“Beating Heart Failure with Healthy Heartbeat”

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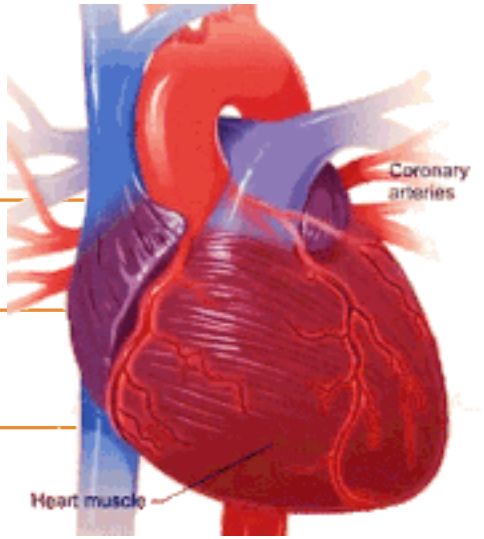
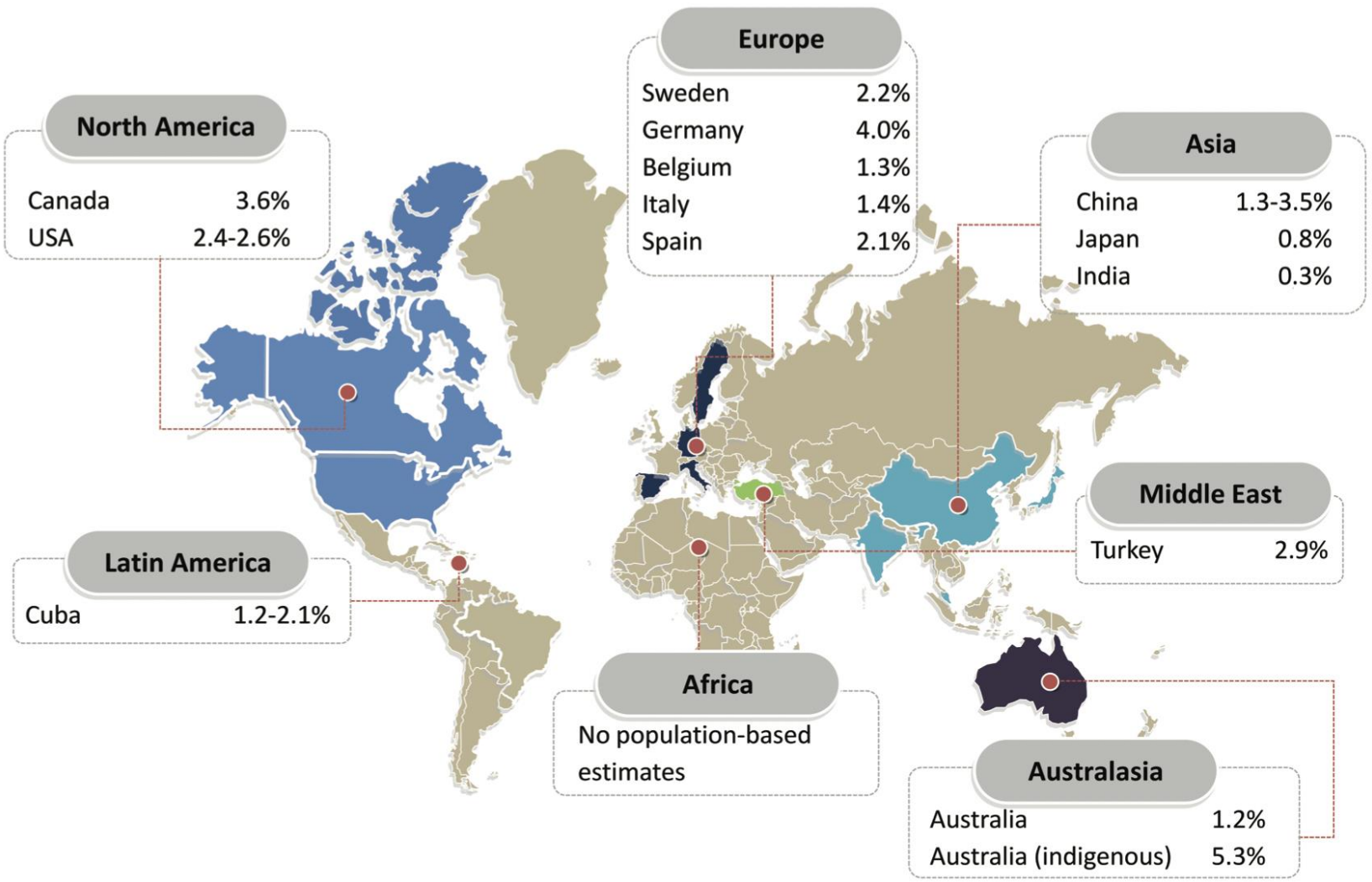


23rd November 2024

HF is an increasingly important public health issue

HF Prevalence in population-based studies[1]



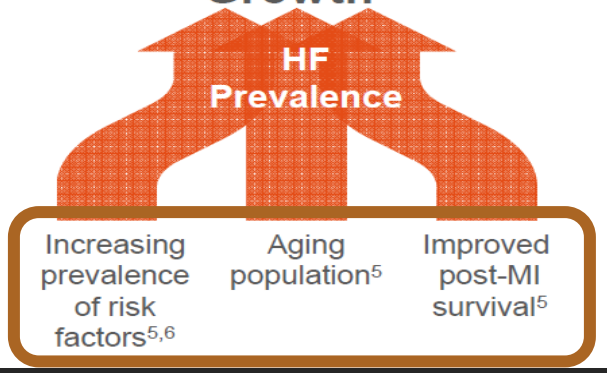
Prevalence[1]

1-3%

of the population in Asia have HF[1]

As many as **1 in 5** people aged 70–80 years have HF[1]

Growth[2]



1. Groenewegen A et al. Eur J Heart Fail 2020;22:1342-56. 2. Jones NR et al. Eur J Heart Fail 2019;21:1306-25.

Prevalence of cardiovascular morbidities in Myanmar

Ko Ko Zaw[1*], Nwe Nwe[2] and Su Su Hlaing[3]

Possible heart Failure prevalence 2.8% (1.5million of 50 million pop:)

Abstract

Background: Cardiovascular diseases (CVDs) are now in a rising trend in South East Asia including Myanmar due to increase in major cardiovascular risk factors in both urban and rural areas, such as smoking, obesity and diabetes

The most common cause of heart failure is CAD, especially after AMI, followed by VHD and dilated cardiomyopathy.

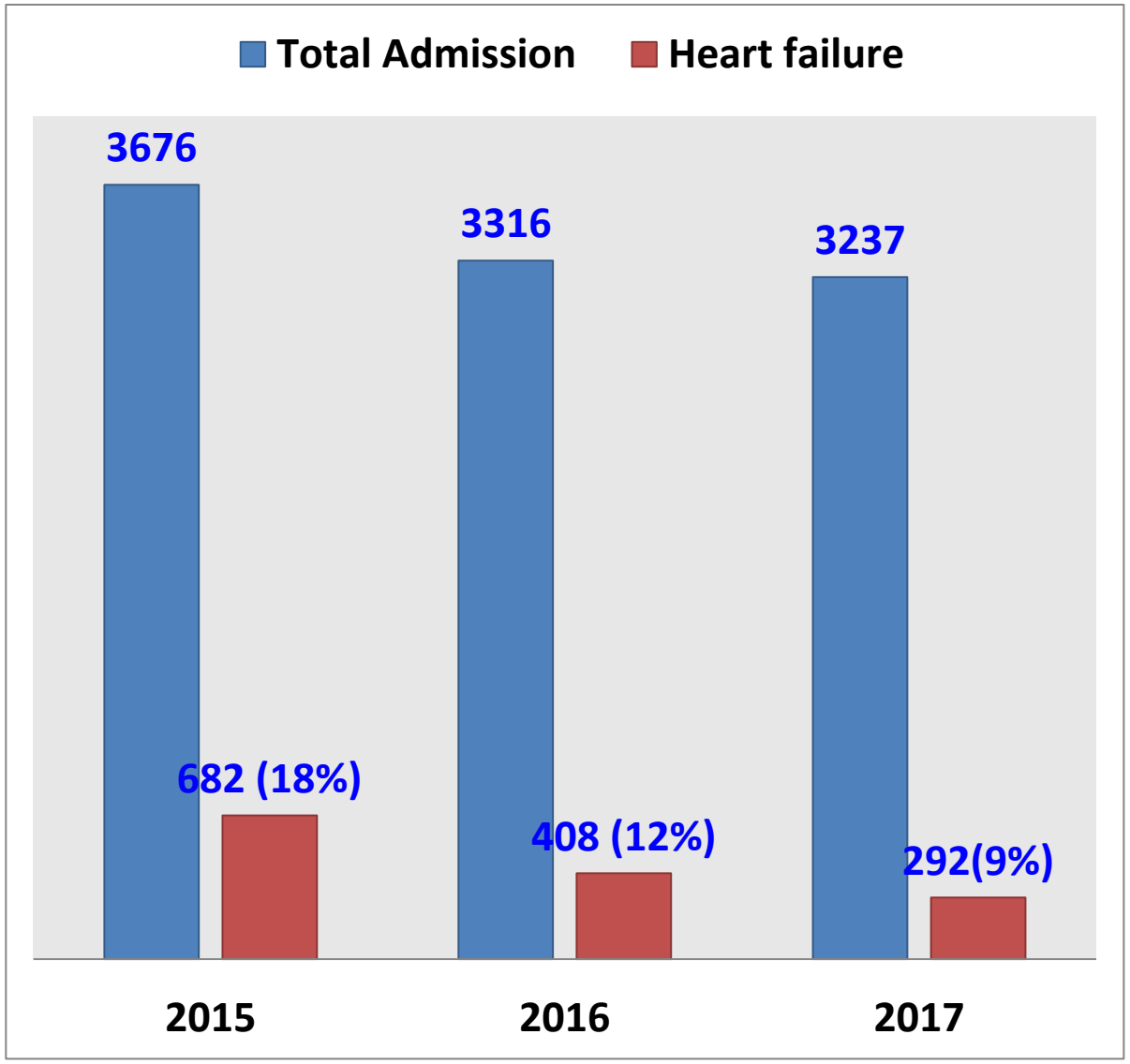
Research Group] to determine the level of reported CVD morbidities in adult population.

Results: Age of the study population ranged from 40 to 99 years with the mean age of 56 years. Seventy-one percent of the study population was women. Nine percent of the study population have suffered from angina according to Rose Angina Questionnaire. Prevalence of possible heart attack, stroke and heart failure was 7.5, 1.5 and 2.8%. Prevalence of hypertension was 51%.

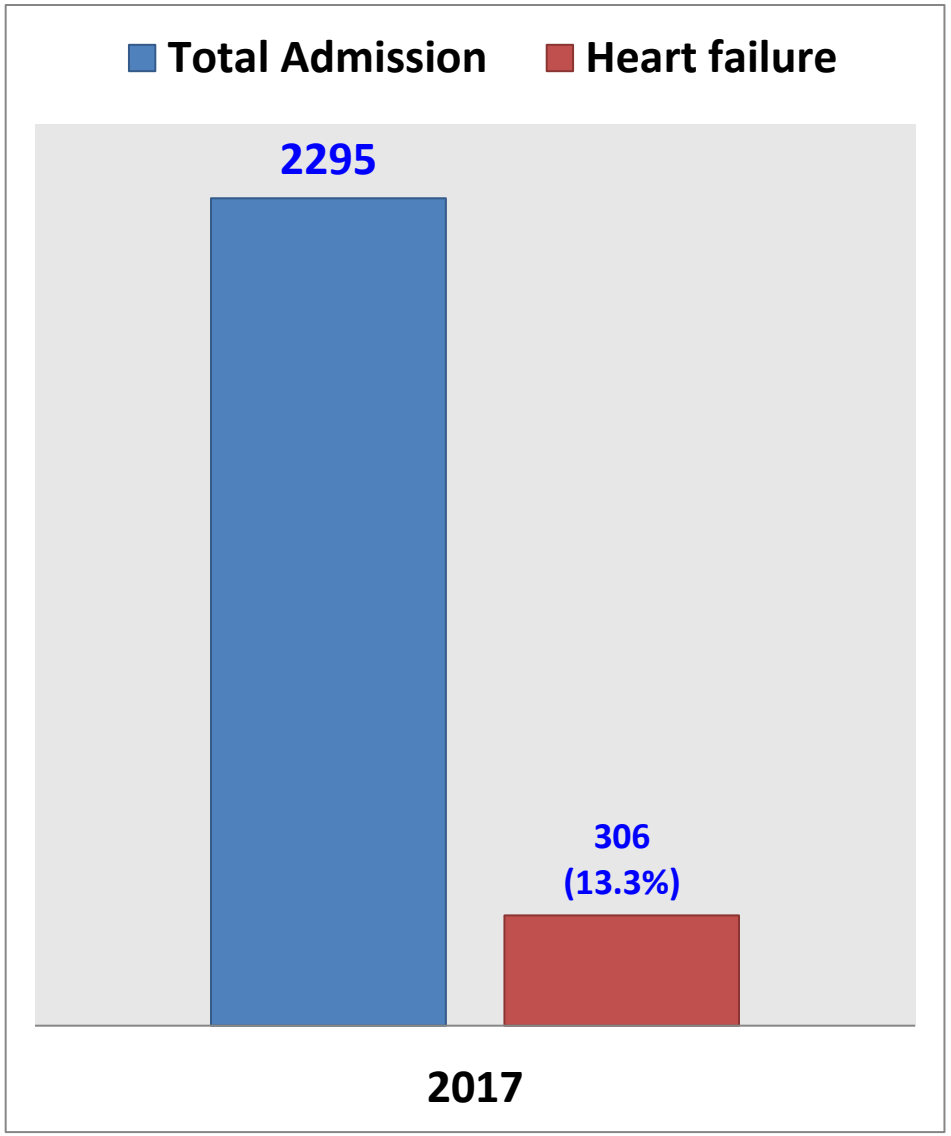
Conclusion: The CVD morbidities are high. There is a need for strengthening prevention and control activities of CVDs.

Keywords: Cardiovascular diseases, CVD, Myanmar, Prevalence, Morbidities

Total number of HF cases in CVM, MGH 2015 to 2017

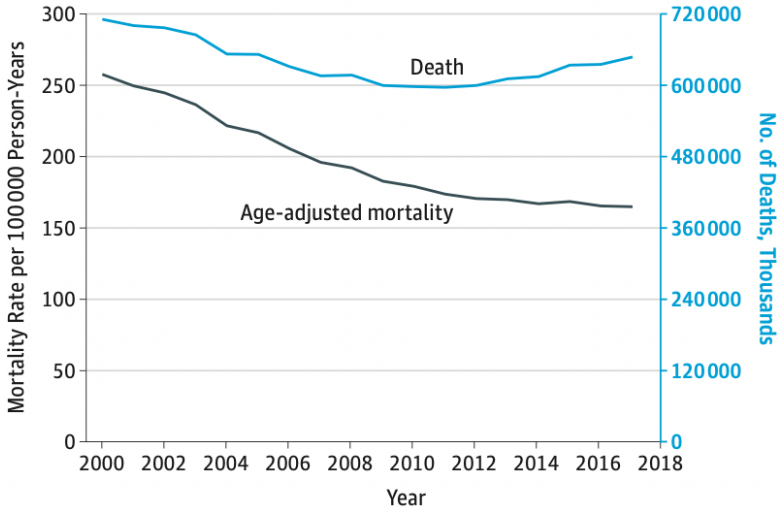


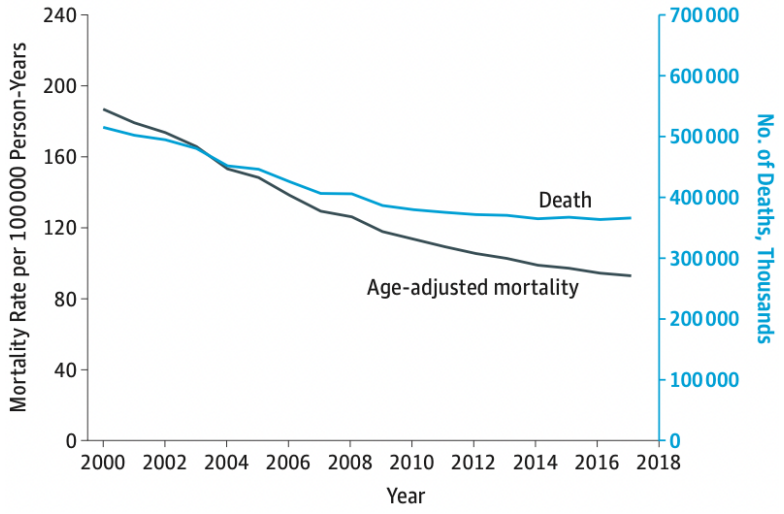
Total number of HF cases in CVM, NOGH 2017

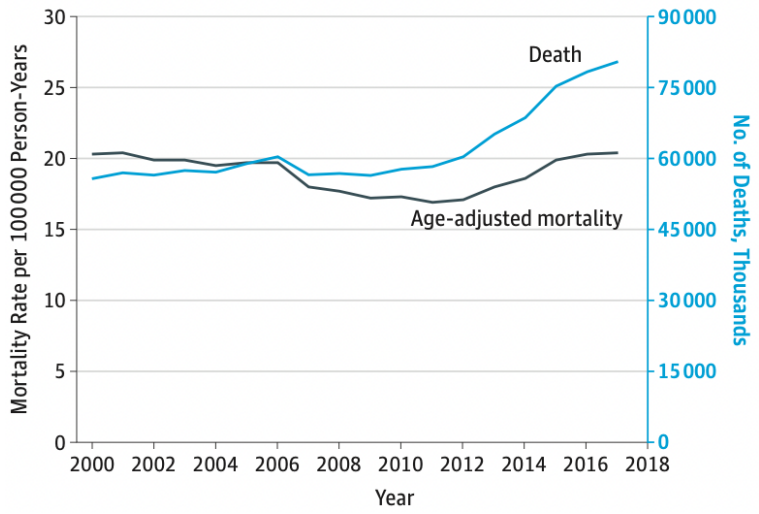


HF is an increasingly important public health issue

Mortality Rates and Number of Deaths in USA[1], 2000 to 2017



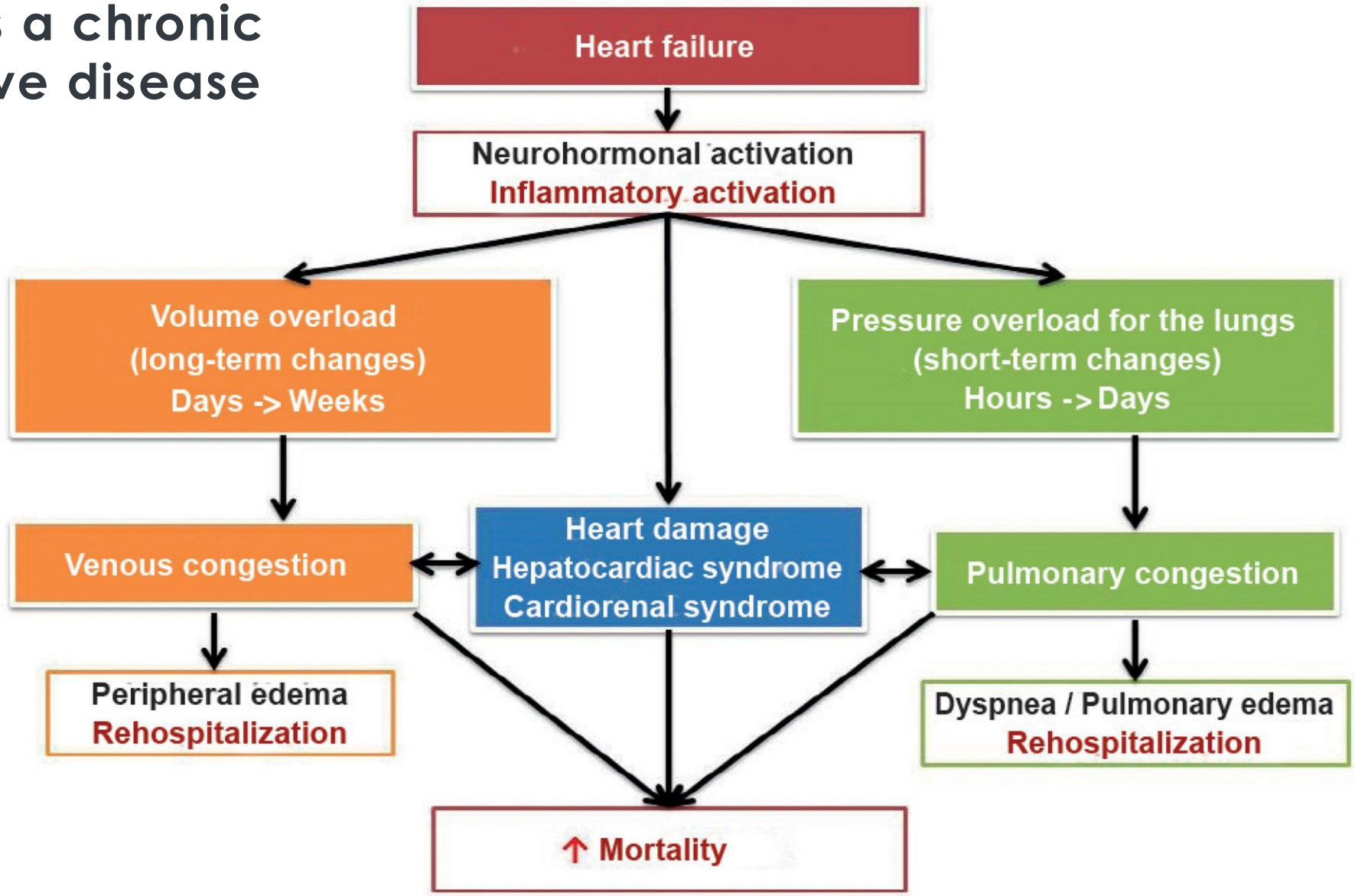




- **Deceleration in the rate of decrease of heart disease mortality** from 2011 to 2017
- Age-adjusted mortality rate **decreased 5.0% for heart disease and 14.9% for CHD** while **increasing 20.7% for heart failure** and 8.4% for other heart diseases
- Explanations:
  - substantial increases in obesity and diabetes rates that began in the mid-1980s (heart disease mortality)
  - rapid population growth in group of adults ≥65 years + increased burden of comorbidities (HF mortality)
  - transition from HFrEF to HFpEF, for which effective evidence-based strategies are still largely lacking[2]

1. Sidney S et al. JAMA Cardiol 2019;4:1280-6. 2. Owan TE et al. N Engl J Med 2006;355:251-9.

Heart failure is a chronic and progressive disease



With several key challenges
heart failure hospitalization

>1 million

Annual hospitalizations both in the United States and Europe[1]

1-4%

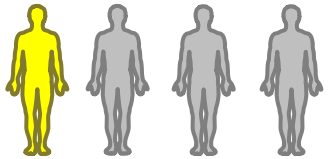
Heart failure hospitalization among total hospital admission[2]

Up to 9/10 patients

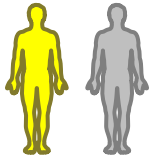
Hospitalized due to worsening chronic heart failure as compared with de novo heart failure[3]

