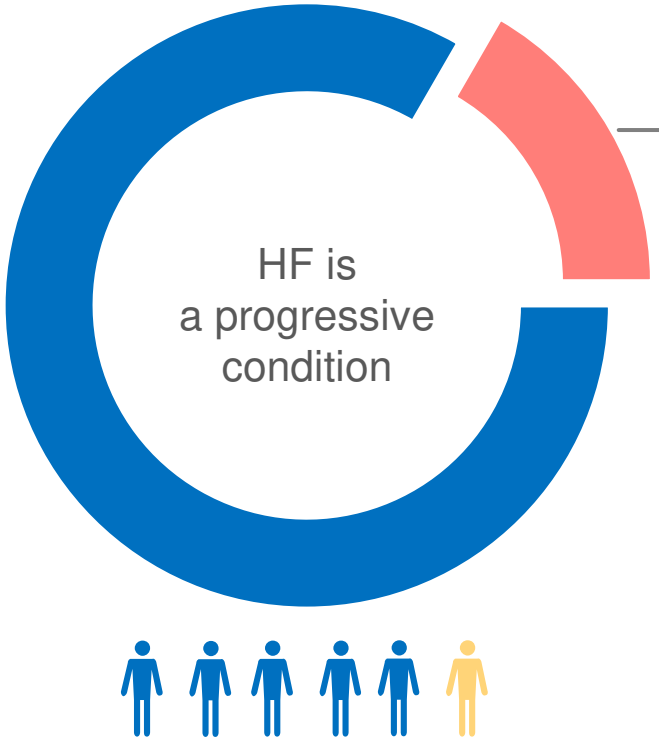
Ponokowski doi.org/10.1002/ehf2.12005

HF, A Progressive Disease



Adapted from Gheorghiade et al. *Am J Cardiol.* 2005 and Cowie et al. *ESC Heart Fail.* 2014.
*Adjustment of and potential addition to current therapy.
a. Gheorghiade M et al. *Am J Cardiol.* 2005;96:11G-17G; b. Cowie MR et al. *ESC Heart Fail.* 2014;1:110-145.

Worsening HF Events



Worsening HF events[a-b]

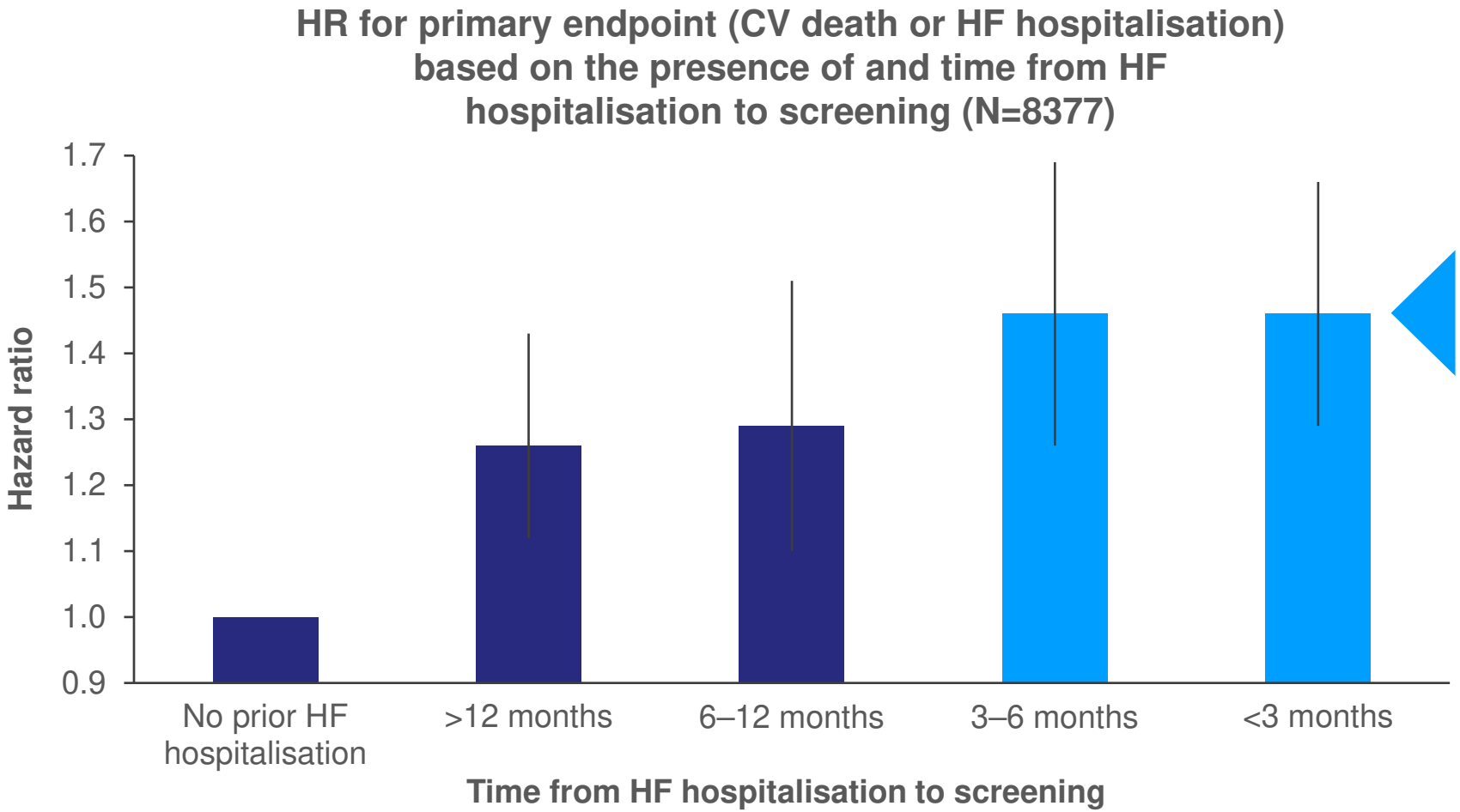
Characterised by:

- Development of progressively **escalating signs and symptoms of HF** requiring intensification of therapy
- Experience of a prior worsening HF event
  - Need for IV diuretics, regardless of setting
  - HF hospitalisation
  - Need for an urgent HF visit

1 in 6 patients develop worsening chronic HF within 18 months of initial diagnosis*[a]

a. Butler J, et al. *J Am Coll Cardiol*. 2019;73:935–944; b. Greene SJ, et al. *JAMA Cardiol*. 2018;3:252–259.

PARADIGM-HF: Risk of CVD/HFH and a Recent Hosp.



Risk of CV death or HF hospitalisation was 46% higher in patients with recent hospitalization vs those with no prior hospitalisation

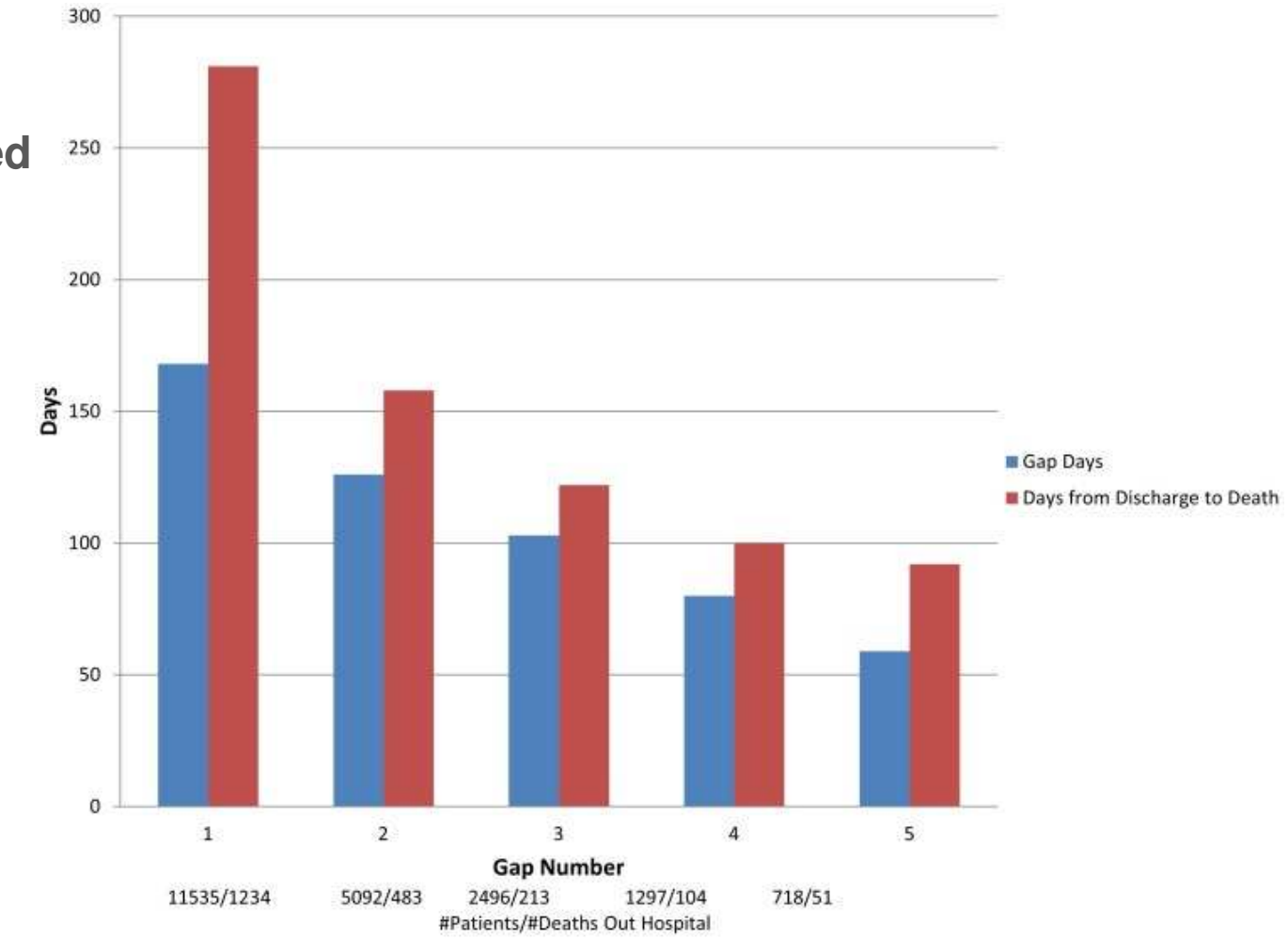
CV, cardiovascular; HF, heart failure; HR, hazard ratio.

1. Solomon SD et al. *JACC Heart Fail.* 2016;4:816–822.

HF: Mind the Gap

Alberta Health

Population-based cohort of 40,667 patients



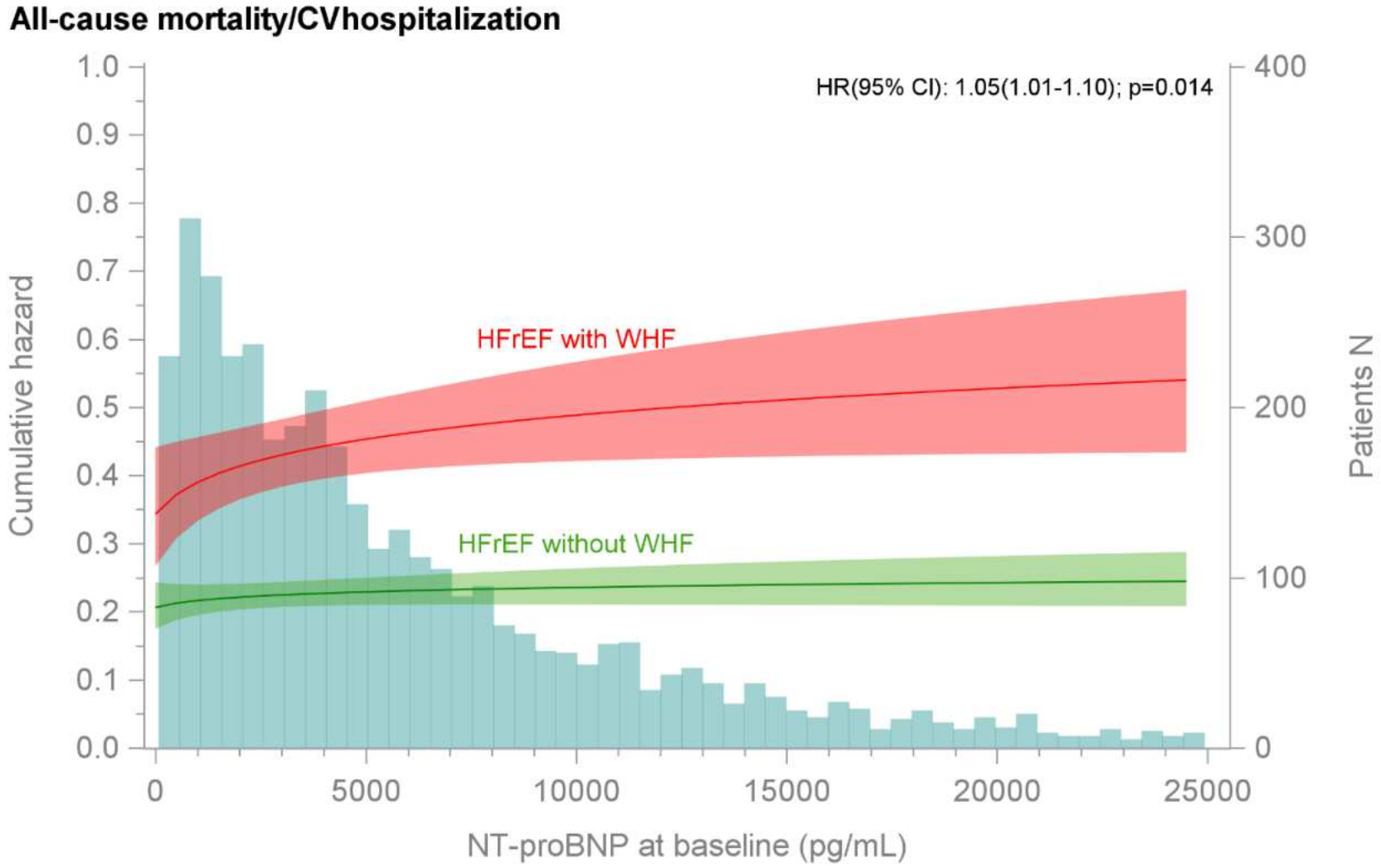
168
Median gap days between 1st and 2nd hospitalizations

Average reduction of 28 gap days for each re-hospitalization

60
Median gap days between 4th and 5th hospitalizations

Bakal JA, *PLoS One*. 2014

WHF in Canada



Sepehrvand, submitted, 2022

Summary

- Highly prevalent globally
- Major hospitalization impact
- Gaps in care in the delivery of the best medications for right patient
- Uncertainty / challenges in clinical care exist

NT-proBNP as a Biomarker-Guided Strategy for HF Management

Lisa M. Mielniczuk, MD, FRCPC

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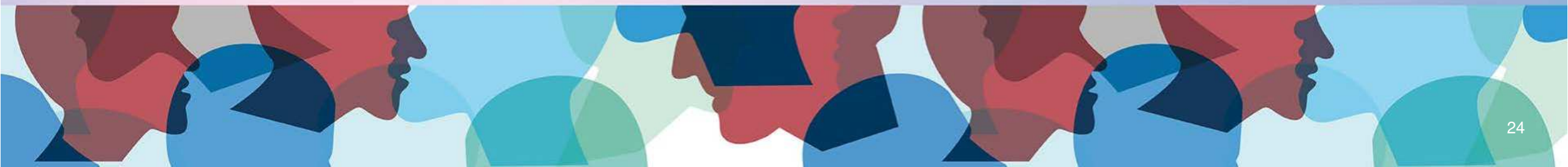
Ottawa, ON



A Recent Clinical Case: Mr. NS

- 76-year-old male with a history of NICM and HFrEF
  - Diagnosed initially in 1997
  - Mild CAD (30% LAD/RCA)
  - CRT-D in 2007
- Paroxysmal atrial fibrillation
- Chronic kidney disease (creatinine 160-170)
- Echo 2020: LVDD 6.2 cm with EF 20%
  - Grade 2 diastolic dysfunction
  - Moderate RV dysfunction
  - 1 + MR with 3+ TR
  - RVSP 30 mmHg

Medications:

- Amiodarone 100 mg daily
- Apixiban 5 mg bid
- Atorvastatin 20 mg daily
- Bisoprolol 2.5 mg daily
- Empagliflozin 10 daily
- Furosemide 80 mg bid
- Sacubitril-valsartan 97-103 mg bid
- Spironolactone 25 mg daily

Can we predict his future risk?

- Baseline FC II symptoms
- Walks 30 min daily
- Baseline BP 85-95 systolic with HR 60-70
- No ER visits or admissions >1 year
- Baseline NTproBNP:
  - 2016: 2938 ng/L
  - 2018: 3348 ng/L
  - 2021: 4507 ng/L

The Next 6 Months…

Worsening symptoms:
- Diuretics increased
- Metolazone added
- Referral for TV clip
- Declined advanced therapies

Recurrent worsening:
- 2 visits at Rapid Intervention Clinic for IV diuretics
- Regular Metolazone
- Spironolactone discontinued

- Stabilization of weight gain
- New baseline NYHA III

Progressive deterioration
- Entresto held
- SGLT2 I held
- Admitted to hospital

Echo: LVEF 15-20%. LVDD 6.2 cm
Moderate RV dysfunction
Torrential TR

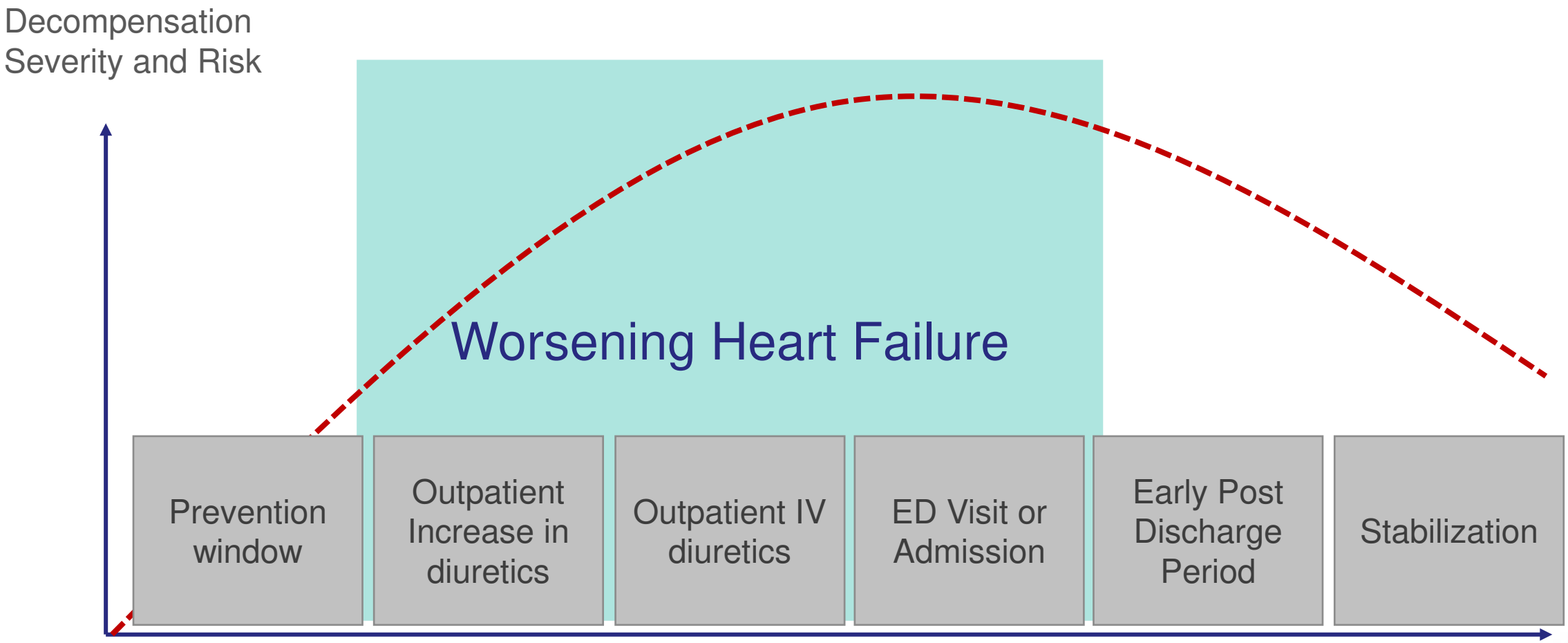
Echo: LVEF 20%, LVDD 6.7
Severe RV dysfunction
Torrential TR

	July	Aug	Sept	January
NTproBNP	6527ng/L	8561	5915	9595
Cr	170-180 umol/l	190	173	251-286
eGFR	36	29	33	18

Questions for Consideration?

