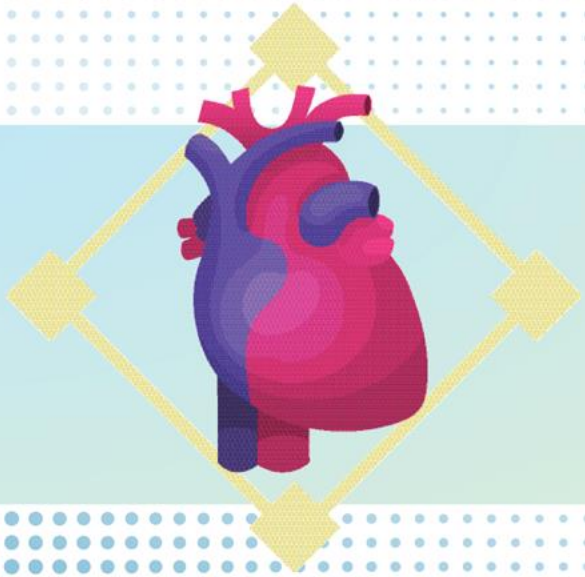

Disruptive Treatment in HF: Combination Therapies for the Home Run

May 10, 2019

Faculty

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Vice President, Research
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Speaker Disclosures
Dr. Nadia Giannetti

- **Consulting Fees/Honoraria:** Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS/Pfizer Alliance, Novartis, Servier
- **Clinical Trials:** Amgen, Boehringer Ingelheim, Merck, Novartis, Pfizer, Servier
- **Speaker Fees:**
- **Other:**

Speaker Disclosures
Dr. Peter Liu

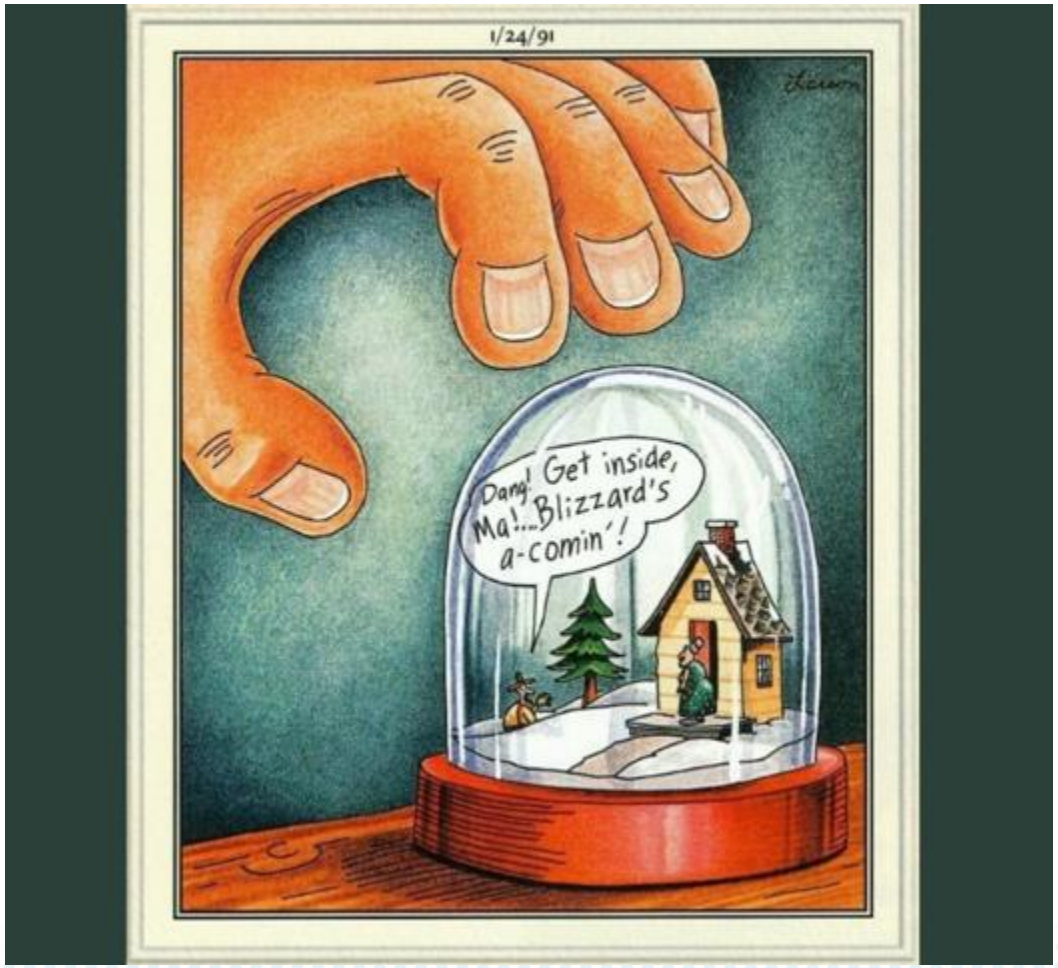
- **Consulting Fees/Honoraria:** Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, Roche, Sanofi, Servier
- **Clinical Trials:** Roche
- **Speaker Fees:**
- **Other:**

Speaker Disclosures
Dr. Kim Connelly

- Received honoraria, advisory board and/or grant support from Merck, Astra Zeneca, Boehringer Ingelheim, Janssen, Servier, Eli Lilly, Ferring and Novo Nordisk

- Holds patent for linagliptin and HF

Speaker Disclosure
Dr. Jonathan Howlett



- **Relationships with commercial interests:**
  - **Grants/Research Support:** AstraZeneca, Merck, Servier, Pfizer, Novartis, Medtronic, Bayer
  - **Speakers Bureau/Honoraria:** Bayer, Servier, Boerhinger Ingleheim, Novartis
  - **Consulting Fees:** General Electric, Government of Canada and Alberta, Novo Nordisk, AstraZeneca, Merck, Servier, Pfizer, Novartis, St. Jude, Bayer
  - **Medical Advisory Board:** Cardiol

Speaker Disclosures
Mr. John Klein

- **Relationships with commercial interests:**
  - **Grants/Research Support:**
  - **Speakers Bureau/Honoraria:** Servier
  - **Consulting Fees:**
  - **Other:**

Learning Objectives

- Reinforce the importance of in-hospital initiation of evidence-based therapies
- Highlight the early impact of HR lowering on heart function
- Recognize the benefits to patients of early optimization of evidence-based therapies in HF

Agenda

Time	Topic	Presenter
11:55 am - 12:00 pm	Welcome and Introduction	Nadia Giannetti, MD
12:00 - 12:05 pm	Call to Action	John Klein
12:05 - 12:20 pm	Optimizing HF Therapies as Early as Possible	Jonathan Howlett, MD
12:20 - 12:25 pm	Panel Discussion	Nadia Giannetti, MD
12:25 - 12:45 pm	Imaging the Heart: Early Impact of Lowering HR on Heart Function	Kim Connelly, MD
12:45 - 12:50 pm	Panel Discussion	Nadia Giannetti, MD
12:50 - 12:55 pm	Tying it all Together	Peter Liu, MD
12:55 - 1:10 pm	Questions and Answers	ALL
1:10 pm	Closing Remarks and Evaluations	Peter Liu, MD

Question 1: Which of the following medical therapies have been shown to improve survival in patients with heart failure?

1. ACE-inhibitors
2. Beta-blockers
3. MRAs
4. ARNIs
5. Ivabradine
6. All of the above
7. 1,2,3
8. 1,2,3,4

Question 2: Which of the following is/are independent predictors of mortality?

1. NYHA class
2. Systolic BP
3. Creatinine
4. LVEF
5. Heart rate
6. All of the above
7. 1,2,3
8. 1,2,3,4

Question 3: What can be said that is true about recovery of LVEF in patients with HFrEF following ACE/BB/MRA?

1) Almost half exhibit some degree of improvement in LVEF
2) 30% will normalize EF
3) More than 70% will still have HFrEF even if they improve EF
4) Men have better EF recovery than women
5) EF improvement does not improve prognosis during the first year

Question 4: What statement best describes your understanding of initiation of in-hospital therapies for HFrEF (assume eligible for all therapies)?

1) Triple therapy should be optimized prior to initiation of any 'new' therapies such as ARNi or SNI

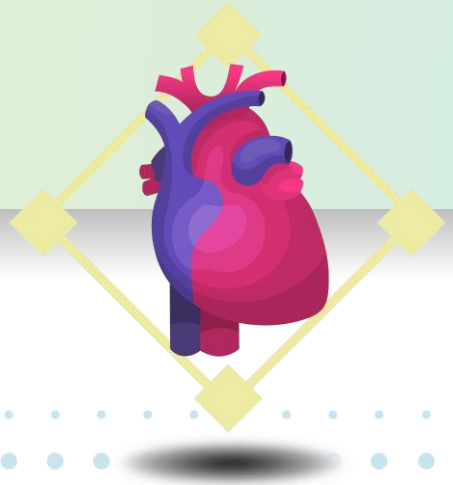
2) Patients should be started on ARNi while in hospital but not SNI

3) Patients should be started on both ARNi and SNI while in hospital

4) New therapies should only be started in outpatient population

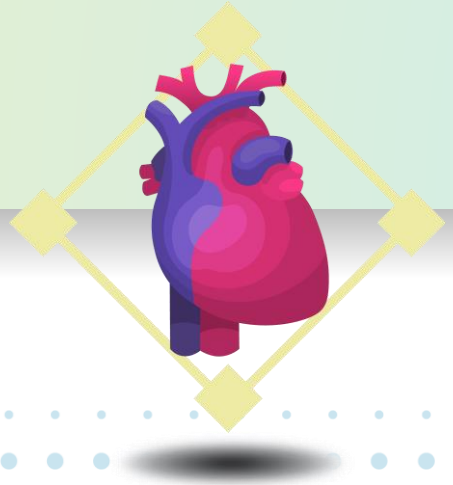
Call to Action

John Klein



Optimizing HF Therapies as Early as Possible

or Why can't HF treatment be more like cancer treatment?

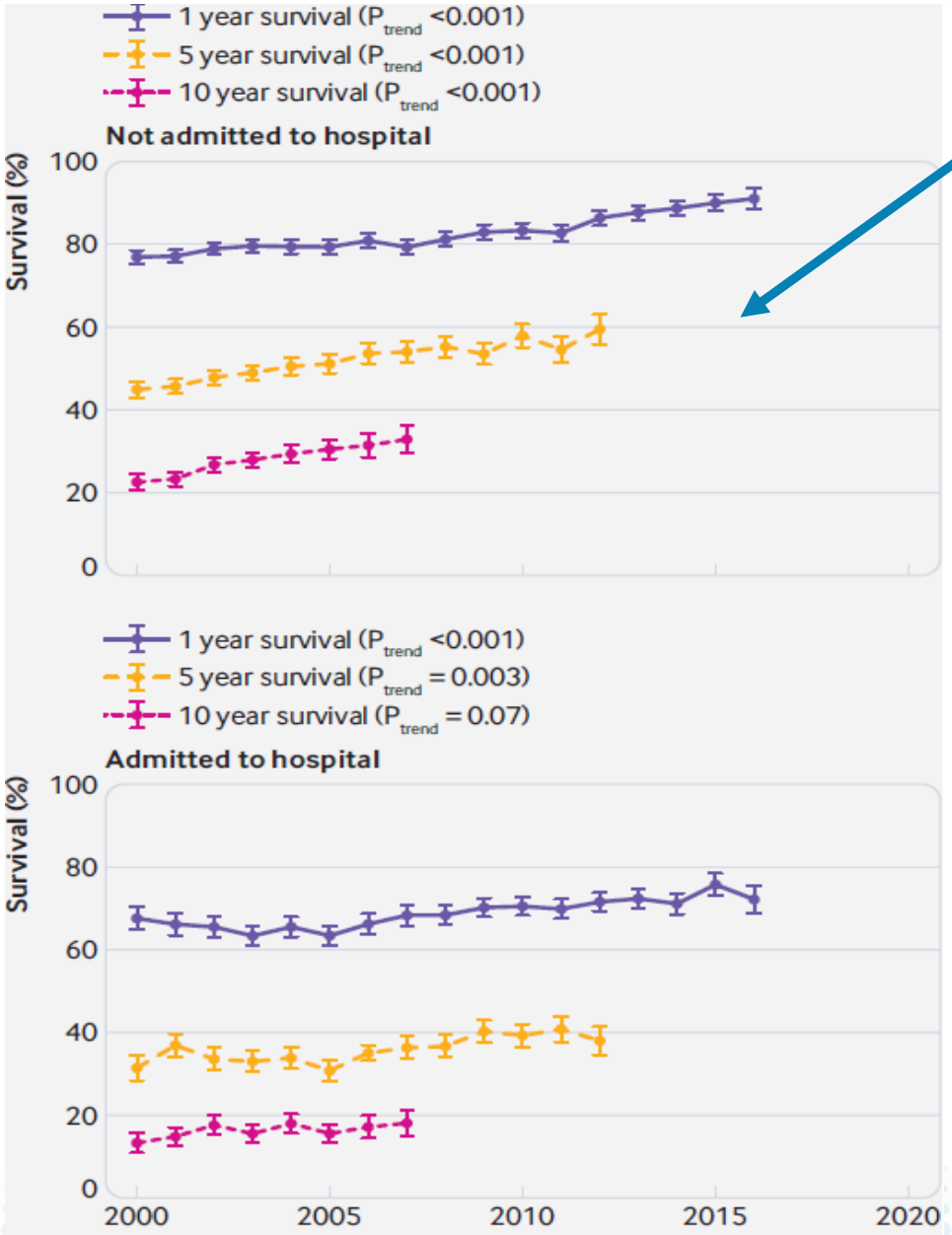


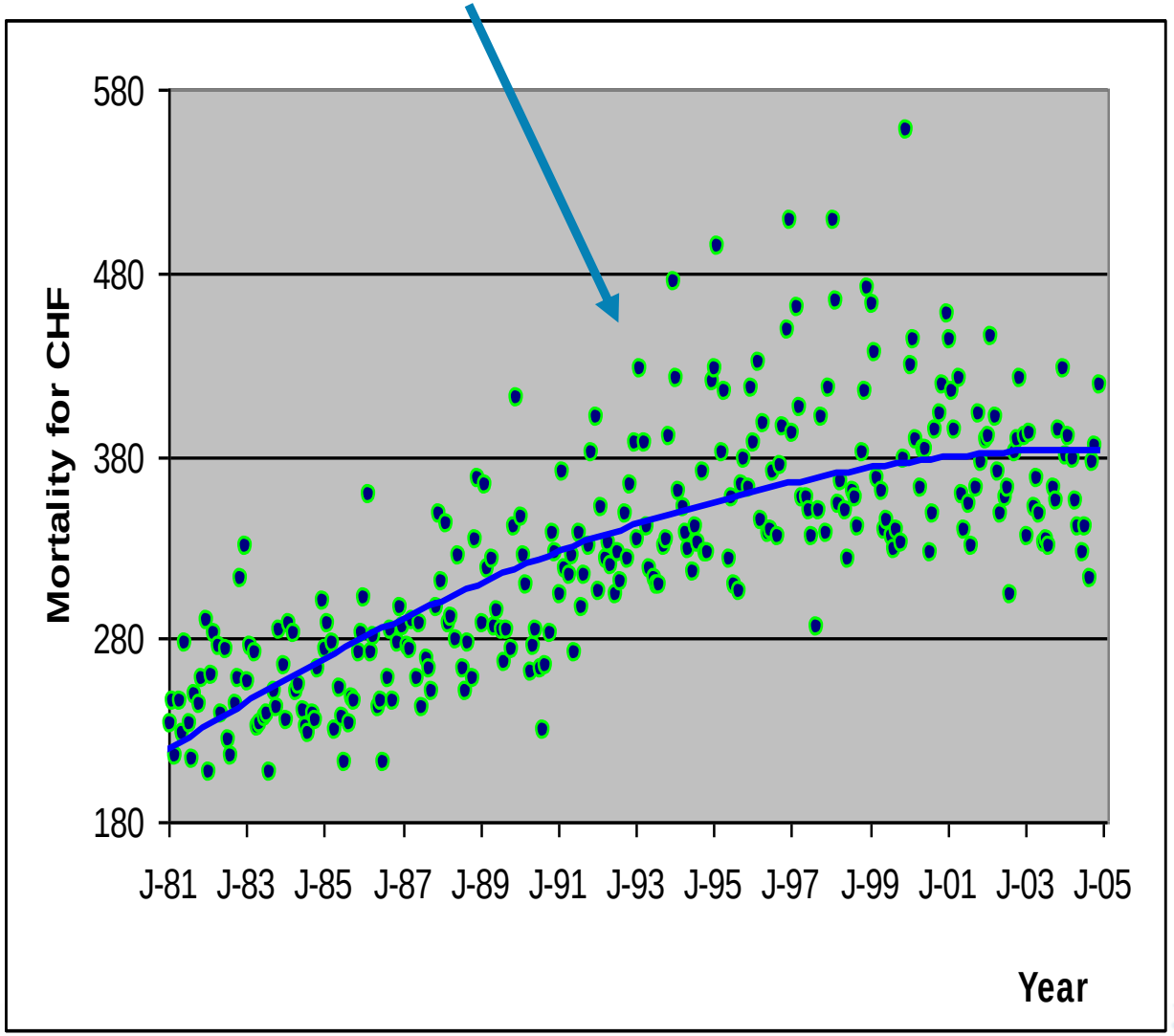
Jonathan Howlett

MD, FRCPC, FACC

Libin Cardiovascular Institute

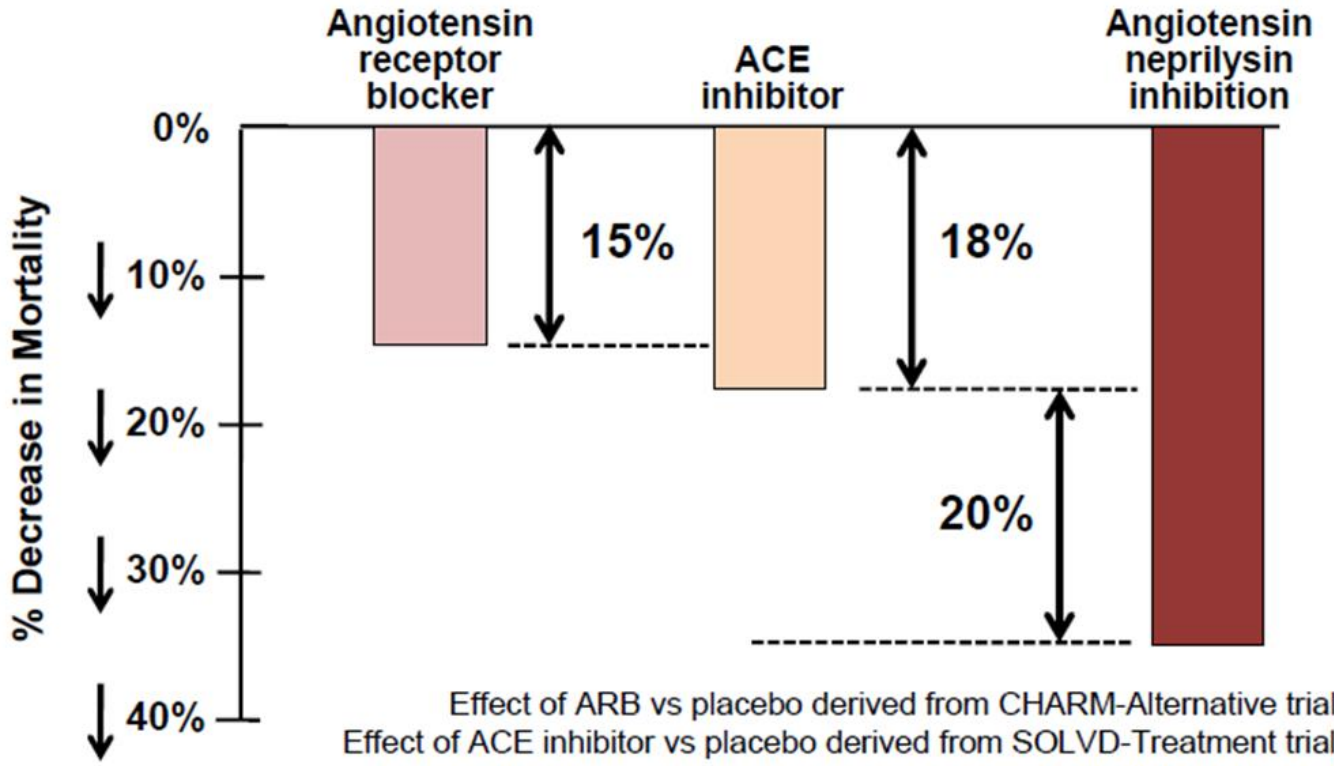
Survival of New Onset HF in UK
Crude CHF Deaths in Canada





thebmj | *BMJ* 2019;364:l223 | doi: 10.1136/bmj.l223

Angiotensin Neprilysin Inhibition with LCZ696 Doubles Effect on Cardiovascular Death of Current Inhibitors of the Renin-Angiotensin System



