Should We Integrate New HF Drugs During In-Hospital Care?

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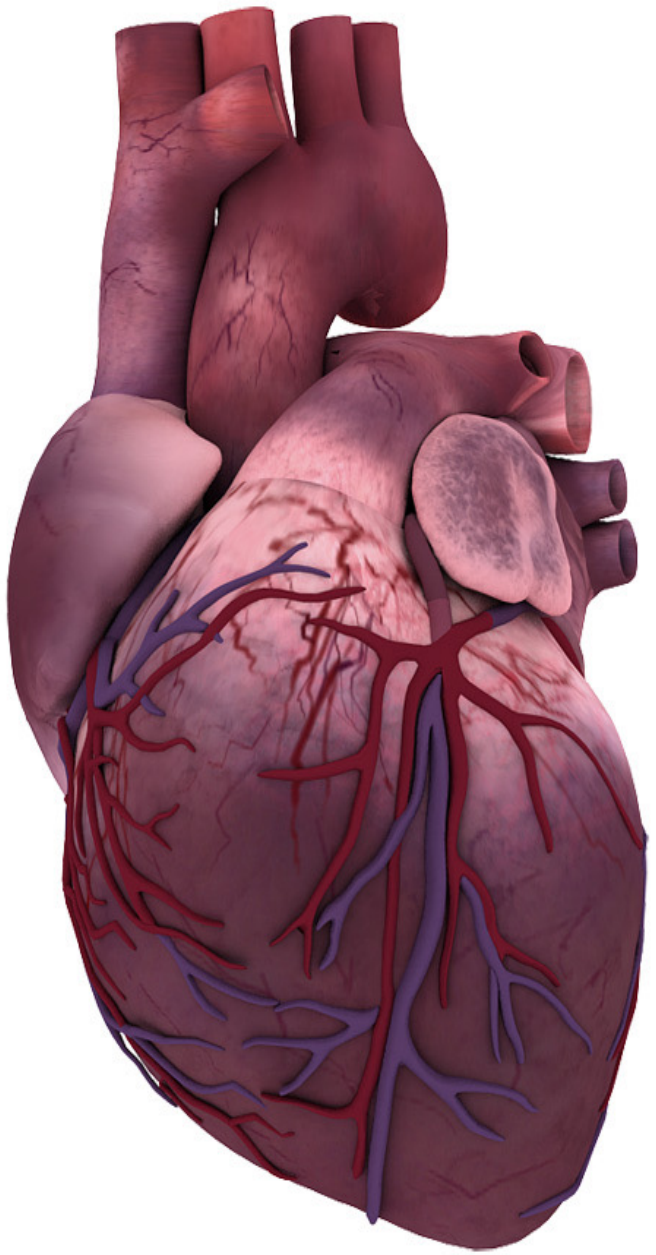
Conflict of Interest Disclosures

- **Speaking/Consulting fees**:

- Servier, Novartis, Astra Zeneca, Boehringer Ingelhiem, Bayer



Heart Failure in Canada

1 MILLION
CANADIANS ARE LIVING WITH HEART FAILURE.

50,000
new cases of heart failure are diagnosed each year, making it the most rapidly rising cardiovascular disease among Canadians.

1 in 5
Canadians over the age of 40 have a risk of developing heart failure.

100,000+
Canadians are hospitalized annually due to heart failure – **the most common reason for hospital admission.**

1.4 MILLION
HOSPITAL STAYS PER YEAR

10 DAYS
the average length of stay for heart failure patients.

26.4 DAYS
of hospital resources used by the average patient in their first year of treatment.

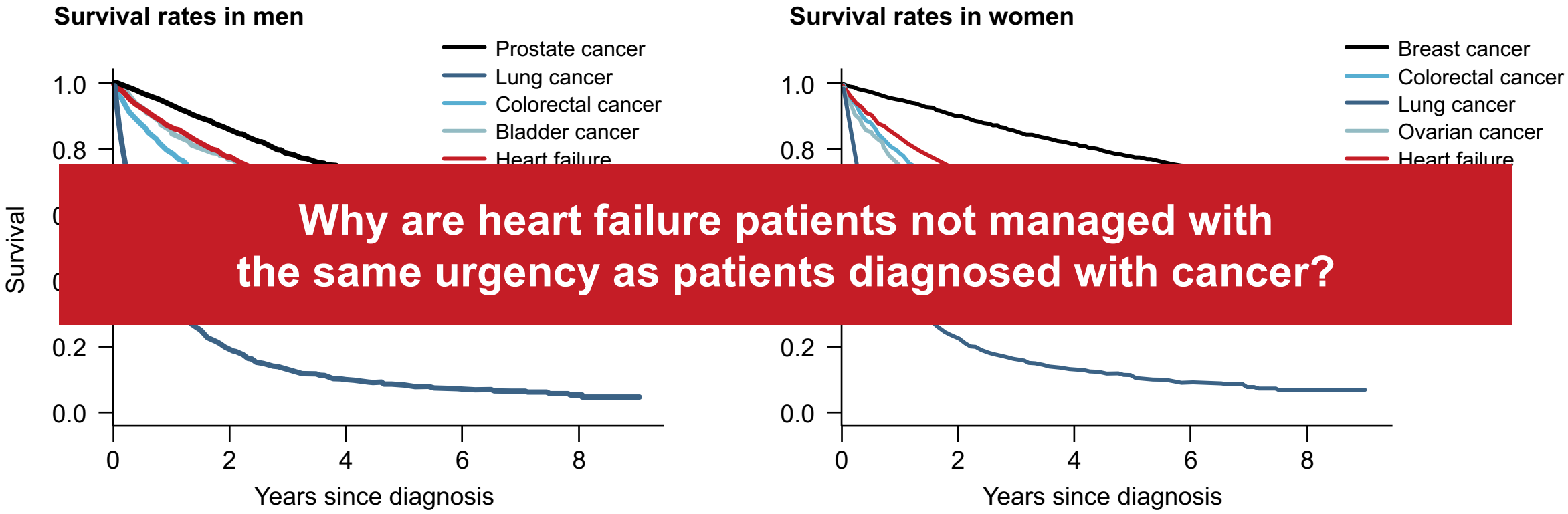
2.1 YEARS
the median survival rate for heart failure patients.

40 TO 50%
of people with congestive heart failure die within five years of diagnosis.

$2.3B
annual cost for managing moderate and severe heart failure patients in Canada.

Mortality rate is higher for heart failure than many cancers

The mortality rate for patients with chronic HF is as high as 50% at 5 years post-diagnosis[1,2,3]

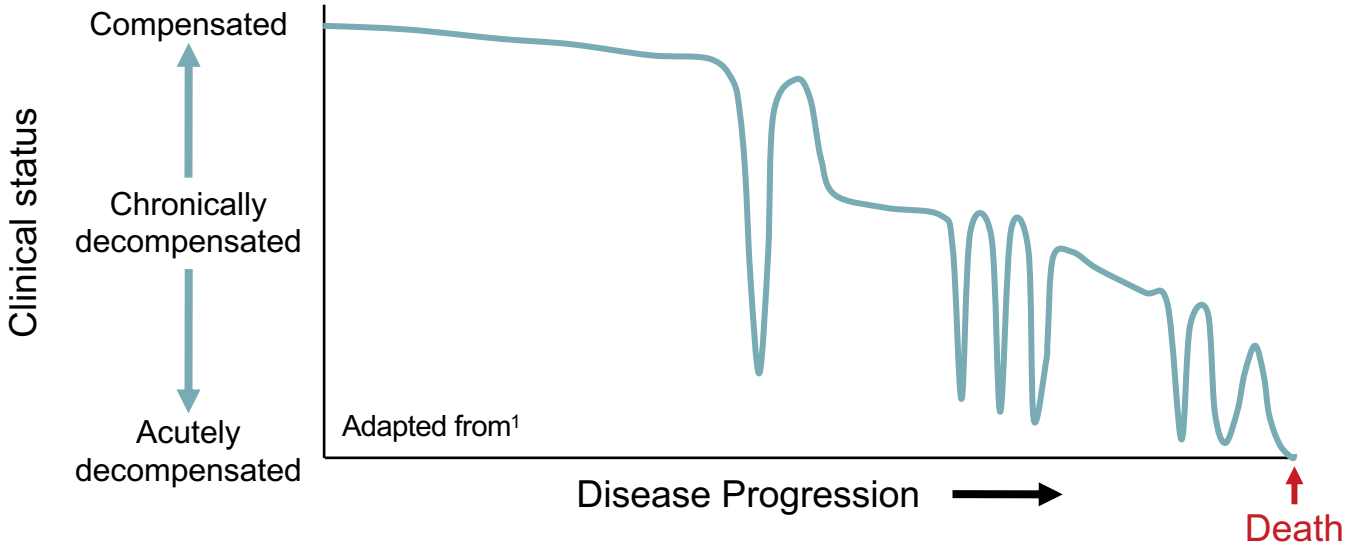


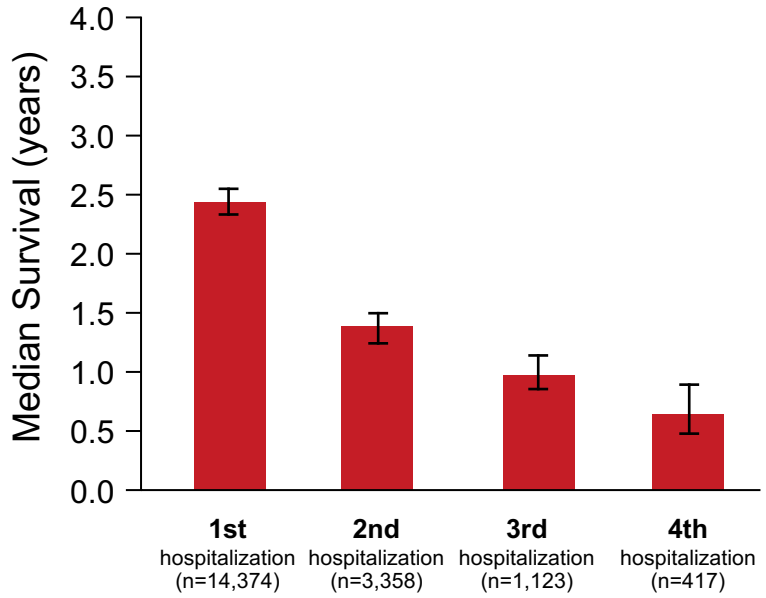
Why are heart failure patients not managed with the same urgency as patients diagnosed with cancer?