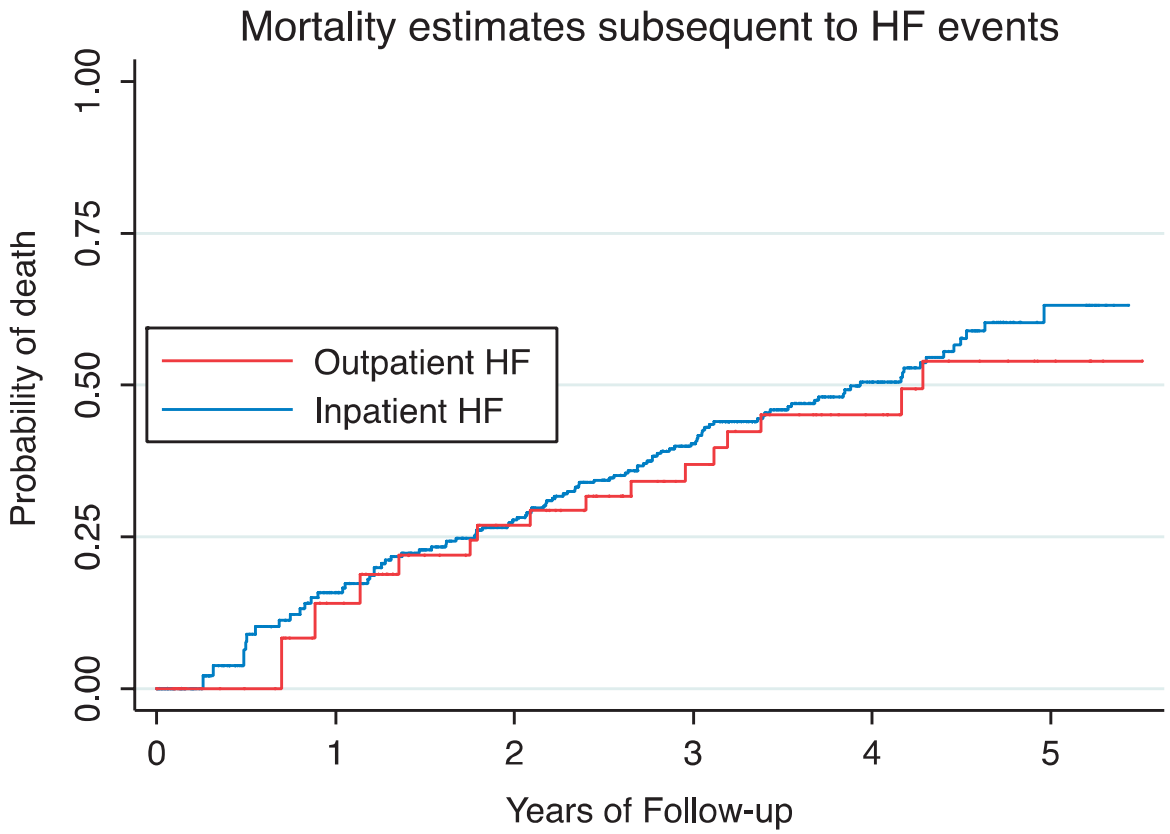
- When /How do we define worsening heart failure?
- Was serial NT-proBNP testing helpful in this case?
- Could we have changed the trajectory of this patient's course?

Worsening Heart Failure



Worsening HF in MADIT-CRT

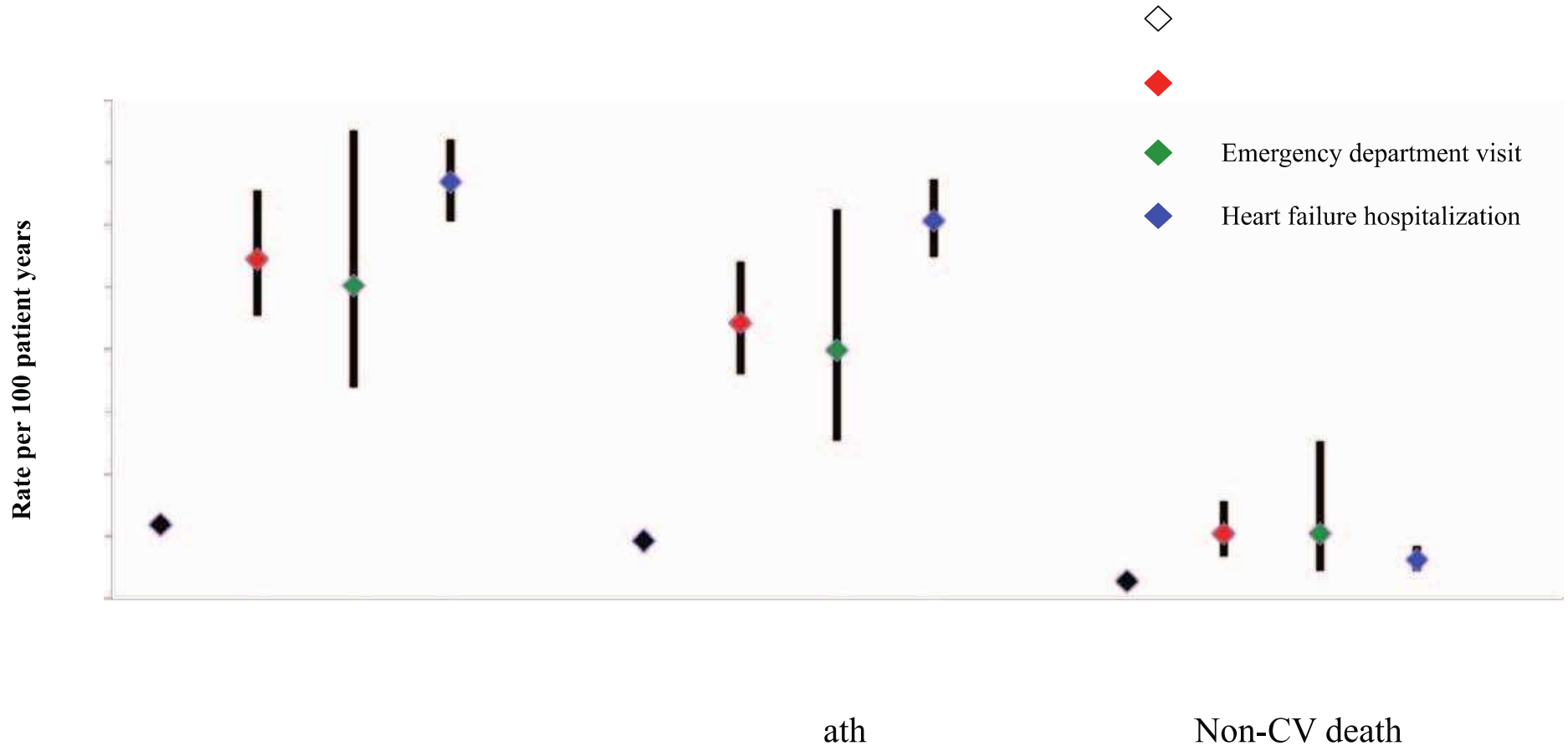
B



Number at risk						
Outpatient HF	0	17	31	23	15	5
Inpatient HF	0	108	180	135	76	13

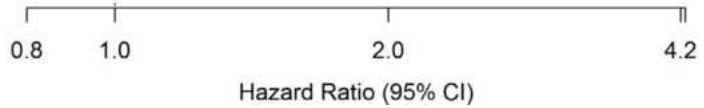
Skali H, Eur J Heat Fail 2014; 16:560-65

Worsening HF in PARADIGM-HF



One-Year Mortality after Intensification of Outpatient Diuretic Therapy

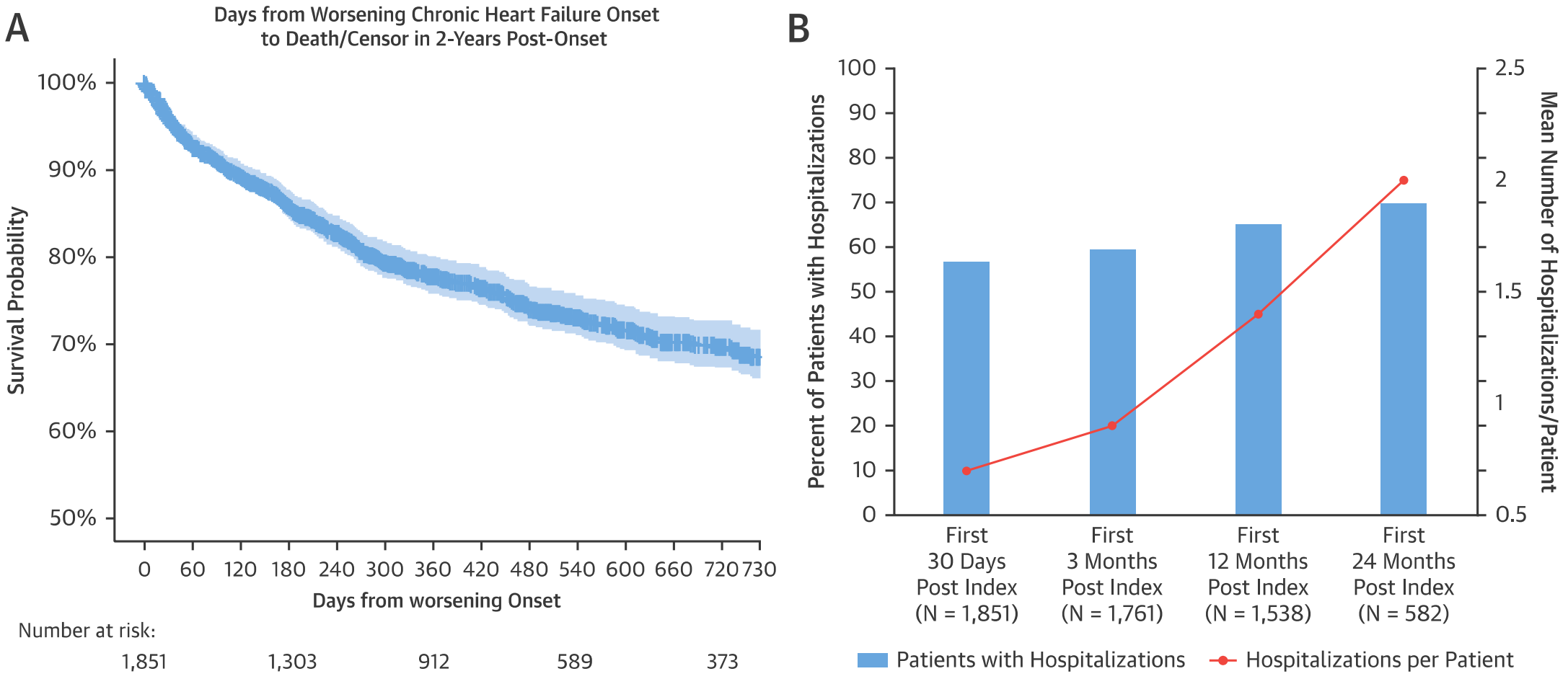
Time since HF diagnosis	Event	$N_{patients}$	N_{deaths} (%)	Hazard ratio (95%-CI)	P-value
Year 1	No worsening	53,794	3,944 (7.3)	1	
	HF hospitalization	3,160	420 (13.3)	1.88(1.70-2.08)	<0.001
	Diuretic intensification	4,517	567 (12.6)	1.49(1.36-1.62)	<0.001
	Both events	942	176 (18.7)	2.31(1.99-2.69)	<0.001
Year 2	No worsening	41,557	2,897 (7.0)	1	
	HF hospitalization	1,122	195 (17.4)	2.39(2.07-2.77)	<0.001
	Diuretic intensification	2,575	357 (13.9)	1.67(1.50-1.87)	<0.001
	Both events	426	83 (19.5)	2.33(1.87-2.90)	<0.001
Year 3	No worsening	32,393	2,340 (7.2)	1	
	HF hospitalization	719	120 (16.7)	2.06(1.71-2.47)	<0.001
	Diuretic intensification	1,800	233 (13.0)	1.48(1.29-1.69)	<0.001
	Both events	285	68 (23.9)	2.95(2.31-3.75)	<0.001
Year 4	No worsening	24,956	1,679 (6.7)	1	
	HF hospitalization	525	90 (17.1)	2.23(1.80-2.76)	<0.001
	Diuretic intensification	1,244	171 (13.8)	1.68(1.44-1.97)	<0.001
	Both events	225	55 (24.4)	3.24(2.48-4.25)	<0.001
Year 5	No worsening	19,185	1,323 (6.9)	1	
	HF hospitalization	348	61 (17.5)	2.19(1.69-2.84)	<0.001
	Diuretic intensification	931	155 (16.7)	1.99(1.68-2.36)	<0.001
	Both events	155	30 (19.4)	2.15(1.49-3.09)	<0.001



Madalaire; JAHA 2020

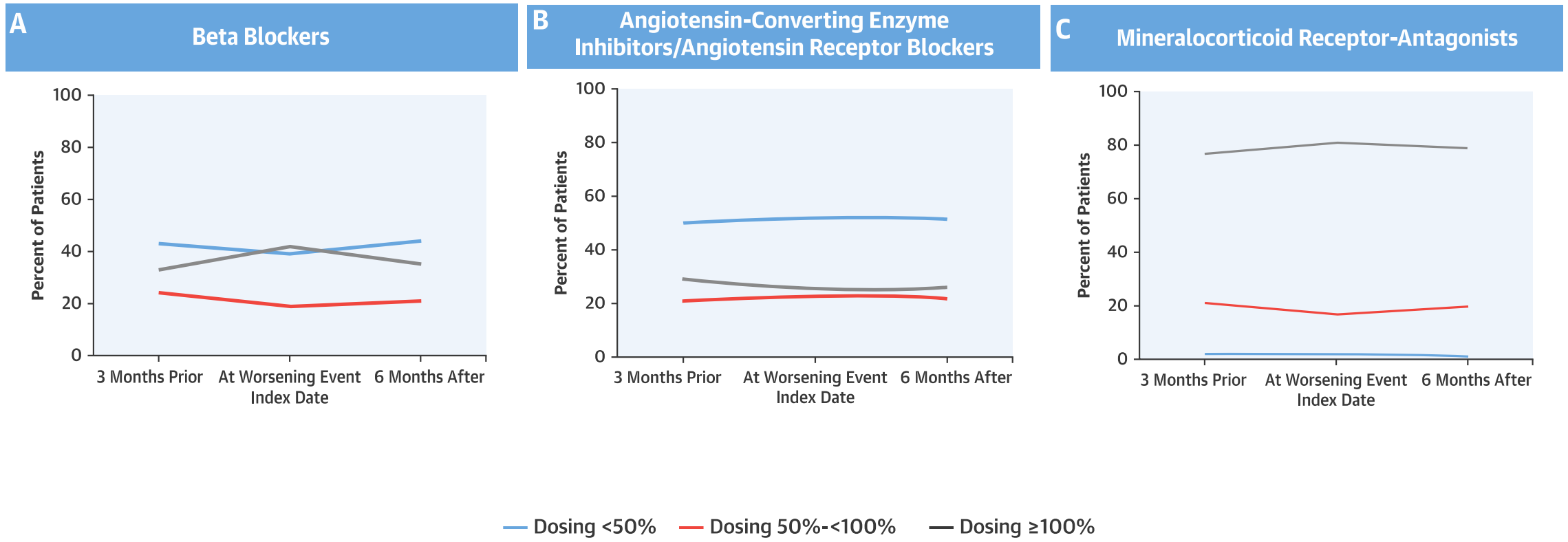
Clinical Course of Patients with HFrEF and Worsening HF

FIGURE 4 Outcomes for Patients With Worsening Heart Failure



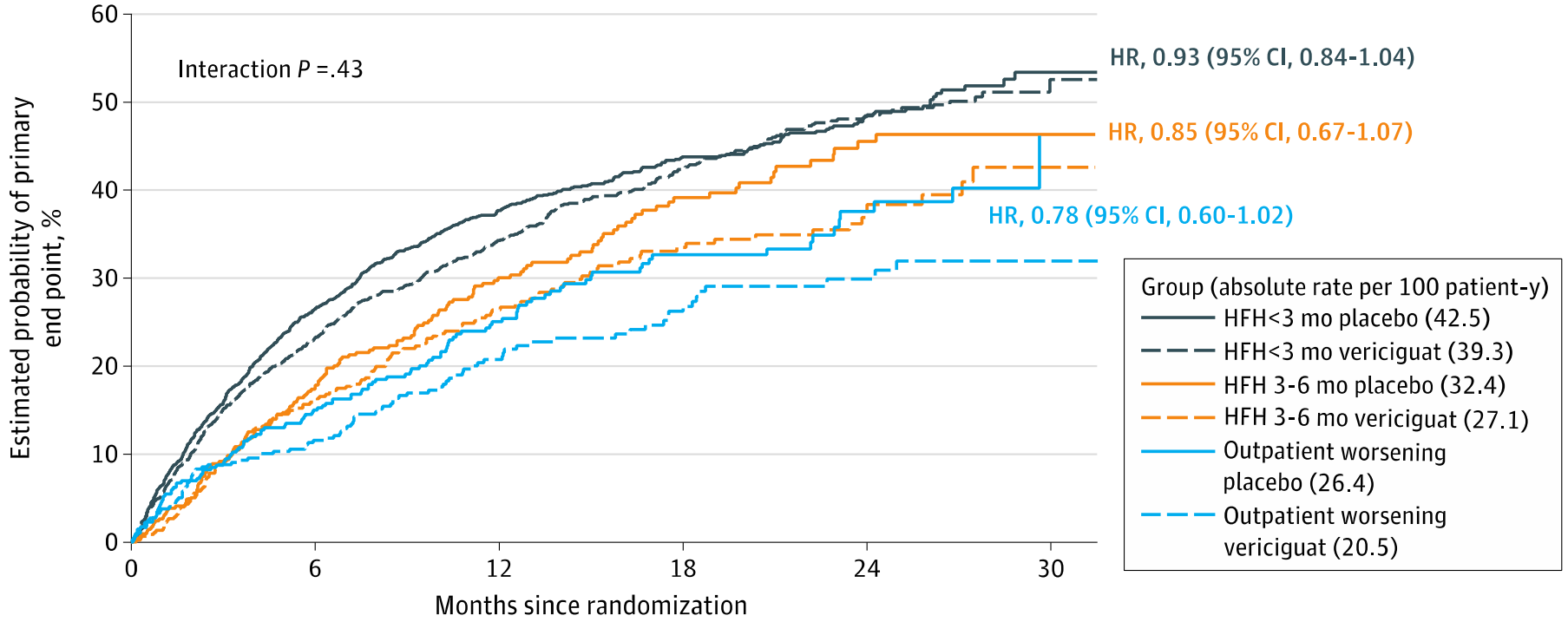
Butler, J. JACC 2019;73:935

Optimization of Medical Therapy Following an Acute Worsening Event



Butler, J. et aL. J Am Coll Cardiol. 2019;73(8):935-44.