5-10 days

Average length of hospital stay[3]



Almost **1 out of 4** hospitalized patients (24%) are rehospitalized for heart failure within the **30-day post discharge period**[4]

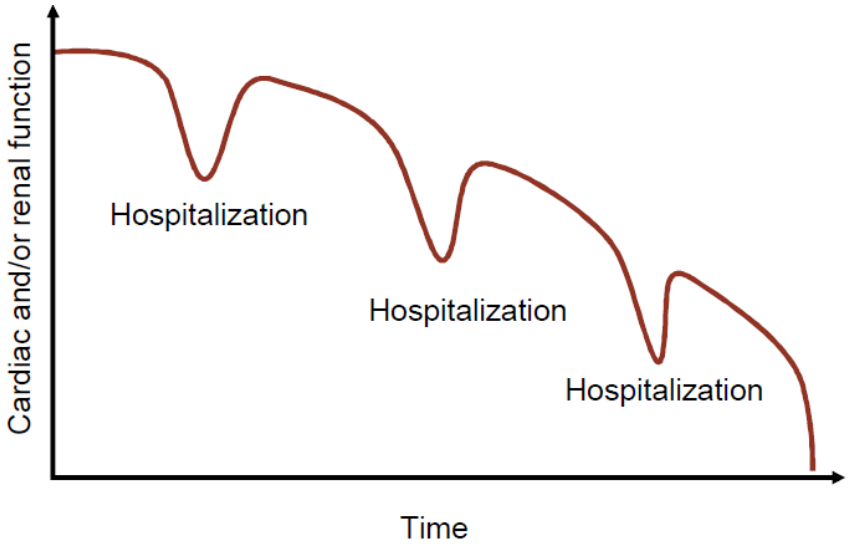


Nearly **1 out of 2** patients (46%) are rehospitalized for heart failure within the **60-day post discharge period**[4]

1. Ambrosy PA et al. The Global Health and Economic Burden of Hospitalizations for Heart Failure. Lessons Learned From Hospitalized Heart Failure Registries. J Am Coll Cardiol. 2014;63:1123–1133 2. Cowie MR et al. Improving care for patients with acute heart failure. 2014. Oxford PharmaGenesis. ISBN 978-1-903539-12-5. Available online at: http://www.oxfordhealthpolicyforum.org/reports/acute-heart-failure/improving-care-for-patients-with-acute-heart-failure. 3. Butler J, Braunwald E, Gheorghiade M. Recognizing worsening chronic heart failure as an entity and an end point in clinical trials. JAMA. 2014;312(8):789-90. 4. O'Connor CM et al. Causes of death and rehospitalization in patients hospitalized with worsening heart failure and reduce left ventricular ejection fraction: results from efficacy of vasopressin antagonism in heart failure outcome stuy with tolvaptan (EVEREST) program. Am Heart J. 2010;159:841-849.e1

PATIENT'S JOURNEY

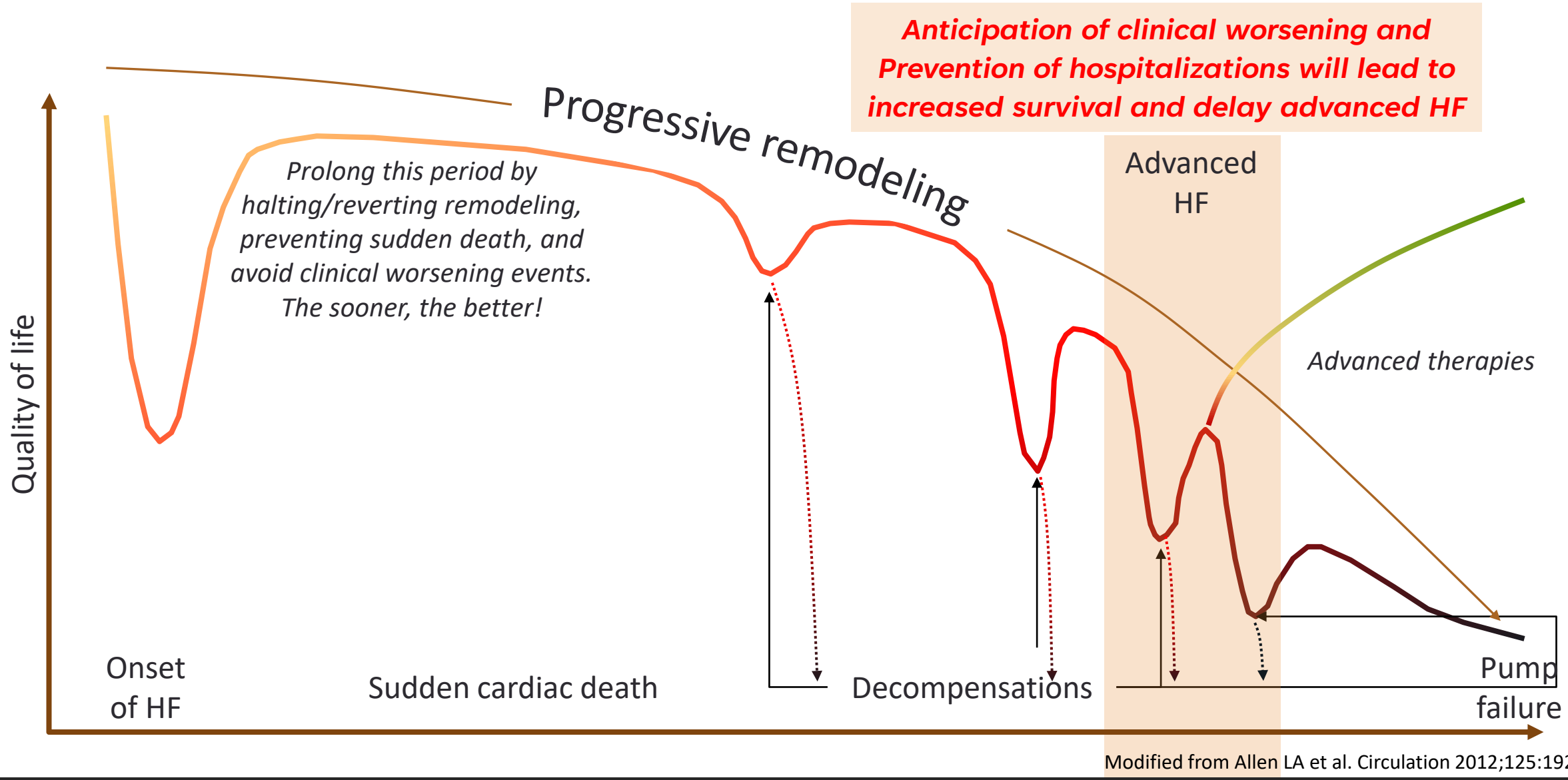
Heart failure patients suffer from recurrent hospitalization



With each hospitalization, there is likely myocardial and renal damage which contributes to progressive LV or renal dysfunction, leading to an inevitable downward spiral.[1]

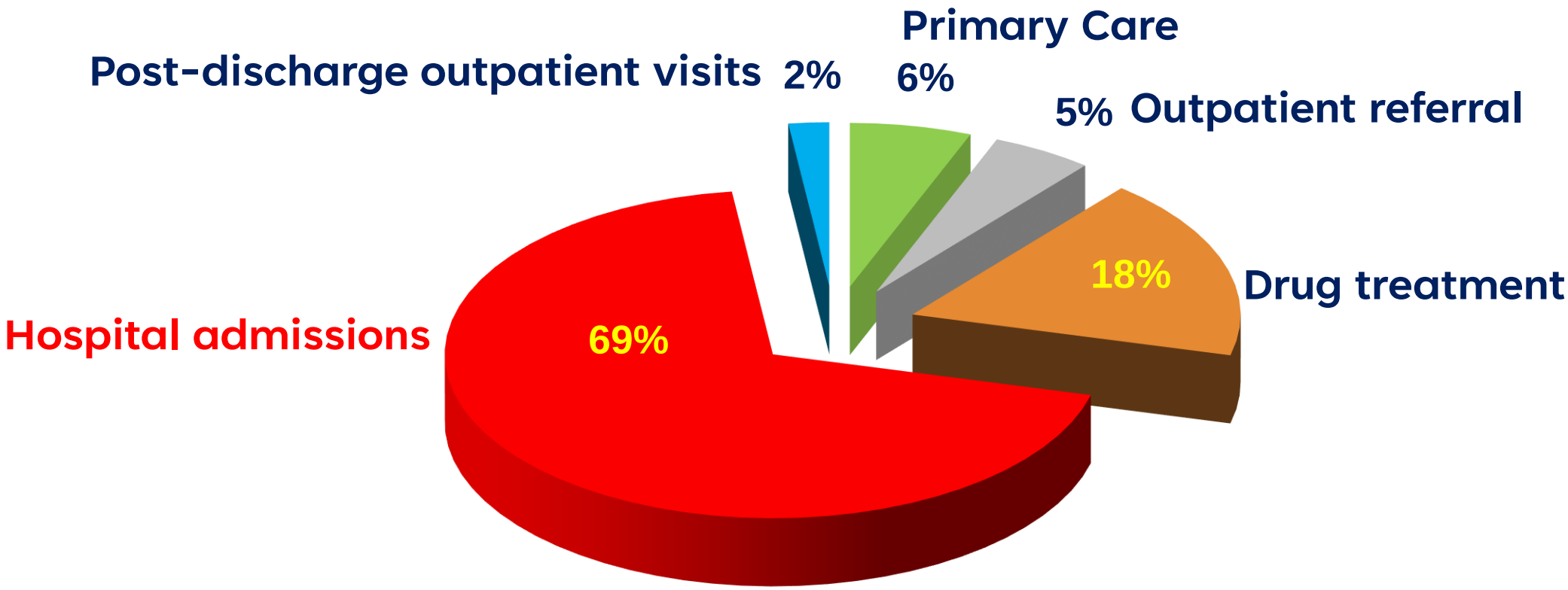
1. Gheorghiade M et al. *Am J Cardiol*. 2005;96:11-17.

Clinical course of heart failure



Modified from Allen LA et al. Circulation 2012;125:1928-52

Economic burden of chronic HF



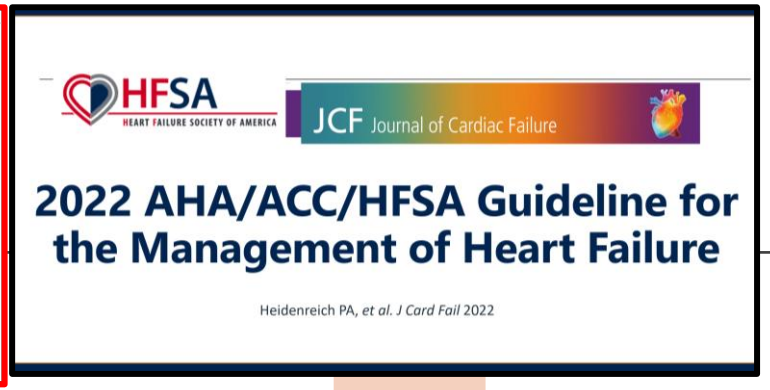
Hospitalization accounts for most CHF-associated costs

Stewart S, et al. *Eur J Heart Fail* 2002;4:361–71.

Medical Treatment for Ambulatory Patients with HFrEF

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

ESC European Society of Cardiology



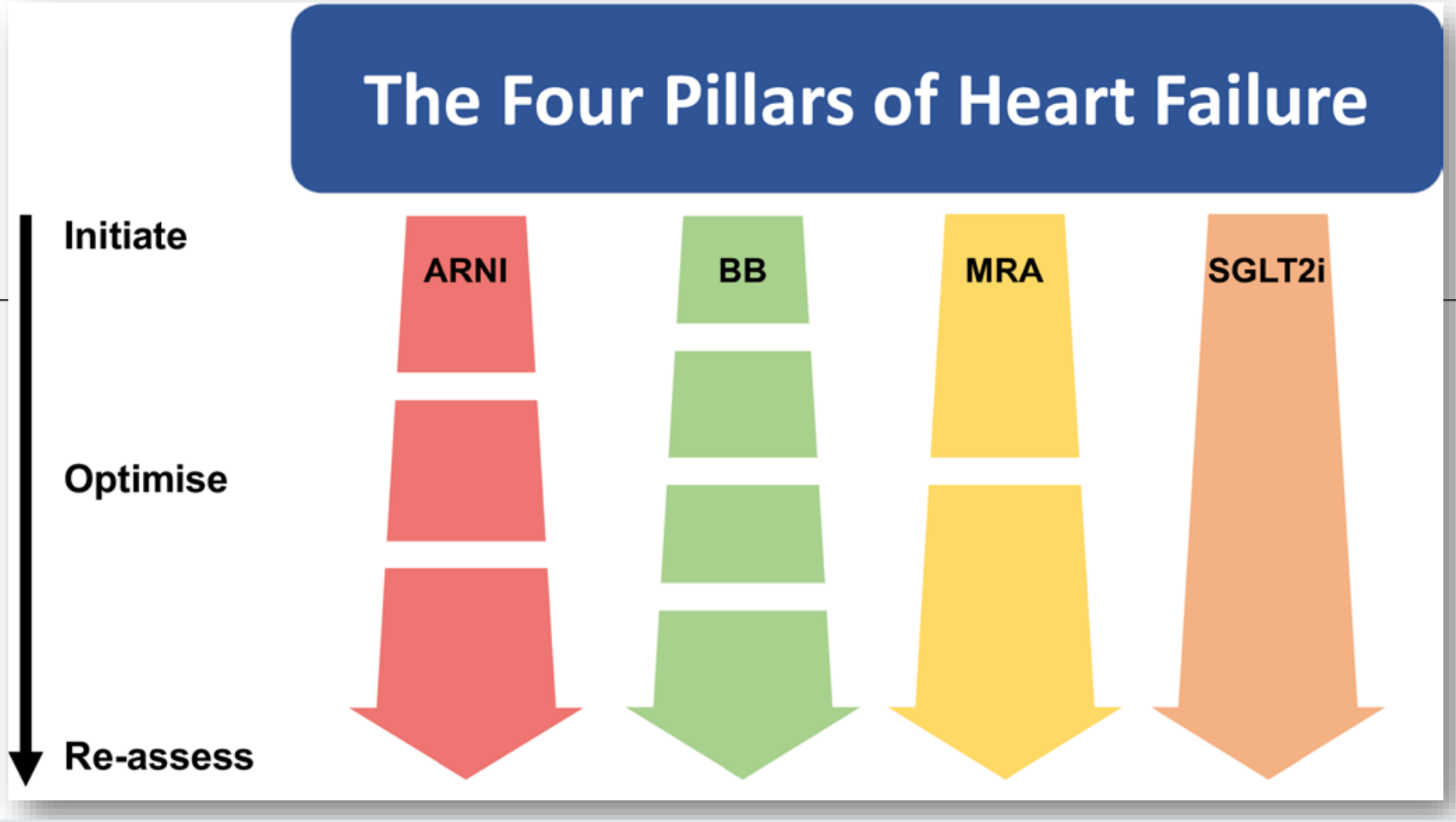
2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Diuretics

- Relieve congestion

- **Neurohormonal agents**
- Modify disease course/reduce HHF/improve mortality
- ACEI/ARB/ARNI,BBs, MRAs,SGLT2i as 4 pillars of therapy

- **Personalised**
- Ivabradine/Digoxin/ H-ISDN
- Device therapy
- Management of co-morbidities: hyperkalemia/iron deficiency anaemia/arrhythmias

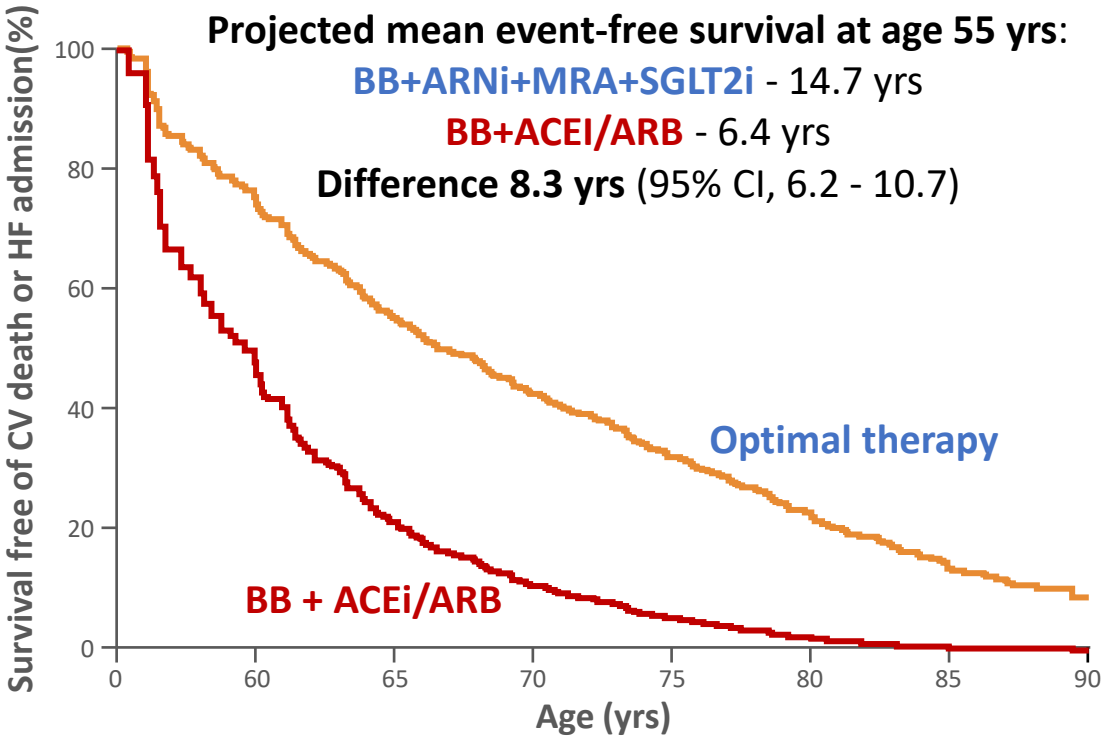


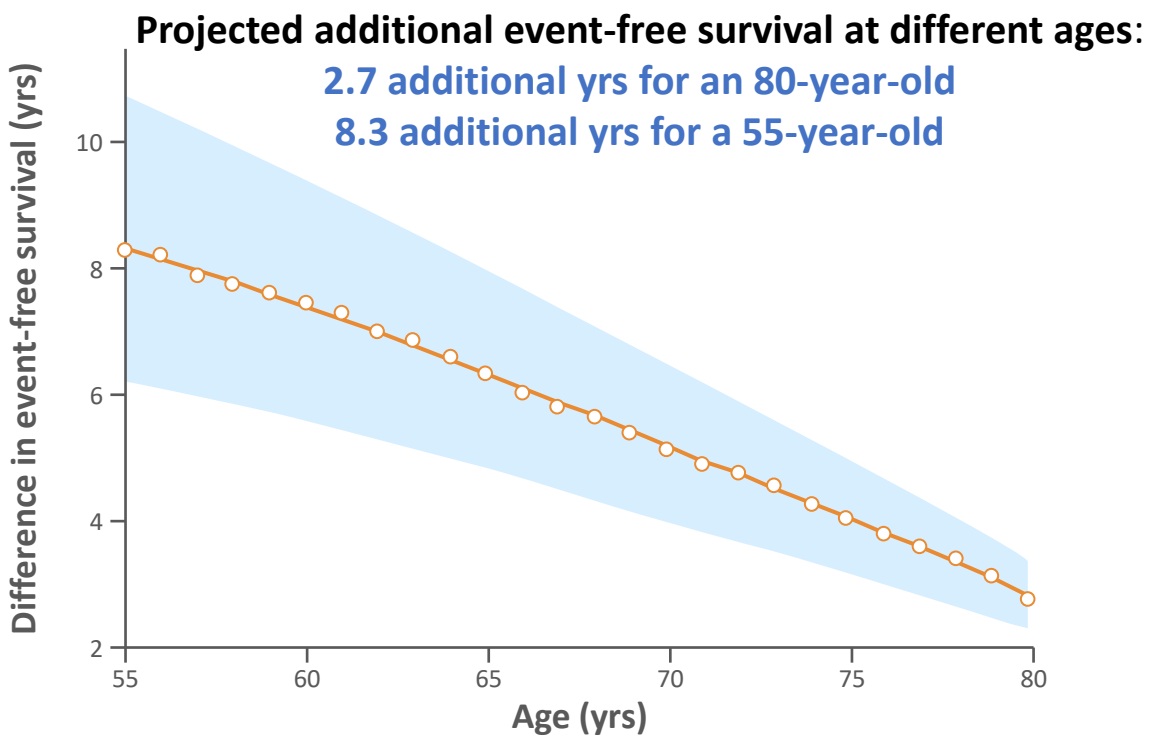
Cumulative risk reduction in all-cause mortality over 24 months if all evidence-based medical therapies are used: Relative risk reduction 72.9%, Absolute risk reduction 25.5%

NNT to prevent death- 4

Oportunities to prolong survival in HFrEF

Survival benefits of optimal, comprehensive disease-modifying drug therapy





Cross-trial analysis of EMPHASIS-HF, PARADIGM-HF and DAPA-HF[1]: Lifetime comprehensive disease-modifying drug therapy (BB, ARNi, MRA, and SGLT2i) reduces the hazard of CV death or HF admission (HR 0.38 [95% CI, 0.30–0.47]) compared with conventional therapy (BB + ACEi/ARB). Depending on the age of therapeutic optimisation, comprehensive disease-modifying drug therapy was estimated to afford 1.4 to 6.3 additional yrs of survival. EMPHASIS-HF control group (93% ACEi/ARB, 87% BB): mean age 69 yrs, 78% male, mean LVEF 26%, prior HF admission 53%.