HF, heart failure

1. Mamas et al. Eur J Heart Fail. 2017;19(9):1095-1104; 2. Benjamin et al. Circulation 2017;135(10):e146-e603; 3. Roger et al. JAMA 2004;292:344–50

Risk increases after every ADHF episode





50% mortality rate at 5 years[3,4]

Median survival (50% mortality) and 95% confidence limits in patients with HF after each HF hospitalization.[2]

1. Gheorghiade et al. Am J Cardiol 2005;96:11G–17G; 2. *Setoguchi et al* Am Heart J 2007;154:26026; 3. Benjamin et al. Circulation 2017;135(10):e146-e603; 4. Roger et al. JAMA 2004;292:344–50

Even in 2017, the CCS Guideline were talking about in hospital initiation…

Criteria for Discharge

Hemodynamically stable

- Presenting symptoms resolved
- Vital signs resolved and stable for > 24 hrs, especially blood pressure & heart rate
- Returned to "dry" weight and stable for > 24 hours on oral diurectics
- Inter-current cardiac illness adequately diagnosed and treated
- Inter-current non-cardiac illness adquately diagnosed and treated

Optimization of CHF therapies

- Chronic oral HF therapy initiated, titrated and optimized (or outpatient plan for same)

Transition of care

- Education initiated, understood by patient and caregivers, continued education planned
- Discharge plan includes clear requirements for follow-up labs, office appointments and further testing
- Timely communication to primary care provider and/or multi-disciplinary disease management program is essential

Ezekowitz et al. Canadian Journal of Cardiology 33 (2017) 1342e1433

ESC guidelines recommend optimization of guideline-directed medical therapy (GDMT) before discharge for HF patients

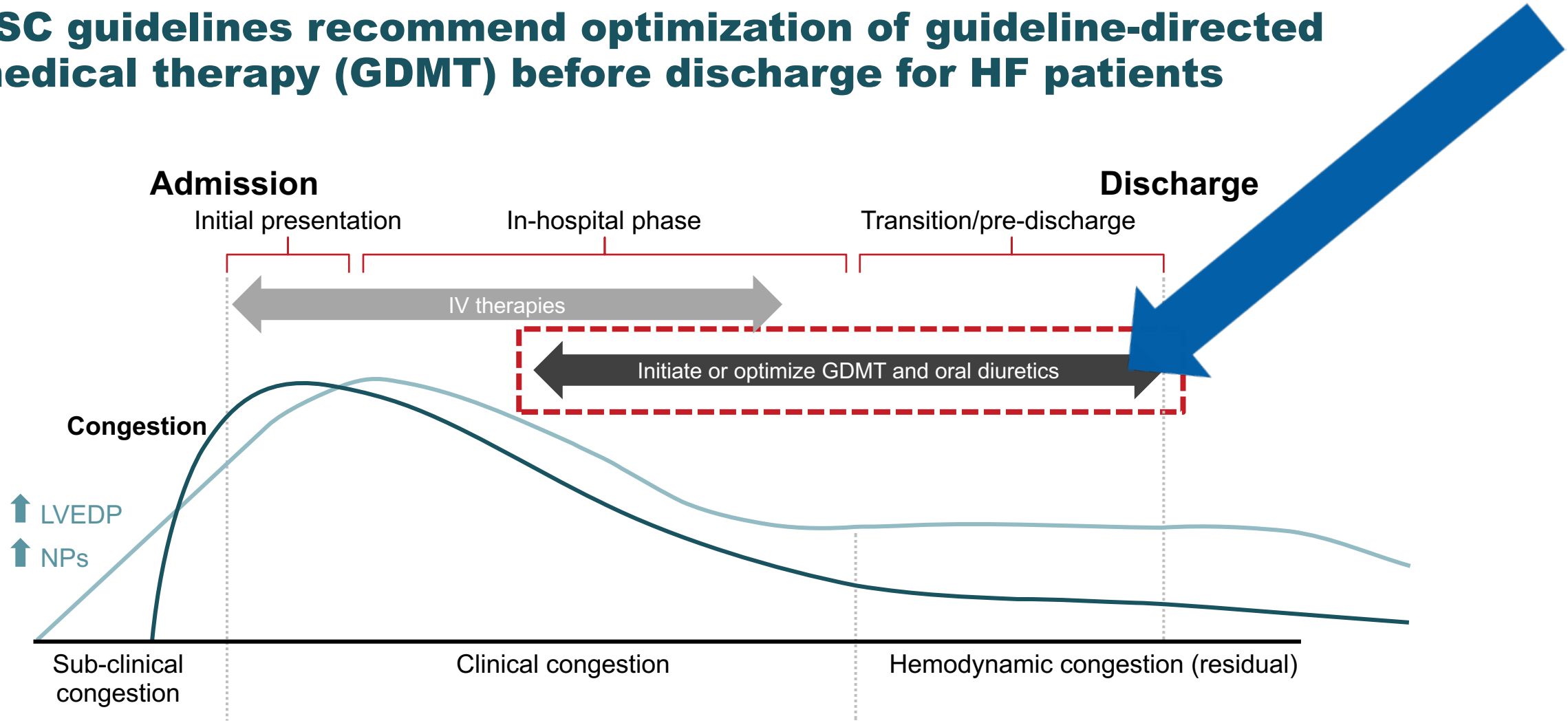


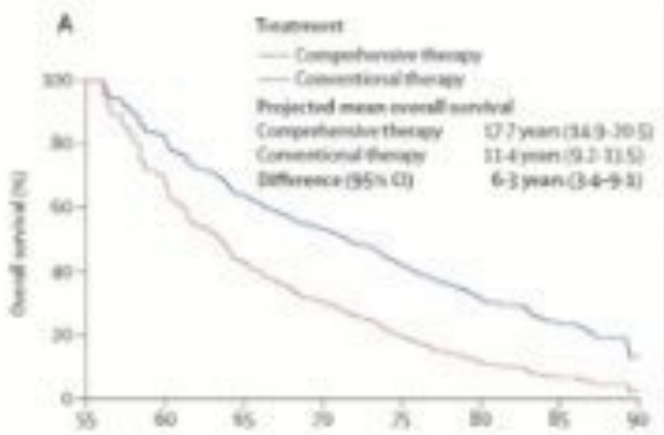
Figure Adapted from Harjola VP et al. European Journal of Heart Failure 2018 Volume: 20, Issue: 7, Pages: 1081-1099; Ponikowski et al. Eur Heart J 2016;37:2129–200

Early Integration of Comprehensive Therapy (ARNI+BB+MRA+SGLT2i)

4 drugs → **5** mechanistic pathways → **6** additional years of survival

- ARNI
- β-blocker
- MRA
- SGLT-2 Inhibitor

- Angiotensin II
- Neprilysin
- Sympathetic nervous system
- Mineralocorticoid
- SGLT-2



Vaduganathan M et al. *Lancet* 2020

Optimization is generally not optimal!

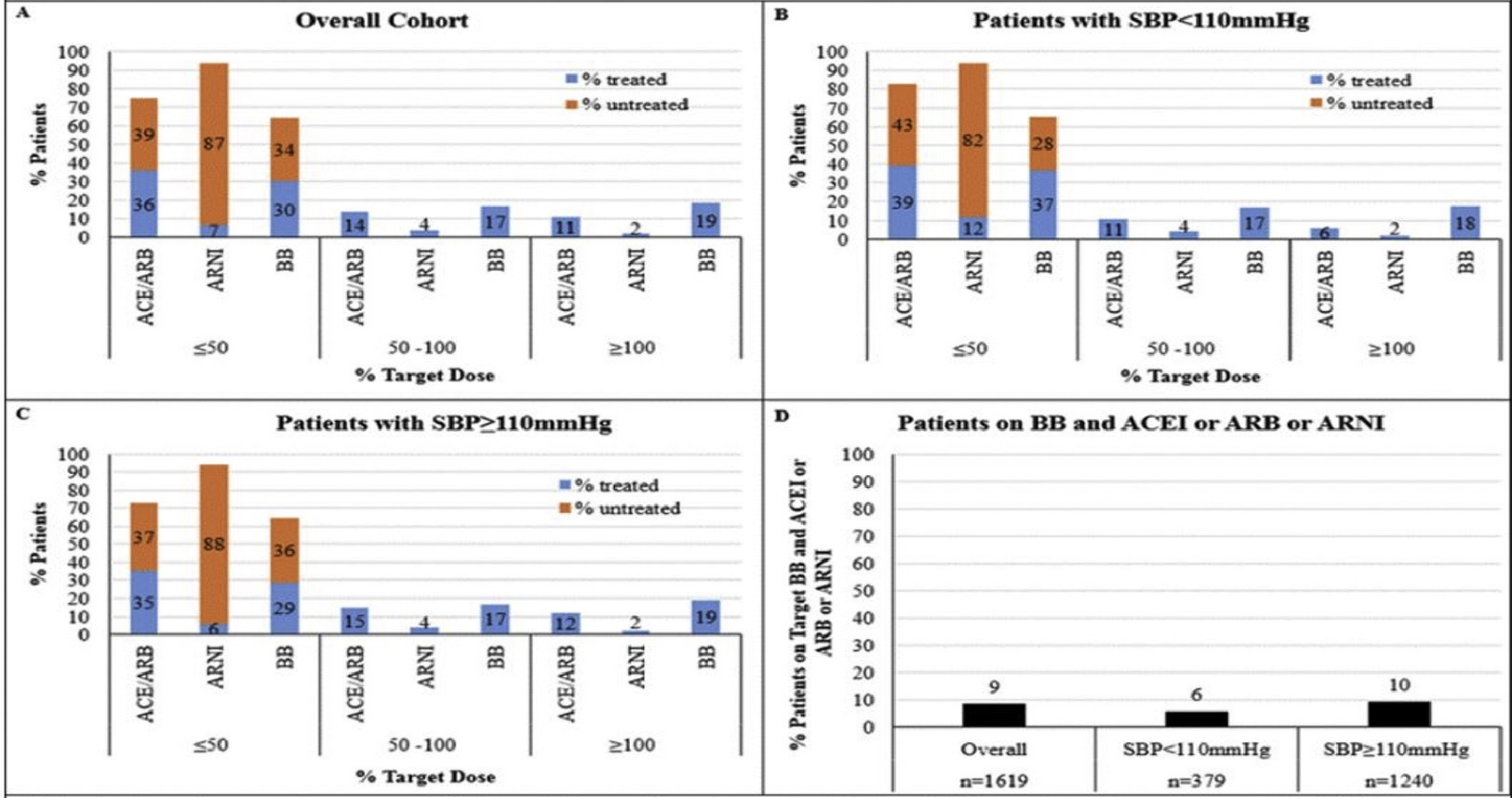
A

CHAMP-HF Registry

3500 real-world patients with HFrEF

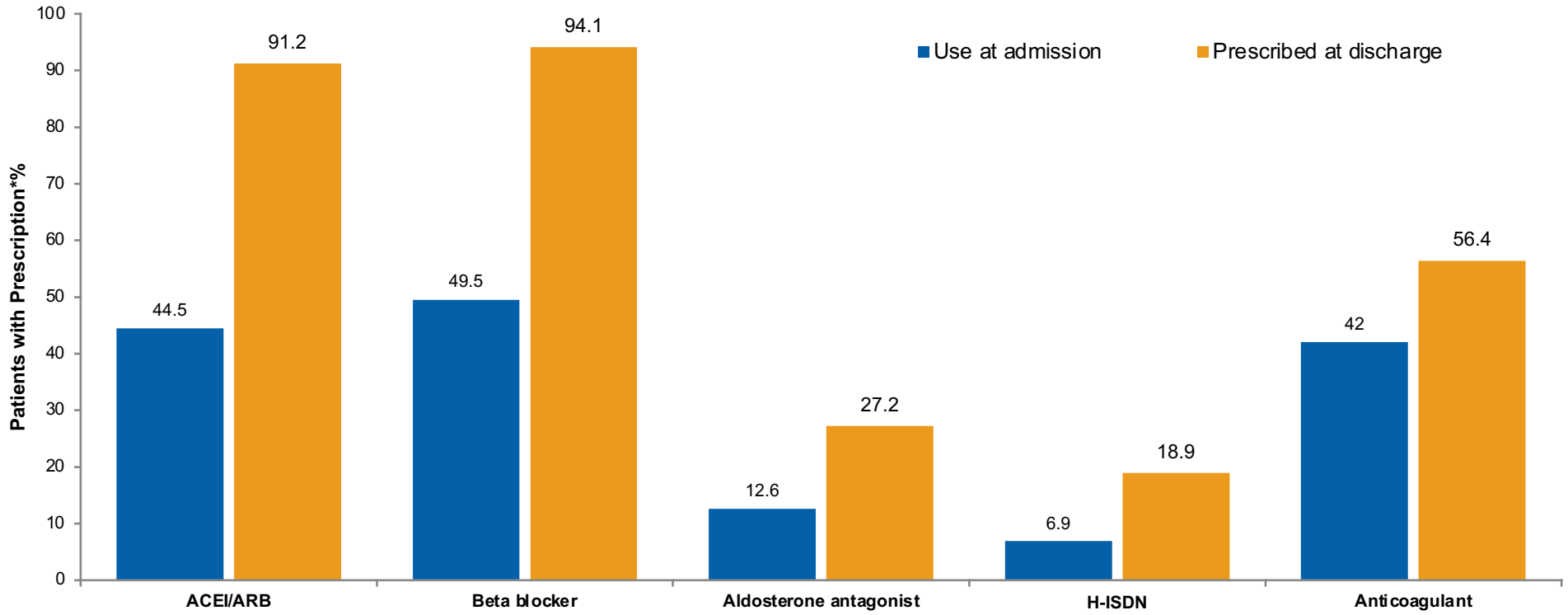
	ACEI/ARB	ARNI	ACEI/ARB/ ARNI	Beta-Blocker	MRA
Without Contraindication and Not Treated	1374	3029	920	1159	2317
Treated	2107	452	2536	2351	1163
With Contraindication	37	37	62	8	38