Worsening HF Events in VICTORIA

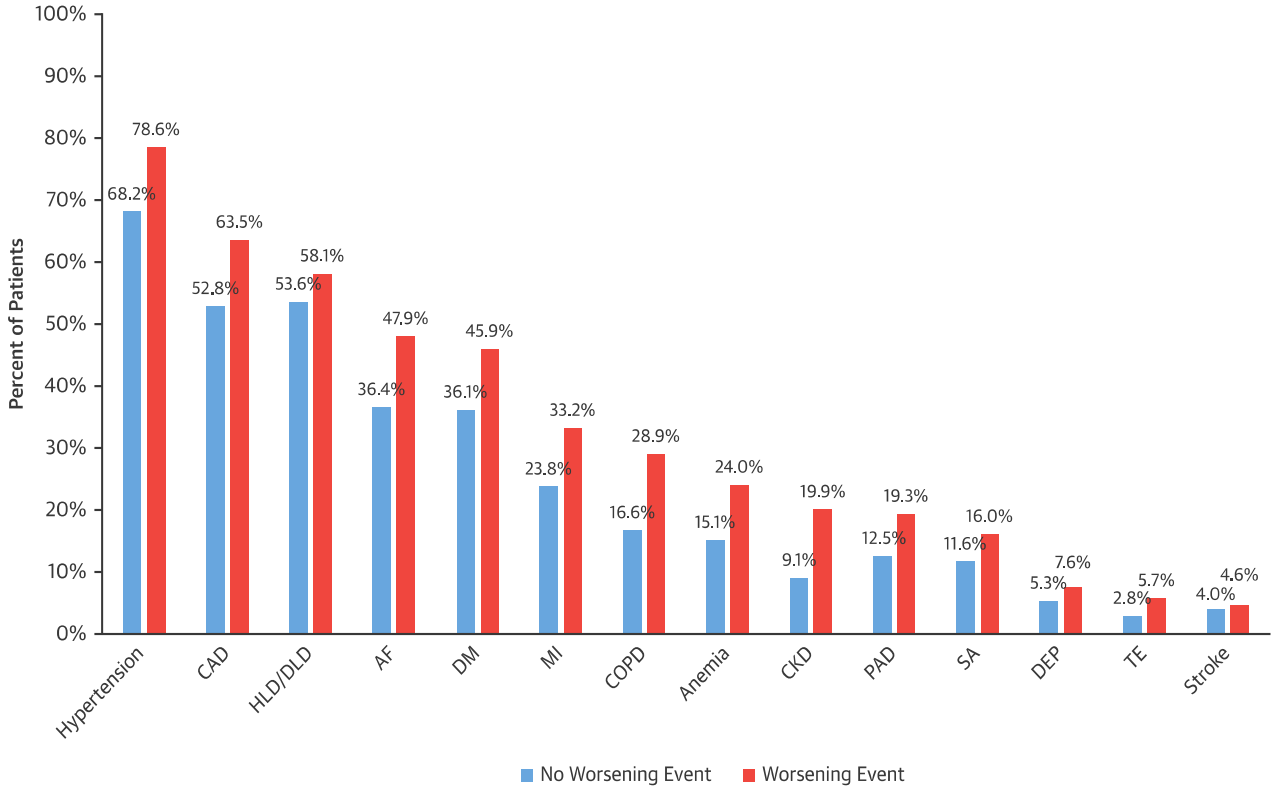


No. at risk

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

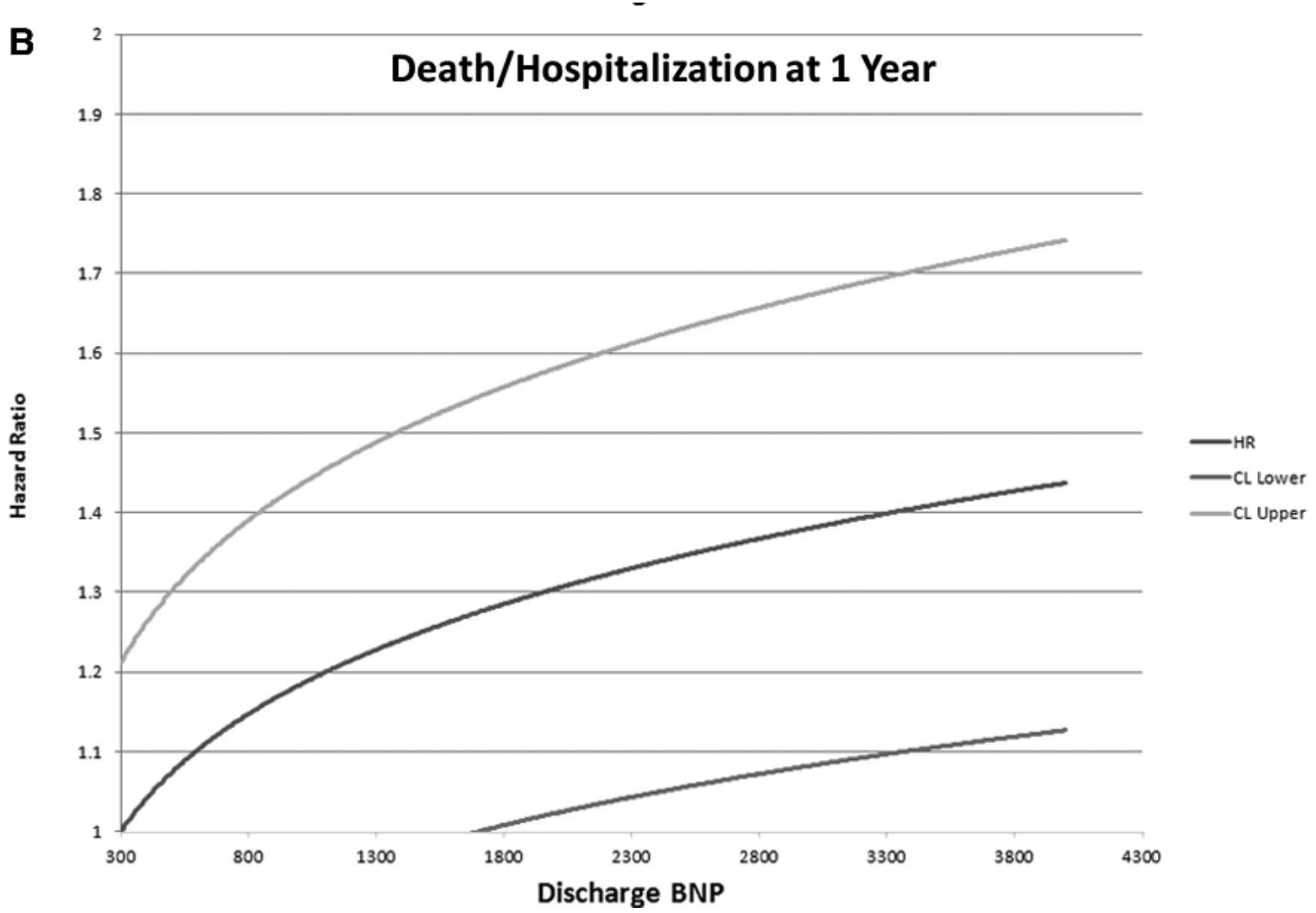
How Do I Recognize Worsening Heart Failure?



- **Who is at Risk?**
  - Multiple co-morbidities
  - Lower EF
  - Absence of GDMT
  - Suboptimal doses of GDMT
- **What does Worsening HF look like?**
  - Escalation of diuretics
  - Urgent visit requiring IV diuretics
  - ER visit
  - Admission

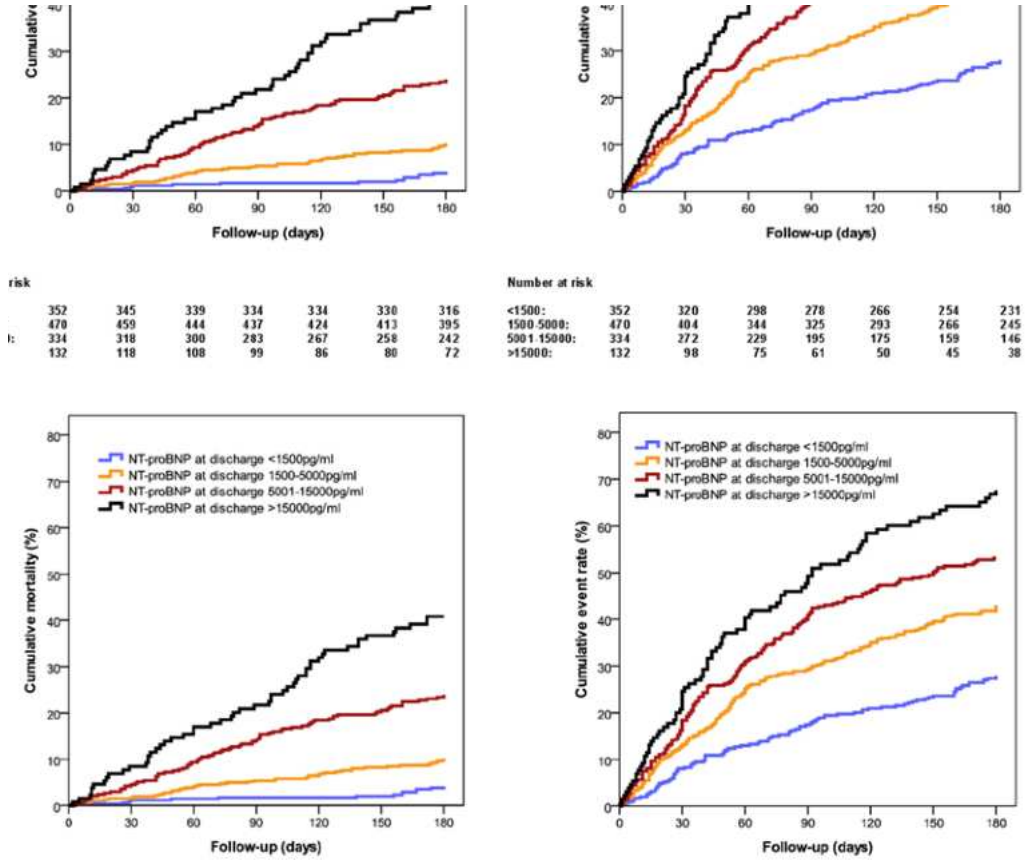
Butler, J. JACC 2019;73:935

Natriuretic Peptides Drive Prognosis in Hospitalized Patients



Kociol R, Circ Heart Fail 2011; 628-36

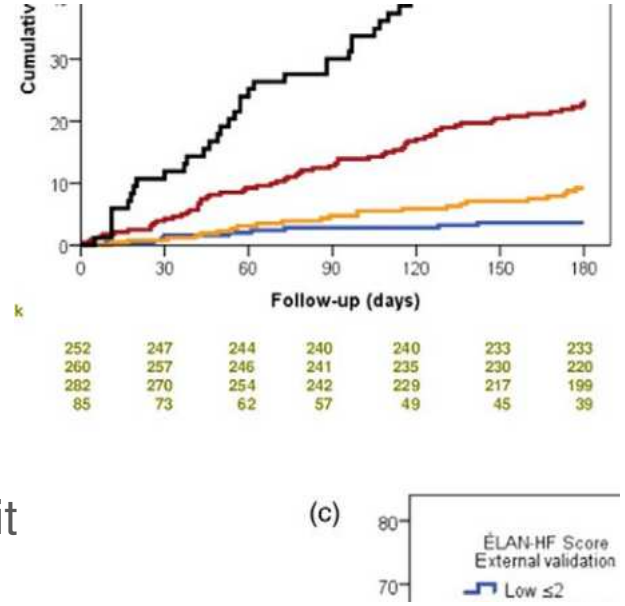
Natriuretic Peptides Drive Prognosis in Hospitalized Patients



Risk Score:

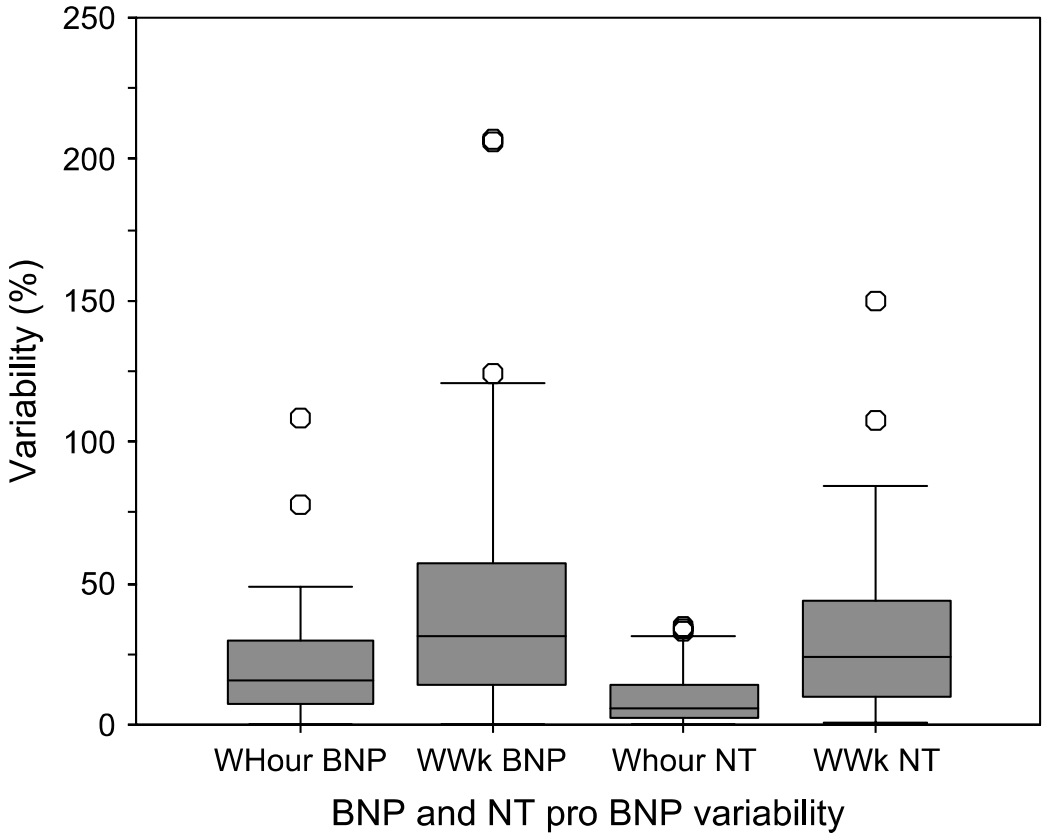
- NT-proBNP reduction <30%
- Absolute value
  - >15,000 (4)
  - 5001-15000 (3)
  - 1500-5000 (1)
- Age>75 years
- Edema at admission
- SBP<115 mmHg at admit
- Na<130 at admit
- Urea at discharge >15
- FC III/IV at discharge

All Cause Mortality



Salah K, Heart 2014; 100:115

Biologic Variability in Natriuretic Peptide Levels



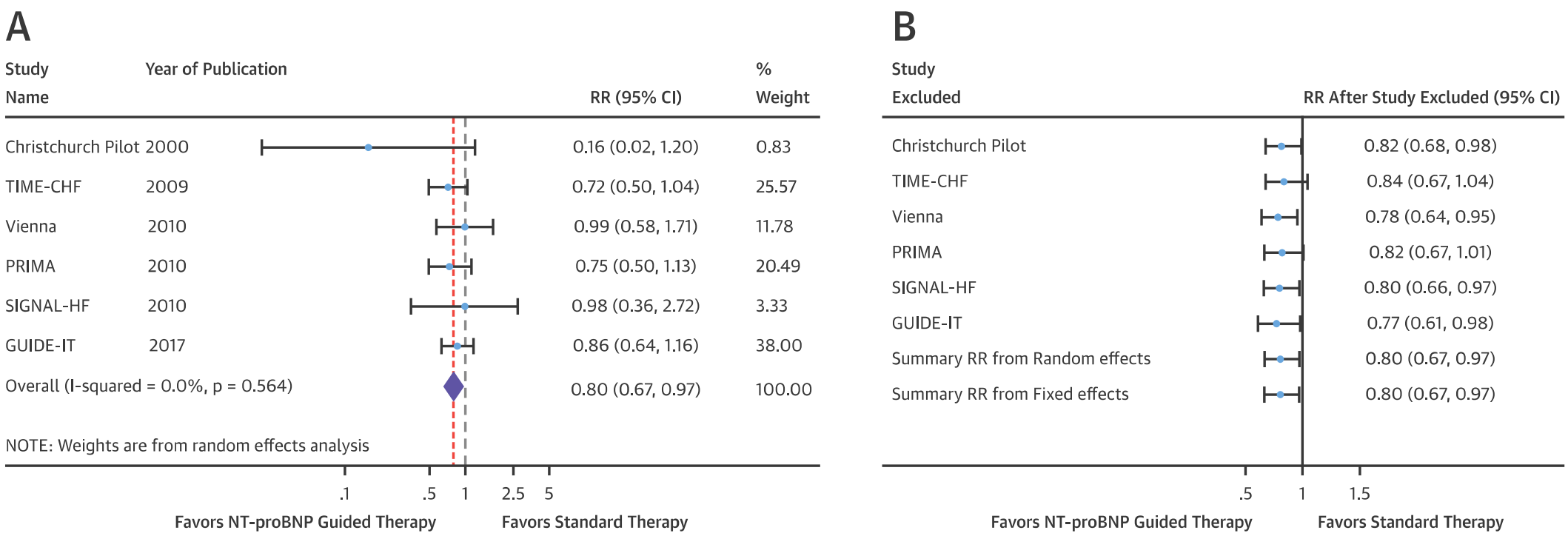
45 stable HF patients

- Mean NTproBNP 781
- Mean BNP 158
- Mean GFR 52

O'Hanlon R; J Card Fail 2007; 13:50-55

Can Natriuretic Peptides be Used to Guide Therapy in Chronic Heart Failure?

