香港中文大學
The Chinese University of Hong Kong

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

35th Anniversary 三十五週年

Every beat matters – the importance of early heart rate control in the new and personalized heart failure management era

Dr. K Kam
Honorary Associate Professor (CUHK)
Prince of Wales Hospital

Framework of my talk

- Heart failure situation in real world and HK
- Why heart rate really matter in management
- GDMT for HFrEF: the fantastic four plus heart rate control
- Post discharge Heart Failure Clinic: Strong-HF

De Marzo V et al. J Intern Med. 2022; doi: 10.111/joinm.13487

Heart failure situation in real world and HK

Huge Gaps in HF care pathway

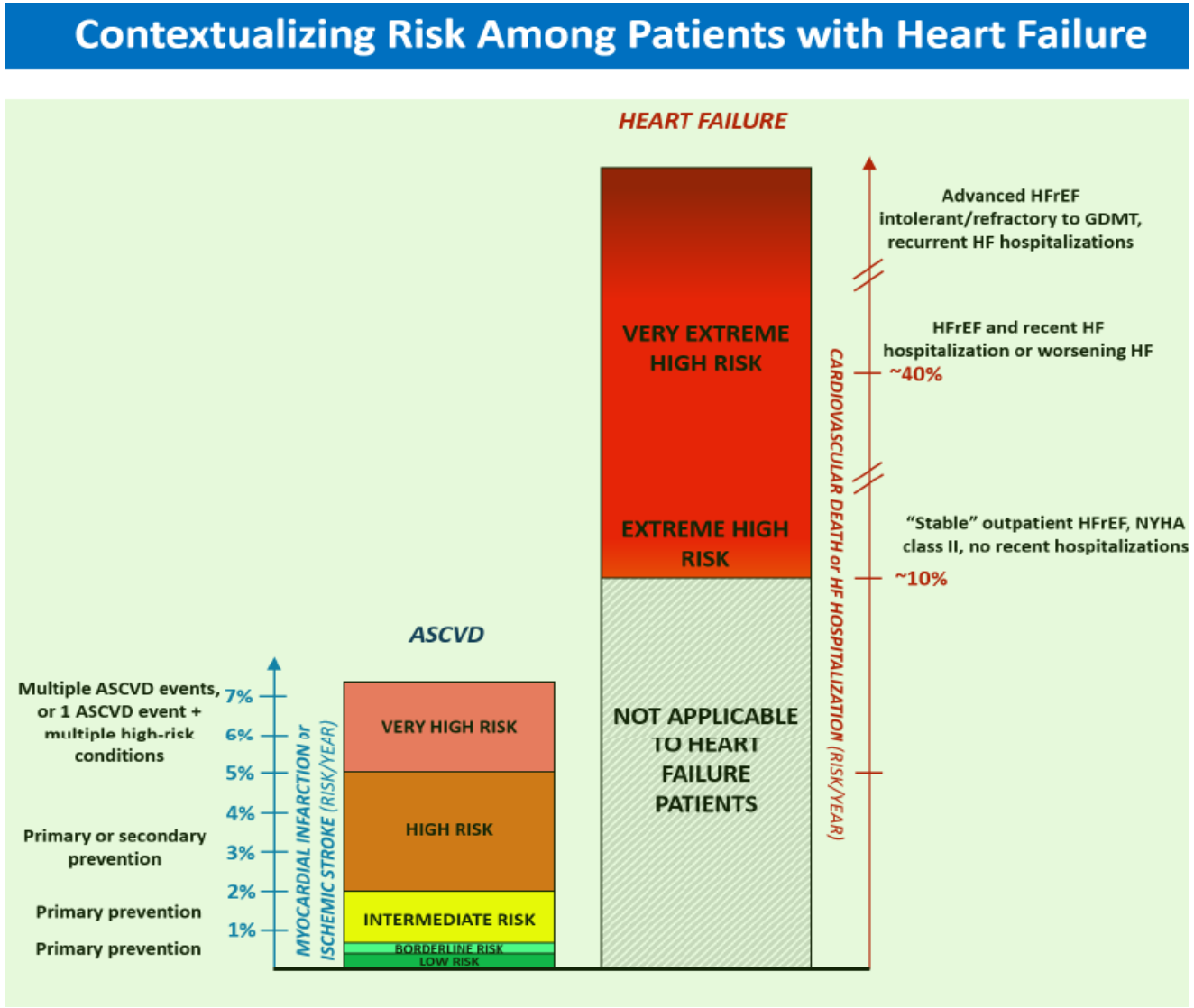
- In Hong Kong, heart failure is the leading cause of admission in Department of Medicine
- Frequent hospitalizations and high readmissions ~25% in one month
  - **21,015 HF admissions in 2019** vs 15,989 HF admissions in 2007 (30% increase)
  - in-patient care contributes to the largest proportion (72.2%) of the total cost

Number of Inpatient and Day Inpatient Discharges and Deaths in Hospitals under the Hospital Authority by Disease Group, 2017 to 2019

Disease group	Detailed list number ICD 10th revision	2017	2018	2019
Hypertensive heart disease	I11	310	274	285
Hypertensive renal disease	I12	925	784	730
Hypertensive heart and renal disease	I13	658	515	429
Secondary hypertension	I15	551	585	559
Acute myocardial infarction	I21-I22	9 210	8 589	8 523
Other ischaemic heart diseases	I20, I23-I25	16 974	16 484	17 454
Pulmonary embolism	I26	607	650	677
Conduction disorders and cardiac arrhythmias	I44-I49	18 196	18 130	18 752
Heart failure	I50	19 636	20 405	21 015
Other heart diseases	I27-I43, I51-I52	5 547	5 821	5 798
Intracranial haemorrhage	I60-I62	7 736	7 675	7 856
Cerebral infarction	I63	10 258	10 562	10 530
Stroke, not specified as haemorrhage or infarction	I64	3 225	3 195	3 069
Other cerebrovascular diseases	I65-I69	3 179	3 238	3 433

Leung et al. BMC Cardiovascular Disorders 2015:15:12 DOI 10.1186/s12872-015-0002-8 and Hospital Authorty Statistical Report

HFrEF patients have a much higher rate of clinical events



ASCVD = atherosclerotic cardiovascular disease CV = cardiovascular HF = heart failure HFrEF = heart failure with reduced ejection fraction HHF hospitalization for heart failure MI =myocardial infarction NYHA = New York Heart Association,

1. Greene SJ, et al. JAMA. 2021;326(22):2261-2262 2. Heidenreich PA, et al. J Am Coll Cardiol. 2022 May 3;79(17):e263-e421 3. McDonagh TA al. Eur Heart J. 2021;42(36):3599-3726.

HF patients are at very high risk of death and hospitalization

9 out of 10 PATIENTS

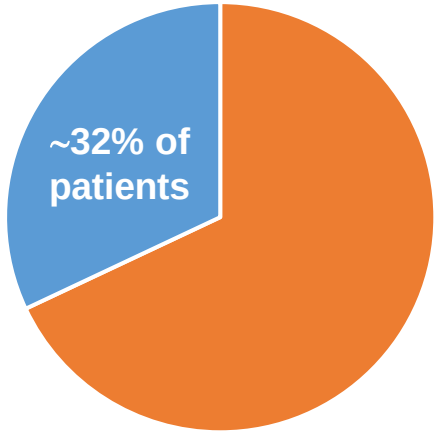
are symptomatic, even with current HF standard of care (SoC)[1,a]

[a]Based on a prospective observational study of 3494 US outpatients with chronic HFrEF in the CHAMP-HF registry; [b]Based on a retrospective analysis of 51,286 patients from a US Military Data Repository admitted to a healthcare facility for the first time for heart failure. During the 7-year study period (2007–2013) patients were assessed for subsequent hHF, comorbidities, and mortality data. No distinction was made between patients with reduced or preserved ejection fraction

CV, cardiovascular; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hHF, hospitalization for heart failure; NYHA, New York Heart Association; SoC, standard of care

1. Khariton Y, et al. *JACC Heart Fail* 2018:6;465–473; 2. Young JB, et al. *Circulation* 2004;110:2618–2626; 3. Lin AH, et al. *Mil Med* 2017;182:e1932–e1937

Nearly one third of patients with HFrEF are at high risk of hospitalization or CV death, including those who appear stable[2]



Based on NYHA classification over a 4-year period, from the 2004 CHARM study

Each hHF increases the risk of mortality further[3,b]

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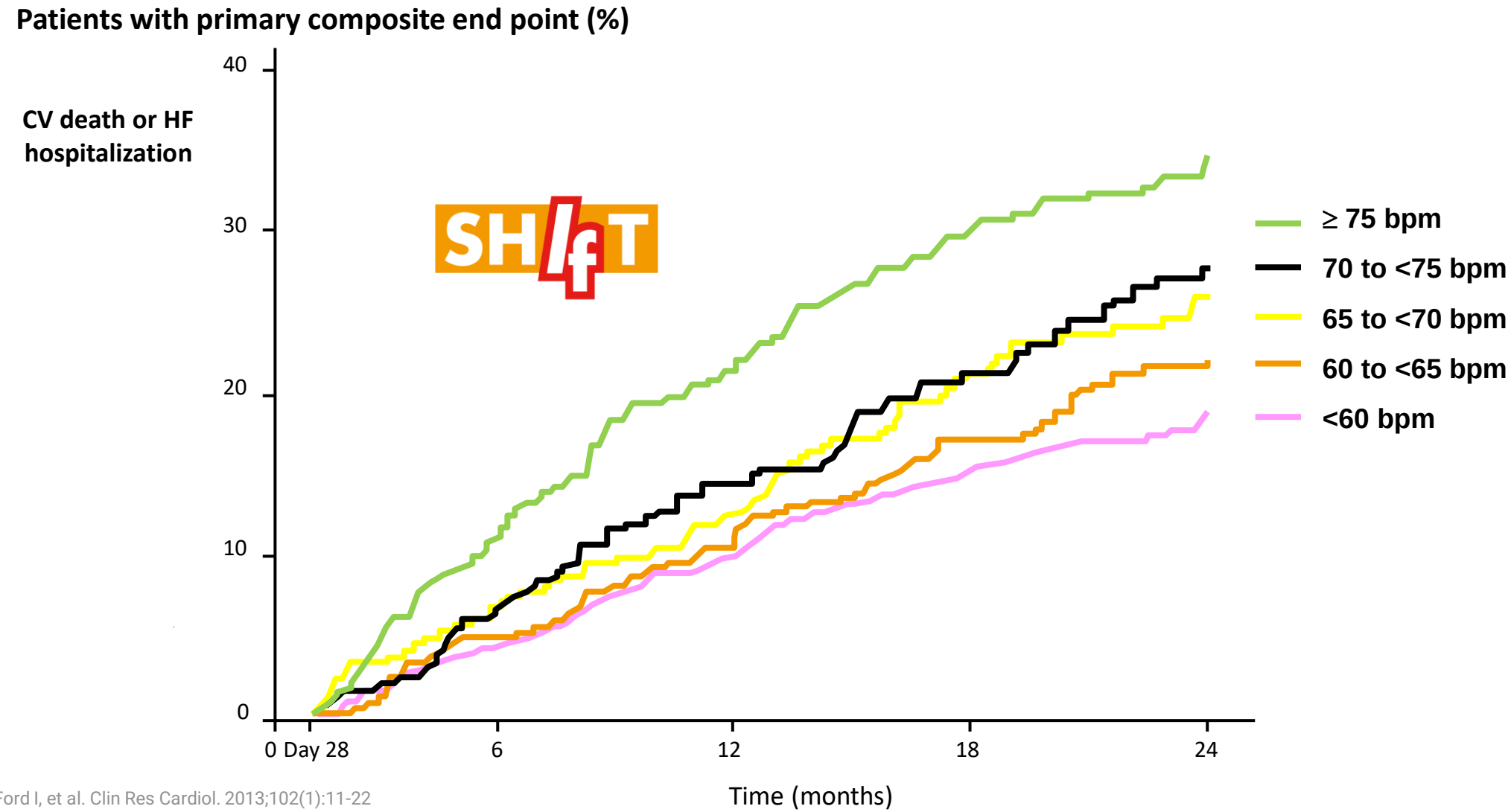
Why heart rate really matters in Mx

Higher event rates are observed for HFrEF patients (in SR) with elevated heart rate



