THE NEW FRONTIER:
Worsening Heart Failure as a Target for Therapy

FRIDAY MAY 7, 2021 / 1:00 – 1:50 PM ET

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

Welcome and Introduction

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Planning Committee & Faculty

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University of Montreal Chair Holder: Foundation Marcelle et Jean Coutu, Cal et Janine Moisan for better practices in advanced heart failure

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Disclosure of Financial Support

- This program has received financial support from Bayer in the form of an educational grant

Mitigating Potential Bias

- Potential Biases are acknowledged and are mitigated by presenting data supported by national and international guidelines, and as follows:
    - Information presented is evidence-based
    - Material has been developed and reviewed by the Planning Committee

Off-label uses of drugs will be discussed and identified as such by the speaker

Accreditation

This event is 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 hour.

Learning Objectives

- Define worsening heart failure across the spectrum of patient presentations and recognize the significant unmet need to optimize outcomes in these patients
- Explore data from the VICTORIA trial and discuss how vericiguat may close the gap on worsening heart failure by addressing a different therapeutic target than currently available therapies
- Diagnose worsening heart failure and apply best practices for in-patient and out-patient management, based on a comprehensive look at the evidence
- Explore different case scenarios of patients with worsening heart failure and apply treatment strategies based on evidence and expert recommendations

Characterizing Worsening Heart Failure

Anique Ducharme, MD, MSc, FRCP
President – Canadian Heart Failure Society
Director, Heart Failure Clinic, Montreal Heart Institute,
Professor of Medicine, University of Montreal
University of Montreal Chair Holder: Foundation Marcelle et Jean Coutu, Cal et Janine Moisan for better practices in advanced heart failure

First….

What is Worsening Heart Failure ?

- Universal definition

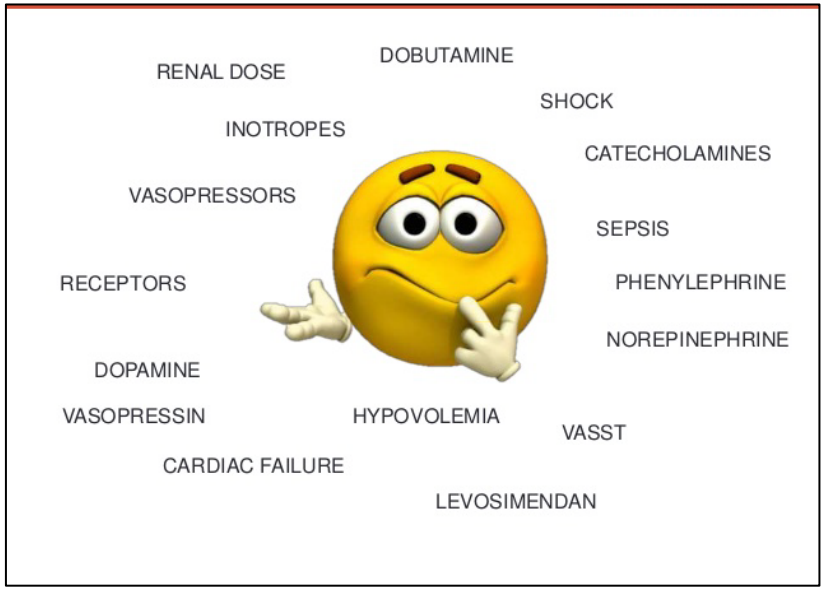
Defining WHF…

- OPTIME-CHF
- RITZ-4
- Pre-RELAX- AHF
- PROTECT
- DOSE
- RELAX-AHF
- REVIVE I
- REVIVE 2
- ROSE

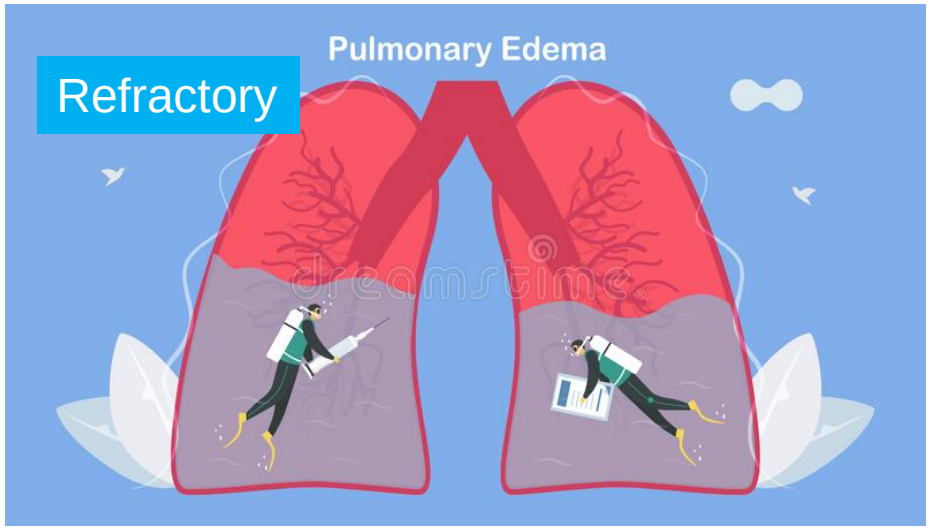
No consensus in definition for endpoints or timing

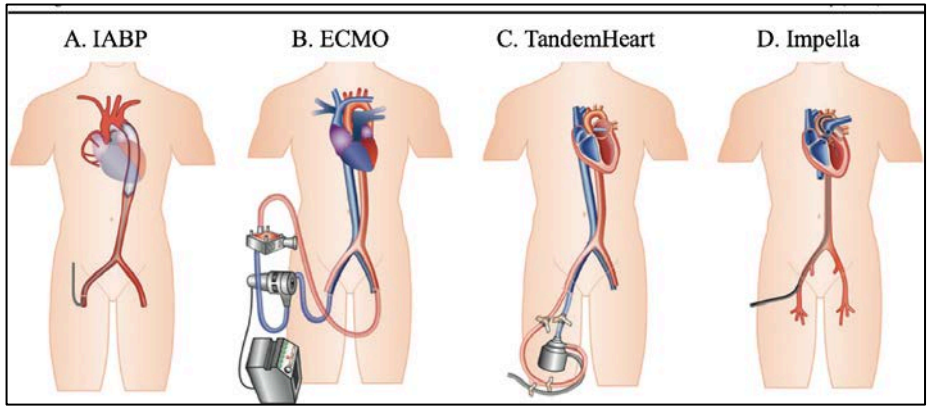
ENDPOINTS

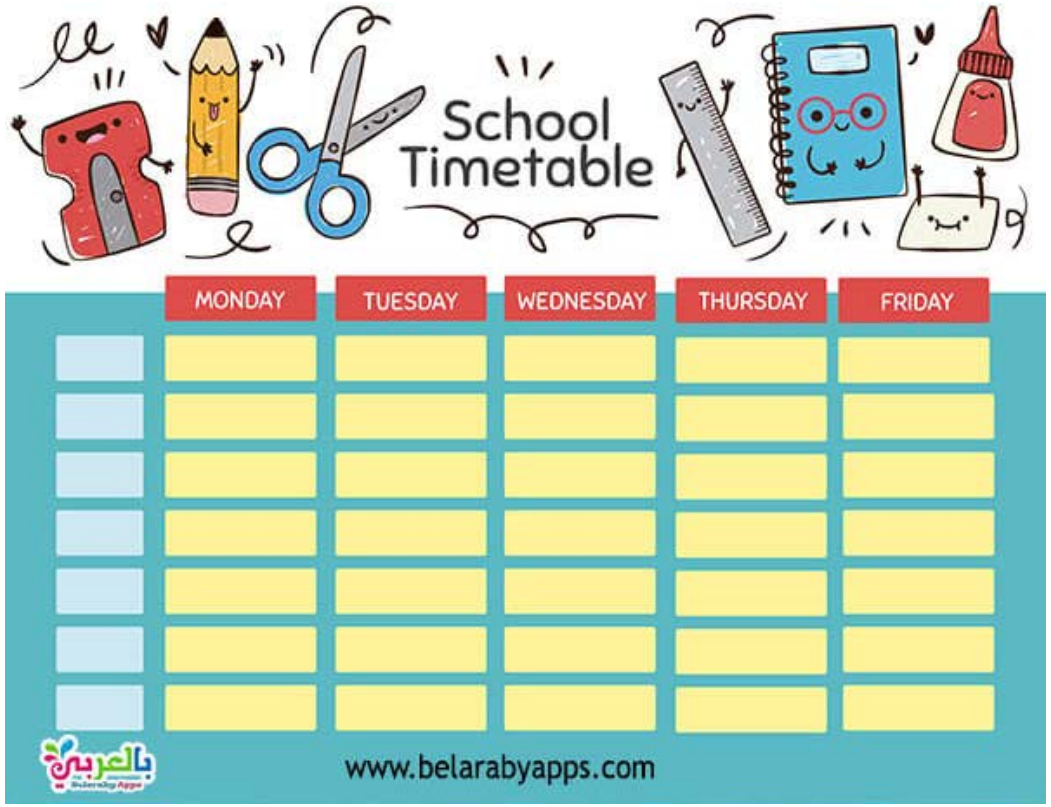
inadequate



Refractory

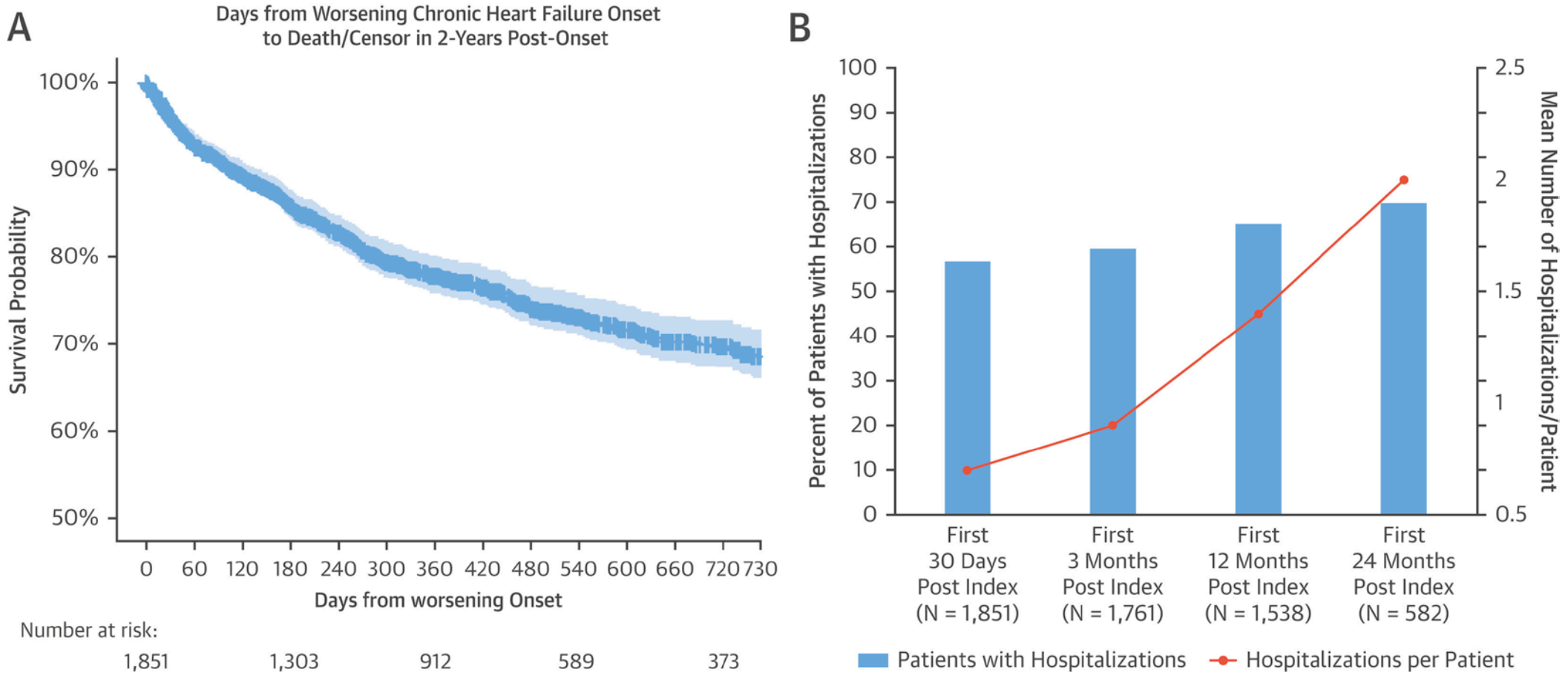






- 48 h after therapy initiation
- 72h..
- 5 days ?
- >24 h after study drug initiation and requiring intervention by day 7/discharge
- 14 days?
- 31 days?
- At 6 h, 24 h, or 5 days, 31 days

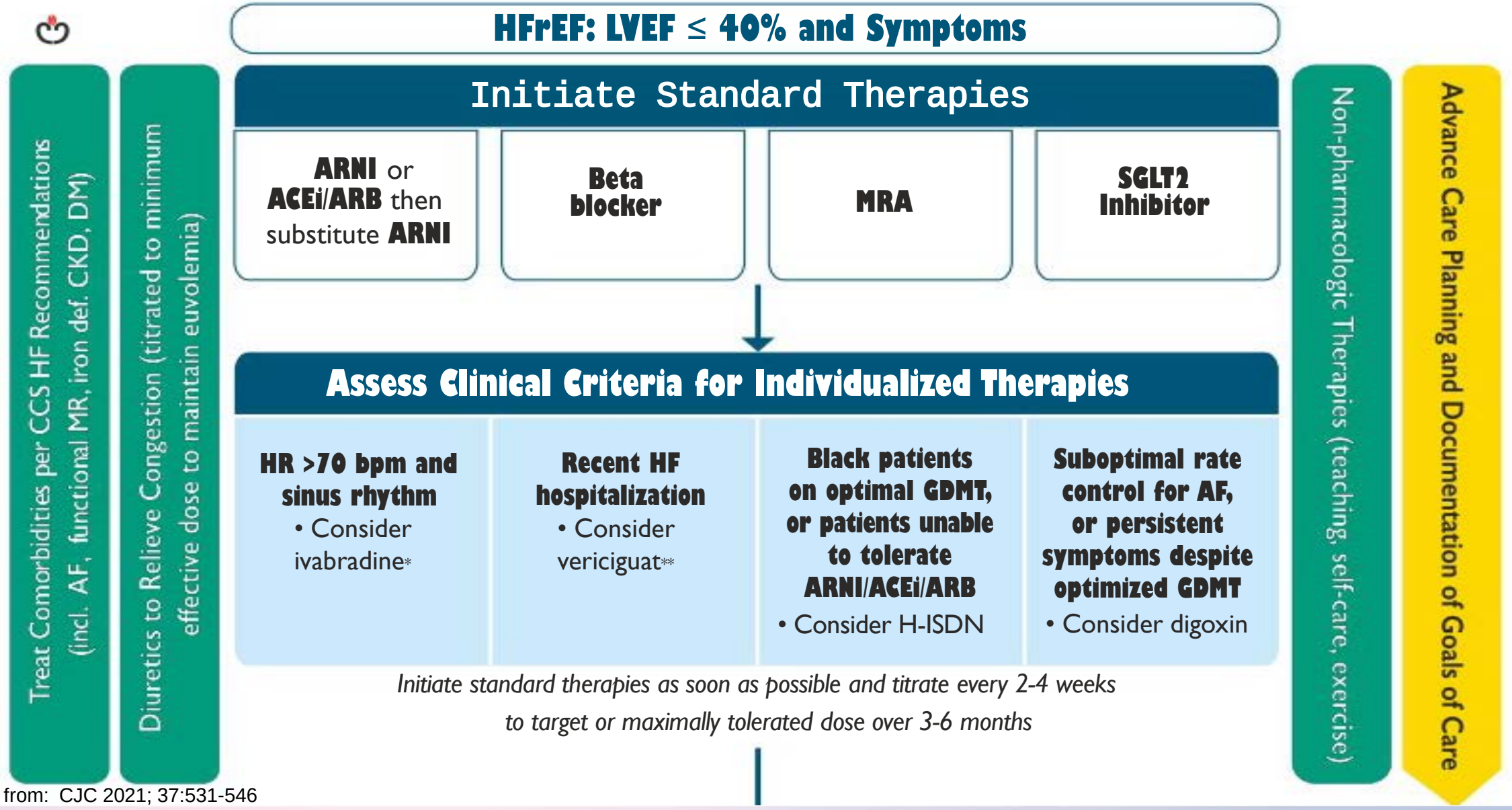
Outcomes for Patients With Worsening Heart Failure



Butler et al. JACC VOL. 73, NO. 8, 2019

- WHF is generally defined as worsening heart failure symptoms and signs requiring an intensification of therapy,
- Incidence : 5% to 42% of hf admissions.
- High risk for adverse outcomes post-discharge,
  - ¼ readmission within a month and
  - ~30% mortality within a year of discharge.
- Developing new therapies for these patients has been challenging, in part due to the lack of reliable surrogate markers to predict future risk.