Effect of ARB vs placebo derived from CHARM-Alternative trial
Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial

Primary composite endpoint and components in patients with HR ≥ 77 bpm at baseline (N=3357)

	Ivabradine (N=1657)				Placebo (N=1700)				Hazard ratio		
	NPY	n	%	PY	NPY	n	%	PY	E	95% CI	p-value
Primary composite endpoint	**2709**	**454**	**27.40**	**16.76**	**2602**	**581**	**34.18**	**22.33**	**0.75**	**[0.67;0.85]**	**0.000006**
Secondary endpoints											
- Hospitalisation for worsening heart failure	2709	298	17.98	11.00	2602	418	24.59	16.07	0.69	[0.59;0.80]	0.0000008
- Cardiovascular death	2984	253	15.39	8.54	2984	312	18.35	10.46	0.81	[0.69;0.96]	0.0137
- Death from any cause	2984	285	17.20	9.55	2984	350	20.59	11.73	0.81	[0.69;0.94]	0.0074
- Death from heart failure	2984	67	4.04	2.23	2984	107	6.29	3.59	0.61	[0.45;0.83]	0.0017

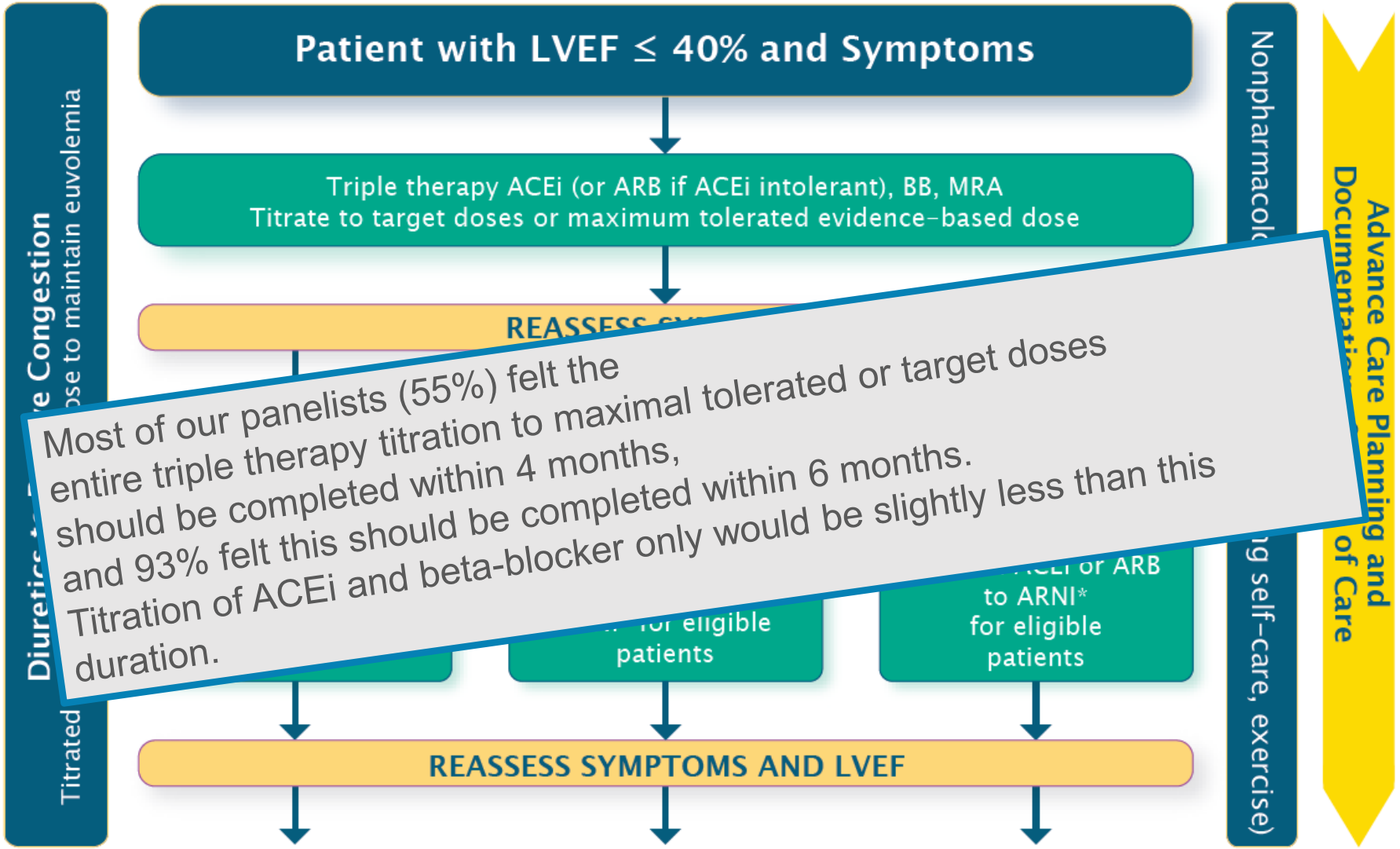
N : number of patients at risk; NPY : number of patients-year; n : number of patients having experienced the endpoint; % : global incidence rate n/Nx100; PY : annual incidence rate number of patients having experienced the endpoint on the whole study for 100 patients-year at risk; E : estimate of the hazard ratio between treatment groups (Ivabradine /Placebo) based on an adjusted Cox s proportional hazards model with beta-blocker intake at randomization as a covariate; 95% CI : 95% Confidence Interval of the estimate (two-sided); p-value : p-value (Wald test)

One year NNT is 18

One year NNT is 46

Swedberg et al. *Lancet* 2010; 376: 875-85; Krum & Sindone. *Heart Lung Circ* 2013; 22: s87-8.

Therapeutic Approach to Patients With HFrEF



Most of our panelists (55%) felt the entire triple therapy titration to maximal tolerated or target doses should be completed within 4 months, and 93% felt this should be completed within 6 months. Titration of ACEi and beta-blocker only would be slightly less than this duration.

Chronic Underdosing of Medications Following HF Discharge

Medication	%*	0 to 30 d	31 to 180 d	181 to 360 d	3 to 5 y	Target Dosage, mg†
Metoprolol‡	59.4%	75 (50 to 125)	75 (50 to 100)	75 (50 to 100)	75 (50 to 100)	200
Carvedilol	12.1%	12.5 (6.25 to 25)	18.75 (9.37 to 37.5)	25 (12.5 to 50)	25 (12.5 to 50)	50
Bisoprolol	5.5%	5 (3.75 to 10)	5 (2.5 to 7.5)	5 (5 to 10)	5 (5 to 10)	10
Other	23.0%	...	...	...	...	...
RASi						
Trandolapril	24.8%	2 (1 to 4)	2 (1 to 3)	2 (1 to 4)	2 (2 to 4)	4
Ramipril	19.8%	5 (3.125 to 7.5)	5 (2.5 to 10)	5 (3.125 to 10)	5 (3.75 to 10)	10
Enalapril	16.0%	10 (7.5 to 20)	10 (5 to 20)	10 (5 to 20)	10 (7.5 to 20)	20
Captopril	11.7%	37.5 (25 to 62.5)	37.5 (25 to 62.5)	37.5 (25 to 62.5)	50 (25 to 62.5)	150
Losartan	9.6%	50 (25 to 75)	50 (25 to 75)	50 (50 to 75)	50 (50 to 75)	50
Candesartan	1.5%	8 (6 to 16)	8 (6 to 16)	8 (8 to 16)	8 (8 to 16)	32
Valsartan	0.6%	120 (80 to 160)	120 (80 to 160)	120 (80 to 160)	80 (80 to 160)	320
Other	16.0%	...	...	...	...	...

(*Circulation*. 2007;116:737-744.)

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In Contemporary Clinical Practice, Only 15–30% of Patients Are Able to Reach the BB Target Dose

Source/Study	Patients	Years	Patients on			References
			BB	BB ≥ 50% target dose	BB ≥ 100% target dose	
CHFN (Canada)	17790	1999-2010	74.6%	-	-	Arnold, EJHF, 2011, 10, S204
ESC-HF (Europe)	3226	2009-2010	87%	-	28.4%	Maggioni, EJHF, 2010, 12, 1076
IMPROVE-HF (US)	15381	2005-2007	86%	-	17.5%	Yancy, AHJ, 2009, 157, 754 Heywood, CHF, 2010, 3, 596
IMPACT-RECO (France)	1919	2005	65%	47%	18%	de Groote, EJHF, 2007, 9, 1205
OPTIMIZE-HF (US)	2373	2003-2004	83.5%	-	14.5%	Fonarow, AJC, 2008, 102, 1524
Shift (worldwide)	6505	2006-2010	89% ¥	56%	26%	Swedberg, Lancet, 2010, 375, 875
EMPHASIS-HF (Worldwide)	2737	2006-2010	87% ¥	39.5%	-	Zannad, NEJM, 2011, 364, 11 Krum, Circ. 2011, 124, A10483
PARADIGM-HF (Worldwide)	8442	2009-2013	93%	-	-	McMurray, NEJM, 2014

Target dose as defined by landmark BB clinical trials
¥ as background therapy

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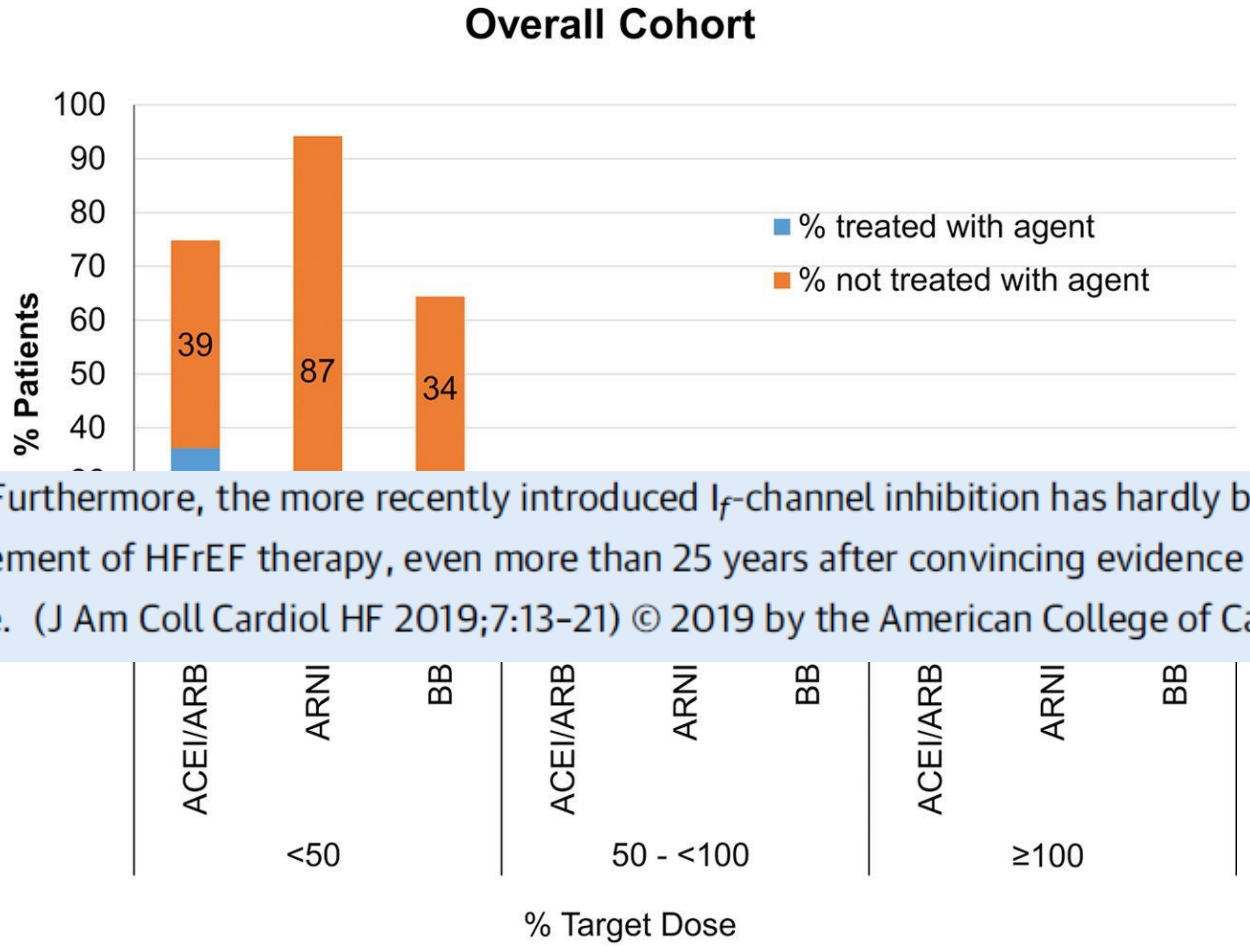
Target Doses of EBMT in the CHECK HF Registry

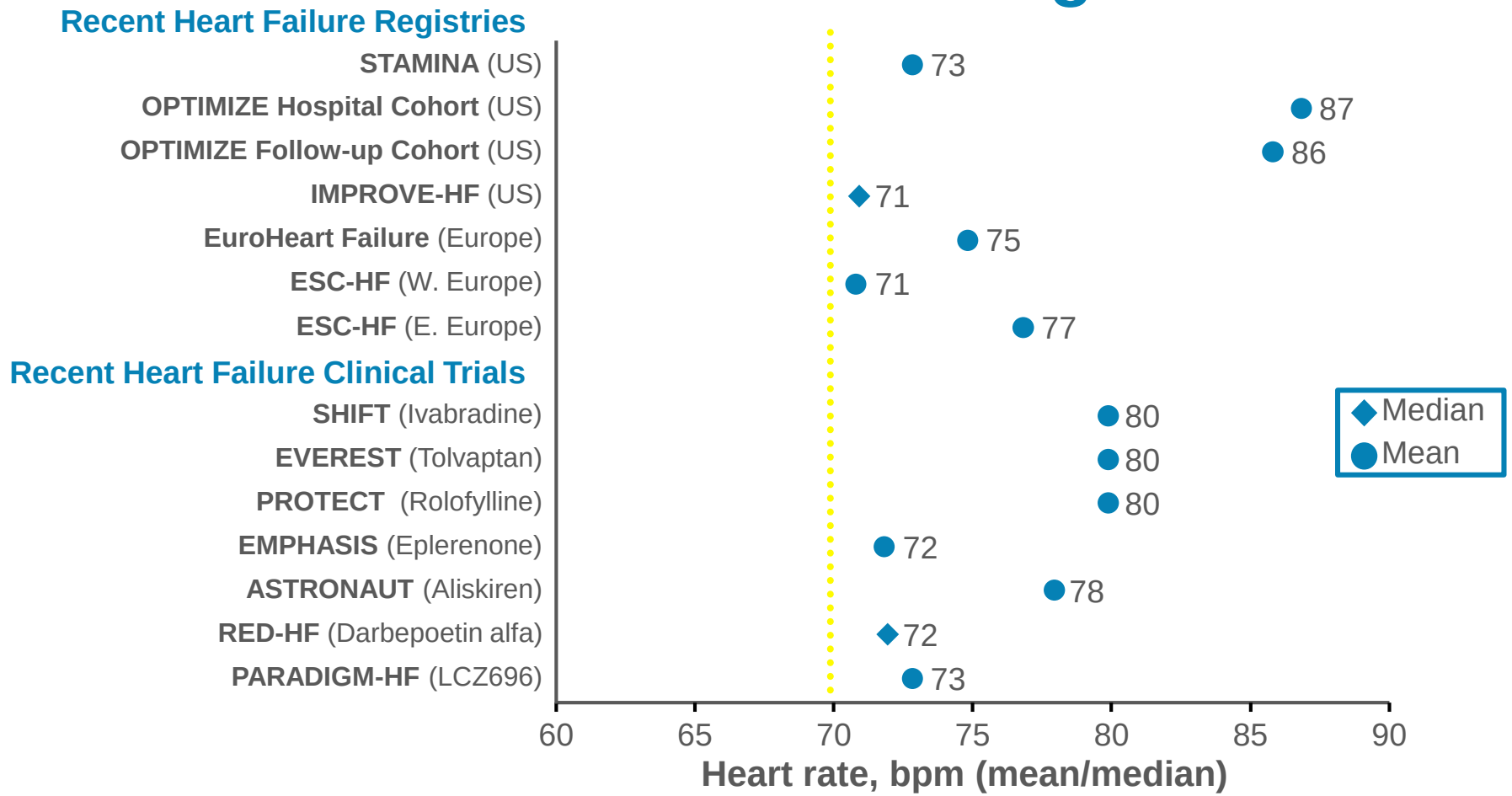


mended by guidelines. Furthermore, the more recently introduced I_f-channel inhibition has hardly been adopted. There is ample room for improvement of HFrEF therapy, even more than 25 years after convincing evidence that HFrEF treatment leads to better outcome. (J Am Coll Cardiol HF 2019;7:13–21) © 2019 by the American College of Cardiology Foundation.

ACEI = angiotensin converting enzyme inhibitor; ARNI =angiotensin receptor- neprilysin inhibitor; ARB = angiotensin receptor blocker; BB = beta blockers, SBP = systolic blood pressure

Poghni A. Peri-Okonny et al. *JCHF* 2019;j.jchf.2018.11.011

Heart Rate Remains Relatively High in Recent Heart Failure Trials and Heart Failure Registries



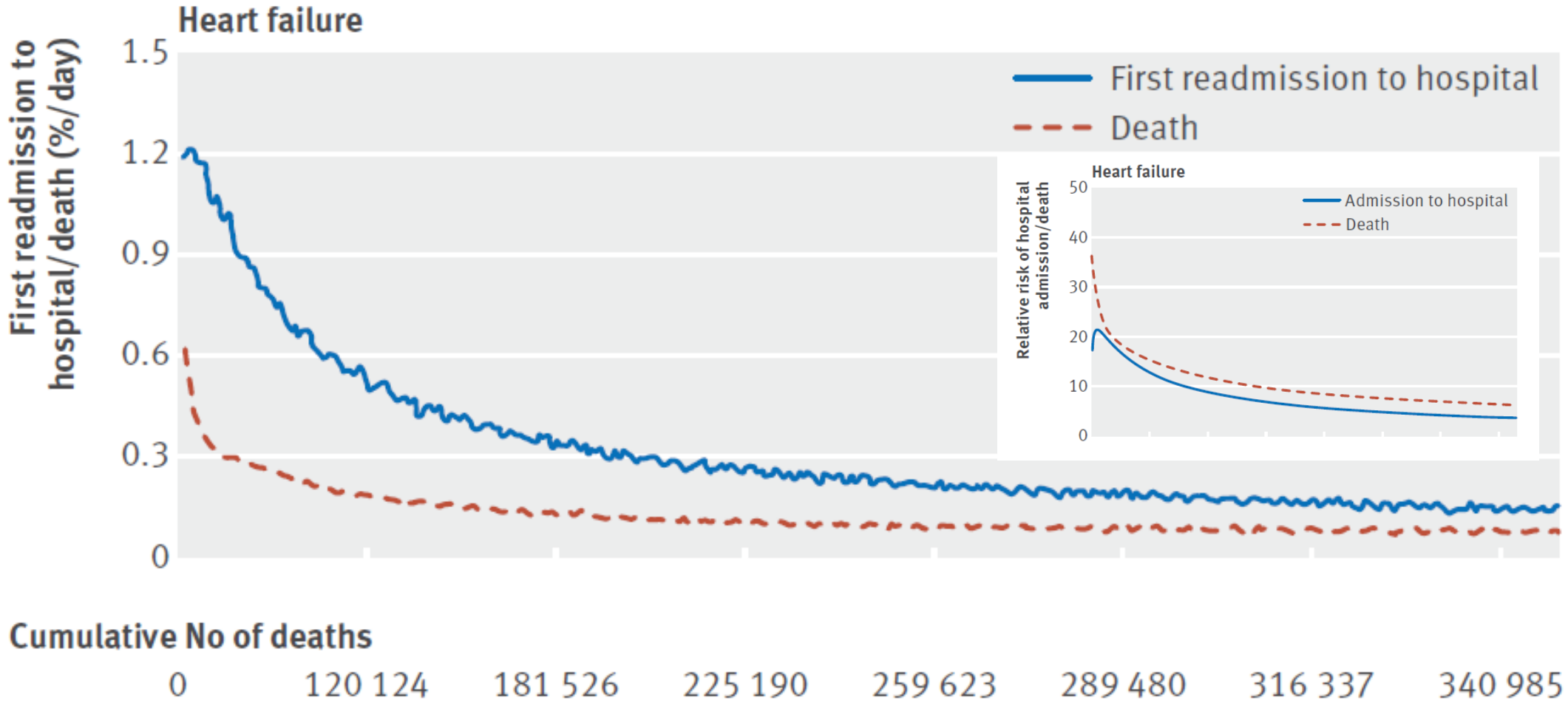
Vs.