Greene et al, JACC 2018



ACEI = Angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, ARNI = angiotensin receptor- neprilysin inhibitor, BB = beta blocker

Hospitalization Provides an Opportunity to Optimize Chronic Heart Failure Therapy



Data from 158,922 patients with heart failure discharged from 271 hospitals participating in the Get With the Guidelines-Heart Failure quality improvement initiative between April 1, 2008, and June 30, 2013

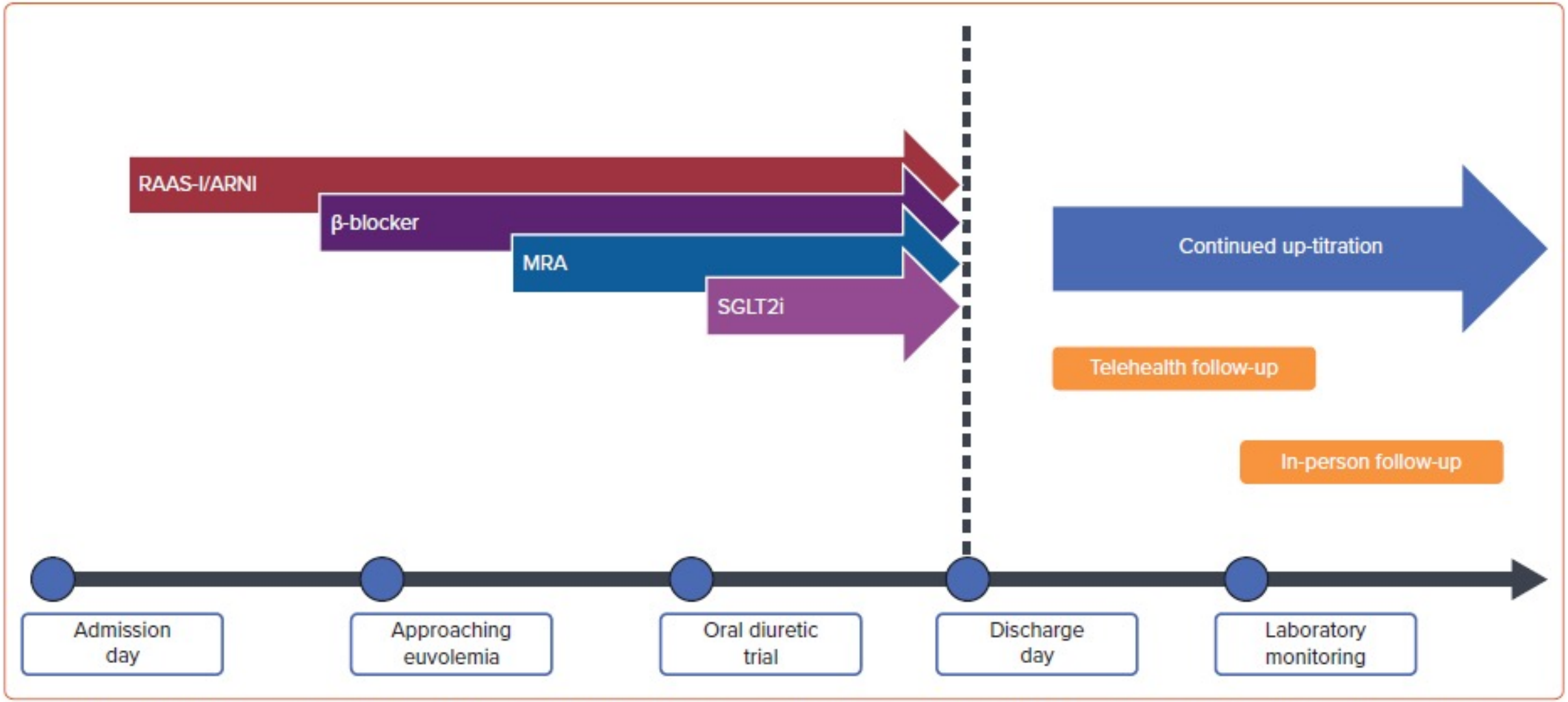
Among patients eligible for specific therapy; *Includes continuing prescription (with use prior to admission) and newly prescribed ACEI/ARB indicates angiotensin converting enzyme inhibitors/angiotensin receptor blockers; H-ISDN, hydralazine-isosorbide dinitrate

*Approximately half of patients presenting with symptoms of HF have reduced LVEF (≤40%).

Allen LA et al. Circulation. 2015;132:1347-1353.

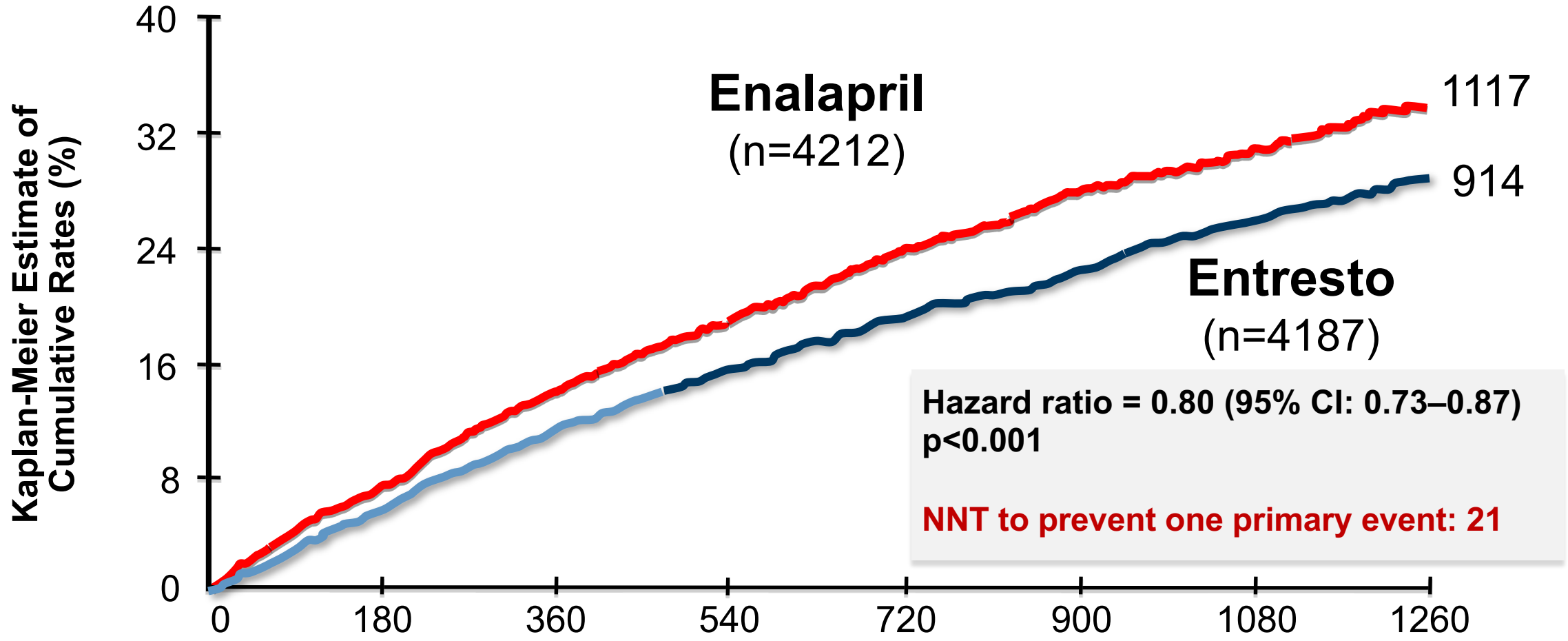
Benjamin EJ et al. Circulation. 2018;137:e67-e492.

Figure 1: Shifting the Paradigm of Guideline-directed Medical Therapy Initiation



A suggested timeline of initiating guideline-directed medical therapy (GDMT) for patients admitted with heart failure with reduced ejection fraction during their hospitalization. ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; MRA = mineralocorticoid receptor antagonist; RAAS-I = renin-angiotensin-aldosterone system inhibitor; SGLT2i = sodium–glucose cotransporter-2 inhibitor.

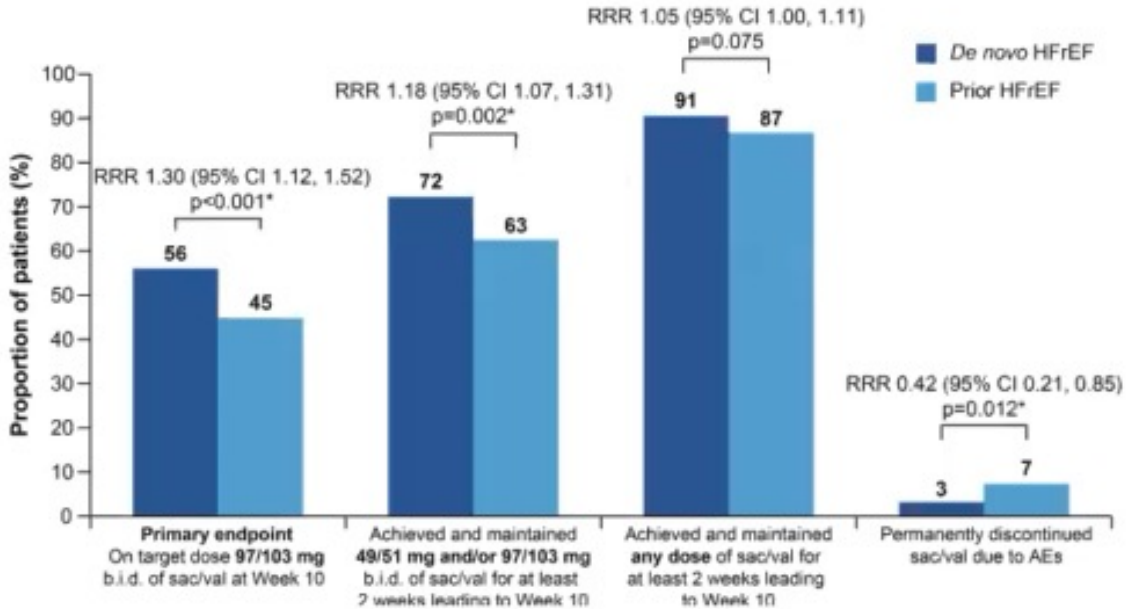
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