Böhm M, Borer J, Ford I, et al. Clin Res Cardiol. 2013;102(1):11-22

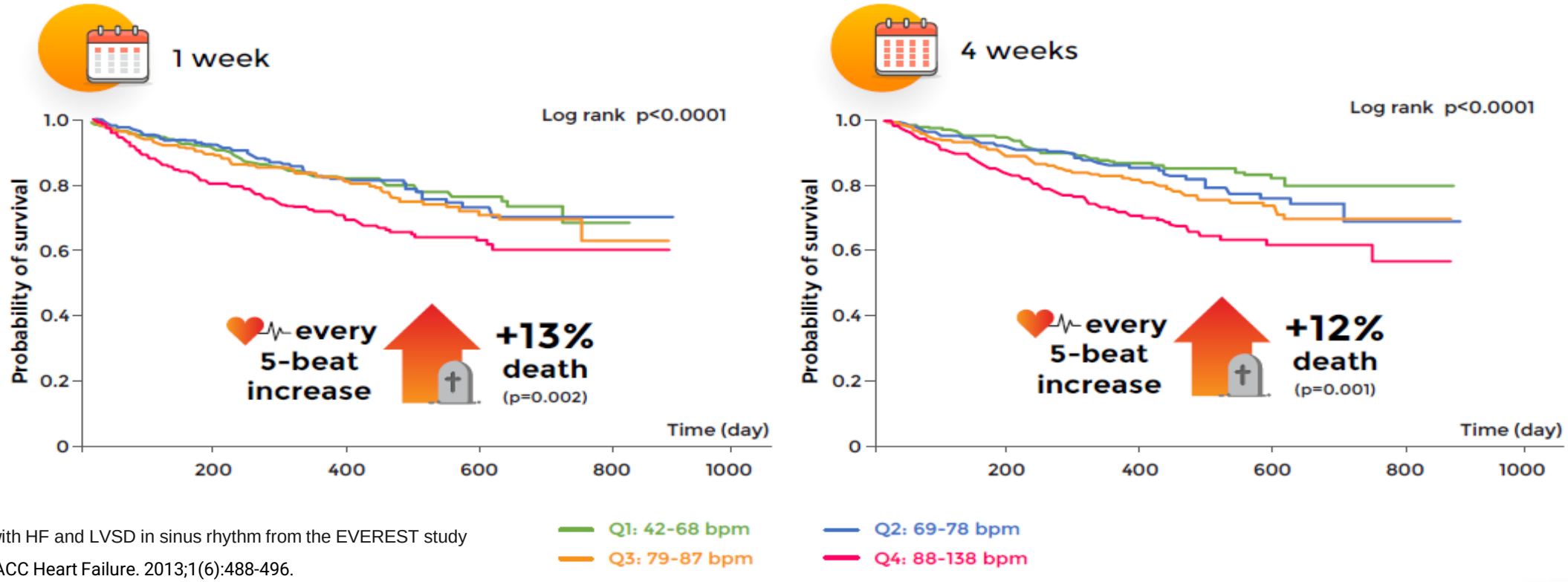
1-week & 4-week post-discharge heart rate predicts mortality

JACC: Heart Failure
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 1, No. 6, 2013
ISSN 2213-1779/$36.00
http://dx.doi.org/10.1016/j.jchf.2013.08.005

CLINICAL RESEARCH

The Prognostic Significance of Heart Rate in Patients Hospitalized for Heart Failure With Reduced Ejection Fraction in Sinus Rhythm



N=1947 patients with HF and LVSD in sinus rhythm from the EVEREST study

Greene JC et al. JACC Heart Failure. 2013;1(6):488-496.

Increased 30-day mortality for HFrEF patients with higher and elevated heart rate at discharge

Original Article

Association of Heart Rate at Hospital Discharge With Mortality and Hospitalizations in Patients With Heart Failure

Marlena V. Habal, MD; Peter P. Liu, MD; Peter C. Austin, PhD; Heather J. Ross, MD; Gary E. Newton, MD; Xuesong Wang, MSc; Jack V. Tu, MD, PhD; Douglas S. Lee, MD, PhD

- Elevated HR at discharge is associated with increased **30-day mortality** and higher readmission rates in HF patients
- Average discharge HR = 76 bpm

	Heart Rate at Discharge (bpm)				
	40–60	61–70	71–80	81–90	>90
Patients (%)	14.6%	23.9%	28.9%	18.7%	13.9%
Hazard ratio for **30-day** mortality	1.06	Referent	1.21	1.70	1.88

61.5% of patients with HR ≥ 70 bpm

Habal MV et al. *Circ Heart Fail* 2014; 7(1):12-20.

- 9097 patients discharged from an HF hospitalization in Ontario (1999–2001 and 2004–2005)

High heart rate remains an important and independent risk factor for HFrEF patients in SR despite background GDMTs including the use of ARNI

	Adjusted hazard ratio		
	Tertile 1 - reference group (≤66 bpm)	Tertile 2 (67-76 bpm)	Tertile 3 (≥77 bpm)
Primary endpoint	1.00	1.19 (1.05, 1.35)	1.24 (1.09, 1.43)
CV death	1.00	1.19 (1.01, 1.40)	1.24 (1.04, 1.47)
HF hospitalization	1.00	1.18 (0.99, 1.39)	1.37 (1.15, 1.63)
All-cause mortality	1.00	1.23 (1.07, 1.42)	1.27 (1.08, 1.48)

Association between heart rate and outcome (tertile analysis)

McMurray JJ et al. N Eng J Med. 2014;371(11):993-1004.

High heart rate remains an important and independent risk factor for HFrEF patients in SR despite background GDMTs including the use of ARNI

ESC European Society of Cardiology

European Journal of Heart Failure (2019)
doi:10.1002/ejhf.1682

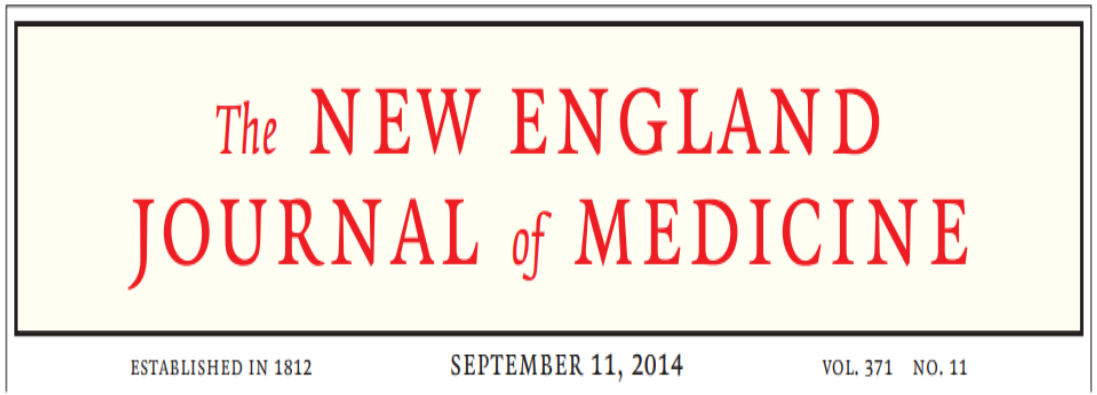
RESEARCH ARTICLE

Relationship between heart rate and outcomes in patients in sinus rhythm or atrial fibrillation with heart failure and reduced ejection fraction

Kieran F. Docherty[1], Li Shen[1], Davide Castagno[2], Mark C. Petrie[1], William T. Abraham[3], Michael Böhm[4], Akshay S. Desai[5], Kenneth Dickstein[6], Lars V. Køber[7], Milton Packer[8], Jean L. Rouleau[9], Scott D. Solomon[5], Karl Swedberg[10], Ali Vazir[11], Michael R. Zile[12], Pardeep S. Jhund[1], and John J.V. McMurray[1]*

Docherty KF et al. Eur J Heart Fail. 2019 Dec 17. doi: 10.1002/ejhf.1682

Around 65% patients from this analysis are from the PARADIGM-HF trial (ARNI study)



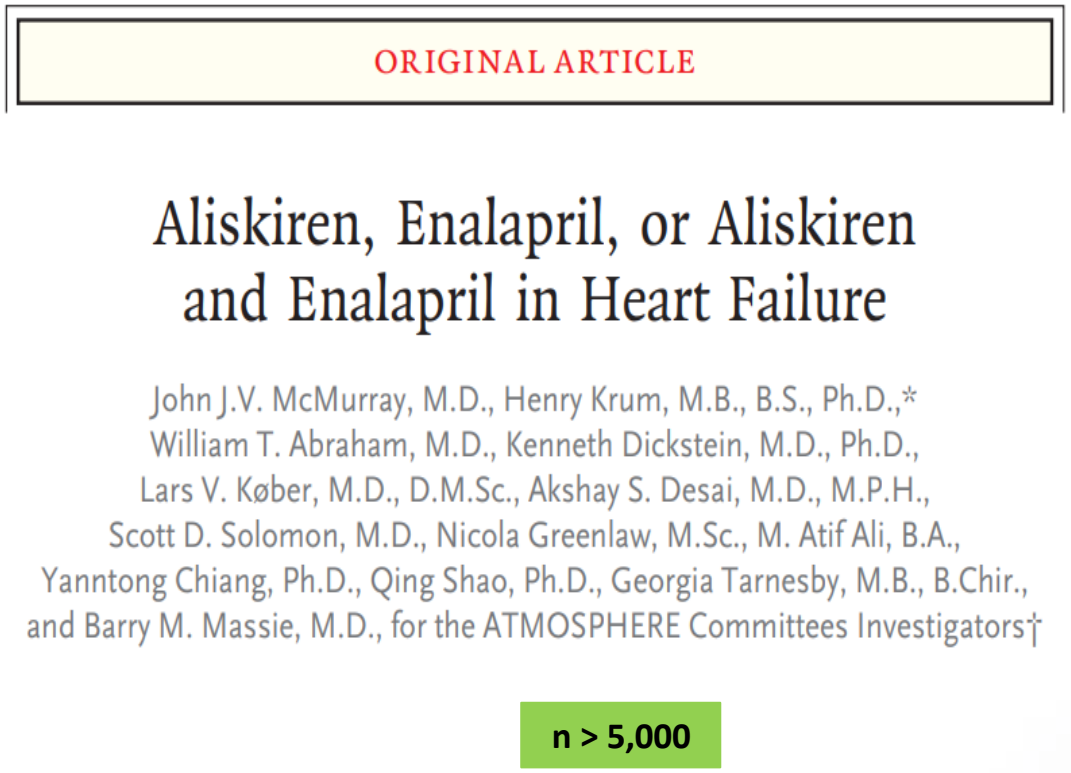
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

n > 8,000



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

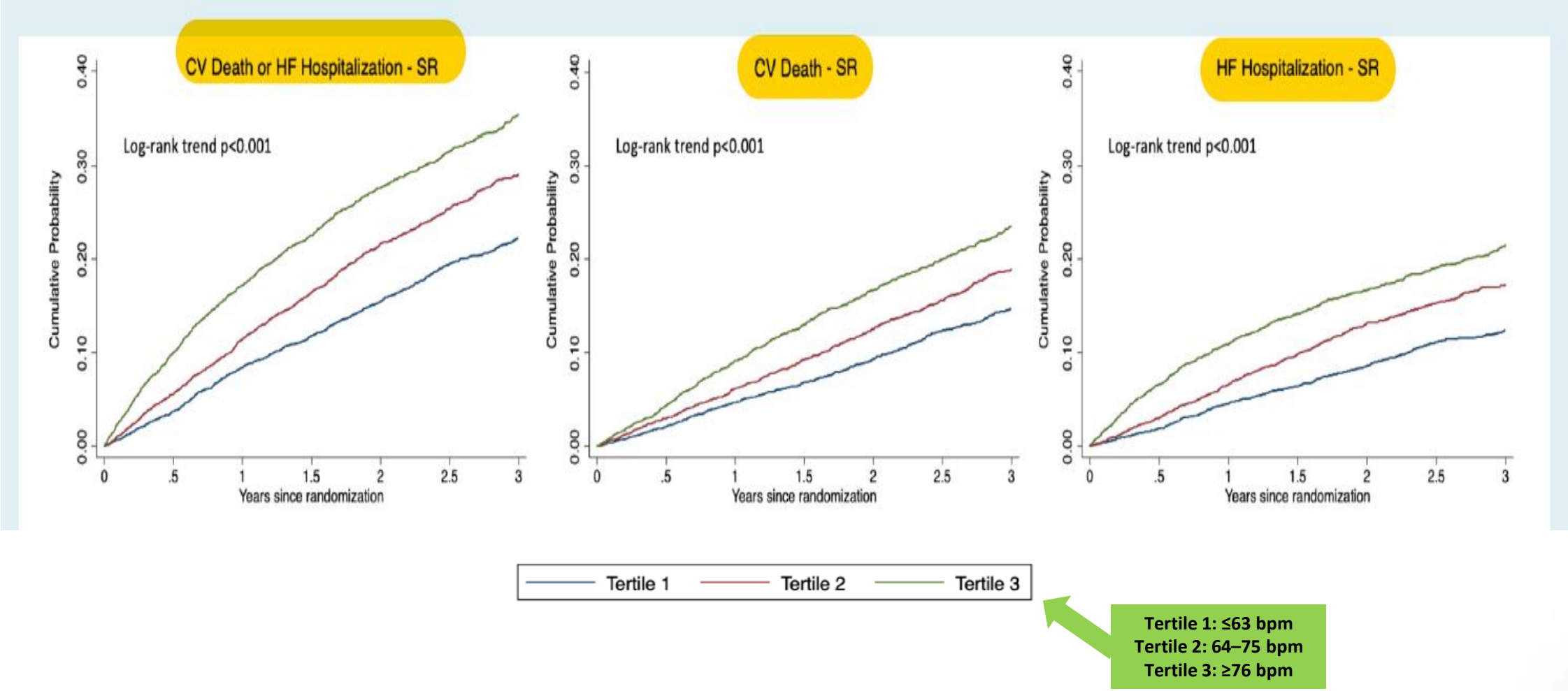
Aliskiren, Enalapril, or Aliskiren and Enalapril in Heart Failure

John J.V. McMurray, M.D., Henry Krum, M.B., B.S., Ph.D.,* William T. Abraham, M.D., Kenneth Dickstein, M.D., Ph.D., Lars V. Køber, M.D., D.M.Sc., Akshay S. Desai, M.D., M.P.H., Scott D. Solomon, M.D., Nicola Greenlaw, M.Sc., M. Atif Ali, B.A., Yanntong Chiang, Ph.D., Qing Shao, Ph.D., Georgia Tarnesby, M.B., B.Chir., and Barry M. Massie, M.D., for the ATMOSPHERE Committees Investigators†

n > 5,000

John J.V. McMurray, et al. N Engl J Med 2014;371:993-1004 (PARADIGM-HF study)
John J.V. McMurray, et al. N Engl J Med 2016; 374:1521-1532 (ATMOSPHERE study)