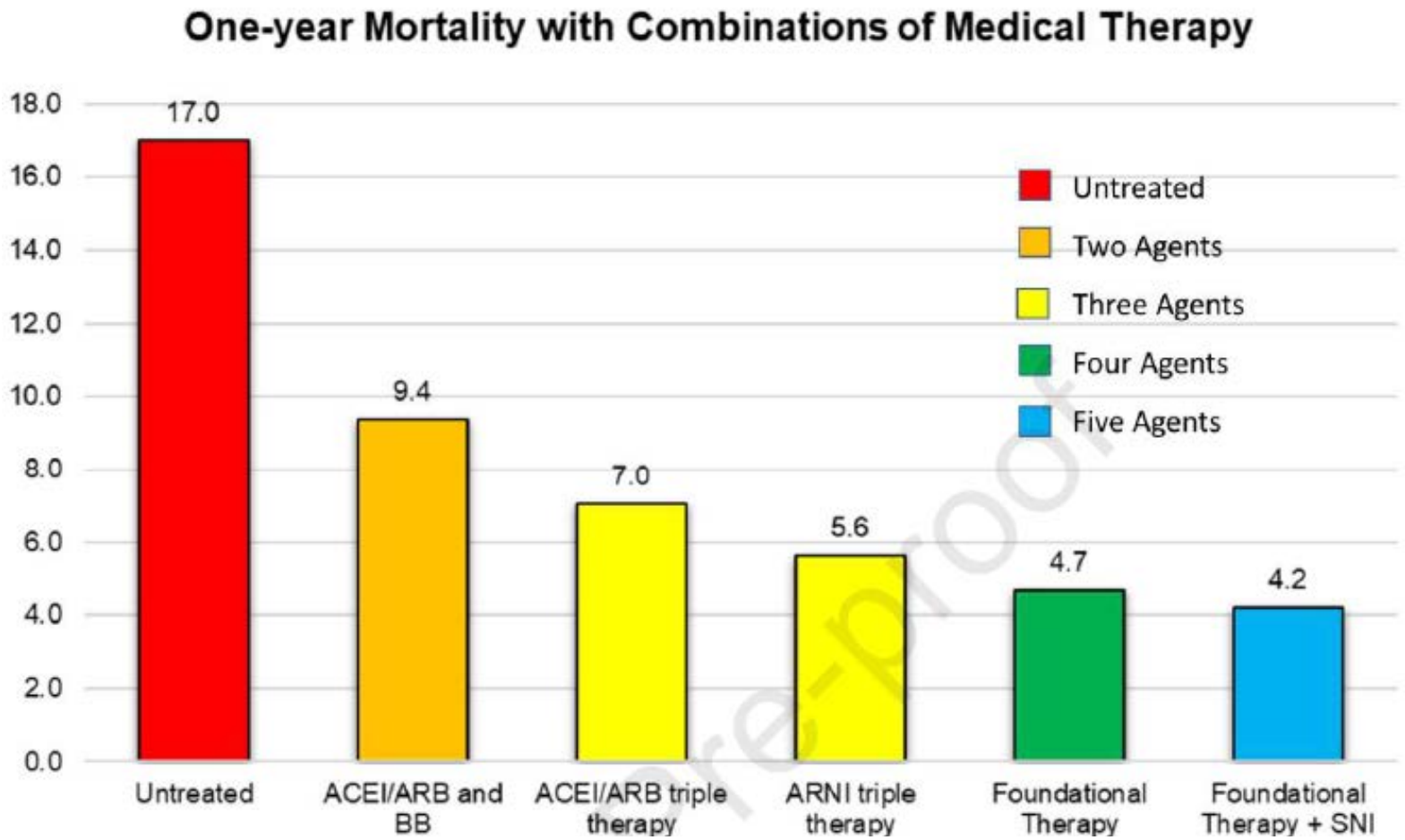
Therapeutic Approach to Patients with Heart Failure and Reduced Ejection Fraction (HFrEF)



Adapted from: CJC 2021; 37:531-546

Targeting the Residual risk

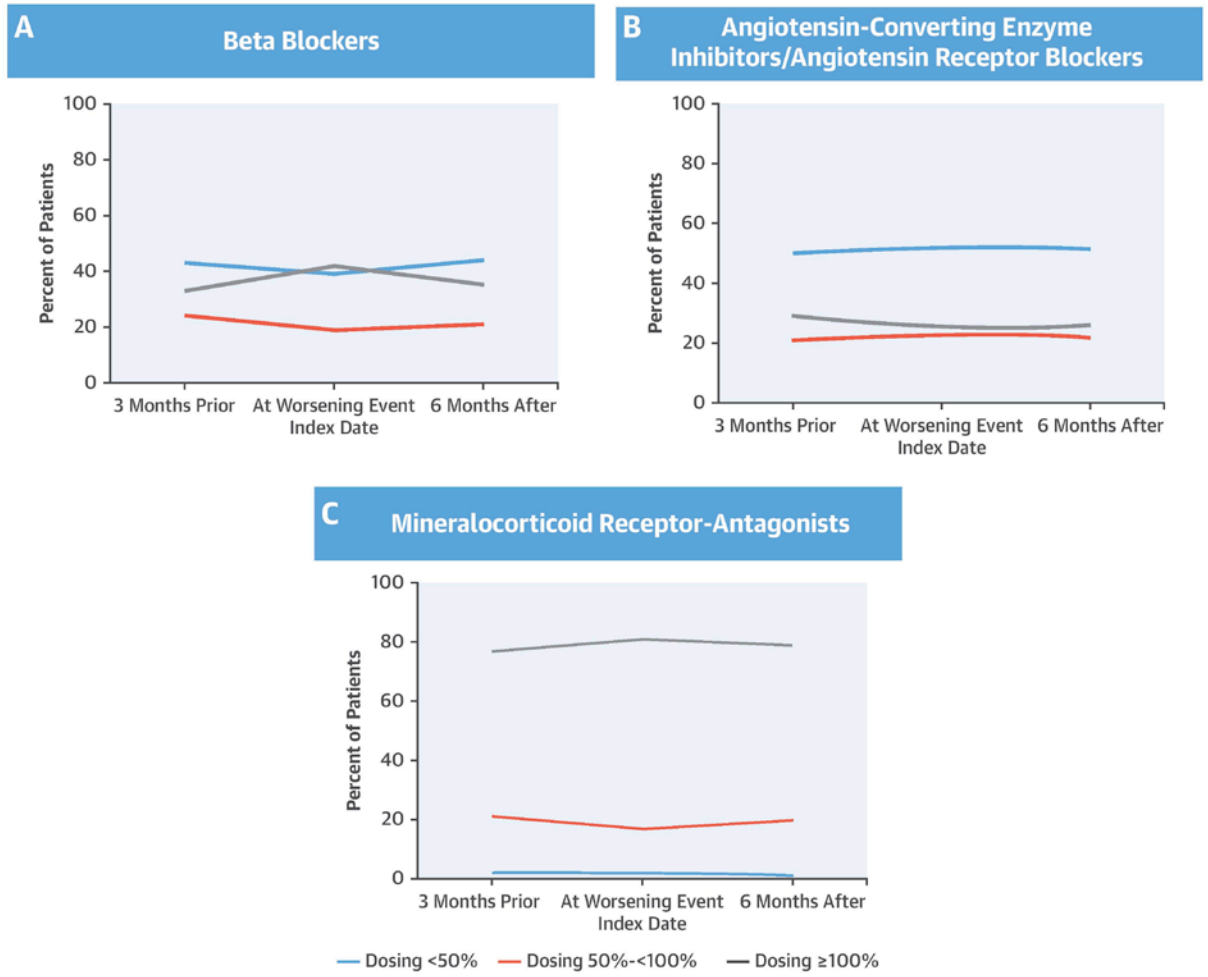
Incremental benefit of combination therapies in HFrEF



Risk reduction with therapy extrapolated from previous estimations of landmark trials
Foundational therapy includes BB, MRA, ARNI, and SGLT2

Miller, CJC, 2021, in press

Treatment Patterns in Patients With HFrEF & WHF: % of Patients on Daily Target Doses



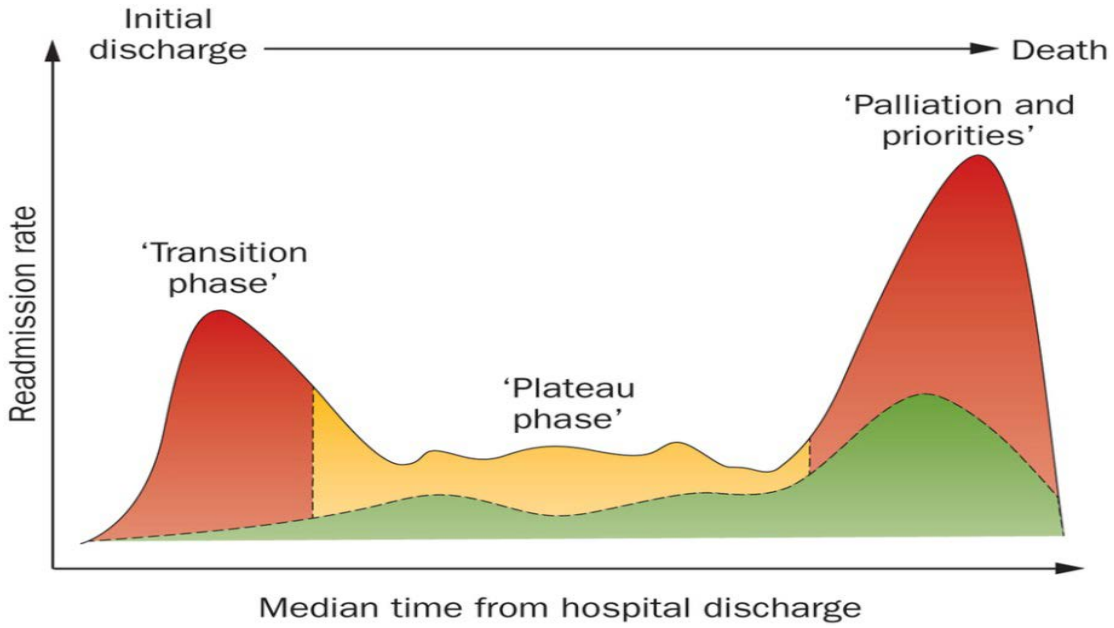
- Before, during, & after the WHF event.
- Overall, patients were generally on significantly suboptimal medical therapy.
- These trends did not change considerably at 6 months, even after a WHF event.

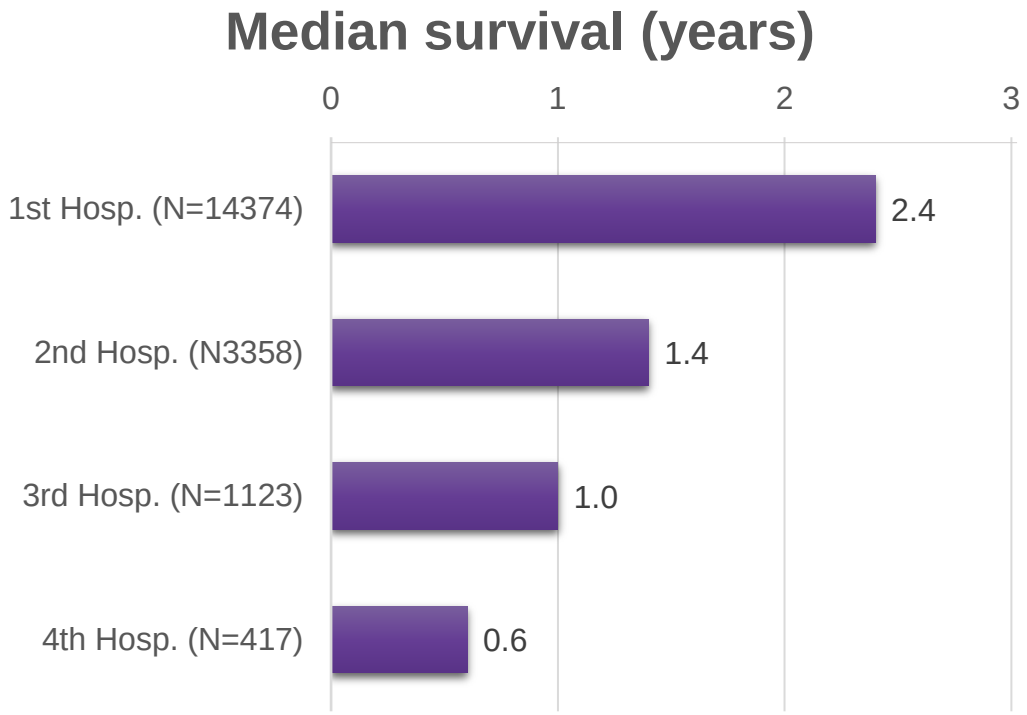
Butler, J. et al. J Am Coll Cardiol. 2019;73(8):935-44.

Hospital Admission: Failure or Opportunity?

Prognosis Following HF Hospitalization in Canada

- Post-discharge transition period is a high-risk phase or vulnerable phase
- **1 in 5 (20%)** patients will be readmitted within 30 days





- The CCS benchmark recommends follow-up within **3** weeks of hospitalization

Setoguchi S et al. *Am Heart J* 2007; 154(2):203-205.

New Data on Soluble Guanylate Cyclase Stimulators in Heart Failure: The VICTORIA trial

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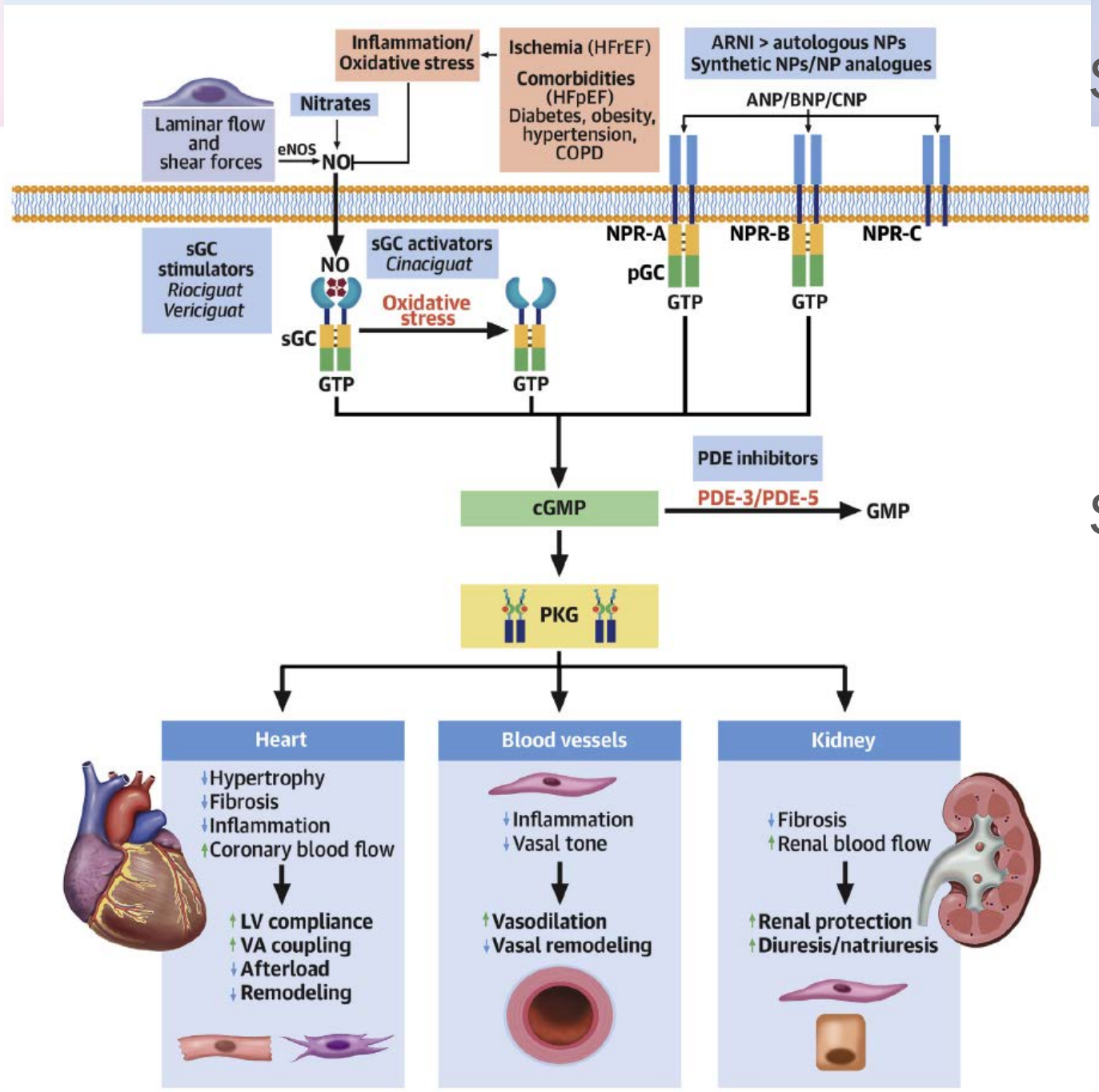
Sacubitril/valsartan

Nitrates

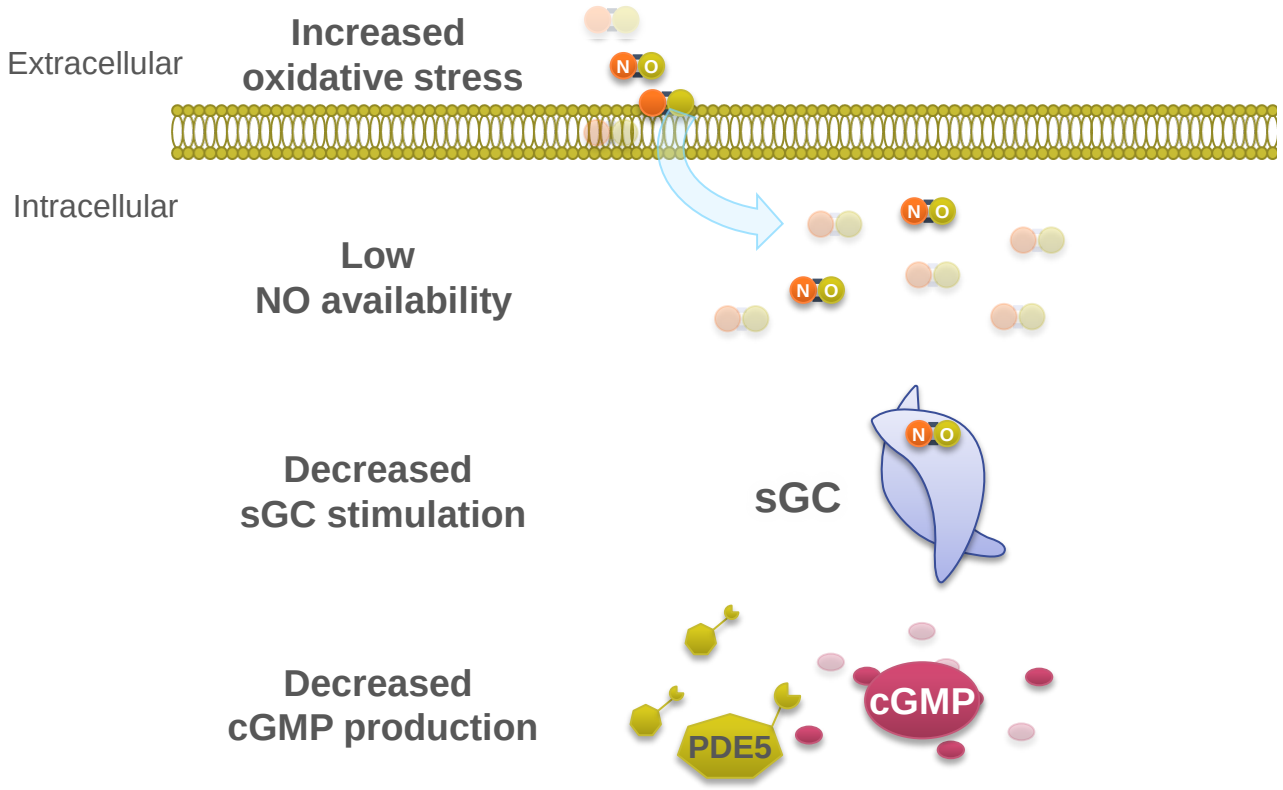
Vericiguat



Sildenafil

Emdin, JACC 2020

Soluble Guanylate Cyclase (sGC)



Clinical Effects of an Impaired sGC-cGMP Pathway

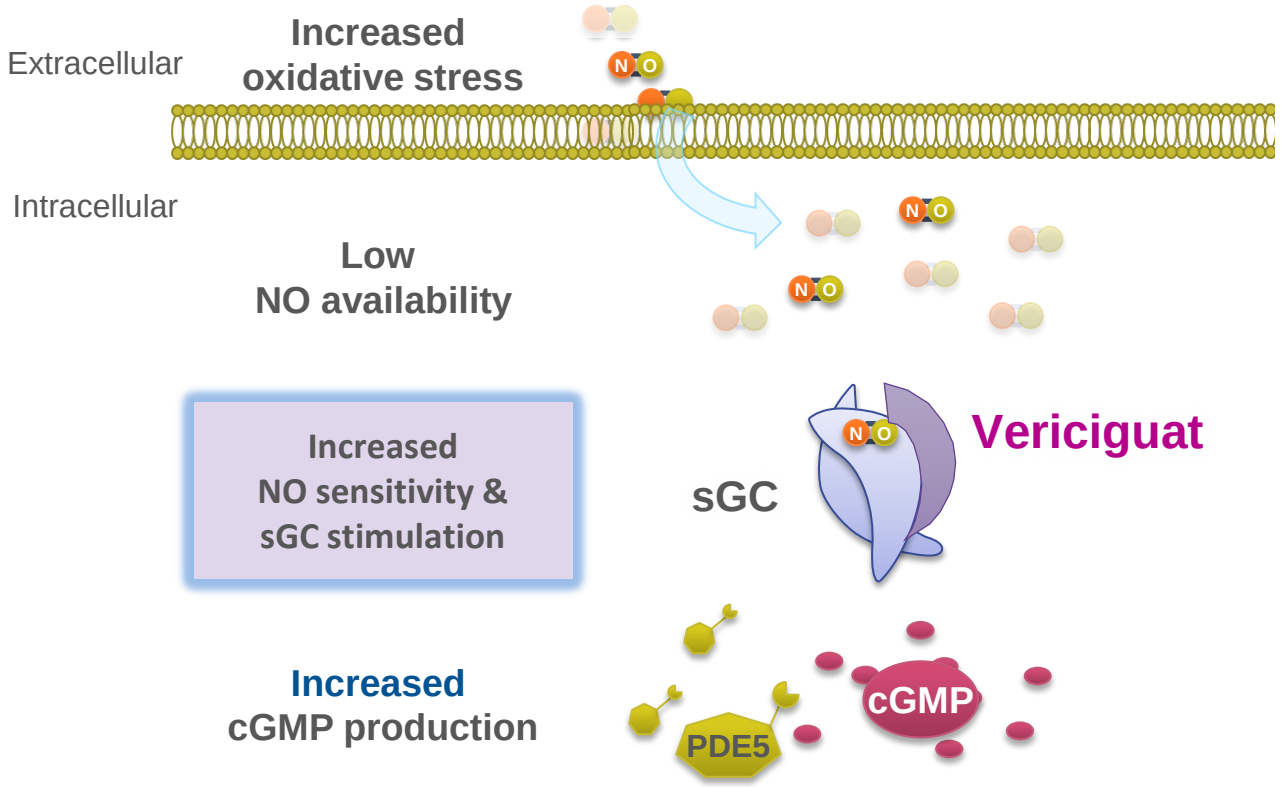
- Progressive myocardial dysfunction
- Adverse left-ventricular remodeling
- Vascular dysfunction
- Increased fibrosis
- Increased inflammation

Oxidative stress and the resulting deficiency in NO can lead to insufficient stimulation of the sGC, decreased production of cGMP, and subsequent cardiovascular dysfunction and HF[1,3]

cGMP=cyclic guanosine monophosphate; HF=heart failure; NO=nitric oxide; PDE5=phosphodiesterase 5; RAAS=renin-angiotensin-aldosterone system; sGC=soluble guanylate cyclase; SNS=sympathetic nervous system.

