CORRIDOR CONSULTS
at Heart Failure Update 2021

Synergistic Role of Beta-Blockers and Ivabradine

SERVIER

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  - **Research**: Novartis, AstraZeneca and Pfizer
  - **Presentation and Advisory Boards:**
    BI, AstraZeneca, Pfizer, Servier, Novartis

HEART FAILURE

2021 UPDATE

The Canadian Cardiovascular Society

IS IT HEART FAILURE AND WHAT SHOULD I DO?

Canadian Cardiovascular Society
Leadership. Knowledge. Community.

HEART FAILURE

CCS HF2021

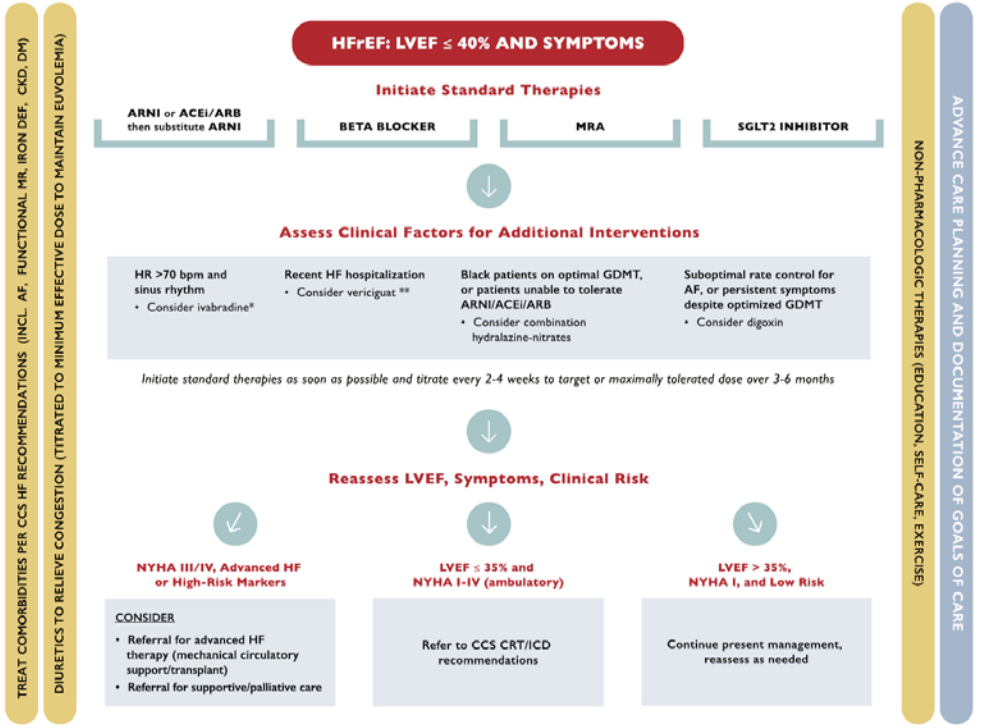


Figure 1. Simplified treatment algorithm for management of heart failure (HF) with reduced ejection fraction (HFrEF). Standard therapies are applicable to most patients with HFrEF for reducing cardiovascular mortality and hospitalization for HF. Additional, pharmacologic therapies should be individualized on the basis of clinical factors as outlined in the text. Every attempt should be made to initiate and titrate therapies with the goal of medication optimization by 3-6 months after a diagnosis of HFrEF. Throughout the patient journey, nonpharmacologic therapies should be prescribed, along with judicious use of diuretics to maintain euvolemia. Evidence also supports interventions to treat important comorbidities including iron deficiency, atrial fibrillation (AF), and functional mitral regurgitation (MR) in selected patients. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CCS, Canadian Cardiovascular Society; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; GDMT, guideline-directed medical therapy; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SGLT, sodium glucose transport. * Health Canada has approved ivabradine for patients with HFrEF and heart rate (HR) ≥ 77 bpm in sinus rhythm. ** Vericiguat is not yet approved for use in Canada.

Challenges in Up-titration of HF Therapies

Additional delays:

- Patients are on other medications, possibly temporarily, that prohibit up-titration
- Lack of resources to manage the up-titration
- Burden of visits for frequent up-titration; clinics are overcrowded
- HF nurses are often key to managing clinic needs, but a team approach is needed

Possible solutions:

- HF clinics to supervise
- Tools for up-titration and monitoring
- Slow pace & goals of up-titration
- Primary care support strategies
- Take maximum advantage of the hospital phase to initiate and titrate therapies
- Remote up-titration and monitoring

HFrEF, heart failure with reduced ejection fraction

Atherton JJ et al. *Card Fail Rev* 2017; 3(1):25-32.

Guidelines

- We recommend that ivabradine be used for patients with HFrEF and symptoms ***despite treatment with GDMT***, a resting ***heart rate ≥ 70 bpm***, and sinus rhythm for the prevention of CV death and HF hospitalization (Strong Recommendation; High Quality Evidence).

Values and preferences. High value is placed on reducing the risk of CV death and HHF when ivabradine is used as adjunctive therapy with standard HF medication treatments in a selected HFrEF population.

Differing criteria for heart rate eligibility have been approved by various regulatory authorities ranging from ***70-77 bpm***, although the trial entry criteria was 70 bpm.