BAD info

- Hosp. represents failure of Rx
- Bests evidence for rapid med change in hospital
- Give decongesting drug when congested
- Give HR lowering drug when HR elevated

- There is no evidence
- It is not safe
- It will prolong hospitalization
- The old ways are best
- We have time after hospitalization to do this

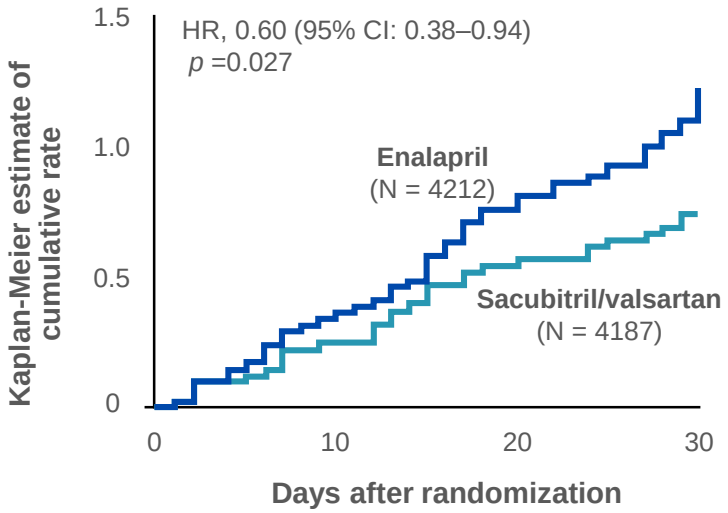
UK HF Audit: Risk of Death or Hospitalization *Starting at Discharge*



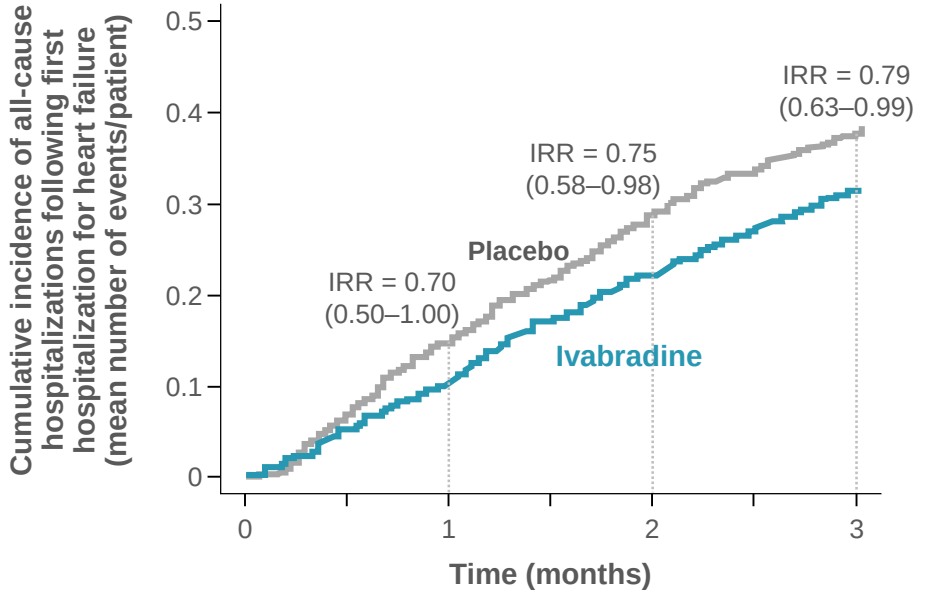
the bmj | *BMJ* 2015;350:h411 | doi: 10.1136/bmj.h411

Early Benefit of Treatment on Hospitalization for Heart Failure

Endpoint – hospitalization for HF



Hospitalization for HF begins to diverge as quickly as 2 weeks.

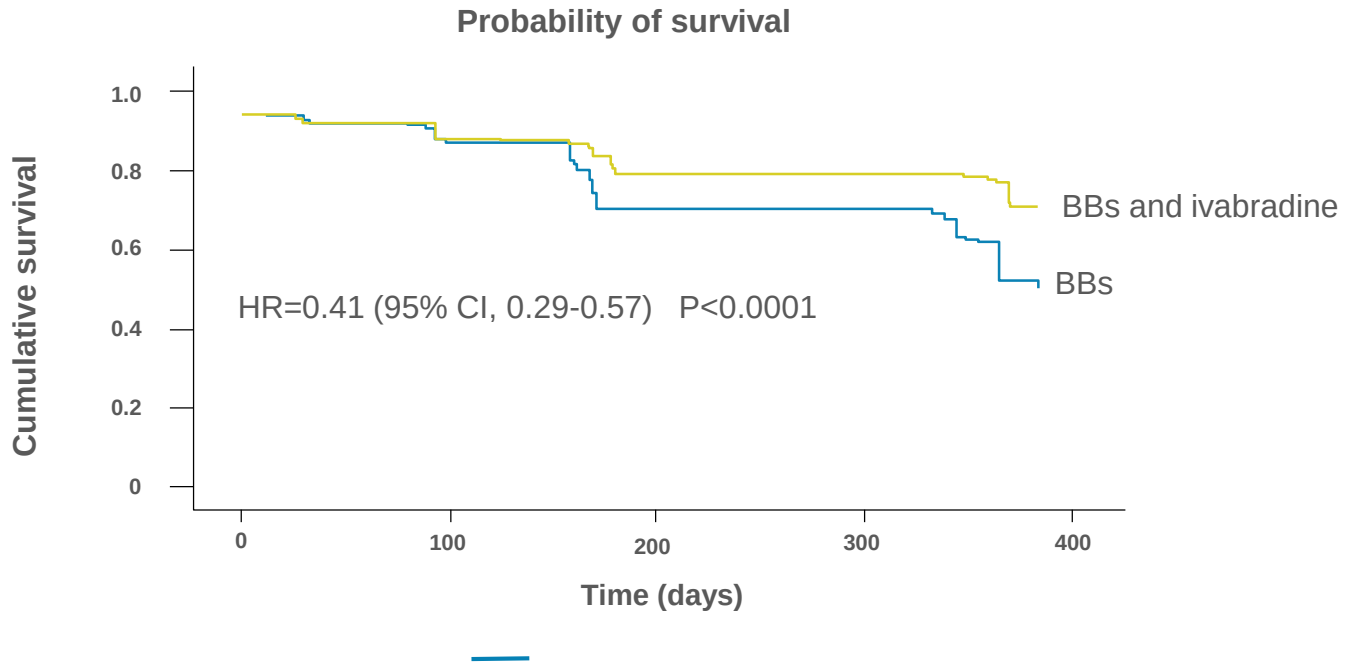


Early treatment with IVA reduces readmission for HF in SHIFT trial.

The curves begin to diverge at 2 weeks for those hospitalized for HF.

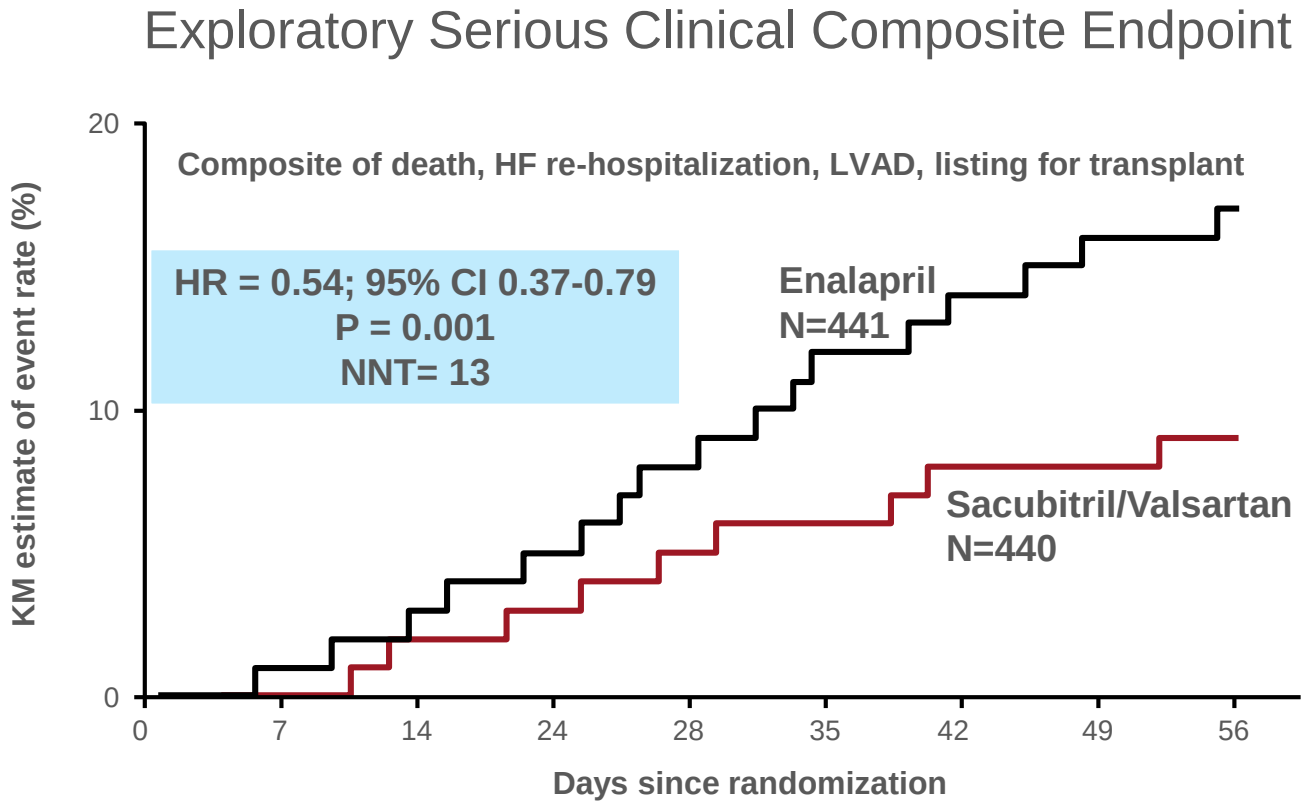
Early Co-administration of Ivabradine and β-blockers During Hospitalization May Reduce Mortality

A retrospective analysis on 370 hospitalized HF patients with heart rate ≥70 bpm (150 BB + ivabradine, 220 BB alone) in the Optimize Heart Failure Care Program from 8 countries (2015-2016)



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

PIONEER-HF



- Exploratory Serious Clinical Composite endpoint was driven by the reduction of risk of death and HF re-hospitalizations

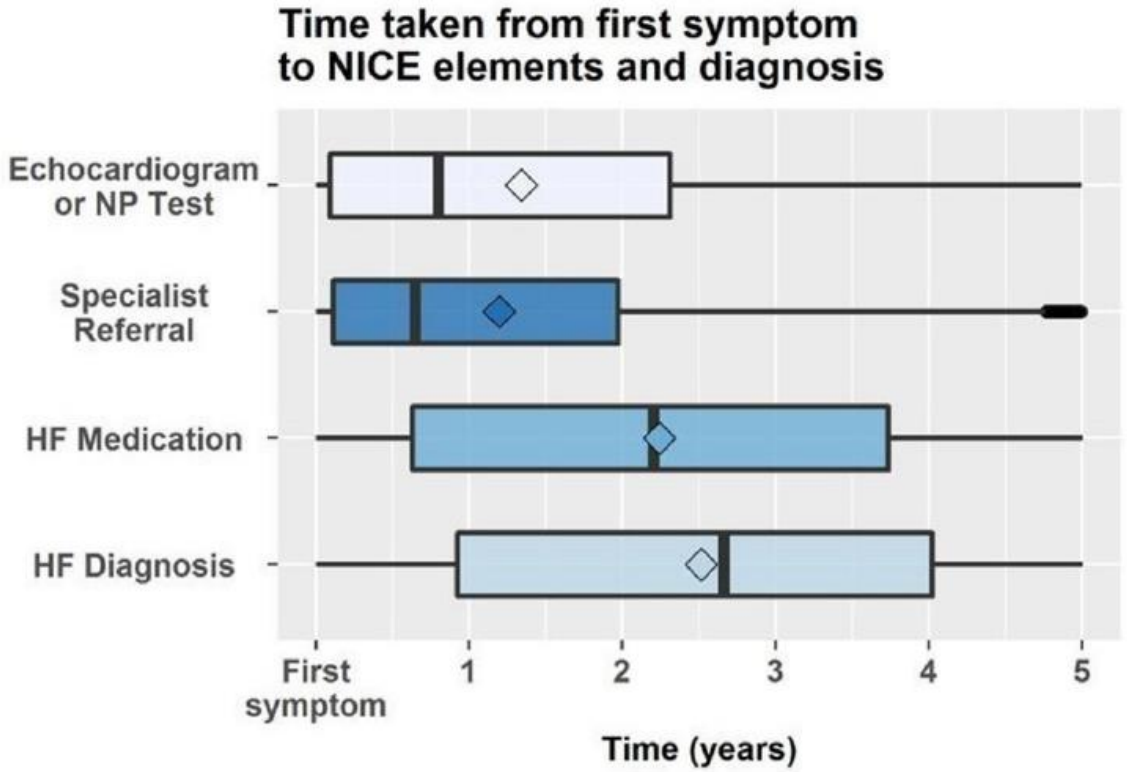
Velazquez EJ et al. nejm.org/doi/full/10.1056/NEJMoa1812851

"*de novo*" HF can be as old as 3 years

ORIGINAL RESEARCH ARTICLE

Adherence to guidelines in management of symptoms suggestive of heart failure in primary care

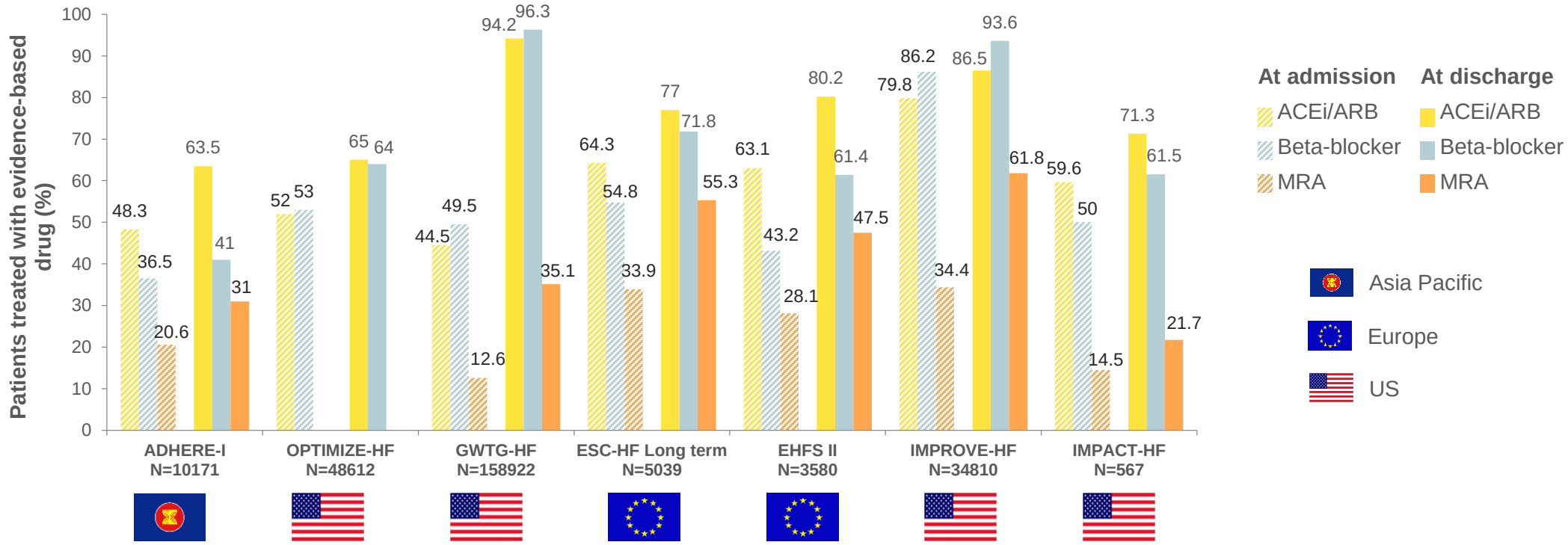
Benedict Hayhoe,[1] Dani Kim,[1,2] Paul P Aylin,[1,2] F Azeem Majeed,[1] Martin R Cowie,[3] Alex Bottle[1,2]



Hayhoe B, *et al*. *Heart* 2018;**0**:1–8. doi:10.1136/heartjnl-2018-313971

Hospitalization Provides an Opportunity for HF Treatment Optimization

Significant increase in the prescription of evidence-based disease-modifying therapies at discharge compared to pre-hospitalization[1-7]

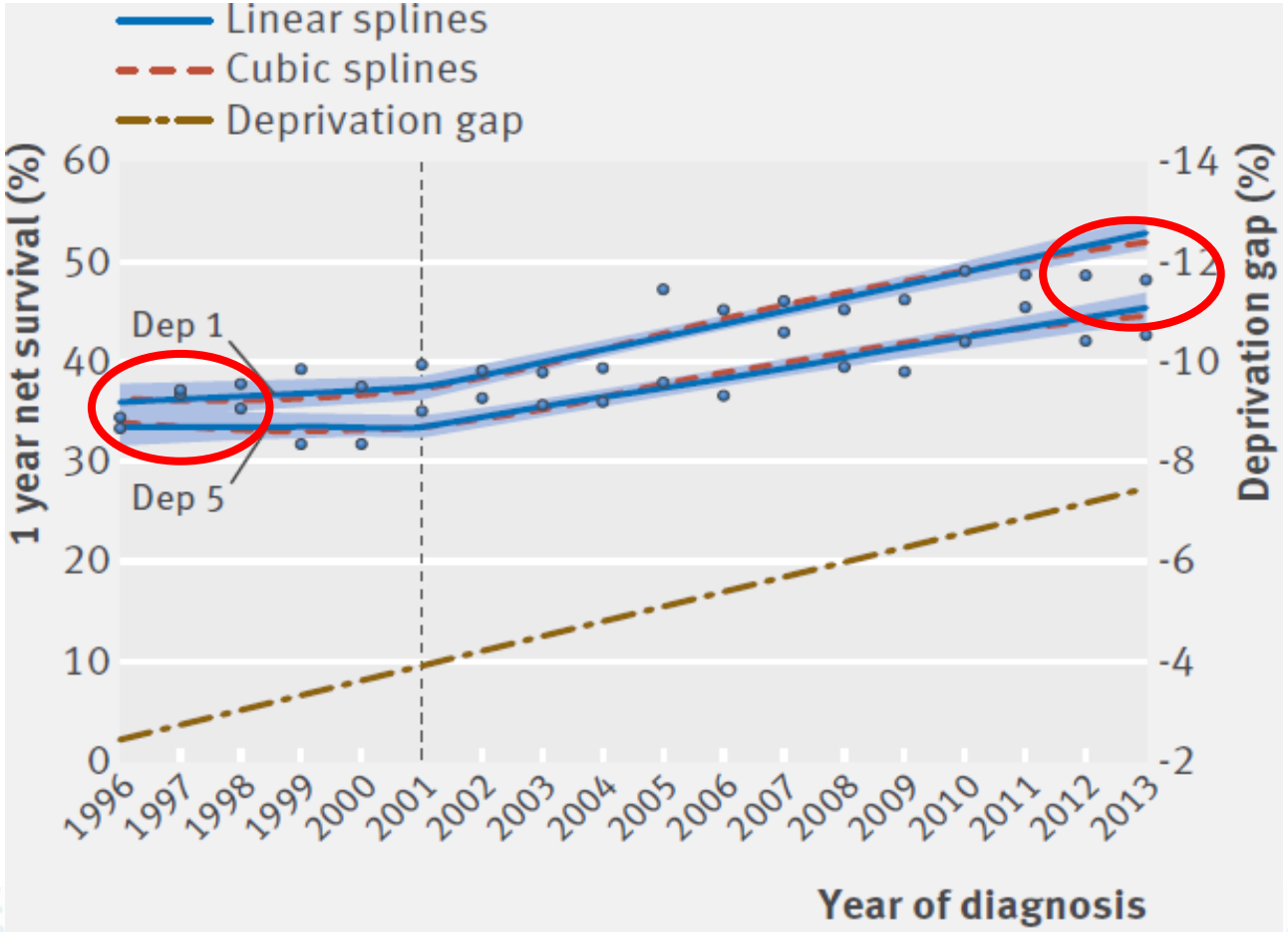


ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HF, heart failure; MRA, mineralocorticoid receptor antagonist