FIGURE 1 All-Cause Mortality Comparison of NT-proBNP-Guided Versus Standard Therapy in Chronic HFrEF



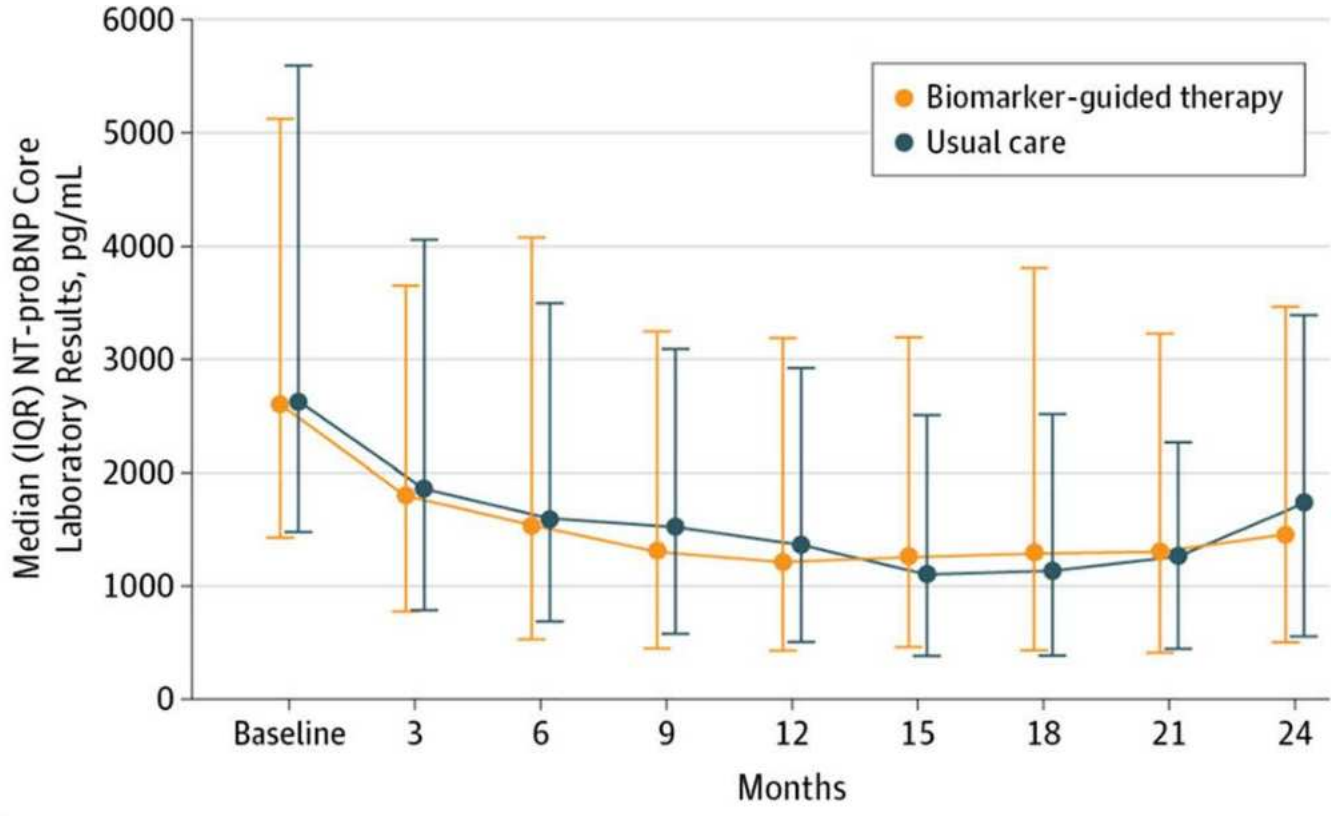
Bajaj N, JACC 2018; 951-5

GUIDE-IT Study

Optimizing Goal Directed Medical Therapy

Felker M; JAMA 2017; 318:713-20

Changes in Natriuretic Peptide Level Over Time



No. of participants									
Biomarker-guided therapy	426	355	305	263	228	180	153	123	105
Usual care	430	347	307	244	225	183	141	116	110

Januzzi; Curr Heart Fail Rep2018; 1537-43

NT-proBNP Level at 90 Days Predicted Prognosis

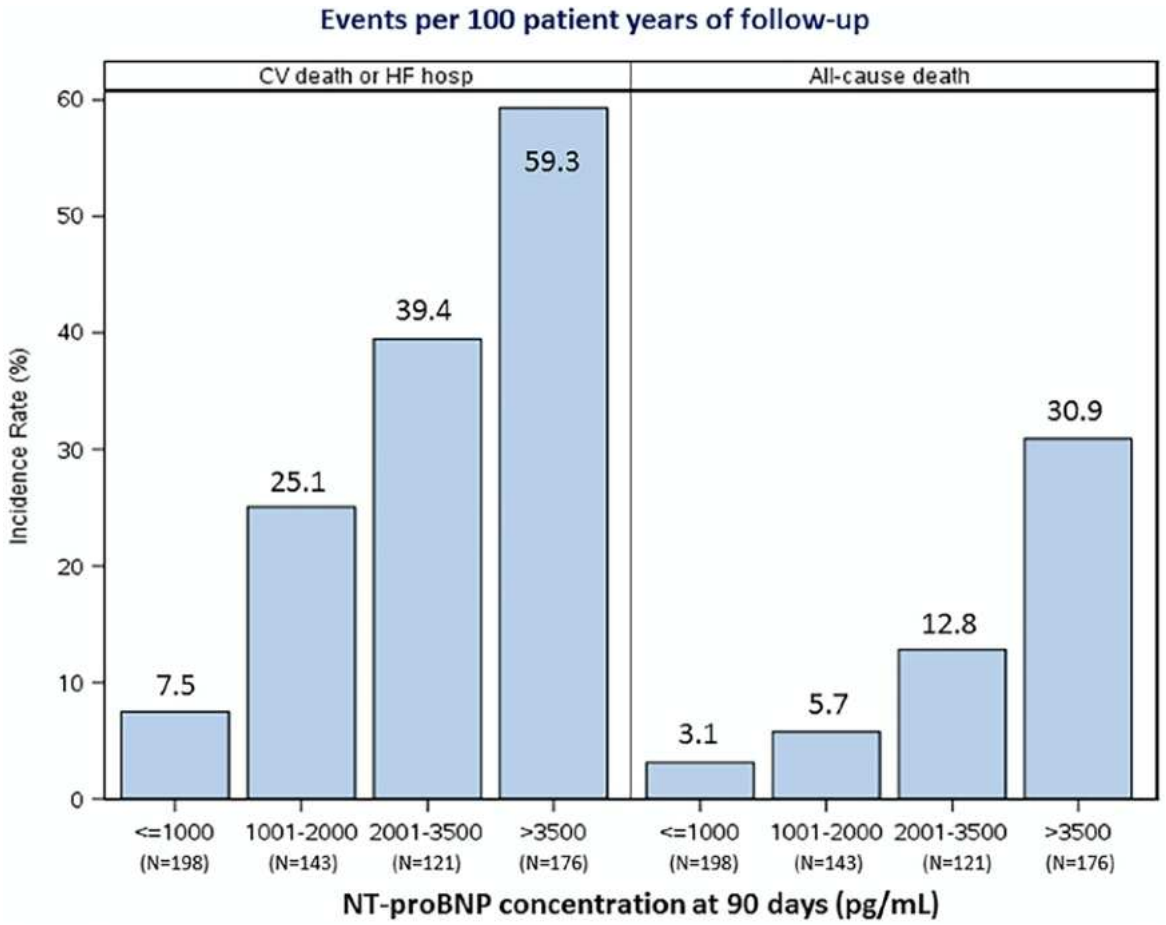


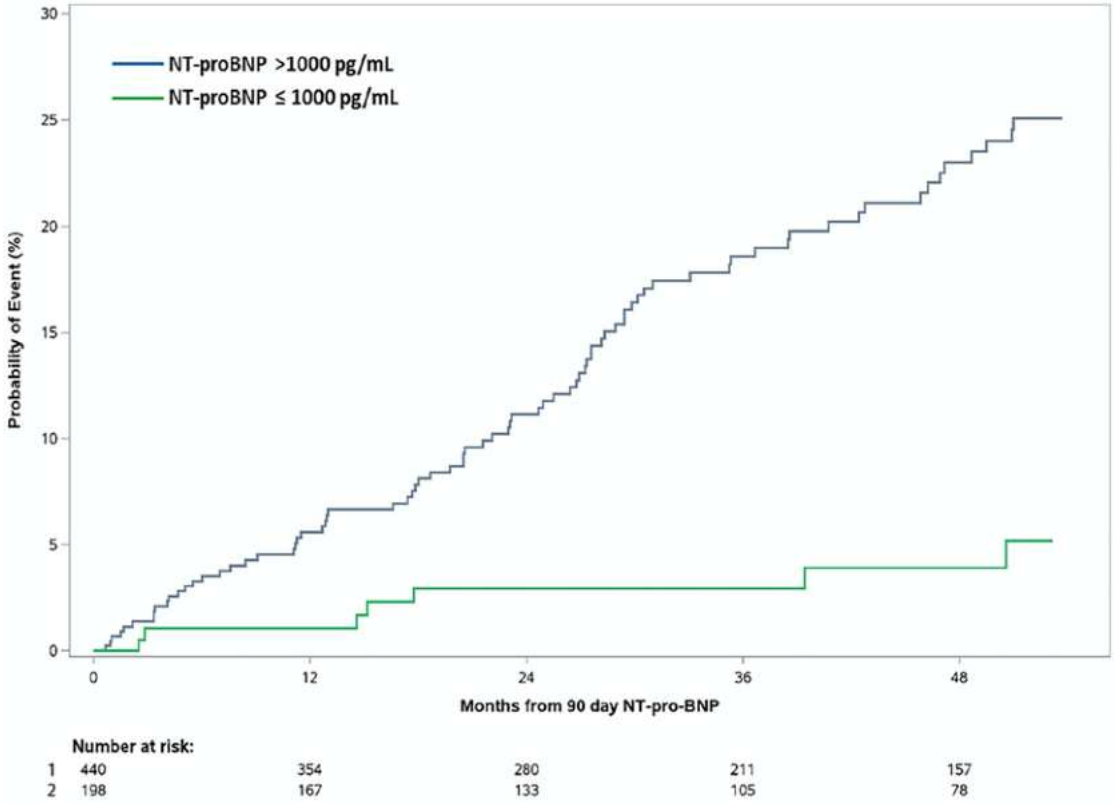
Figure 2: Rates of CV death or HF hospitalization and all-cause mortality as a function of NT-proBNP categories at 90 days.

Higher concentrations of NT-proBNP by 90 days after randomization were associated with worse outcomes.

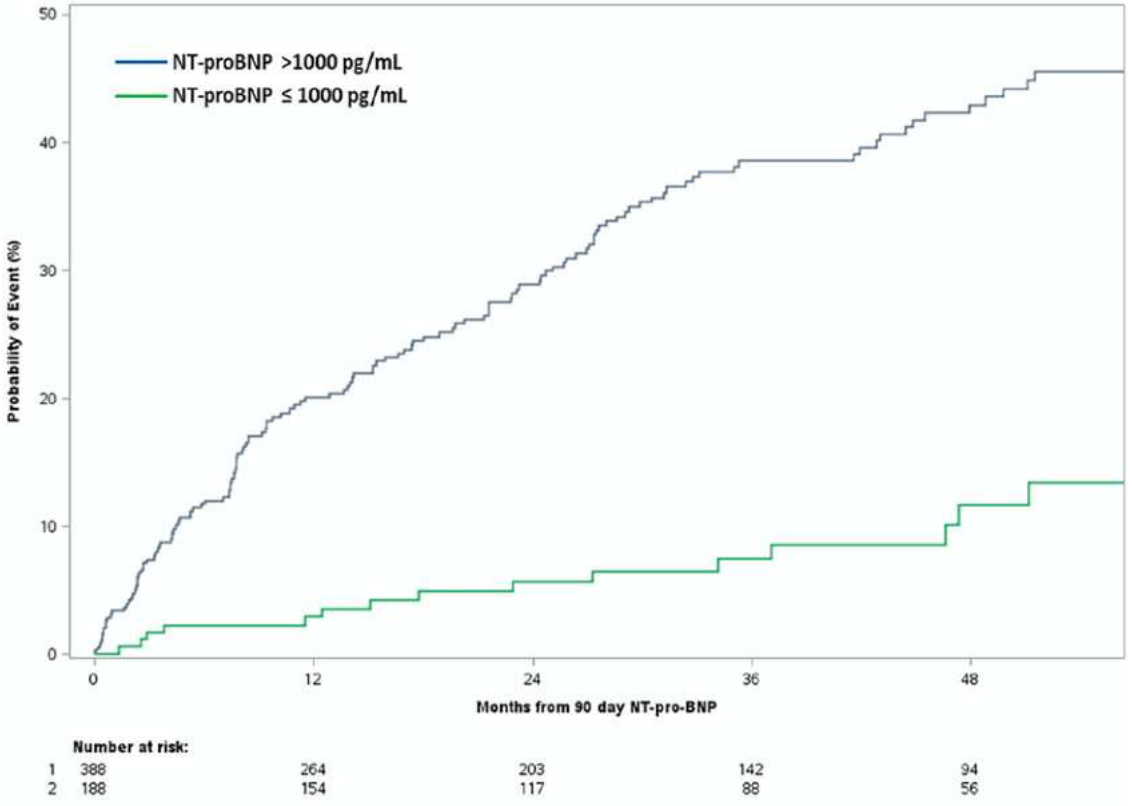
Januzzi, J. JACC 2019; 74:1205-1217

The Power of Prognosis

CV Death or HF Hospitalization

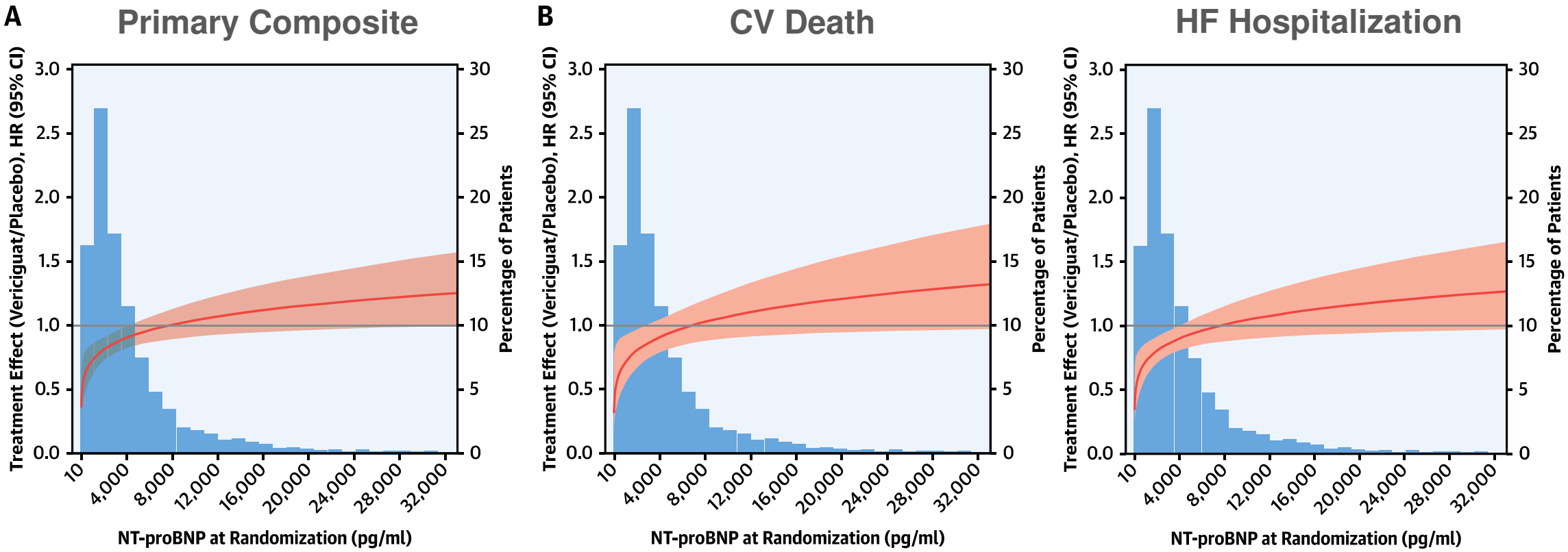


All Cause Mortality



Januzzi, J. JACC 2019; 74:1205-1217

NT-proBNP and Clinical Outcomes in VICTORIA



:ardiol HF. 2020;8(11):931-9.

Ezekowitz, J. JACC 2020:931

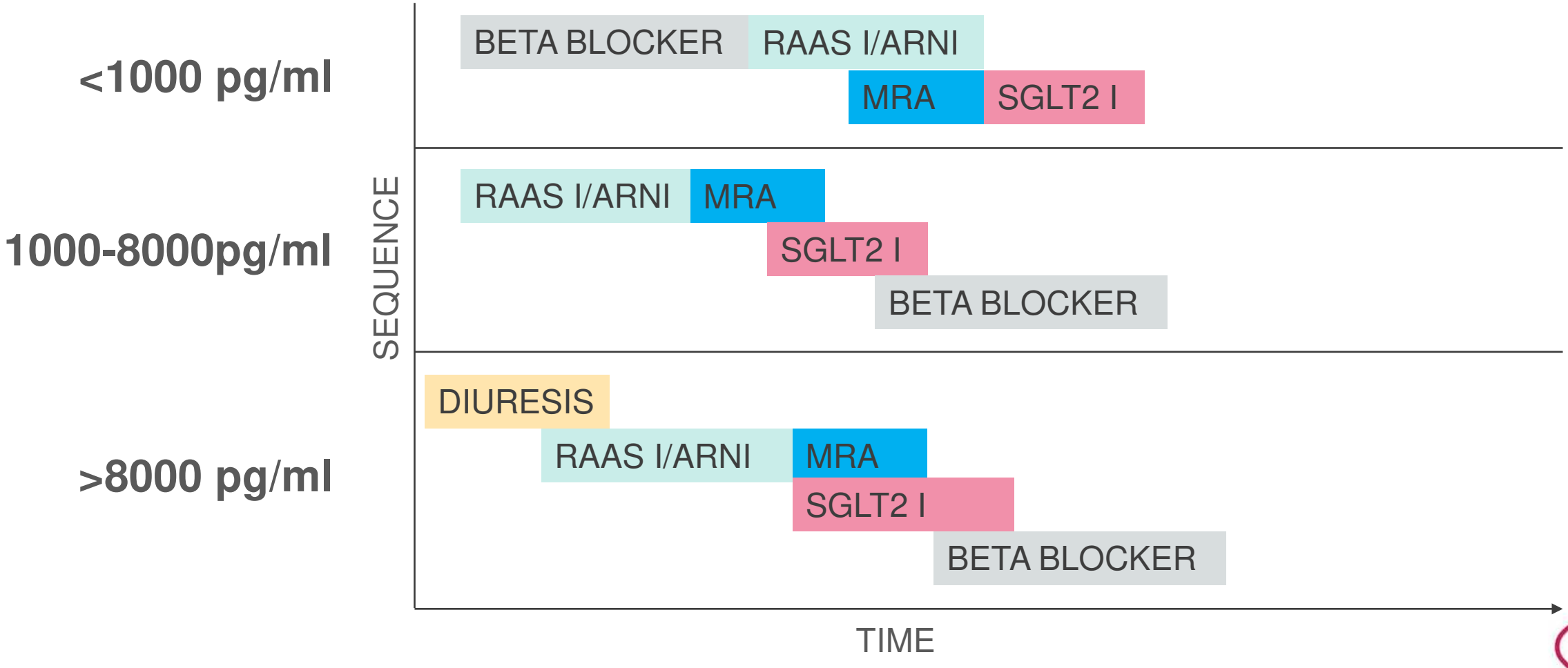
When is This Approach Actually Helpful?