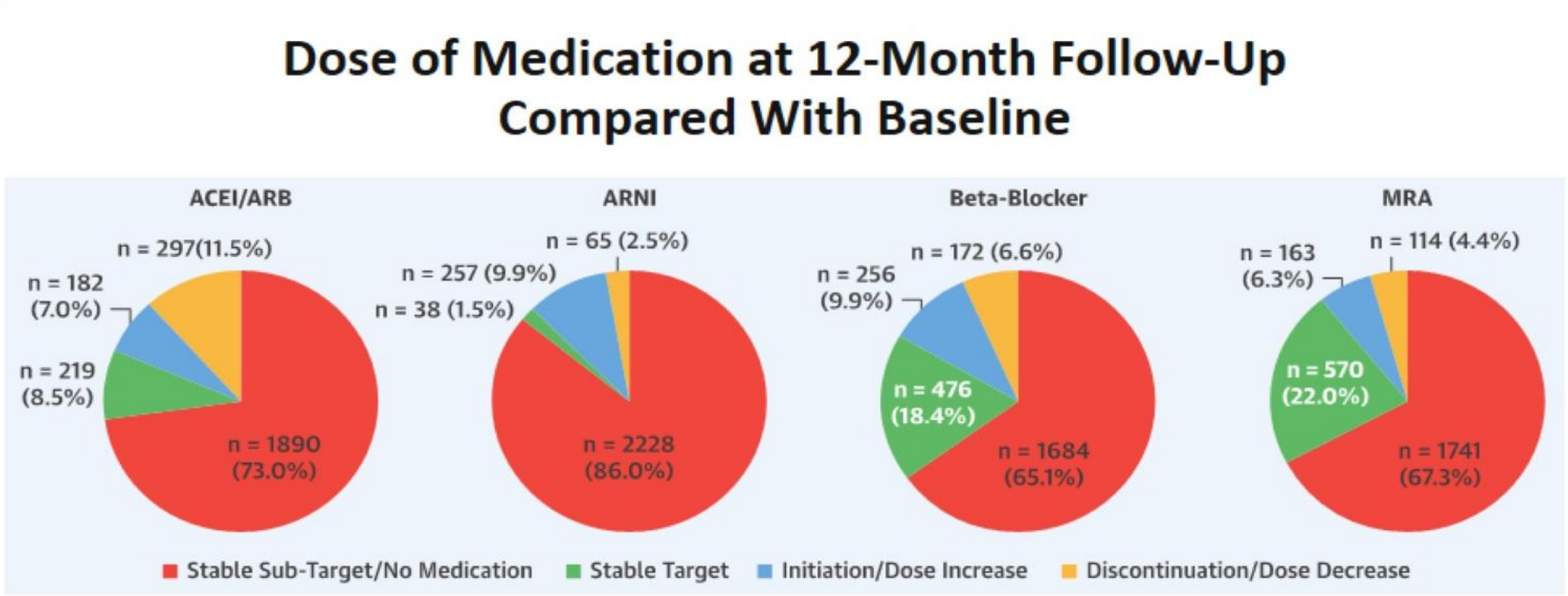
Gaps in the Use of GDMT: Data from the CHAMP-HF Registry

In adjusted models, older age, lower BP, more severe functional class, renal insufficiency and recent HHF generally favored lower medication utilization or dose

	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

3518 outpatients from 150 practices with chronic HFrEF receiving at least 1 oral medication for management of HF included in analysis.
Greene Sj, et al. *J Am Coll Cardiolo*. 2018;72:351-366.

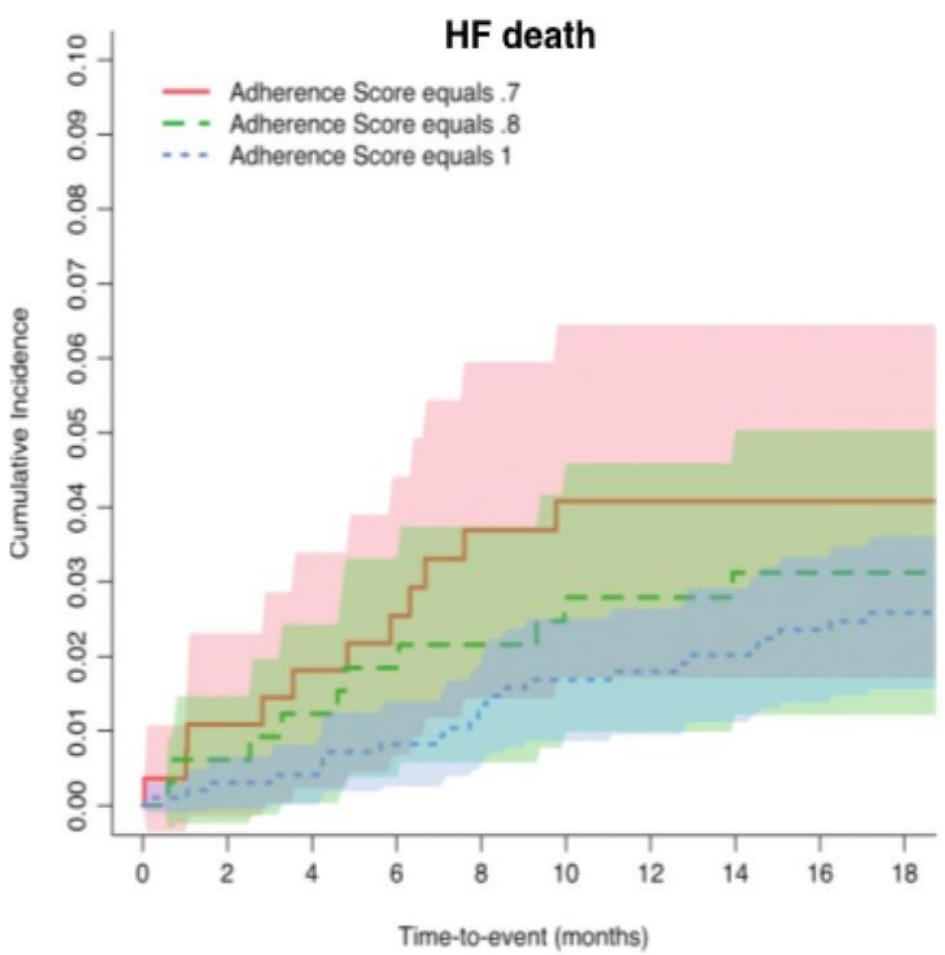
Titration of GDMT in HFrEF: Data from CHAMP-HF

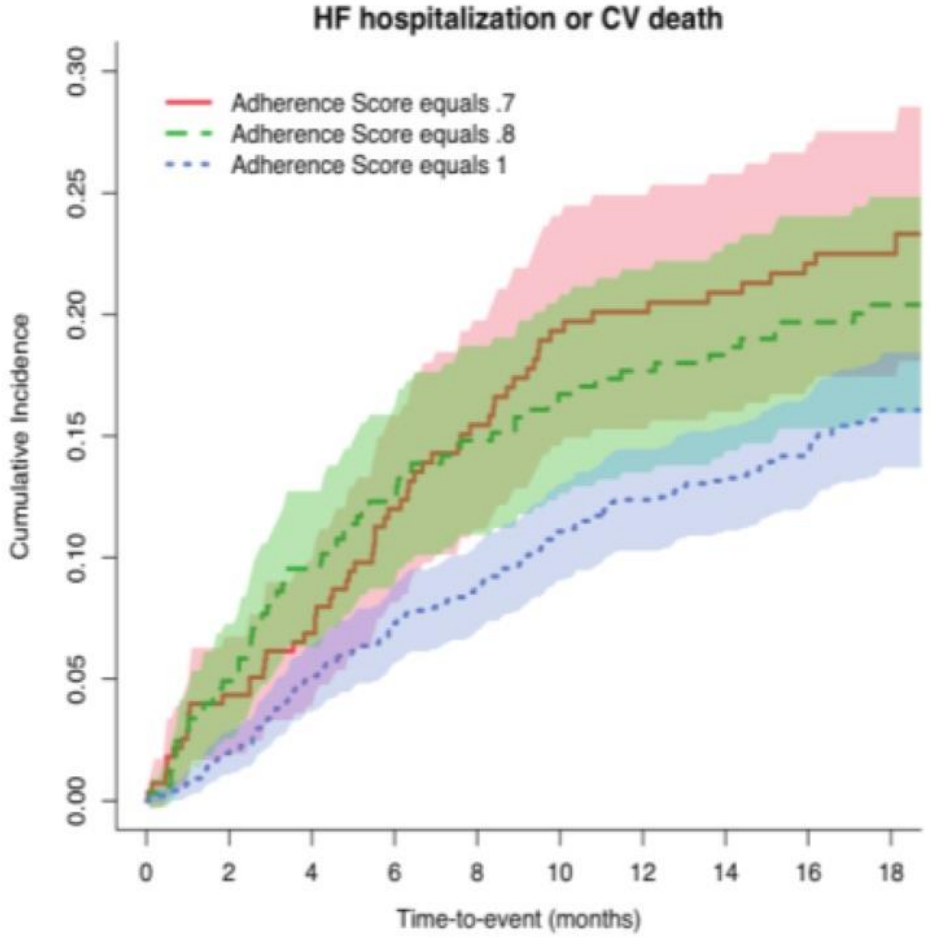


- Over 12 months, < 1% of patients were simultaneously treated with target doses of ACEI/ARB/ARNI, beta-blocker, and MRA
- Medical reasons were the most common reasons for discontinuations and dose decreases of each therapy, but the relative contributions from patient preference, health team, and systems-based reasons varied by medication

Greene Sj, et al. *J Am Coll Cardiolo*. 2019;73: 2365-2383.

QUALIFY: Suboptimal Adherence to GDMT Associated with Reduced Outcomes in HFrEF

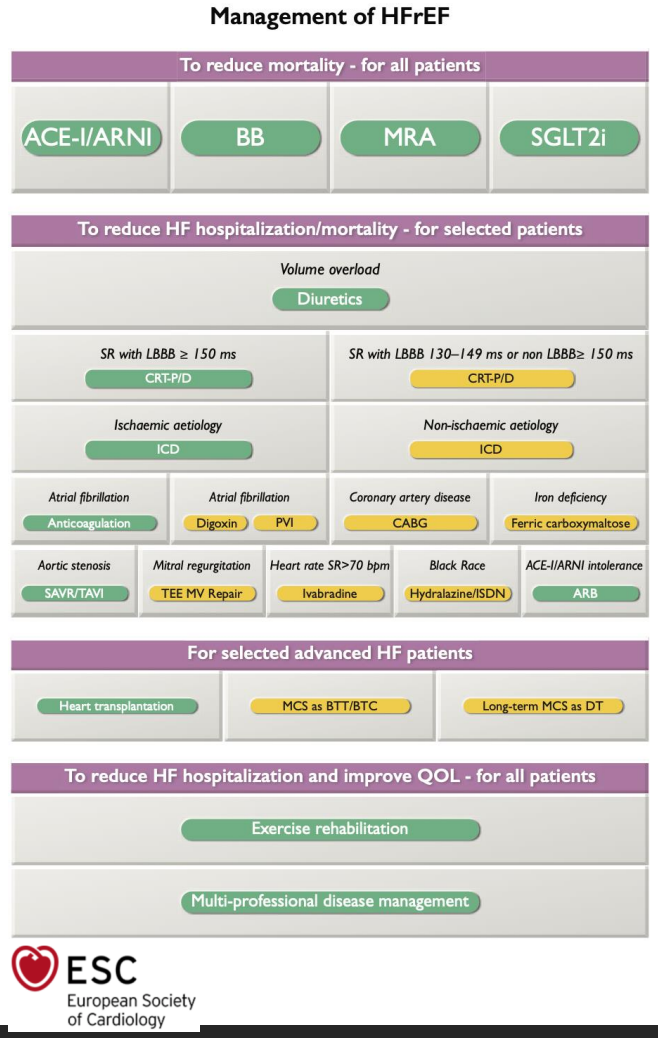


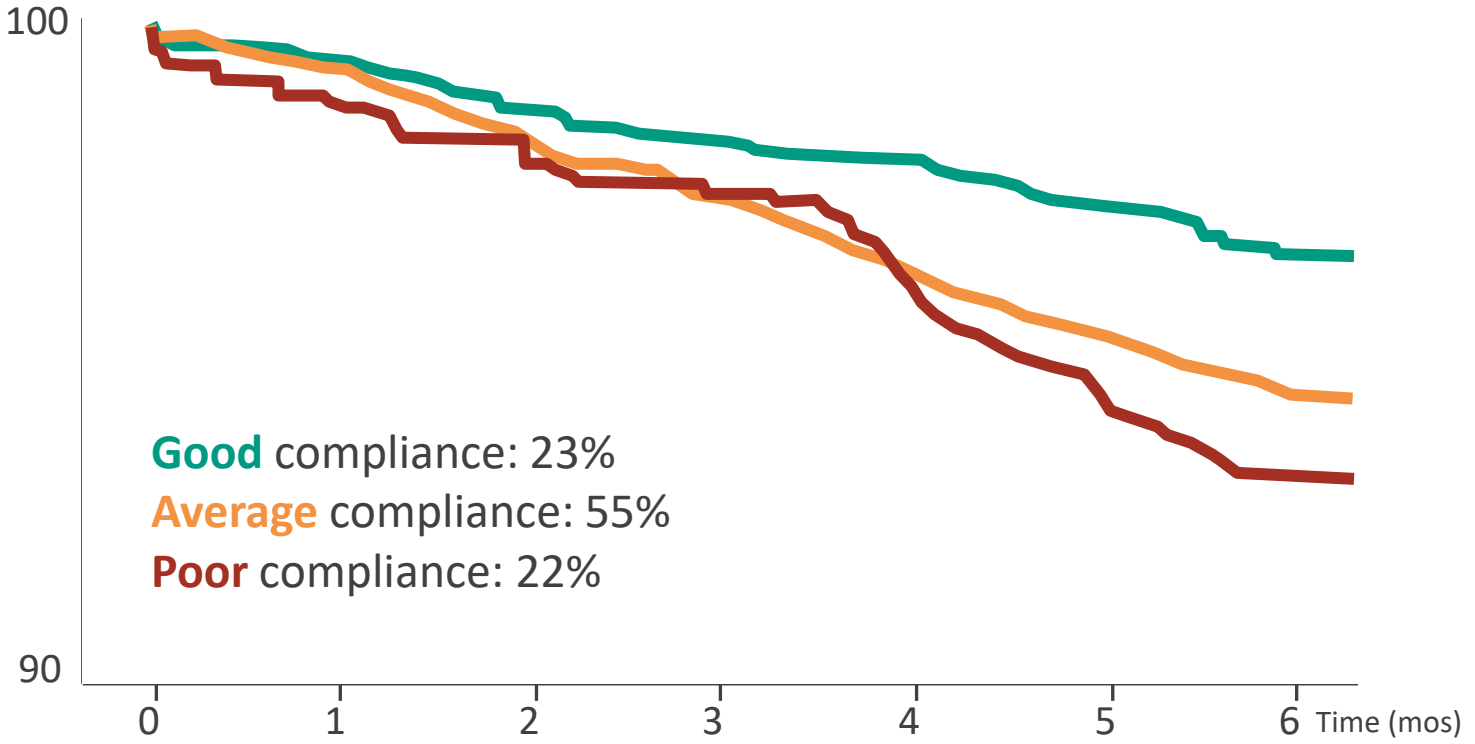


18 months follow up data on 6118 ambulatory patients with HFreF from 549 centres in 36 countries.
Komajda M, et al. *Eur j Heart Fail*. 2019;21:921-929.

Missed oportunities to prolong survival in HFrEF

Impact of physician adherence to guidelines on overall survival





QUALIFY registry[1]: 6669 Pts w/ HFrEF and HF hospitalization 1-15 mos. Guideline adherence score: ACEi, ARB if ACEi not tolerated, BB, MRA (NYHA II-IV) and ivabradine (NYHA II-IV, SR ≥70-75 bpm). Maximum points if drug prescribed at ≥50% maximum recommended dose in absence of a contraindication. 18 months follow up data in 6,118 Pts[2]: HF death and the composite of CV death or HF hospitalizations were predicted by adherence score.

1. Komajda M et al. Eur J Heart Fail 2017; 19: 1414. 2. Komajda M et al. Eur J Heart Fail 2019; 21: 921.

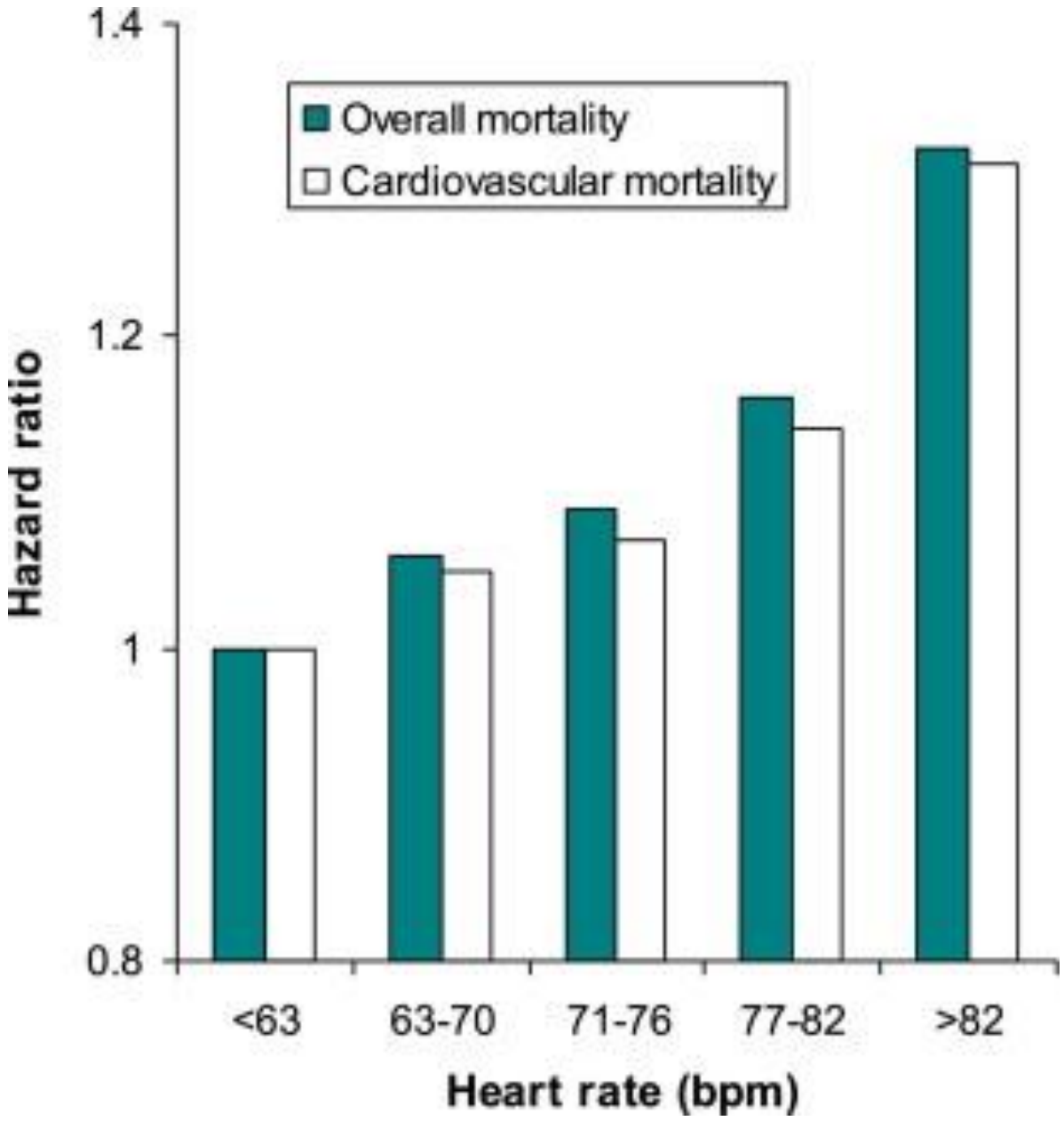
Challenges and Limitations of Current HFrEF Therapy: Summary

- **Patients with HFrEF are at high risks for adverse outcomes**
- **optimizing treatment of HFrEF with existing therapies remains a key therapeutic goal**
- **There is still significant room for additional improvement in the treatment of patients with HFrEF**

The cardiovascular risk factor “resting heart rate”

Resting heart rate as a risk marker and risk factor

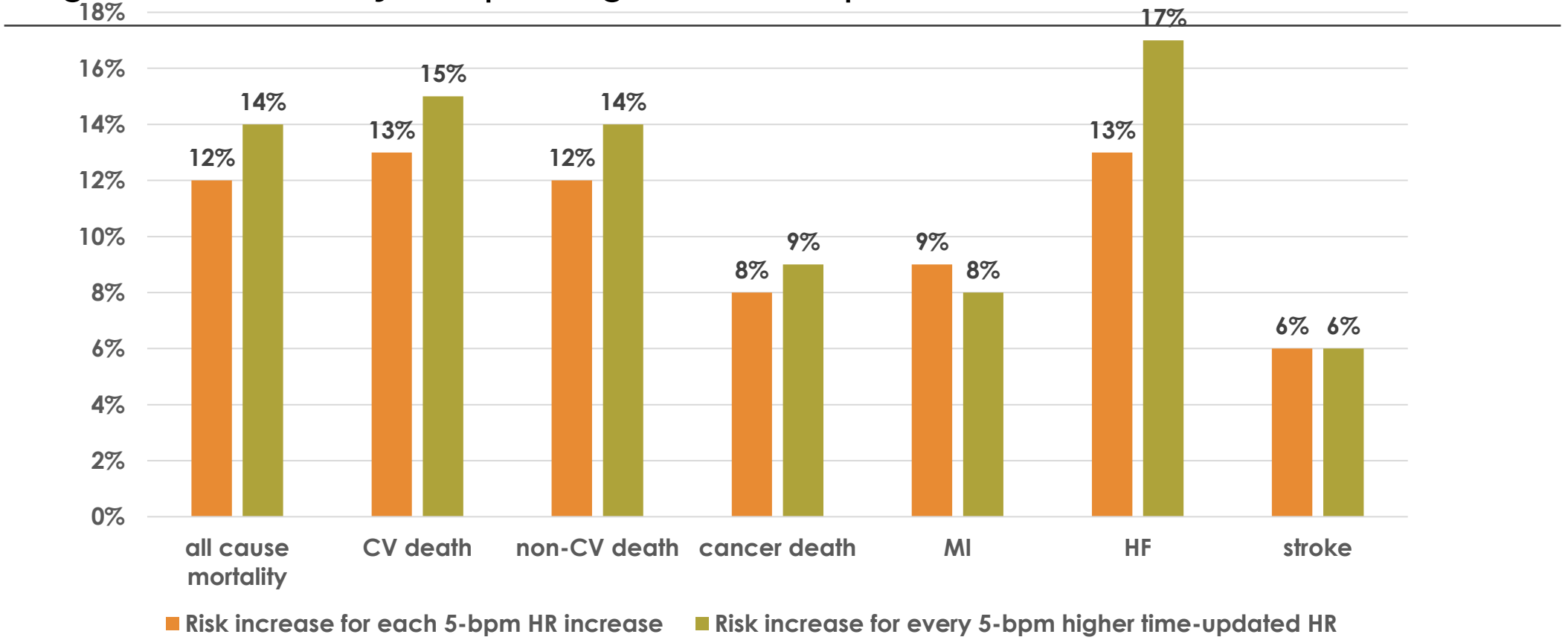
- **An elevated heart rate causes shortening of the duration of the whole cardiac cycle, predominantly at the cost of diastolic duration because systolic time remains fairly stable.**
- **The association of HR and diastolic duration is not linear, showing disproportionate shortening of diastolic time with rising HR.**
- **In contrast, slow HR induce prolongation of diastolic duration, thereby improving coronary blood flow and oxygen supply, as perfusion of coronary arteries occurs mainly in diastole.**



Fox K, Borer JS, Camm AJ, et al; Heart Rate Working Group. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol*. 2007; 50(9):823–830

Associations between HR and adverse outcomes

Increased risk of adverse outcomes with each 5-bpm increase in HR from the peceding visit and every 5-bpm higher time-updated HR*