Heart rate of around 60 bpm seem to be an ideal target heart rate for HFrEF patients in sinus rhythm



Tertile 1: ≤63 bpm
Tertile 2: 64–75 bpm
Tertile 3: ≥76 bpm

Docherty KF et al. Eur J Heart Fail. 2019 Dec 17. doi: 10.1002/ejhf.1682

Significant reduction in CV events, HF biomarker level, as well as QoL improvement is demonstrated for ≥10 bpm reduction at 12 months from study baseline

	Sinus rhythm ($n = 7756$)	
	Event rate (95% CI)	Adjusted HR (95% CI)
CV death or HF hospitalization		
≤ −10 bpm	10.0 (8.7–11.4)	0.74 (0.63–0.87); $P < 0.001$
< +/−10 bpm	9.9 (9.2–10.5)	1.00 (Referent)
≥ +10 bpm	14.5 (13.1–16.0)	1.52 (1.34–1.72); $P < 0.001$
CV death		
≤ −10 bpm	6.4 (5.4–7.5)	0.82 (0.67–1.01); $P = 0.060$
< +/−10 bpm	5.7 (5.3–6.2)	1.00 (Referent)
≥ +10 bpm	8.6 (7.6–9.8)	1.53 (1.31–1.80); $P = <0.001$
HF hospitalization		
≤ −10 bpm	5.2 (4.3–6.3)	0.69 (0.55–0.87); $P = 0.001$
< +/−10 bpm	5.6 (5.1–6.1)	1.00 (Referent)
≥ +10 bpm	8.4 (7.4–9.7)	1.60 (1.36–1.89); $P < 0.001$
Pump failure death		
≤ −10 bpm	1.4 (1.0–2.0)	0.73 (0.48–1.13); $P = 0.163$
< +/−10 bpm	1.4 (1.2–1.7)	1.00 (Referent)
≥ +10 bpm	1.9 (1.5–2.5)	1.51 (1.08–2.10); $P = 0.015$
Sudden cardiac death		
≤ −10 bpm	2.9 (2.3–3.7)	0.82 (0.61–1.12); $P = 0.218$
< +/−10 bpm	2.5 (2.2–2.9)	1.00 (Referent)
≥ +10 bpm	3.2 (2.6–3.9)	1.20 (0.94–1.55); $P = 0.150$
All-cause death		
≤ −10 bpm	7.7 (6.6–8.9)	0.83 (0.69–1.00); $P = 0.050$
< +/−10 bpm	6.9 (6.4–7.5)	1.00 (Referent)
≥ +10 bpm	10.0 (8.8–11.2)	1.51 (1.31–1.75); $P < 0.001$

HFrEF patients in sinus rhythm with a heart rate reduction at 12 months have significant improvement in CV outcomes and QoL, as well as reduction in HF biomarker (NT-proBNP)

	Sinus rhythm			
	≤ −10 bpm ($n = 1274$)	< +/−10 bpm ($n = 4943$)	≥ +10 bpm ($n = 1539$)	*P*-value for trend
Increase in KCCQ at 12 months ≥ 5 points	423 (33.2%)	1399 (28.3%)	369 (24.0%)	<0.001
Decrease in KCCQ at 12 months ≥ 5 points	272 (21.4%)	1139 (23.0%)	421 (27.4%)	<0.001
Mean (±SD) change in NT-proBNP at 12 months (pg/mL)[a]	−414 ± 2272	59 ± 2294	424 ± 2754	<0.001

KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide

J Card Fail. 2019 Dec 17. doi: 10.1002/ejhf.1682

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GDMT for HFrEF: the fantastic four plus HR control

GDMT – the fantastic four pillars

ESC European Society of Cardiology
European Heart Journal (2021) **42**, 3599–3726
doi:10.1093/eurheartj/ehab368

ESC GUIDELINES

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Circulation
Volume 145, Issue 18, 3 May 2022; Pages e895-e1032
https://doi.org/10.1161/CIR.0000000000001063

American Heart Association.

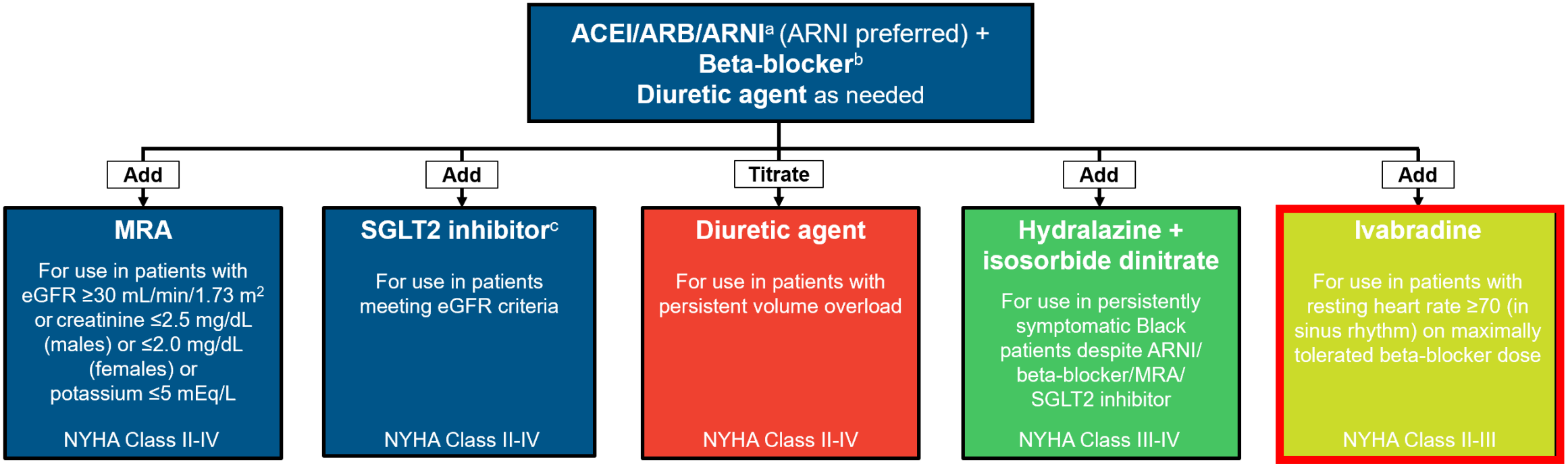
AHA/ACC/HFSA CLINICAL PRACTICE GUIDELINE

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

For ALL patients	ACEI/ARNI	BB	MRA	SGLT2i
	ARNI (ACEI/ARB)	BB	MRA	SGLT2i
For SELECTED patients	Ivabradine	ARB	Vericiguat	
	Ivabradine	H-N	Vericiguat	

1. McDonagh TA, et al. European Heart Journal (2021) 42, 3599-3726
2. Paul A. Heidenreich et al. Circulation Volume 145, Issue 18, 3 May 2022; Pages e895-e1032

2021 ACC Expert Consensus Now Includes SGLT-2i as a Component of First-Line Treatment for Patients With HFrEF



- ARNIs, beta-blockers[b], MRAs and SGLT2 inhibitors are first-line medications for all patients with HFrEF.
- SGLT2 inhibitors should be added for patients with chronic HFrEF who are already receiving ARNI/ACEI/ARB, beta-blocker and MRA, if not contraindicated.
- Achieving target or maximally tolerated doses of other HFrEF therapies is not necessary before adding SGLT2 inhibitors.

Blue boxes indicate first-line therapy.

[a]ACEI/ARB should only be considered in patients with contraindications, intolerance or inaccessibility to ARNI; [b]Evidence-based beta-blocker (carvedilol, metoprolol succinate, or bisoprolol); [c]DAPA is the only SGLT2 inhibitor with an FDA-approved indication for the treatment of HFrEF.

Maddox TM et al. Online ahead of print. *J Am Coll Cardiol*. 2021.

Incremental benefits of ivabradine on top of GDMT are well proven

JIM Original Article

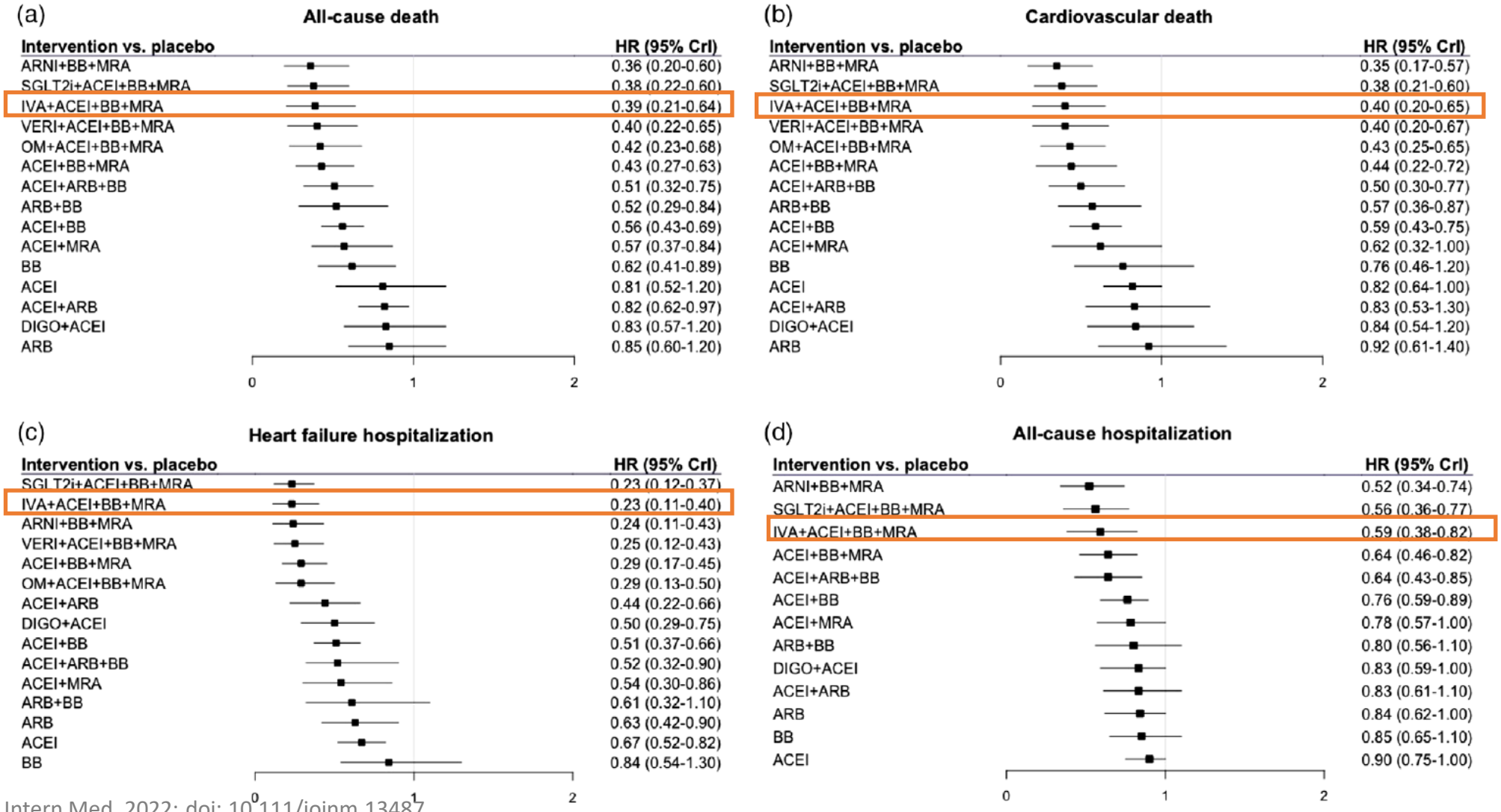
doi: 10.1111/joim.13487

Network meta-analysis of medical therapy efficacy in more than 90,000 patients with heart failure and reduced ejection fraction

Vincenzo De Marzo[1], Gianluigi Savarese[2], Lucia Tricarico[3,4], Sofia Hassan[1], Massimo Iacoviello[3,4], Italo Porto[1,5] & Pietro Ameri[1,5]

De Marzo V et al. J Intern Med. 2022; doi: 10.111/joinm.13487

Incremental benefits of GDMTs are well proven - ivabradine vs SGLT2i with backbone therapy on board



De Marzo V et al. J Intern Med. 2022; doi: 10.111/joinm.13487

One size does not fit all – BP / P / Cr / K / AF vs SR

ESC European Society of Cardiology
European Journal of Heart Failure (2021) **23**, 872–881
doi:10.1002/ejhf.2206

POSITION PAPER

Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology

What is the heart rate/rhythm/BP/GFR/K+ ?

Rosano GMC et al. *Eur J Heart Fail.* 2021;23(6):872-881.

Patient profiling in HFrEF for tailoring medical therapy: consensus document of the ESC Heart Failure Association

Black—drugs that should be given to patients;

Red—drugs that should be reduced or discontinued

Blue—drugs that should be added.