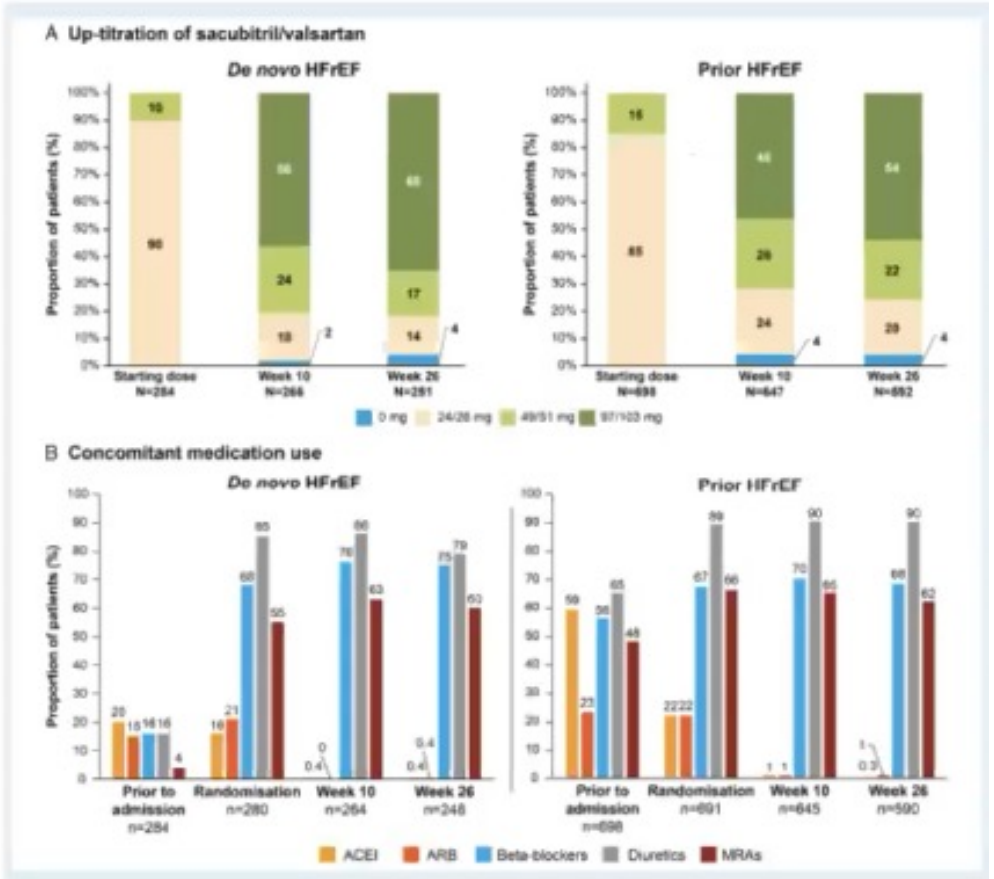


Patients at Risk

Entresto	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

TRANSITION Study





Senni et al; Eur J HF 2020; 22:303-312

TRANSITION: randomized trial of pre-discharge vs. post-discharge initiation of sacubitril/valsartan

	PRE-DISCHARGE	POST-DISCHARGE
Serious adverse events :	**18,9%**	**17,7%**
Cardiac failure:	7,0%	7,7%
Acute renal injury:	1,2%	1,4%
Hypotension:	0,8%	0,4%
Hyperkalemia:	0,6%	0,4%
Mortality:	**2,6%**	**2,0%**

PREDICTORS FOR SUCCESSFUL SAC/VAL DOSE UP-TITRATION (200 mg BID)

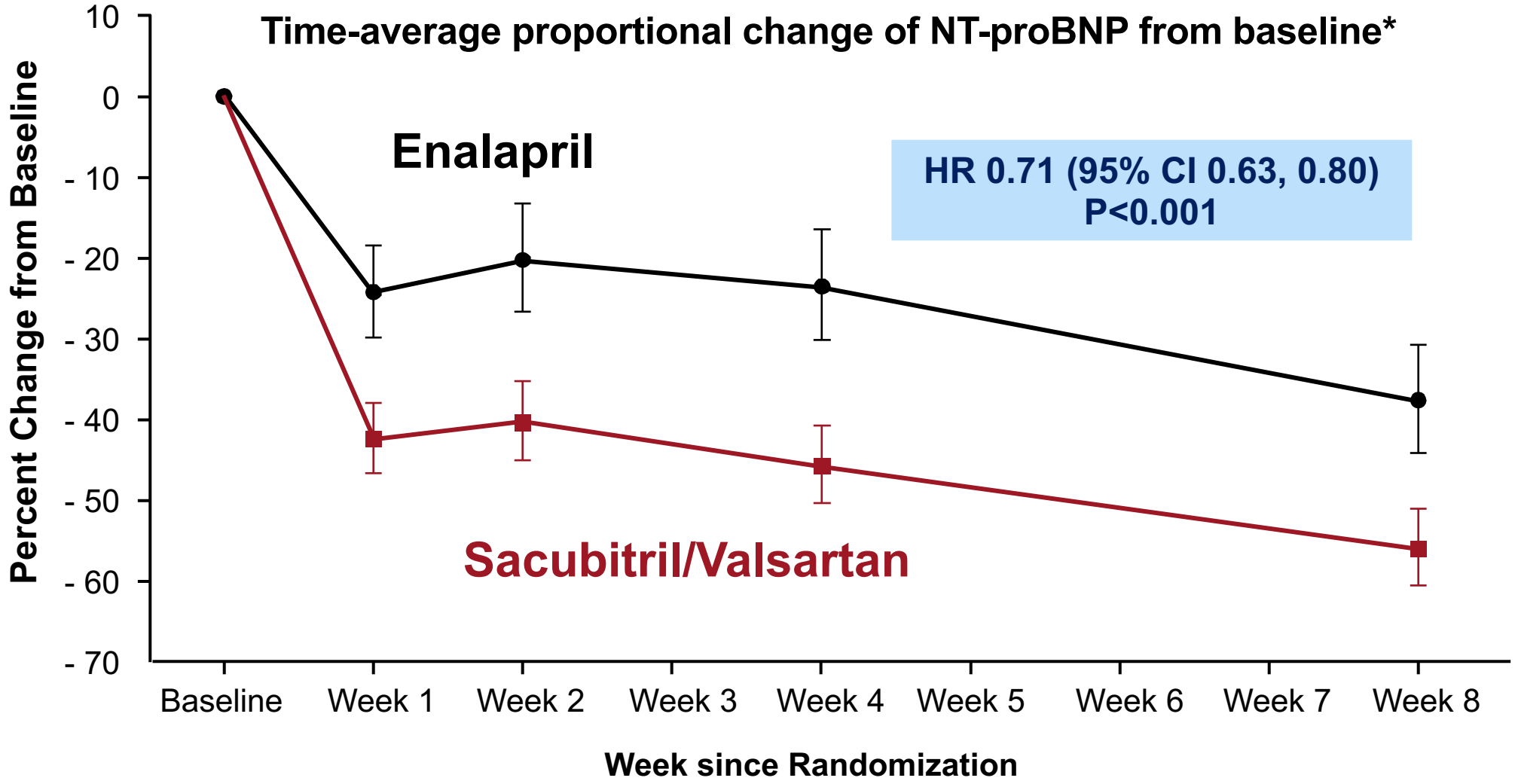
Age :	**<65 vs. >65 y.o**
eGFR:	> 60 vs. <60 ml.min.1,73m^2
SBP	**>120 vs 100 to 120 mm Hg**
Prior HF:	y/n
Hypertension:	**y/n**
AF:	y/n
Start dose	100 vs 50 mg BID
Treatment:	post vs pre discharge

Wachter R, et al. Abstract P6531.
European Society of Cardiology Congress; Aug. 25-29, 2018; Munich.

TRANSITION

PIONEER-HF

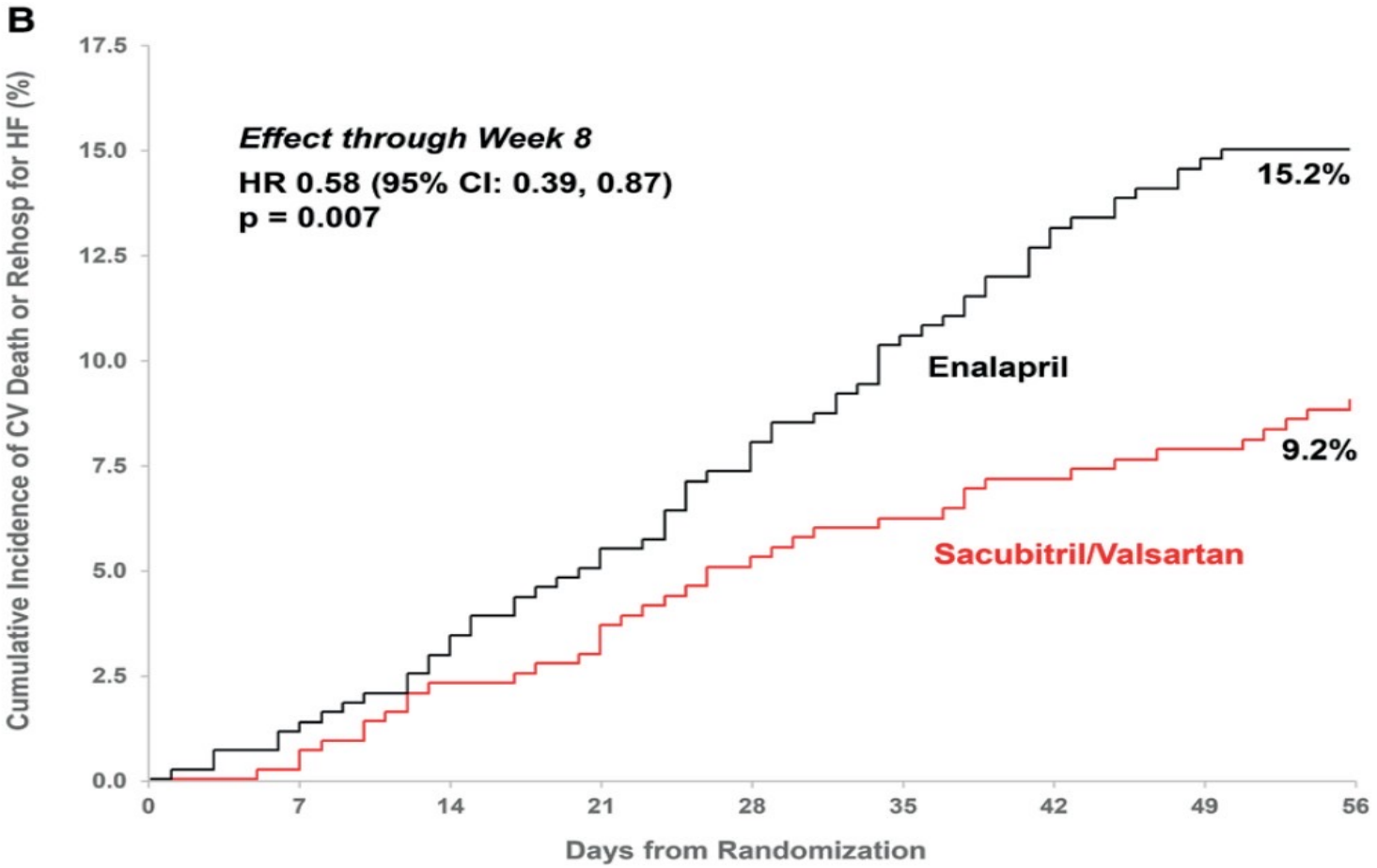
Primary Endpoint



*Percentage (%) change from baseline to mean of weeks 4 and 8

Velazquez EJ et al. nejm.org/doi/full/10.1056/NEJMoa1812851

PIONEER-HF: CV Death or HF Rehospitalization



Significant Clinical Benefits within 30 Days

Morrow, et al. *Circulation* 2019;139:2285-2288

PIONEER-HF

Safety

Key Safety Outcomes no. (%)	Sacubitril/ Valsartan (n=440) (%)	Enalapril (n=441) (%)	RR Sac/Val vs Enalapril (95% CI)
Worsening renal function[a]	60 (13.6)	65 (14.7)	0.93 (0.67-1.28)
Hyperkalemia	51 (11.6)	41 (9.3)	1.25 (0.84-1.84)
Symptomatic hypotension	66 (15.0)	56 (12.7)	1.18 (0.85-1.64)
Angioedema events[b]	1 (0.2)	6 (1.4)	0.17 (0.02-1.38)