1. Breitenstein S et al. *Handb Exp Pharmacol*. 2017;243:225-247. 2. Buys ES et al. *Cardiovasc Res.* 2008;79(1):179-186. 3. Gheorghiade M et al. *Heart Fail Rev*. 2013;18(2):123-134. 4. Data on file.

sGC and HF: vericiguat



Clinical Effects of Vericiguat on an Impaired sGC-cGMP Pathway

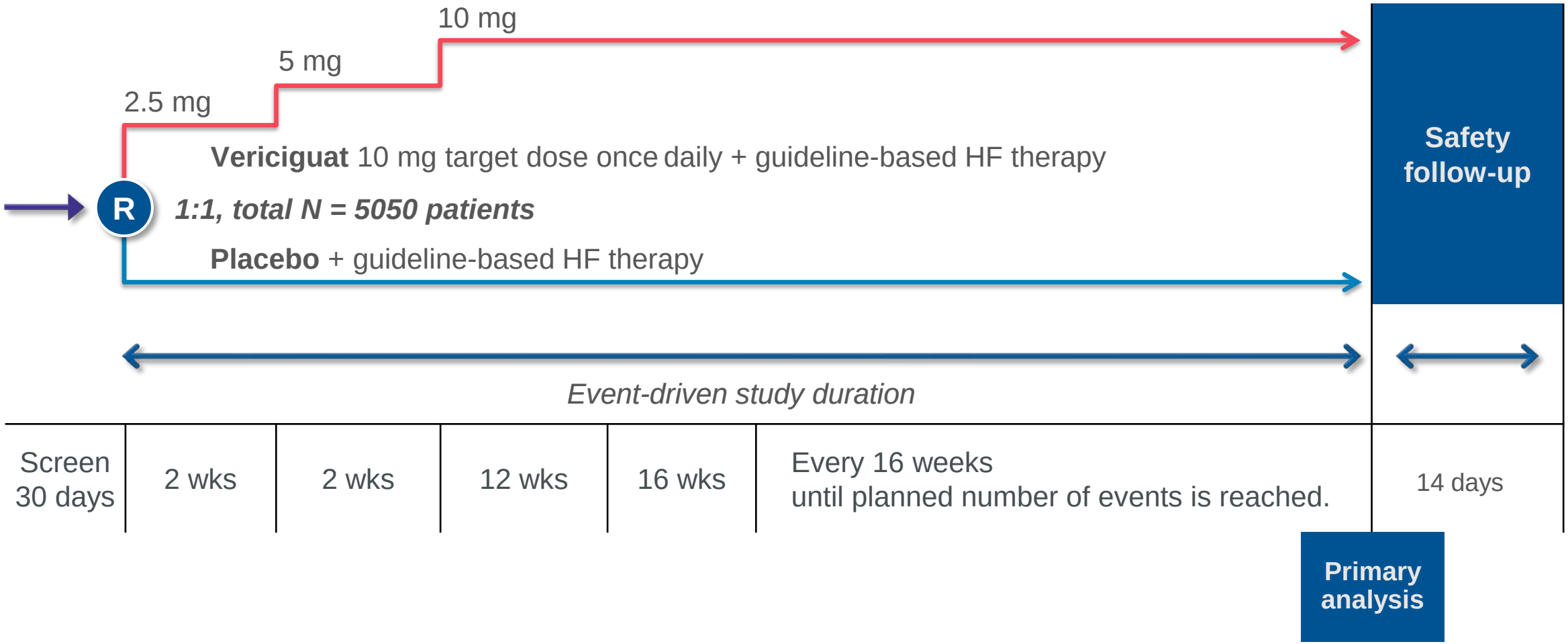
- **Improved** myocardial function
- **Reduced** left-ventricular remodeling
- **Improved** vascular function
- **Decreased** fibrosis
- **Decreased** inflammation

Vericiguat directly and selectively stimulates sGC to increase cGMP production even under low-NO conditions in HF4

cGMP=cyclic guanosine monophosphate; HF=heart failure; NO=nitric oxide; PDE5=phosphodiesterase type 5; sGC=soluble guanylate cyclase.

1. Breitenstein S et al. *Handb Exp Pharmacol*. 2017;243:225-247. 2. Buys ES et al. *Cardiovasc Res.* 2008;79(1):179-186. 3. Gheorghiade M et al. *Heart Fail Rev*. 2013;18(2):123-134. 4. Armstrong PW et al. *JACC Heart Fail*. 2018;6(2):96-104.

VICTORIA Design



VICTORIA: Inclusion Criteria

"Chronic HF"

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

after

"Worsening event"

- 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

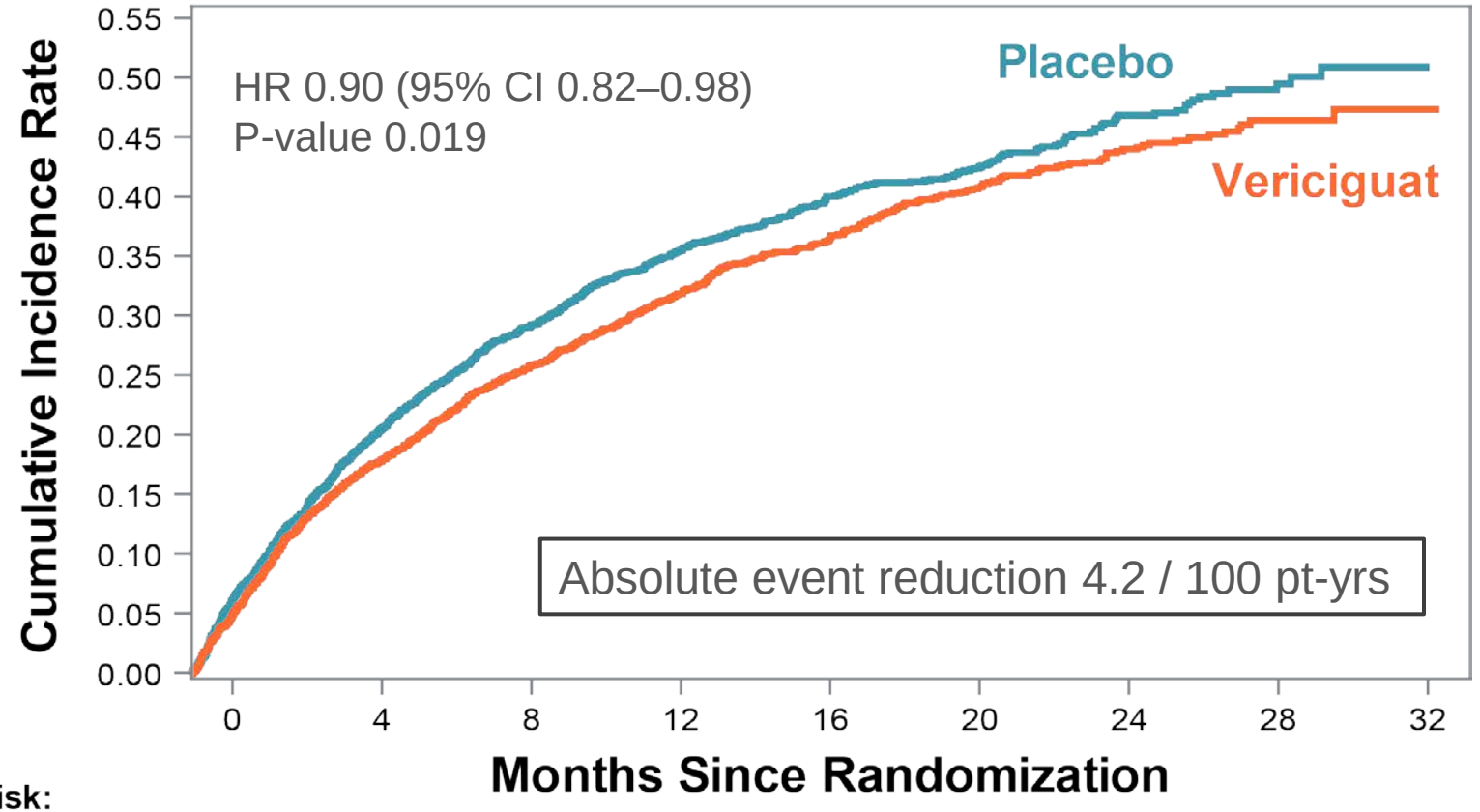
Patients may have been randomized as an inpatient or outpatient but must have met criteria for clinical stability (e.g., SBP ≥ 100 mmHg, off IV treatments ≥ 24 hours)

30-day screening period without run-in

Baseline Characteristics

	Vericiguat (N=2526)	Placebo (N=2524)
Age mean (SD)	67.5 (12.2)	67.2 (12.2)
Female sex	605 (24.0%)	603 (23.9%)
Index event at Randomization		
HF hospitalization < 3 mos	1673 (66.2%)	1705 (67.6%)
HF hospitalization 3 to 6 mos	454 (18.0%)	417 (16.5%)
IV diuretic for HF < 3 mos (no hospitalization)	399 (15.8%)	402 (15.9%)
EF % (SD)	29.0 (8.3)	28.8 (8.3)
NYHA class III–IV baseline,	1045 (41.4%)	1024 (40.6%)
NT-proBNP Median (25^{th} – 75^{th}) pg/mL	2804 (1572- 5380)	2821(1548 – 5206)
Triple guide-based therapy *	1480 (58.7%)	1529 (60.7%)
ICD, BV pacemaker (or both) *	813 (32.2%)	802 (31.8%)

VICTORIA: CVD/HFH

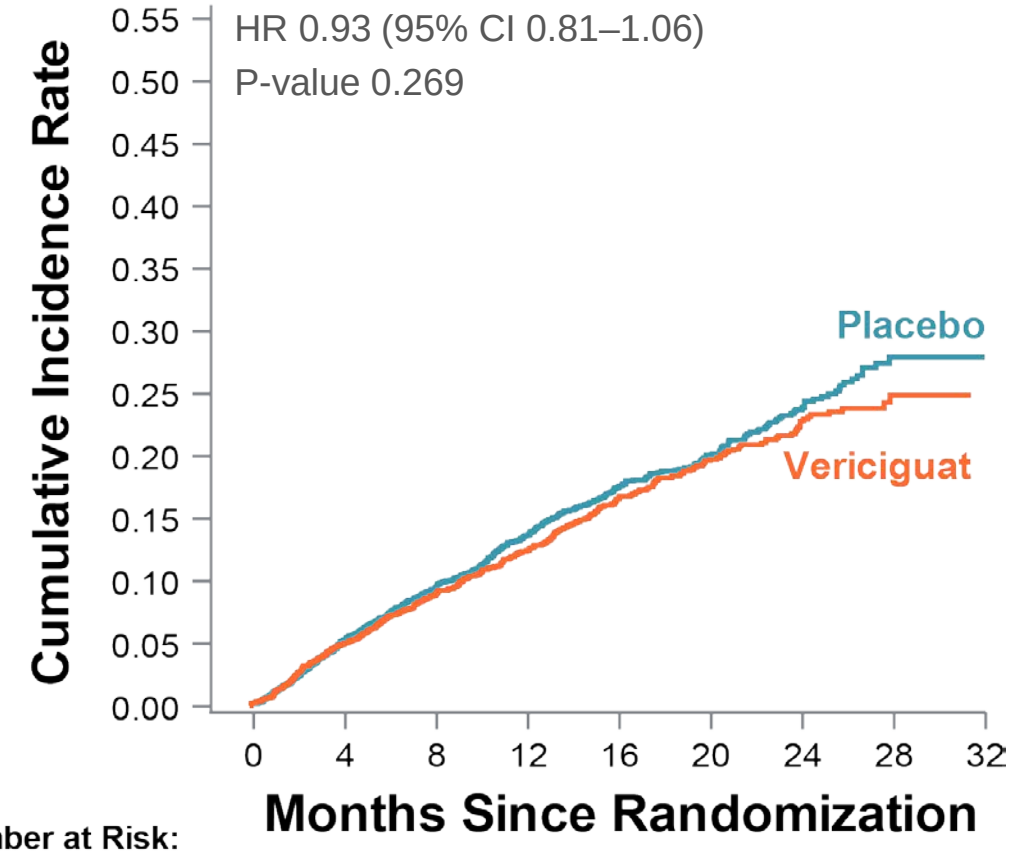


Number at Risk:									
Vericiguat	2526	2099	1621	1154	826	577	348	125	1
Placebo	2524	2053	1555	1097	772	559	324	110	0

VICTORIA, NEJM 2020

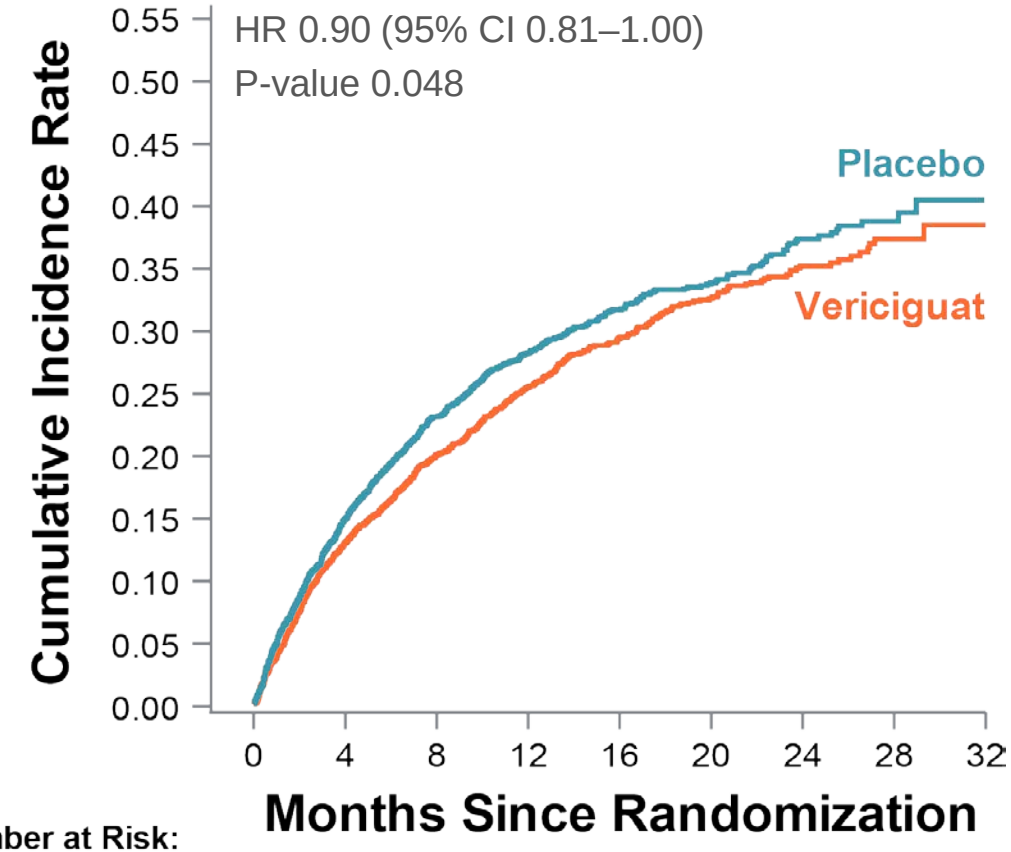
VICTORIA: Secondary Outcomes

Cardiovascular Death



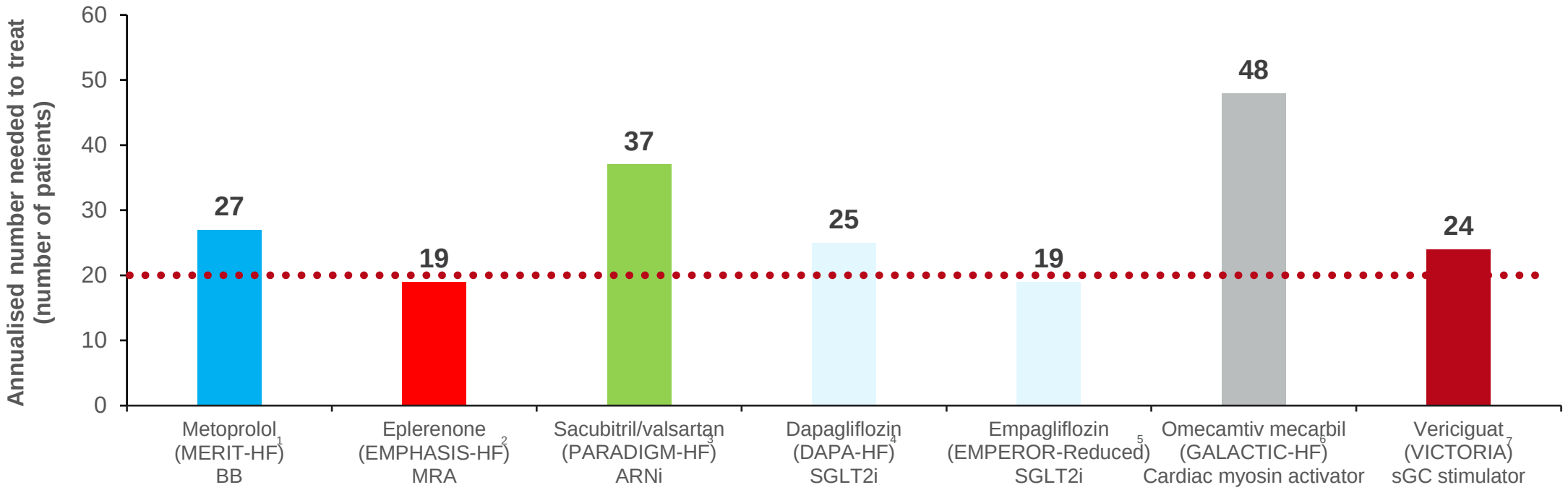
Number at Risk:									
Vericiguat	2526	2376	1968	1468	1070	779	487	185	1
Placebo	2524	2370	1951	1439	1045	768	471	157	0

First HF Hospitalization



Number at Risk:									
Vericiguat	2526	2098	1620	1153	825	577	348	125	1
Placebo	2524	2052	1554	1096	771	558	323	110	0

Annualised NNTs for primary endpoint



Safety & Tolerability

- Symptomatic hypotension / syncope more common with vericiguat
- No adverse effects of vericiguat on either electrolytes or renal function
- Serious AE were similar: vericiguat (32.8%), placebo (34.8%)
- More anemia developed with vericiguat (7.6%) than placebo (5.7%)

- At 12 months, 10 mg target dose achieved: vericiguat (89.2%), placebo (91.4%)

Summary

- Vericiguat was significantly more effective than placebo in reducing:
  - The composite of CV death or HF hospitalization
  - HF hospitalization (first and recurrent)
  - There was directionally aligned reduction in CV death
- Vericiguat titrated to 10mg was generally safe and well tolerated
- There was excellent application of guideline-based HF therapy and patient follow-up
- NNT = 24 patients x 10.8 months

Tackling WHF: When and How?