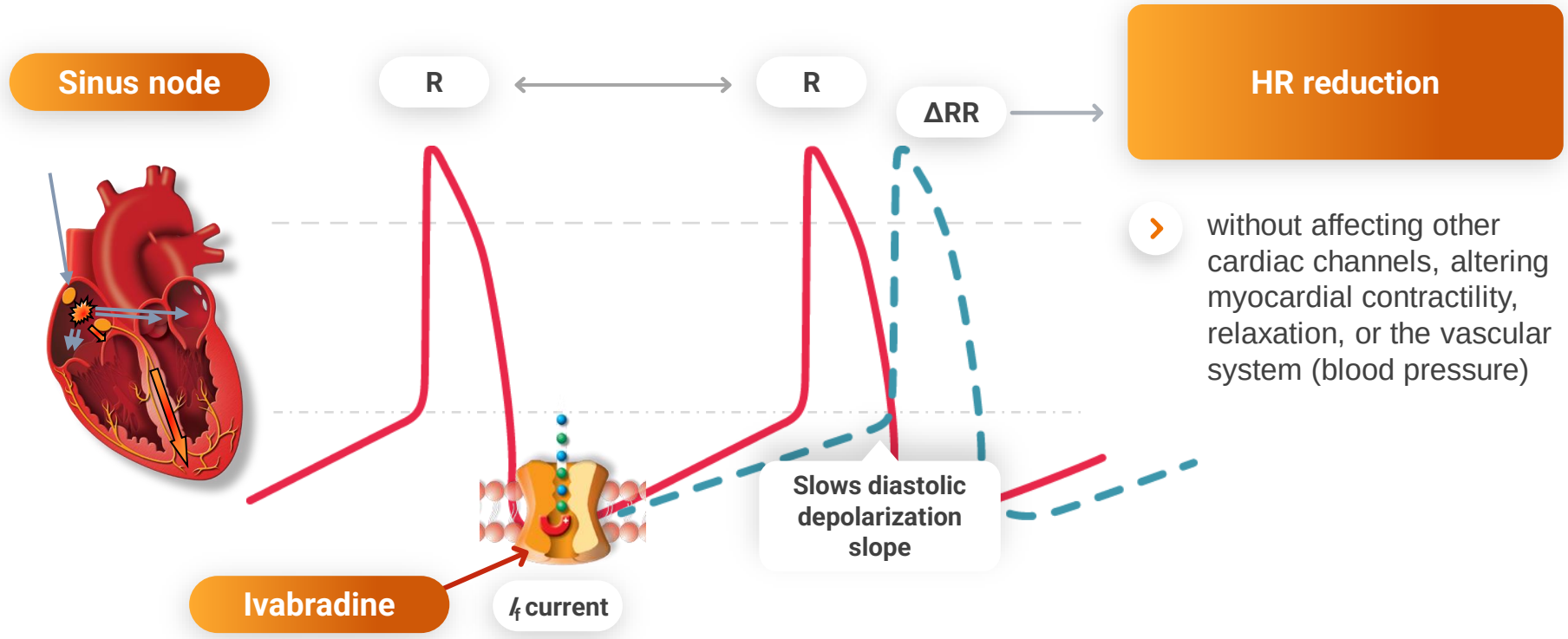
*In patients with predominant chronic coronary syndrome, BP threshold is 120/80 mm Hg

ACE= angiotensin-converting enzyme; AF= atrial fibrillation; ARB= angiotensin II receptor blocker; ARNI= angiotensin receptor neprilysin inhibitor; BP= blood pressure; bpm= beats per minute; CDK= chronic kidney disease; eGFR= estimated glomerular filtration rate; ESC= European Society of Cardiology; MRA= mineralocorticoid receptor antagonist; HFrEF= heart failure with reduced ejection fraction; HR= heart rate; SGLT2I= sodium-glucose cotransporter-2 inhibitors.

Rosano GMC et al. Eur J Heart Fail. 2021;23(6):872-881

Ivabradine reduces heart rate by selective inhibition of the sinus node If current

Ivabradine reduces HR via specific and selective inhibitory effect on I_f current* in sinoatrial node cells



* I_f is the main current of diastolic depolarization that leads to the generation of a new potential action

bpm= beats per minute; HR= Heart rate

Di Francesco D, Camm AJ. Drugs. 2004 64(16):1757-1765

SHIFT main study – Study design and patient population

In 6505 patients with:

- Moderate to severe chronic HF
  - NYHA class II-IV
- Left ventricular ejection fraction ≤ 35%
- HR ≥ 70 bpm
- Sinus rhythm

Ivabradine group (**n=3241**); Placebo group (**n=3264**)

Ivabradine dose:
starting dose – 5 mg bid, after 2 weeks dose was increased to 7.5 mg bid*

*At least 70% of patients were at the target dose of 7.5 mg bid

Median study duration: 23 months

Baseline clinical and demographic characteristics

Demographic characteristics	Ivabradine group	Placebo group
Age, years	**60.7 (11.2)**	**60.1 (11.5)**
Sex	**2462 (76%)**	**2508 (77%)**
Ethnic origin		
White	**2879 (89%)**	**2892 (89%)**
Asian	**268 (8%)**	**264 (8%)**
Other	**94 (3%)**	**108 (3%)**

Cardiac parameters	Ivabradine group	Placebo group
Heart rate, bpm	**79.7 (9.5)**	**80.1 (9.8)**
SBP, mm Hg	**122.0 (16.1)**	**121.4 (15.9)**
LVEF, %	**29·0% (5.1)**	**29.0% (5.2)**
eGFR, mL/min/1.73 m^2	**74.6 (22.9)**	**74.8 (23.1)**

NYHA Class	Ivabradine group	Placebo group
II	**1585 (49%)**	**1584 (49%)**
III	**1605 (50%)**	**1618 (50%)**
IV	**50 (2%)**	**61 (2%)**

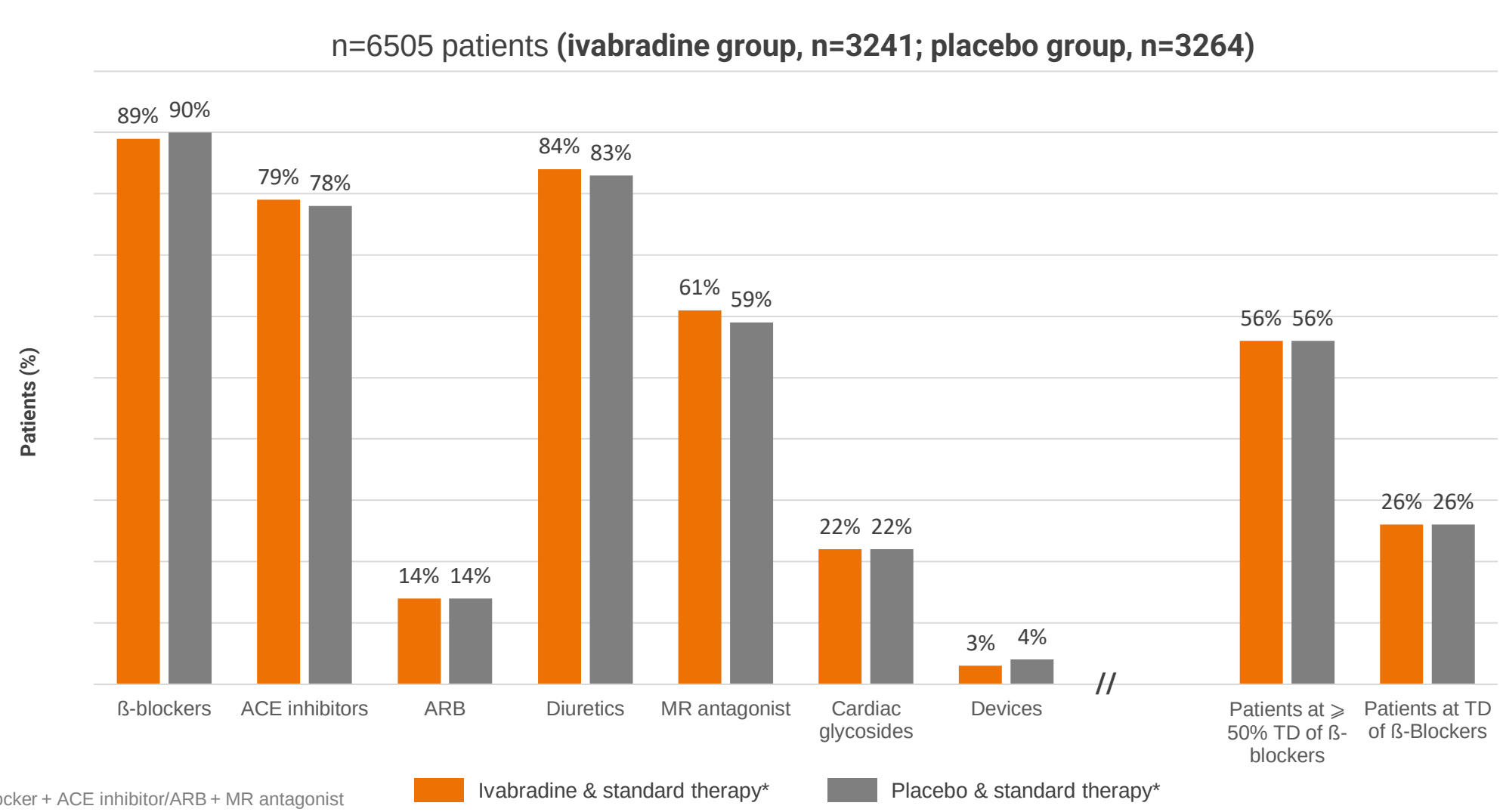
Medical history	Ivabradine group	Placebo group
Ischemic	**2215 (68%)**	**2203 (67%)**
Hypertension	**2162 (67%)**	**2152 (66%)**
Diabetes	**973 (30%)**	**1006 (31%)**

Data are number of patients (%) or mean (SD).

bpm= beats per min; bid= twice daily; eGFR= estimated glomerular filtration rate; HF= heart failure; HR= heart rate; LVEF= left-ventricular ejection fraction; NYHA= New York Heart Association; SBP=systolic blood pressure; SHIFT= Systolic Heart failure treatment with the If inhibitor ivabradine trial

Swedberg K et al. *Lancet*. 2010;376:875-885

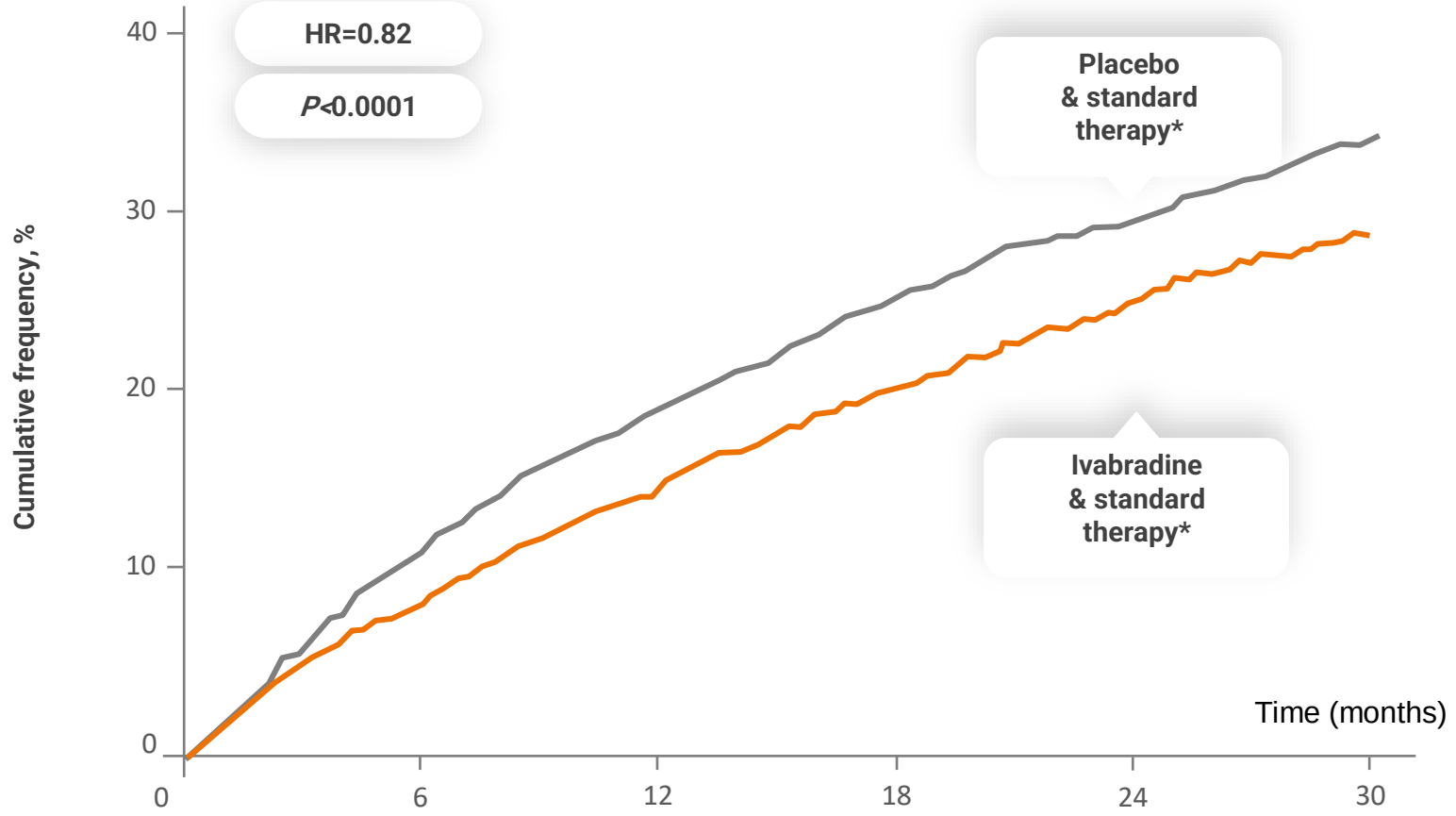
GDMT in both arm



* β-blocker + ACE inhibitor/ARB + MR antagonist

Significant reduction in CV mortality or HF hospitalization (primary endpoint)