Table 1. Quality of available evidence to support the use of each HFrEF therapy according to clinical setting

	Quality of evidence supporting recommendation		
HFrEF drug therapy	Chronic ambulatory HF	New-onset HF	HF hospitalization*
Sacubitril-valsartan	High	Low	Moderate
ACEI/ARB	High	High	High†
β-blockers	High	High	High
MRAs	High	High	High†
SGLT2 inhibitors	High	N/A	N/A‡
Ivabradine	High	N/A	N/A
Vericiguat	Moderate	N/A	NA
Digoxin	Moderate	Low	Low
H-ISDN	Moderate	Low	Low

There are now 6 medications and 2 devices that reduce all cause mortality in patients with HFrEF

Therapy	NNT Mortality 1 year	NNT Mortality 5 years
Medications		
ACEi/ARB	92	18
Beta blocker	40	8
MRA	75	15
SNI- Ivabradine	45	9
ARNi	80	14
SGLT2i	67	16
Devices		
ICD	70	14
CRT pacing	70	14

Fonarow, JAMA Cardiol, 2018; 3(12);1226-31.
Swedberg Lancet 2009

Ivabradine

Recommendation 15. We recommend that ivabradine be used for patients with HFrEF and symptoms despite treatment with GDMT, a resting heart rate ≥70 bpm, and sinus rhythm for the prevention of CV death and HF Hospitalization (Strong Recommendation; High-Quality Evidence).

Values and preferences. High value is placed on reducing the risk of CV death and HHF when ivabradine is used as adjunctive therapy with standard HF medication treatments in a selected HFrEF population. Differing criteria for heart rate eligibility have been approved by various regulatory authorities ranging from 70-77 bpm, although the trial entry criteria was 70 bpm.

Practical tip. Ivabradine has no direct effect on BP, myocardial contractility, or renal function and as such is well tolerated in patients who are unable to initiate or titrate b-blockers for these reasons.

Practical tip. Ivabradine may be considered for patients with either stable or decompensated chronic HFrEF who are intolerant of b-blockers, with a resting heart rate in sinus rhythm of >70 bpm.

Practical tip. Typical reductions in resting sinus heart rate after treatment with b-blockers range from 10-15 bpm, with little change (< 5 bpm) between low and high doses. This consideration might assist in the decision to use further medications for sinus heart rate control.

Practical tip. Ivabradine is well tolerated in older adults and can be initiated at 2.5 mg twice daily.

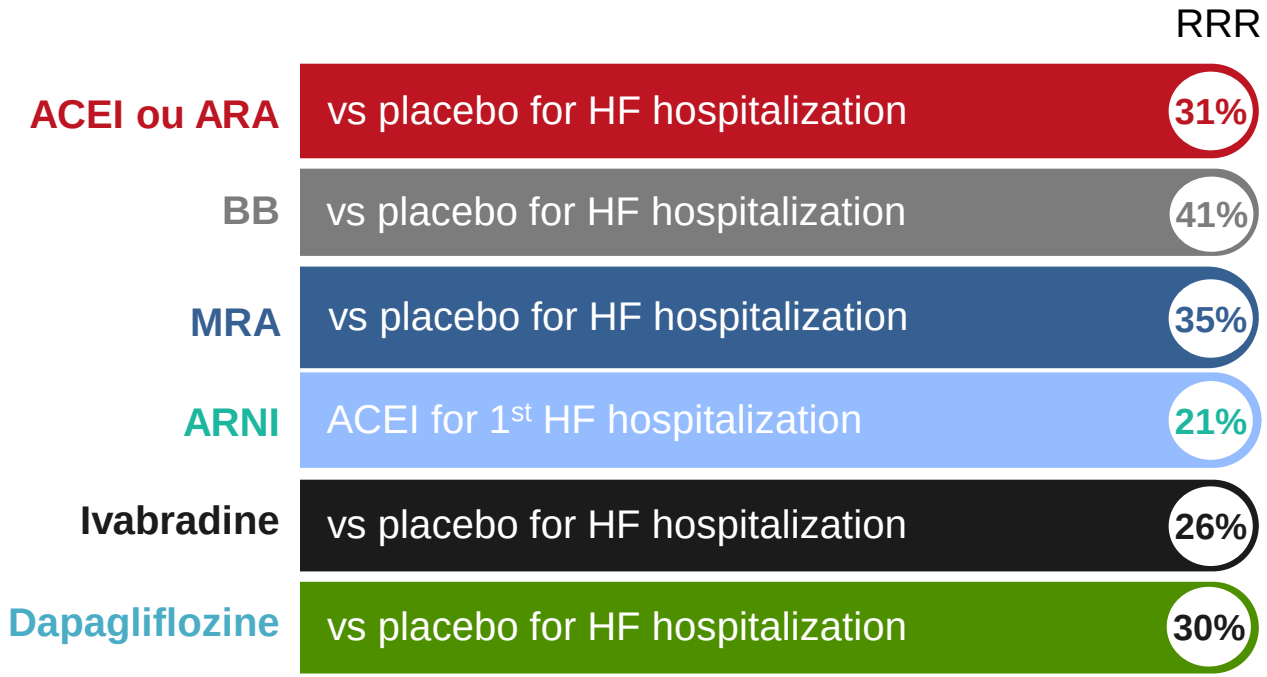
Practical tip. Ivabradine should be avoided in patients with advanced liver disease.

Carvedilol Produces Dose-Related Improvements in Left Ventricular Function and Survival in Subjects With Chronic Heart Failure MOCHA study

Table 3. Maintenance Doses Achieved, ECG Ventricular Rates, and Blood Pressures During and at End of Maintenance Therapy (±SD)

		Carvedilol		
	Placebo	6.25 mg BID	12.5 mg BID	25 mg BID
Maintenance dose, mg/d (n)	... (81)	6.25±0 (82)	12.3±1.1 (86)	23.7±4.0 (84)
Heart rate, bpm				
Baseline	83±16	86±15	80±13	84±17
2 mo	81±13	73±16	68±14	67±12
4 mo	80±14	71±15	66±12	67±14
6 mo	80±12	70±21	68±12	67±13