Jonathan Howlett MD, FRCPC, FCCS, FHFSA (Hon)
Clinical Professor of Medicine, University of Calgary
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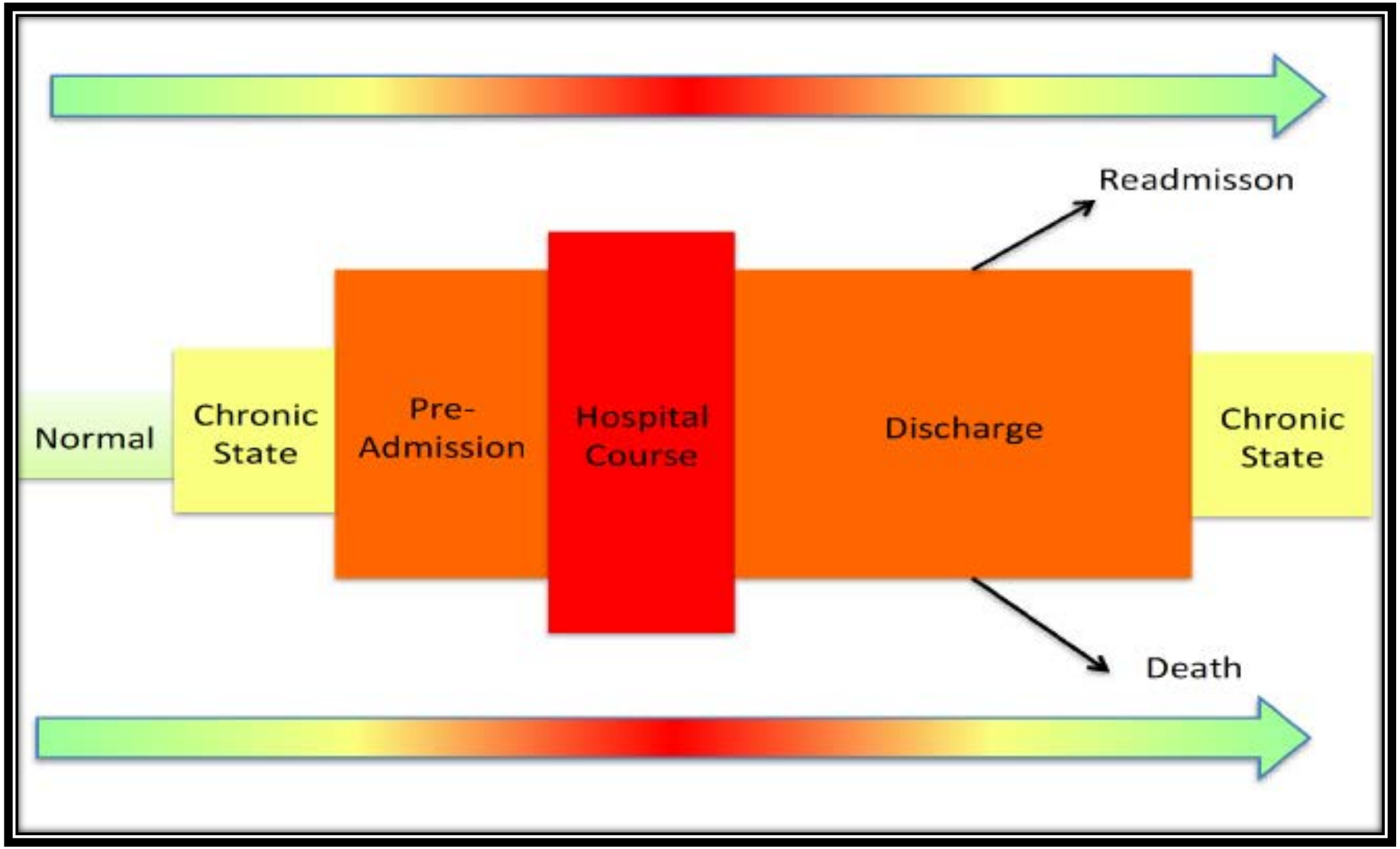
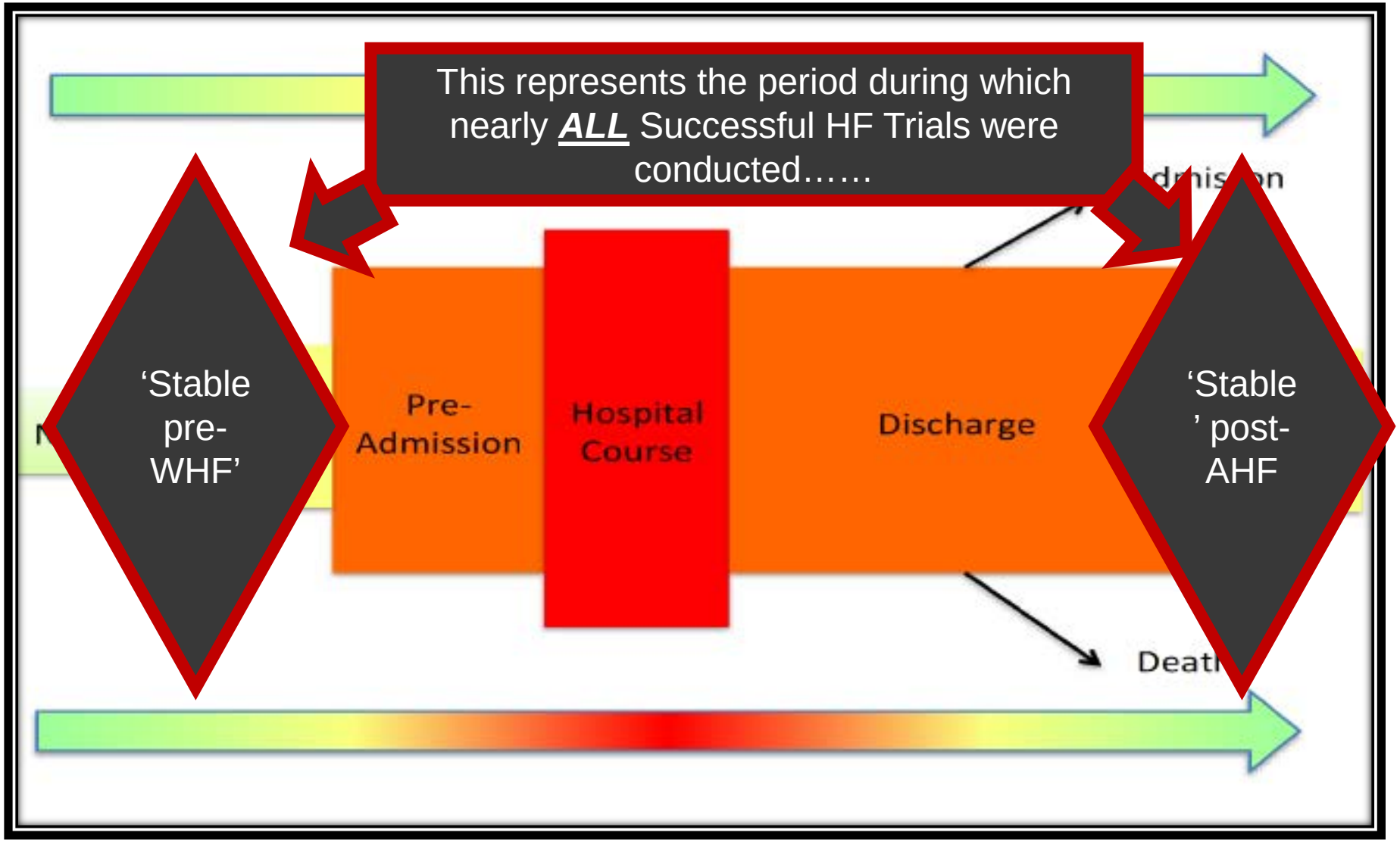
Past & Founding President, Canadian Heart Failure Society
Calgary, Alberta

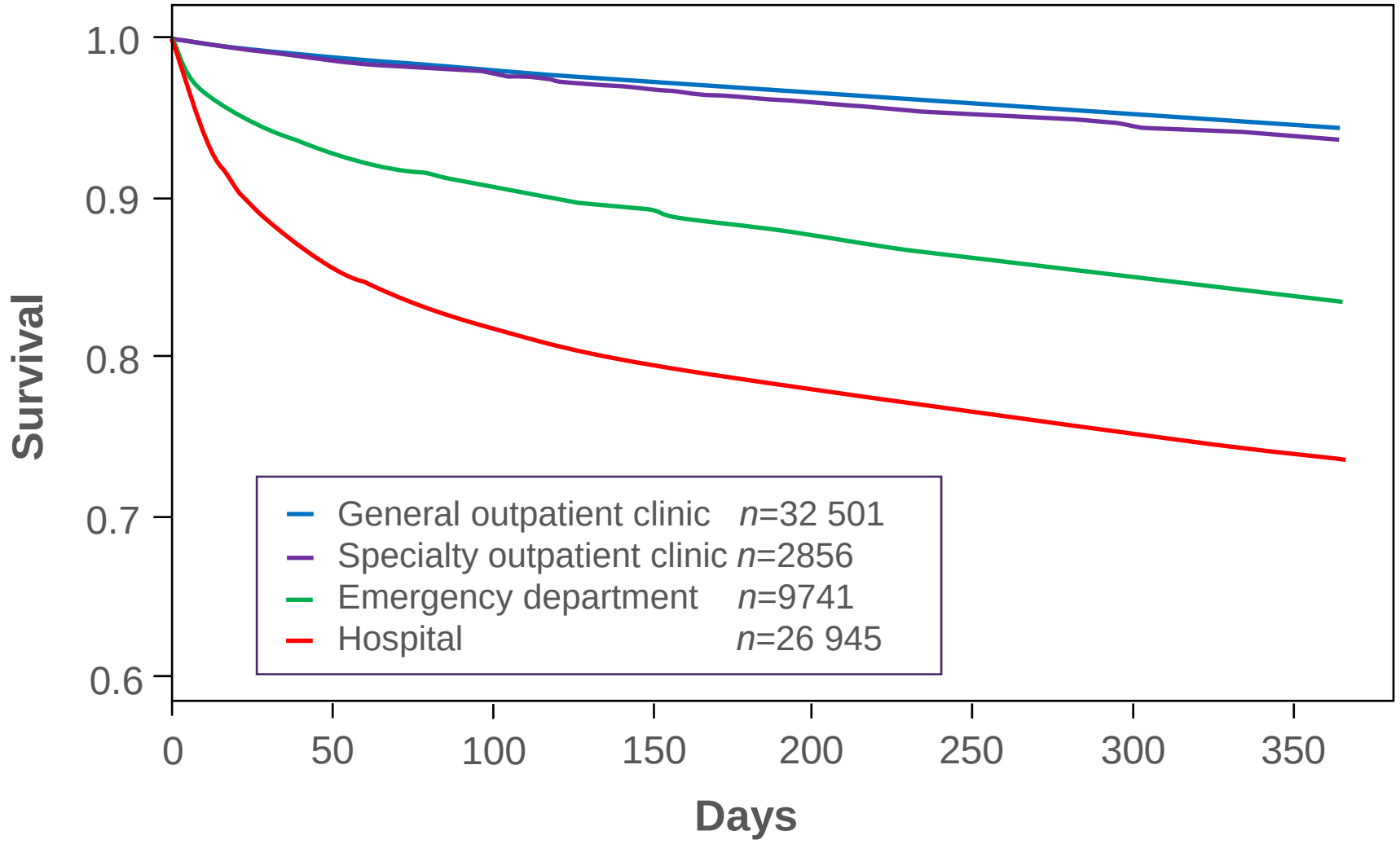
Timing of Clinical Trials in the HF Journey



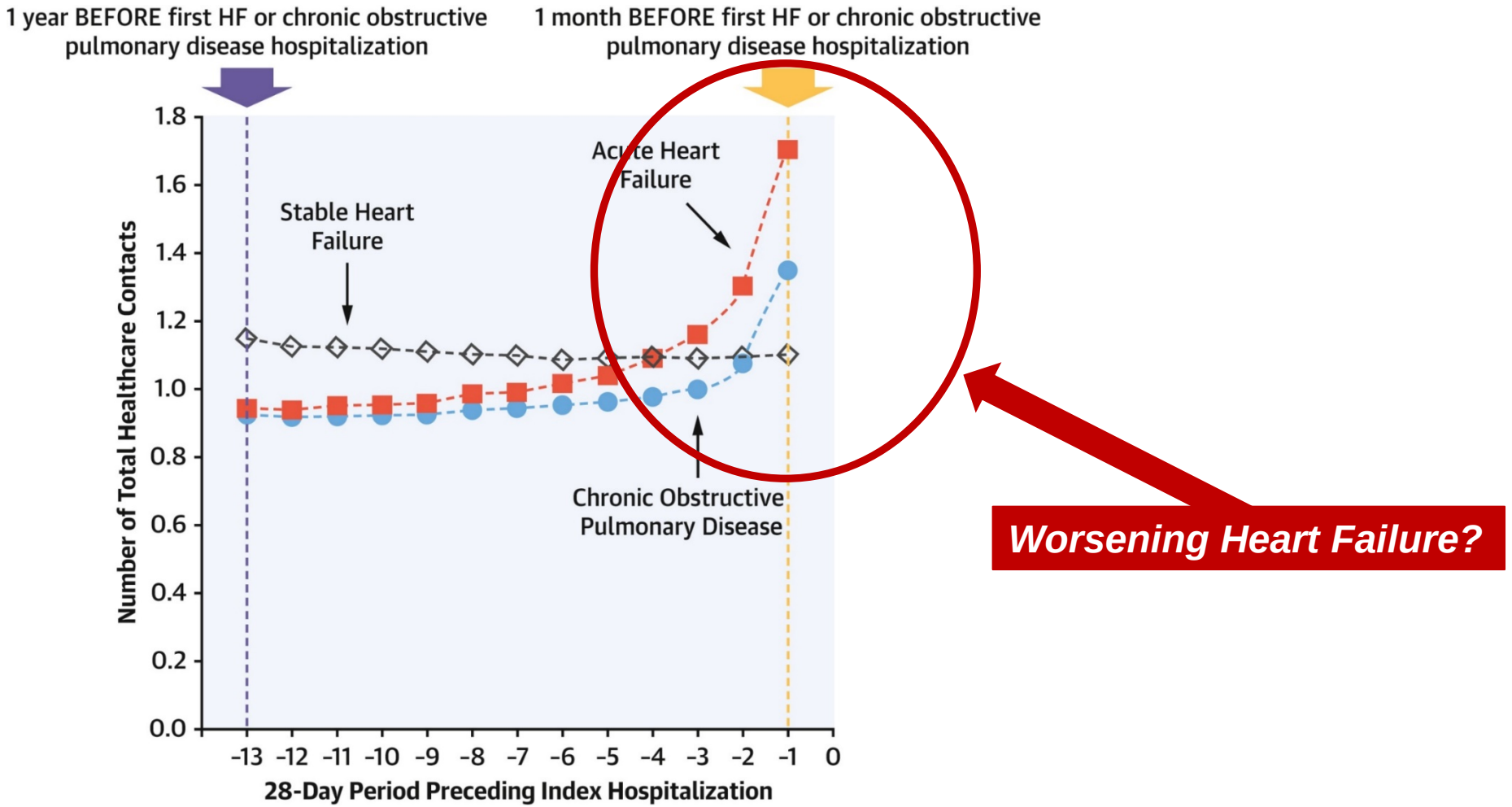
Timing of Clinical Trials in the HF Journey



Survival Curves after Index Visit for Heart Failure in Different Location of Initial HF Diagnosis