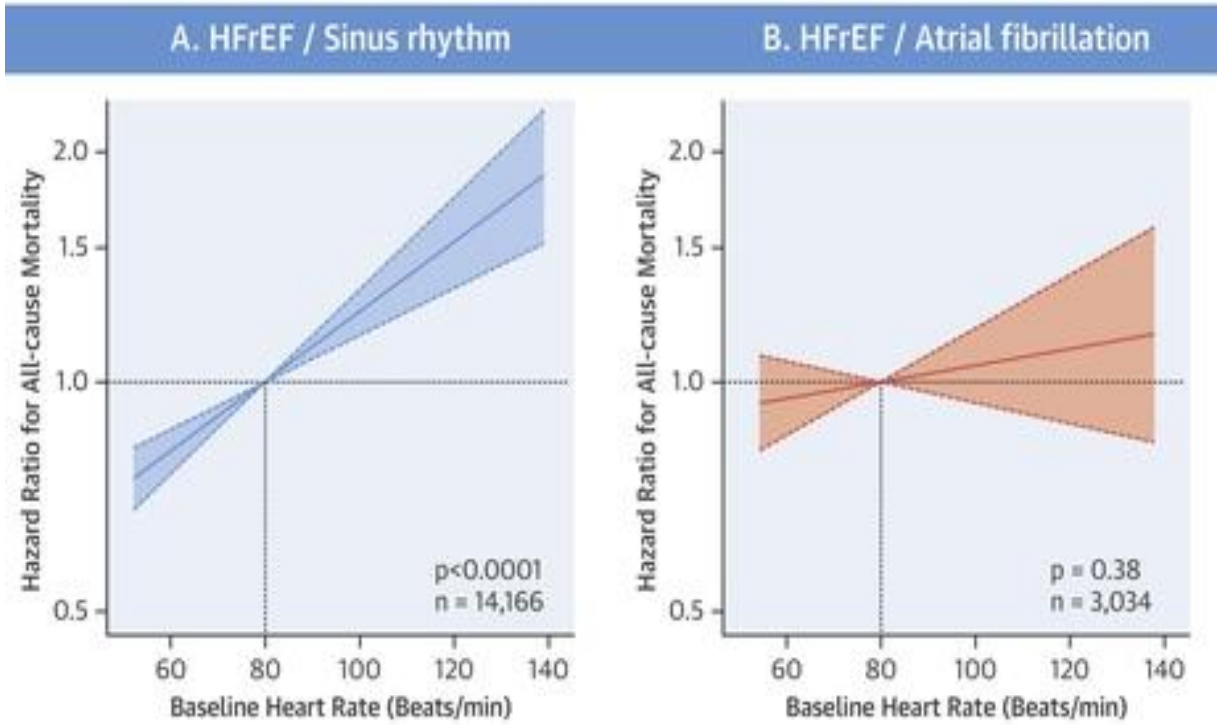


(*) Time-updated HR is the most recent HR value measured before the occurrence of an event or at the end of a study
HR: heart rate; bpm: beats per minute; CV: cardiovascular; MI: myocardial infarction; HF: heart failure

Association of heart rate with outcomes in HFrEF

Simple marker to help improve patients' lives

- These results[1] conclusively demonstrate the predictive value of pulse rate measured at time of diagnosis of HFrEF and during patient follow up
- A **lower pulse rate** at the time diagnosis and across follow-up encounters was strongly associated with **lower risk of mortality and hospitalization outcomes**, **independent of BB treatment and dose**
- Patients who had a **pulse rate ≥70 bpm in the past 6 months had 36% ↑mortality, 25% ↑all-cause hospitalizations, and 51% ↑HF hospitalization**, compared to patients with pulse rates <70 bpm
- Meta-analysis of 11 RCTs of BB in HF patients in SR showed significant positive linear association between HR at time of enrollment and all-cause mortality[2]

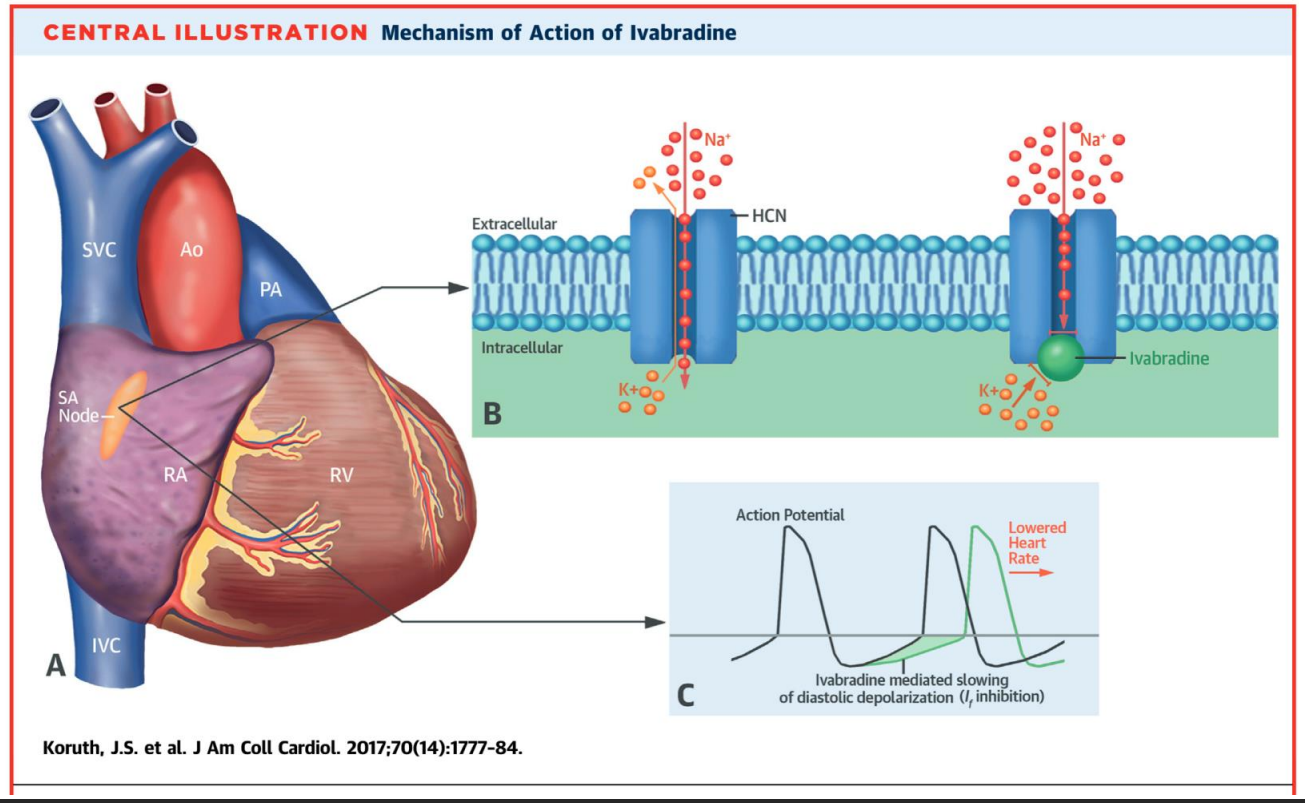


Veterans Affairs (VA) national cohort: 51,194 incident HFrEF cases (67 ± 12 years, 98% male) between 2006 and 2012. Average of 6.3 ± 3.6 pulse measurements per patient updated at 6 month intervals over a median follow-up of 3.2 years. Objective: examine the associations of both baseline (time of HF diagnosis) and serially measured pulse rates, with mortality and days hospitalized per year for HF and for any cause.

1. Kurgansky KE et al. BMC Cardiovasc Dis 2020; 20: 92. 2. Kotecha D et al. J Am Coll Cardiol 2017;69:2885-96.

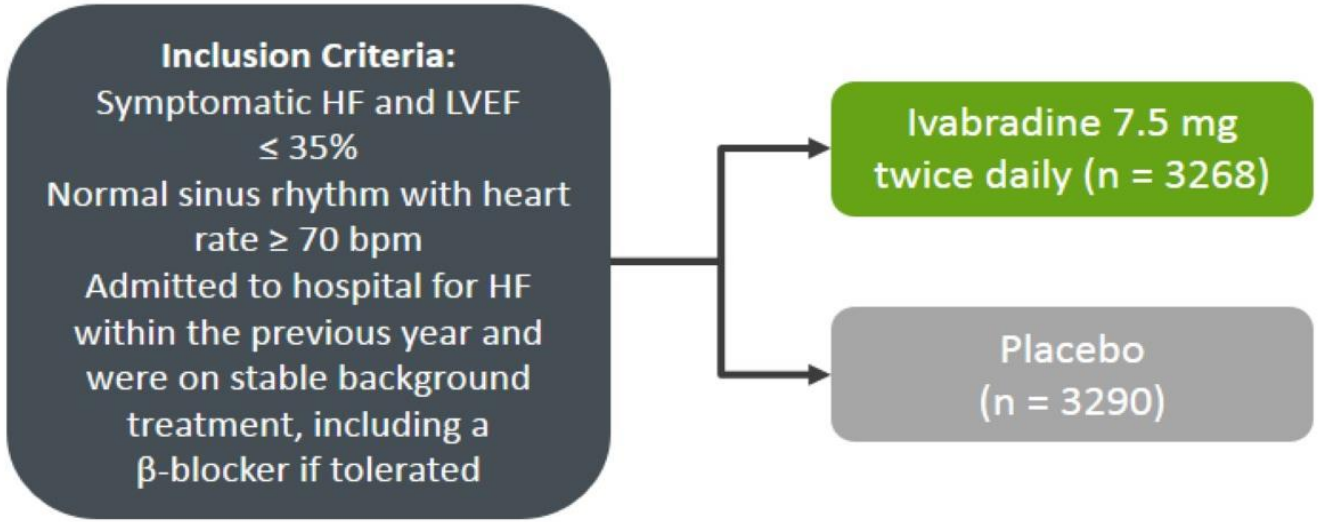
Ivabradine

- Works on the sino-atrial node funny current slowing heart rate
- No effect on blood pressure
- No effect on contractility



Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial

- Randomized, double-blind, placebo-controlled, parallel-group study; 6558 patients randomly assigned
- Study duration: median, 22.9 months; maximum ,41.7months



Primary efficacy: composite of CV death or hospital admission for worsening HF

Bohm M et al. Lancet 2010; 376: 886

Ivabradine improves outcomes in HFrEF

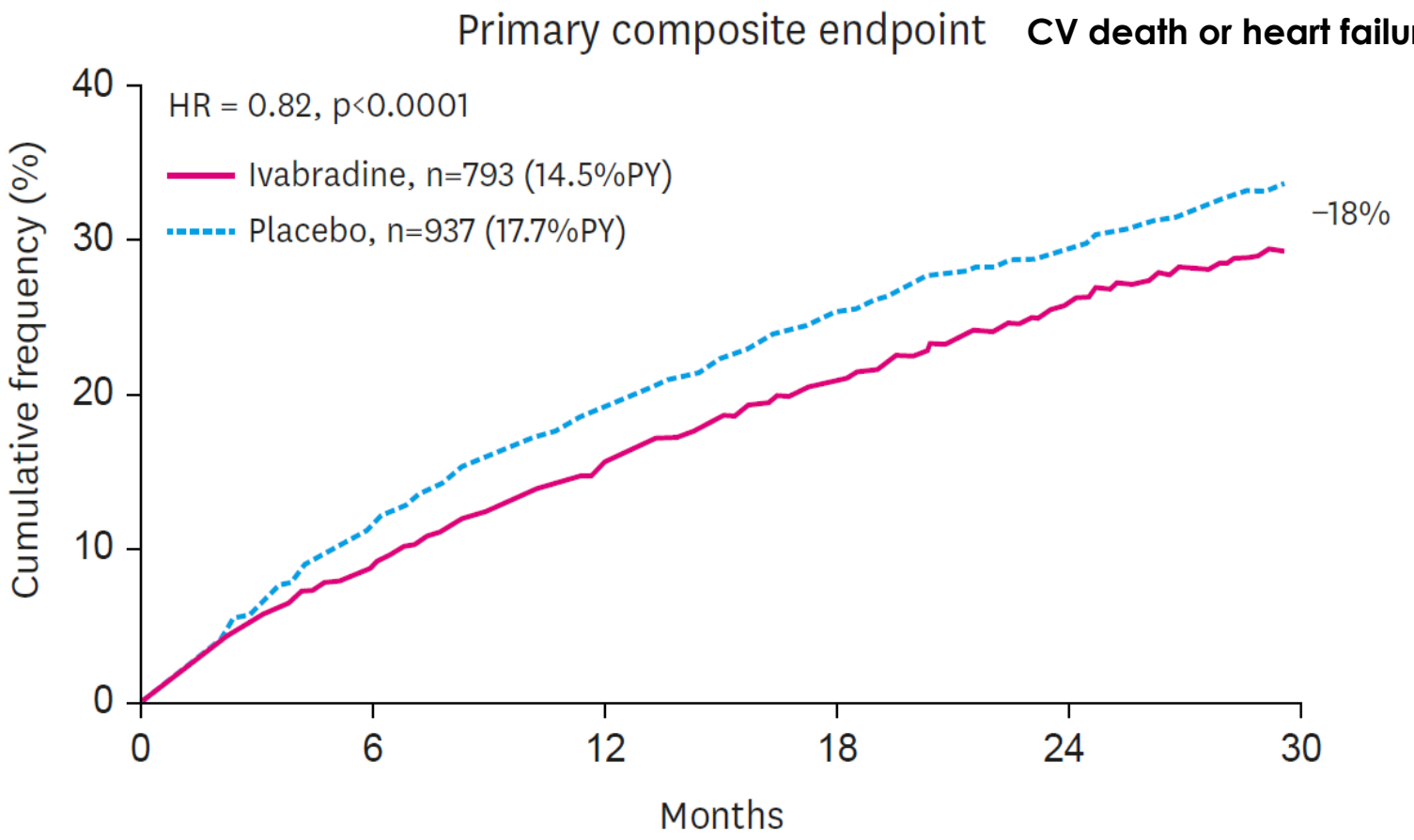


Figure 3. Kaplan Meier cumulative event curves for the primary composite endpoint (cardiovascular death or heart failure hospitalization) for ivabradine or placebo. Primary results of the SHIFT study. Modified according to 10.
HR = hazard ratio; SHIFT = Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial.

Bohm M et al. Lancet 2010; 376: 886

Baseline HR is a predictor of endpoints on placebo

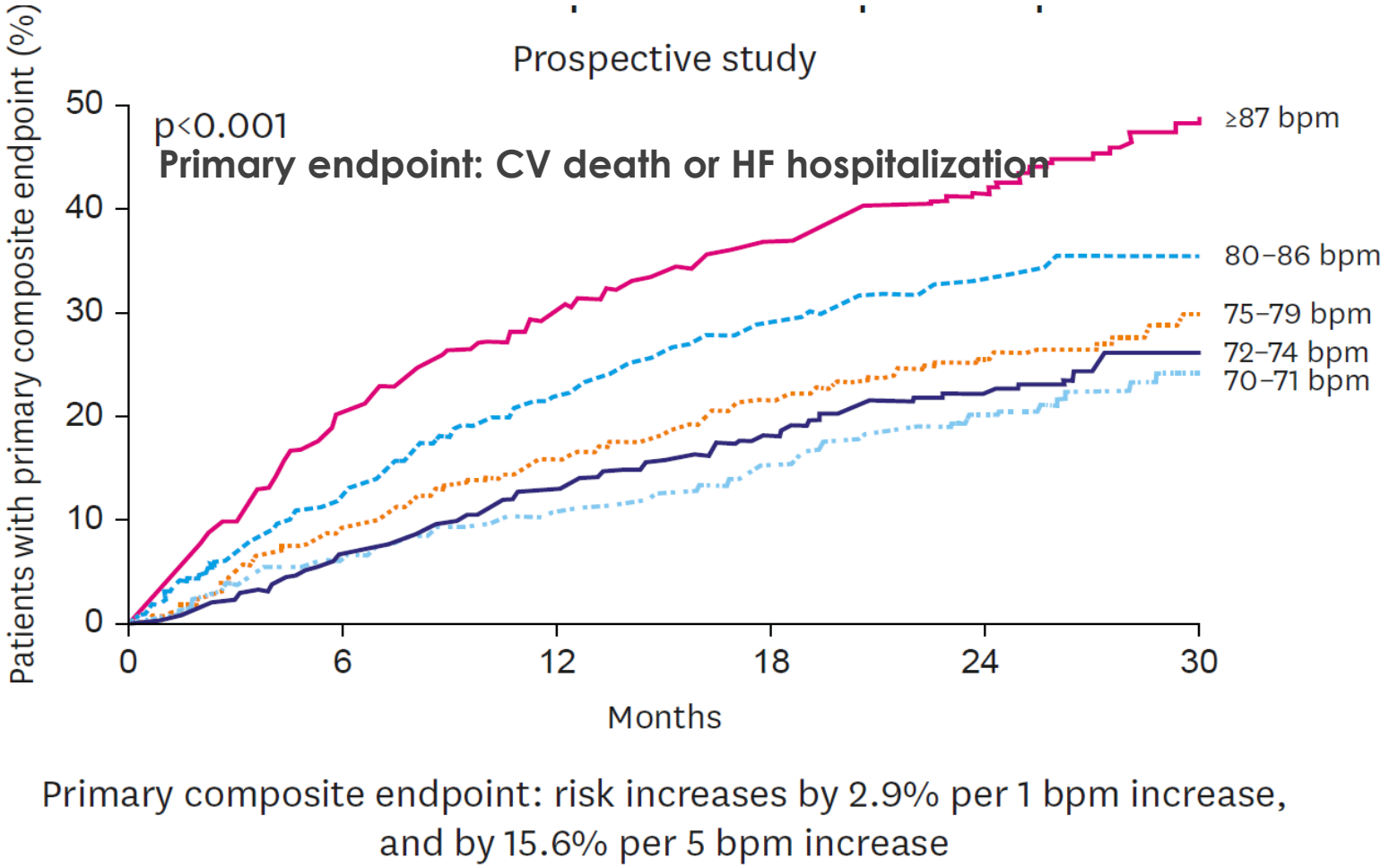
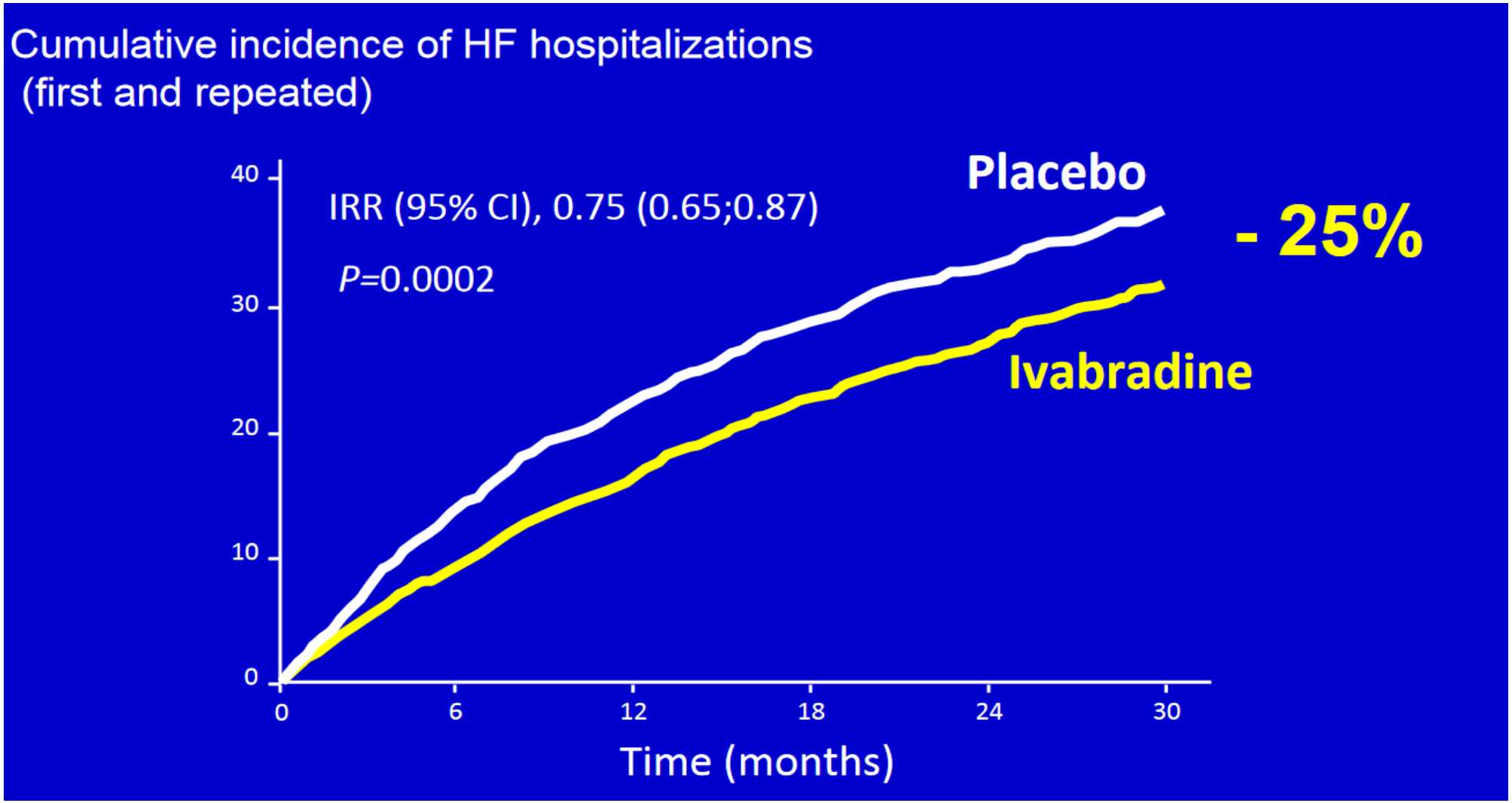


Figure 2. Kaplan Meier cumulative event curves for the primary composite endpoint (cardiovascular death or heart failure hospitalization) according to patient groups defined by quintiles of heart rate at 28 days on placebo. Log rank p values show the difference between the groups. Modified according to 7.

Bohm M et al. Lancet 2010; 376: 886

Ivabradine effect (on the top of guideline based treatment), heart rate reduction and HF hospitalizations

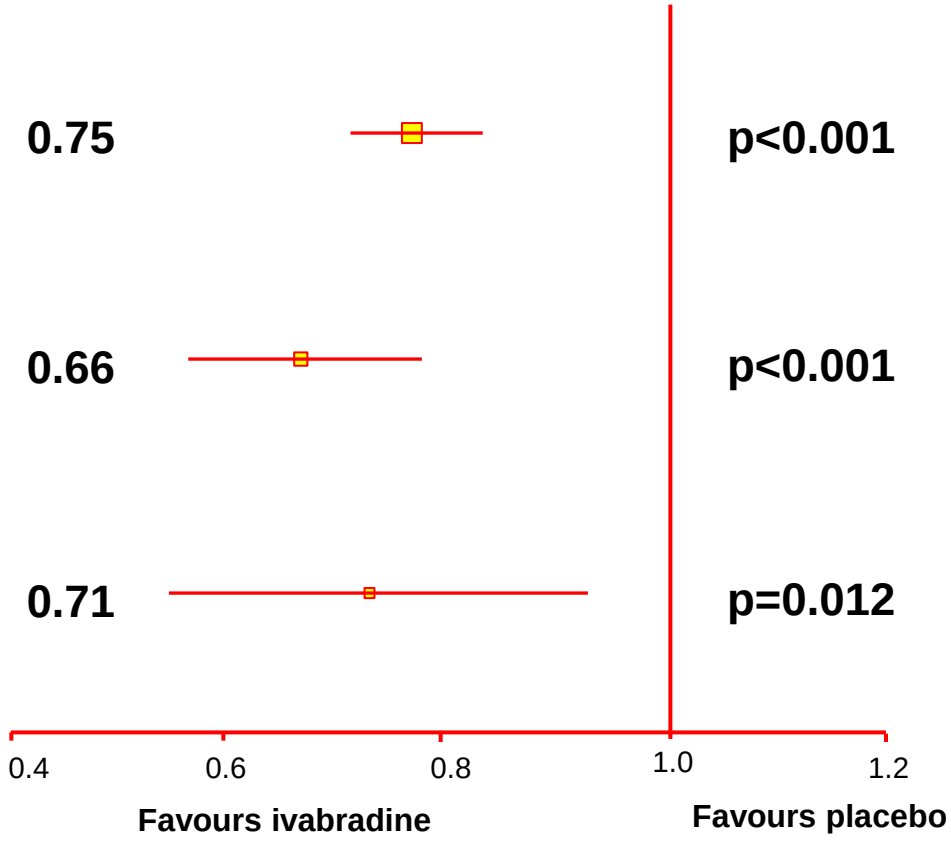


Borer JS, et al. Eur Heart J. 2012;33: 2813-20.