[a] SCr ≥0.5 with simultaneous eGFR reduction of ≥25%
[b] Positively adjudicated angioedema cases.
RR, Relative risk

Velazquez EJ et al. nejm.org/doi/full/10.1056/NEJMoa1812851

Updated recommendations

- We recommend that an ARNI be used in place of an ACEI or ARB, in patients with HFrEF, who remain symptomatic despite treatment with appropriate doses of GDMT to decrease CV death, HF hospitalizations, and symptoms

  Strong Recommendation; High-Quality Evidence

- We recommend that patients admitted to hospital for acute decompensated HF with HFrEF should be switched to an ARNI, from an ACEI or ARB, when stabilized and before hospital discharge

  Strong Recommendation; Moderate-Quality Evidence

- We suggest that patients admitted to hospital with a new diagnosis of HFrEF should be treated with ARNI as first-line therapy, as an alternative to either an ACEI or ARB

  Weak Recommendation; Moderate-Quality Evidence

McDonald, Virani, et al, Can J Cardiol 2021

Canadian Cardiovascular Society

McDonald, Virani, et al., *Canadian Journal of Cardiology:* https://doi.org/10.1016/j.cjca.2021.01.017

ESC European Society of Cardiology

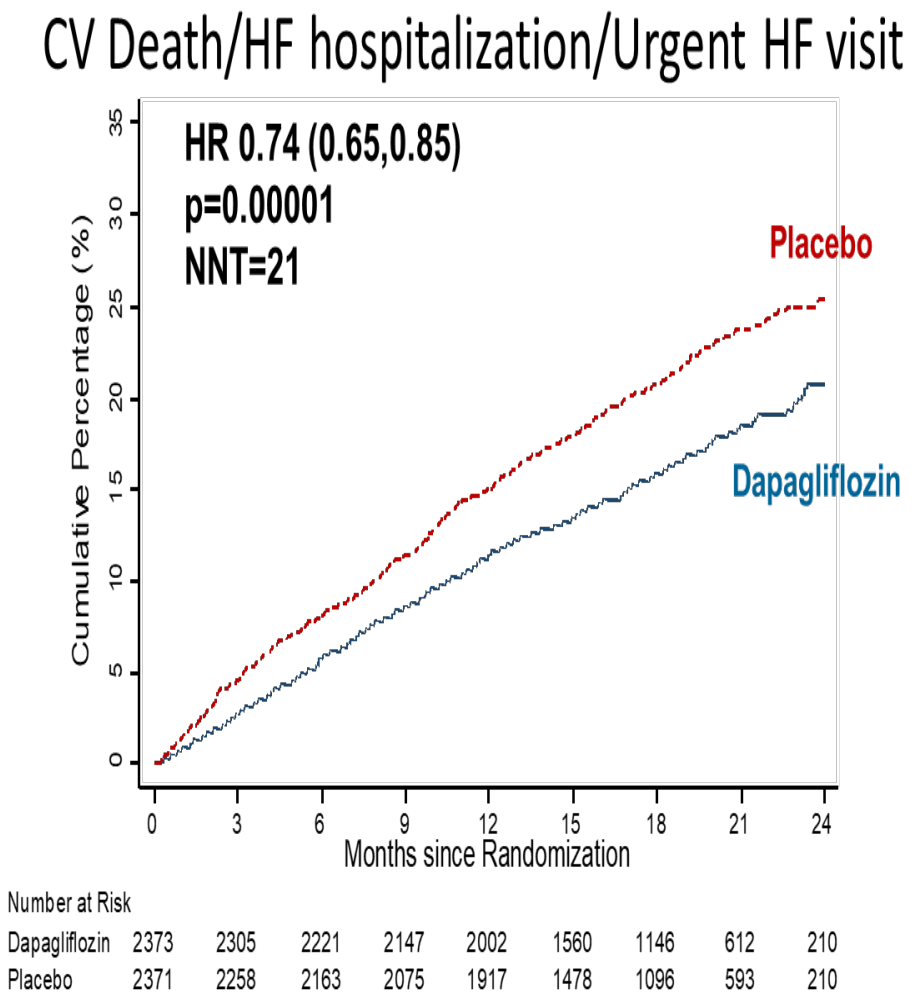
European Journal of Heart Failure (2021)
doi:10.1002/ejhf.2191

STUDY DESIGN PAPER

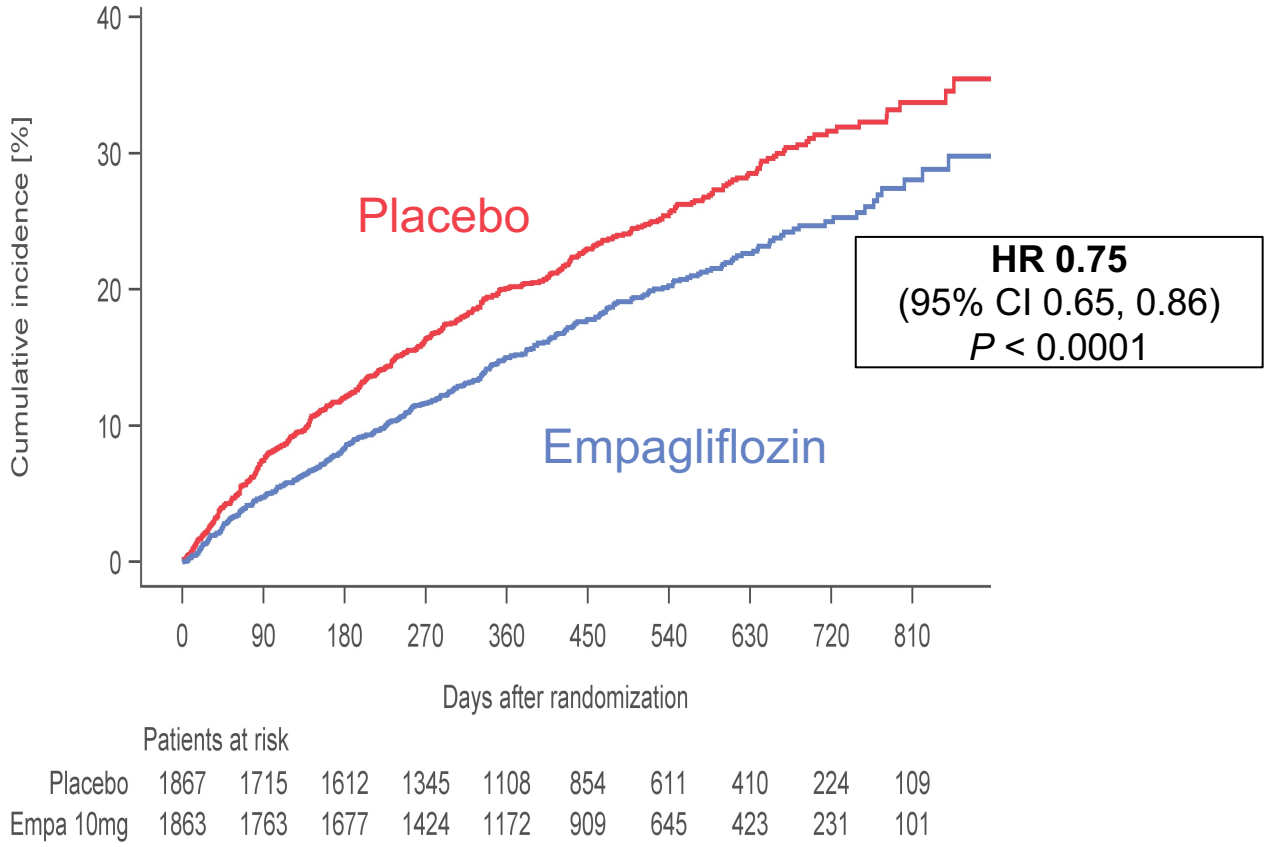
Prospective ARNI vs. ACE inhibitor trial to DetermIne Superiority in reducing heart failure Events after Myocardial Infarction (PARADISE-MI): design and baseline characteristics

Karola S. Jering[1], Brian Claggett[1], Marc A. Pfeffer[1]*, Christopher Granger[2], Lars Køber[3], Eldrin F. Lewis[4], Aldo P. Maggioni[5], Douglas Mann[6], John J.V. McMurray[7], Jean-Lucien Rouleau[8], Scott D. Solomon[1], Philippe G. Steg[9], Peter van der Meer[10], Margaret Wernsing[11], Katherine Carter[11], Weinong Guo[11], Yinong Zhou[11], Martin Lefkowitz[11], Jianjian Gong[11], Yi Wang[11], Bela Merkely[12], Stella M. Macin[13], Urmil Shah[14], Jose C. Nicolau[15], and Eugene Braunwald[16]