- When a low target of NP is attempted (BNP< 100 or NT-proBNP<1000)
- Therapies MUST be adjusted to achieve these goals
- A change in therapy would NOT otherwise have been made if the NP measurement had not been performed

Personalization of Goal Directed Medical Therapy

- Beware of the patient with persistently high NP levels after optimization of volume status
- NP levels best addressed in context of renal function, age and body size
- Never interpret in isolation

NT-proBNP Guided Management in Treatment Naïve Heart Failure



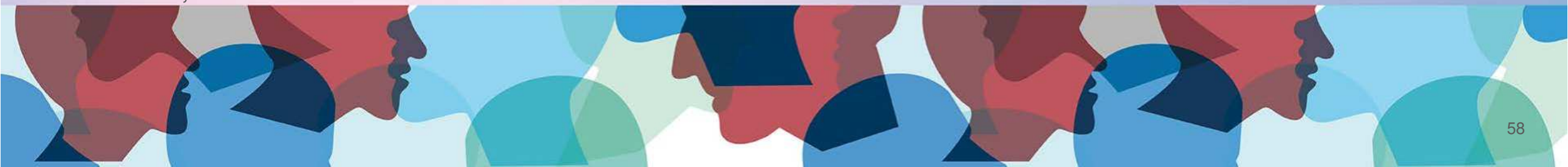
SUMMARY

- WORSENING HEART FAILURE
  - Characterized by change in clinical status
    - Escalation of diuretics
    - Intravenous therapy
    - ER visit
    - Hospitalization
  - Significant increase in risk of future events
- NT-proBNP can help to identify patient at increased risk
  - Value in risk stratification at critical time points
  - Routine use /measurement
    - Only if a change in clinical management is anticipated

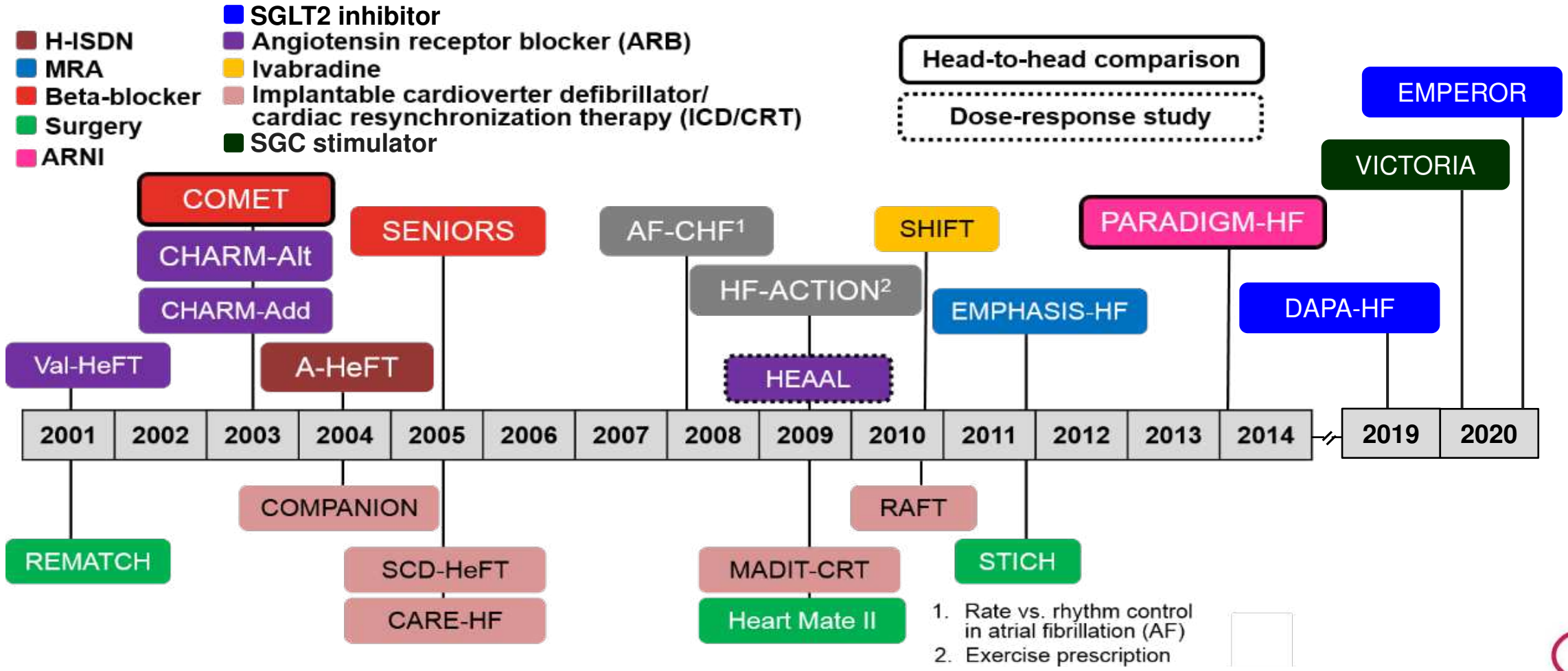
Patient Management Strategies and Treatment Options:

What, When, How

Javed Butler, MD, MPH, MBA
Baylor University Medical Center
Baylor Scott and White Health
Dallas, TX



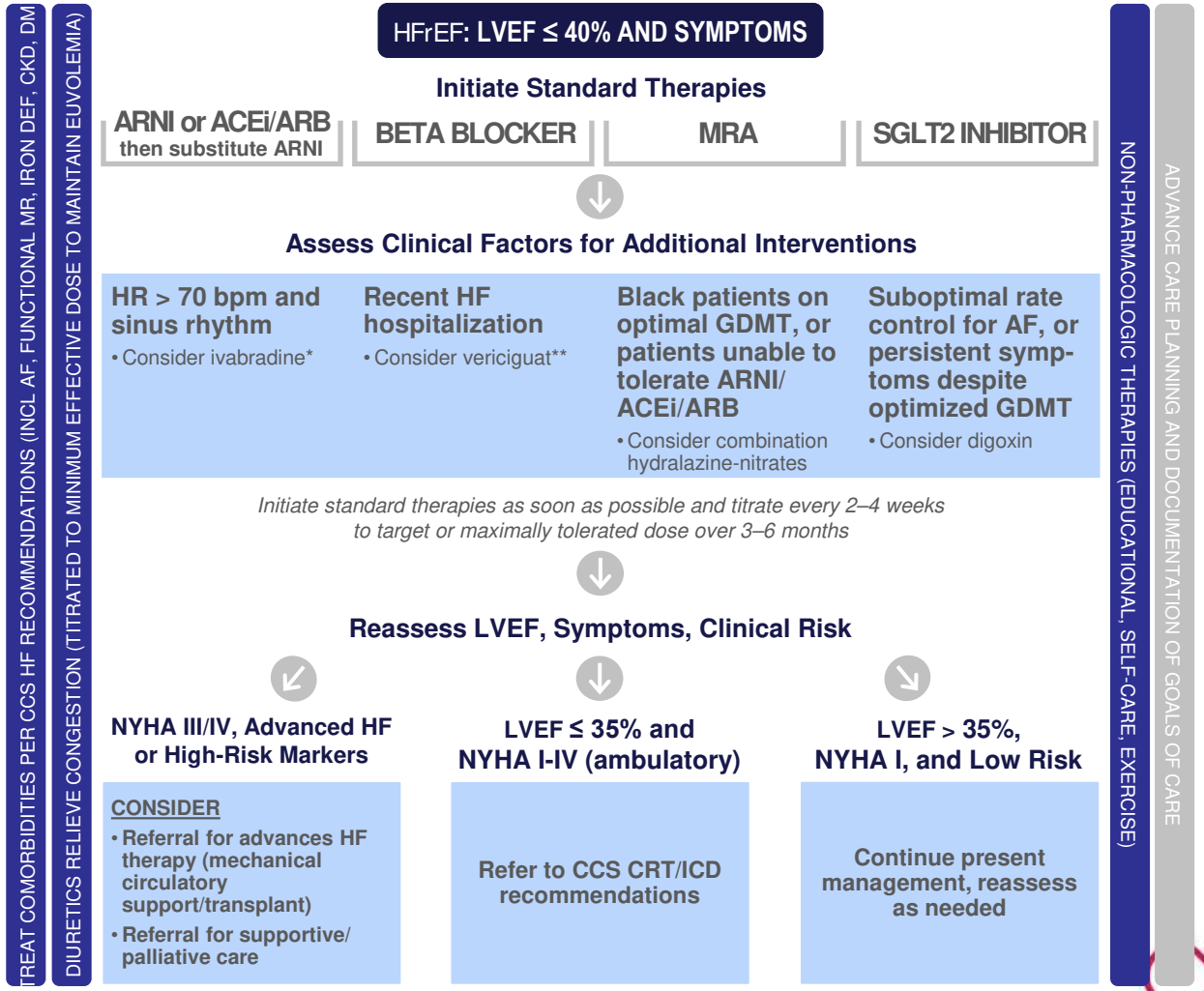
HFrEF: Positive trials 2001–2020



Adapted from: McMurray JJV. Eur J Heart. 2015;36:3467-70.

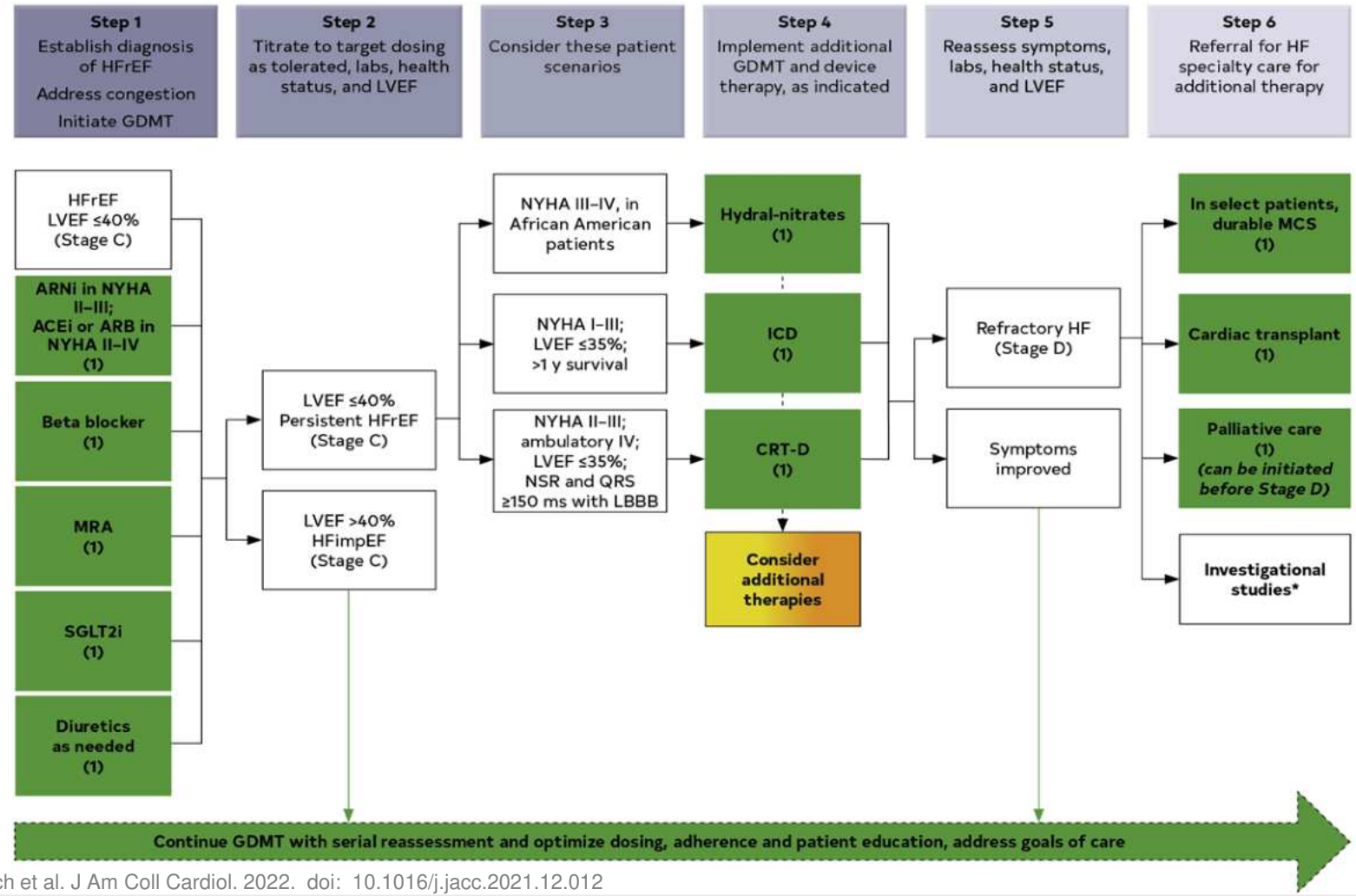
2021 CCS/CHFS HFrEF Guidelines Update: Therapeutic Approach to Patients With HFrEF

- We recommend that in the absence of contraindications, patients with HFrEF be treated with **combination therapy including one evidence-based medication from each of the following categories:**
  - **ARNI (or ACEI/ARB);**
  - **β-blocker;**
  - **MRA; and**
  - **SGLT2 inhibitor**



CCS/CHFS heart Failure Guidelines Update: Defining a new Pharmacologic Standard of care for Heart Failure with Reduced Ejection Fraction. Canadian Journal of Cardiology 37 (2021) 531-546

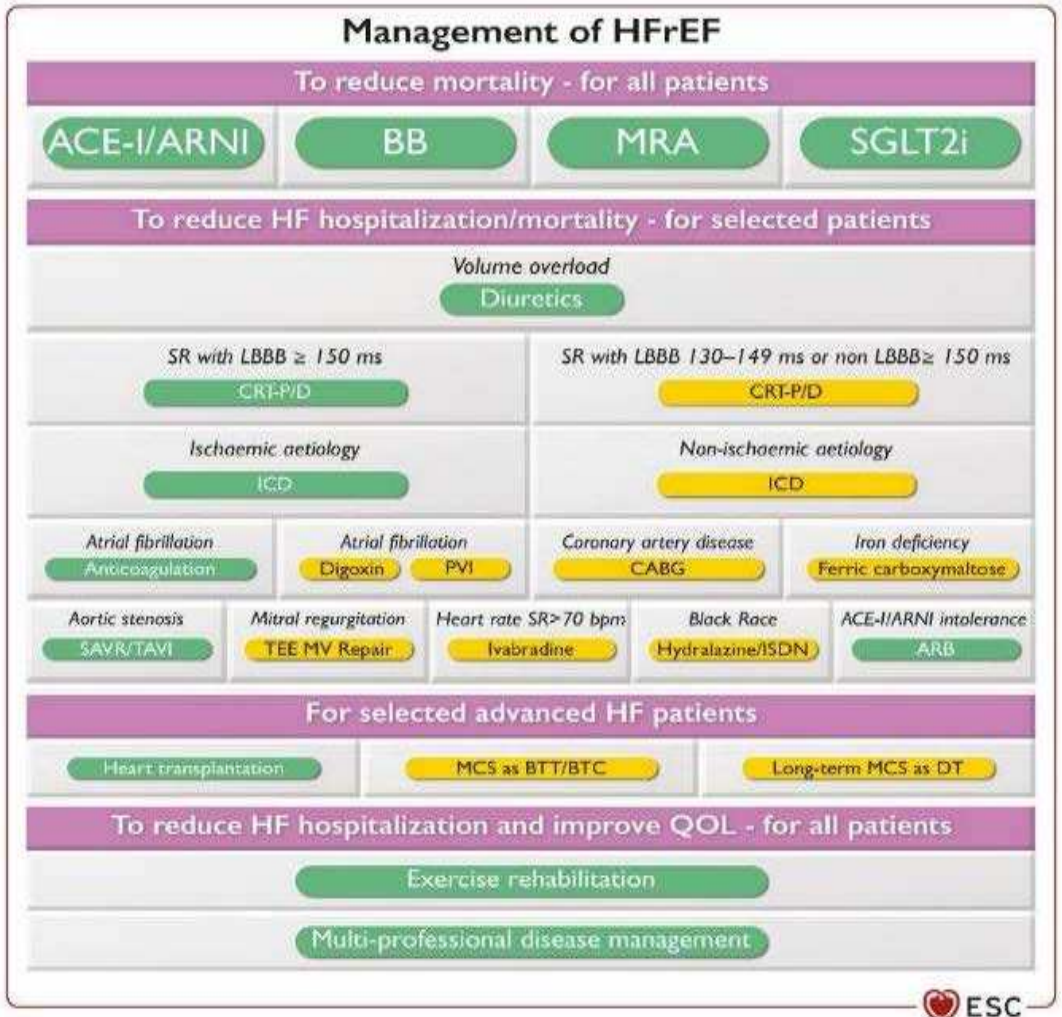
Treatment of HFrEF Stages C and D



- Guideline-directed medical therapy (GDMT) for heart failure (HF) with reduced ejection fraction (HFrEF) now includes 4 medication classes that include sodium-glucose cotransporter-2 inhibitors (SGLT2i).
- **If patients have chronic symptomatic HFrEF with NYHA class II or III symptoms and they tolerate an ACEi or ARB, they should be switched to an ARNi because of improvement in morbidity and mortality**
- In patients with symptomatic chronic HFrEF, SGLT2i therapy provides intermediate economic value

Heidenreich et al. J Am Coll Cardiol. 2022. doi: 10.1016/j.jacc.2021.12.012

Strategic Phenotypic Overview of the Management of Heart Failure with Reduced Ejection Fraction



Class I = Green.
Class IIa = Yellow.

The Figure shows management options.

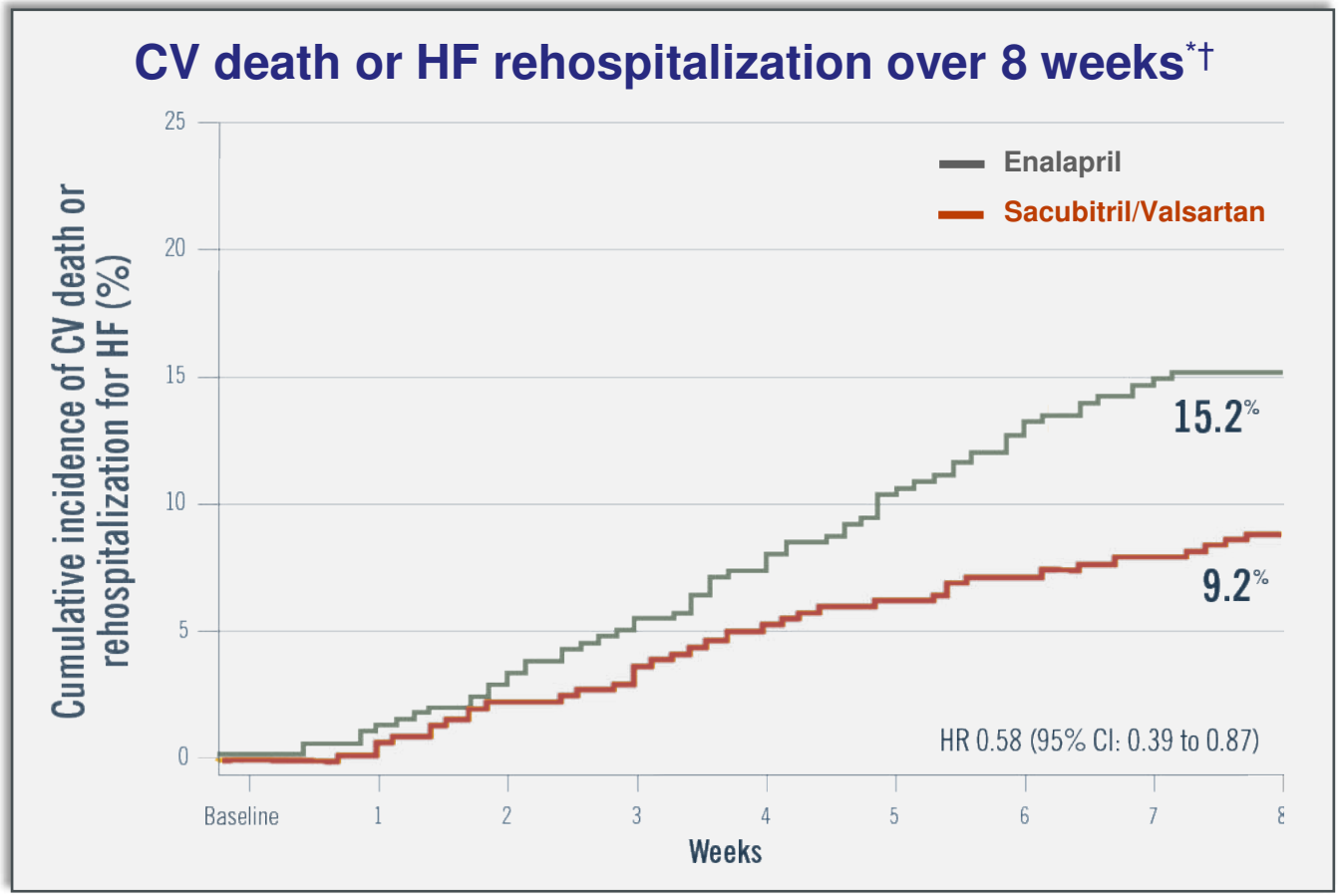
See the specific tables for those with Class IIb recommendations.

McDonagh T & Metra M et al. EHJ & EJHF 2021.