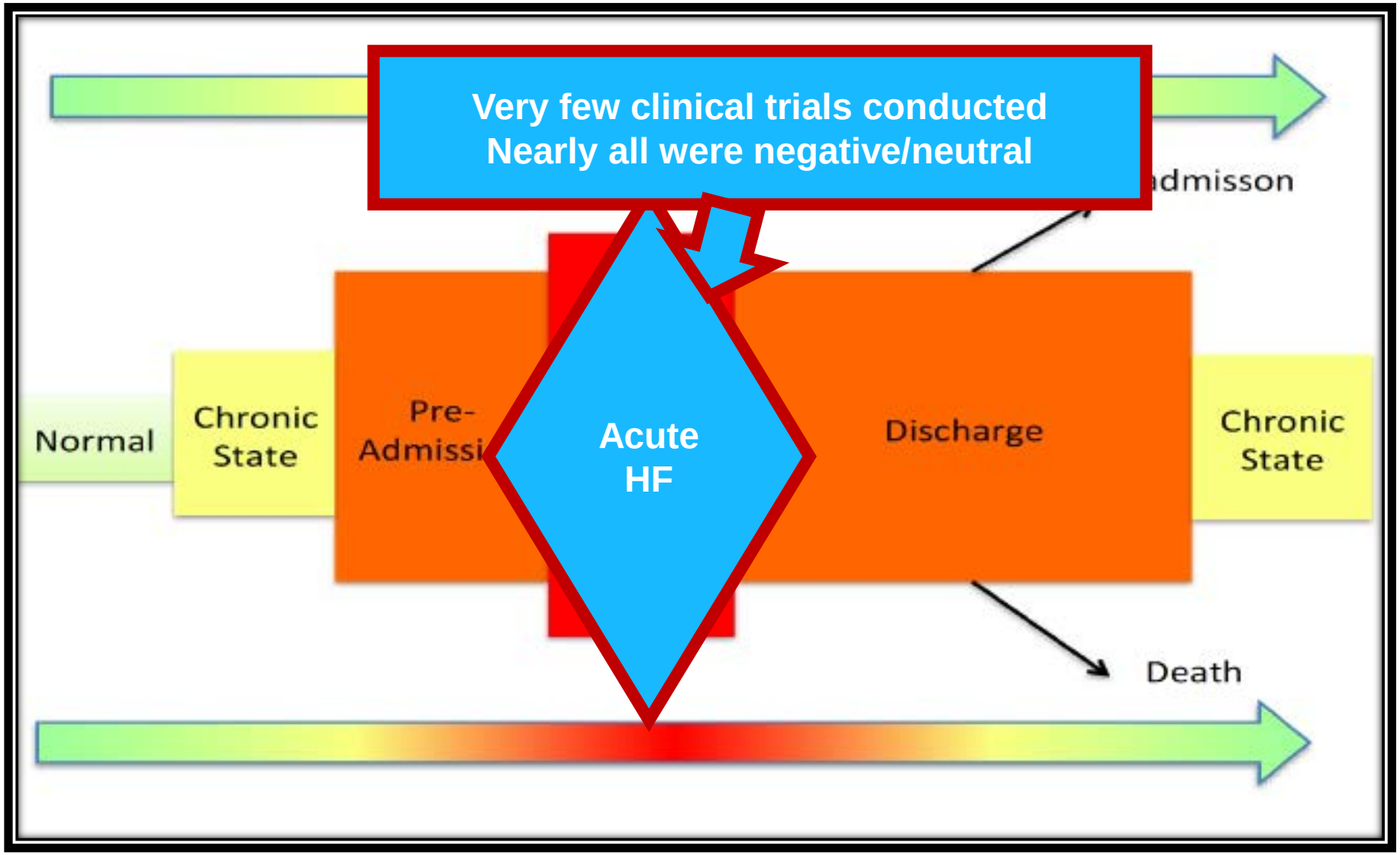


Ezekowitz JA. Eur J HF 2011;13:142-7



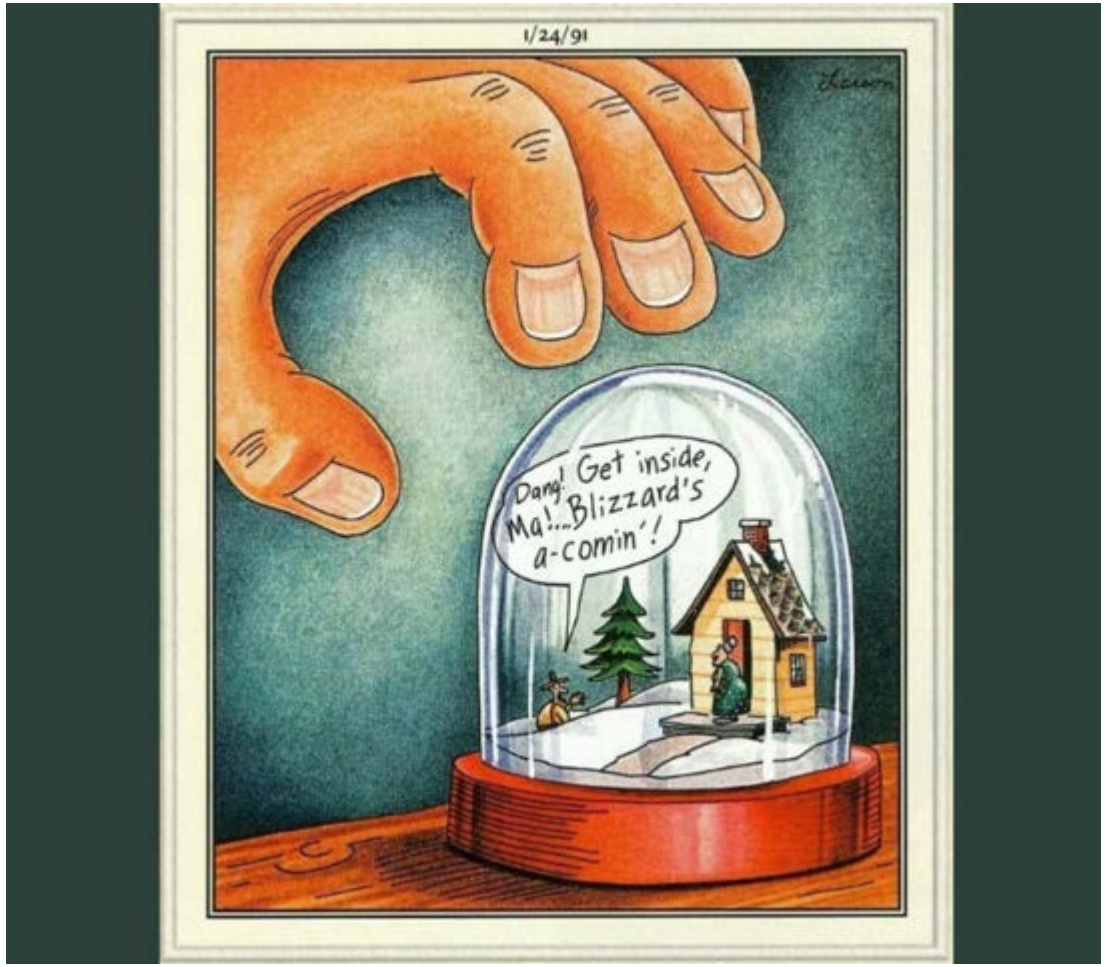
Anderson K, Ross HJ, Austin PC, Fang J, Lee DS. J Am Coll Cardiol HF. 2020 Dec, 8 (12) 1024–1034

Timing of Clinical Trials in the HF Journey



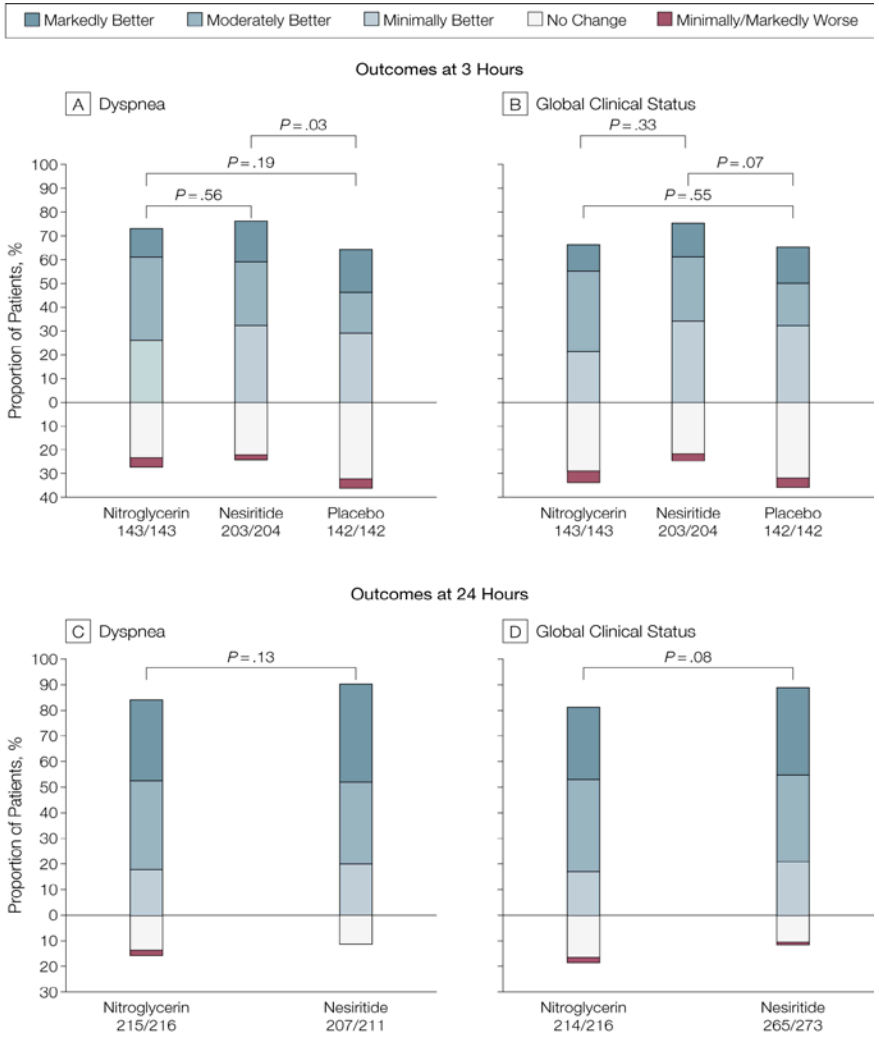
Lesson 1: Size and Outcomes Matter

- Small vs. Large trials
- Dyspnea as primary endpoint



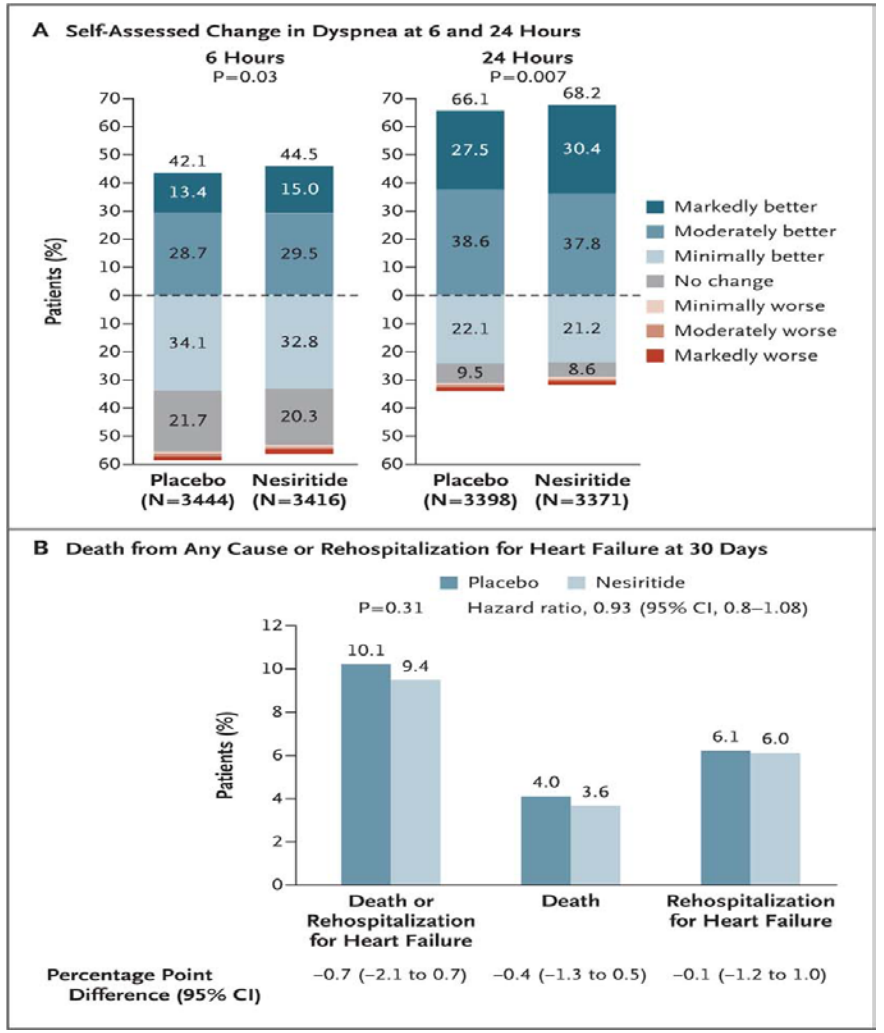
Lesson 1: Size and Outcomes matter….

VMAC, n=489: Improved dyspnea



doi: 10/1093/ehjcvp/pvaa1323

ASCEND HF, n=6769: nothing more…



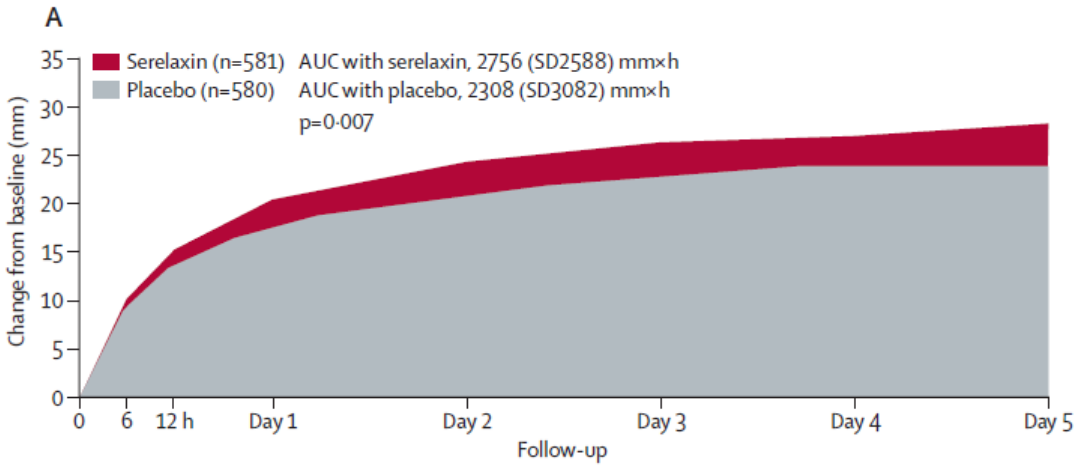
N Engl J Med 2011;365:32-43

Lesson 2: Consistency Matters

- Look for complementary measures to dyspnea
  - Volume
  - Diuretic use
  - Other symptoms
- Look for consistency of other endpoints
  - Repeat hospitalization
  - iv diuretic or escalation of Rx (i.e. WHF)
  - Mortality
  - Time course of outcome

Lesson 2: Consistency Matters

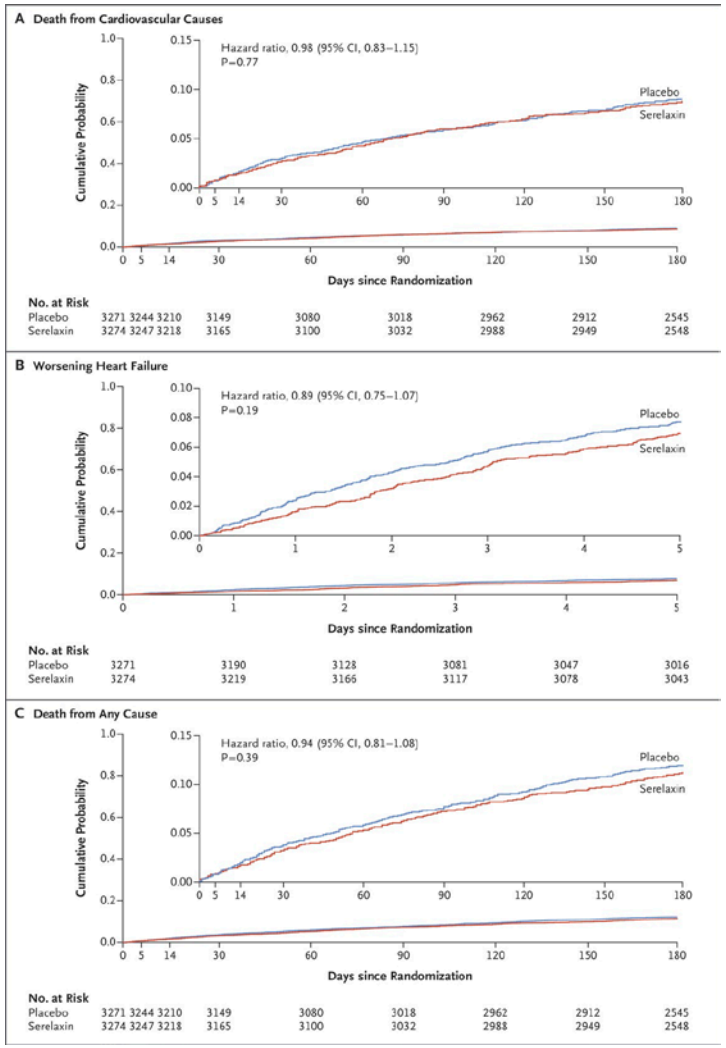
RELAX AHF, n=1161: CV Mortality?



	Placebo	Serelaxin	Treatment effect (95% CI)	p value	
Study day of moderately or markedly improved dyspnoea before day 5**	1·9 (2·1)	1·5 (1·9)	−0·4 (−0·6, −0·2)*	0·002‖	
Study day of worsening heart failure before day 5††	5·5 (1·4)	5·8 (0·9)	0·3 (0·1, 0·4)*	0·0009‖	
Worsening heart failure before 14 days	91 (KM 15·7%)	66 (KM 11·4%)	0·70 (0·51, 0·96)‡‡	0·024§§	
Total intravenous loop diuretic dose before day 5 (mg)¶¶	213 (358)	161 (265)	−52 (−88, −15)*	0·006†	
Total oral loop diuretic dose before day 5 (mg)††	183 (189)	193 (195)	10 (−12, 32)*	0·382†	
All-cause death or readmission to hospital for heart or renal failure before day 60	77 (KM 13·4%)	77 (KM 13·4%)	1·01 (0·74, 1·38)‡‡	0·959§§	X
Days alive out of hospital before day 30	20·4 (6·83)	20·9 (6·44)	0·5 (−0·3, 1·3)*	0·293‖	X
Cardiovascular death before day 180‖‖	55 (KM 9·6%)	35 (KM 6·1%)	0·63 (0·41, 0·96)‡‡	0·028§§	X
Days in intensive care unit or cardiac care unit	3·9 (7·0)	3·5 (7·1)	−0·3 (−1·1, 0·5)*	0·029‖	
Death before day 30	19 (KM 3·3%)	12 (KM 2·1%)	0·63 (0·30, 1·29)‡‡	0·202§§	X
Death or worsening heart failure or readmission to hospital for heart failure before day 30	110 (KM 19·0%)	90 (KM 15·6%)	0·79 (0·60, 1·04)‡‡	0·089§§	X
Cardiovascular death or readmission to hospital for heart or renal failure before day 30	40 (KM 6·9%)	43 (KM 7·5%)	1·08 (0·70, 1·66)‡‡	0·726§§	X
Cardiovascular death or readmission to hospital for heart or renal failure before 30 days after discharge	42 (KM 7·4%)	50 (KM 8·9%)	1·21 (0·80, 1·82)‡‡	0·360§§	X

Teerlink, Lancet 2013: doi.org/10.1016/S0140-6736(12)61855-8

RELAX AHF2, n= 6545: Nope!