HF Medication and Impact on Hospitalization



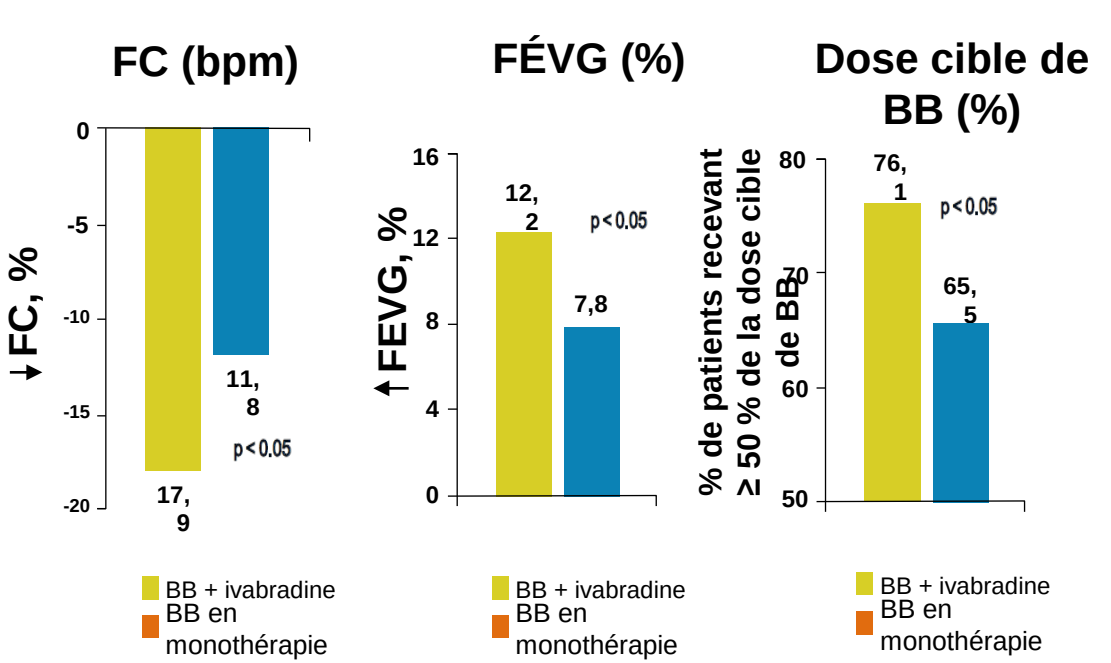
Synergistic Effect of Early Treatment of Ivabradine with BBs vs. BB Alone

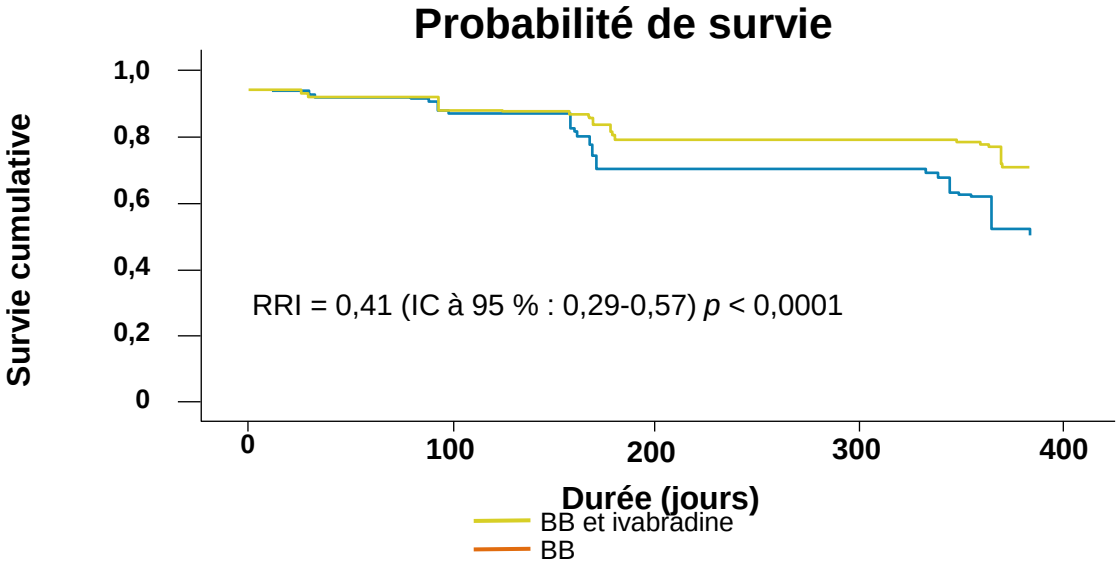
	Type of study	No. patients			FU (months)	Outcomes (IVA+BB vs BB alone)		
		Total	IVA + BB	BB alone		Heart rate	LVEF	Hospitalization and/or mortality
Lopatin et al. 2018	Prospective non randomized	370	150	220	12	↓	↑	↓
ETHIC-AHF 2016	RCT	71	33	38	12	↓	↑	↓
Bagriy et al. 2015	Prospective non randomized	69	33	36	5	↓	NA	NA
Lesmes et al. 2015	RCT	43	21	22	1	↓	NA	↓
CARVIVA HF 2011	RCT	80	42	38	3	↓	NA	NA
SHIFT 2010	RCT	6505	3241	3264	23	↓	↑	↓

Lopatin et al., Int. J Cardiol., 2018, 260, 113-117
Hidalgo FJ et al. Int J Clin Cardiol. 2017; 4:093
Bagriy, JACC, 2013, 61, E700
Lesmes, EJHF, 2015
Volterrani, IJC, 2011, 151, 218
Swedberg, Lancet, 2010, 376: 875-85