n=6 505 patients **(ivabradine group, n=3241; placebo group, n=3264)**



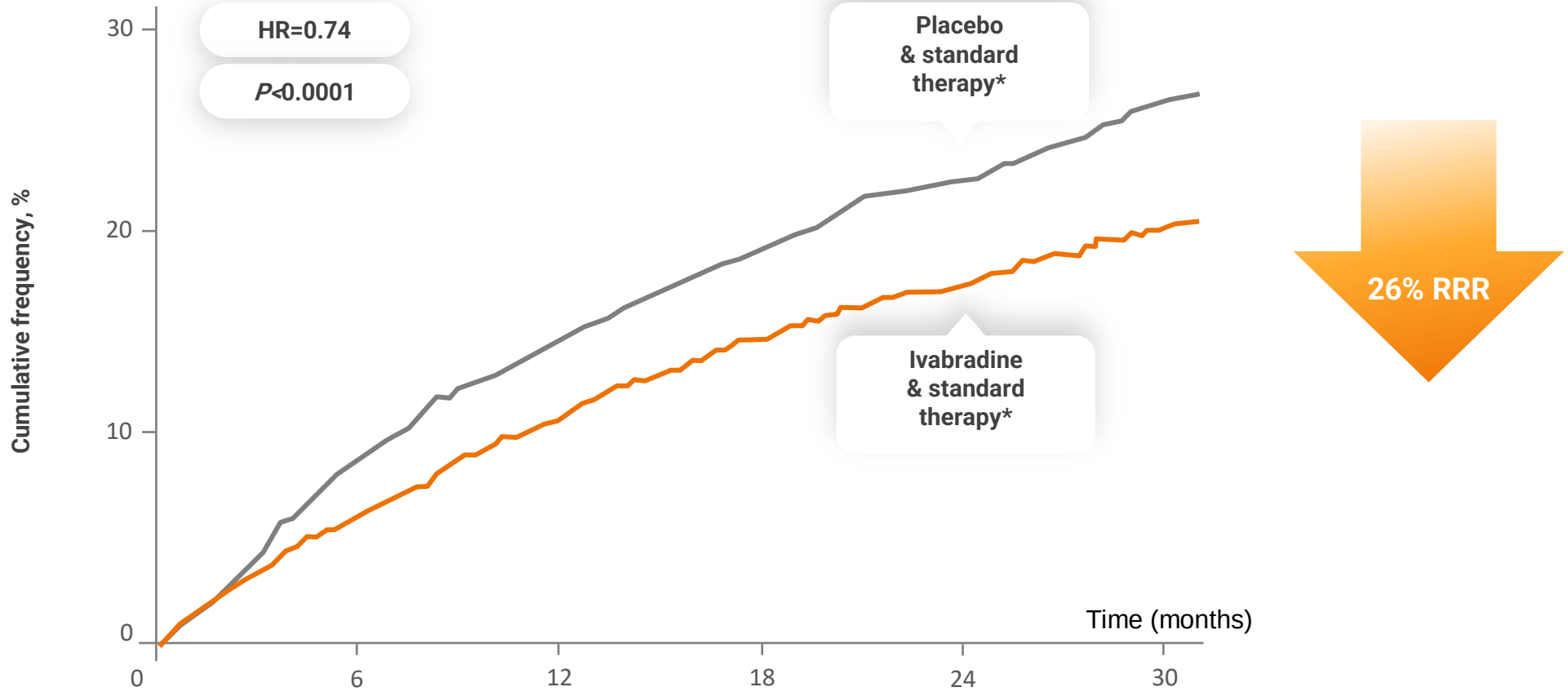
18% RRR

NNT for 1 year: 26

* β-blocker + ACE inhibitor/ARB + MR antagonist

Significant reduction in HF hospitalizations

n=6505 patients **(ivabradine group, n=3241; placebo group, n=3264)**



* β-blocker + ACE inhibitor/ARB + MR antagonist

SHIFT sub study on LV remodeling function (from echocardiography)

EUROPEAN SOCIETY OF CARDIOLOGY®

European Heart Journal (2011) **32**, 2507–2515
doi:10.1093/eurheartj/ehr311

FASTTRACK
ESC CLINICAL TRIAL UPDATE

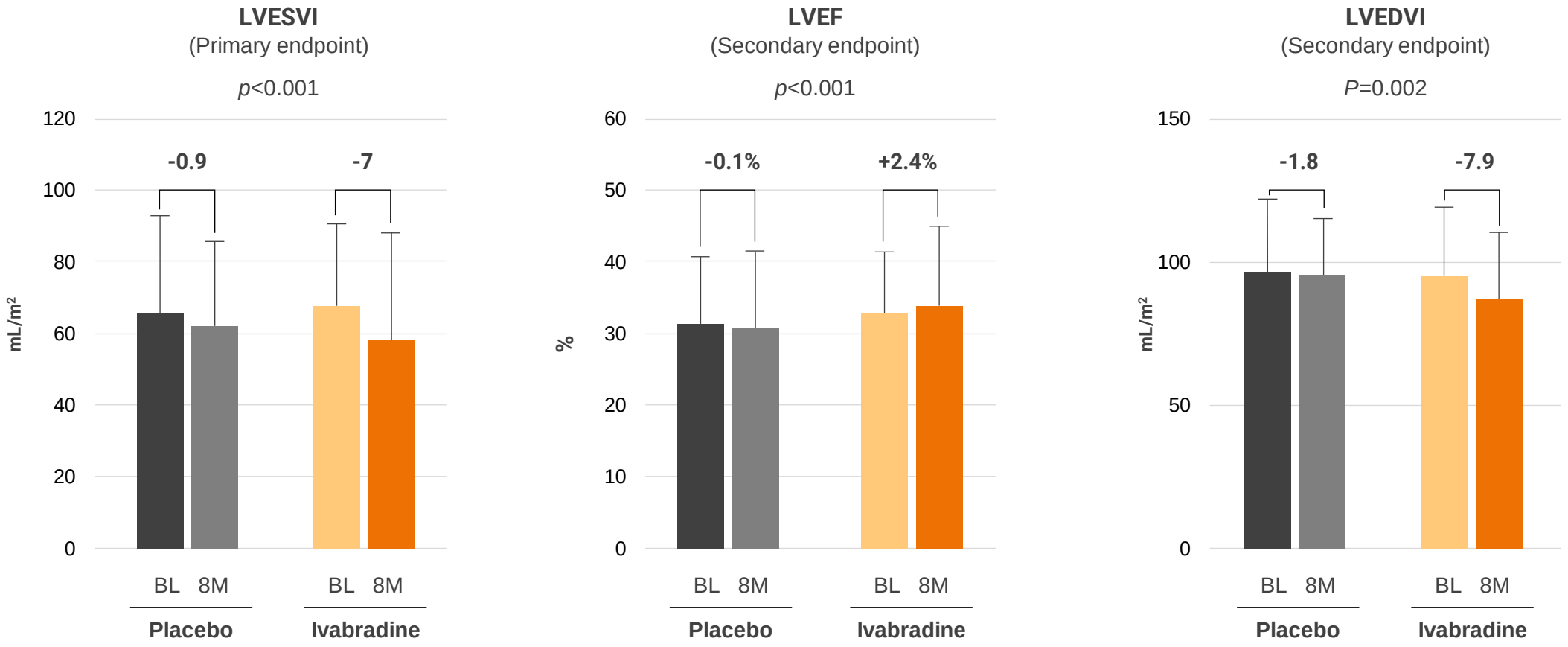
Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography substudy

Jean-Claude Tardif[1]*, Eileen O'Meara[1], Michel Komajda[2], Michael Böhm[3], Jeffrey S. Borer[4], Ian Ford[5], Luigi Tavazzi[6], and Karl Swedberg[7], on behalf of the SHIFT Investigators

Tardif JC et al. *Eur Heart J*. 2011;32:2507-2515

Ivabradine reverses cardiac remodeling

Echocardiography substudy from SHIFT; n= 611 patients with HFrEF
(Ivabradine group, n= 304; placebo group, n=307)



SHIFT sub study on LV unload

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Heart Failure

Selective Heart Rate Reduction With Ivabradine Unloads the Left Ventricle in Heart Failure Patients

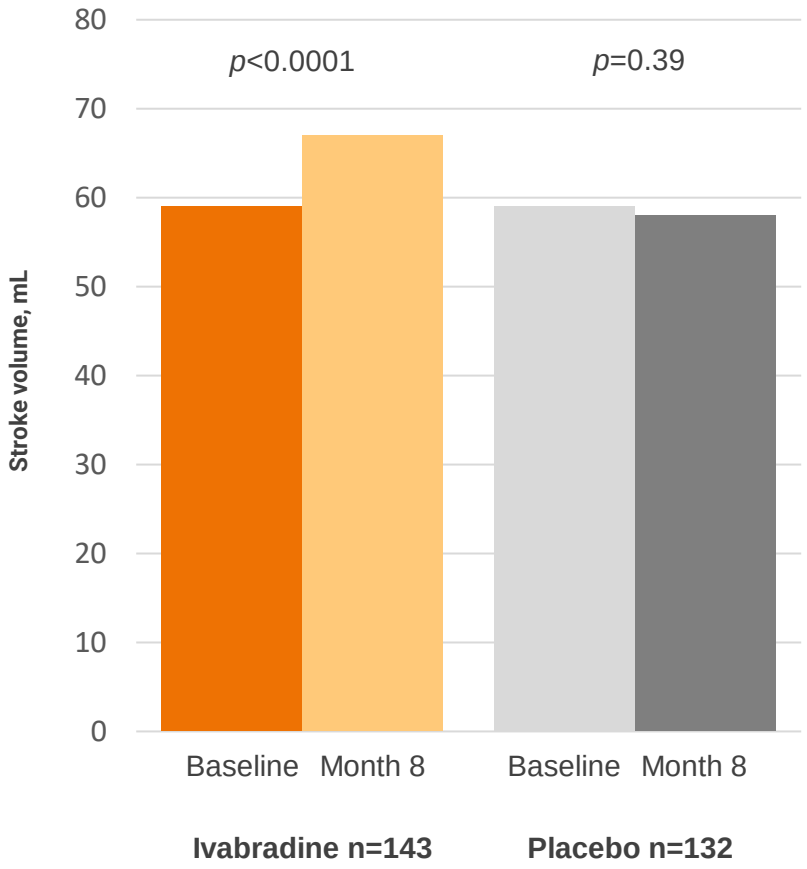
Jan-Christian Reil, MD,* Jean-Claude Tardif, MD,† Ian Ford, MD,‡ Suzanne M. Lloyd, MSc,‡ Eileen O'Meara, MD,† Michel Komajda, MD,§ Jeffrey S. Borer, MD,|| Luigi Tavazzi, MD,¶ Karl Swedberg, MD,# Michael Böhm, MD*

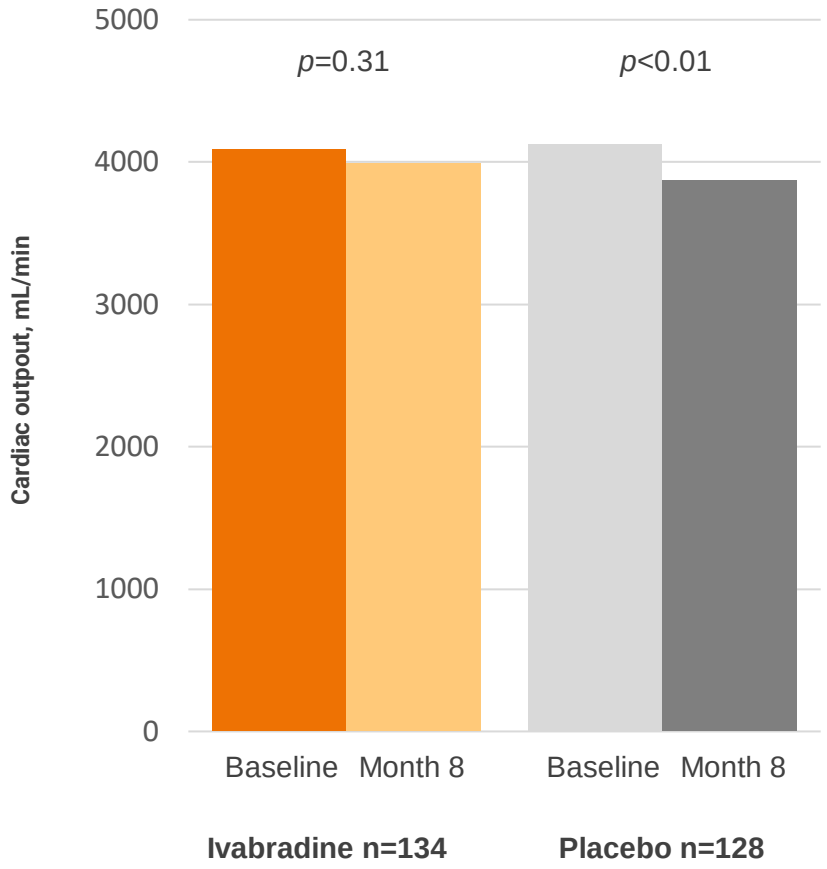
Homburg/Saar, Germany; Montreal, Quebec, Canada; Glasgow, United Kingdom; Paris, France; Brooklyn and New York, New York; Cotignola, Italy; and Gothenburg, Sweden

Reil JC et al. *J Am Coll Cardiol.* 2013;62:1977-1985.