Inpatient Initiation of Sacubitril/Valsartan Reduced Risk of CV Death or HF Rehospitalization*† vs Enalapril *(Post hoc analysis)*[1]

PIONEER-HF

CV death or HF rehospitalization over 8 weeks*†



Sacubitril/Valsartan

42% RRR

IN CV DEATH OR HF READMISSIONS

6.0% ARR

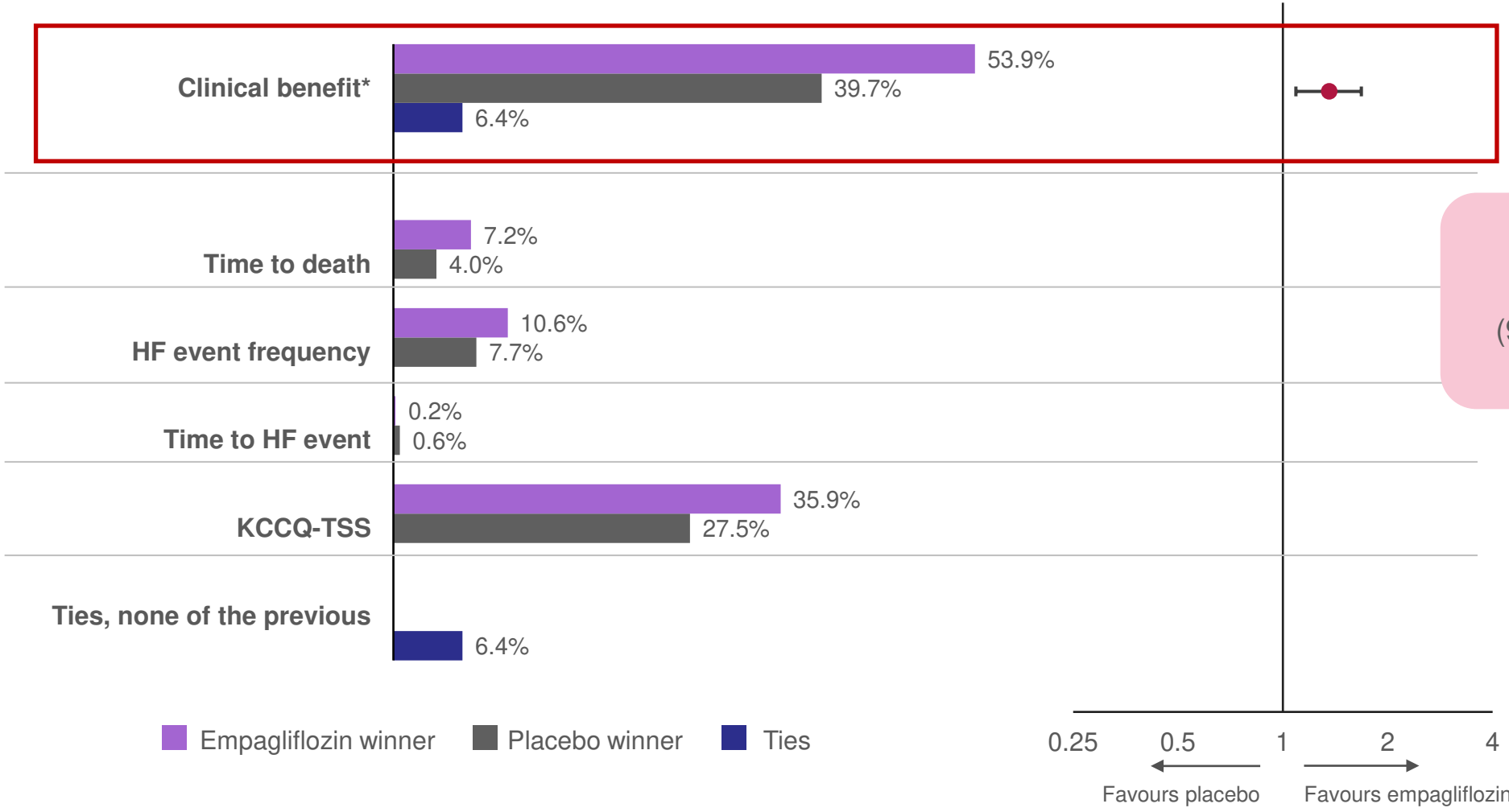
ARR, absolute risk reduction; CV, cardiovascular; RRR, relative risk reduction

*Readmission was defined as the first hospitalization after inpatient initiation of study drug.[2]

†CV death and HF rehospitalizations (8-week, double-blind followed by 4-week, open-label period) events have been adjudicated as definite or probable. A patient is counted only once.

1. Morrow et al. Circulation. 2019; 139(19):2285-2288. 2. Velazquez EJ et al. *N Engl J Med.* 2019;380(6):539-548.

EMPULSE: Patients treated with empagliflozin were 36% more likely to experience a clinical benefit than those who received placebo



Stratified win ratio: 1.36
(95% CI: 1.09, 1.68)
p=0.0054

Empagliflozin: Superior in 53.9% of comparisons

Placebo: Superior in 39.7% of comparisons

ESC 2021 Heart Failure Guidelines: Oral therapy should be initiated during hospitalization and promptly optimized around discharge

Recommendations	Class I[a]	Level[b]
It is recommended that patients hospitalized for HF be carefully evaluated to exclude persistent signs of congestion before discharge and to optimize oral treatment.	I	C
It is recommended that evidence-based oral medical treatment be administered before discharge.	I	C
An early follow-up visit is recommended at 1-2 weeks after discharge to assess signs of congestion, drug tolerance and start and/or uptitrate evidence-based therapy.	I	C

*Class of recommendation: [b]Level of evidence.
HF = heart failure.
McDonagh TA eet al. nline ahead of print. *Eur Heart J.* 2021.

In-Hospital Initiation of Quadruple Medical Therapy for HFreEF

Hospitalized **Post-Discharge** →

	Day 1-4	Days 7-14	Days 14-28	Days 21-42	Beyond
ARNI	Continue	Titrate, as tolerated	Titrate, as tolerated		• Maintenance / further optimization of quadruple therapy • Consideration of EP device therapies/ Mitraclip • Consideration of add-on medical therapies or advanced therapies, if refractory • Manage comorbidities
Beta-blocker	Titrate, as tolerated	Titrate, as tolerated	Titrate, as tolerated		
MRA	Continue	Titrate, as tolerated	Continue		
SGLT2i	Continue	Continue	Continue		
	Low starting doses Prioritize beta-blocker titration	Benefits of each Rx demonstrated within 30 days of initiation Cumulative benefits within 30 days (>75% relative risk reduction)			Focus on complete set of quadruple medical therapies being implemented

In-Hospital Initiation

More likely to be treated

More likely to tolerate

More likely to fill prescription

More likely to adhere

More likely to persist

More likely to feel better

More likely to be home

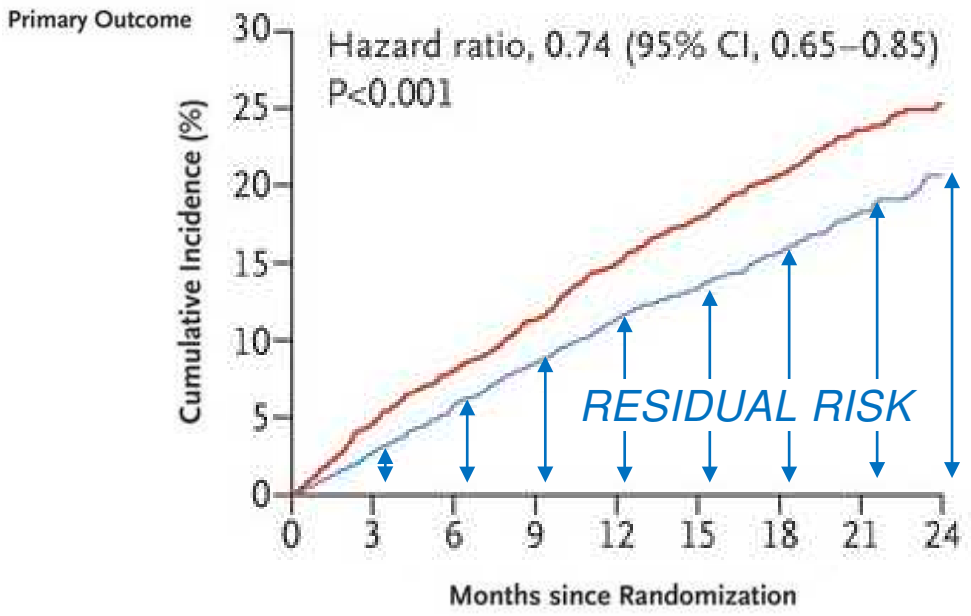
More likely to survive

In press: Greene et al. Eur J HF: 10.1002/ejhf.2382

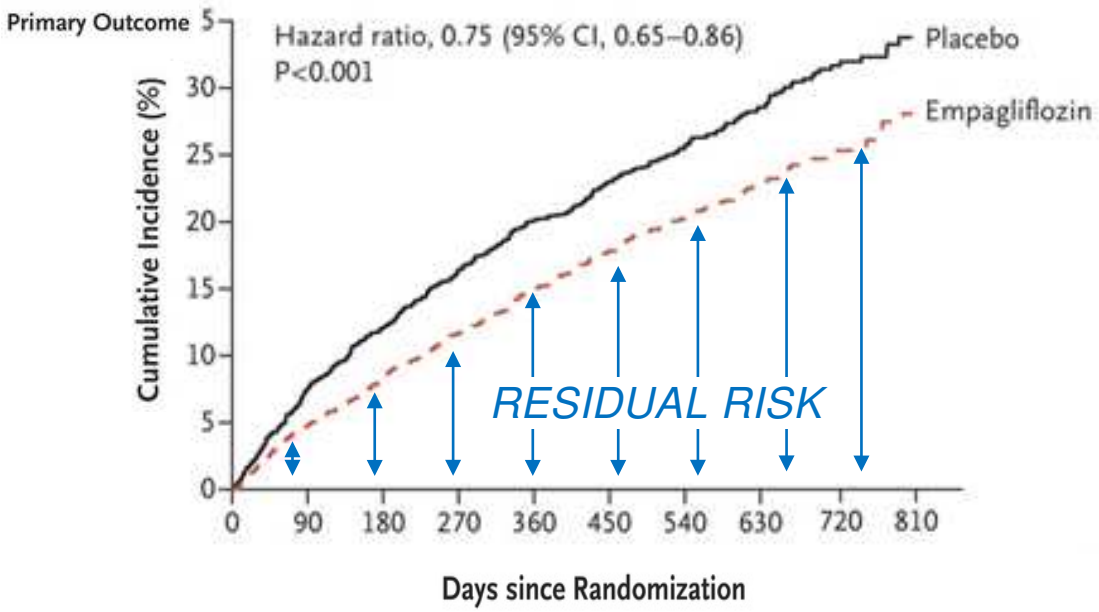
Residual Risk

Improvements made. But more needed!

DAPA-HF McMurray NEJM 2019



EMPEROR-Reduced Packer NEJM 2020

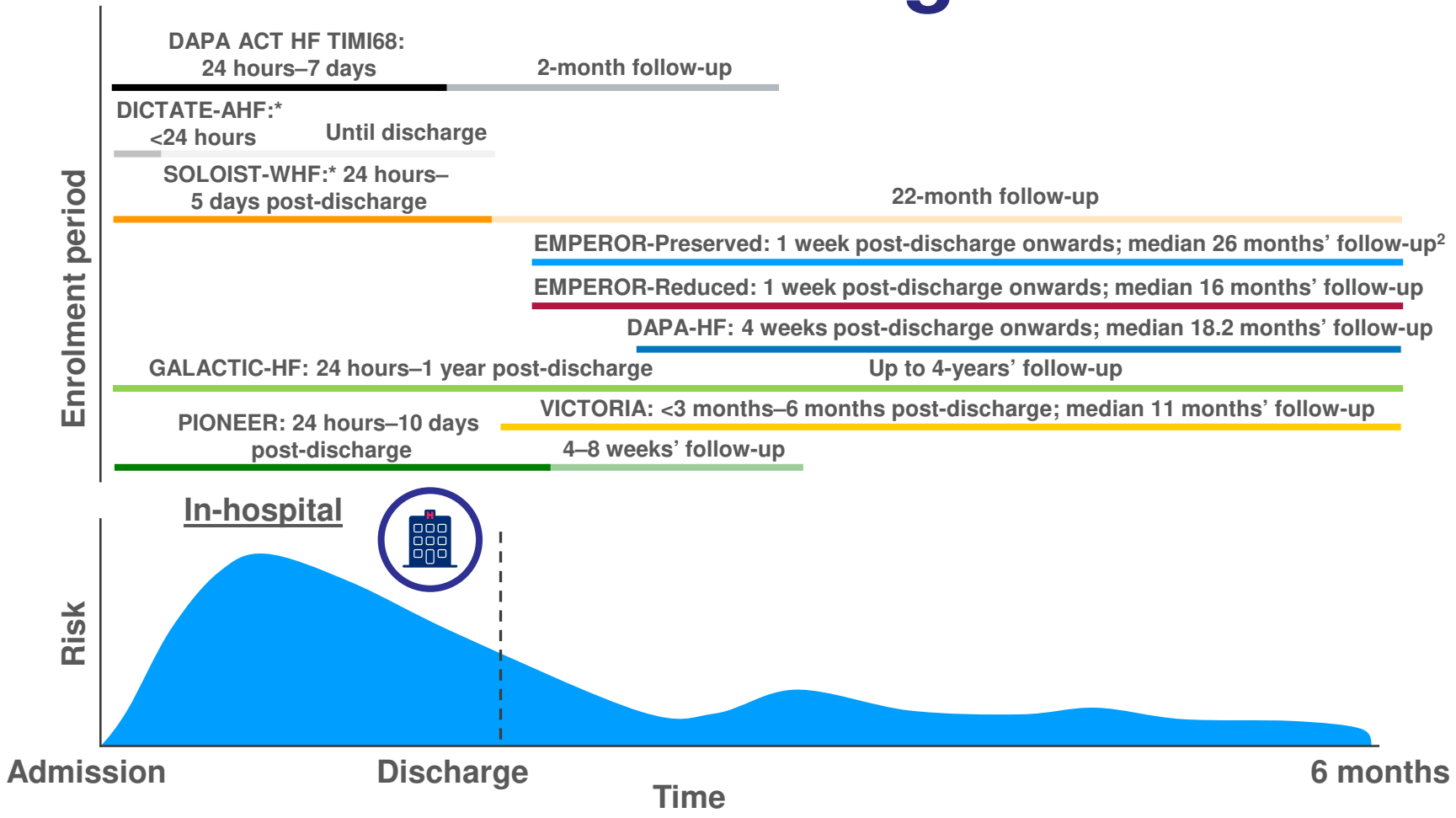


Trajectory of Stage C Heart Failure

New Onset/De Novo HF:	Resolution of Symptoms:	Persistent HF:	Worsening HF:
• Newly diagnosed HF • No previous history of HF	• Resolution of symptoms/ signs of HF Stage C with previous symptoms of HF with persistent LV dysfunction → HF in remission with resolution of previous structural and/or functional heart disease*	• Persistent HF with ongoing symptoms/signs and/or limited functional capacity	• Worsening symptoms/ signs/functional capacity

Heidenreich et al. J Am Coll Cardiol. 2022. doi: 10.1016/j.jacc.2021.12.012

Enrollment Window and Follow Up Duration in Various Acute/Worsening HF trials



Medical Therapy for Heart Failure With Reduced Ejection Fraction

The CHAMP-HF Registry

Stephen J. Greene, MD,[a,b] Javed Butler, MD, MPH, MBA,[c] Nancy M. Albert, PhD,[d] Adam D. DeVore, MD, MHS,[a,b] Puza P. Sharma, MBBS, MPH, PhD,[e] Carol I. Duffy, DO,[e] C. Larry Hill, PhD,[a] Kevin McCague, MA,[e] Xiaojuan Mi, PhD,[a] J. Herbert Patterson, PharmD,[f] John A. Spertus, MD, MPH,[g] Laine Thomas, PhD,[a] Fredonia B. Williams, EdD,[h] Adrian F. Hernandez, MD, MHS,[a,b] Gregg C. Fonarow, MD[i]

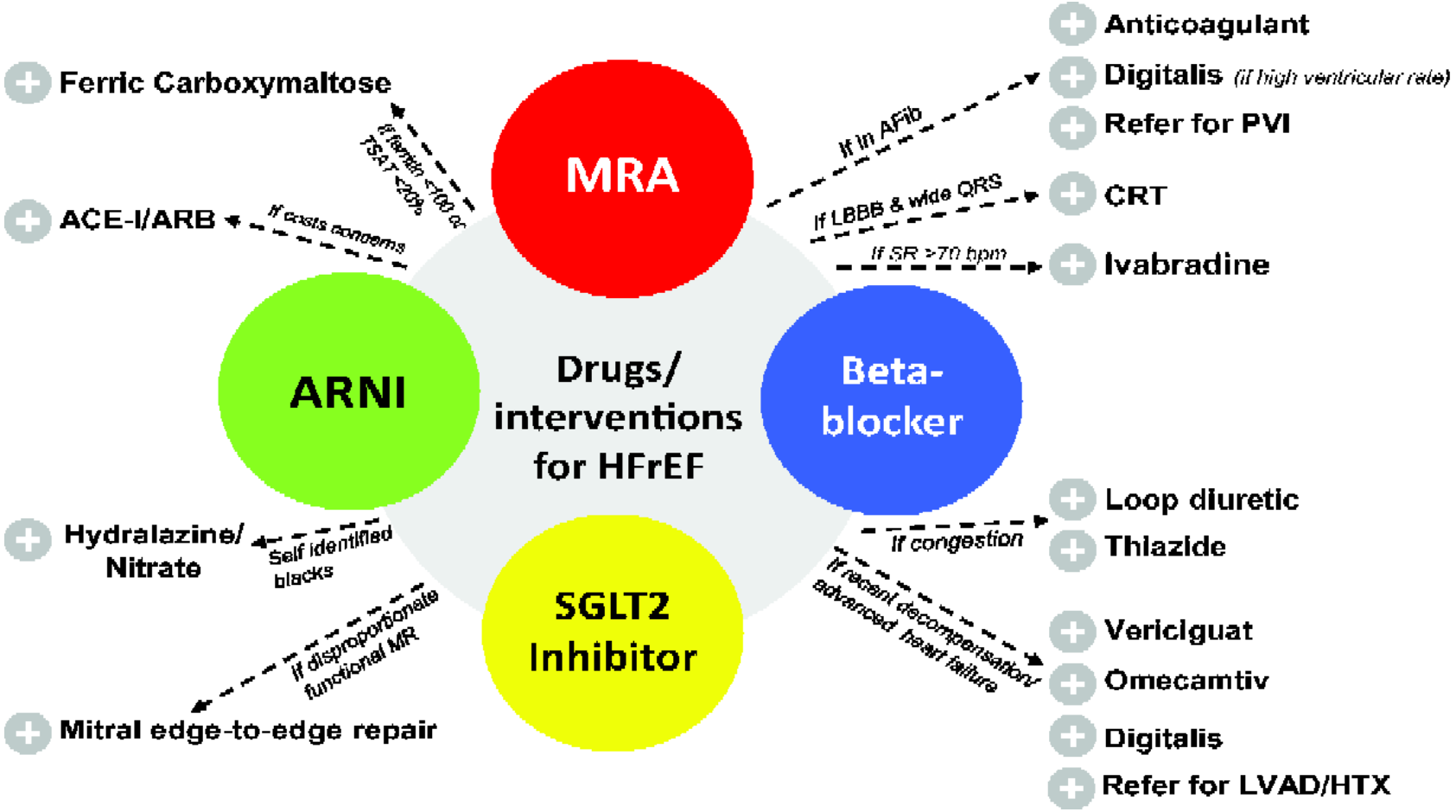
% Eligible Patients <u>NOT</u> Receiving Therapy:

- ACEI/ARB/ARNI – **27%**
- Beta-blocker – **33%**
- MRA – **67%**

<25% of eligible patients receive "triple therapy"
(ACEI/ARB/ARNI + BB + MRA)