Recurrence of HF hospitalization

Total-time approach

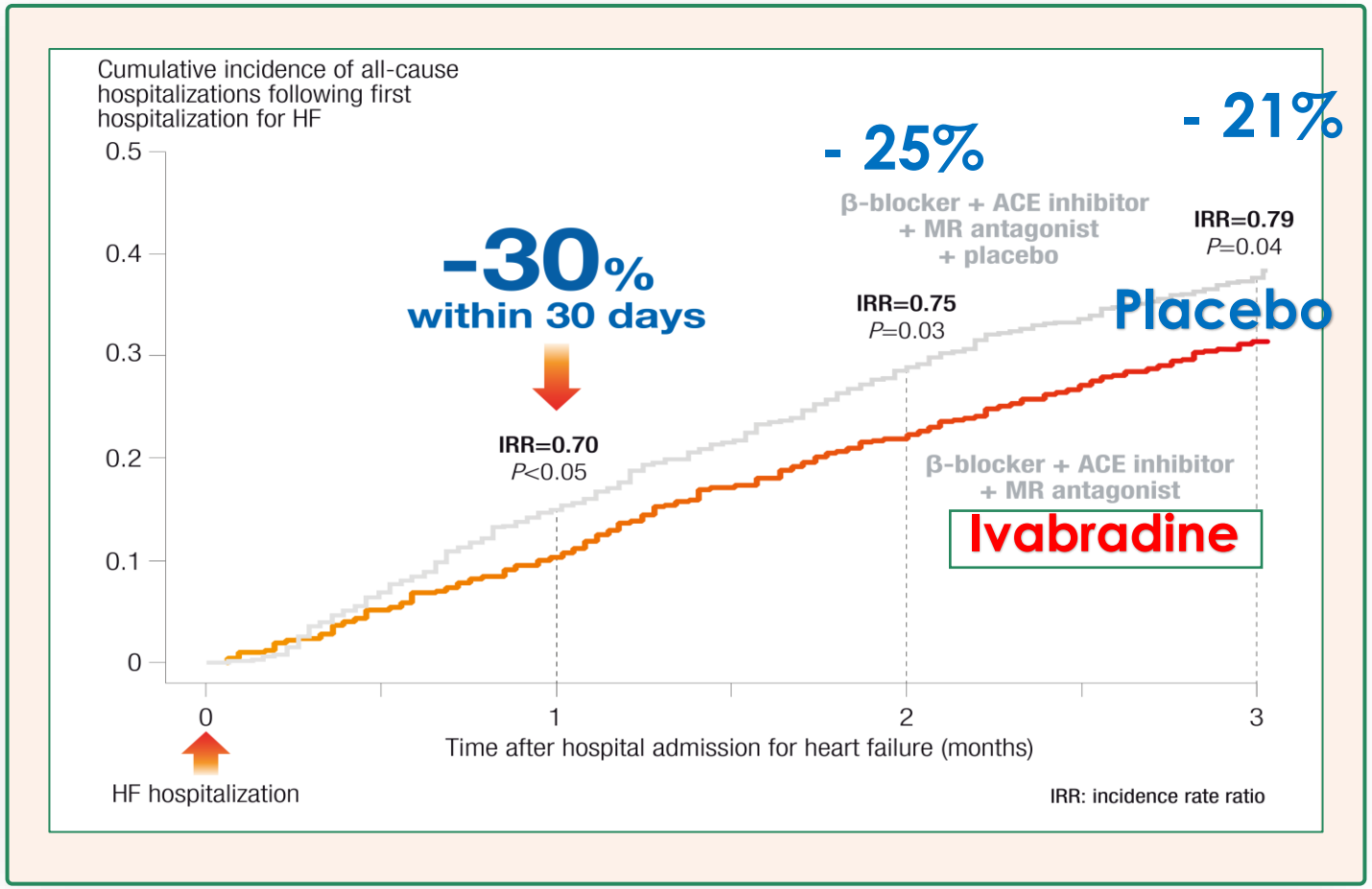
	Ivabradine (n=3241)	Placebo (n=3264)	Hazard ratio	*p*-value
First hospitalization	514 (16%)	672 (21%)	0.75	p<0.001
Second hospitalization	189 (6%)	283 (9%)	0.66	p<0.001
Third hospitalization	90 (3%)	128 (4%)	0.71	p=0.012



Reduces the risk of early re-admissions when initiated Ivabradine BEFORE DISCHARGE

Earlier is better

Any hospitalization within 3 months of hospital discharge



Komajda M et al. Eur J Heart Fail 2016; 18: 1182

SHIFT trial: Mortality and Hospitalization

	Primary Endpoint	Mortality Endpoints			Other Endpoints	
	CV death or hospital admission for worsening HF	All-cause mortality	CV mortality	Death from HF	Hospital admission for worsening HF	CV death, or hospital admission for worsening HF, or hospital admission for nonfatal MI
Ivabradine group (n=3241)	793 (24%)	503 (16%)	449 (14%)	113 (3%)	514 (16%)	825 (25%)
Placebo group (n=3264)	937 (29%)	552 (17%)	491 (15%)	151 (5%)	672 (21%)	979 (30%)
HR (95% CI)	0.82 (0.75, 0.90)	0.90 (0.80, 1.02)	0.91 (0.80, 1.03)	0.74 (0.58, 0.94)	0.74 (0.66, 0.83)	0.82 (0.74, 0.89)
***P* Value**	< .0001	.092	.128	.014	< .0001	< .0001

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

Ivabradine improves outcomes in HFrEF

6505 patients with HF and LVEF≤35%, NYHA II-IV, SR ≥70 bpm, and at least one HF hospitalization in the past 12 months.

Effects in subgroup of patients with baseline HR ≥75 bpm

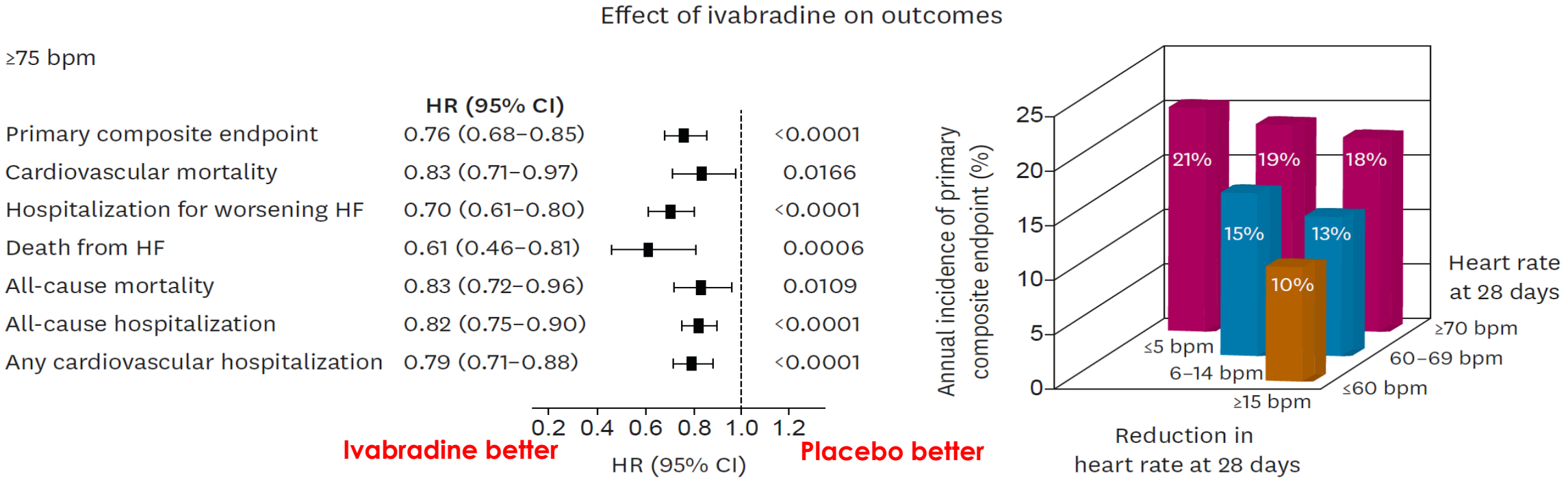


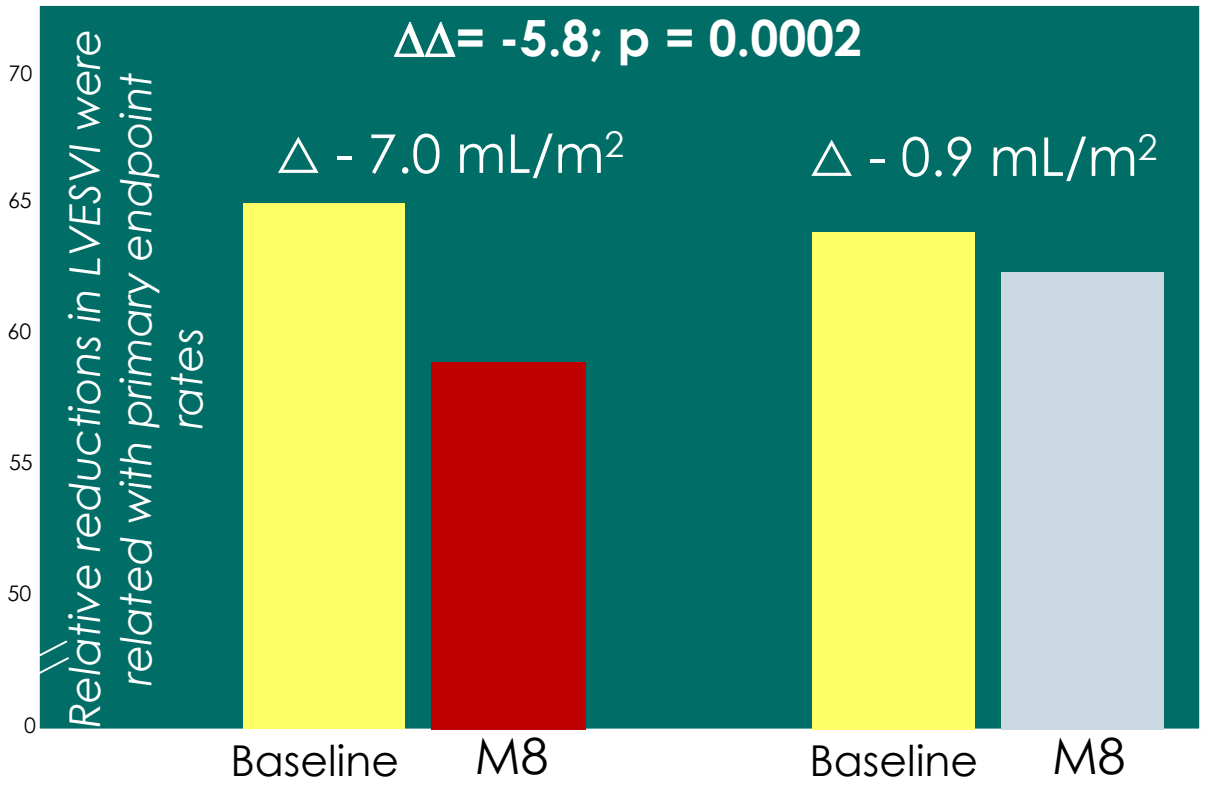
Figure 4. Forest plots (left) demonstrating the hazard ratio (with 95% CIs) for the primary composite endpoint (cardiovascular death or HF hospitalization), cardiovascular mortality, hospitalization for worsening of HF, death from HF, all-cause mortality, all-cause hospitalization and any cardiovascular hospitalization for ivabradine compared to placebo. On the right hand side, the annual incidents of the primary composite endpoint are given according to heart rate achieved after up-titration of ivabradine at 28 days or reduction of heart rate at 28 days. Please note that all endpoints were significantly reduced and this reduction is closely associated with heart rate achieved and heart rate reduction in patients with chronic HF at a heart rate ≥ 75 bpm. Modified according to 24.
CI = confidence interval; HF= heart failure; HR = hazard ratio.

Bohm M et al. Lancet 2010; 376: 886

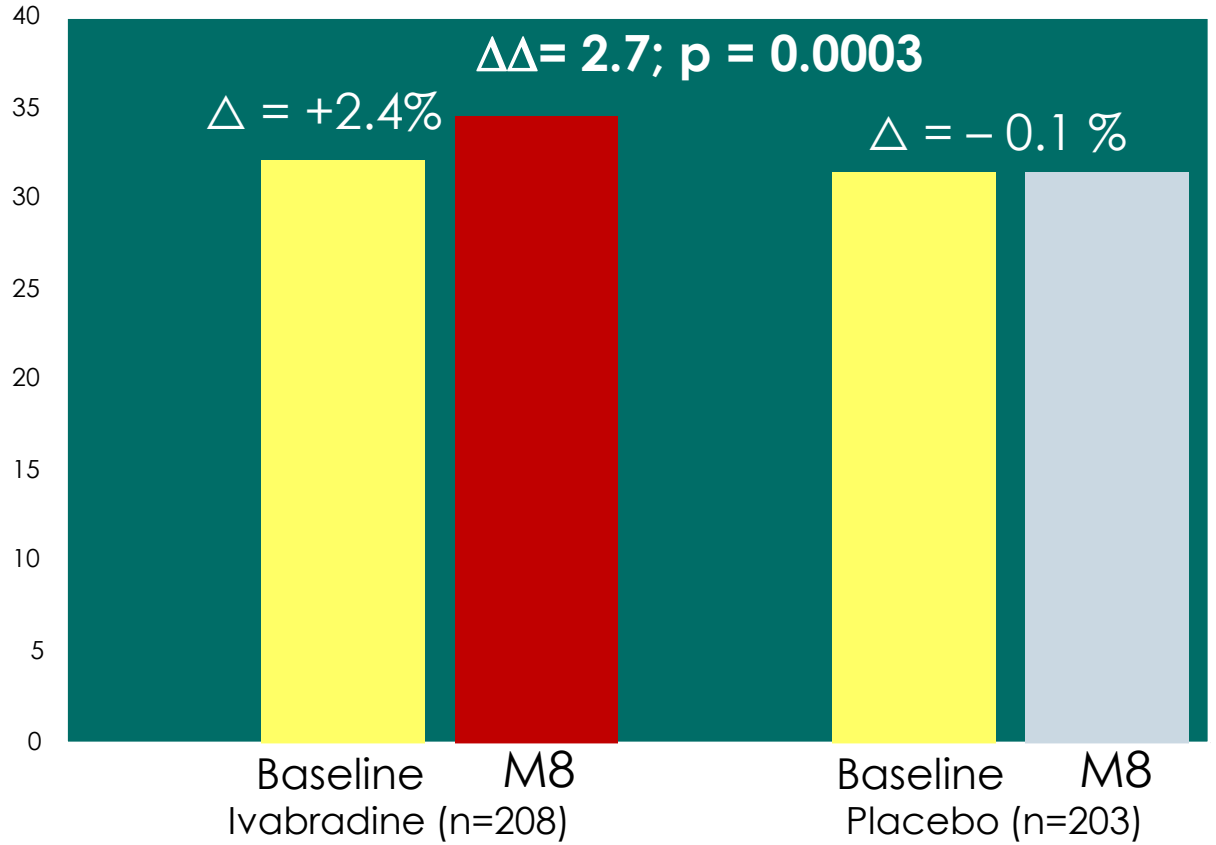
Ivabradine improves outcomes in HFrEF

Mechanism of benefit includes reverse remodeling

LV endsystolic volume index



LV ejection fraction



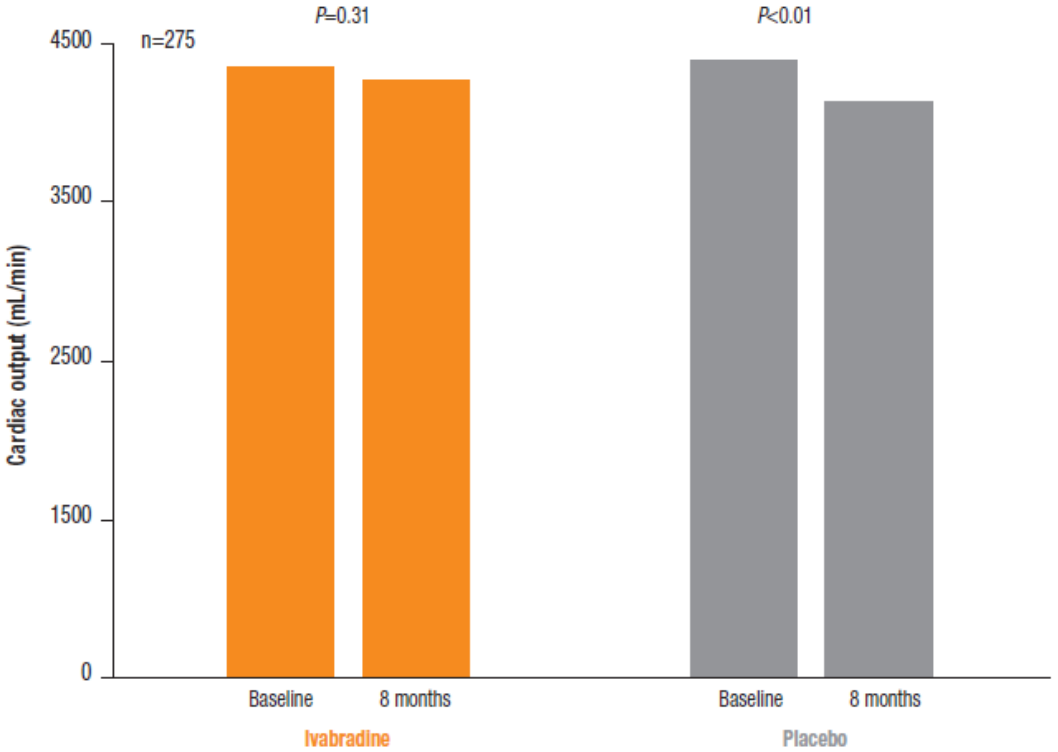
SHIFT: 6505 patients with HF and LVEF≤35%, NYHA II-IV, SR ≥70 bpm, and at least one HF hospitalization in the past 12 months. Patients were randomly assigned to ivabradine titrated to a maximum of 7.5 mg bid or matching placebo. Echo substudy included 613 patients.

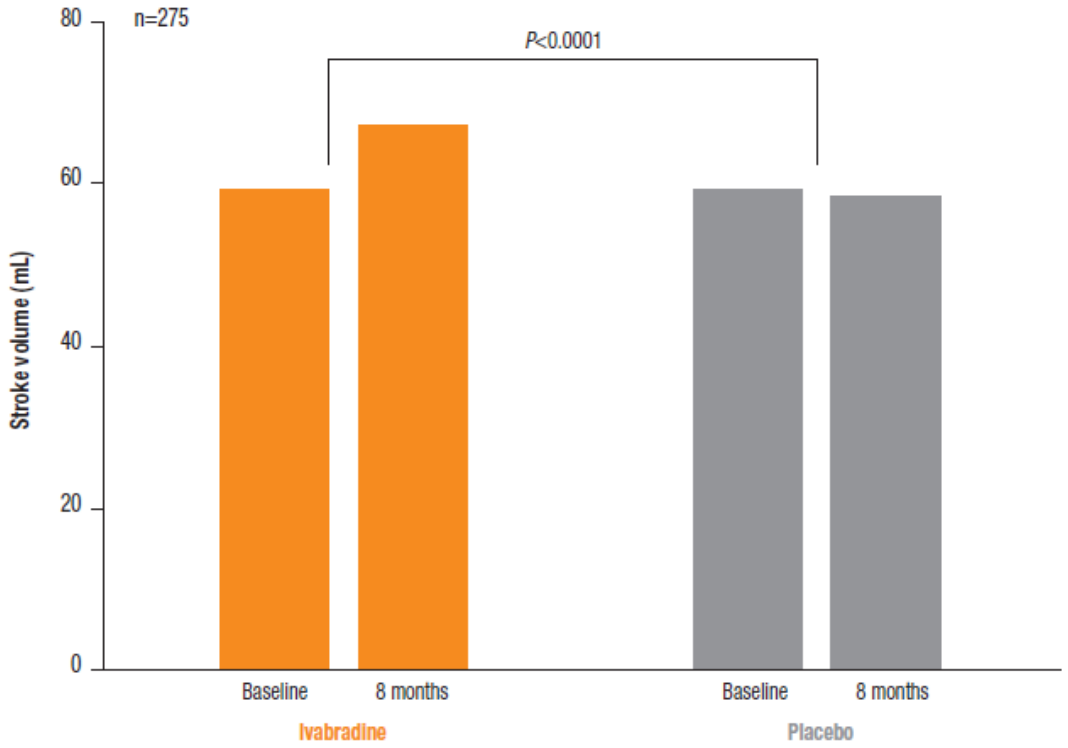
Medical therapy at baseline included 91% ACEi/ARB and 90% BB. Median follow up 23 months. Primary endpoint: CV death or HF hospitalization.