1. Atherton et al. *J Card Fail* 2012;18:82–8; 2. O'Connor et al. *Am Heart J* 2008;156:662–73; 3. Allen et al. *Circulation* 2015;132:1347–53; 4. Maggioni et al *Eur J Heart Fail* 2013;15:1173–84; 5. Nieminen et al. *Eur Heart J* 2006;27:2725–36; 6. Fonarow et al. *Circulation* 2010;122:585–96; 7. O'Connor et al. *J Card Fail* 2005;11:200–5

Impact of National Cancer Policies on Cancer Survival Trends and Socioeconomic Inequalities in England, 1996–2013: Population-based Study

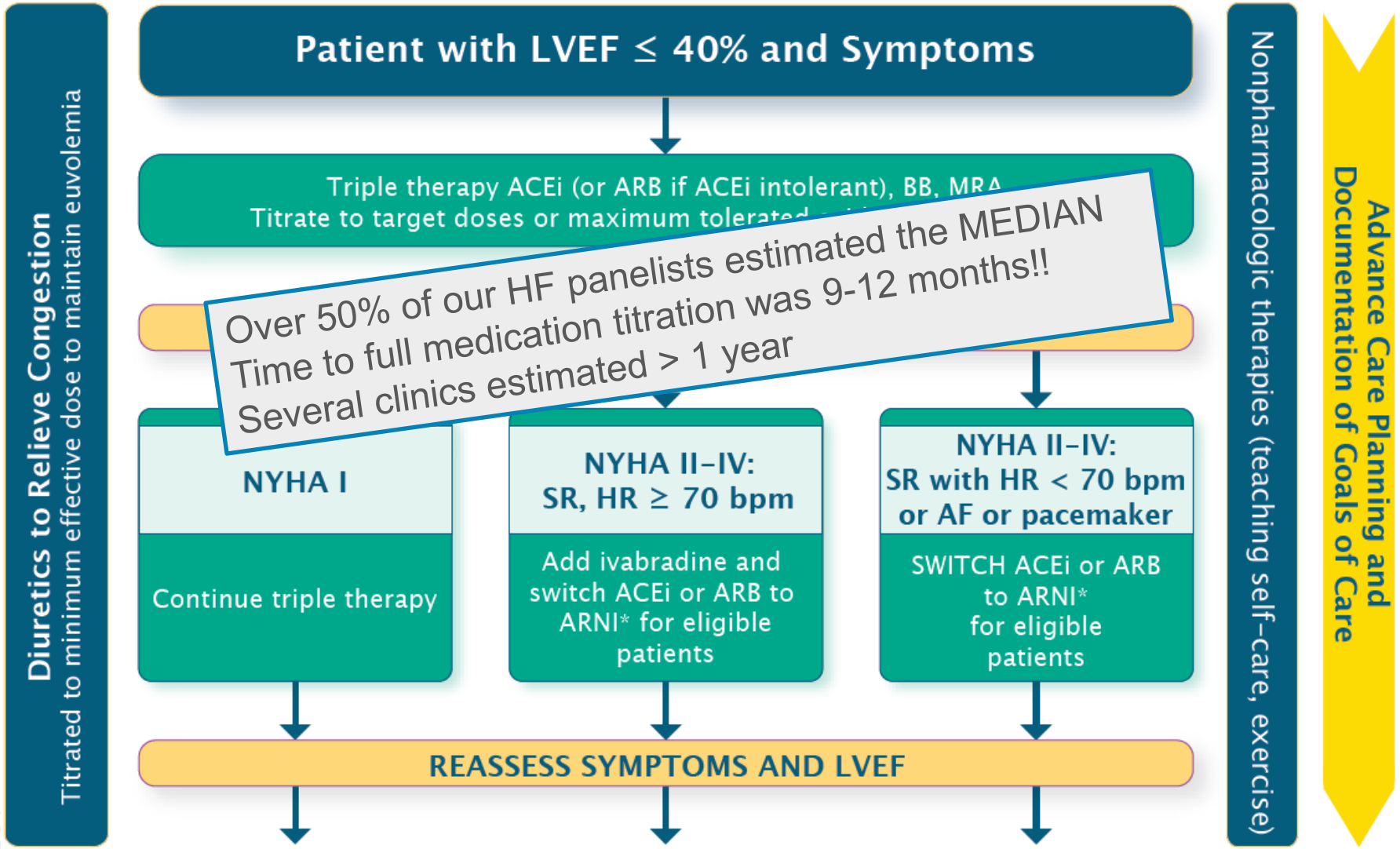
Aimilia Exarchakou, Bernard Rachet, Aurélien Belot, Camille Maringe, Michel P Coleman



This is a 16% absolute increase over 20 years which is 50% more than HF increase in similar time

thebmi | BMJ 2018;360:k764 | doi: 10.1136/bmj.k764

Therapeutic Approach to Patients with HFrEF



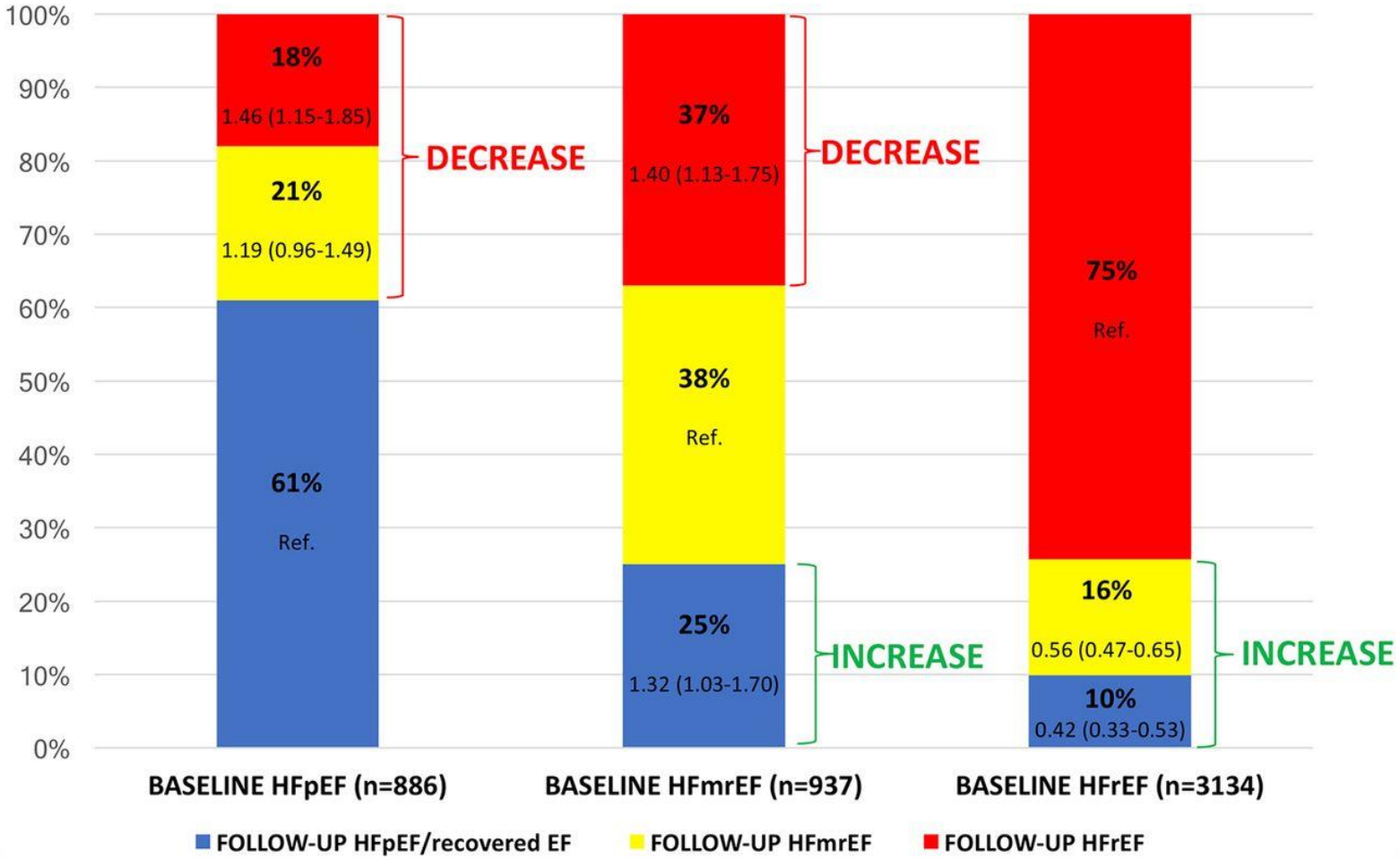
Breast Cancer vs. Heart Failure

- **Similarities:**
  - Common
  - Life threatening
  - Poor quality of life
  - Early treatment improves mortality
  - Improving mortality rates
  - Highest long term risk for mortality in those surviving 2 yrs is CV death
- **Differences:**
  - Malignant vs. degenerative
  - Well organized advocacy groups
  - Combination therapy upfront
  - Early access to treatment
  - National reporting strategy
  - Dedicated formulary committee


Stardate 8130.3:
"THE NEEDS OF THE MANY OUTWEIGH
THE NEEDS OF THE FEW"

LVEF Trends Following Initial Diagnosis of HF

Median Time to Maximal EF Change 14 Months



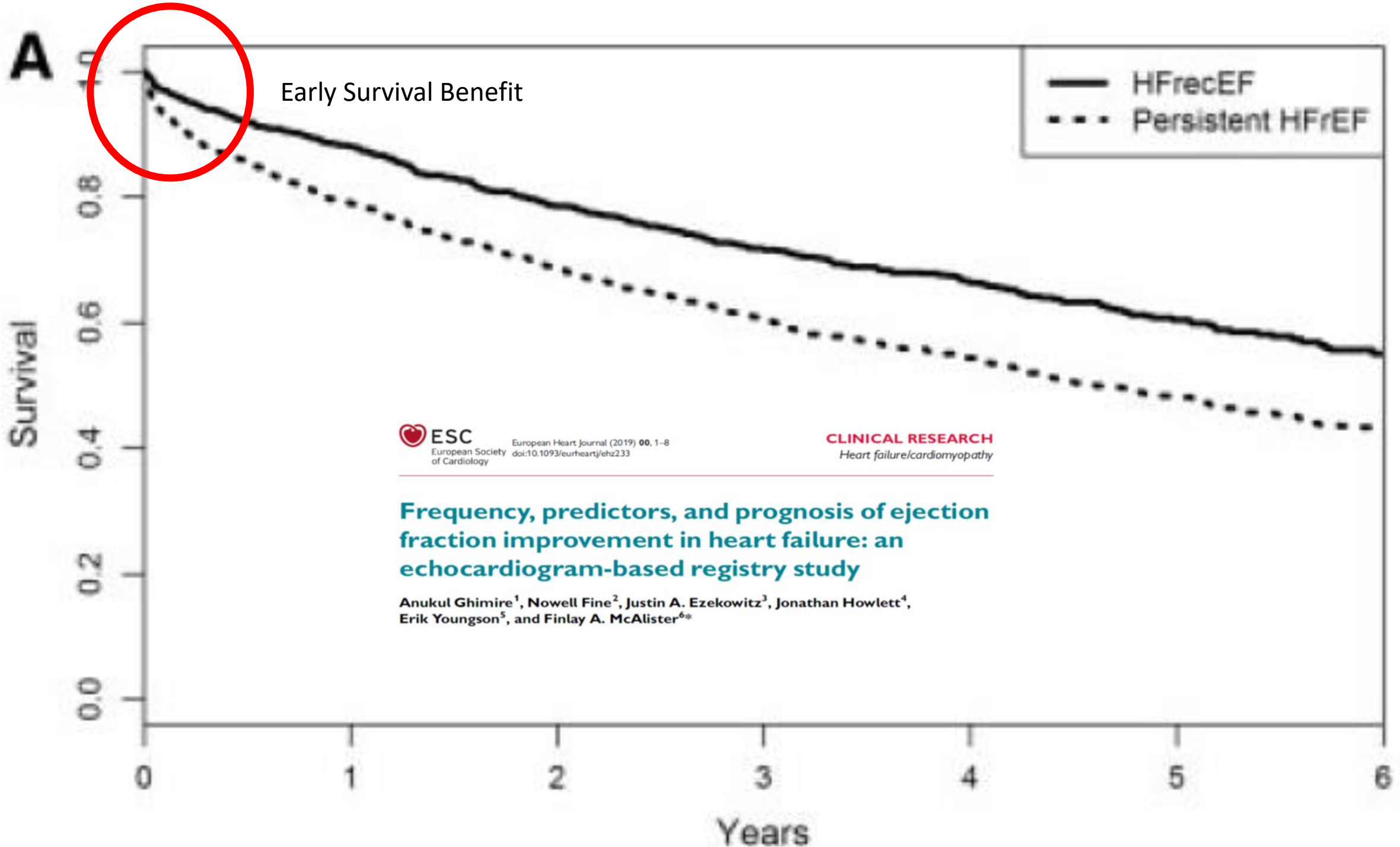
THE MANY

Nearly 75% will need consideration of new therapies when finished titration, however long it takes

THE FEW

Only 25% possibly could have avoided ARNi and SNI

Gianluigi Savarese et al. *JCHF* 2019;j.jchf.2018.11.019



ESC European Society of Cardiology
European Heart Journal (2019) 00, 1–8
doi:10.1093/eurheartj/ehz233

CLINICAL RESEARCH
Heart failure/cardiomyopathy

Frequency, predictors, and prognosis of ejection fraction improvement in heart failure: an echocardiogram-based registry study

Anukul Ghimire[1], Nowell Fine[2], Justin A. Ezekowitz[3], Jonathan Howlett[4], Erik Youngson[5], and Finlay A. McAlister[6]*

How well would this go over?

- You have breast cancer
- We will start with some old drugs and see how you do.
  - We will see you every couple of months
  - We may have to try several times to ensure you are on the highest drug dose of each
- If THAT does not work, we will have to make sure we have done everything we can about you being on all of the other drugs at their optimal levels.
- If you do not respond well to this, we will see if you qualify for 1 or both of 2 newer drugs.
- Once that is done, we will see about getting another drug, but we need to do 3 separate visits first while on the older drugs to see if you qualify.
- If you are hospitalized in the meantime, we might have to start over again as someone might stop one or more of your older drugs…

Time for a Disruption in HF Treatment: Cluster Titration (CT) for HFrEF

Cluster A: Diuretic & SGLTi	Cluster B: ARNi & MRA	Cluster C: BB & SNI
Encounter 1		
Start 1st Med Cluster A	Start 1st med Cluster B	Start 1st med Cluster C
Encounter 2 (whenever feasible)		
Start 2nd med Cluster A	Start 2nd med Cluster B	Start 2nd med Cluster B
Encounter 3 & ongoing (whenever feasible)		
Diuretic titration	Easiest cluster B titration	Alternate Cluster C titration

Three Disruptions for the Treatment of Acute HF

Problem:

1) SLOW uptake and use of EBMT
2) LONG titration even when it happens leaving complications in its wake
3) HIGH hospital readmission and poor patient experience

Disruption:

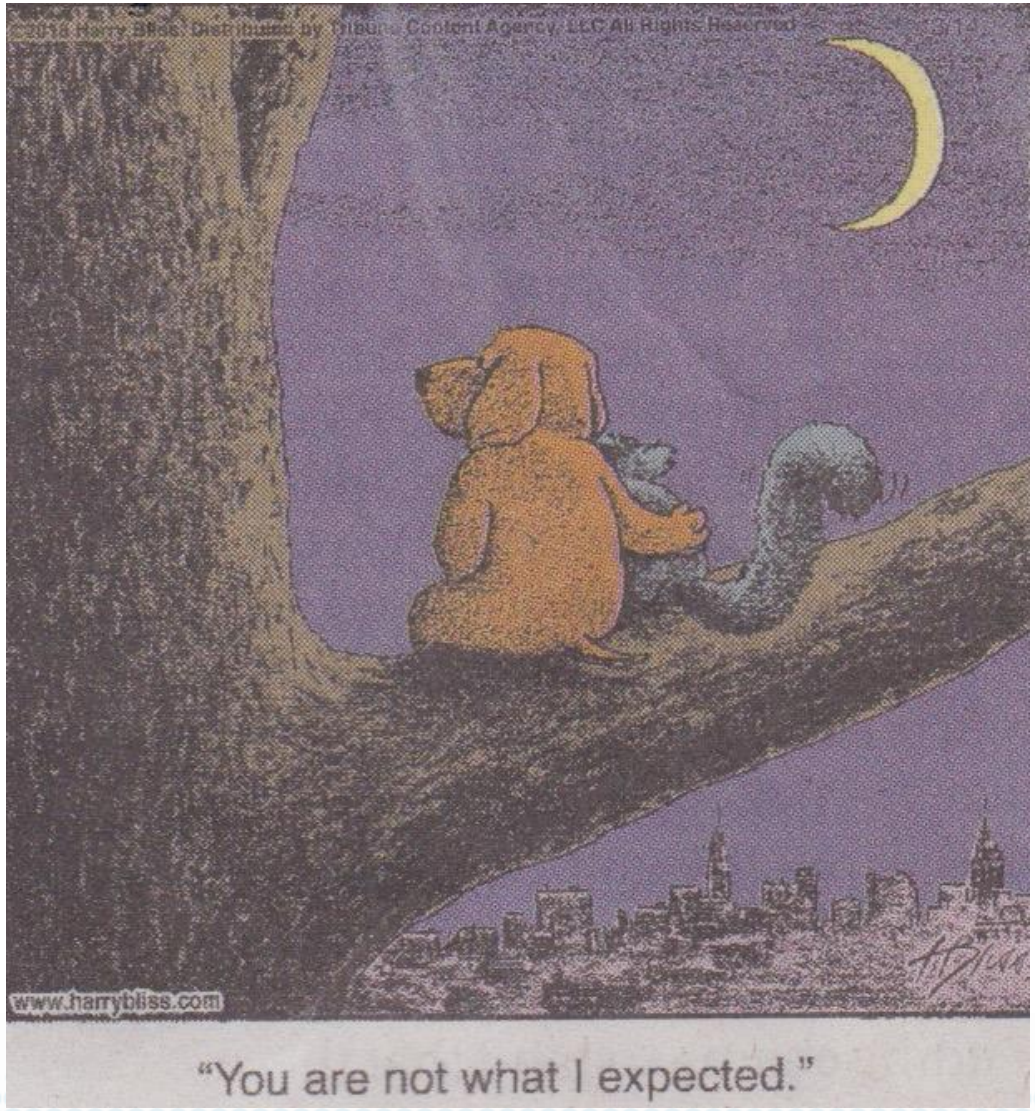
a) STOP ACE, GET BNP and LVEF on admission

b) Start ALL medical therapies upfront with Cluster titration

Pragmatic, easiest titration

c) EARLY follow up with PCP and specialist – 7 days (one or the other)