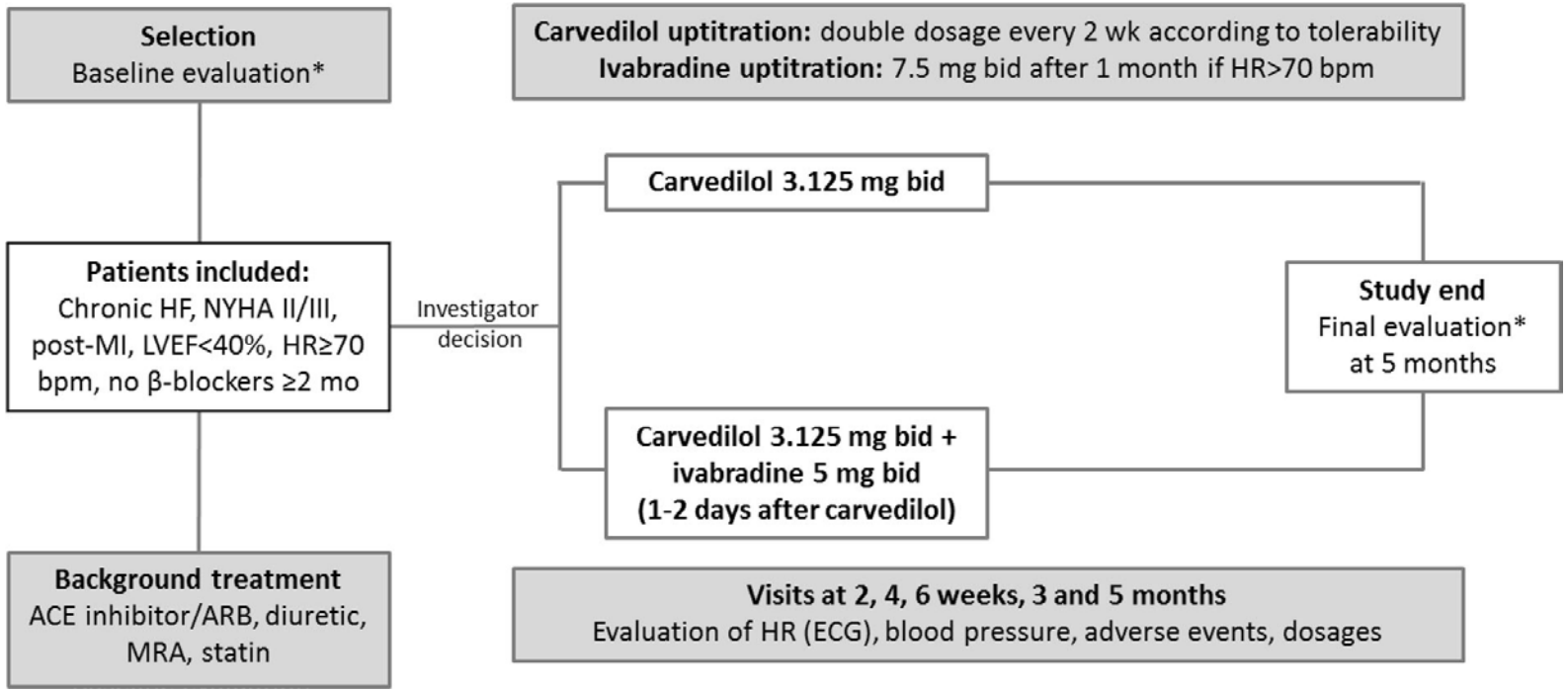
The synergistic effect of early concomitant administration of ivabradine and beta-blockers during hospitalization is safe and improves patients outcomes

Une analyse rétrospective de 370 patients hospitalisés atteints d'IC et présentant une fréquence cardiaque ≥ 70 bpm (150 sous BB + ivabradine, 220 sous BB en monothérapie) dans le cadre du programme Optimize Heart Failure Care mené dans 8 pays (2015-2016)