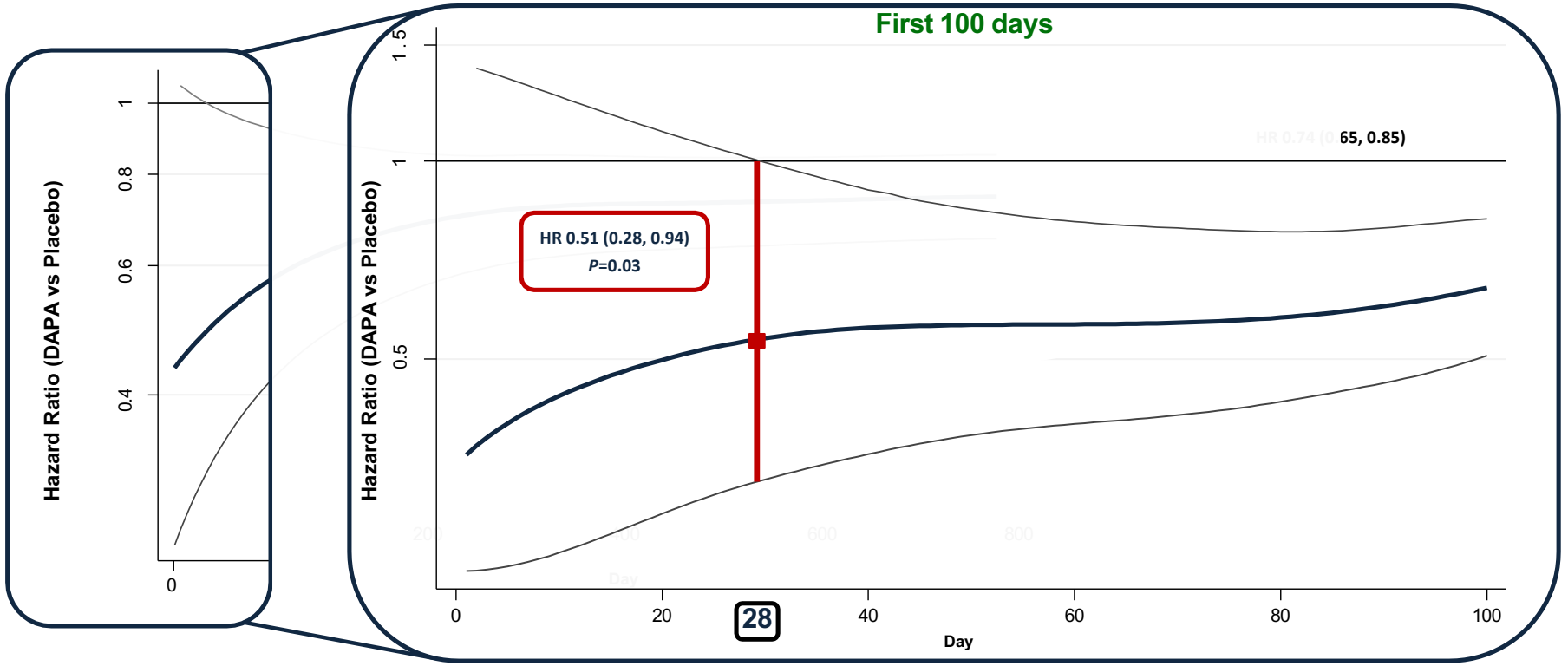
DAPA-HF and EMPEROR-Reduced



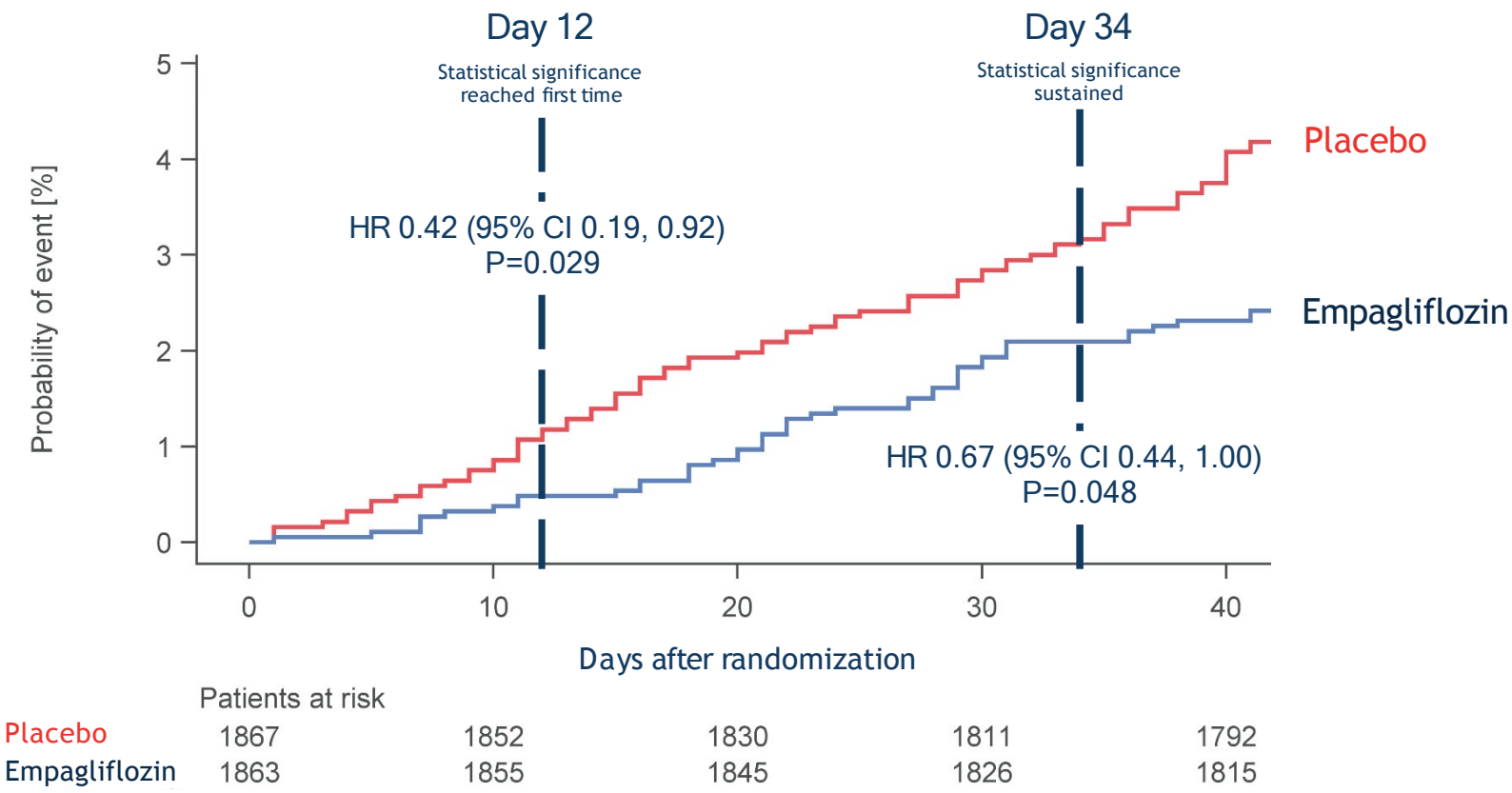
Time to Cardiovascular Death or Hospitalization for Heart Failure (Primary Endpoint)



Early Benefit of Dapagliflozin on CV Death or WHF

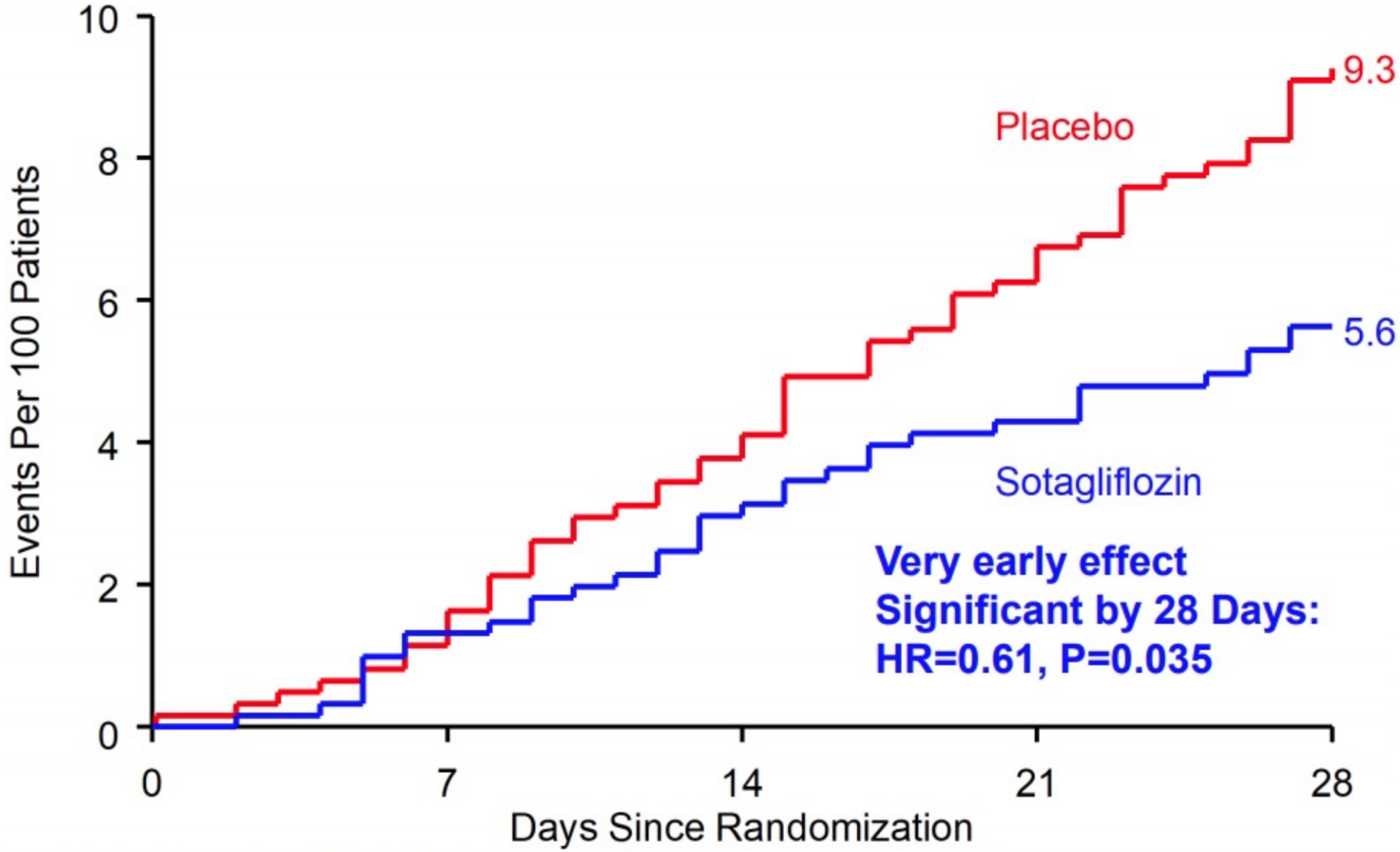


Sabatine MS et al. Presented at: AHA Scientific Sessions; November 16-18, 2019; Philadelphia, PA.


Day 12
Statistical significance reached first time
Day 34
Statistical significance sustained
Placebo
Empagliflozin
HR 0.42 (95% CI 0.19, 0.92)
P=0.029
HR 0.67 (95% CI 0.44, 1.00)
P=0.048
Probability of event [%]
0
1
2
3
4
5
0
10
20
30
40
Days after randomization
Patients at risk
Placebo 1867 1852 1830 1811 1792
Empagliflozin 1863 1855 1845 1826 1815

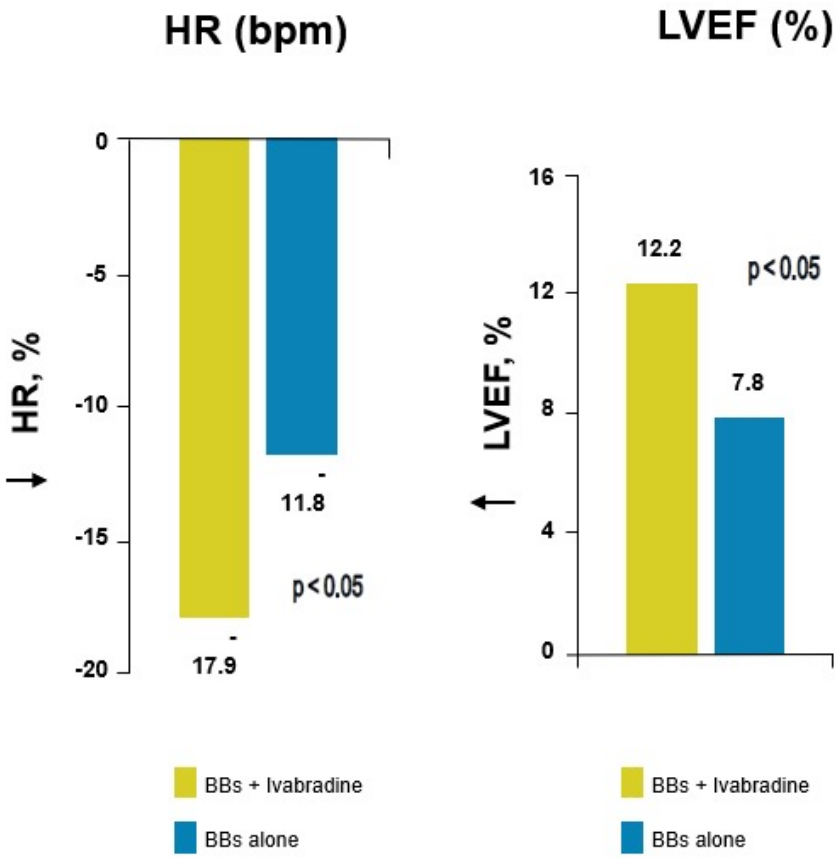
Primary Efficacy: Total CV Death, HHF, and Urgent HF Visit – Significant by 28 Days