Greene SJ et al. *JACC* 2018

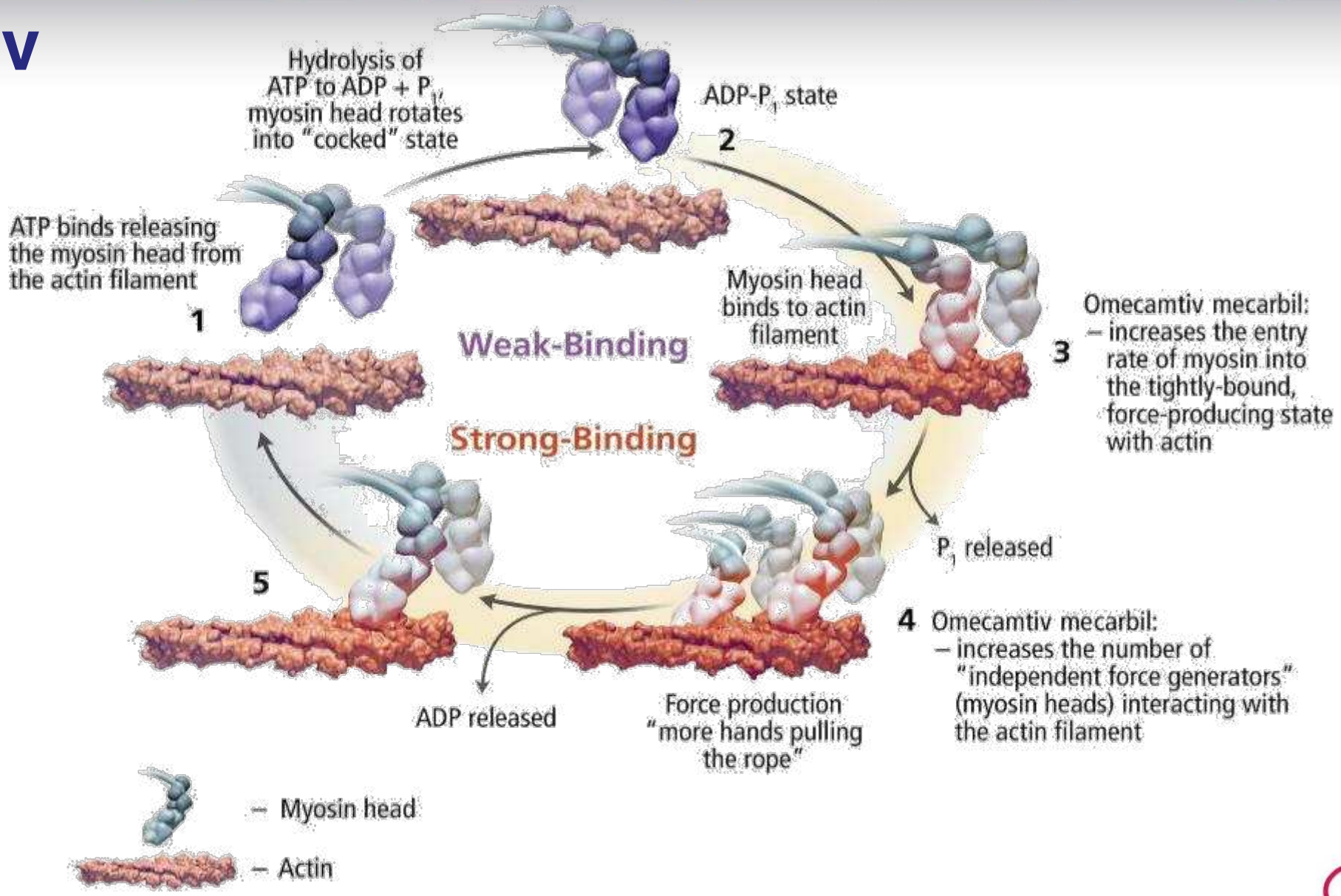
Therapy Options for Patients with HFrEF



ESC European Society of Cardiology

Johann Bauersachs, Heart failure drug treatment: the fantastic four, *European Heart Journal*, 2021;, ehaa1012, https://doi.org/10.1093/eurheartj/ehaa1012

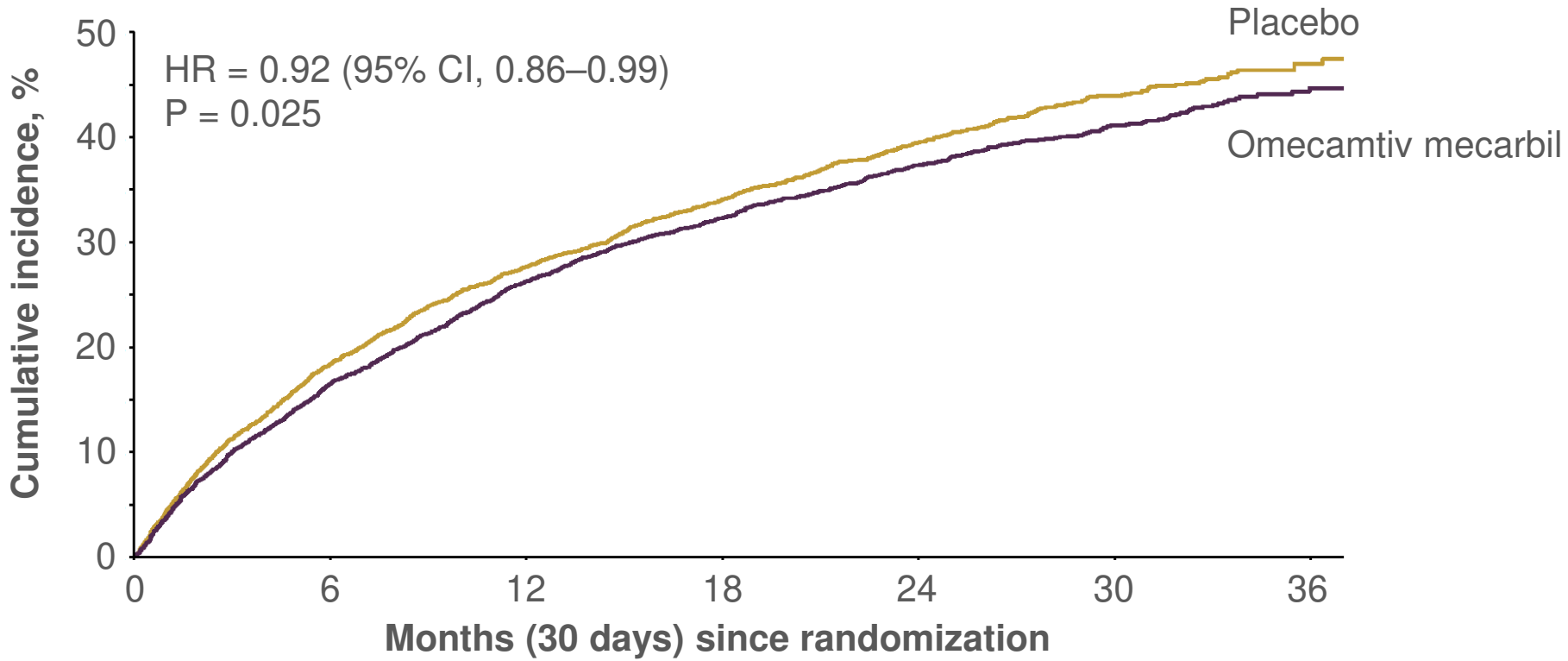
Omecamtiv Mecarbil



Ahmad, T. Lindenfeld, J et al. (2019), Why has positive inotropy failed in chronic heart failure? Lessons from prior inotrope trials. Eur J Heart Fail. doi:10.1002/ejhf.1557

GALACTIC-HF: Primary Composite Endpoint

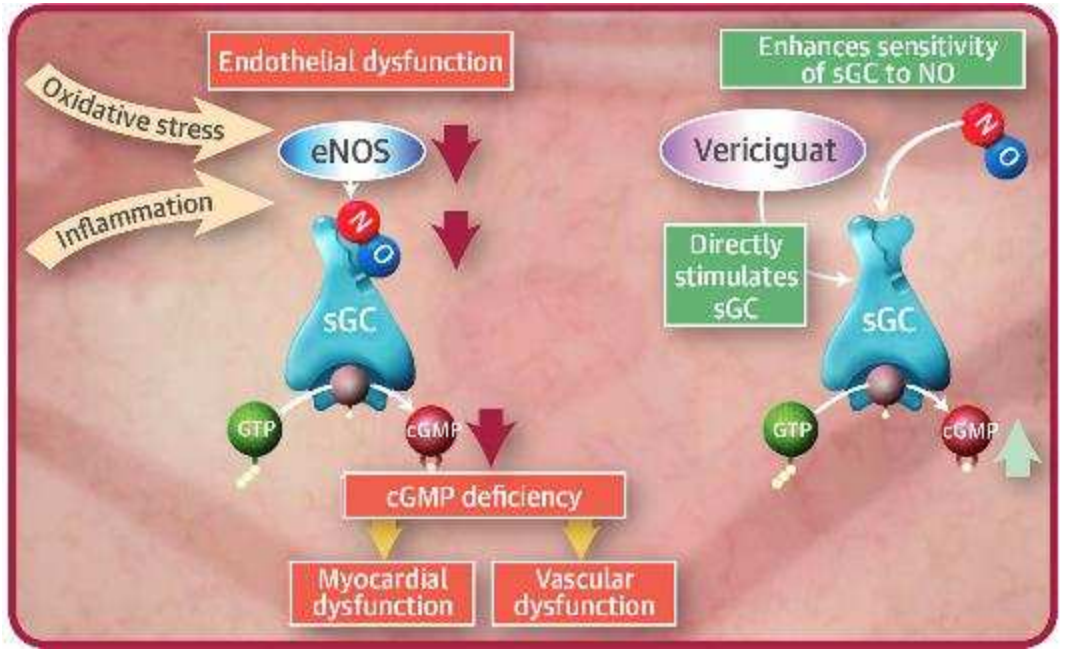
Time to first Heart Failure event or Cardiovascular death



Patients at risk, n							
Placebo	4112	3310	2889	2102	1349	647	141
Omecamtiv mecarbil	4120	3391	2953	2158	1430	700	164

Vericiguat stimulates soluble Guanylate Cyclase (sGC)

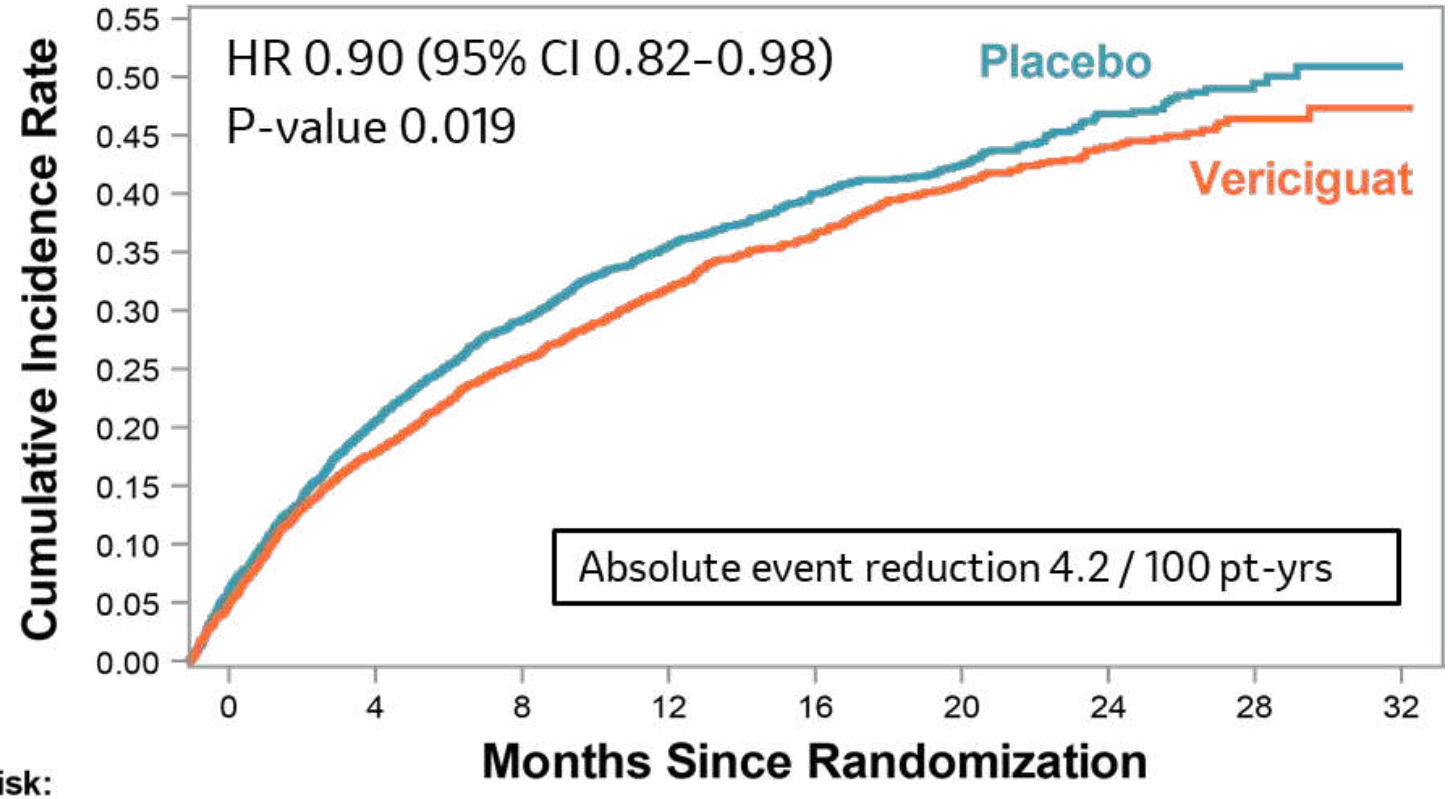
- **Vericiguat** has a dual mode of action:
  - sGC stimulator directly stimulates sGC via a different binding site, independently of NO
  - sGC stimulator sensitizes sGC to endogenous NO by stabilizing the NO–sGC Binding
- **cGMP** plays an important role in:
  - **Vasodilation**
  - **anti-proliferative effects**
  - **anti-fibrotic effects**
  - **anti-inflammatory effects**
- Impairments in NO-sGC-cGMP signalling have been implicated in the development of heart failure



JACC: Heart Failure 2018;6(2):96-104

VERICIGUAT stimulates sGC to increase cGMP production
Treating HFrEF patients with Vericiguat can restore signaling of a suppressed pathway.

VICTORIA: Vericiguat Reduces CVD and HFH in High-Risk Patients Following a Worsening Event



Number at Risk:									
Vericiguat	2526	2099	1621	1154	826	577	348	125	1
Placebo	2524	2053	1555	1097	772	559	324	110	0

Median treatment duration for primary end point: 10.8 mo

Annual NNT: 24

VICTORIA Armstrong NEJM 2020

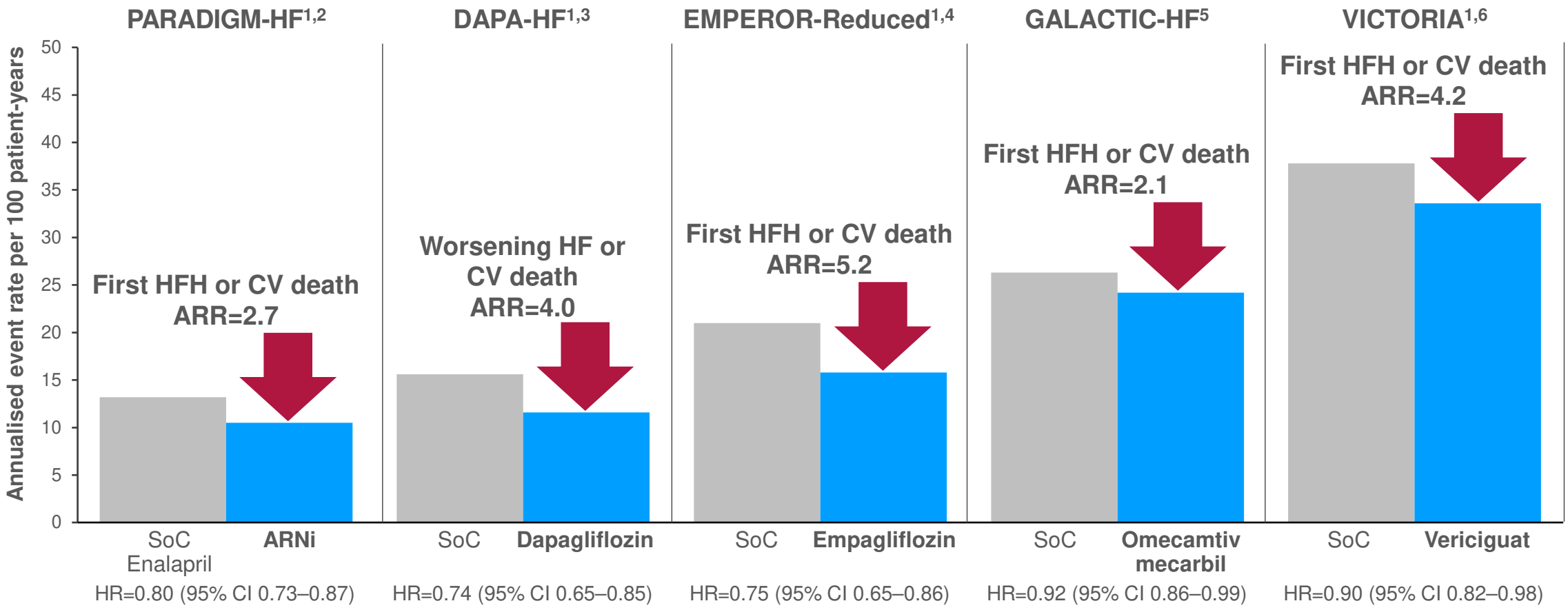
VICTORIA in Context: Annualised Event Rate (Events per 100 Patient-Years at Risk)

	PARADIGM-HF[1,2]		DAPA-HF[1,3]		EMPEROR-Reduced[1,4]		GALACTIC-HF[5]		VICTORIA[1,6]	
	Comparator	Sacubitril/ Valsartan	Comparator	Dapagliflozin	Comparator	Empagliflozin	Comparator	Omecamtiv mecarbil	Comparator	Vericiguat
Median follow-up	27 months		18 months		16 months		22 months		11 months	
Hazard ratios (95% CI) for key outcomes										
Primary endpoint	0.80 (0.73–0.87)		0.74 (0.65–0.85)		0.75 (0.65–0.86)		0.92 (0.86–0.99)		0.90 (0.82–0.98)	
CV death	0.80 (0.71–0.89)		0.82 (0.69–0.98)		0.92 (0.75–1.12)		1.01 (0.92–1.11)		0.93 (0.81–1.06)	
First HFH	0.79 (0.71–0.89)		0.70 (0.59–0.83)		0.69 (0.59–0.81)		0.95 (0.87–1.03)		0.90 (0.81–1.00)	
Annualised event rate (events per 100 patients at risk)										
Primary endpoint	13.2	10.5	15.6	11.6	21.0	15.8	26.3	24.2	37.8	33.6
ARR	**2.7**		**4.0**		**5.2**		**2.1**		**4.2**	
CV death	7.5	6.0	7.9	6.5	8.1	7.6	10.8	10.9	13.9	12.9
ARR	**1.5**		**1.4**		**0.6**		**-0.1**		**1.0**	
First HFH	7.7[7]	6.2[7]	9.8	6.9	15.5	10.7	19.1	18.0	29.1	25.9
ARR	**1.6**		**2.9**		**4.8**		**1.1**		**3.2**	

Each HF study was independently conducted, and no head-to-head HF studies have been completed that allow for direct comparison of the efficacy and/or safety of one drug versus another.
ARR, absolute rate reduction; CI, confidence interval; CV, cardiovascular; HF, heart failure; HFH, heart failure hospitalisation

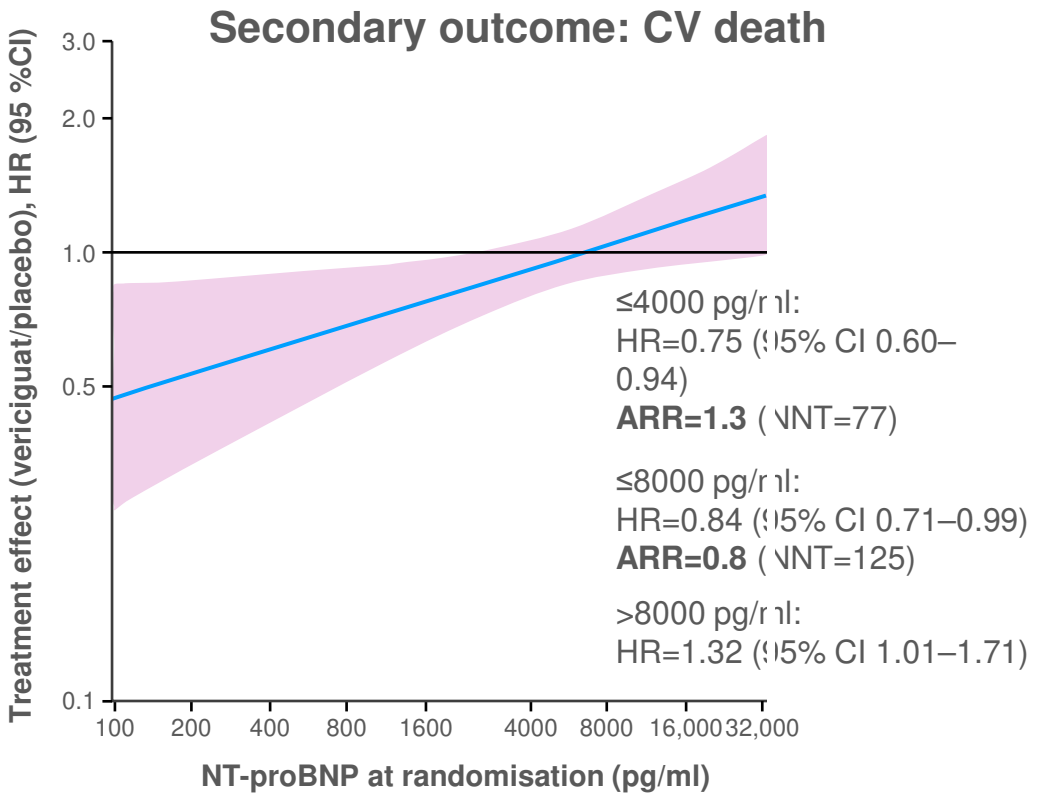
1. Butler J et al. *Eur J Heart Fail.* 2020;22:1991–1993; 2. McMurray JJ et al. *N Engl J Med.* 2014;371:993–1004; 3. McMurray JJV et al. *N Engl J Med.* 2019;381:1995–2008; 4. Packer M et al. *N Engl J Med.* 2020;383:1413–1424; 5. Teerlink JR et al. *N Engl J Med.* 2021;384:105–116; 6. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893; 7. McMurray JJV et al. *Eur Heart J.* 2015;36:434–439.