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

Ivabradine and cardiac haemodynamic parameters[1]

Cardiac output is maintained as stroke volume increases [SHIFT study]



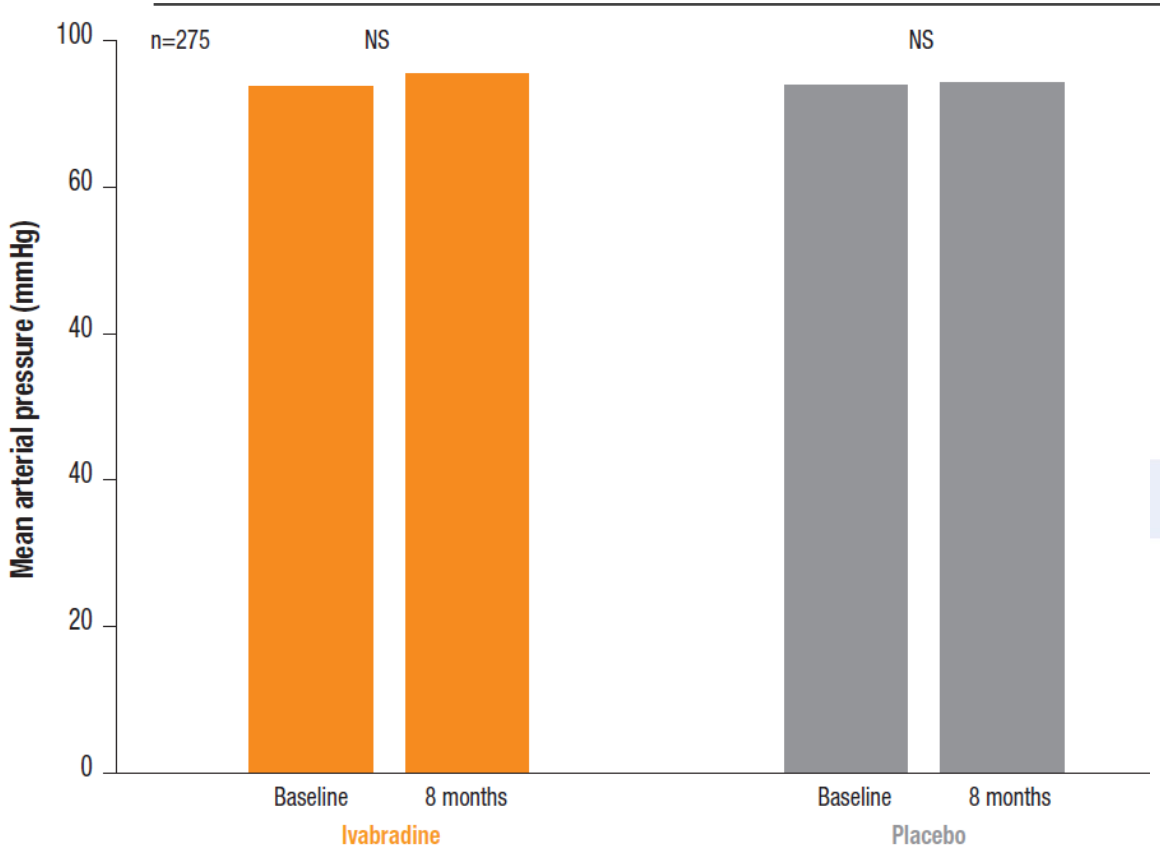


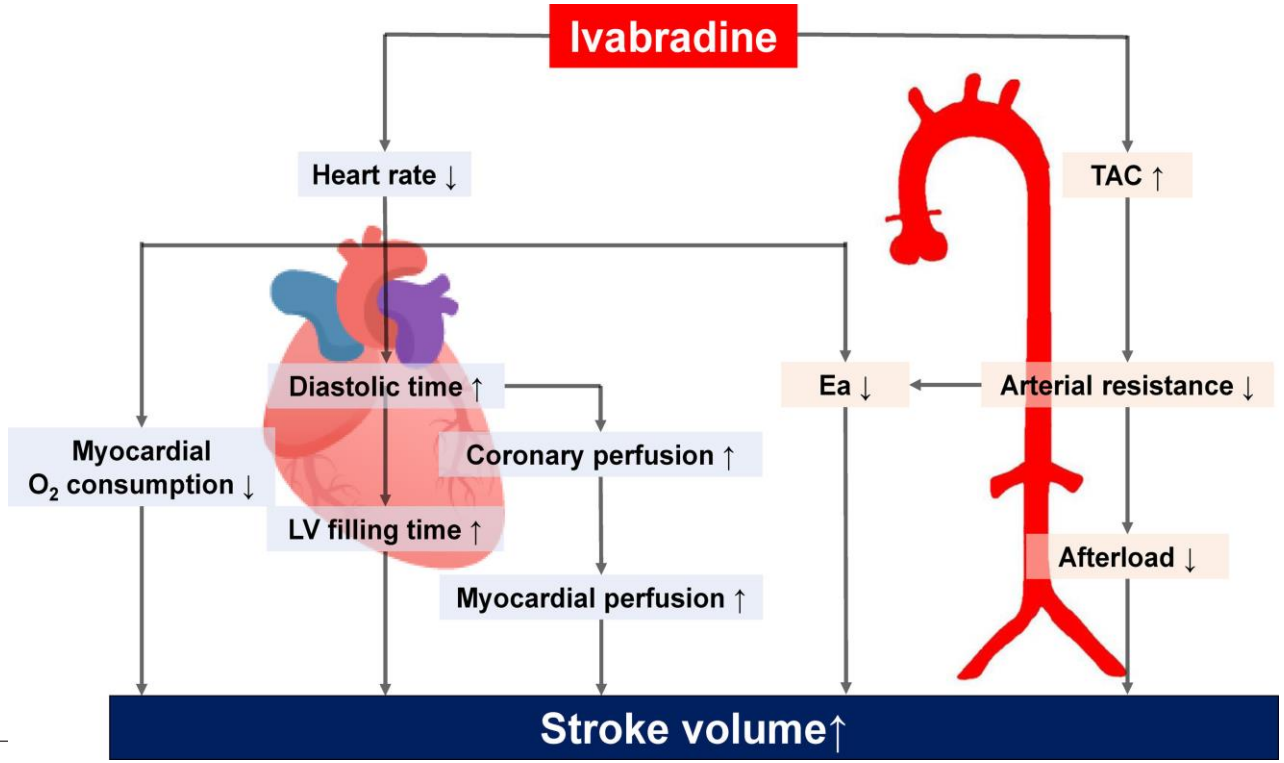
Ivabradine or placebo is given on top of guideline-recommended therapy including ACE inhibitor, β-blocker, mineralocorticoid receptor antagonist

1. Reil JC, Tardif JC, Ford I, et al. Selective heart rate reduction with ivabradine unloads the left ventricle in heart failure patients. *J Am Coll Cardiol*. 2013;62(21):1977-1985

Ivabradine and cardiac haemodynamic parameters[1]

Blood pressure is maintained in heart failure patients [SHIFT study]





Ivabradine or placebo is given on top of guideline-recommended therapy including ACE inhibitor, β-blocker, mineralocorticoid receptor antagonist

1. Reil JC, Tardif JC, Ford I, et al. Selective heart rate reduction with ivabradine unloads the left ventricle in heart failure patients. *J Am Coll Cardiol*. 2013;62(21):1977-1985

Ivabradine and beta-blocker combination therapy

Treatment synergies

	B-Bloq	Ivab
Heart rate	↓	↓
Systolic volume	↓	↑
Cardiac output	↓	↔
Blood pressure	↓	↔

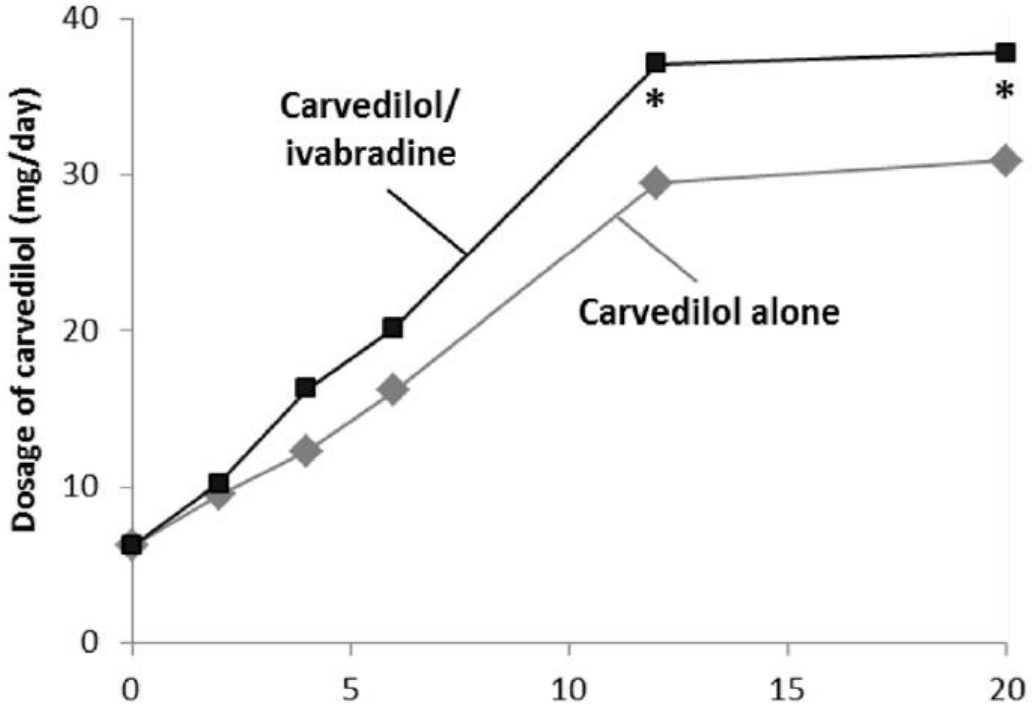
- In the normal heart, increasing the HR (e.g., exercise) has a positive inotropic effect and ↑velocity of both ventricular contraction and relaxation
- In the HF-rEF heart, the opposite occurs, and this explains the intolerance to exercise: impaired Ca entry into myocardial cells and less proteins available to transport Ca back into the sarcoplasmic reticulum
- **Reducing HR in HFrEF is useful because it increases the force of contraction**
- **Ivabradine increases systolic volume**

Luo J et al. J Mol Cell Cardiol 2006;40:64. Janssen PML et al. J Mol Cell Cardiol 2007;43:523. De Ferrari GM et al. Eur J Heart Fail 2008;10:550.

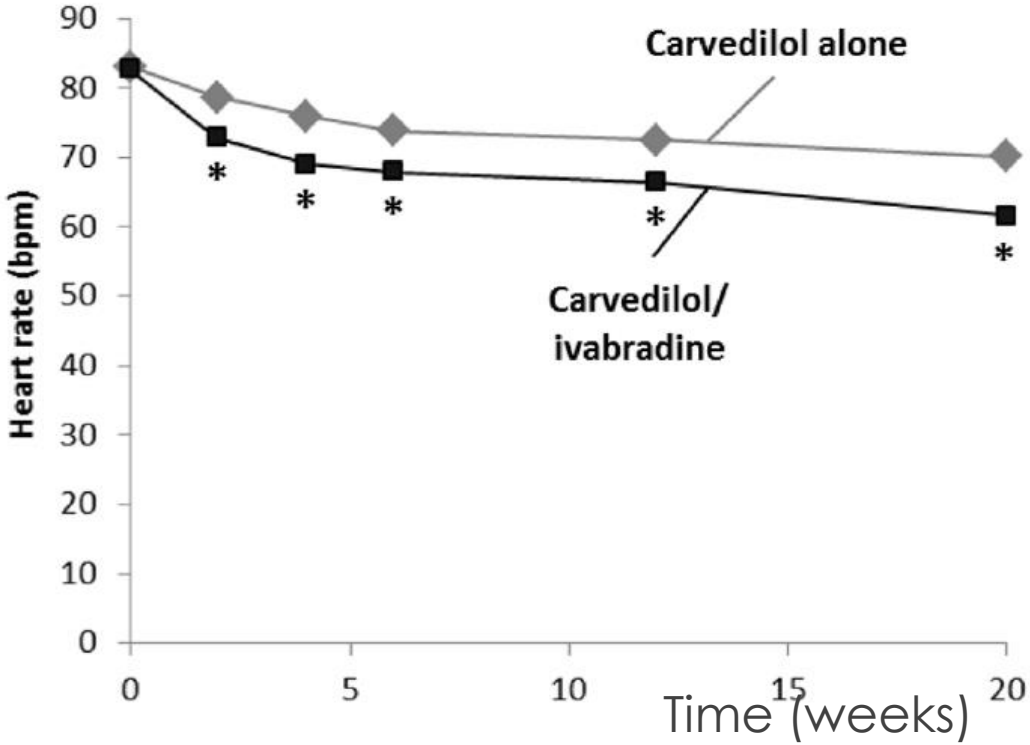
Ivabradine and carvedilol combination therapy

Early benefits

Facilitates carvedilol titration



Improves HR reduction

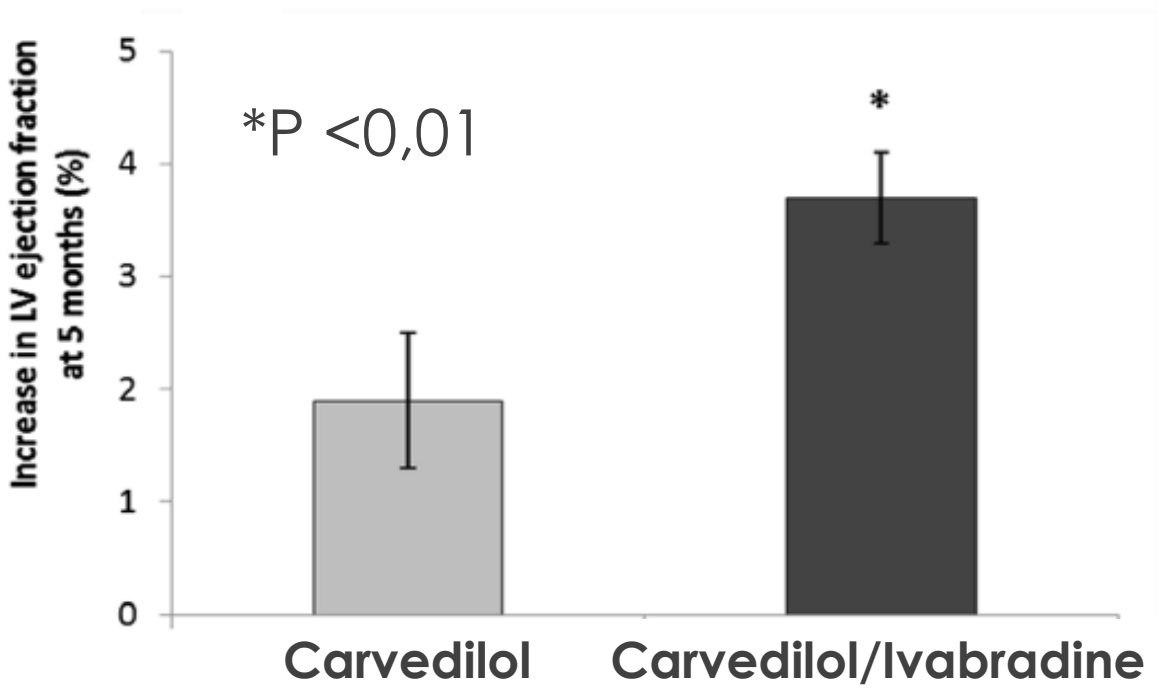


69 Pts with prior MI and HFrEF in NYHA II/III, SR ≥70, not on BB. Carvedilol 3.125 mg bid, dose doubled q2 weeks up to maximal tolerated dose (max 25 mg bid). Ivabradine 5 mg bid started on 2nd /3rd day, increased to 7.5 mg bid at 1 month if HR ≥70.

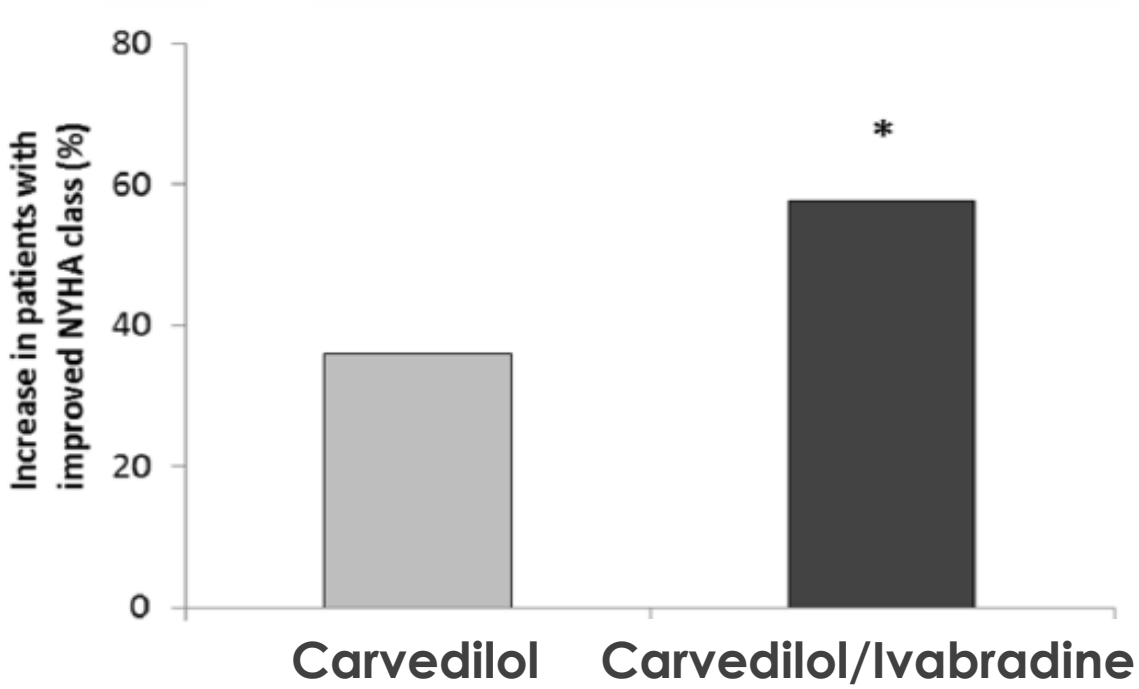
Ivabradine and carvedilol combination therapy

Early benefits

Improves systolic function



Improves functional capacity



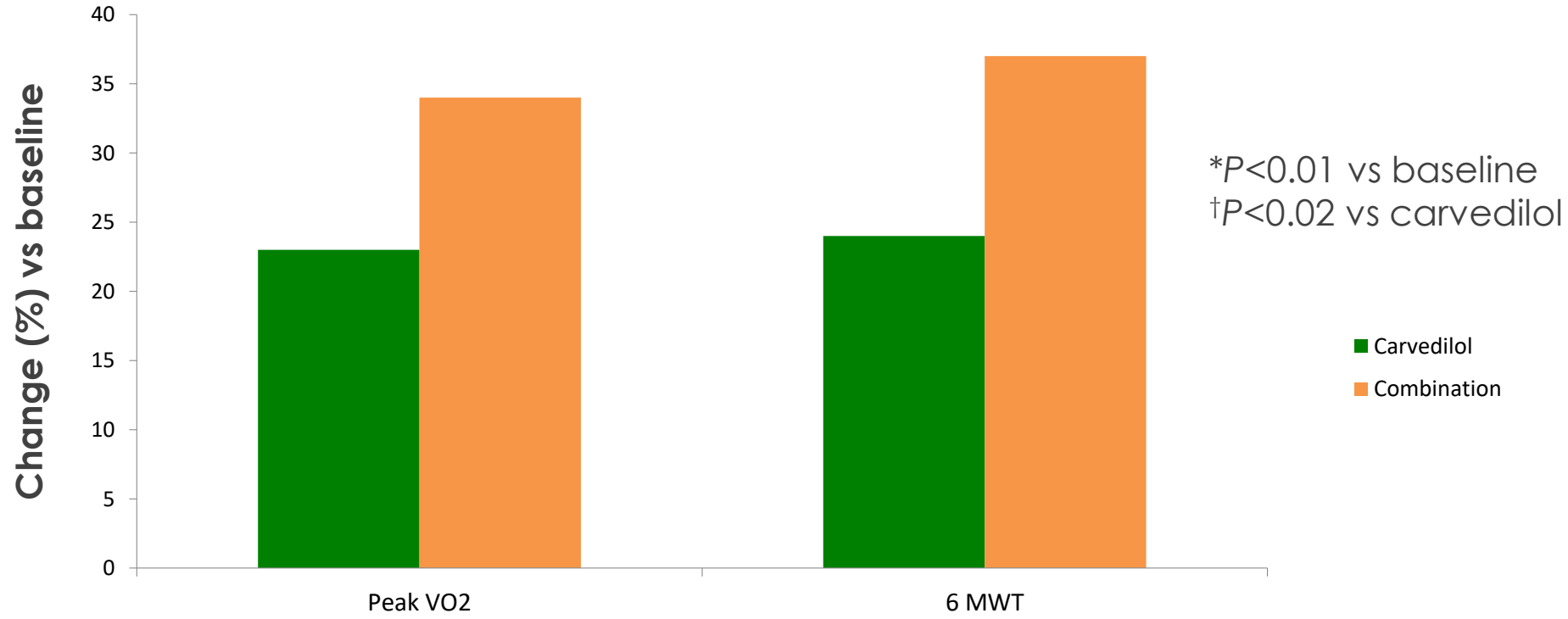
69 Pts with prior MI and HFrEF in NYHA II/III, SR ≥70, not on BB. Carvedilol 3.125 mg bid, dose doubled q2 weeks up to maximal tolerated dose (max 25 mg bid). Ivabradine 5 mg bid started on 2nd /3rd day, increased to 7.5 mg bid at 1 month if HR ≥70.

Bagriy AE et al. Adv Ther 2015;32:108

Ivabradine and carvedilol combination therapy

Early benefits

Improves exercice capacity at 12 weeks

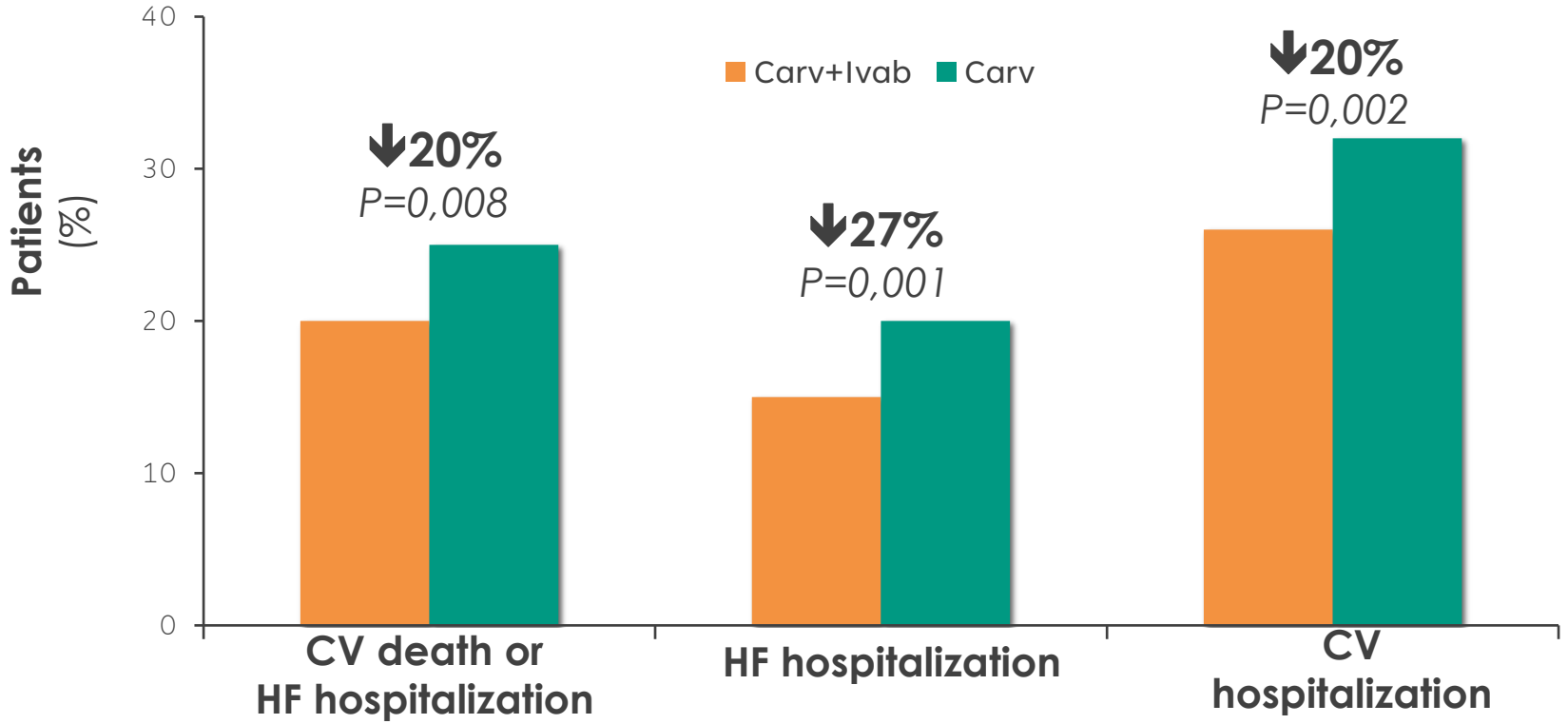


CARVIVA-HF: 121 HFrEF patients in NYHA II or III. ACEi taken in maximum tolerated doses.