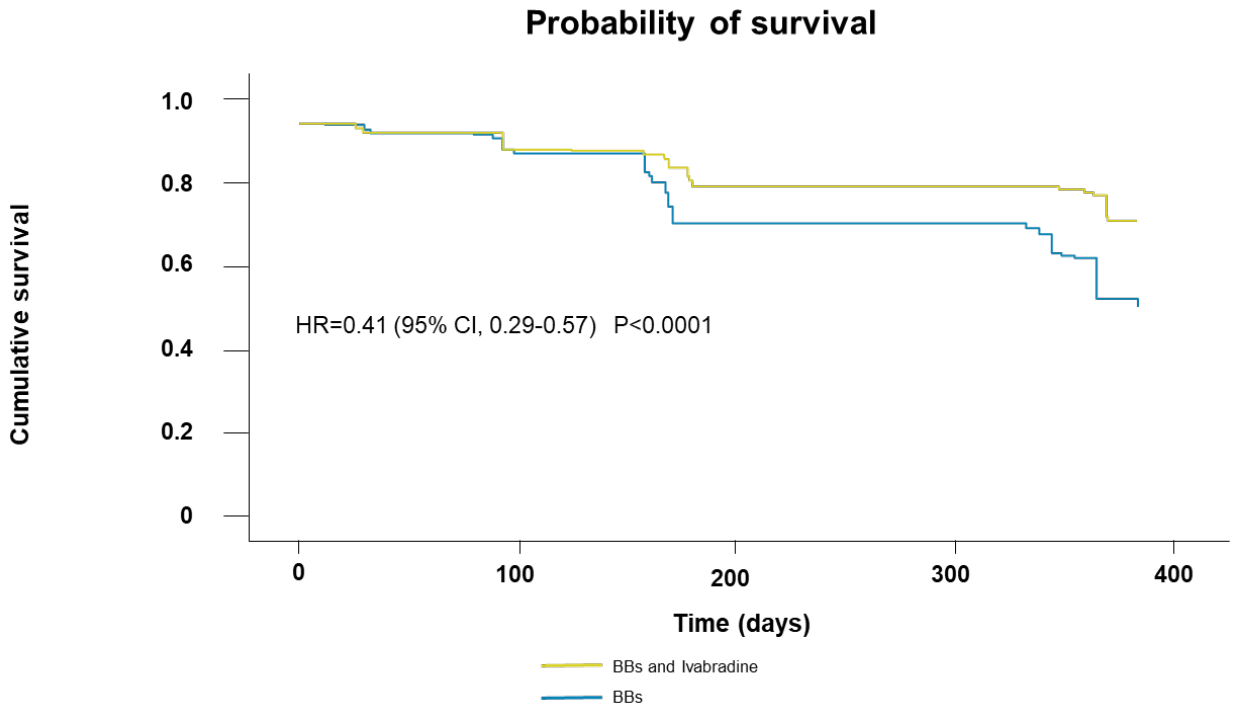
SOLOIST



Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

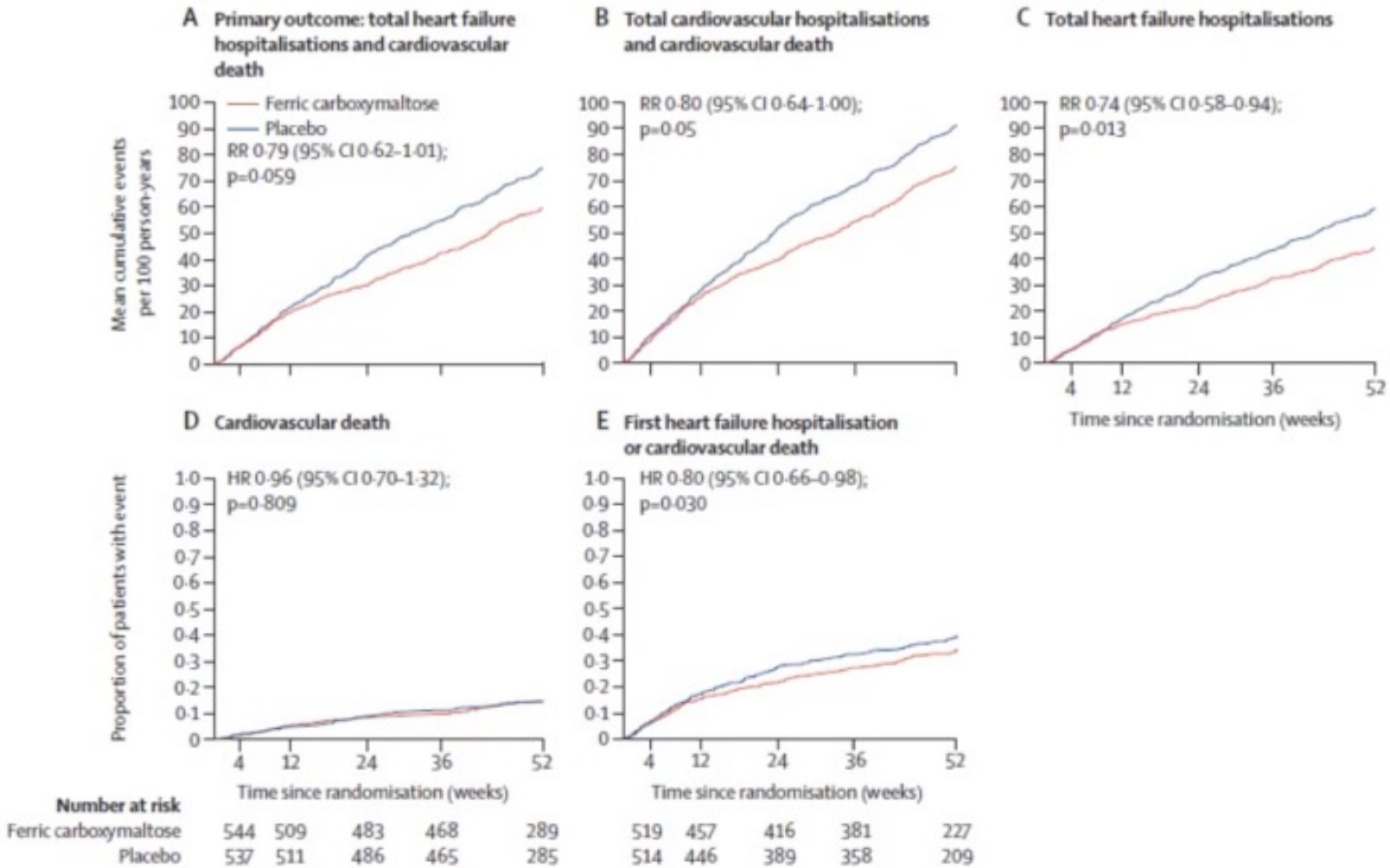
Early co-administration of ivabradine and β-blockers during hospitalization is safe and may improve survival





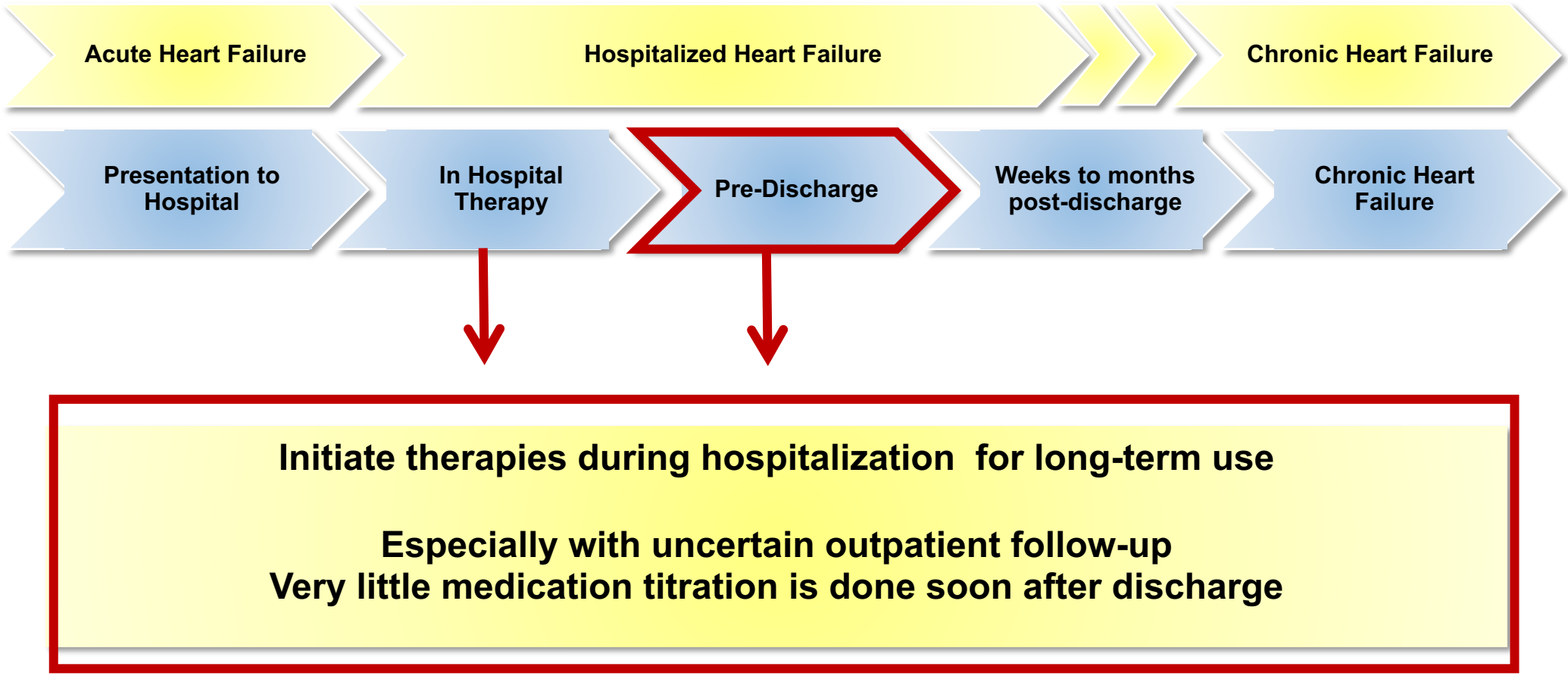
Lopatin et al., *Int. J Cardiol., 2018, 260, 113-117*