Ivabradine increases stroke volume and maintains cardiac output in long-term use

Echocardiography substudy from SHIFT (275 patients)

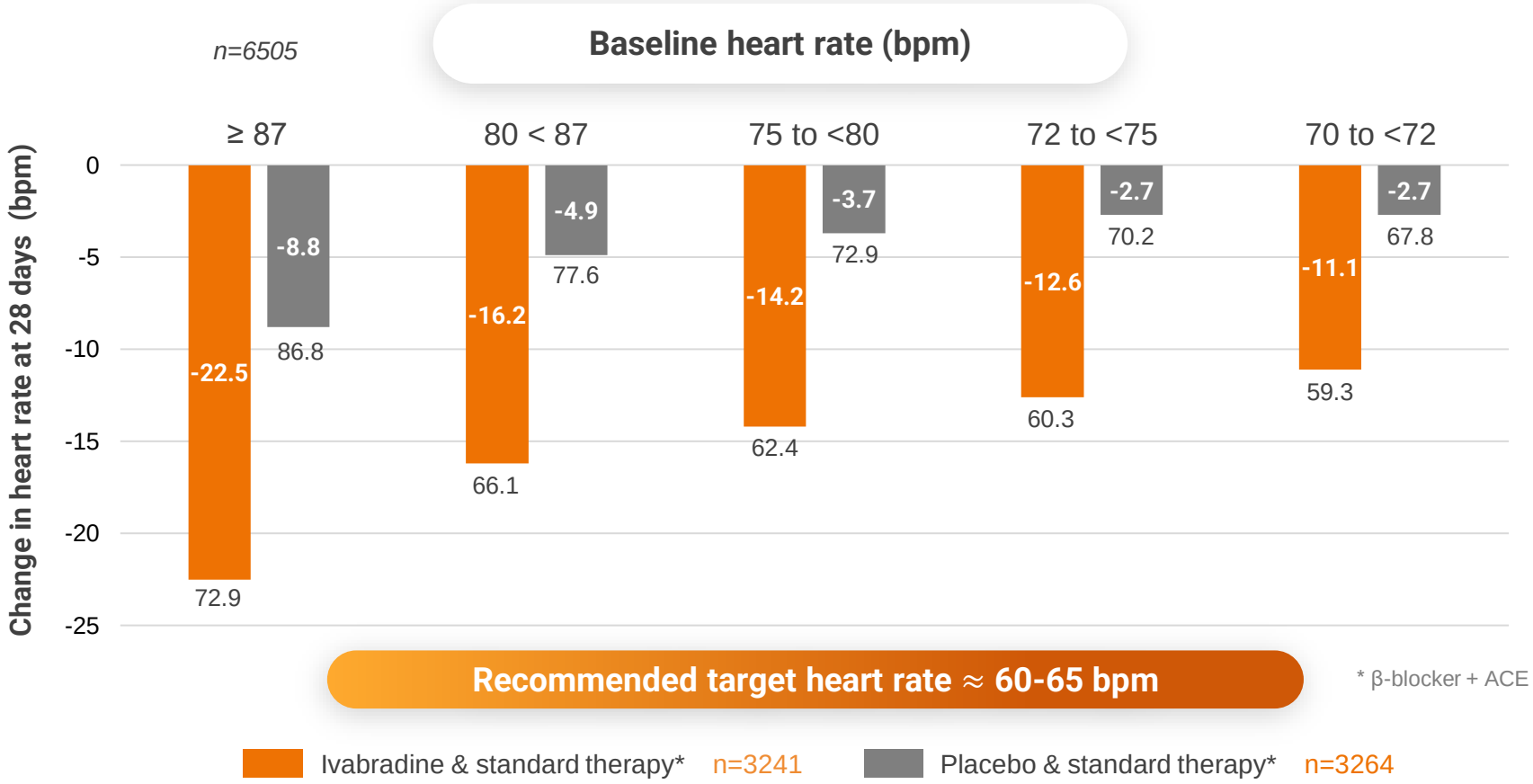




Reil JC et al. *J Am Coll Cardiol*. 2013;62:1977-1985.

Baseline dependent heart rate reduction

Heart rate reduction with ivabradine according to baseline heart rate in patients with HFrEF



Böhm M et al. *Lancet.* 2010;376(9744):886-894

SHIFT sub study on HFrEF patients with baseline heart rate ≥75 bpm

Clin Res Cardiol (2013) 102:11–22
DOI 10.1007/s00392-012-0467-8

ORIGINAL PAPER

Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study

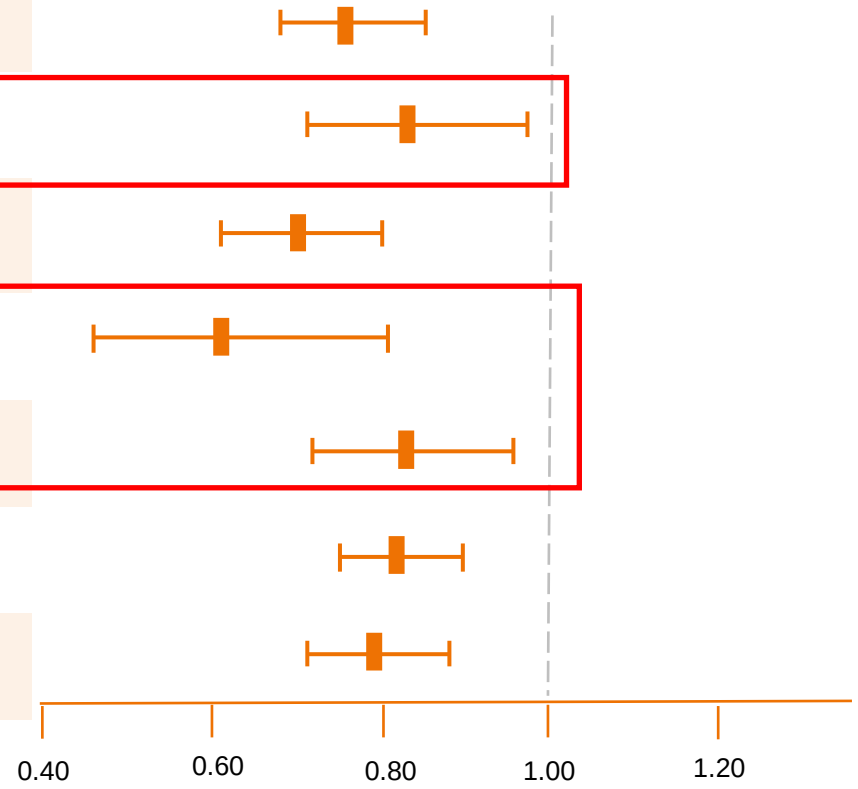
Michael Böhm · Jeffrey Borer · Ian Ford · Jose R. Gonzalez-Juanatey · Michel Komajda · Jose Lopez-Sendon · Jan-Christian Reil · Karl Swedberg · Luigi Tavazzi

Böhm M et al. *Clin Res Cardiol*. 2013;102:1-12

Greater magnitude of benefits including significant mortality reductions for HFrEF patients with baseline heart rate ≥75 bpm

n=4150 patients (**ivabradine group, n=2052; placebo group, n=2098**)

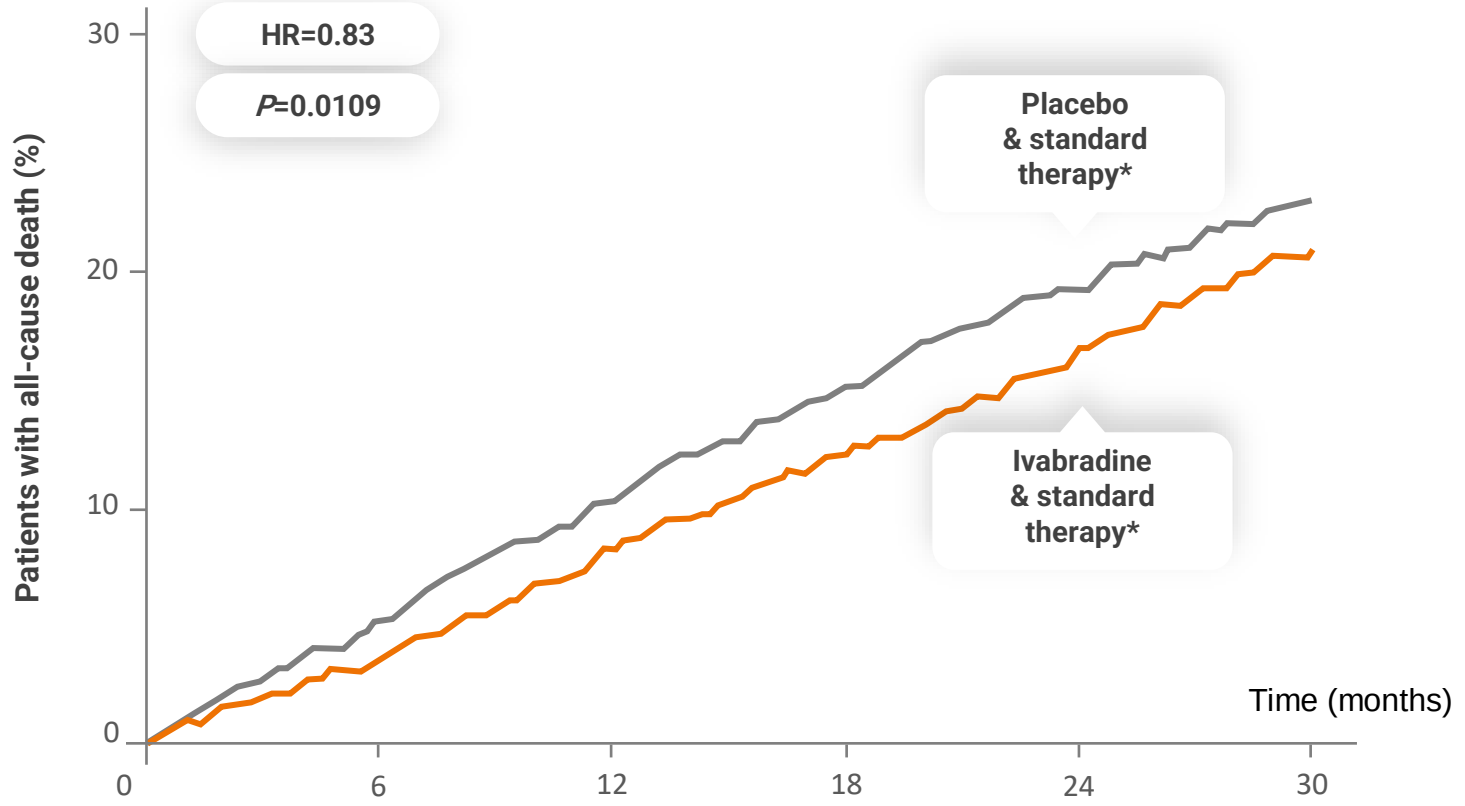
	HR	95% CI	*P*
Cardiovascular death or hospital admission for worsening HF	0.76	0.68-0.85	<0.0001
Cardiovascular mortality	0.83	0.71-0.97	0.0166
Hospitalization for worsening HF	0.70	0.61-0.80	<0.0001
Death from HF	0.61	0.46-0.81	0.0006
All-cause mortality	0.83	0.72-0.96	0.0109
All-cause hospitalization	0.82	0.75-0.90	<0.0001
Cardiovascular hospitalization	0.79	0.71-0.88	<0.0001



bpm= beats per minute; CI= confidence interval; HR= hazard ratio; HF= heart failure; HFrEF= heart failure with reduced ejection fraction; SHIFT= Systolic Heart failure treatment with the If inhibitor ivabradine Trial

Significant reduction in all-cause death in HFrEF patients with baseline heart rate ≥ 75 bpm

n=4150 patients **(ivabradine group, n=2052; placebo group, n=2098)**



17% RRR

NNT for 1 year: 51

* β-blocker + ACE inhibitor/ARB + MR antagonist

RRR= Relative risk reduction; NNT= Number needed to treat; BPM= Beats per minute; HFrEF= Heart failure with reduced ejection fraction; HR= Hazard ratio; SHIFT= Systolic heart failure treatment with the I*f* inhibitor ivabradine trial; MR= Mineralocorticoid receptor; ARB= Angiotensin receptor blockers; ACE= Angiotensin Converting enzyme

Komajda M. *Eur Heart J Suppl.* 2015;17:G30-G36

SHIFT sub study on recurrent hospitalization for HF

EUROPEAN SOCIETY OF CARDIOLOGY®

European Heart Journal (2012) **33**, 2813–2820
doi:10.1093/eurheartj/ehs259

FASTTRACK
CLINICAL TRIAL & REGISTRY UPDATE

Effect of ivabradine on recurrent hospitalization for worsening heart failure in patients with chronic systolic heart failure: the SHIFT Study