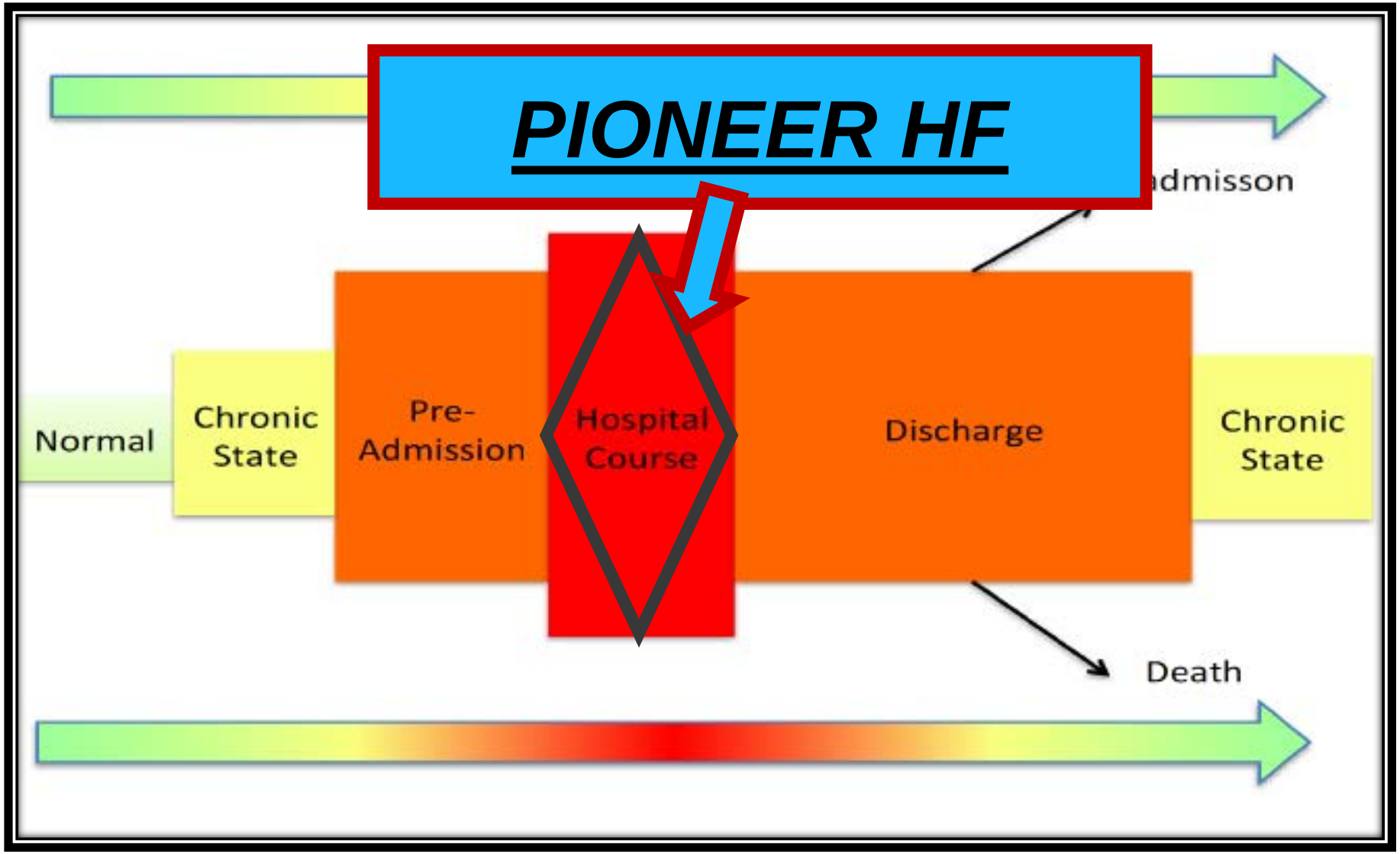
Metra M et al. NEJM 2019;381:716-726

Studies of In-hospital EBMT Initiation: Randomized

Medication	Studies, (n)	Primary Result	Outcomes
ACE/ARB	nil	---	----
Beta blockers	**1, (363)**	**Increased use 3 months**	**No difference**
MRA	2 (560)	No difference in hospital outcomes	No difference in follow up outcomes
Ivabradine	**3 (220)**	**Lower HR, BNP at discharge**	**Improved symptoms, EF, HR, exercise dur.**
ARNi	**2 (1480)**	**Well tolerated at 6ws Lower NT BNP 60 d**	**Lower repeat hospitalization**

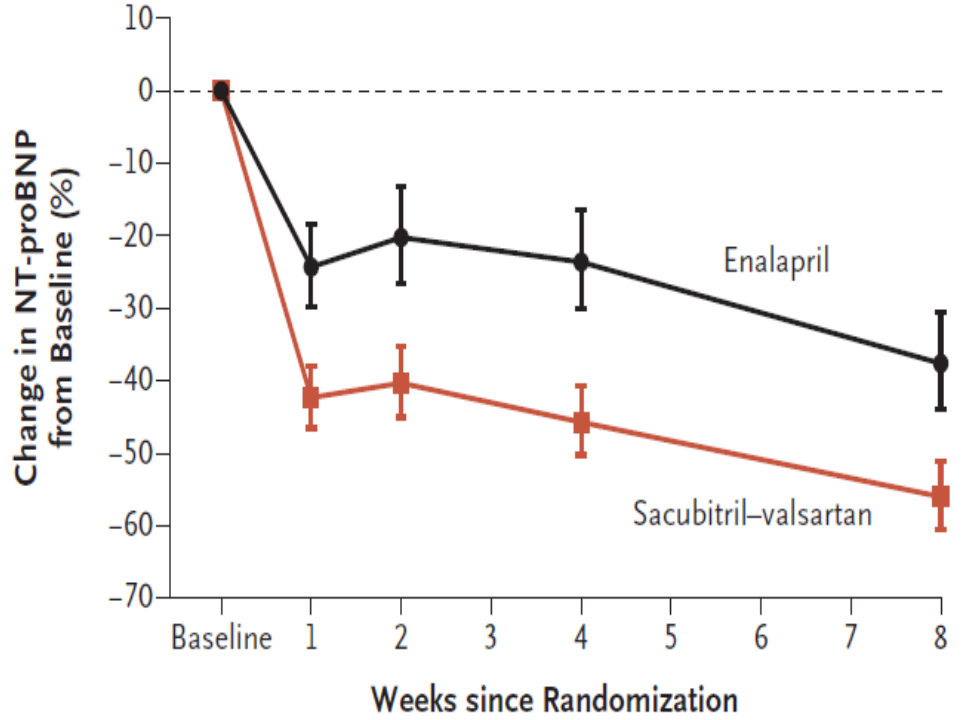
Lesson 3: In AHF there is still hope!

Timing of Clinical Trials in the HF Journey



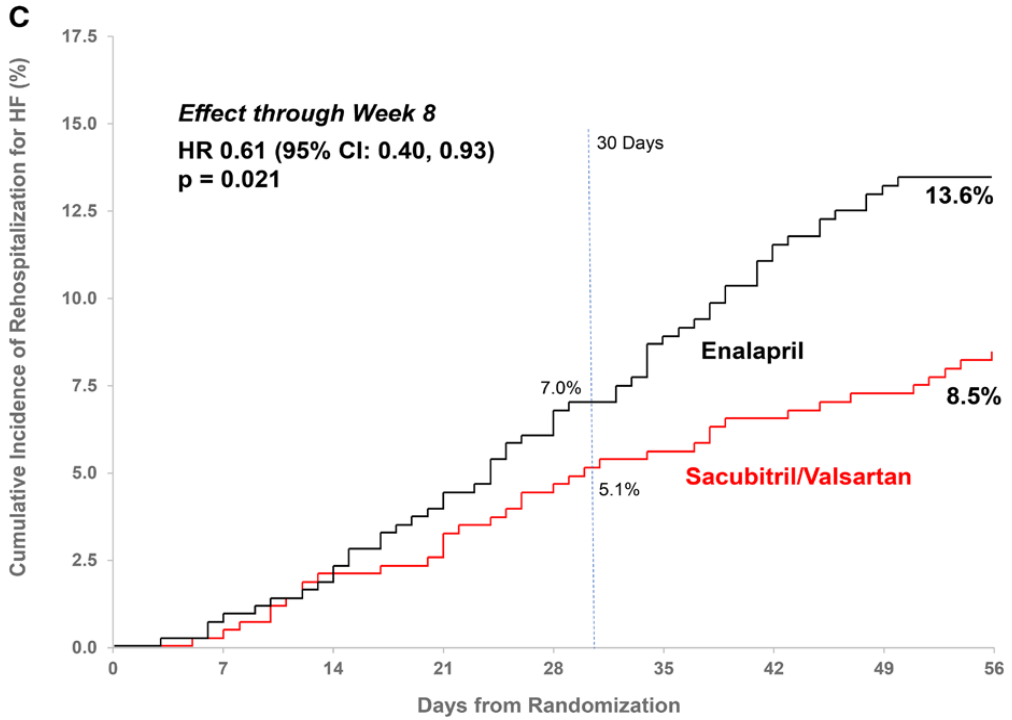
PIONEER-HF Study:

ARNI in acute HF associated with greater reduction in NTproBNP compared with ACEi



No. at Risk

Enalapril	394	359	351	350	348
Sacubitril–valsartan	397	355	363	365	349

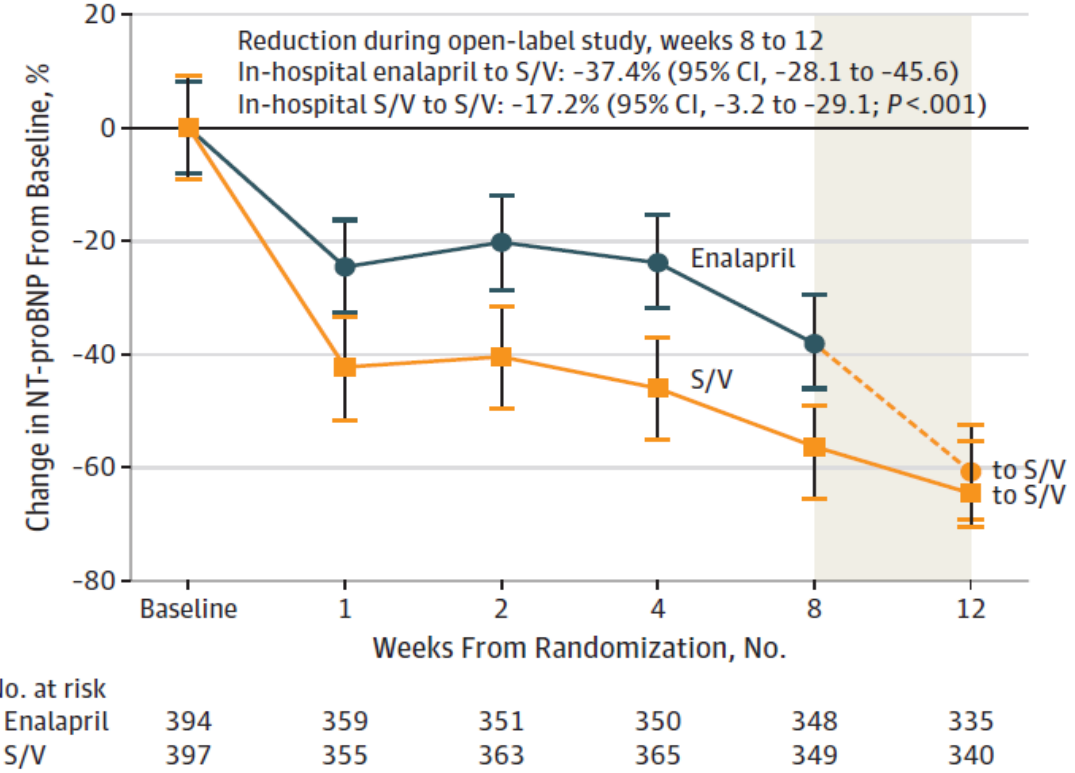


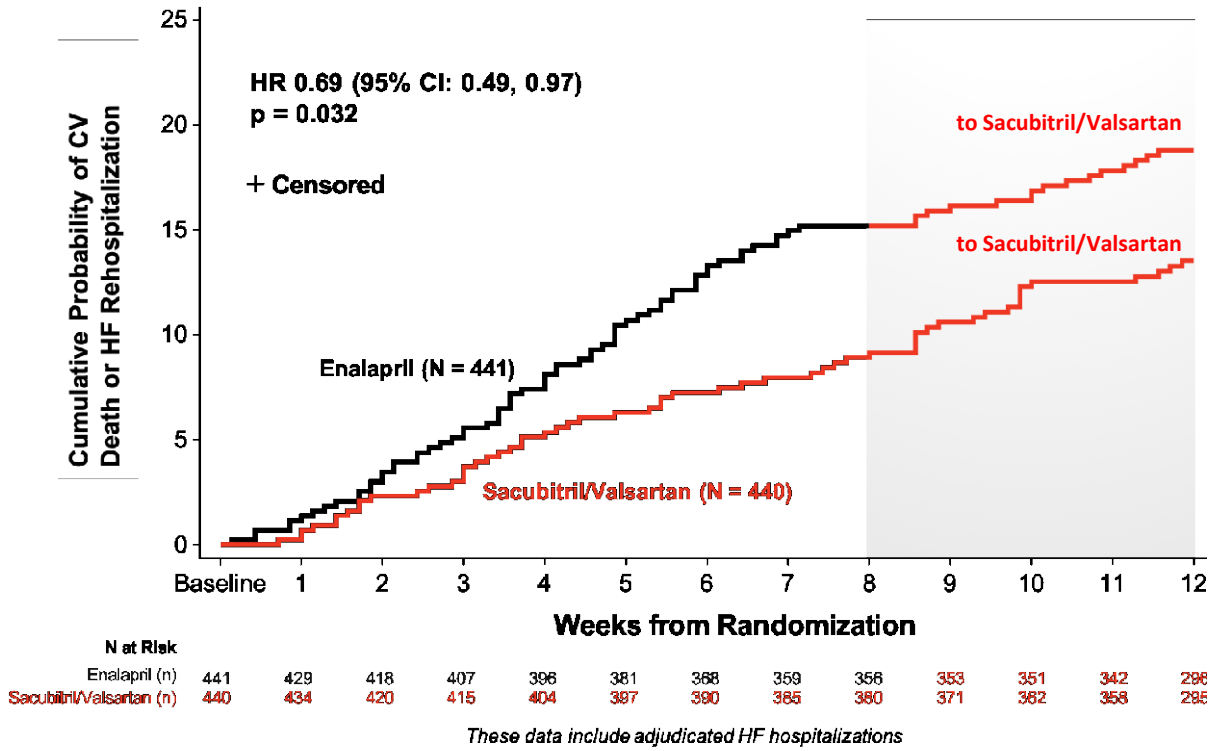
- 880 patients, hospitalized for worsening HF randomized to enalapril vs sac-val once stabilized
- 1/3 had de novo HF

Velazquez et al, New Eng J Med 2019

PIONEER-HF Study:

Open label extension

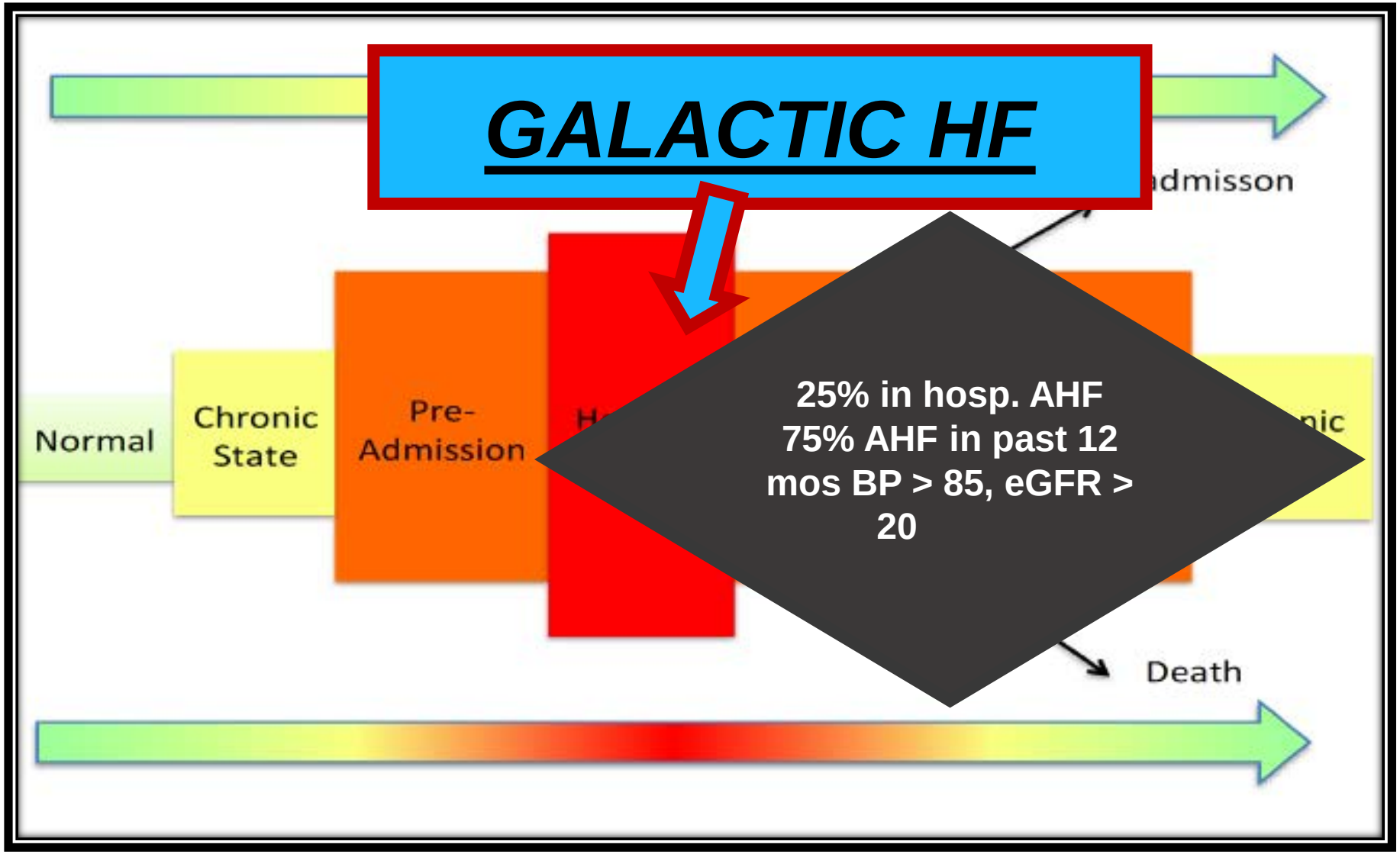




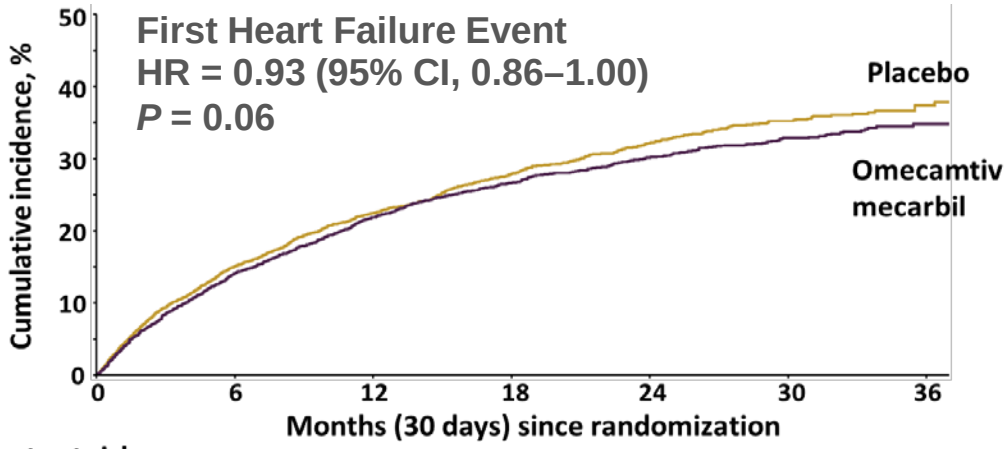
- Open label extension:
  - Further reduction in NTproBNP (both groups)
  - In-hospital sac-val group experienced lower incidence of death or re-hospitalization over 12 weeks follow-up