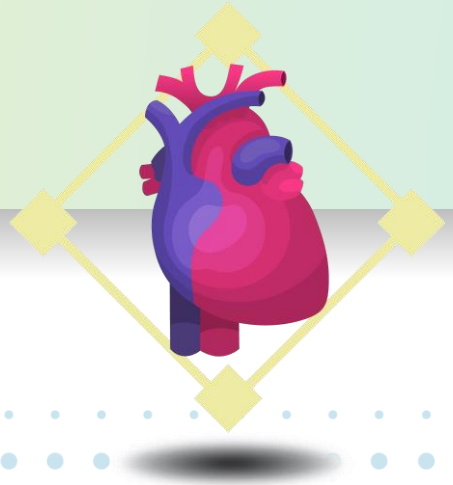
Let the Hospital be Your Friend…



Imaging the Heart: Early Impact of Lowering HR on Heart Function

Kim Connelly

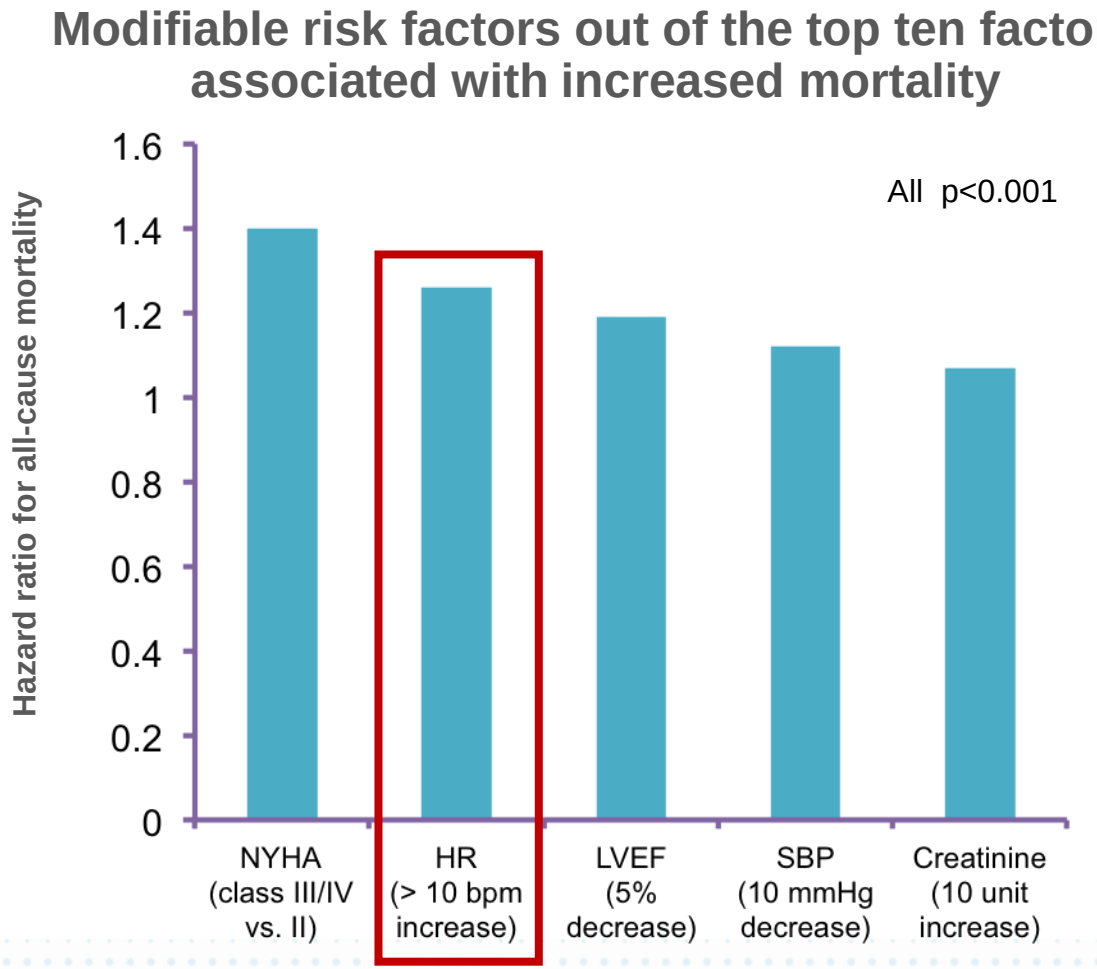
MBBS, FRACP, PhD



Objectives

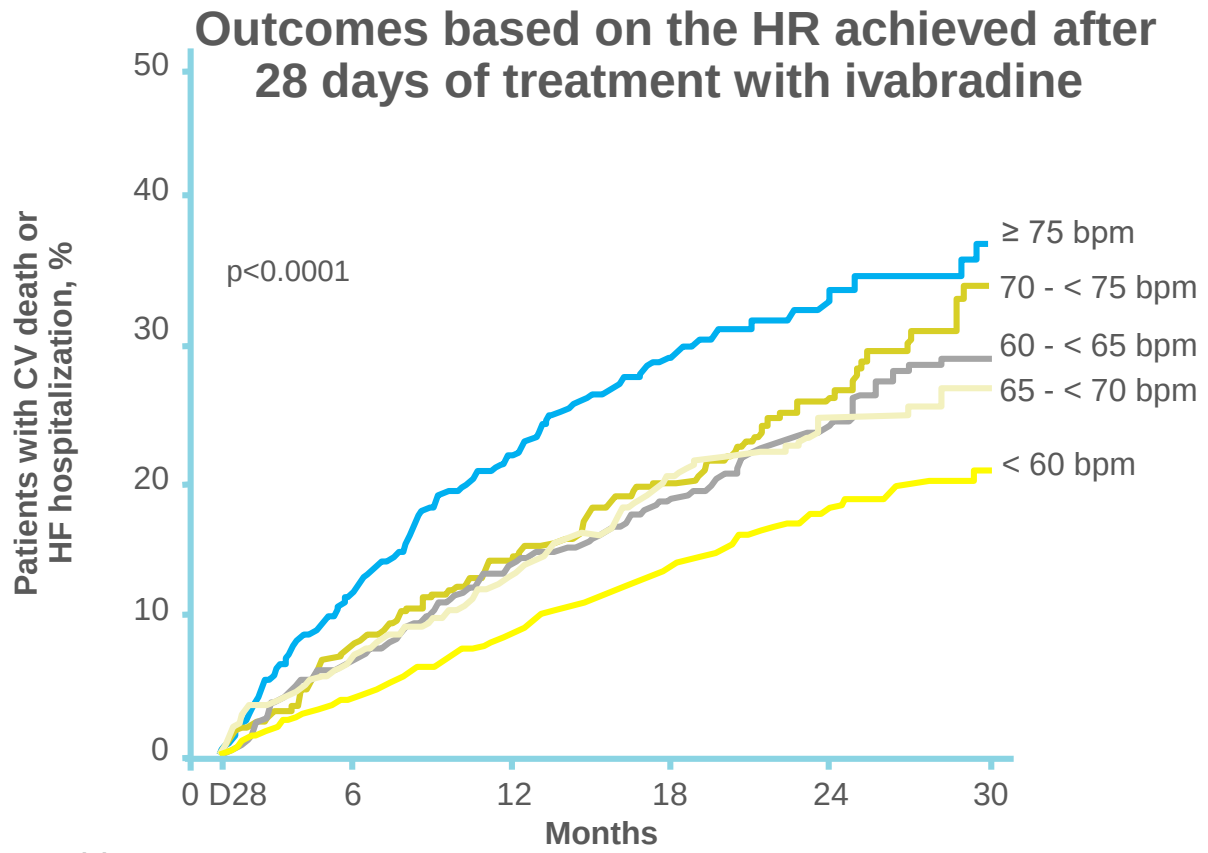
- Discuss HR as an independent risk factor for adverse CV outcomes
- Review impact of HR modulation upon cardiac functional outcomes
- Discuss potential mechanism behind beneficial effects

Heart Rate is Independently Linked to a Significant Increase in All-cause Mortality



Ford et al. *Int J Cardiol* 2015;184: 163-9 (Shift sub-analysis).

Lowering Heart Rate Impacts on Prognosis



No. at risk						
≥ 75 bpm	527	451	376	291	141	47
70 to < 75 bpm	344	314	276	221	116	41
65 to < 70 bpm	444	404	358	287	149	62
60 to < 65 bpm	605	556	488	407	176	59
< 60 bpm	1 192	1 132	1 004	842	414	162

Böhm et al. *Lancet* 2010; 376: 886-94.

Independent Risk Factor: Prognostic of Heart Rate from the PARADIGM-HF Study

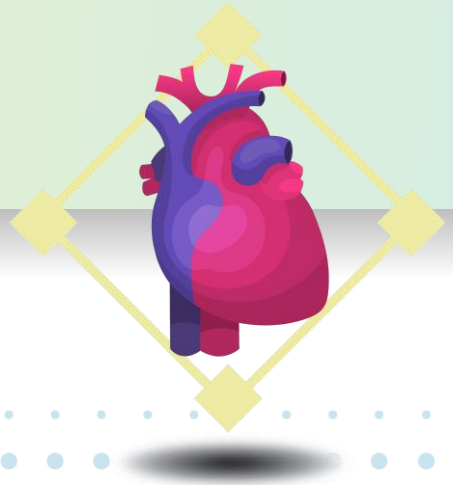
8399 patients from Paradigm-HF

- Baseline HR: 72bpm
- End of study HR: 72bpm

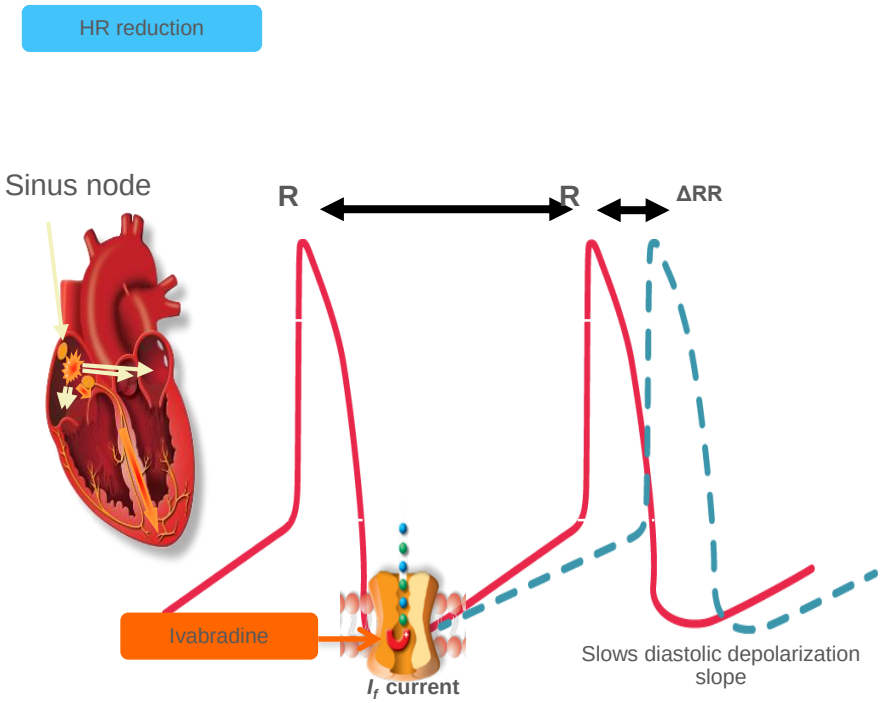
	Adjusted hazard ratio		
	Tertile 1- Reference Group (≤ 66 bpm)	Tertile 2 (67-76 bpm)	Tertile 3 (≥ 77 bpm)
Primary endpoint	1.00	1.19 1.05-1.35	1.24 1.09-1.43
CV Death	1.00	1.19 1.01-1.40	1.24 1.04-1.47
Heart failure hospitalizations	1.00	1.18 0.99-1.39	1.37 1.15-1.63
All-cause Mortality	1.00	1.23 1.07-1.42	1.27 1.08-1.48

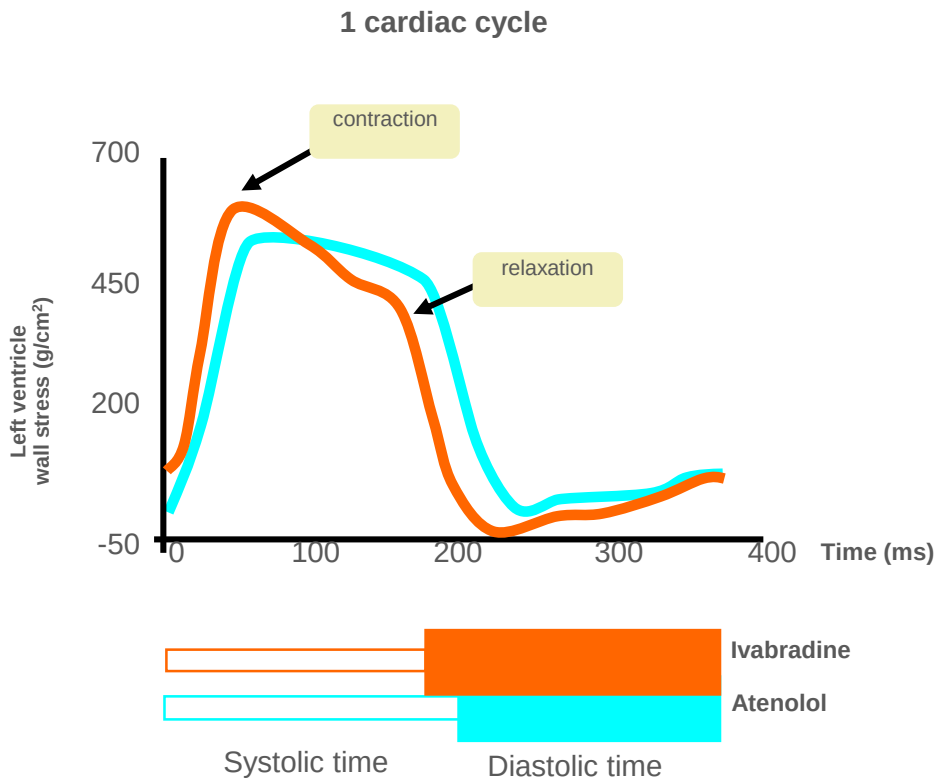
McMurray, *NEJM*, 2014, 371, 993-1004
Castagno D, et al. Poster presented at Heart Failure, May 21–24, 2016, Florence, Italy

Ivabradine: Heart Rate Reduction and Benefits on Mortality/Morbidity



Ivabradine MOA and Physiological Effect



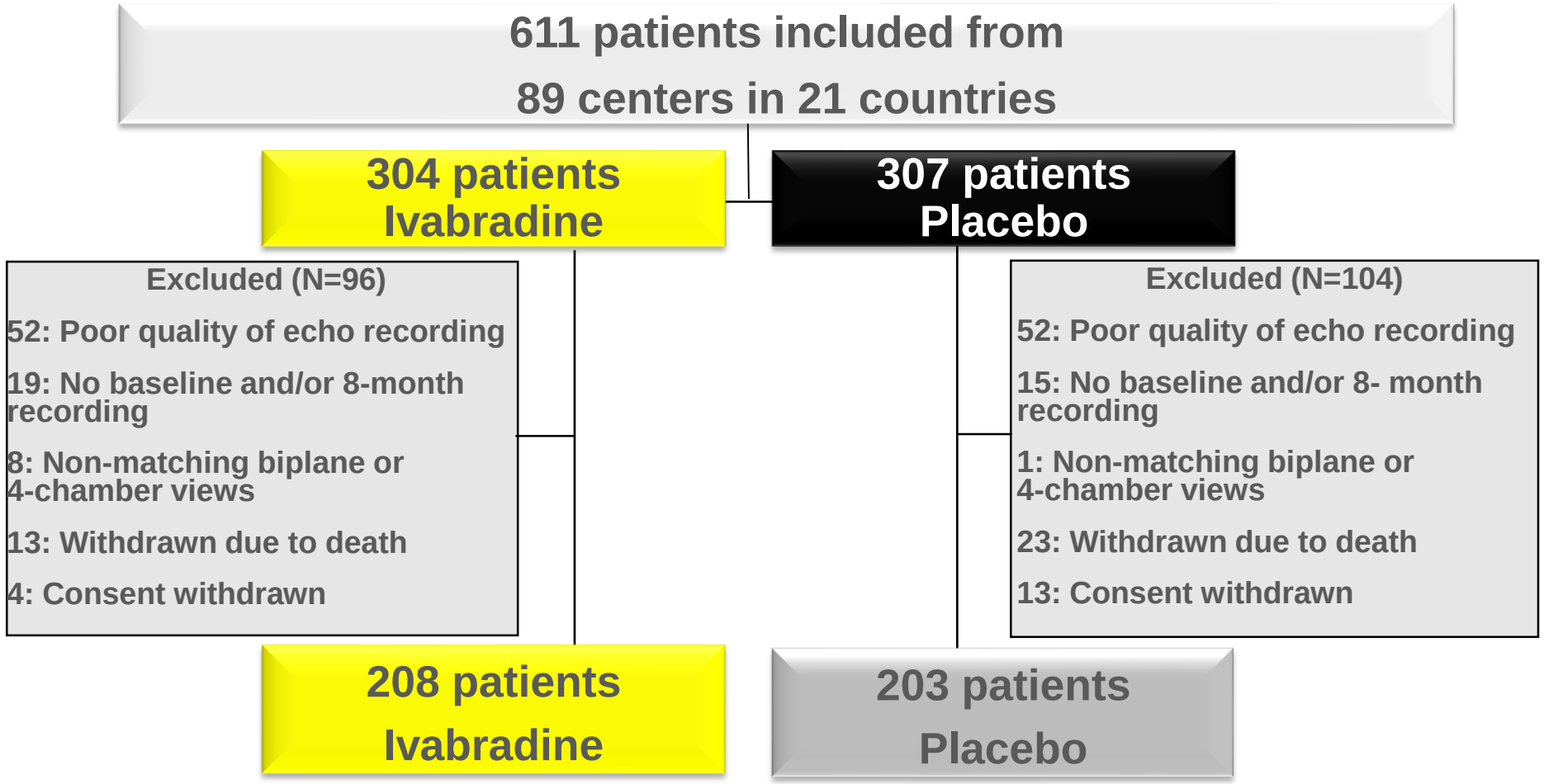


DiFrancesco & Camm. Drugs 2004; 64 (16): 1757-65.
Colin et al. *Am J Physiol Heart Circ Physiol* 2002; 282: H672-9
Reil JC et al. *JACC* 2013, 62, 1977-1985

Background

- Cardiac remodeling is central to the pathophysiology of heart failure (HF) and is a prognostic factor in patients with HF
- Left ventricular (LV) enlargement and reduced ejection fraction are powerful predictors of outcomes in heart failure
- Therapeutic effects of drugs and devices on LV remodeling are associated with their longer-term effects on mortality

Sub-study Population



Median follow-up after 8-month echocardiogram: 16.1 months

Tardif JC, O'Meara E, Komajda M, et al. *Eur Heart J*. 2011;32(20):2507-15
www.shift-study.com

Baseline Characteristics

	Ivabradine N=304	Placebo N=307
Mean age, years	60	59
Male, %	80	82
Mean BMI, kg/m^2	28	28
Mean HF duration, years	4	4
HF ischaemic cause, %	67	65
NYHA class II, %	48	46
NYHA class III, %	51	53
Mean LVEF, %	32	32
Mean HR, bpm	78	79
Mean systolic BP, mm Hg	121	119
Mean diastolic BP, mm Hg	75	75

Tardif JC, O'Meara E, Komajda M, et al. *Eur Heart J.* 2011;32(20):2507-15
www.shift-study.com