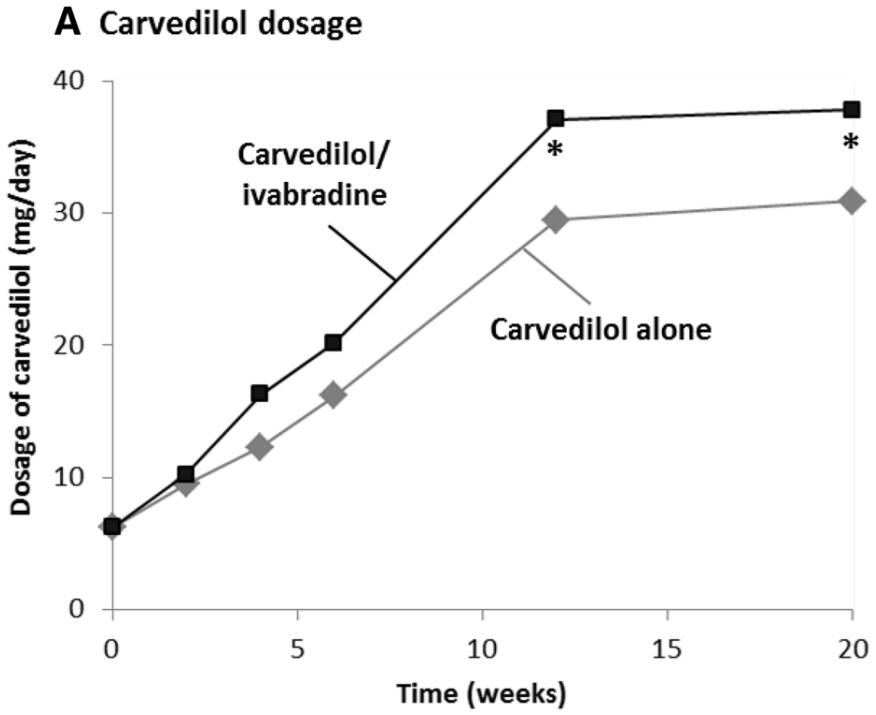


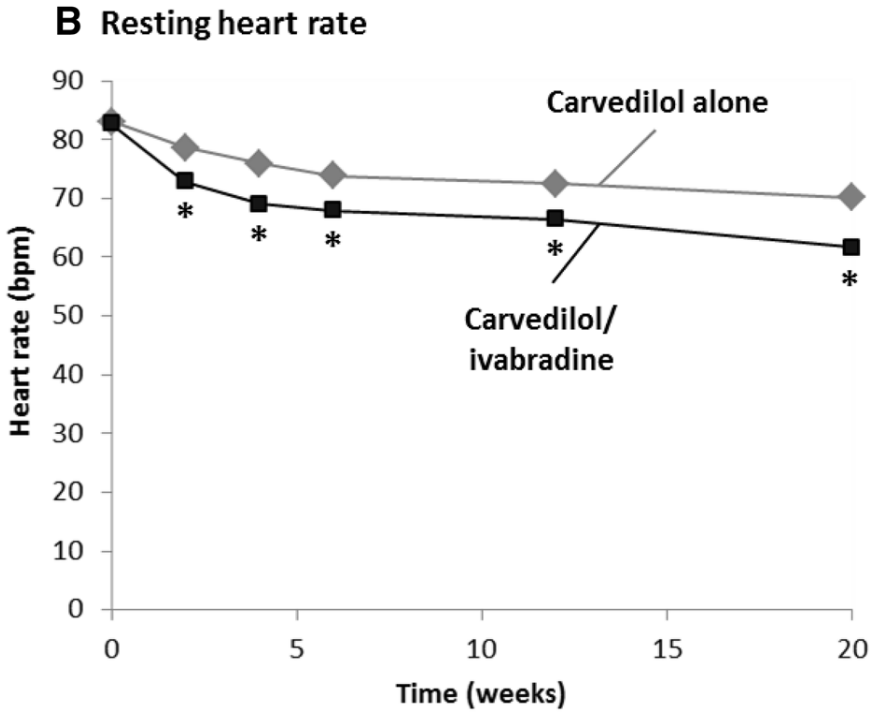
Addition of ivabradine to the beta-blocker improves exercise capacity in patients with systolic heart failure



69 patients patients with ischemic chronic HF
in sinus rhythm
Previous MI
HR ≥ 70 bpm
NYHA class II-III
BB and Iva naive

Combination Therapy Achieves Higher Dosage of Carvedilol





Most common reasons for not reaching BB TD : hypotension, dizziness and worsening HF

➢Higher tolerated dose of carvedilol (37.4mg vs 29.6mg)

ESC HEART FAILURE
ESC Heart Failure (2021)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13182

ORIGINAL RESEARCH ARTICLE

Combination of ivabradine and sacubitril/valsartan in patients with heart failure and reduced ejection fraction

Ying-Hsiang Lee[1,2†], Po-Lin Lin[2,3†], Wei-Ru Chiou[2,4], Jin-Long Huang[5,6], Wen-Yu Lin[7], Chia-Te Liao[8], Fa-Po Chung[6,9], Huai-Wen Liang[10], Chien-Yi Hsu[6,11,12] and Hung-Yu Chang[6,13*]

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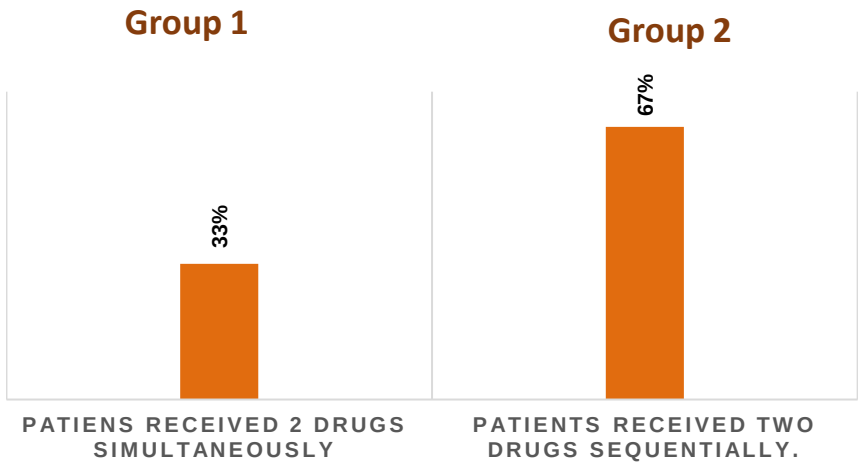
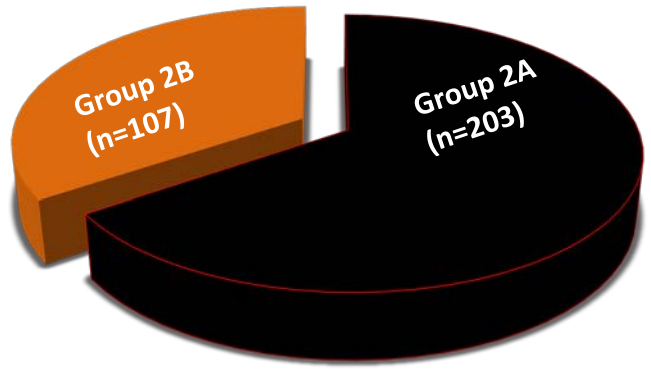
Should we give a combination of Sac/Val and Ivabradine at the same time or sequentially

1,853 patients with symptomatic HFrEF

Inclusion criteria: male or female, symptomatic patients with HFrEF, age > 20 years old, treated with both ivabradine and sacubitril/valsartan (S/V) treatment; patient with HR≥ 70bpm before ivabradine treatment.