AFFIRM-AHF: Ferric Carboxymaltose in Iron Deficient Acute HF Patients

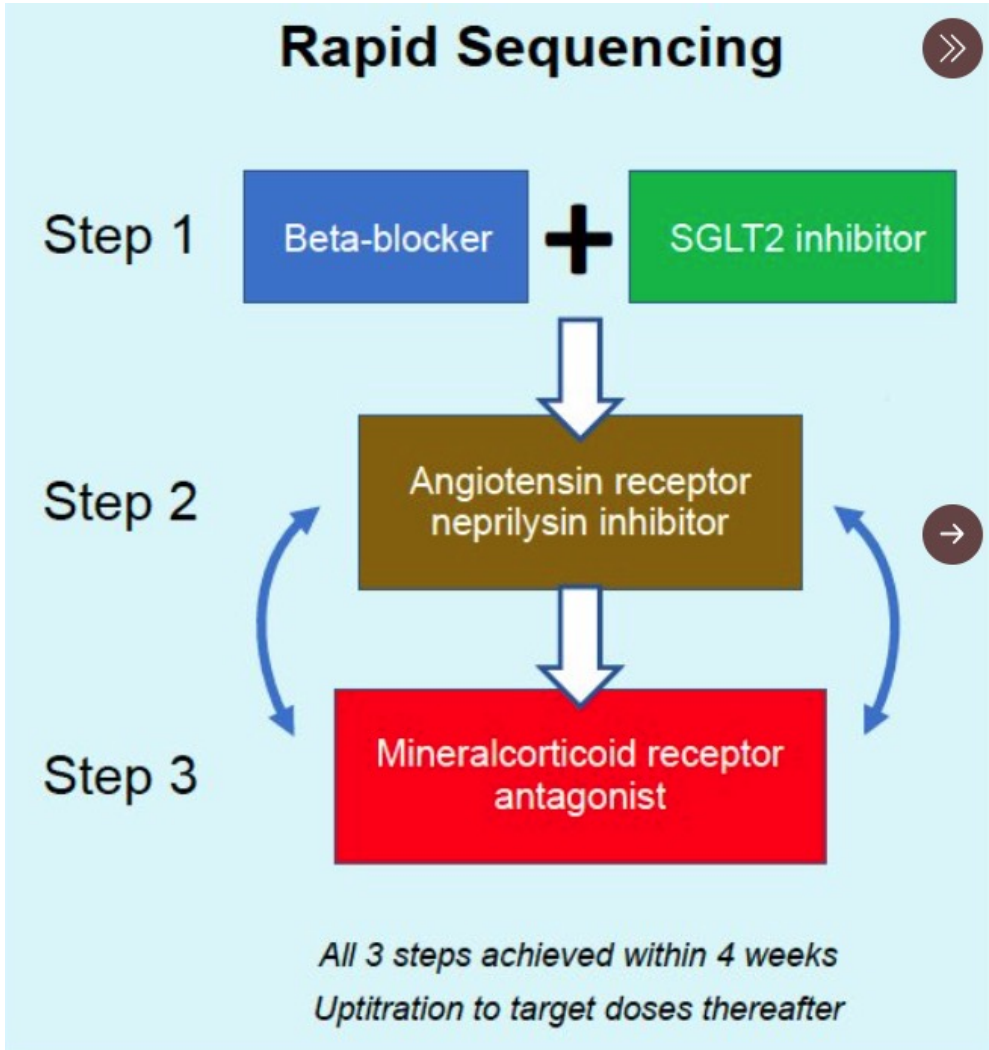


Poikowski, Lancet 2020; 396:1895

Hospitalization is a key moment to optimize treatment



Marti NC et al. Timing and duration of interventions in clinical trials for patients with hospitalized heart failure. *Circ Heart Fail* 2013;6:1095-1101.


Rapid Sequencing
Step 1
Beta-blocker
SGLT2 inhibitor
Step 2
Angiotensin receptor neprilysin inhibitor
Step 3
Mineralcorticoid receptor antagonist
All 3 steps achieved within 4 weeks
Uptitration to target doses thereafter

Cluster Scheme

Initiation and Titration of Foundational Therapy for Heart Failure with LVEF < 40%

Red- Face to face visit with prescriber preferred | Blue- Either face to face or virtual visit with prescriber | Orange- Virtual visit with prescriber preferred

Cluster A: Diuretic & SGLTi	+	Cluster B: ARNi & MRA	+	Cluster C: Beta Blocker & SNI*

Encounter 1 (Usually face-to-face, up to 3 medication initiations)

Start Preferred Cluster A Medication	Start Preferred Cluster B Medication	Start Preferred Cluster Medication*

1- 2 Weeks

Encounter 2 (whenever feasible, up to 3 medication initiations)

Titrate Cluster A Medication	Start Second Cluster B Medication	Adjust Cluster C Medication*

1- 2 Weeks

Encounter 3 & ongoing (whenever feasible, up to 3 medication titrations)

Diuretic titration as needed	Cluster B Medication titration	Cluster C Medication Titration*

1- 2 Weeks

Goal Foundational Therapy- Continue to actively manage as necessary

Addition of Personalized Therapies as dictated by clinical presentation and setting (see Table 2)

Recommended Total Time for Titration ≤ 12 weeks (3 months)

Canadian Journal of Cardiology 2021 37632-643DOI: (10.1016/j.cjca.2020.12.028)

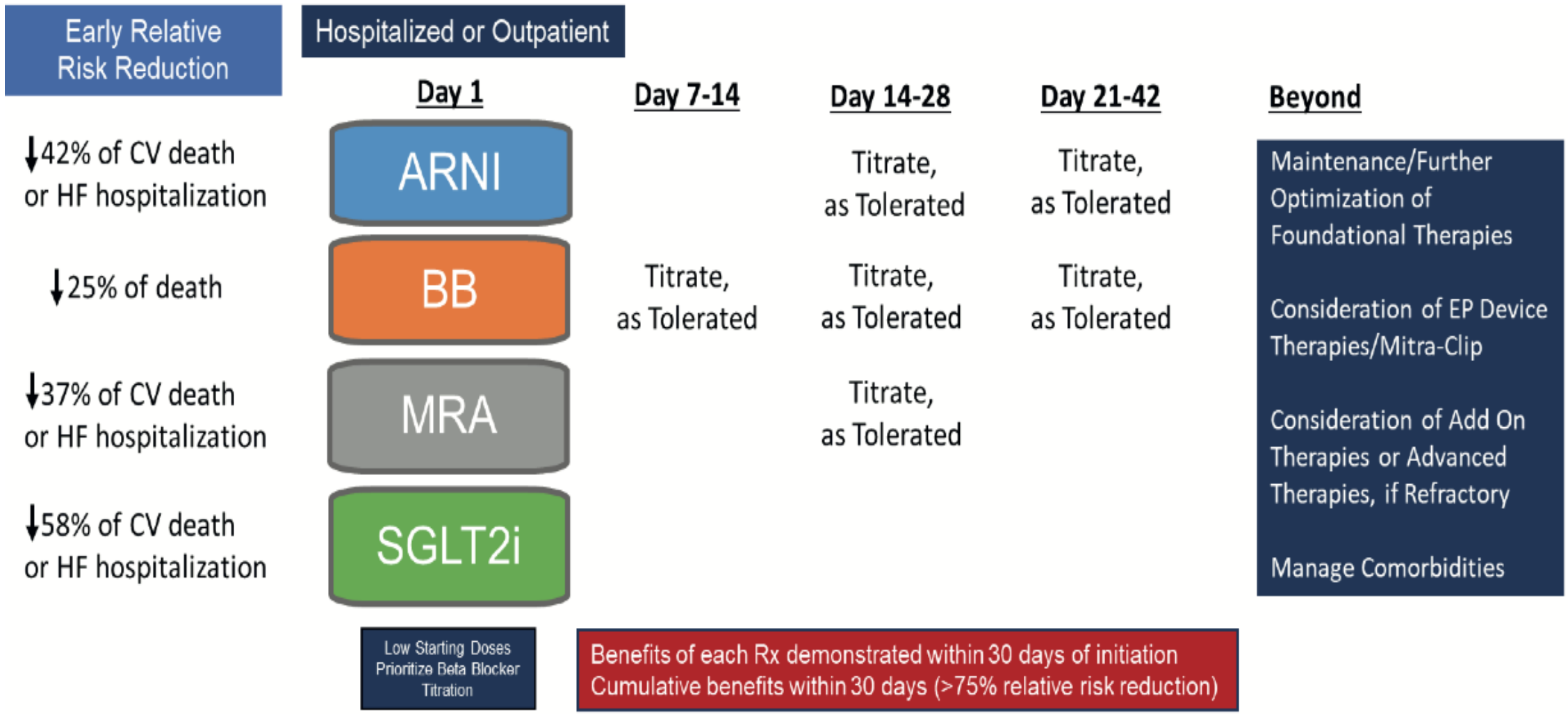
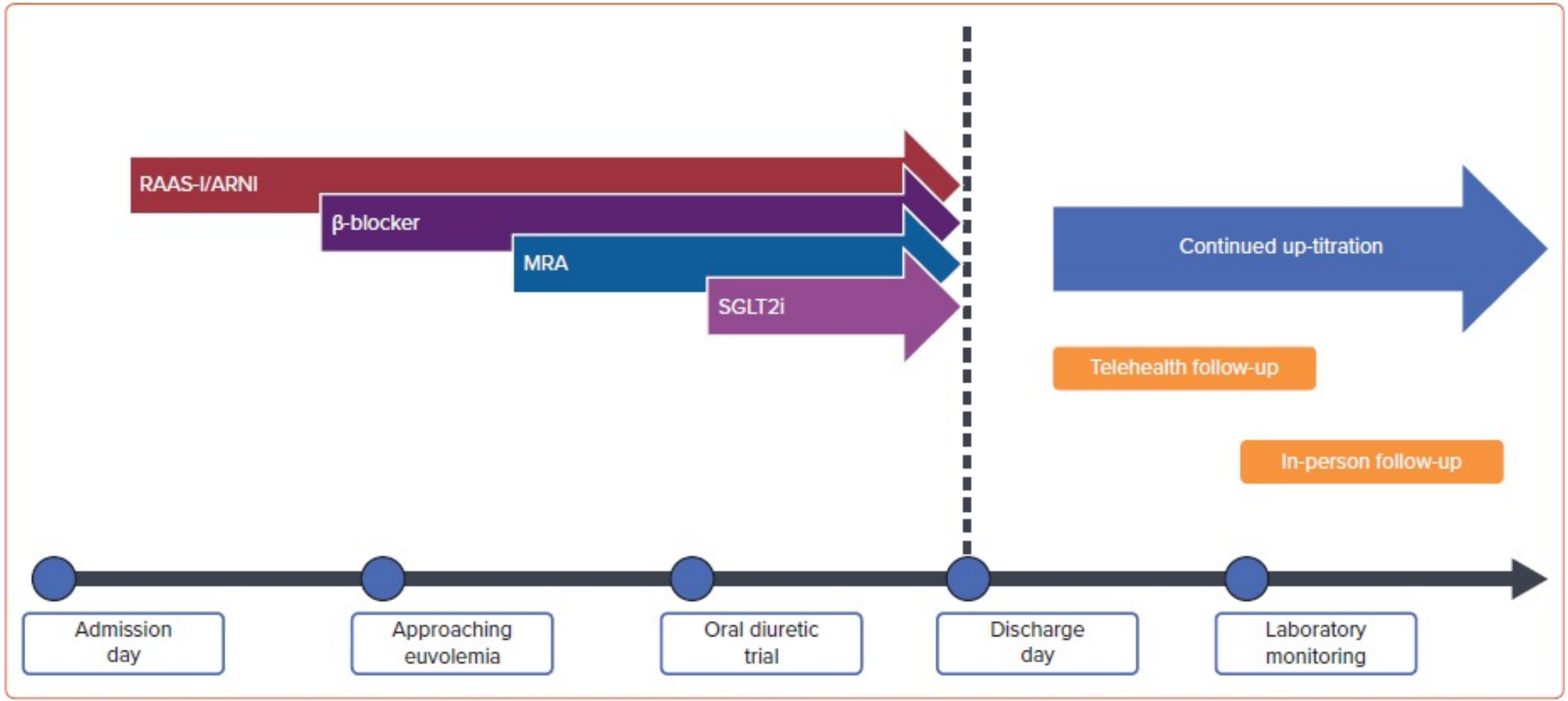

Early Relative Risk Reduction
Hospitalized or Outpatient
Day 1
Day 7-14
Day 14-28
Day 21-42
Beyond
↓42% of CV death or HF hospitalization
ARNI
Titrate, as Tolerated
Titrate, as Tolerated
Maintenance/Further Optimization of Foundational Therapies
↓25% of death
BB
Titrate, as Tolerated
Titrate, as Tolerated
Titrate, as Tolerated
Consideration of EP Device Therapies/Mitra-Clip
↓37% of CV death or HF hospitalization
MRA
Titrate, as Tolerated
Consideration of Add On Therapies or Advanced Therapies, if Refractory
↓58% of CV death or HF hospitalization
SGLT2i
Manage Comorbidities
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)

Figure 1: Shifting the Paradigm of Guideline-directed Medical Therapy Initiation



A suggested timeline of initiating guideline-directed medical therapy (GDMT) for patients admitted with heart failure with reduced ejection fraction during their hospitalization. ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; MRA = mineralocorticoid receptor antagonist; RAAS-I = renin-angiotensin-aldosterone system inhibitor; SGLT2i = sodium–glucose cotransporter-2 inhibitor.