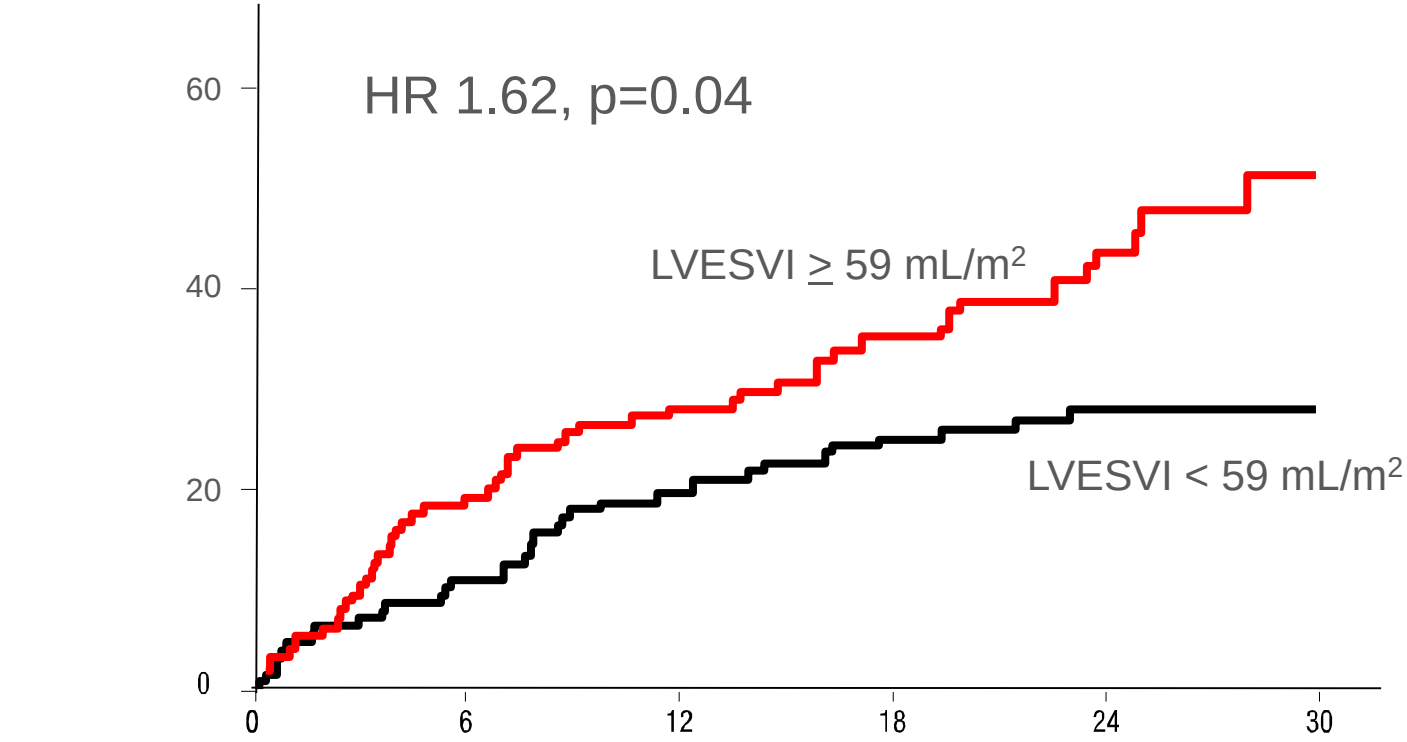
Baseline Background Treatment

	Ivabradine N=304	Placebo N=307
Beta-blocker, %	92	92
ACE inhibitor, %	80	83
ARB, %	17	12
Diuretic (excludes antialdo), %	87	87
Aldosterone antagonist, %	74	71
Digitalis, %	27	32
Devices, %	3	4

Tardif JC, O'Meara E, Komajda M, et al. *Eur Heart J*. 2011;32(20):2507-15
www.shift-study.com

LV End-systolic Volume Index and Outcome in the Placebo Group

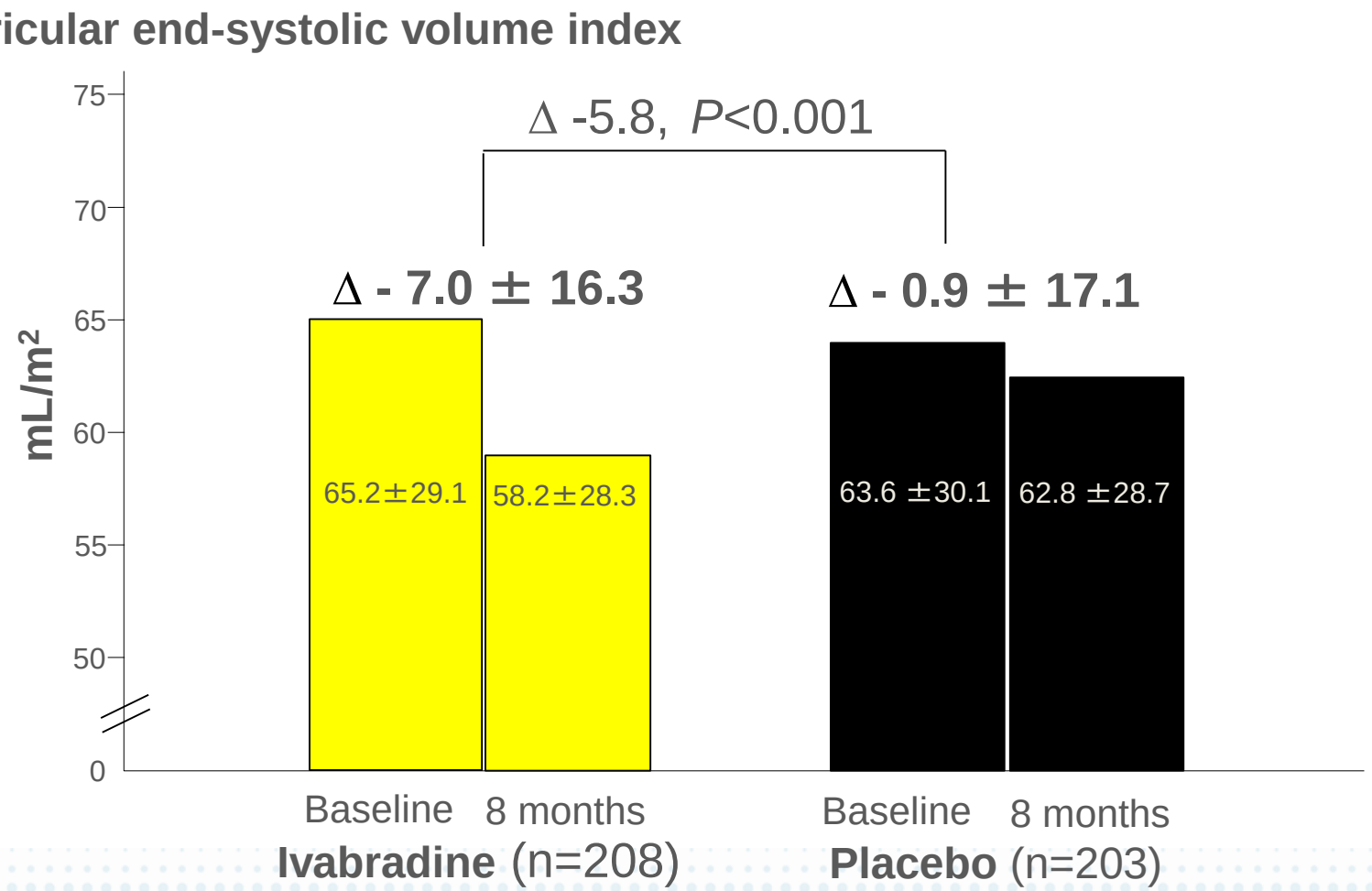
Patients with primary composite endpoint, %



Number at risk						
LVESVI ≥59 mL/m²	131	104	93	84	38	13
LVESVI <59 mL/m²	132	118	107	100	49	19

Tardif JC, O'Meara E, Komajda M, et al. *Eur Heart J*. 2011;32(20):2507-15
www.shift-study.com

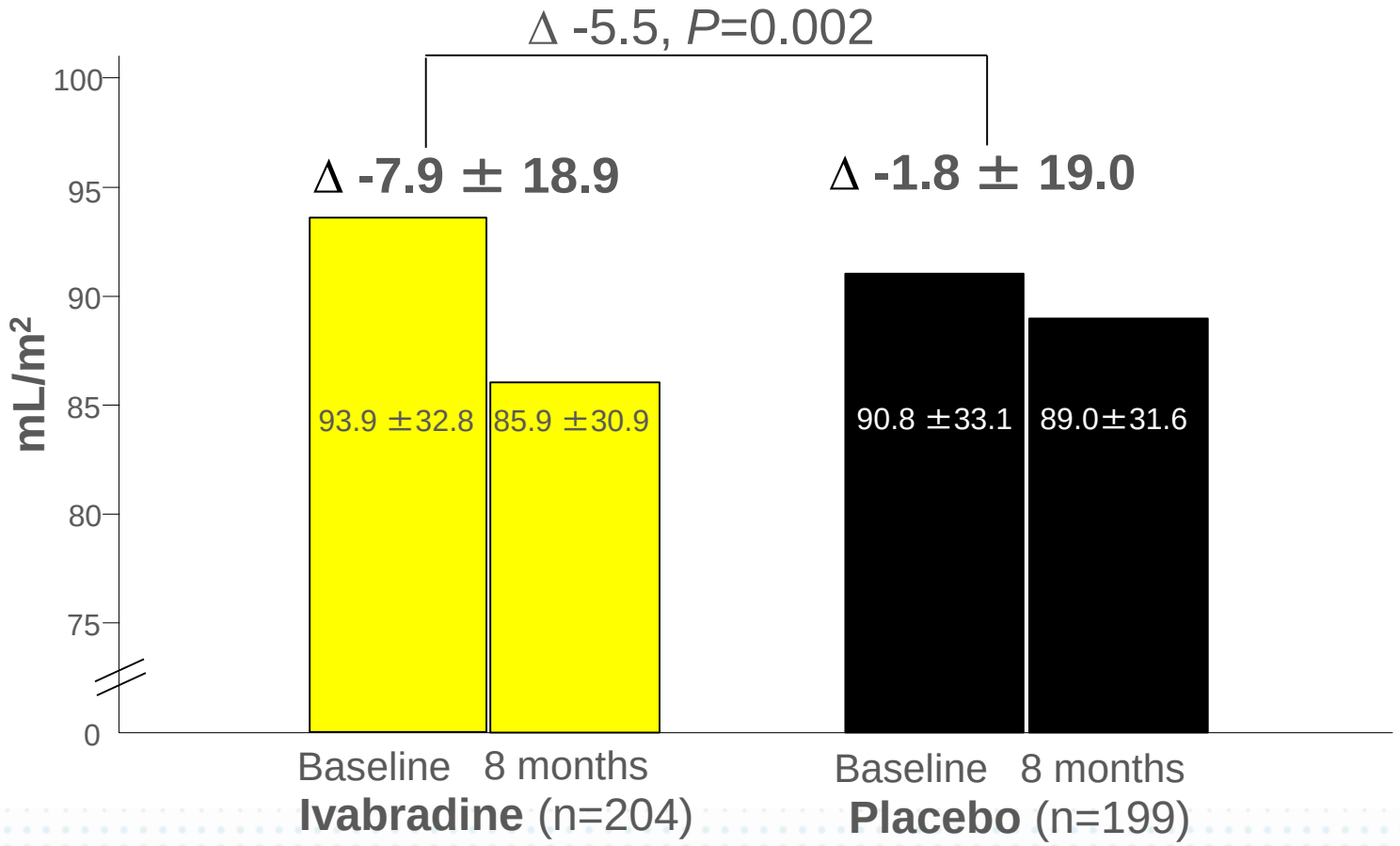
Primary Endpoint: Change in LVESVI from Baseline to 8 Months



Tardif JC, O'Meara E, Komajda M, et al. *Eur Heart J*. 2011;32(20):2507-15
www.shift-study.com

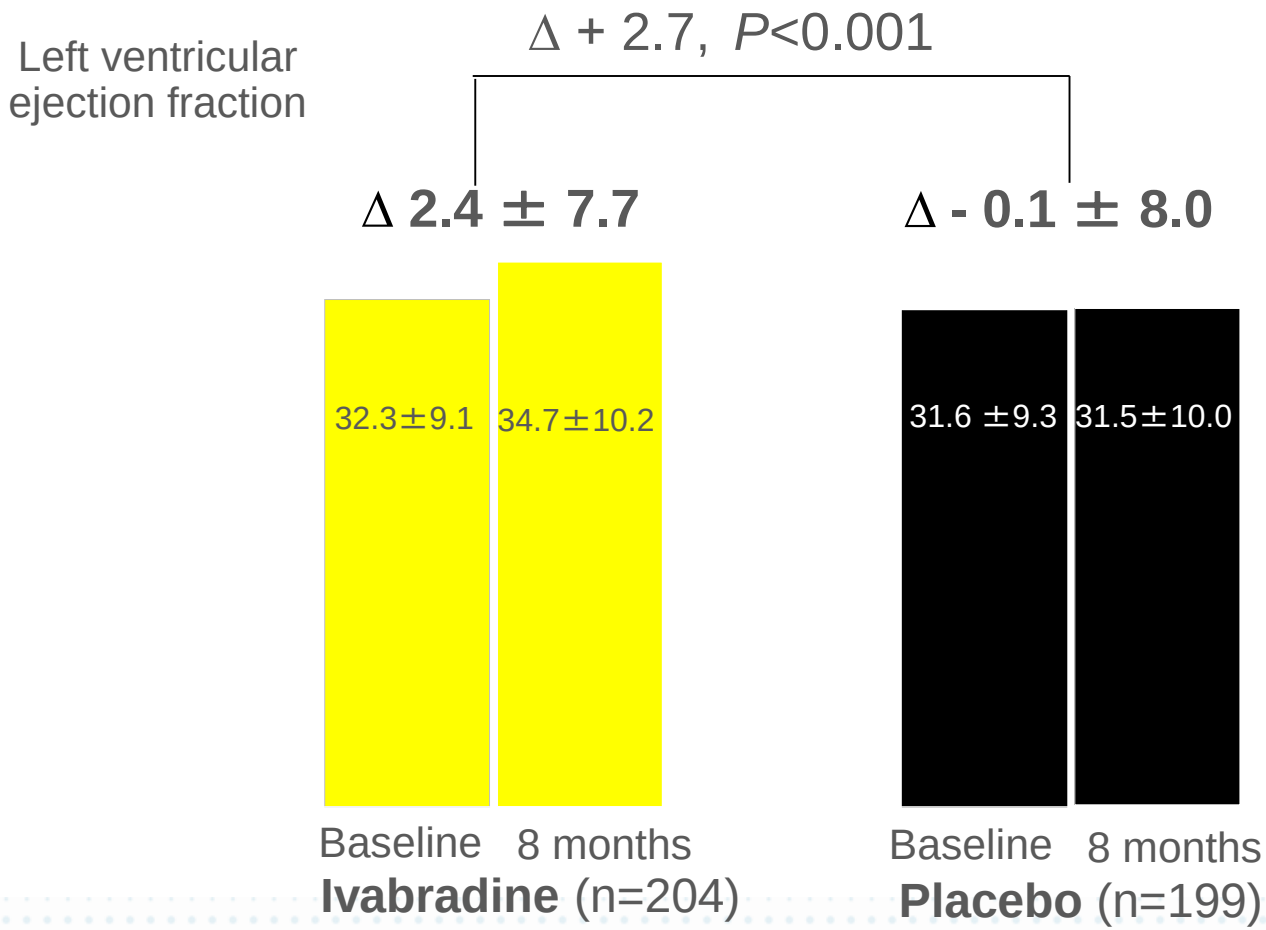
Secondary Endpoint: Change in LVEDVI from Baseline to 8 Months

Left ventricular end-diastolic volume index



Tardif JC, O'Meara E, Komajda M, et al. *Eur Heart J*. 2011;32(20):2507-15
www.shift-study.com

Secondary Endpoint: Change in LVEF from Baseline to 8 Months



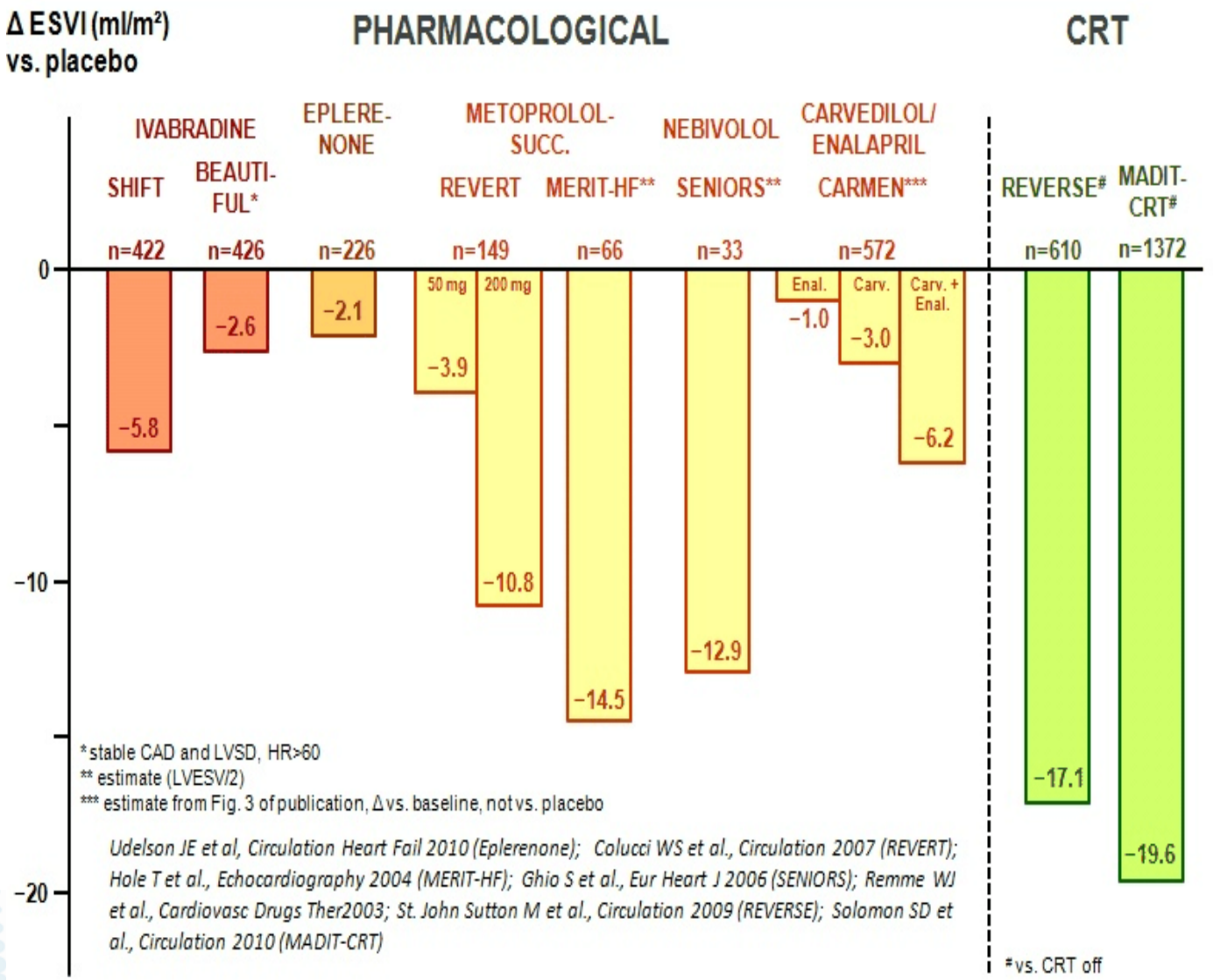
Tardif JC, O'Meara E, Komajda M, et al. *Eur Heart J*. 2011;32(20):2507-15
www.shift-study.com

Summary of Changes in HR, LV End-Systolic/End-Diastolic Volume Indexes

	Ivabradine n=304	Placebo n=307	P
Change in resting HR at 8 months, bpm	- 14.7	- 5.8	<0.001
Change in LVESVI at 8 month, mL/m^2	- 7.0	- 0.9	<0.001
Change in LVEDVI at 8 month, mL/m^2	- 7.9	- 1.8	0.002

Tardif JC, O'Meara E, Komajda M, et al. *Eur Heart J*. 2011;32(20):2507-15
www.shift-study.com

SHIFT Compared to Prior Echo HF Studies



Impact of Evidence-based Therapies on LVEF

	Number of Studies (n)	ΔEF (IC 95%)	Mean Follow-up (weeks)
Bisoprolol	1 (28)	12,0 (4,4-19,6)	52
Metoprolol CR	4 (587)	4,5 (1,8-7,1)	25,5
Enalapril	6 (431)	3,7 (1,5-5,9)	24
Spironolactone	3 (185)	3,0 (1,9-4,1)	25,7
CRT	4 (1052)	2,7 (1,9-3,5)	21
Ivabradine	1 (411)	2.7 (1.3-4.2)	35

Conclusions

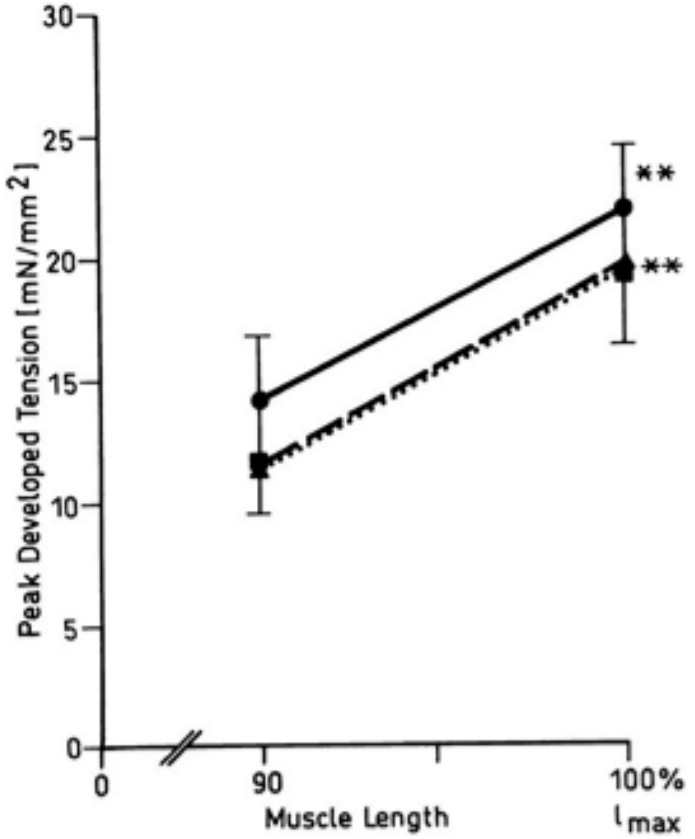
- Heart rate reduction with ivabradine reverses left ventricular remodeling in patients with heart failure and LV systolic dysfunction:
  - Marked reductions of LV volumes
  - Significant improvement of LV ejection fraction
- These results suggest that ivabradine modifies disease progression in patients with HF receiving background therapy

Tardif JC, O'Meara E, Komajda M, et al. *Eur Heart J*. 2011;32(20):2507-15
www.shift-study.com

But what about mechanism?