464 patients received ivabradine and Sacubitril/Valsartan

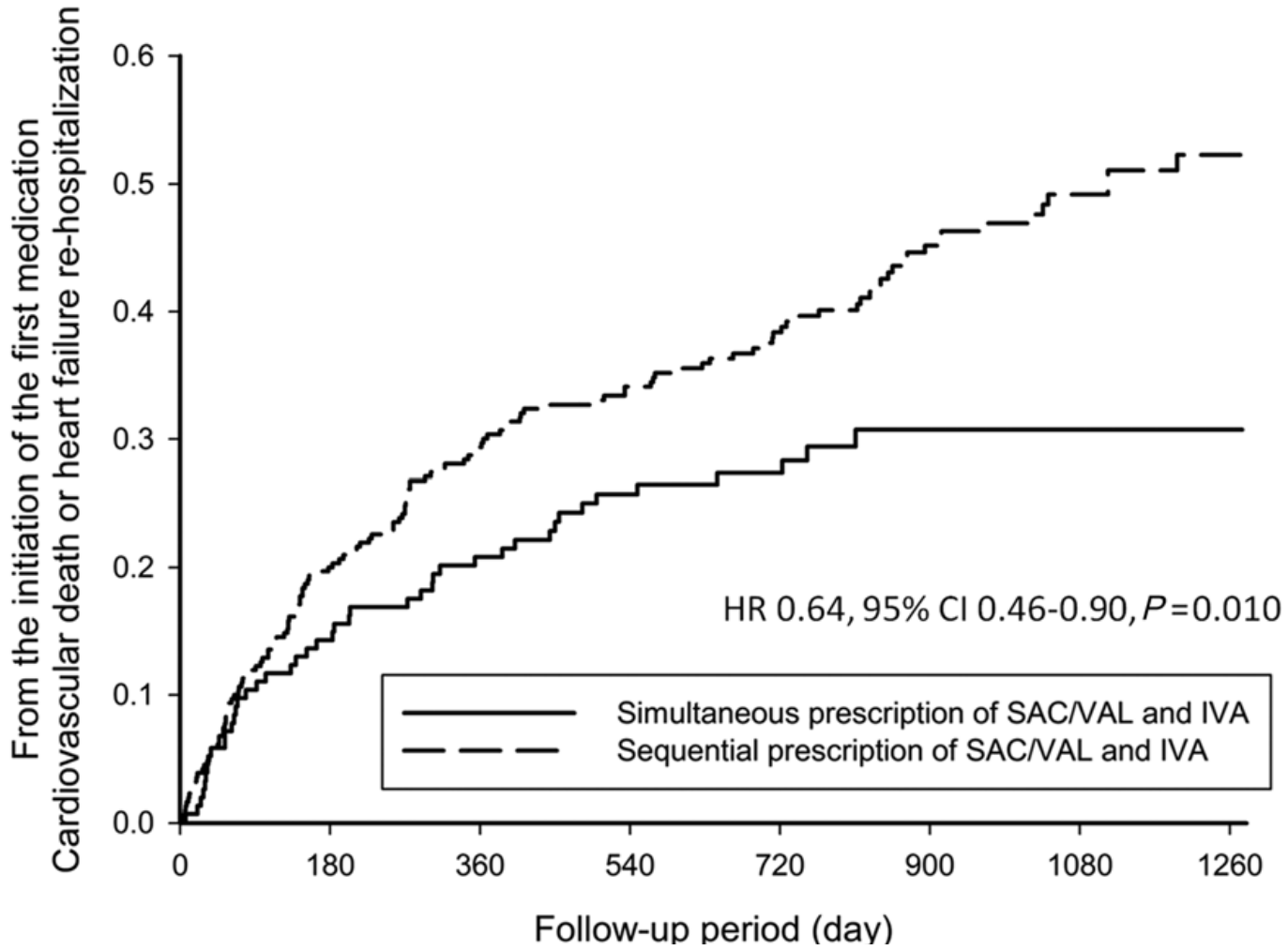




- Patients received ivabradine first, followed by sacubitril/valsartan
- Patients received sacubitril/valsartan first, followed by ivabradine

Lee YH et al. *ESC Heart Fail*. 2021; doi: 10.1002/ehf2.13182.

CV death and recurrent hospitalisation



Lee YH et al. *ESC Heart Fail*. 2021; doi: 10.1002/ehf2.13182.

HF Hospitalization: Failure or Success?

Why Consider Initiating New Therapies for HF in Hospital ?

- No RCT data for initiation / continuation of ACEIs / ARBs in hospital
- Low-dose B-blocker pre-discharge initiation in hemodynamically stable patients was well-tolerated and improved rehospitalization rate and functional status at 6 months
- Initiation of Spironolactone in hospital is associated with reduced arrhythmias and further reduced congestion
- Several data show that hospital initiation leads to increased long-term outpatient use.

ARB, angiotensin receptor blocker

Bhagat AA et al. *JACC Heart Fail* 2019; 7(1):1-12.