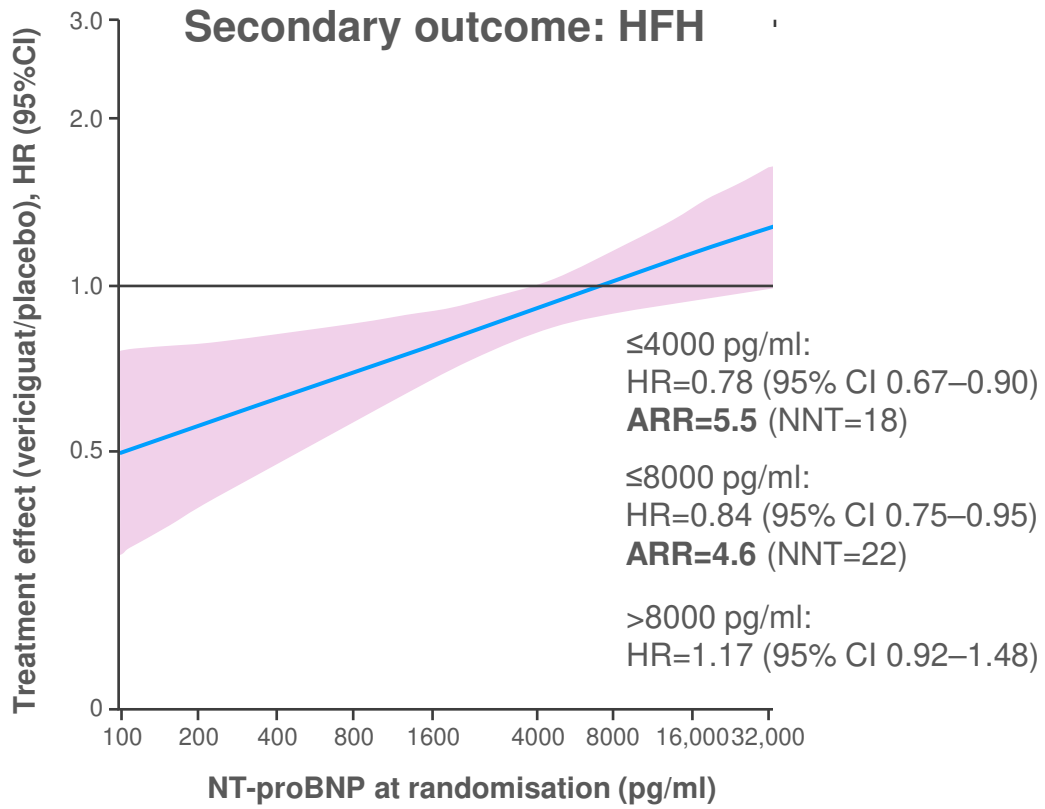
Contemporary HF Outcome Trials
Primary Endpoint Absolute Rate Reduction



Each HF study was independently conducted, and no head-to-head HF studies have been completed that allow for direct comparison of the efficacy and/or safety of one drug versus another.
ARNi, angiotensin receptor–neprilysin inhibitor; ARR, absolute rate reduction; CI, confidence interval; CV, cardiovascular; HF, heart failure; HFH, heart failure hospitalisation; HR, hazard ratio; SoC, standard of care.
1. Butler J et al. *Eur J Heart Fail.* 2020;22:1991–1993; 2. McMurray JJ et al. *N Engl J Med.* 2014;371:993–1004; 3. McMurray JJV et al. *N Engl J Med.* 2019;381:1995–2008; 4. Packer M et al. *N Engl J Med.* 2020;383:1413–1424; 5. Teerlink JR et al. *N Engl J Med.* 2021;384:105–116; 6. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893.

VICTORIA: NT-proBNP and Clinical Outcomes



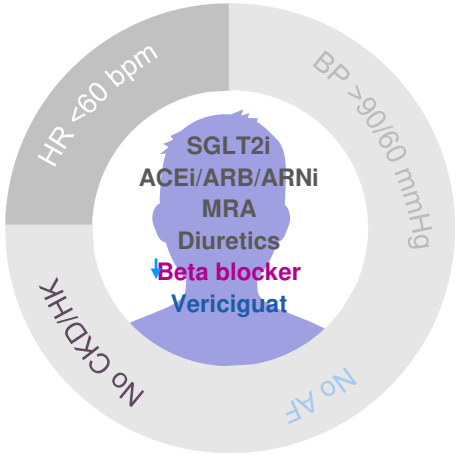


For patients with NT-proBNP ≤8000 pg/ml, the treatment effect of vericiguat extended to both CV death and HFH

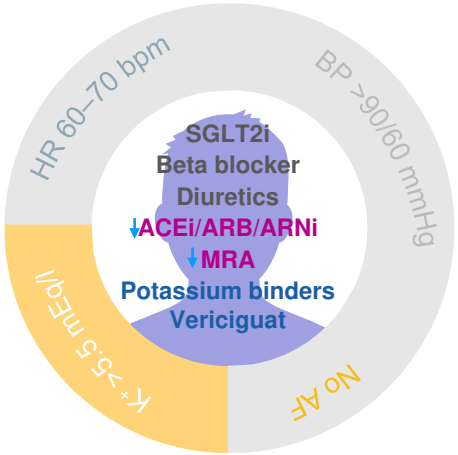
Adjusted for MAGGIC risk score and presented on the log scale. NNT values calculated from 1/ARR.
CI, confidence interval; CV, cardiovascular; HFH, heart failure hospitalisation; HR, hazard ratio; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; NT-proBNP, N-terminal pro-brain natriuretic peptide.
1. Ezekowitz JA et al. *JACC Heart Fail*. 2020;8:931–939.

Tailored therapy with vericiguat can be considered when foundational drugs are reduced, discontinued or not tolerated[1]

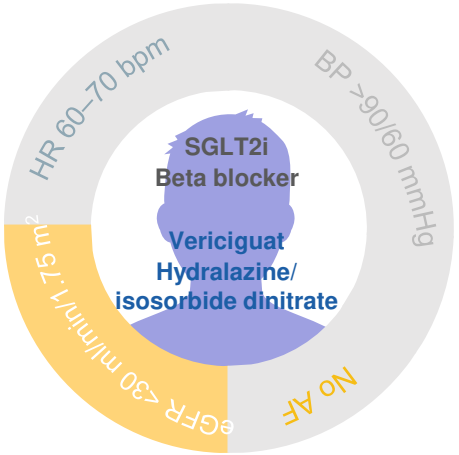
Addition of vericiguat should be considered:



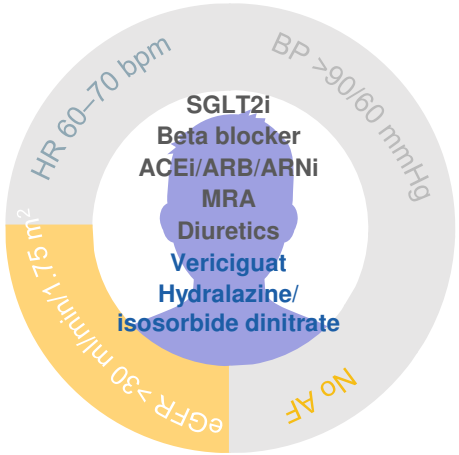
HR <60 BPM



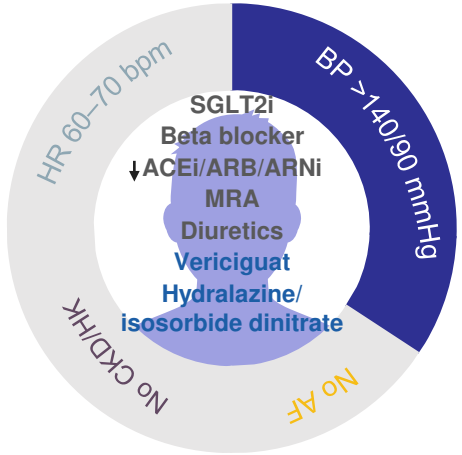
K+ >5.5 mEq/L



eGFR <30 mL/min/1.73 m²



eGFR >30 mL/min/1.73 m²



BP >140/90 mmHg

Black text, drugs that should be given to patients; red text, drugs that should be reduced or discontinued; blue text, drugs that should be added.
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HK, hyperkalemia; HR, heart rate; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose co-transporter 2 inhibitor.

Reference: 1. Rosano GMC *et al. Eur J Heart Fail* 2021; https://doi.org/10.1002/ejhf.2206.

Where Does Vericiguat Fit?

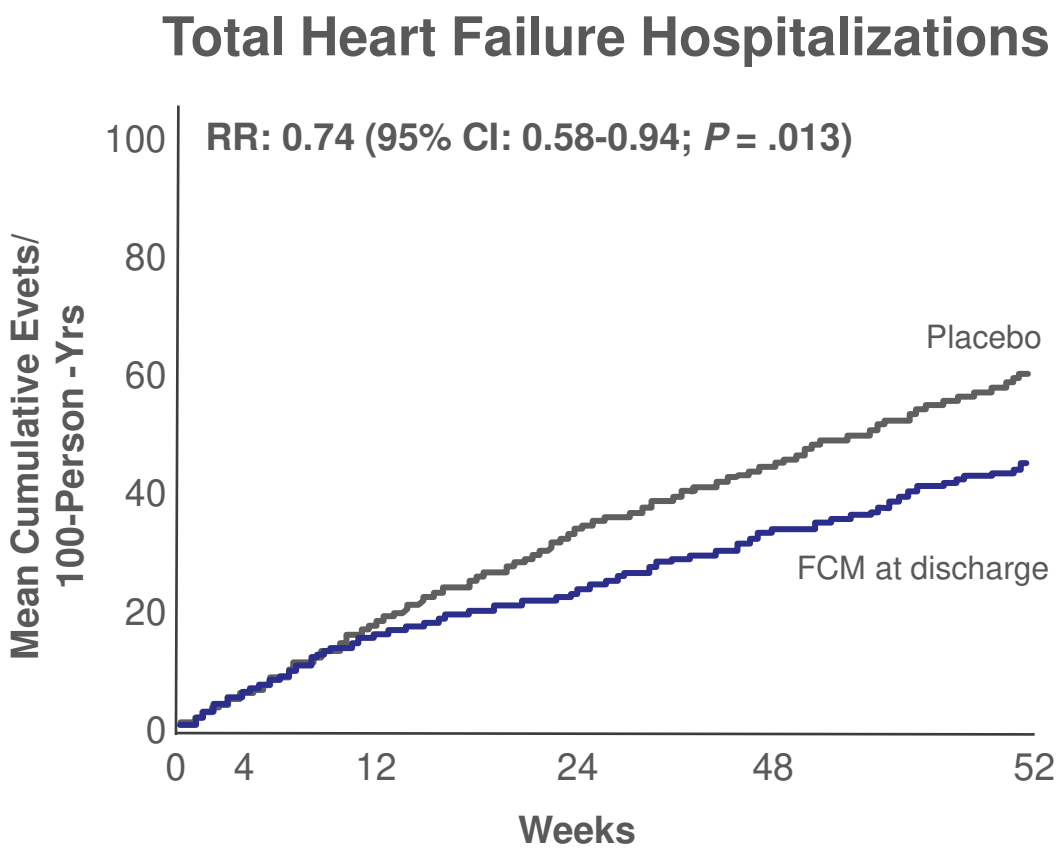
- **On standard of care and develop worsening heart failure**
- **Unable to tolerate standard therapy**
  - Vericiguat is safe and well-tolerated
    - Blood pressure
    - Heart rate
    - Renal function
    - Potassium
- **Among those with NT-proBNP <8000**
  - Mortality estimates similar to other therapies
- **Upstream high-risk population**
  - Definition of worsening HF?
  - Further studies in HFrEF patients without recent worsening HF?

Omecamtiv Mecarbil for Patients with HFrEF

- **Which Patients?**
  - GALACTIC-HF Patients: Symptomatic (NYHA II-IV), LVEF ≤35%, elevated NP (+ Higher Risk Element; i.e. NYHA III: HR 0.87 (0.79, 0.96); p=0.007; NNT 22)
  - Caution in patients in Atrial Fibrillation on Digoxin?

- **When?**
  - Inpatient or Outpatient
  - No adverse effect on Blood pressure, Heart rate, Potassium Homeostasis or Renal Function
  - No interference with GDMT
  - Adverse event profile similar to placebo

Ferric Carboxymaltose: AFFIRM-AHF
Iron-Deficient Patients Discharged After Acute Heart Failure

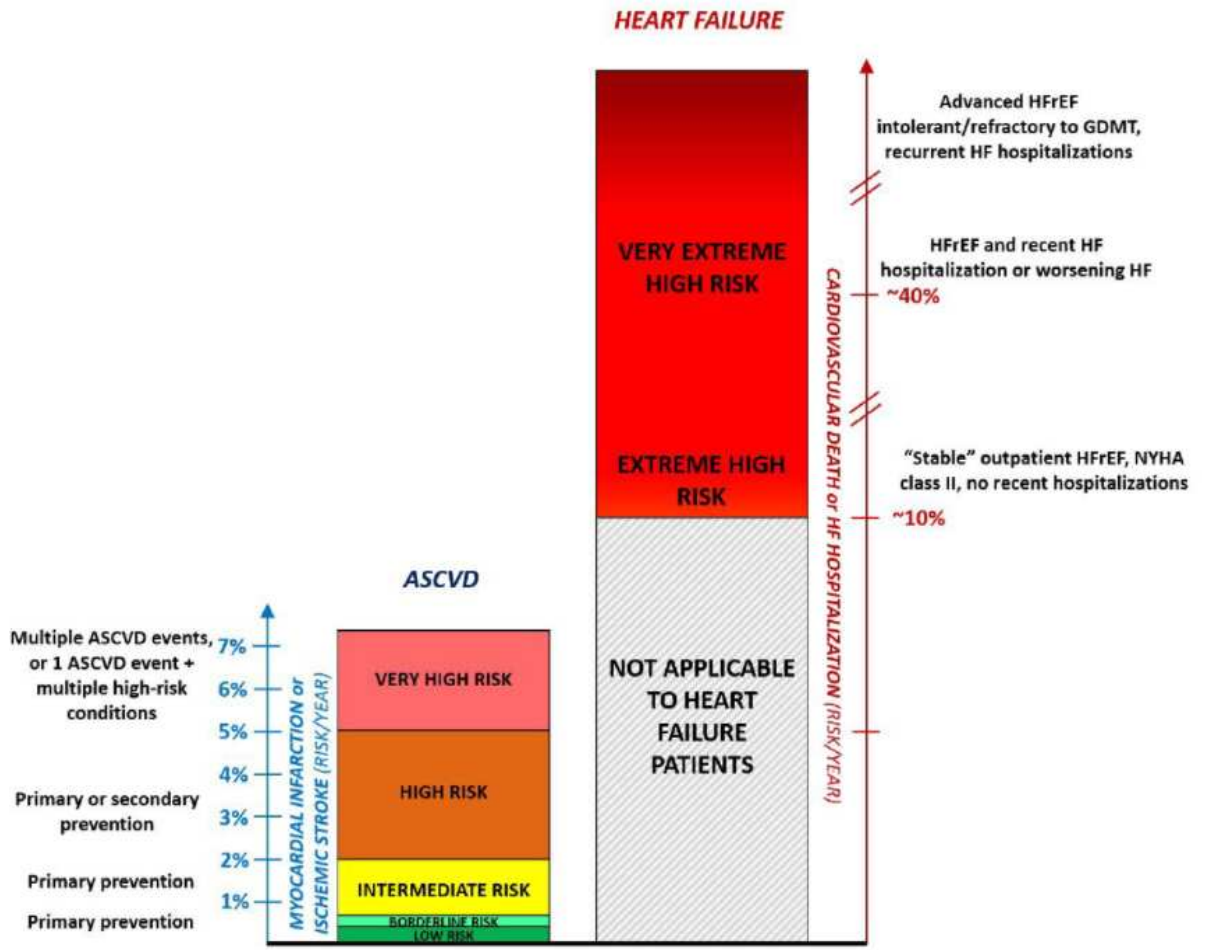


- International, randomized, double-blind, placebo-controlled phase IV trial
- Iron-deficient adults hospitalized for acute HF, LVEF < 50%
- N = 550 Placebo; N = 559 FCM
- **Treatment with ferric carboxymaltose (FCM) was safe and reduced the risk of heart failure hospitalizations**
- No apparent effect on the risk of cardiovascular death

FCM = Ferric Carboxymaltose; LVEF = Left Ventricular Ejection Fraction

Ponikowski P, et al. Lancet. 2020;396(10266):1895-1904.

Contextualizing Risk Among Patients with Heart Failure



Greene SJ, Butler J, Fonarow GC. Contextualizing Risk Among Patients With Heart Failure. *JAMA.* Published online November 15, 2021. doi:10.1001/jama.2021.20739

Key Learnings

- All patients with HFrEF can be characterized as extremely high risk of CV death and hospitalizations
- Residual risk exists even in patients optimized on heart failure GDMT therapies
- Worsening heart failure can be identified in your patients needing:
  - Escalation of diuretics
  - Urgent visit requiring IV diuretics
  - ER visit
  - Admission
- NT-proBNP can help to identify patient at increased risk of hospitalizations and death
- To increase adherence to guidelines, foundational therapy (MRA, BB, SGLT2i, ARNI) should be initiated in-hospital and promptly optimized around discharge
- Vericiguat can be added to standard of care with patients developing worsening heart failure, or as tailored therapy when foundational drugs are reduced, discontinued or not tolerated

HF-iDOC Heart Failure Identification and Optimization in the Community

CHFS SCIC Canadian Heart Failure Society / Société canadienne d'insuffisance cardiaque

The 2022 HF-iDOC program is a CHFS EMR-based quality improvement initiative that identifies heart failure patients with reduced ejection fraction (HFrEF) identified through electronic medical records (EMR) and analyzes adherence to GDMT. Participating physicians utilize Accuro™ (QHR Technologies Inc.)

60 cardiologists participated to date

To date, **2000 patients** with left ventricular EF≤40% between September 2020 and September 2021 were involved in the practice assessment

The protocol of HF-iDOC has been reviewed and approved by an independent ethics review board

If you are an Accuro user and would like to participate in HF-iDOC and present your data to colleagues in your region, or for more information about the program, please contact Jenna Reyenga at jenna@eocipharma.com