Velazquez et al, N Engl J Med 2019
Devore et al, JAMA Cardiol 2020

Timing of Clinical Trials in the HF Journey

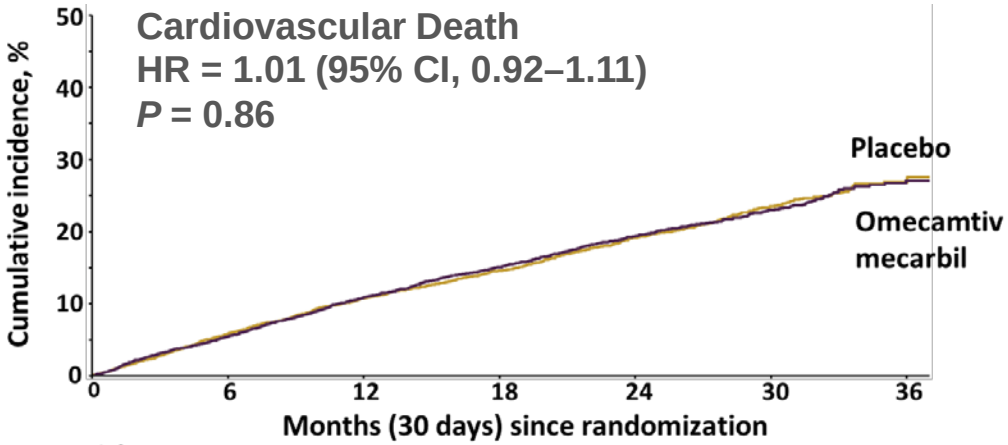


Primary Composite Components and KCCQ TSS



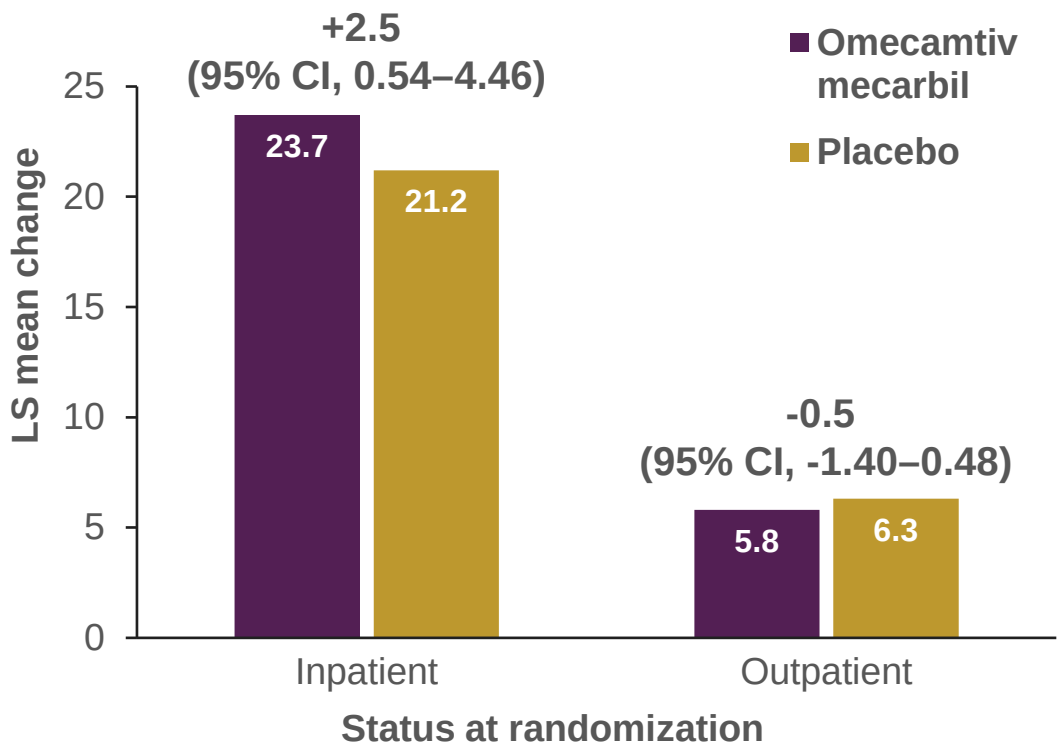
Patients at risk, n

Placebo	4112	3309	2889	2102	1348	647	141
OM	4120	3391	2953	2156	1430	699	164

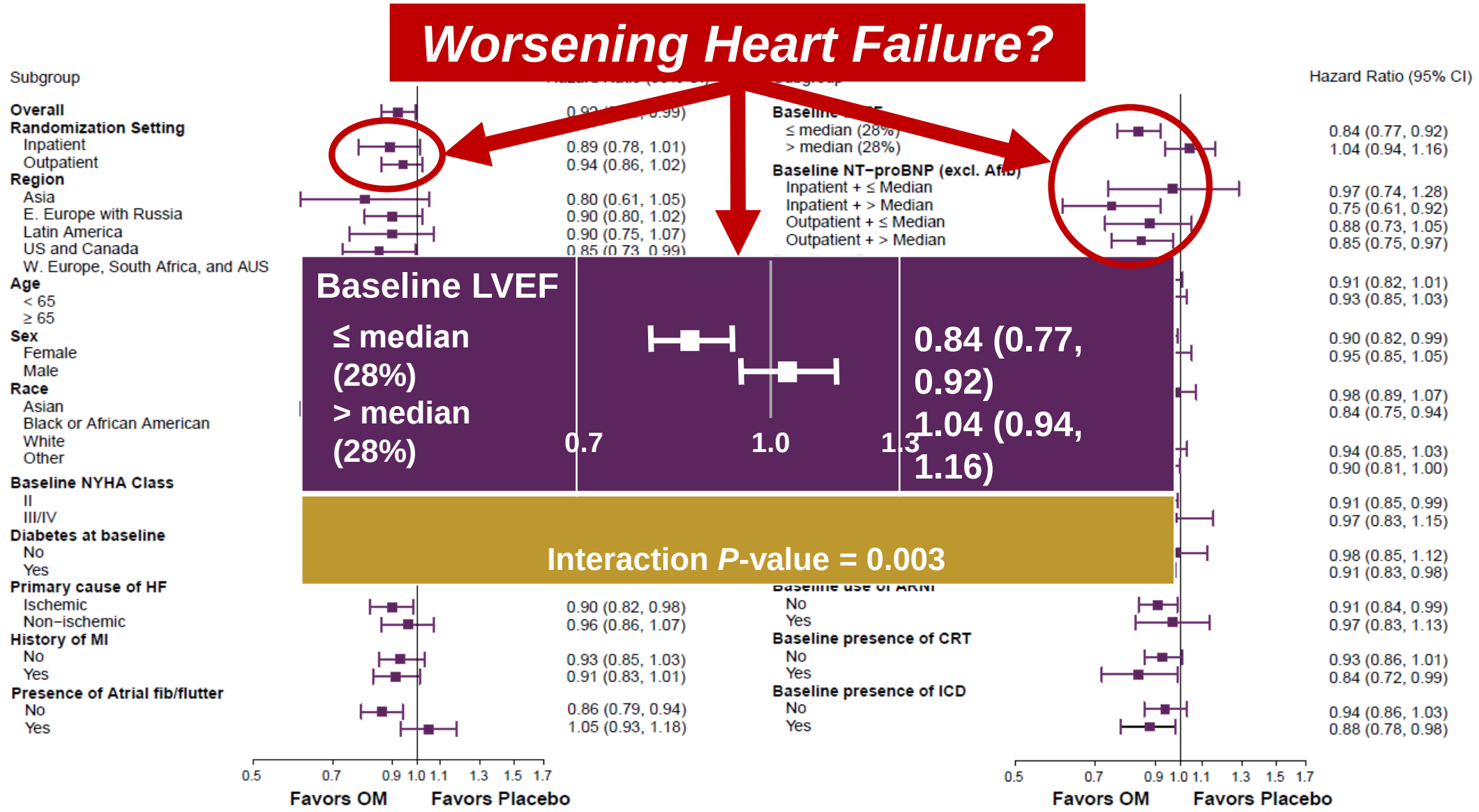


Patients at risk, n

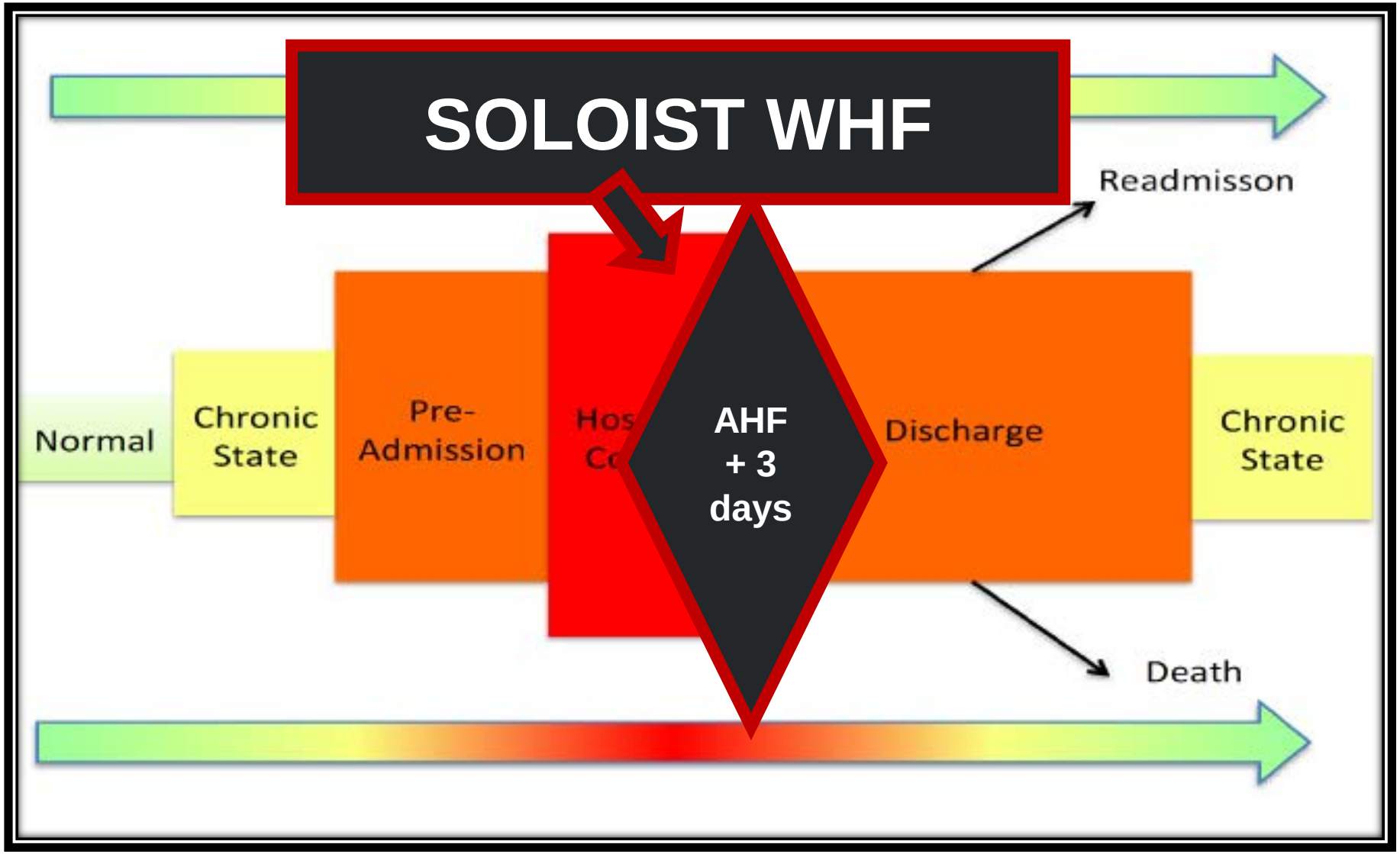
Placebo	4112	3821	3560	2722	1788	885	201
OM	4120	3838	3556	2710	1838	903	224



Primary Outcome: Subgroup Results

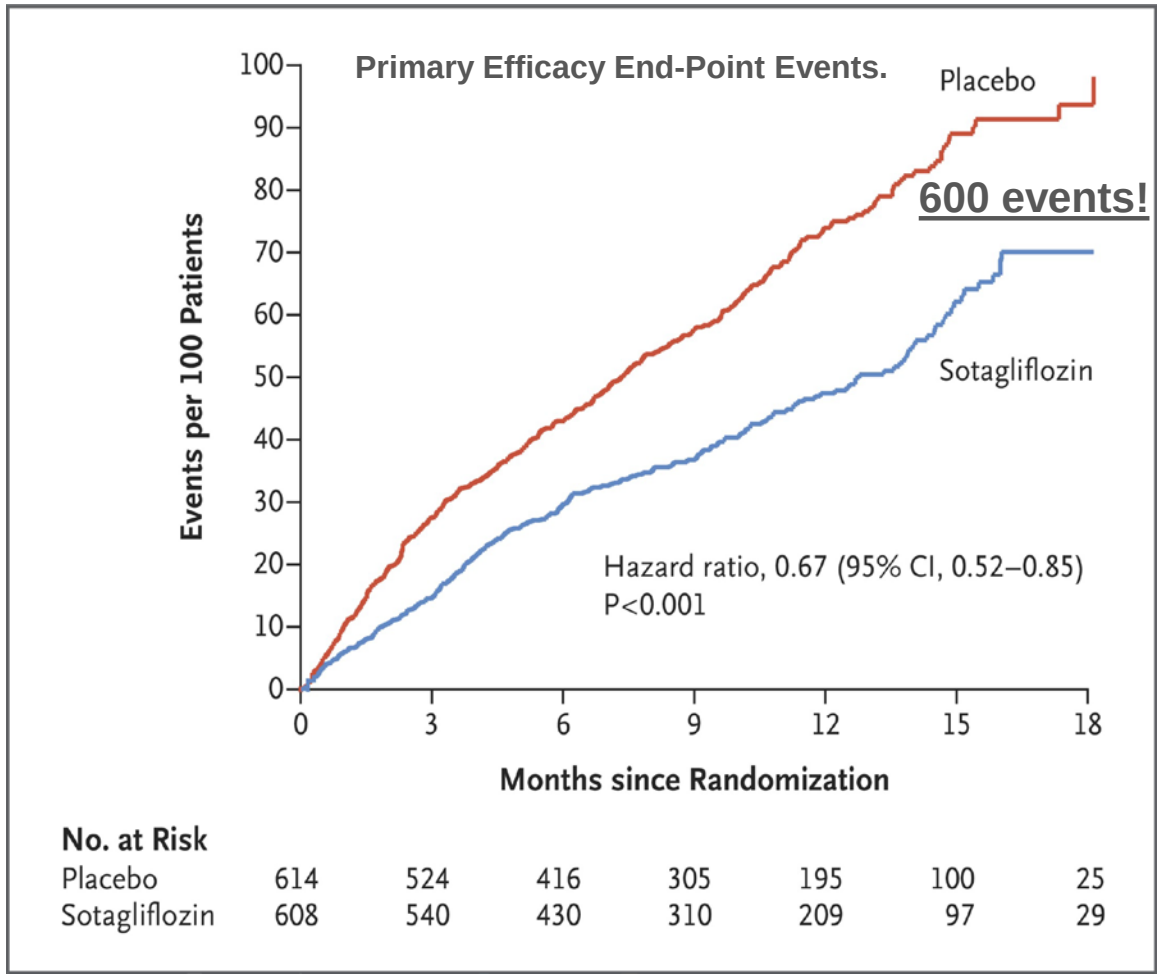


Timing of Clinical Trials in the HF Journey



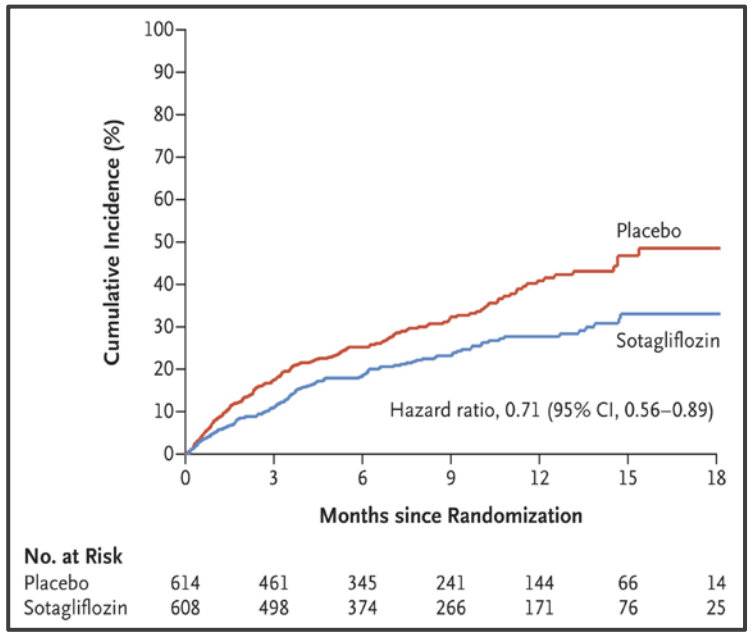
SOLOIST WHF Trial: Hosp + Vulnerable

SOLOIST, n= 1222: Impressive results!



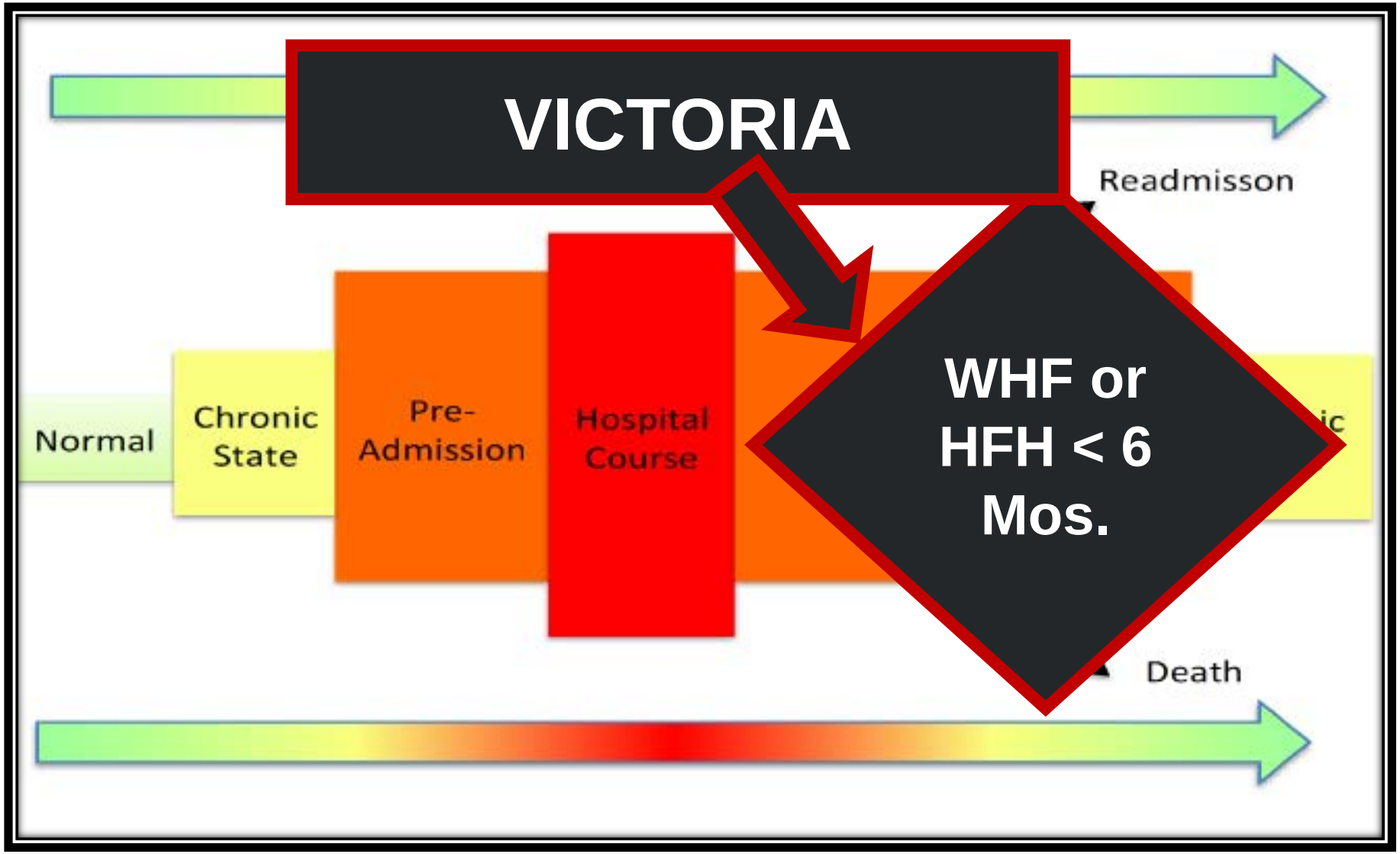
- **But keep in mind:**
  - Altered primary endpoint
  - 50% initiated after discharge
  - Stopped early
  - Events were not adjudicated
    Reduces by ~30%

First Occurrence of Either Death from Cardiovascular Causes or Hospitalization for Heart Failure.