EARLY Impact of High HR at Discharge

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

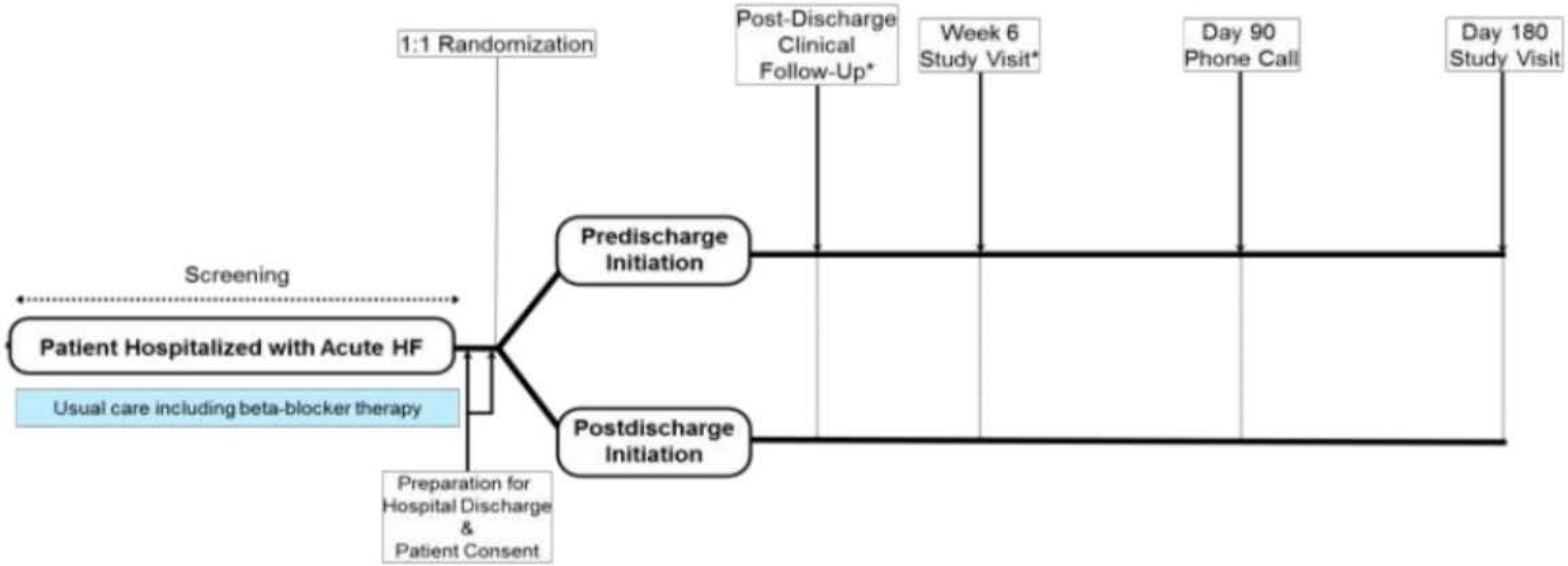
9097 patients discharged following HF hospitalization in Ontario (1999-2001 and 2004-2005)

	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
P value	0.720	Referent	0.185	<0.001	<0.001

➢ 61.5% of patients with HR ≥ 70 bpm

Habal, Circ Heart Fail. 2014 Jan 1;7(1):12-20

PRIME-HF

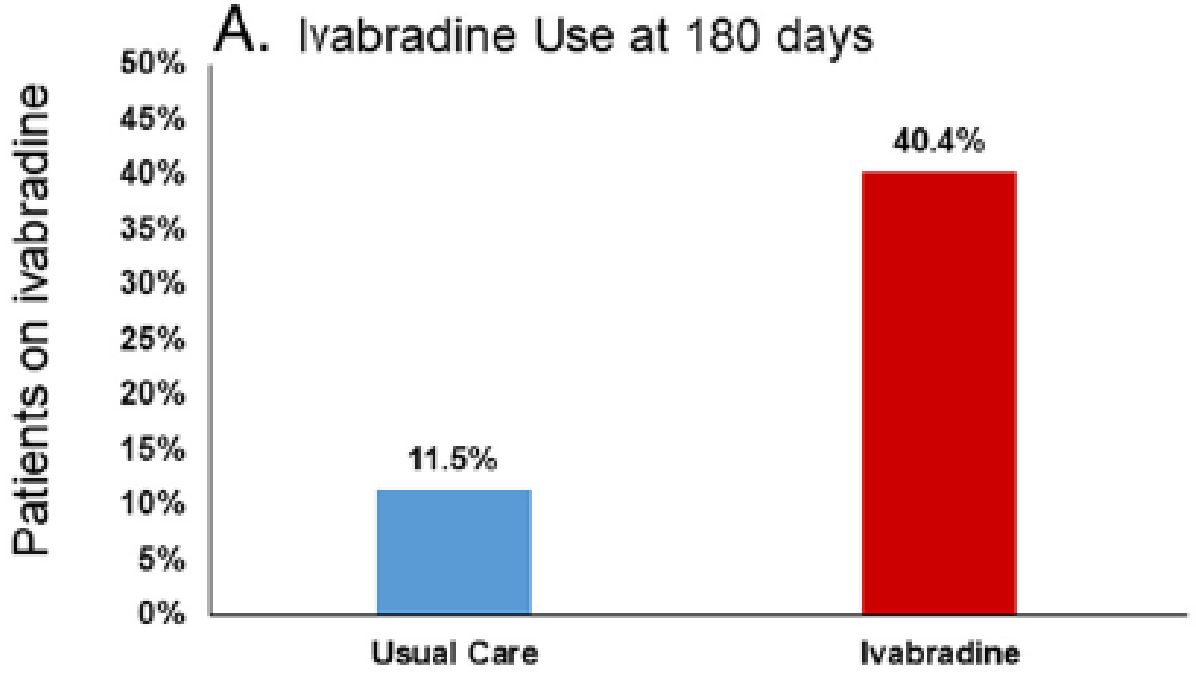


- Primary Endpoint: Uptake of ivabradine at 180 days post-discharge
- Secondary: QOL, HR, beta-blocker use and dose
- Ancillary Study – wearable technology

DukeMedicine

PRIME-HF

(PRIME-HF)
Pre-discharge Introduction of Ivabradine



PRIME-HF

https://newsroom.heart.org/news/few-people-with-heart-failure-take-guideline-recommended-drug-especially-if-not-started-while-hospitalized?preview=fe3e

Mentz et al., Am Heart J, 2020;223:98-105

Ivabradine is effective and safe in acute decompensated HFrEF

10 patients with ADSHF, in sinus rhythm, LVEF < 40%, HR > 70bpm and optimally treated