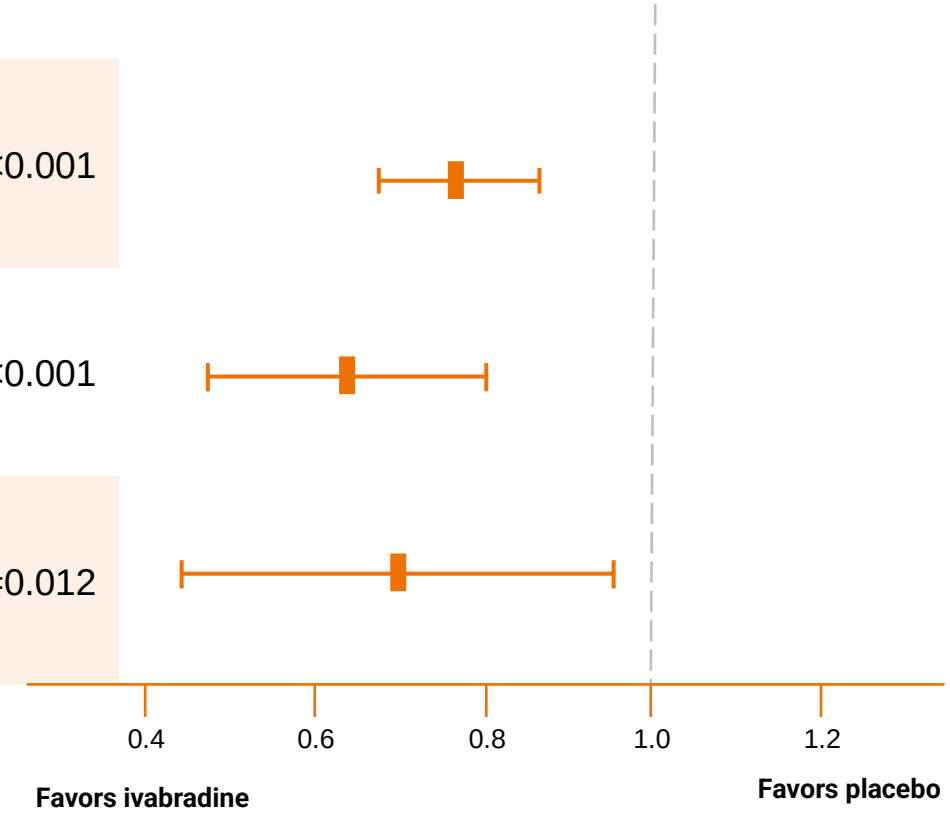
Jeffrey S. Borer[1]*, Michael Böhm[2], Ian Ford[3], Michel Komajda[4], Luigi Tavazzi[5], Jose Lopez Sendon[6], Marco Alings[7], Esteban Lopez-de-Sa[6], and Karl Swedberg[8], on behalf of the SHIFT Investigators

Borer J et al. *Eur Heart J* . 2012;33(22):2813-2820

Significant reduction in repeated HF hospitalizations for HFrEF patients

n=6505 patients **(ivabradine group, n=3241; placebo group, n=3264)**

	Ivabradine & standard therapy*	Placebo & standard therapy*	Hazard ratio	*P*-value
First hospitalization	514 (16%)	672 (21%)	0.75	*P*<0.001
Second hospitalization	189 (6%)	283 (9%)	0.66	*P*<0.001
Third hospitalization	90 (3%)	128 (4%)	0.71	*P*=0.012



* β-blocker + ACE inhibitor/ARB + MR antagonist

CUHK/PWH - Ivabradine Data (Registry from MHFC and Cardiac Clinic)

Paradigm SHIFT in Heart Failure Management: Ivabradine to Reduce Recurrent Hospitalization in Real-Life Practice

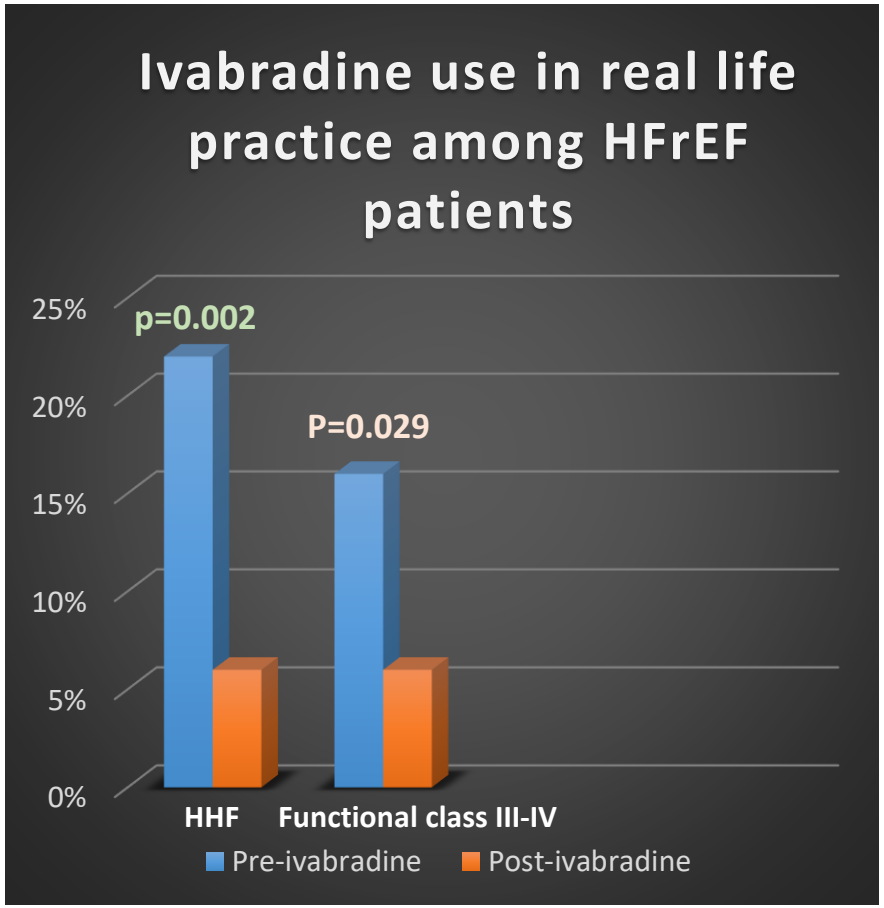
KKH Kam , XT Wang, YS Chan , E Fung, APW Lee
Division of Cardiology, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong

Objectives: Heart failure with reduced ejection fraction (HFrEF) is marked by progressive deterioration, reduced quality of life, high mortality and morbidity. Frequent readmission is common among heart failure population. According to Hospital Authority Statistical Report, heart failure is the leading cause of admission in Cardiology. In-patient care contributed more than 70% of medical cost in heart failure management. In SHIFT trial, ivabradine has been proven to decrease hospital admissions for worsening heart failure. This retrospective analysis aims to evaluate the effect of heart rate reduction by the selective sin us-node inhibitor ivabradine on clinical outcomes among HFrEF patients in real-life clinical situation.

Methods: Patient who has been diagnosed of heart failure of reduced ejection fraction, left ventricular ejection fraction < 35% diagnosed by echocardiography, sinus rhythm with heart rate >70bpm and started ivabradine would be recruited into the study. Those patients who could not tolerate betablocker would be excluded. The primary endpoint was hospital admission for worsening heart failure. Secondary endpoint was the change in functional class.

Results: Clinical data of 50 patients have been extracted from clinical management system (CMS) The baseline demographics and clinical outcomes before and after the use of ivabradine were analyzed. The average age of patient was 60+/-8 and 70% of them were male. At baseline, the average ejection fraction 28 +/-5% and 16% of patients were belonged to NYHA class III to IV status The mean blood pressure was 123/72mmH g and mean heart rate was 84.9bpm. 72% of patients have been started on guideline directed medical therapy with the to combination of betablocker and angiotensin converting enzyme (or angiotensin receptor blocker) +/- mineralocorticoid receptor antagonist. 11 of them (i.e. 22%) have been hospitalized due heart failure in recent three months. Median follow-up was 8.7 months. 84% of patients were taking ivabradine 5mg bd while rest of the them were on 2.5mg bd. Post-treatment phase , the average ejection fraction 30+/-6% (NS) remained similar to baseline. The blood pressure was static with mean BP 117/67mmHg (NS) but mean heart rate has been deceased to 74.1 bpm, p=0.0016. As for the primary endpoint, recurrent heart failure hospitalization has been reduced to 3 episodes only with OR 0.22 (95% CI: 0.1-0.58), p=0.002. The proportion of patients in NYHA class III to IV has significantly dropped to 6% with OR 0.34 (95% CI: 0.12-0.9), p=0.029. 4% of patients complained of mild dizziness but none of them experience phosphenes

Conclusions: Our results echo the finding in Shift Trial, heart-rate reduction with ivabradine has significantly improved the clinical outcomes of heart failure



J HK Coll Cardiol, Vol 26 April 2018

Fantastic four plus heart rate control

Trial (N; median follow-up month)	Drug	Background Rx.	CV death/HHF HR (95%CI)	HHF HR (95%CI)	CV death HR (95%CI)	All-cause mortality HR (95%CI)
EMPHASIS-HF (N=2737; 21 months)	Eplerenone vs placebo	ACEI/ARB 94% BB 87% MRA n/a	**0.66 (0.56–0.78)**	**0.61 (0.50–0.75)**	**0.77 (0.62–0.96)**	**0.78 (0.64–0.95)**
SHIFT (N=6558; 22.9 months)	Ivabradine vs placebo	ACEI/ARB 93% BB 90% MRA 60%	**0.82 (0.75–0.90)**	**0.74 (0.66–0.83)**	0.91 (0.80–1.03)	0.90 (0.80–1.02)
PARADIGM-HF (N=8399; 27 months)	Sacubitril/ valsartan vs Enalapril	ACEI/ARB 100% BB 93% MRA 56%	**0.80 (0.73–0.87)**	**0.79 (0.71–0.89)**	**0.80 (0.71–0.89)**	**0.84 (0.76–0.93)**
DAPA-HF (N=4744; 18.2 months)	Dapagliflozin vs placebo	ACEI/ARB/ARNI 94% BB 96% MRA 71%	**0.75 (0.65–0.85)**	**0.70 (0.59–0.83)**	**0.82 (0.69–0.98)**	**0.83 (0.71–0.97)**
EMPEROR-reduced (N=3730; 16 months)	Empagliflozin vs placebo	ACEI/ARB/ARNI 89% BB 95% MRA 71%	**0.75 (0.65–0.86)**	**0.69 (0.59–0.81)**	0.92 (0.75–1.12)	0.92 (0.77–1.10)
VICTORIA (N=5050; 10.8 months)	Vericiguat vs placebo	ACEI/ARB/ARNI 88% BB 93% MRA 70%	**0.90 (0.82–0.98)**	0.90 (0.81–1.00)	0.93 (0.81–1.06)	0.95 (0.84–1.07)

Real Case

- Presentation
  - M/71, recurrent HF hospitalization x 5 in recent 6 months in 2023
  - NYHA class III, SOBOE, mild chest discomfort
  - P/E: JVP elevated, ankle edema, chest diffuse crep and wheeze

- PMH:
  - HT, DM, mild CRF with 150, BPH
  - Hx of old anterior MI with PCI to LAD in 2020

- ECG: SR/80, Q at V2-3, no ST depression, CXR cardiomegaly, congested
- Coro 2023: no ISR at LAD, no significant lesion, Echo 2023: EF 32%, LAD territory akinesia, mod functional MR, RVSP 62mmHg

- Medication
  - Entresto 100mg bd, bisoprolol 10mg daily, spironolactone 25mg daily, dapaglifozin 10mg daily, furosemide 40mg daily, tamsulosin 0.4mg daily, protaphane 8 units om and aspirin 80mg daily

Ambulatory Heart Failure Clinic

- BP 90/53mmHg P 72 (regular pulse)
- Cr 160, K 5.3, NT-ProBNP 2800pg/ml
- NYHA class III
- Chest clear, persistent ankle edema up to shin

ECG: SR/70, Q at V2-3, QRS duration 110ms, no LBBB

What will you do next?

A) Add digoxin 62.5mcg daily
B) Add ivabradine 5mg bd
C) CRT-D implantation
D) Increase spironolactone to 50mg daily
E) Increase sacubitril / valsartan (ARNI) to 150mg bd

What will you do next?

A) Add digoxin 62.5mcg daily

B) Add ivabradine 5mg bd

C) CRT-D implantation

D) Increase spironolactone to 50mg daily

E) Increase sacubitril / valsartan (ARNI) to 150mg bd

IIa	B-R	Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HF*r*EF (LVEF ≤35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (37-40).

Titrated Ivabradine to 7.5mg bd

- Given iv frusemide
- NYHA class II, SOB and chest pain resolved
- Latest BP 102/58mmHg, P 63
- RFT Cr 137 K 4.9
- No more re-hospitalization
- Able to handle household chores without SOB
  - Including dusting, scrubbing floor…

	Pre-ivabradine	Post-ivabradine	P value
N	50	50	NS
Age	60	60	NS
Sex	Men (70%)	Men (70%)	NS
GDMT (A+BB+MRA)	72%	75%	NS
NYHA class III-IV	16%	6%	OR 0.34 (95% CI: 0.12-0.9), P=0.029
EF	28±5%	30±6%	NS
BP	123/72mmHg	117/67mmHg	NS
Heart rate	84.9 bpm	74.1 bpm	P=0.0016
Recurrent HF hospitalization	11	3	OR 0.22 (95% CI: 0.1-0.58), p=0.002

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35th Anniversary 三十五週年

Post discharge Heart Failure Clinic: Strong-HF

Hospitalized HF

Goals for Optimization and Continuation of GDMT		
1	C-LD	3. For patients admitted with HF, treatment should address reversible factors, establish optimal volume status, and advance GDMT toward targets for outpatient therapy.[6]

In-hospital initiation of GDMT is good

- EVBB: IMPACT-HF
- ARNI: PIONEER
- MRA: ATHENA-HF
- SGLT2i: EMPULSE

1. Gattis WA, O'Connor CM, et al. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. J Am Coll Cardiol. 2004 May 5;43(9):1534-41
2. Velazquez EJ et al; PIONEER-HF Investigators. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. N Engl J Med. 2019 Feb 7;380(6):539-548.
3. Butler J, et al. National Heart Lung and Blood Institute Heart Failure Clinical Research Network. Efficacy and Safety of Spironolactone in Acute Heart Failure: The ATHENA-HF Randomized Clinical Trial. JAMA Cardiol. 2017 Sep 1;2(9):950-958.
4. Voors AA, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nat Med. 2022 Mar;28(3):568-574.