Ivabradine and carvedilol combination therapy

Long term benefits

Increased life expectancy and survival free from HF hospitalizations



SHIFT-Carvedilol: 6505 patients with HF and LVEF≤35%, NYHA II-IV, SR ≥70 bpm, and at least one HF hospitalization in the past 12 months. Patients were randomly assigned to ivabradine titrated to a maximum of 7.5 mg bid or matching placebo.

Medical therapy at baseline included 91% ACEi/ARB and 90% BB. Median follow up 23 months. Primary endpoint: CV death or HF hospitalization. 2596 Dts tratados com Carvedilol (45% dos tratados com BB).

Bocchi EA et al. Cardiology 2015;131:218

Meta-Analysis of Observational Studies in Epidemiology

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Heart rate and outcomes in patients with heart failure with preserved ejection fraction

A dose–response meta-analysis

Xiaoke Shang, MD[a], Rong Lu, MD[b], Mei Liu, MD[b], Shuna Xiao, MD[c], Nianguo Dong, MD, PhD[a,*]

positive relationships were significant in patients with SR but not in those with AF. Higher heart rate in SR is a risk factor for adverse outcomes in patients with HFpEF.

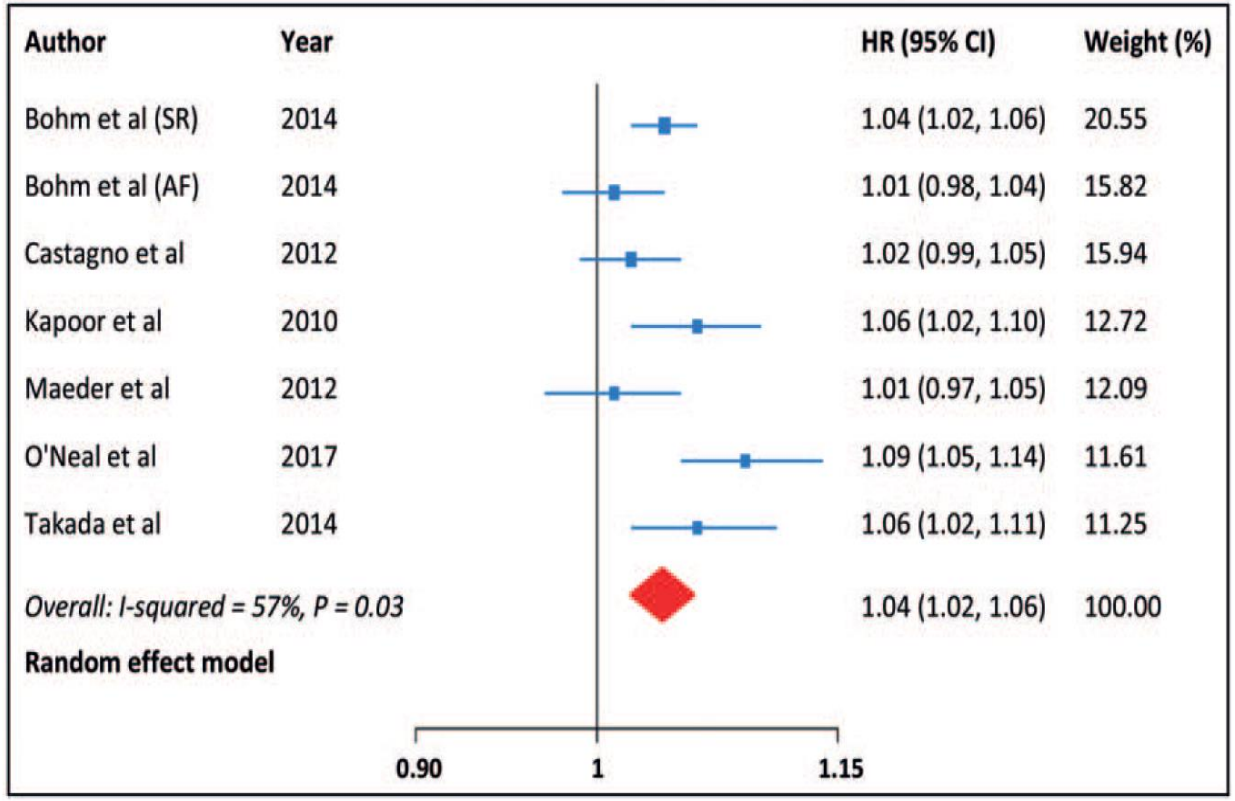

Figure 2. All-cause death for each 10 bpm increase in heart rate.

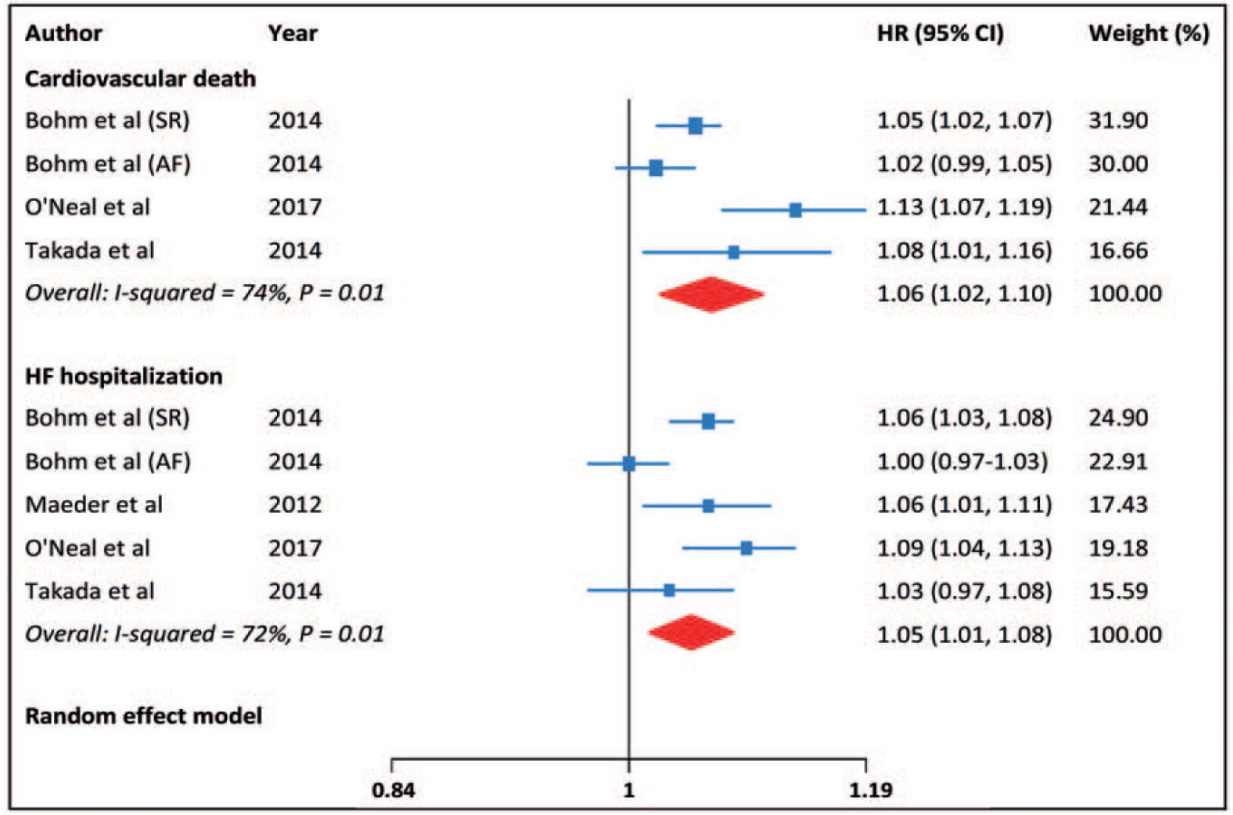

Figure 5. Cardiovascular death and HF hospitalization for each 10 bpm increase in heart rate.

Heart Rate and Outcomes in Hospitalized Patients With Heart Failure With Preserved Ejection Fraction

Phillip H. Lam, MD,[a,b,c] Daniel J. Dooley, MD,[a,b,c] Prakash Deedwania, MD,[a,d] Steven N. Singh, MD,[b,e] Deepak L. Bhatt, MD, MPH,[f,g] Charity J. Morgan, PhD,[h] Javed Butler, MD, MPH, MBA,[i] Selma F. Mohammed, MD, PhD,[c] Wen-Chih Wu, MD,[j,k] Gurusher Panjrath, MD,[l] Michael R. Zile, MD,[m,n] Michel White, MD,[o] Cherinne Arundel, MD,[b,l,p] Thomas E. Love, PhD,[q] Marc R. Blackman, MD,[a,b,l] Richard M. Allman, MD,[r] Wilbert S. Aronow, MD,[s,t] Stefan D. Anker, MD, PhD,[u,v] Gregg C. Fonarow, Ali Ahmed, MD, MPH[a,l,x]

CONCLUSIONS

In hospitalized older patients with **HFpEF**, a **discharge HR <70 beats/min** was independently associated with a **lower risk of all-cause mortality**, but had no association with all-cause or HF readmission. These findings suggest that the beneficial association of a lower HR and improved survival observed in patients with HFrEF might extend to those with HFpEF. Future studies are needed to develop and test interventions that might improve outcomes in patients with HFpEF and elevated HR.

TABLE 2 Outcomes in Propensity Score-Matched Patients

	Events			
	Heart Rate ≥70 Beats/Min (n = 2,031)	Heart Rate <70 Beats/Min (n = 2,031)	Hazard Ratio (95% CI)	p Value
All-cause mortality	70 (1,422)	65 (1,317)	0.86 (0.80-0.93)	<0.001
All-cause readmission	89 (1,810)	90 (1,830)	1.01 (0.95-1.08)	0.681
Heart failure readmission	48 (966)	47 (956)	0.93 (0.85-1.02)	0.111
All-cause readmission or all-cause mortality	97 (1,964)	97 (1,968)	1.01 (0.94-1.07)	0.880
Heart failure readmission or all-cause mortality	84 (1,702)	80 (1,632)	0.90 (0.84-0.96)	0.002

Values are % (n) unless otherwise indicated.
CI = confidence interval.

Vascular Health and Risk Management

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REVIEW

Advances in the management of heart failure: the role of ivabradine

Ivabradine in HF with preserved ejection fraction?

In a small study of 61 patients, ivabradine (5mg bd. for 7days) had a significant beneficial effect on maximal exercise capacity in patients with HFPEF. The study showed an improvement in diastolic function during exercise, including an improvement in LV filling pressures.[2]

2. Kosmala W et al,. *J. Am.Coll. Cardiol.* 62(15), 1330–1338 (2013).

Table 1 Types of heart failure with prognostic relevance of resting heart rate (sinus rhythm) and role of the pacemaker current inhibitor ivabradine

Role of heart rate/ ivabradine	HFrEF chronic stable	HFpEF chronic stable	Acute/ decompensated HF	Post-cardiac transplantation	Peripartum CM	Shock and MODS	ROSC after OHCA
Heart rate is prognostically relevant	Yes	Yes	Yes	?	Yes	Yes	Yes
Ivabradine reduces heart rate	Yes	Yes	Yes	Yes	Yes	Yes	?
Ivabradine improves prognosis	Yes	?	?	?	?	?	?
Ivabradine approved for use in EU/USA	Yes	No	No	No	No	No	No
Combination of ivabradine + beta-blocker feasible	Yes	Yes	Yes	?	Yes	?	?

Note: For patients with HFmrEF, no prospective trials with ivabradine are yet available.

Abbreviations: CM, cardiomyopathy; EU, European Union; HF, heart failure; HFmrEF, heart failure with mild-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MODS, multiple organ dysfunction syndrome; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation.

When to use ivabradine[1]

Ivabradine is indicated in chronic heart failure with systolic dysfunction in patients with:

- √ NYHA II to IV class
- √ sinus rhythm
- √ HR ≥ 75 bpm

- in combination with standard therapy including β-blocker therapy
- or when β-blocker therapy is contraindicated or not tolerated.

1. Procoralan (European Medicines Agency) Summary of Product Characteristics.

Clinical assessment before discharge: the key to avoid readmissions

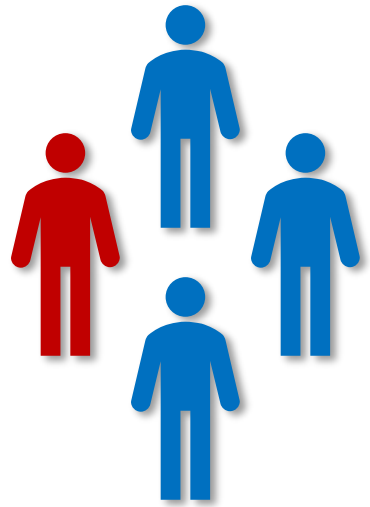
Optimization before discharge is the key action in HF care

Acute HF In-hospital → **Chronic HF Outpatient**

"Vulnerable phase"

Acute phase treatment	Transition treatment	Long term treatment
Intravenous therapy	Intravenous therapy Initiate/up-titration oral GDMT	Optimized oral GDMT

The risk is particularly high within 30 days after hospitalization. Early post-discharge assessment is key: further adjustments to therapy will be required.



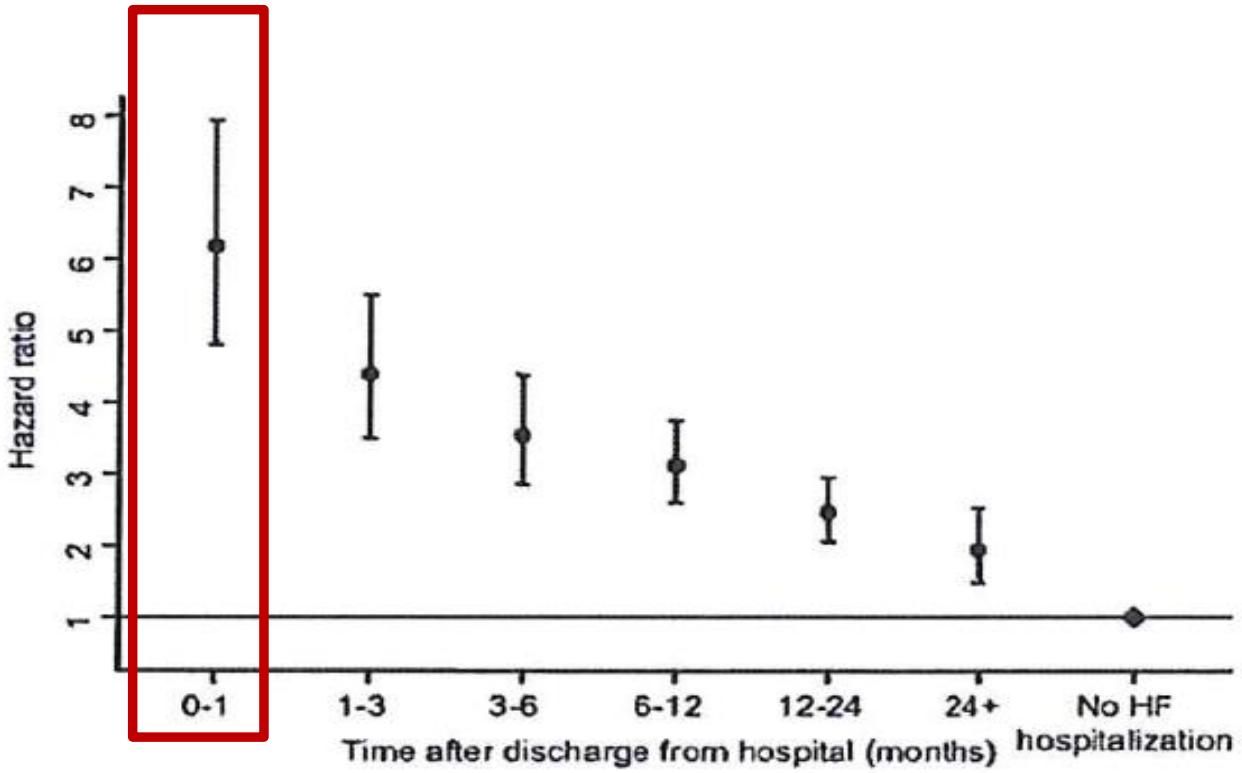
Nearly **1 out of 4** patients are readmitted for HF **within 30 days** following discharge.

Source: Global heart failure awareness program
O'Connor CM et al. Am Heart J. 2010 May;159:841-849

PATIENT'S JOURNEY

Mortality is particularly high in the early phase after hospitalization

All-cause mortality after discharge for HF is high during the 1st month[1]



1. Mørti NC et al. Timing and duration of interventions in clinical trials for patients with hospitalized heart failure. *Circ Heart Fail.* 2013;6:1095-1101. - Changes in risk profile after hospitalization. Hazard ratio of all-cause mortality after discharge from hospital for first hospitalization.

Clinical variables essential for the long-term patient outcomes

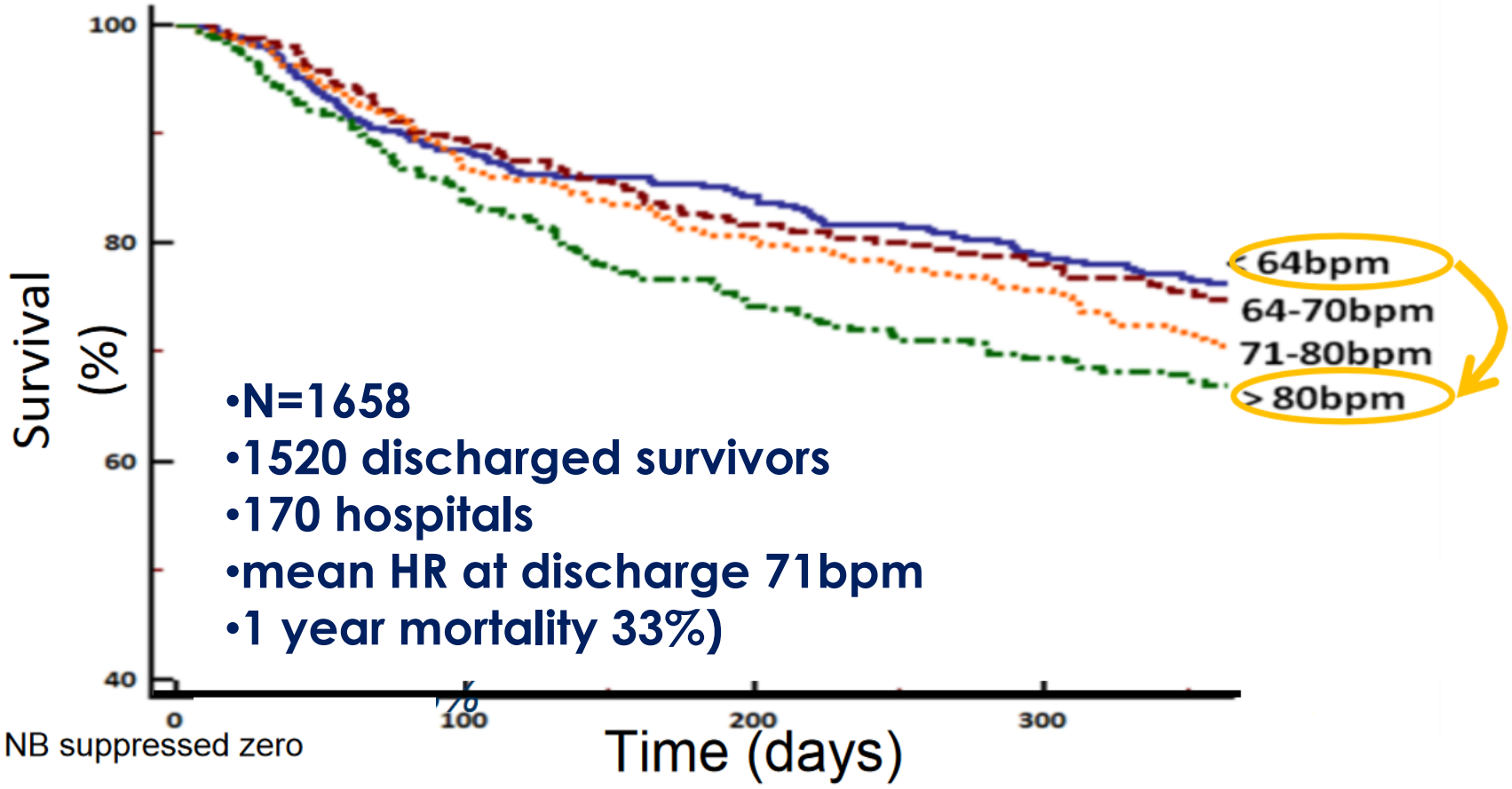
	Prevention of fluid overload	Symptomatic improvement	Prognostic improvement
Clinical			
Signs of congestion	**+++**	**+**	**++**
blood pressure	+	?	+
Heart rate	**?**	**+**	**+**
ECG			
QRS duration (for CRT)	+	++	+++
AF / tachyarrhythmias	+ ?	+	++
Laboratory examinations			
myocardial viability	+	+	++ (?)
natriuretic peptides	++	+	+
renal function / electrolytes	+	+ / 0	+ / ++ (?)
anaemia / iron deficiency	?	++	+

www.escardio.org/guidelines

EUROPEAN SOCIETY OF CARDIOLOGY®

Metra M et al. Circulation 2010;122:1782-5

Heart rate at discharge: reliable predictor of one-year mortality



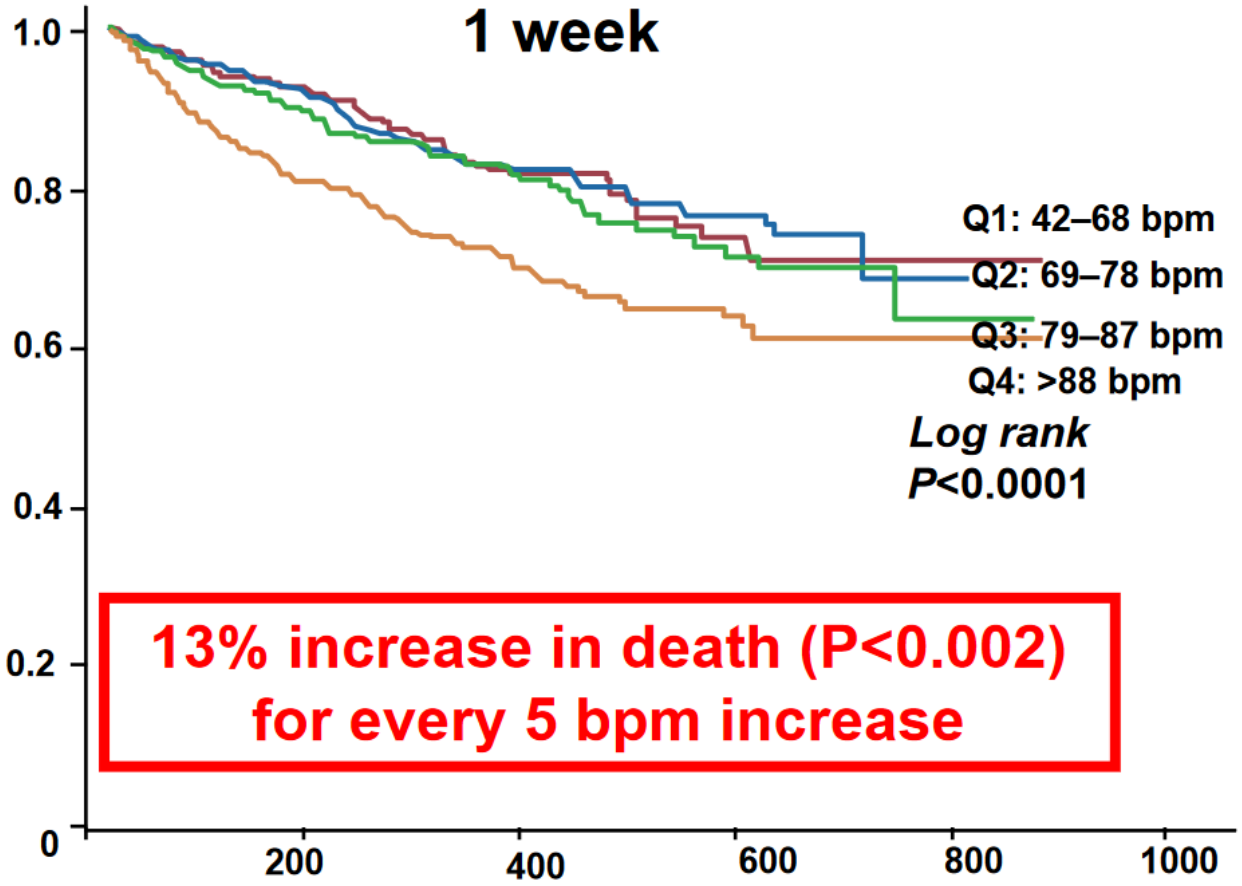
- N=1658
- 1520 discharged survivors
- 170 hospitals
- mean HR at discharge 71bpm
- 1 year mortality 33%)