Better Filling Increases Contractility

Developed force



Healthy heart

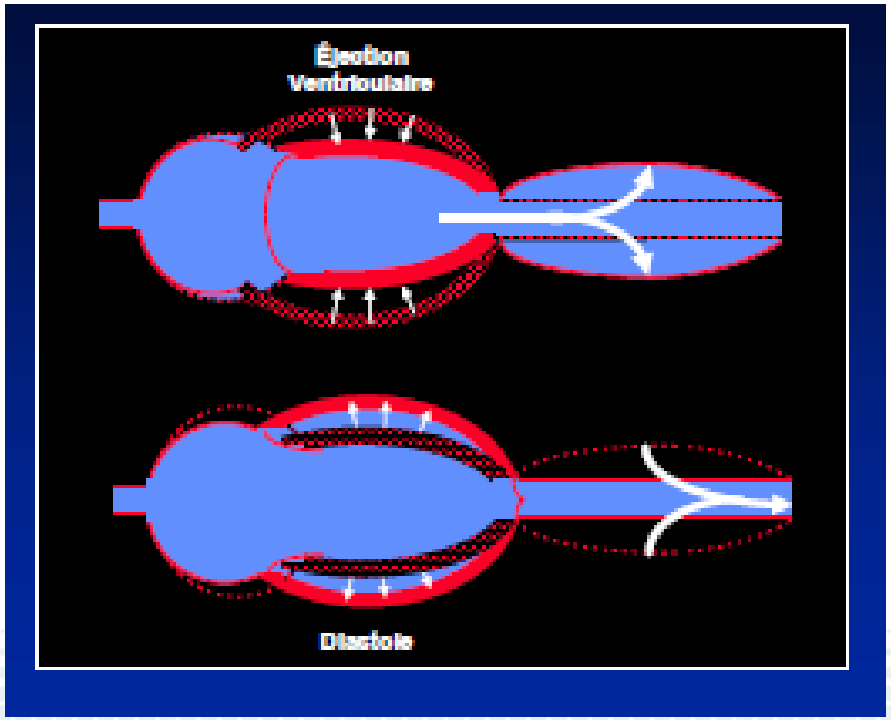
Failing heart

Muscle length

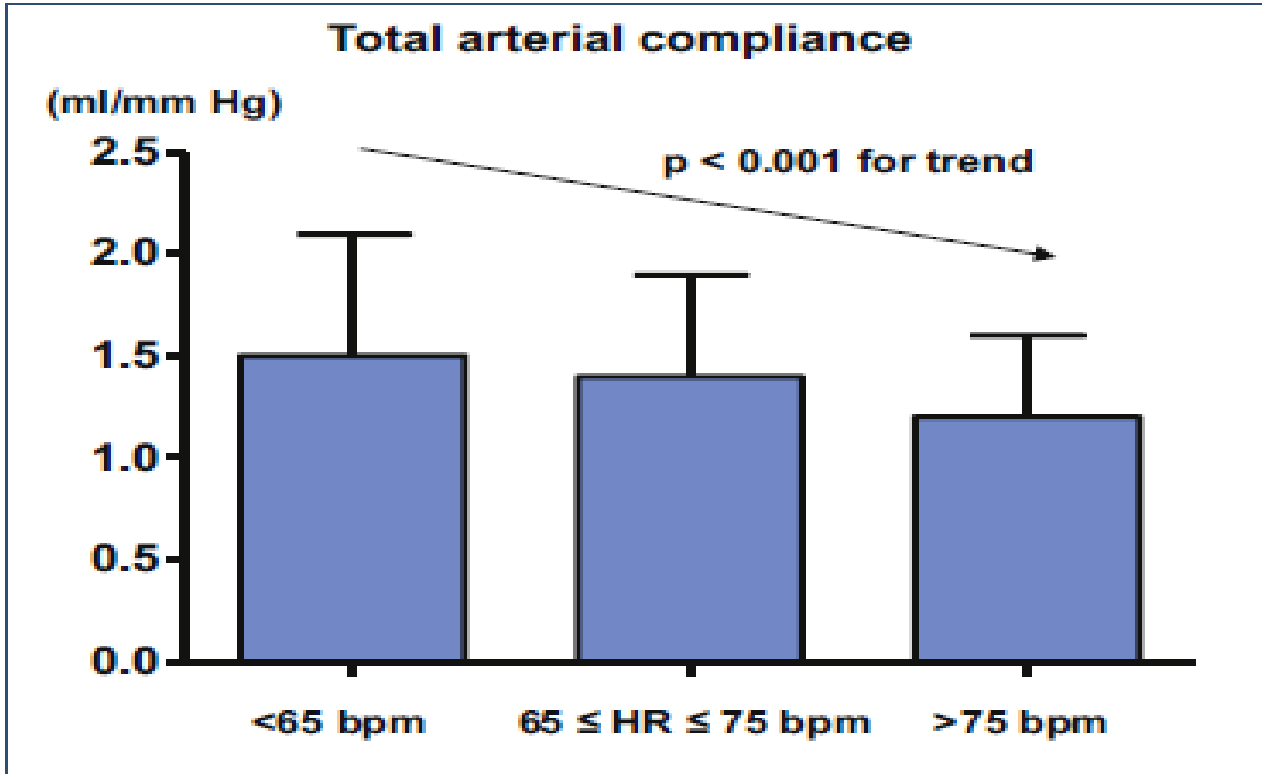
Holubarsch C. et al. *Circulation* 1996

Link Between Afterload and Aortic Elastance

- Afterload has two principal components:
  - Fixed component: total peripheral resistance = Pam/Qc
  - Pulsatile component: arterial compliance



As Heart Rate Increases, Arterial Compliance Decreases



Reil J-C al. *JACC* 2013

Cross-Over Study in Permanently Paced Systolic Heart Failure Patients

Table I Baseline characteristics of the 12 patients who completed the study

Age (years)	68 ± 8
Male/female	11/1
NYHA class (II/III)	7/5
LVEF (%)	23 ± 10
Ischaemic/non-ischaemic	7/5
Treatment, *n* (%)	
ACEI/ARA2, *n* (%)	12 (100%)
Beta-blocker, *n* (%)	12 (100%)
Spironolactone, *n* (%)	7 (58%)
Furosemide[a] (mg/day)	72 ± 16
Amiodarone, *n* (%)	3 (25%)
Digoxin, *n* (%)	3 (25%)
Atrial fibrillation, *n* (%)	2 (17%)
Pacing heart rate (b.p.m.)	62.9 ± 5.0

[a]All patients received furosemide.

Logeart D et al. *Eur J HF* 2009

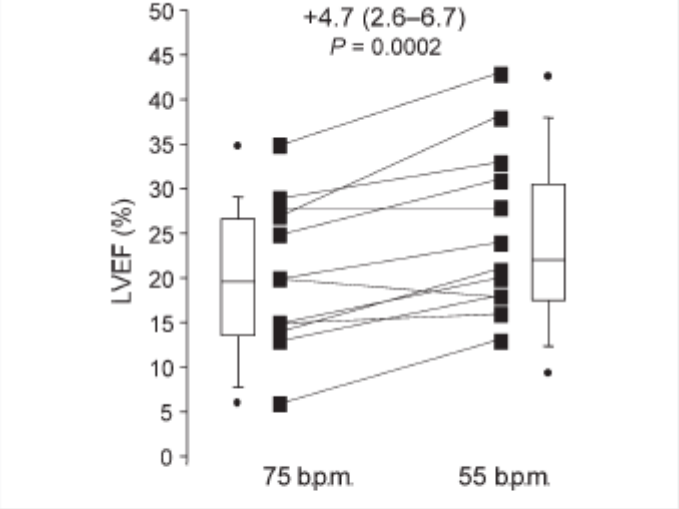


Figure 1 Left ventricular ejection fraction (LVEF) at the end of the two 3-month periods, according to the tested pacing rate. Box-plots show median, 50th and 75th percentiles.

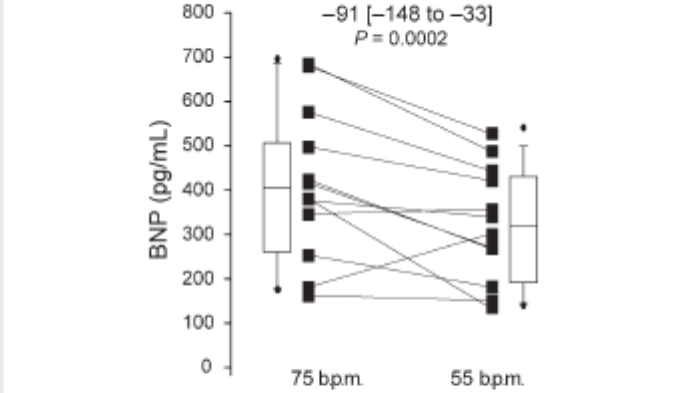
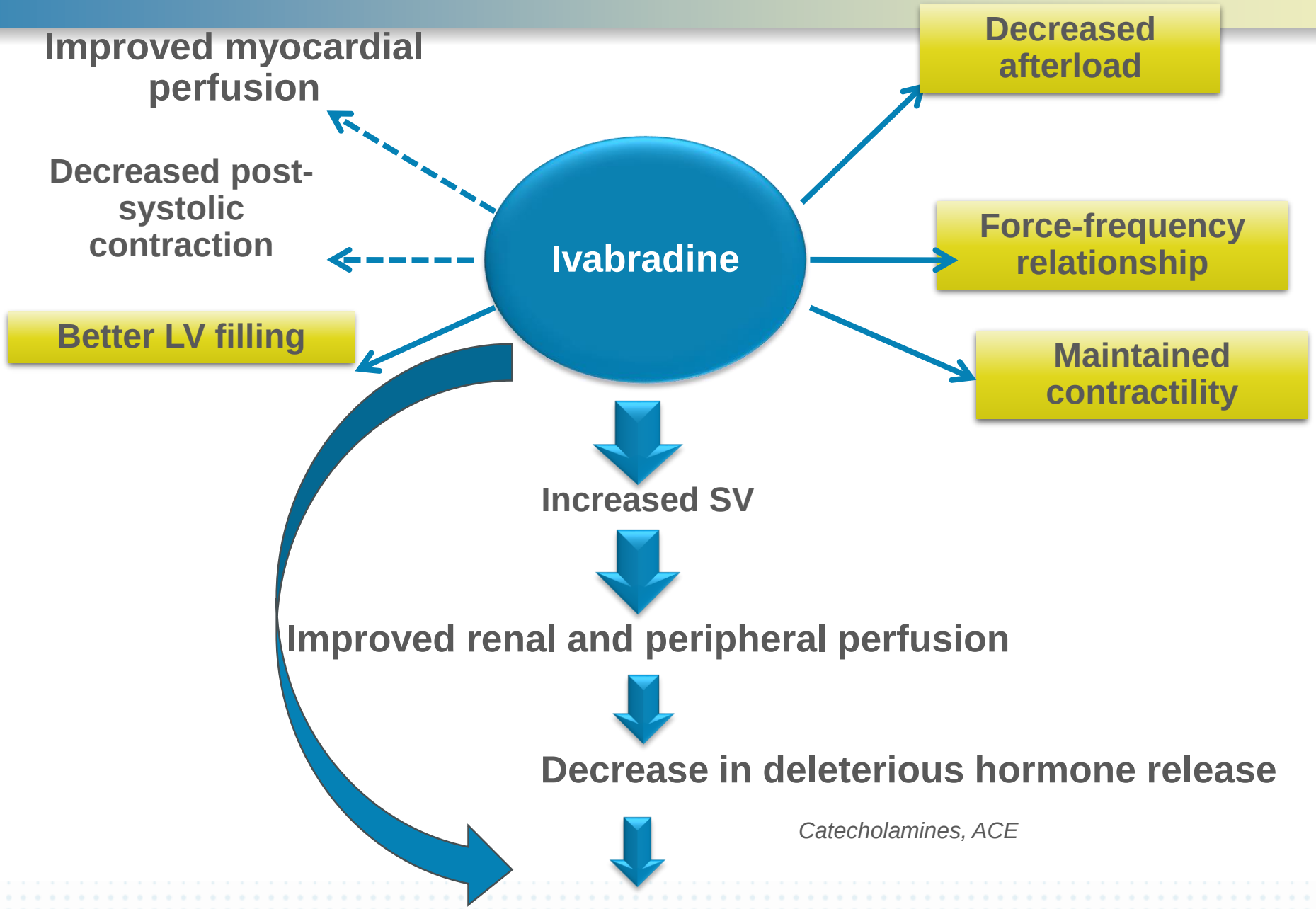


Figure 2 Blood B-type natriuretic peptide (BNP) levels at the end of the two 3-month periods, according to the tested pacing rate. Box-plots show median, 50th and 75th percentiles.

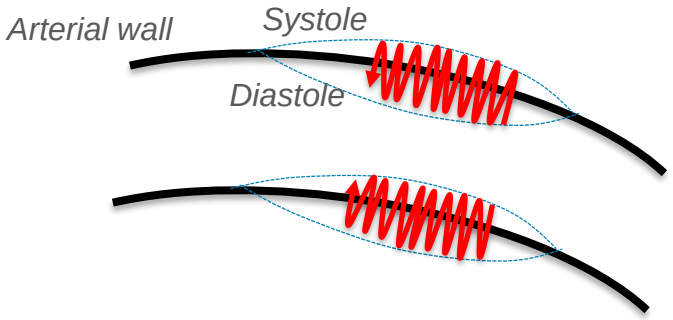
Table 2 Systolic blood pressure and echographic results at the end of the two 3-month periods

Mean ± 1SD	Systolic blood pressure (mmHg)	LV end-diastolic diameter (mm)	LV end-systolic diameter (mm)	Stroke volume (mL)	Cardiac index (L/min/m^2)	Doppler, E/E_a
55 b.p.m.	112.5 ± 17.1	70.0 ± 6.2	63.0 ± 6.9	67 ± 28	2.03 ± 0.33	11.9 ± 3.3
75 b.p.m.	110.0 ± 15.7	69.4 ± 6.2	61.6 ± 7.1	49 ± 21	1.93 ± 0.34	13.2 ± 3.2
Delta 55–75 b.p.m.	+2.5 ± 4.9	+0.6 ± 2.3	−1.4 ± 1.9	+18 ± 15	+0.10 ± 0.24	−1.3 ± 2.3
P-value	0.10	0.19	0.03	0.001	0.17	0.07

Logeart D et al. *Eur J HF* 2009


Improved myocardial perfusion
Decreased post-systolic contraction
Better LV filling
Ivabradine
Decreased afterload
Force-frequency relationship
Maintained contractility
Increased SV
Improved renal and peripheral perfusion
Decrease in deleterious hormone release
Catecholamines, ACE
Reverse remodelling

How could reducing heart rate improve arterial elastance?



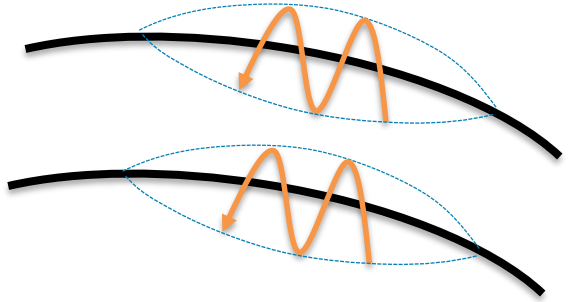
Placebo

↑ number of contraction/relaxation cycles

↑ muscle tone (↓ elasticity)

↑ afterload

↓ stroke volume



Ivabradine

↓ number of contraction/relaxation cycles

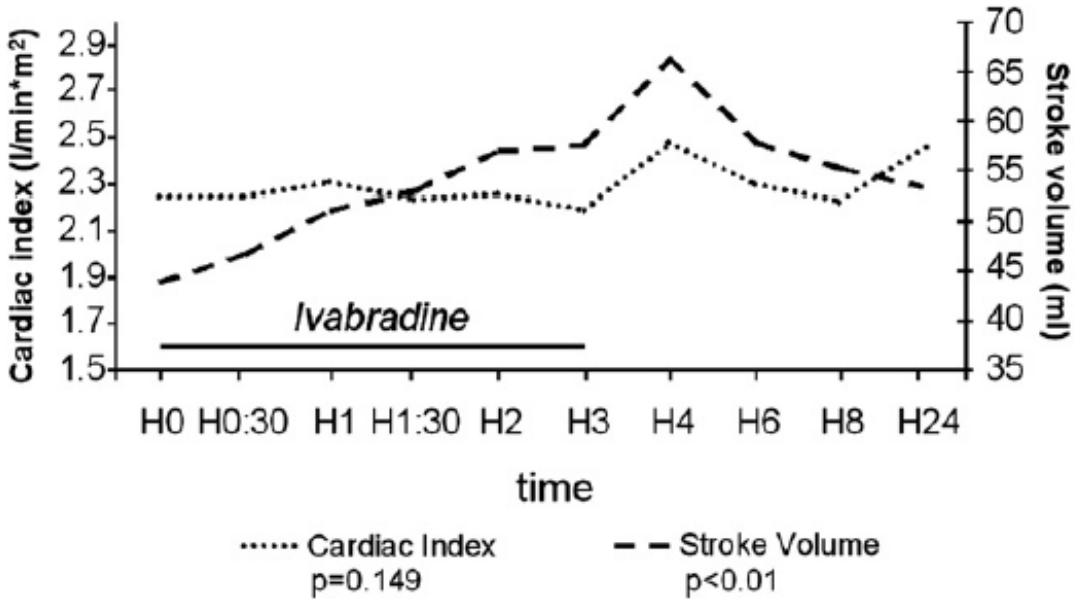
↓ muscle tone (↑ elasticity)

↓ afterload

↑ stroke volume

Ivabradine Infusion Leads to an Immediate Increase in Stroke Volume

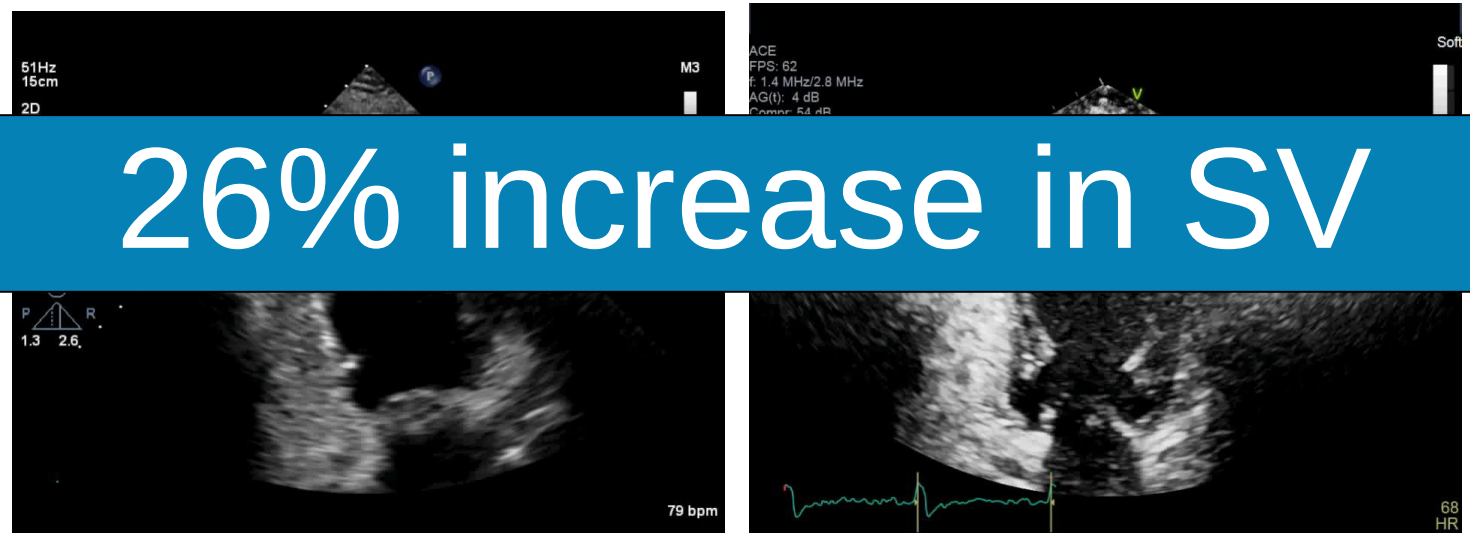
10 severe heart failure patients (NYHA III), with advanced systolic dysfunction (Mean LVEF 21%) and HR ≥ 80 bpm treated with ACE I and beta-blockers



→ In severe systolic heart failure patients IV administration of ivabradine leads to a significant 51% increase in stroke volume.