- Decrease HR at discharge (-21.8 bpm)
- Improve NYHA by 1 or 2 classes at discharge
- Safe

Sargento, Am J Cardiovasc Drugs, 2014

17 patients with ADSHF, in sinus rhythm, LVEF < 40%, HR > 70bpm and optimally treated

- Decrease HR at discharge(-21.7 bpm)
- Safe

Troncoso, EJHF, 2015

21 patients with ADSHF, in sinus rhythm, LVEF < 40% and HR > 70bpm, initiated with BB

- Decrease HR at discharge (-22 bpm) and 28 days later (-29 bpm)
- Safe

Lesmes, EJHF, 2015

17 patients with ADSHF, in sinus rhythm and HR > 70bpm

- Decrease HR by 23 bpm after 6 months
- Improve NYHA class by 1.1 after 6 months
- Increase LVEF by 5% after 6 months
- Safe

Darabantiu, EJHF, 2015

29 patients with ADHF

- Decrease HR by 19 bpm at discharge
- No change in BP
- Safe

Heart Rate as a Predictor of Events in PARADIGM-HF

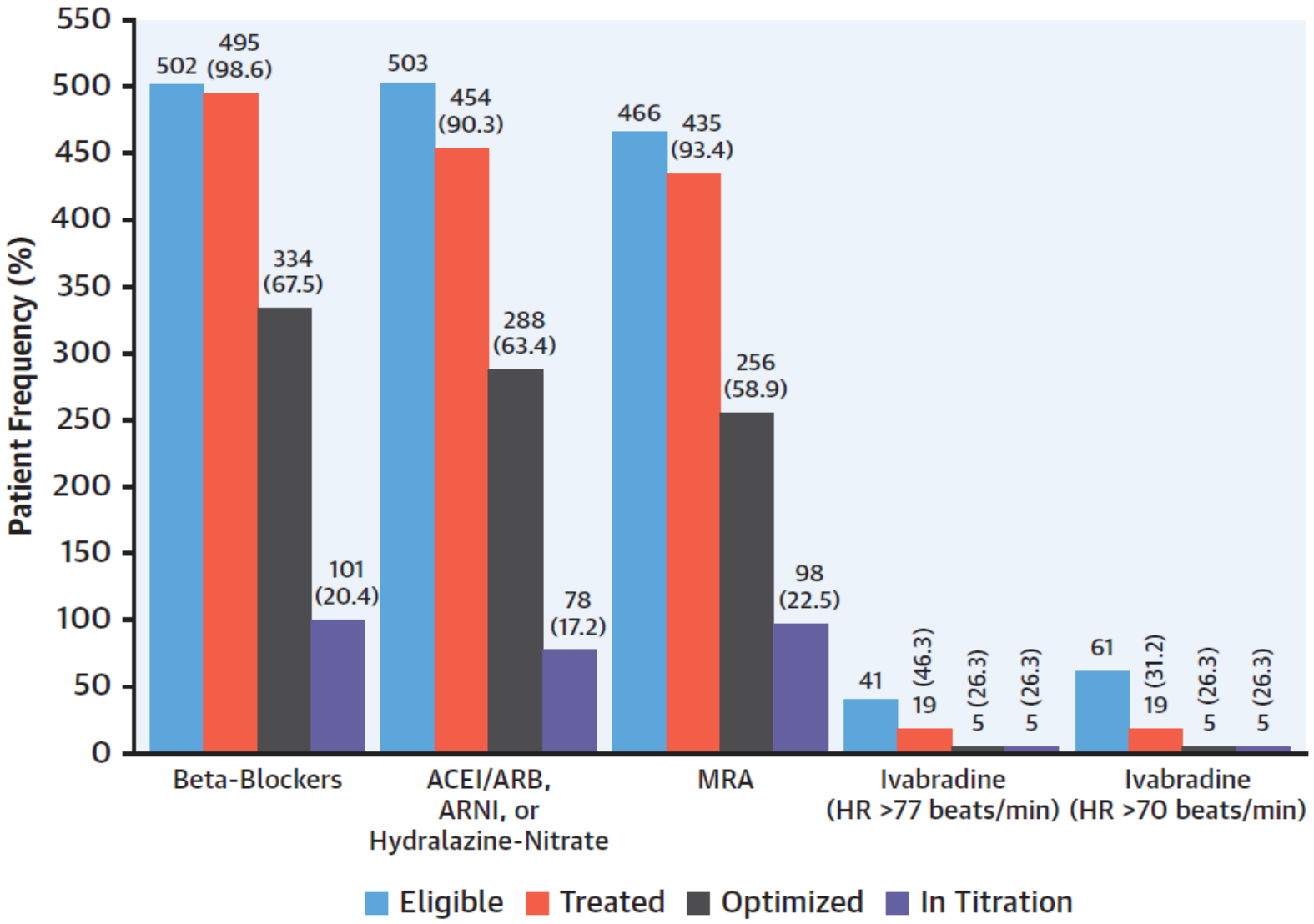
8399 patients de Paradigm-HF
-HR at randomisation 72bpm
-HR end of study: 72bpm
Sub group of patients in sinus rythem

	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
Heart failure hospitalizations	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

McMurray, NEJM, 2014, 371, 993-1004
Castagno D, et al. Poster presented at Heart Failure, May 21–24, 2016, Florence, Italy

Limits of HF treatments

MHI study



Side Effect of BBs

- Introduction and titration of BB
- Fatigue
- Weakness
- Exercise intolerance
- Low output
- Short-term pain for long-term gain should append within 4-8 weeks

Conclusion

- All pillars are important
- Side-effects are common
- Elevated HR should be adressed
- Consider all drugs for all patients including in-hospital