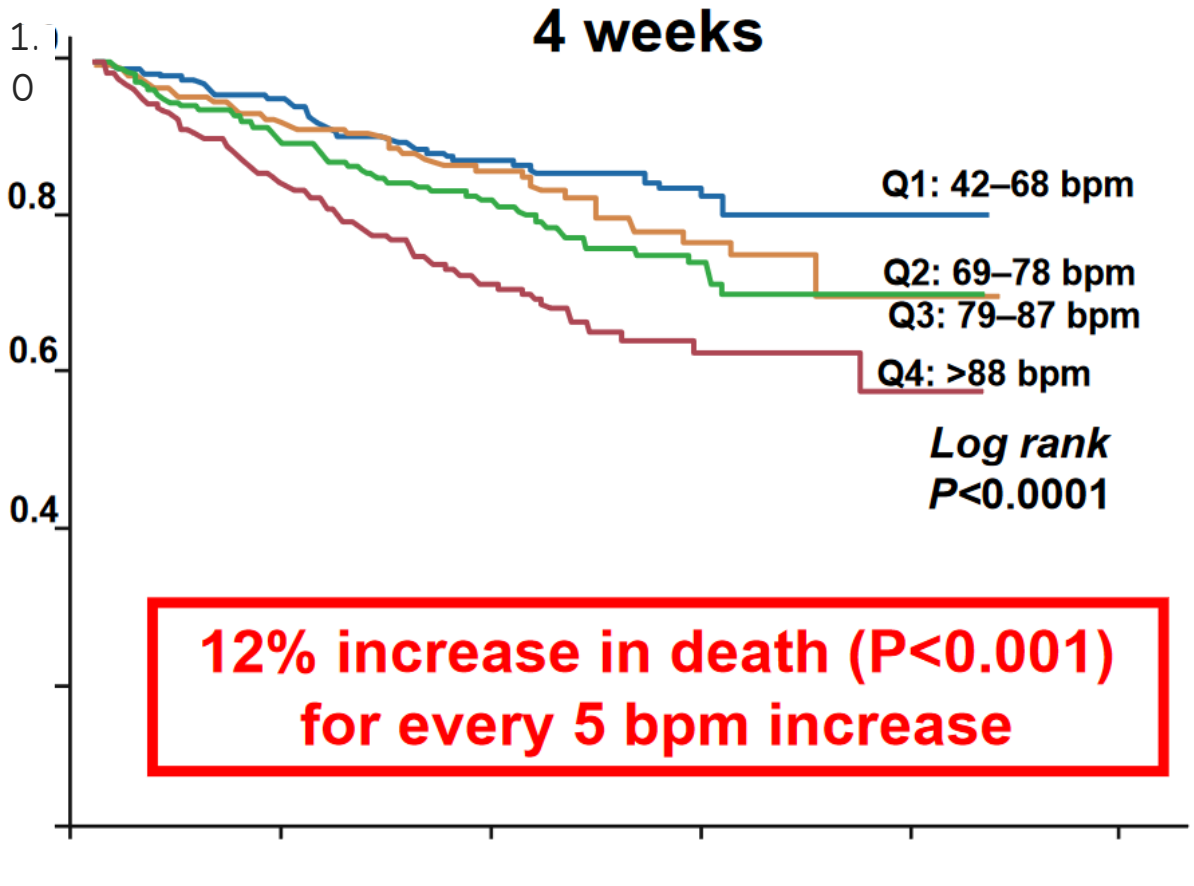
41% increaase in one year mortality (p=0.01)

Logeart D et al. EHJ 2012;33:485 (Abst Suppl)

One and four week post discharge heart rate vs. mortality

EVEREST Trial (n=1947 HF pts)





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

Pre-discharge and early post-discharge care

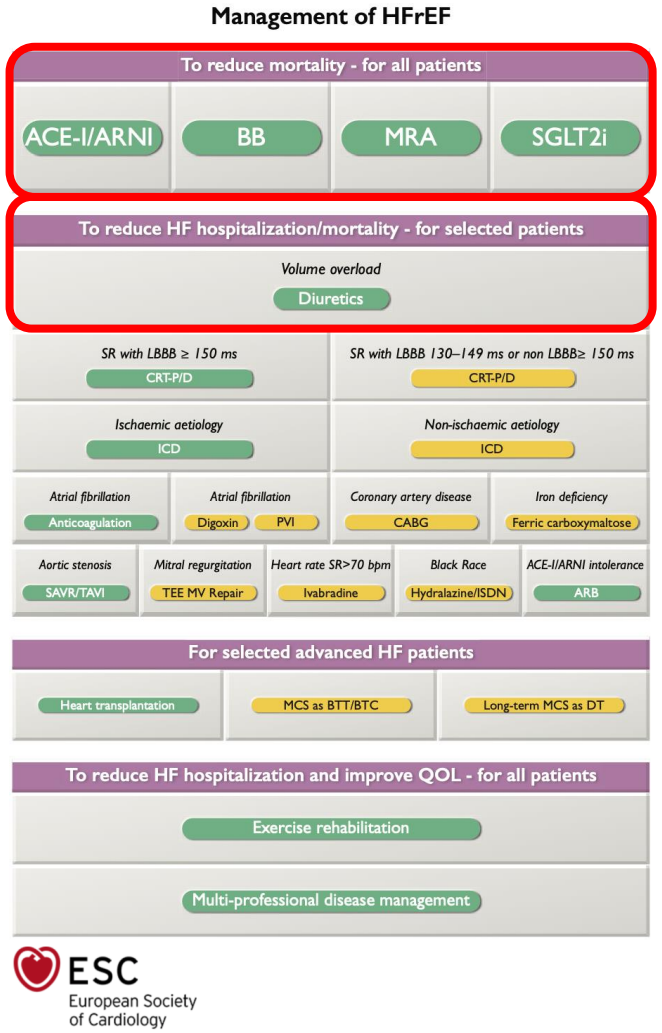
! *No time to waste* !

ESC European Society of Cardiology

Recommendations[1]	Class	Level
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 NEW!
It is recommended that **evidence based oral medical treatment be administered before discharge**	I	C NEW!
An **early follow-up visit** is recommended at 1-2 weeks after discharge to assess signs of congestion, drugs' tolerance and start and/or uptitrate evidence-based therapy	I	C NEW!
Ferric carboxymaltose should be considered in symptomatic HF patients recently hospitalized for HF and with LVEF <50% and iron deficiency, defined as serum ferritin <100 ng/mL or serum ferritin 100-299 ng/mL with TSAT <20%, to improve symptoms and reduce the risk of HF hospitalization[2]	IIa	B NEW!

1. McDonagh TA et al. Eur Heart J 2021;42:3599. 2. Ponikowski P et al. Lancet 2020;396:1895-904.

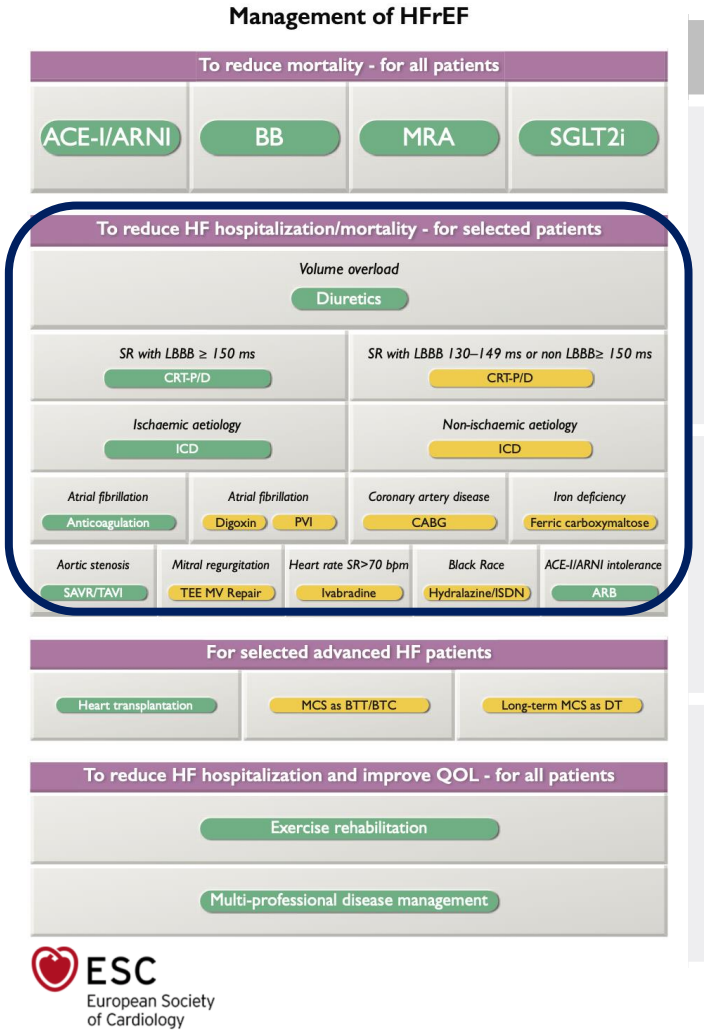
Guidelines for the management of HF with reduced EF



Drugs recommended in all patients with HFrEF	Class	Level
ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death	I	A
Beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death	I	A
MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death	I	A
Dapagliflozin or **empagliflozin** are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death	I	A NEW!
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death	I	B

Initiation of sacubitril/valsartan in ACE-I naïve (i.e. de novo) patients with HFrEF may be considered (IIb-B) NEW!

Guidelines for the management of HF with reduced EF



Drugs recommended in selected patients with HFrEF[1]	Class	Level
Ivabradine should be considered in symptomatic patients with LVEF ≤35%, in SR and a resting HR ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I/ARNi and an MRA, to reduce the risk of HF hospitalization and CV death	IIa	B
Ivabradine should be considered in symptomatic patients with LVEF ≤35%, in SR and a resting HR ≥70 bpm who are unable to tolerate or have contraindications for a beta-blocker to reduce the risk of HF hospitalization and CV death	IIa	C
Vericiguat may be considered in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I/ARNi, a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization[2]	IIb	B

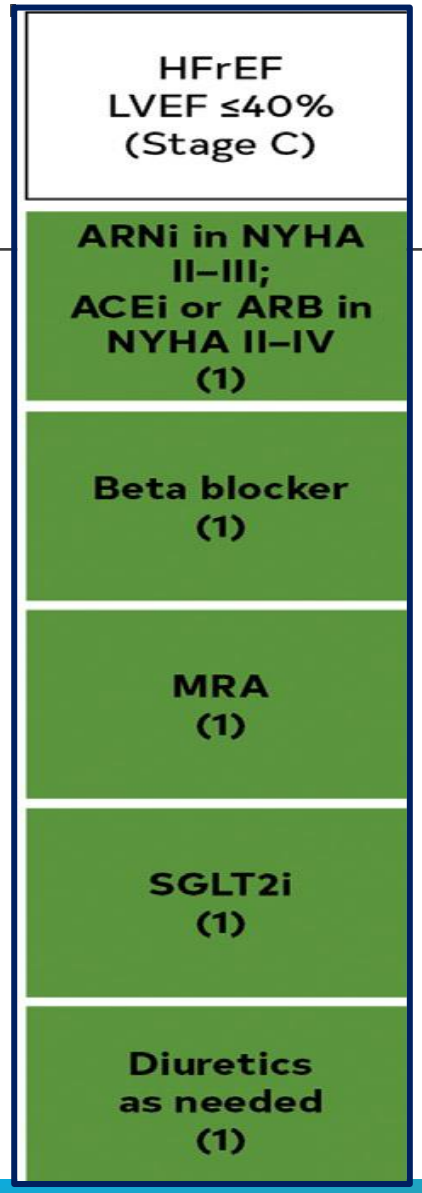
Currently, omecamtiv mecarbil is not licensed for use in HF. However, in the future it may be able to be considered, in addition to standard therapy for HFrEF to reduce the risk of CV mortality and HF hospitalization[3]

1. McDonagh TA et al. Eur Heart J 2021;42:3599-726. 2. Armstrong P et al. N Engl J Med 2020;382:1883-93. 3. Teerlink J et al. N Engl J Med 2021;384:105-16.

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

Developed in partnership with the Heart Failure Society of America

GDMT for HFrEF



Consider Additional Therapies Once GDMT Optimized

NYHA II–III; HFrEF; NSR; heart rate ≥70 bpm; on maximally tolerated beta blocker	**Ivabradine (2a)**
NYHA II–IV; LVEF <45%; recent HFH; or IV diuretics; elevated NP levels	**Vericiguat (2b)**
Symptomatic HFrEF	**Digoxin (2b)**
HF NYHA II–IV	**PUFA (2b)**
Patients with HF with hyperkalemia while taking RAASi	**Potassium binders (2b)**

AMERICAN COLLEGE of CARDIOLOGY FOUNDATION

HFSA HEART FAILURE SOCIETY OF AMERICA

American Heart Association.

Ivabradine

COR	LOE	Recommendation
2a	B-R	1. For patients with symptomatic (NYHA class II to III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDMT, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of ≥70 bpm at rest, ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death.[1,2]

in those advanced HF patients in whom tachycardia persists and where the use of BBs is limited due to hypotension

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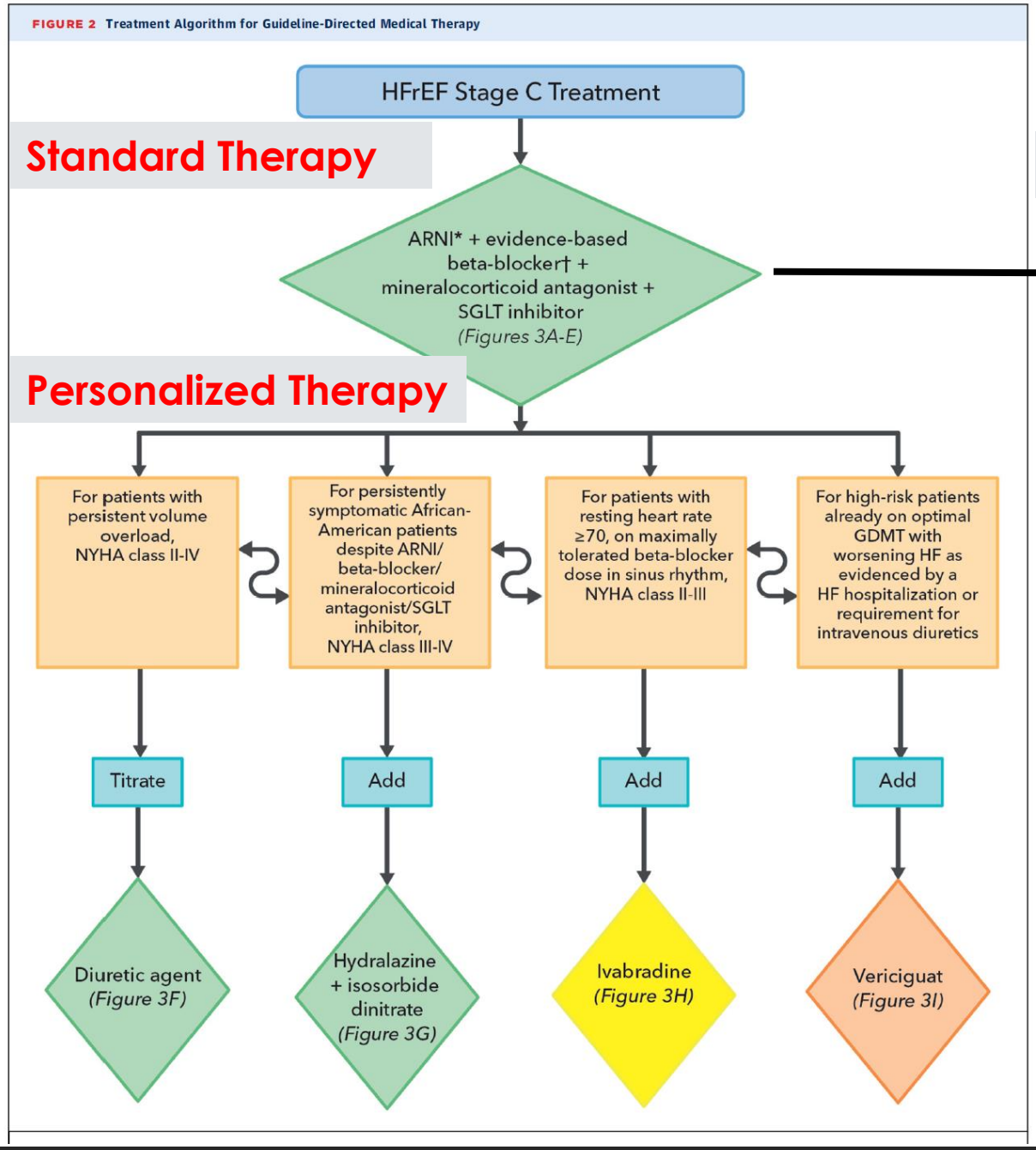
EXPERT CONSENSUS DECISION PATHWAY

2024 ACC Expert Consensus Decision Pathway for Treatment of Heart Failure With Reduced Ejection Fraction

A Report of the American College of Cardiology Solution Set Oversight Committee



Personalized Therapy

Selected patients → ICD/CRT

- Symptom despite standard therapy → Titrate → digoxin
- Iron deficiency → Add → Iv iron
- K+ 5.5mmol/l with RAASi → Add → Patiromer K+ binders
- Suitable coronary anatomy → Add → Surgical revascularization

Reasonable to use omega3 fatty acid to reduce mortality and hospitalization

“The heart rate goal”

- reduction of HR to < 60/min or at least for a reduction of 10 bpm in patients with HFrEF and sinus rhythm of ≥ 75 bpm, either by **betablocker alone** or by the **combination of betablocker plus ivabradine**.
- **the lower HR limit is either 50 bpm or symptomatic bradycardia.**
- As many HFrEF patients under beta-blocker have a HR ≥ 75 bpm there is a need for a combination therapy of betablocker plus ivabradine in these patients

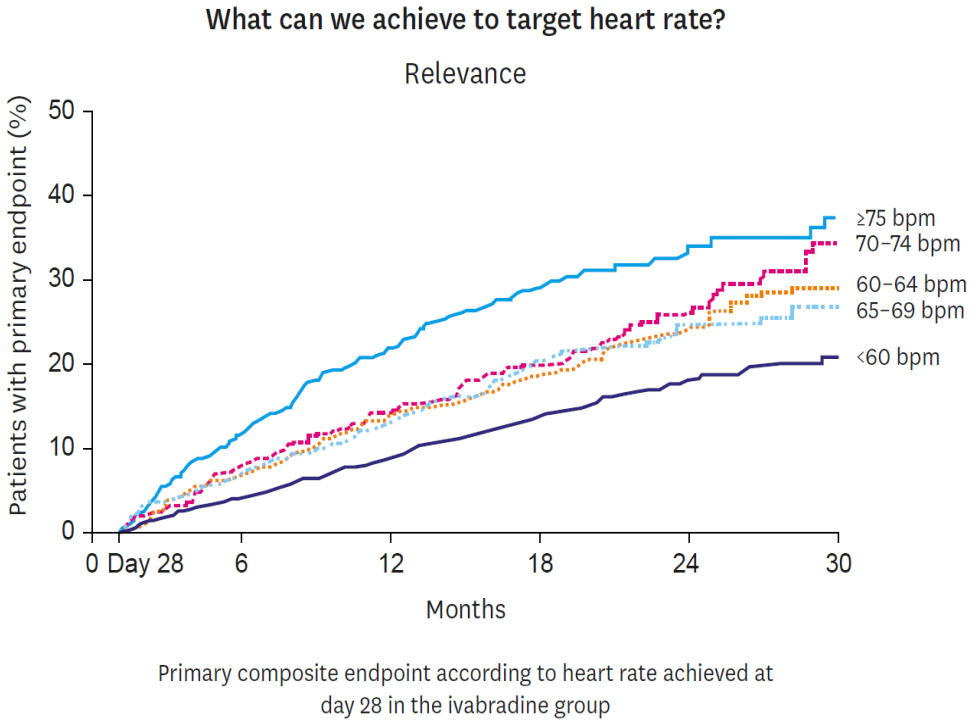


Figure 7. Kaplan Meier cumulative event curves for the primary composite endpoint (cardiovascular death or heart failure hospitalization) according to patient groups defined by quintiles of heart rate achieved at 28 days on treatment with ivabradine. Log rank p-values show the difference between the groups. Modified according to 7.

Conclusions

- **Adherence to clinical practice guidelines is the principal solutions to improve the prognosis of patients with HFrEF.**

- **Two barriers:**
  Adherence of the physicians to guideline
  Adherence of the patient to the prescribed medication

- **High heart rate**, both at the time of diagnosis and during follow-up, is **strongly associated with increased risk of adverse outcomes in HFrEF** patients, **independent of the use of beta-blockers**

- Since the risk is particularly high within 30 days after hospitalization, **ivabradine Pure HR reducing agent** should be initiated before discharge to improve patient outcomes and health care cost.

23rd November 2024

Thank You