Bhatt DL et al. N Engl J Med 2021;384:117-128

Timing of Clinical Trials in the HF Journey



VICTORIA: Primary and secondary outcomes

	Vericiguat (N=2526)		Placebo (N=2524)		Treatment Comparison	
	%	Events/ 100 Pt-Yrs	%	Events/ 100 Pt-Yrs	HR (95%)*	P-value†
PRIMARY COMPOSITE OUTCOME	35.5	**33.6**	38.5	**37.8**	0.90 (0.82–0.98)	**0.019**
HF hospitalization	27.4		29.6			
Cardiovascular death‡	8.2		8.9			
SECONDARY OUTCOMES						
Cardiovascular death	16.4	**12.9**	17.5	**13.9**	0.93 (0.81–1.06)	0.269
HF hospitalization	27.4	**25.9**	29.6	**29.1**	0.90 (0.81–1.00)	**0.048**
Total HF hospitalizations		**38.3**		**42.4**	0.91 (0.84–0.99)	**0.023**
Secondary composite outcome	37.9	**35.9**	40.9	**40.1**	0.90 (0.83–0.98)	**0.021**
HF hospitalization	27.4		29.6			
All-cause mortality‡	10.5		11.3			
All-cause mortality	20.3	**16.0**	21.2	**16.9**	0.95 (0.84–1.07)	0.377

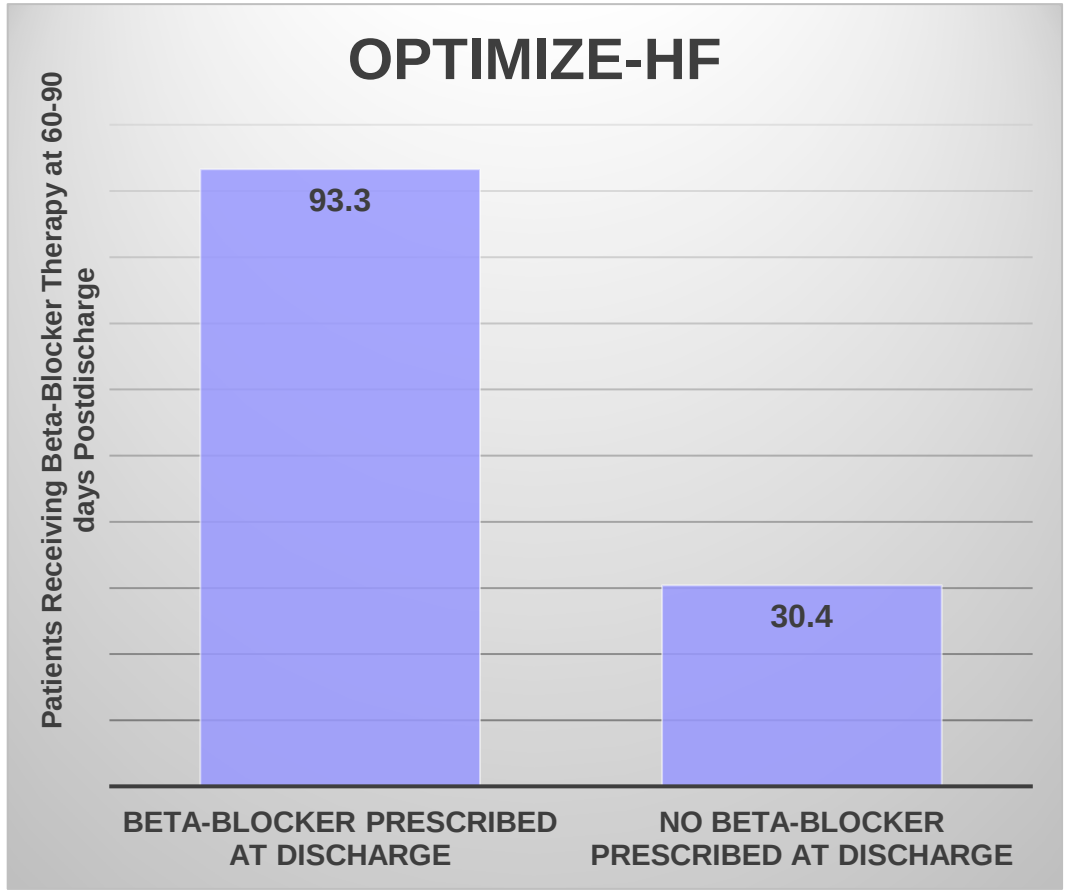
Armstrong et al. N Engl J Med 2020

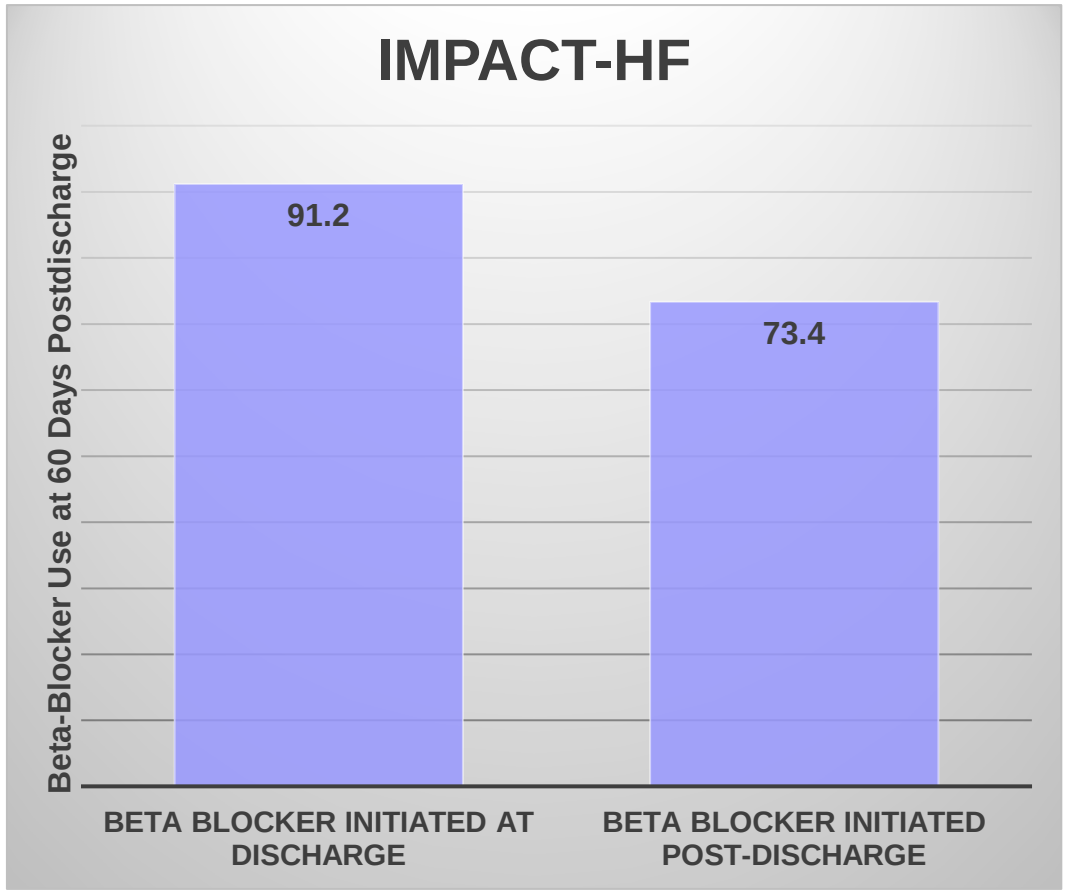
Lesson 4

- Newer therapies are SUPPLEMENTARY to and not REPLACEMENT for Foundational Therapy

Post-Discharge Treatment Compliance

- Patients Leaving the Hospital on GDMT May Have Improved Treatment Adherence at 60 and 90 days



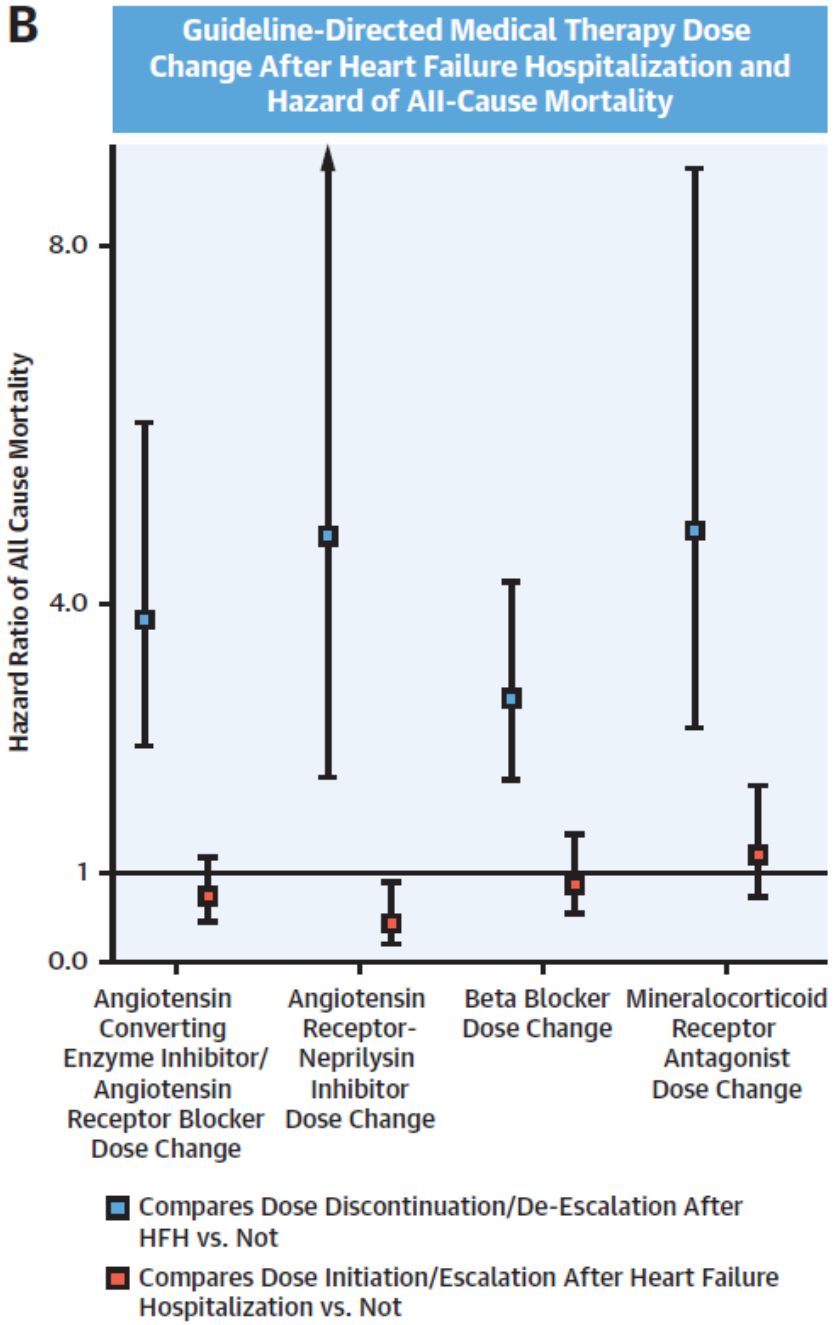


MED/ENT/0380

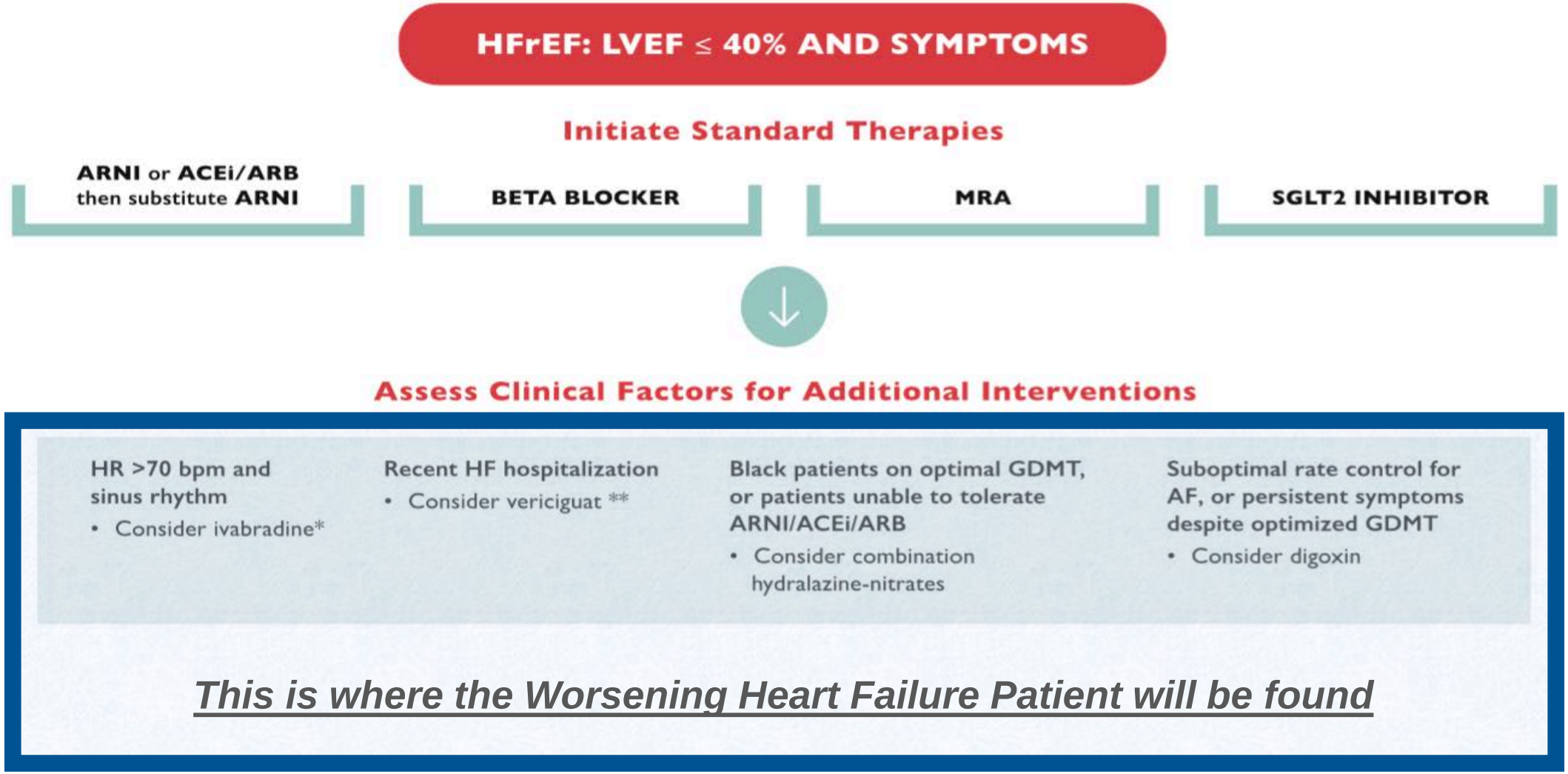
- *initiation of a beta-blocker did not affect length of stay (LoS)
- OPTIMIZE, Organized Programto Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure. GDMT, Guideline Directed Medical Therapy
- 1.Fonarow GC et al. *Am Heart J.* 2007;153:82.e1282.e11
- 2. Gatis WA et al. JACC. 2004;43(9):1534-1541

Observational studies:

Supporting role of EBMT in HFH



Srivastava, JACC HF 2020


HFrEF: LVEF ≤ 40% AND SYMPTOMS
Initiate Standard Therapies
ARNI or ACEi/ARB then substitute ARNI
BETA BLOCKER
MRA
SGLT2 INHIBITOR
Assess Clinical Factors for Additional Interventions
HR >70 bpm and sinus rhythm
• Consider ivabradine*
Recent HF hospitalization
• Consider vericiguat **
Black patients on optimal GDMT, or patients unable to tolerate ARNI/ACEi/ARB
• Consider combination hydralazine-nitrates
Suboptimal rate control for AF, or persistent symptoms despite optimized GDMT
• Consider digoxin
This is where the Worsening Heart Failure Patient will be found

Tackling HF: When and How?

- *Size* and *Outcomes* matter
- Look for *Consistency*
- There IS *HOPE* for acute HF
- Personalized Rx *Supplemental, to EBMT*
  - Adding selected therapies to Foundational therapy has value (ARNi, SGLTi, GCs)
    - *Probably* benefits if added even in hospital
  - Pure, acute HF with novel therapies is a tough nut to crack
    - Ensure *Foundational therapy* is on board
    - Stay tuned for more data

Case Studies

Justin Ezekowitz, MBBCh, MSc
Anique Ducharme, MD, MSc, FRCP
Jonathan Howlett, MD, FRCPC, FCCS FHSFA(Hon)

Patient 1: Pre-discharge

76-year-old male patient with HFrEF admitted 6 days ago with decompensated HF. Intravenous diuretic given with substantial weight loss and improved symptoms.

- History of DM, HTN, CKD, arthritis, poor hearing (runs in family). CRT-D in 2019. To be discharged in am. Changed to oral diuretic yesterday, weight unchanged today.
- EF 38%.
- BP 128/87 mmHg
- HR 68 bpm
- eGFR 46, K 4.5 mmol/L
- Key HF Medications
  - Sacubitril/valsartan 24/26 mg BID
  - Bisoprolol 7.5 mg daily

Patient 2: Referral

Referred after discharge from ER on weekend. Seen for increased SOB, give IV furosemide with good result and send home. Seeing 1 week after ER visit.

- Nondiabetic, CKD, HTN, Obesity, COPD stable, dyslipidemia, Prior CABG with EF 29%. ICD since 2016, narrow QRS.
- eGFR 20
- BP 98/70 mmHg
- HR 68 bpm, NSR
- Medication
  - ARNI (Sacubitril/valsartan 50 mg BID)
  - Carvedilol 12.5 bid
  - Spironolactone 12.5 od
  - Furosemide 80 mg po od