9.2. Maintenance or Optimization of GDMT During Hospitalization

Recommendations for Maintenance or Optimization of GDMT During Hospitalization Referenced studies that support the recommendations are summarized in the Online Data Supplements.		
COR	LOE	Recommendations
1	B-NR	1. In patients with HFrEF requiring hospitalization, preexisting GDMT should be continued and optimized to improve outcomes, unless contraindicated.[1–5]
1	B-NR	2. In patients experiencing mild decrease of renal function or asymptomatic reduction of blood pressure during HF hospitalization, diuresis and other GDMT should not routinely be discontinued.[6–11]
1	B-NR	3. In patients with HFrEF, GDMT should be initiated during hospitalization after clinical stability is achieved.[2,3,5,12–18]
1	B-NR	4. In patients with HFrEF, if discontinuation of GDMT is necessary during hospitalization, it should be reinitiated and further optimized as soon as possible.[19–22]

Click to edit Master title style

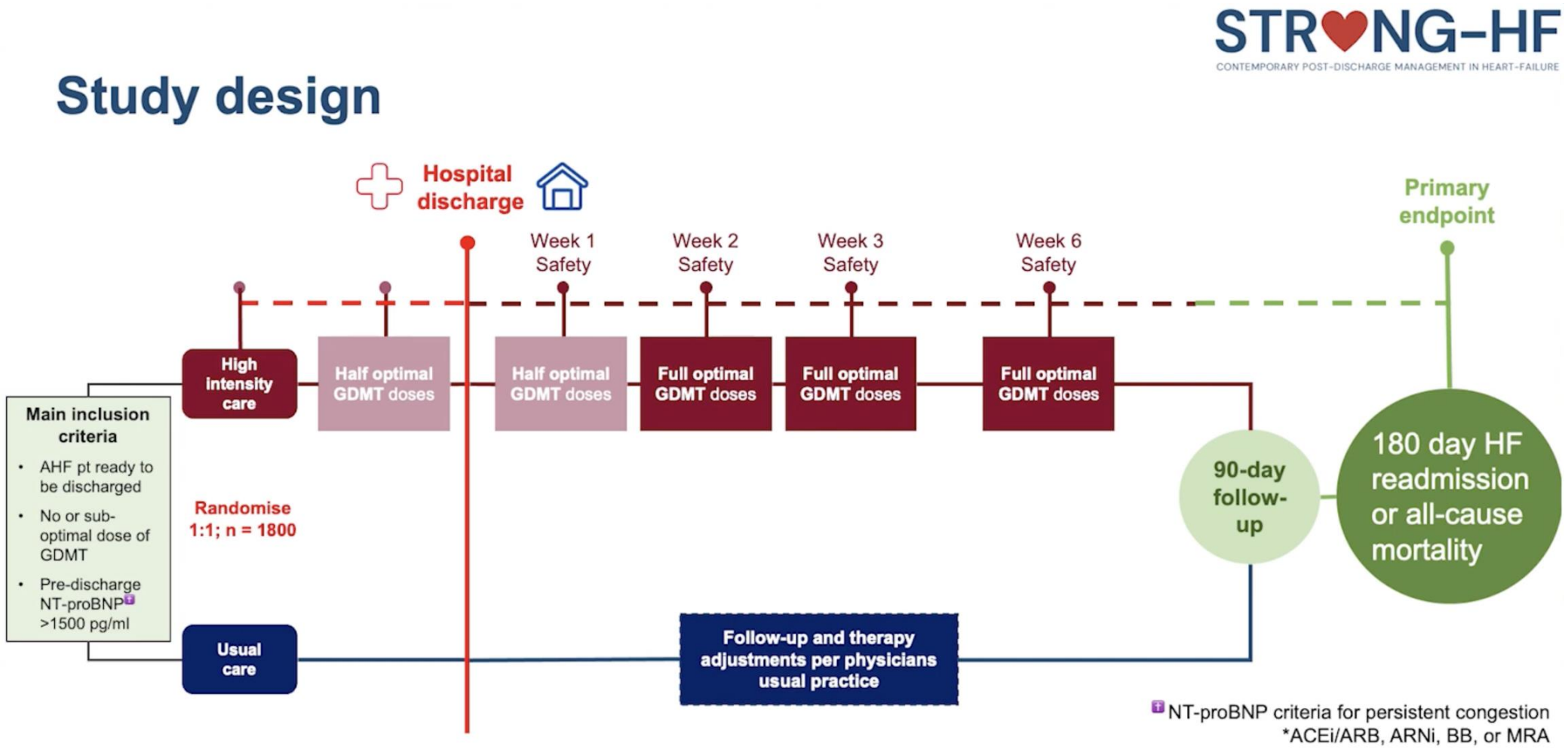
Recommendations	Class[a]	Level[b]
It is recommended that patients hospitalized for HF be carefully evaluated to exclude persistent signs of congestion before discharge and to optimize oral treatment.	I	C
It is recommended that evidence-based oral medical treatment be administered before discharge.	I	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

[a] Class of recommendations. [b] Level of evidence.

ACC/AHA guideline on post-d/c care of acute HF cases

1	B-NR	2. In patients hospitalized with worsening HF, patient-centered discharge instructions with a clear plan for transitional care should be provided before hospital discharge.[5,6]
2a	B-NR	3. In patients hospitalized with worsening HF, participation in systems that allow benchmarking to performance measures is reasonable to increase use of evidence-based therapy, and to improve quality of care.[7–10]
2a	B-NR	4. In patients being discharged after hospitalization for worsening HF, an early follow-up, generally within 7 days of hospital discharge, is reasonable to optimize care and reduce rehospitalization.[11,12]

Strong-HF trial : rapid titration of GDMT under close FU with NT-ProBNP



ACEi, angiotensin converting enzyme inhibitors; AHF, acute heart failure; ARB, angiotensin receptor blockers; BB, beta blockers; GDMT, guideline-directed medical therapies; HF, heart failure; MRA, mineralcorticoid receptor antagonists; NT-proBNP, N-terminal pro B-type natriuretic peptide

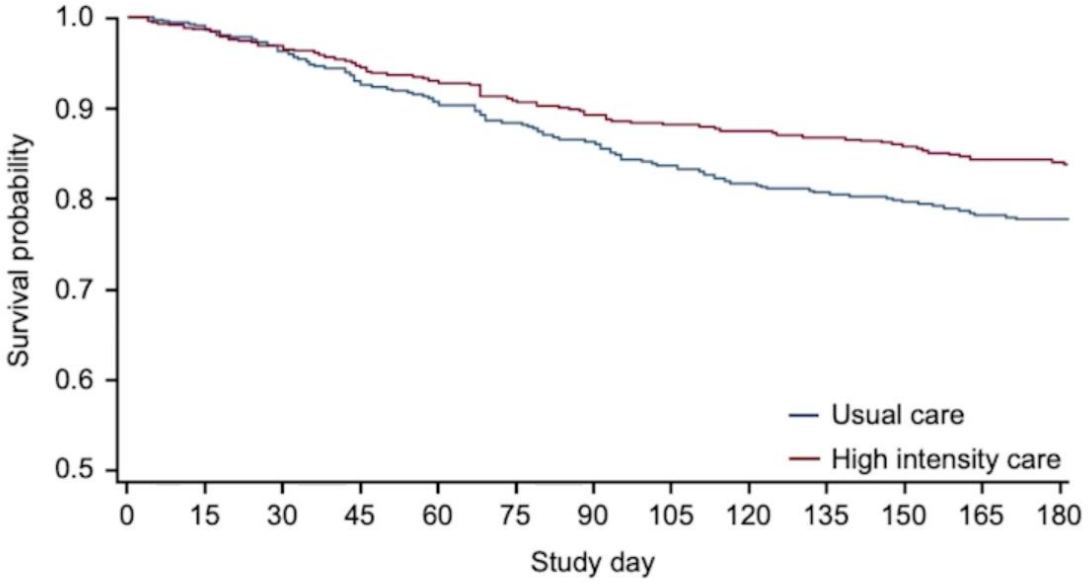
Primary endpoint: 180-day HF readmissio

DESIGN: randomized, parallel

PATIENTS: 1,078

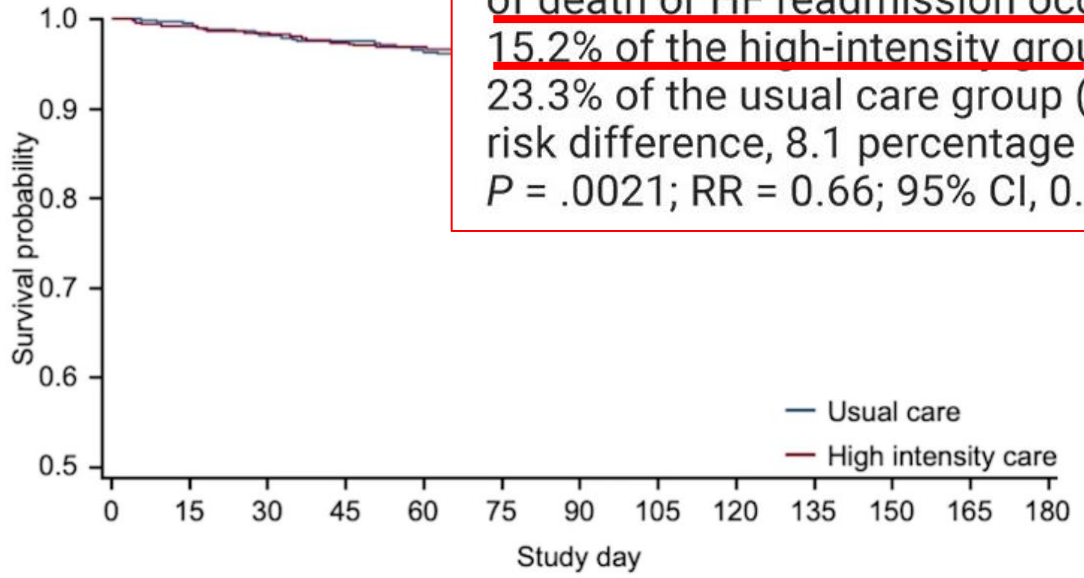
RESULTS: At 90 days, compared with usual care, more patients in the high-intensity group had been uptitrated to full doses of renin-angiotensin blockers (55% vs. 2%), beta-blockers (49% vs. 4%) and MRAs (94% vs. 46%). At 180 days, the primary endpoint of death or HF readmission occurred in 15.2% of the high-intensity group and 23.3% of the usual care group (adjusted risk difference, 8.1 percentage points; *P* = .0021; RR = 0.66; 95% CI, 0.5-0.86).

All-cause death or HF readmission through Day 180



180-day RD 7.3%, 95% CI: 2.4–12.1; p=0.0034

All-cause mor



180-day RD 1.9%, 95% CI: 1.7–5.5; p=0.3068

Mebazza A, et al. *Lancet*. 2022;doi:10.1016/S0140-6736(22)02076-1.

Heart Failure Clinic Flowchart

Target population O
- HFrEF patients, self ambulatory
- NYHA Class II-IV
- Recent HF hospitalization
- Cognitively Intact

Exclusion X
- Severe conditions that limit life expectancy
- Primary valvular disease
- Primary cardiomyopathy e.g. HCM, RCM
- ESRF

Clinical Evaluation
- BP / P
- Resting ECG
- Echocardiography
- Lab Test (CBC, RLFT, sTSH, Hba1c, FL, NT-Pro BNP)

Education
- Self-monitoring of Heart Failure symptoms & Weight
- Sodium/Fluid Restriction
- Flexible diuretic regimen
- Medicine compliance
- Lifestyle modification
- Flu vaccination

↑ **Self-Management Concept**

- **Medicine optimization**
  (according to international HF guidelines*)
- Medicine Counselling
- HF Hotline

Follow Up
- 2-4 week interval
- Medicine optimization and dose titration
- Reinforce education

HF optimization

Standard outpatient clinic
(usually scheduled 12 weeks)

Baseline demographics

	Strong HF cohort (542 intensive FU)	PWH cohort (97)
Age	63+/-14	65+/-12
Sex (Male%)	61%	75%
Average EF	36+/-13%	36+/13%
EF <=40%	68%	69.1%
HFpEF (EF>=50%)	14%	26%
NT-ProBNP	4120	4625
Average visits in 3 months	~5	~3-4
NYHA class	3-4	~3

Outcomes in 3 months

	Strong HF cohort (542 intensive FU)	PWH cohort (97)
All cause mortality	3.3%	1%
HF hospitalization / urgent HF visits through A&E	6.9% (<-9.5%)	7%
Average EF in 3 months	NA	44% (8% increase)
EF <=40%	NA<-68%	37.5%<-69.1%
NT-ProBNP	-2764pg/ml	-2831pg/ml

Outcomes in 3 months

	Strong HF cohort (542 intensive FU)	Reduce HF cohort (97)
BP difference	-3.7mmHg	-8mmHg
BW difference	-1.8kg	No change
NYHA class	**-1.36**	**-1.5**

Unpublished data

Conclusion

- HFrEF is becoming more prevalent due to aging population and contribute a large proportion of heart failure hospitalization (hHF)
- GDMT including BB, RAASi, MRA SGLT-2i – 4 pillars are highly effective in bringing down CV mortality and hHF
  - Heart rate control provide extra benefit in HF outcome esp HR >=75bpm
- ESC and ACC/AHA guidelines recommend early follow up 1-2/52 after HF admission to optimize fluid status, fine titration of GDMT according to NT-ProBNP and BW so as to reduce hHF