Ferrari GM et al. *Eur J Heart Failure* 2008

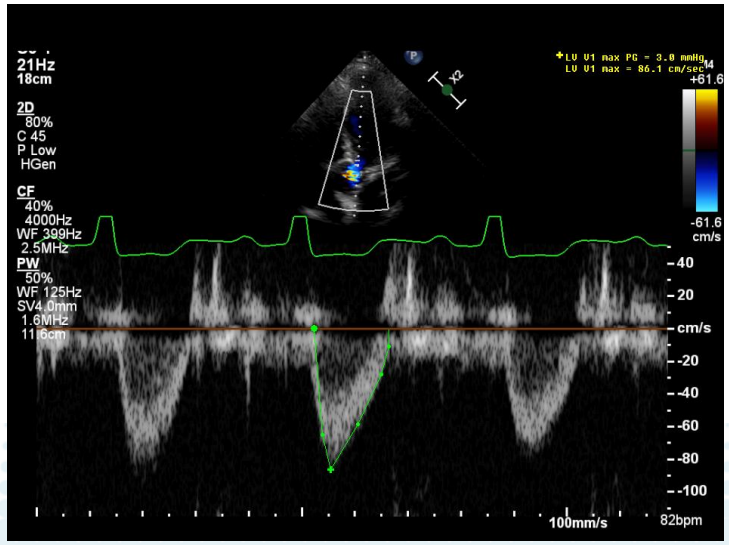
Acute Effects: 9 Days Post-IVA Administration...

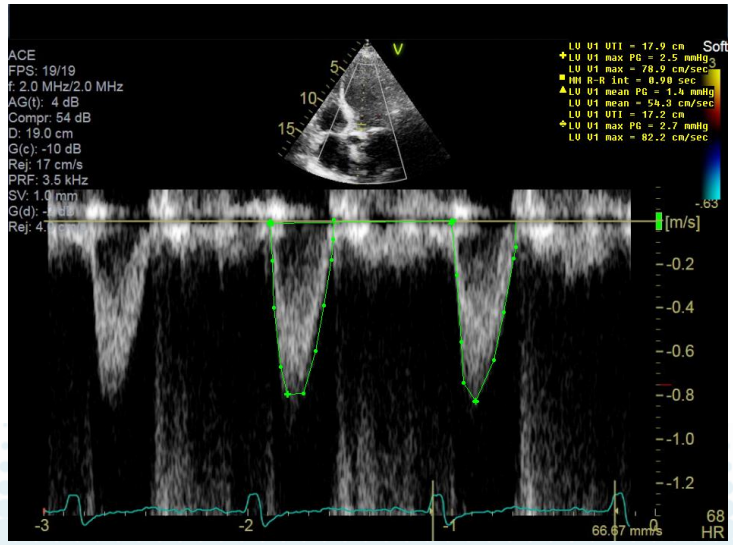


26% increase in SV

SV=

46ml



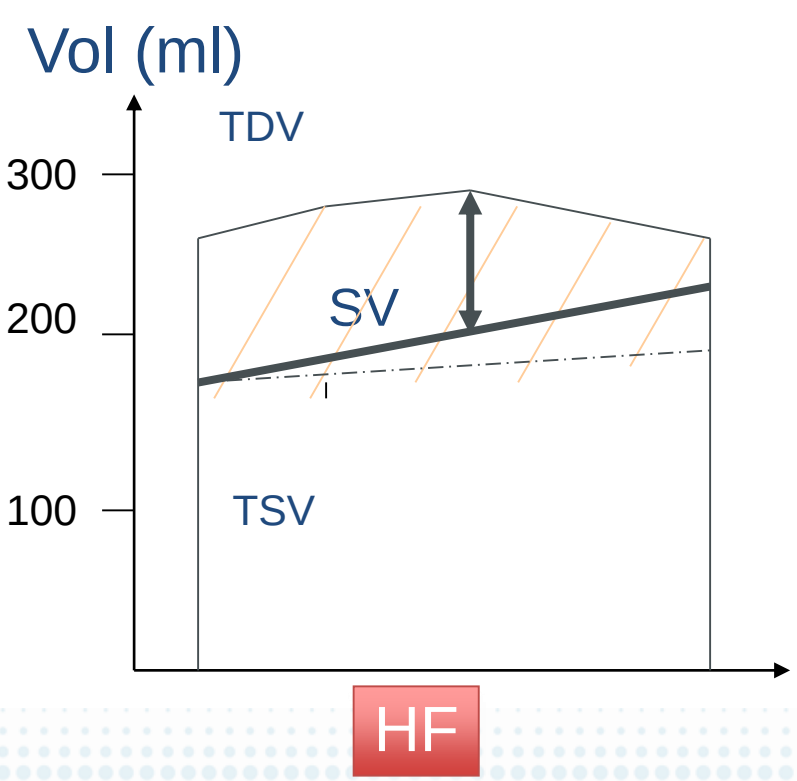


SV=

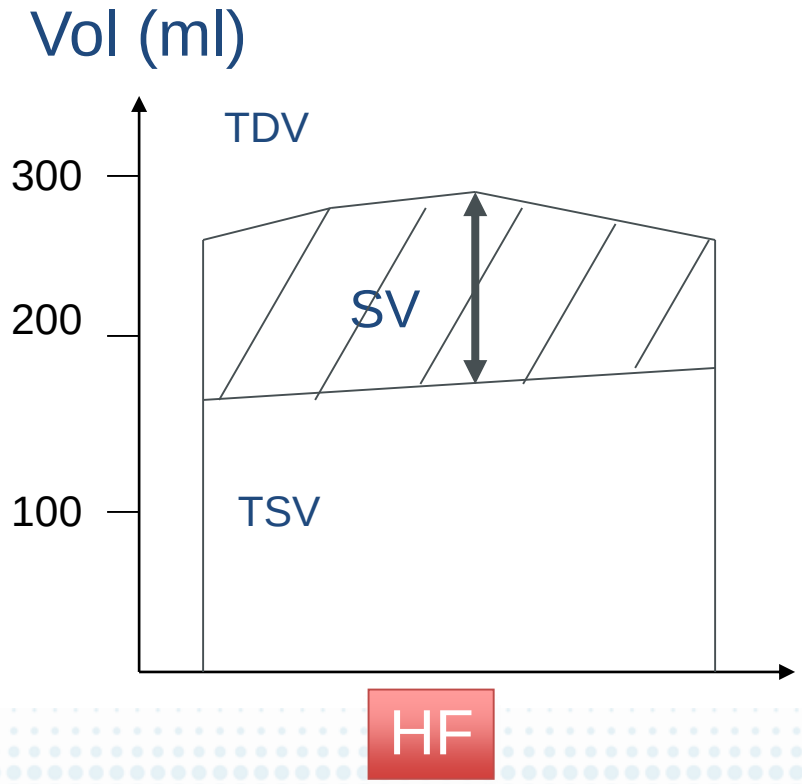
58ml

Immediate Effects on Stroke Volume

Beta-blocker:
HR and inotropic reduction



Ivabradine:
Pure HR reduction



Beta-blocker Infusion Has No Effect on Stroke Volume

24 patients with heart failure (FEVG < 40%), beta-blocker infusion IV

TABLE 5. Hemodynamic Response to Metoprolol Versus Propranolol in Patients With Congestive Heart Failure

	Metoprolol (n=12)	Propranolol (n=12)
Heart rate, bpm		
Pre	91±3	85±3
Post	73±2*	72±2*
Ejection fraction, %		
Pre	20±2	27±2‡
Post	24±3*†	27±3
LVEDV, mL		

TABLE 5. Continued

	Metoprolol (n=12)	Propranolol (n=12)
Systolic function		
LVSP, mm Hg		
Pre	136±10	143±9
Post	120±7*	131±9*
SVI, mL/M^2		
Pre	26±2	31±2
Post	29±3	31±2

SVI: Stroke Volume Index (Volume d'éjection systolique)

Haber HL et al. *Circulation* 1993

Increased Stroke Volume Persists Over the Long Term

Echocardiography study in 275 heart

months)

Table 3 Influence of Selective Heart Rate Reduction With Ivabradine on Hemodynamic Parameters After 8 Months of Treatment Compared With Placebo

Parameter	Ivabradine (n = 143)	Placebo (n = 132)	p Value
Heart rate, beats/min			
At baseline	71 ± 12	71 ± 11.0	0.71
At 8 months	60 ± 10	68 ± 12	<0.0001
Change from baseline to 8 months	−11 ± 13	−2 ± 12	<0.0001
p Value vs. baseline	<0.0001	0.015	
Pulse pressure, mm Hg			
At baseline	47 ± 12	45 ± 11	0.28
Stroke volume, ml			
At baseline	59 ± 16	59 ± 16	0.80
At 8 months	67 ± 16	58 ± 16	<0.0001
Change from baseline to 8 months	9 ± 17	−1 ± 16	<0.0001
p Value vs. baseline	<0.0001	0.39	
At 8 months	92.8 ± 10.5	92.4 ± 10.4	0.73
Change from baseline to 8 months	1.2 ± 10.7	1.5 ± 10.3	0.80
p Value vs. baseline	0.18	0.09	
Stroke volume, ml			
At baseline	59 ± 16	59 ± 16	0.80
At 8 months	67 ± 16	58 ± 16	<0.0001
Change from baseline to 8 months	9 ± 17	−1 ± 16	<0.0001
p Value vs. baseline	<0.0001	0.39	

Reil J-C al. *JACC* 2013

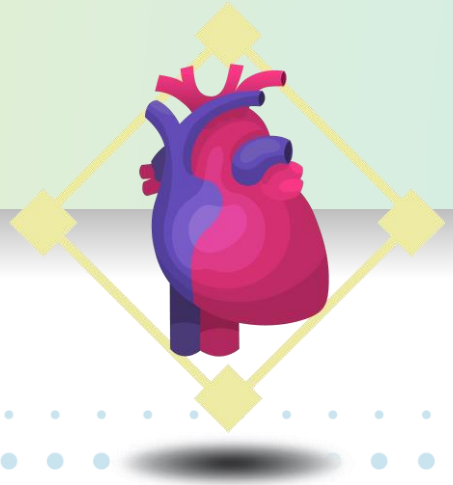
Conclusions

- Elevated HR is an adverse prognostic factor
- Pure HR reduction improves outcomes
- Reducing HR results in reverse remodeling
- Effects are independent of and additive to neurohormonal blockade
- Ivabradine is safe and well tolerated
- Ivabradine is indicated by CCS guidelines for HFrEF patients in SR

Tying it all Together

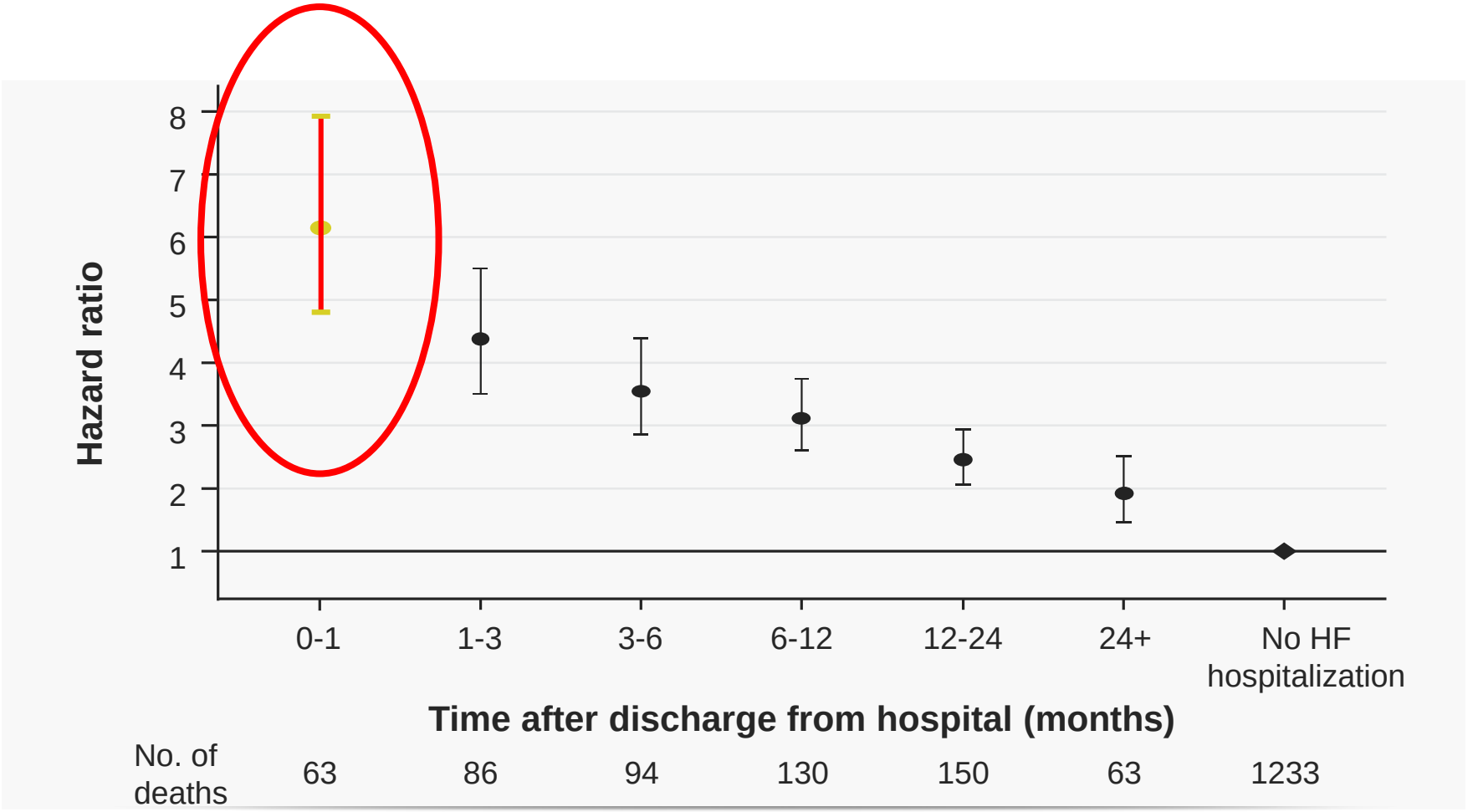
Peter Liu

MD, FRCPC



High Mortality in Hospitalized HF Patient – the “Vulnerable Paradox”

High Mortality in Hospitalized HF Patient – the "Vulnerable Paradox"



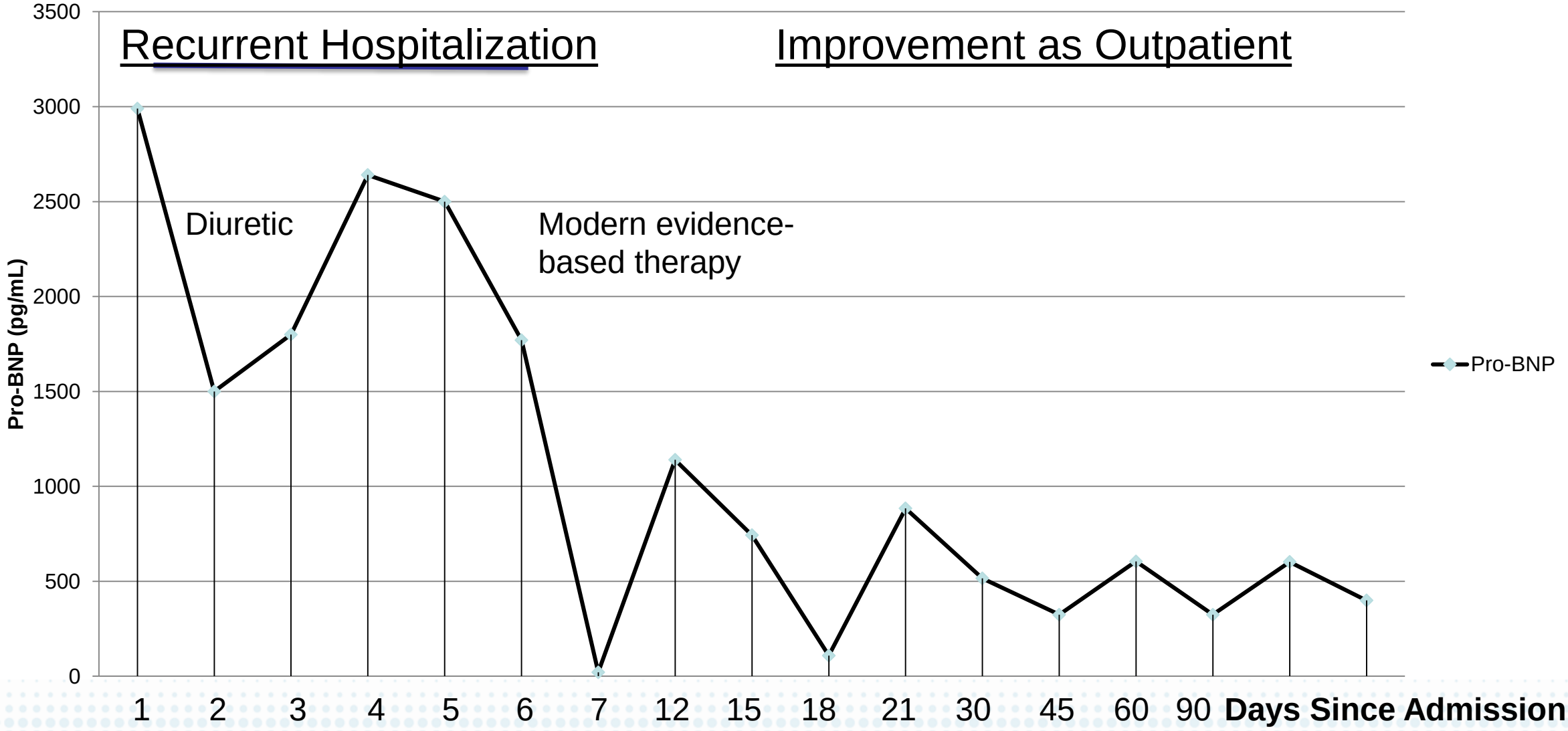
Solomon et al. Circulation 2007;116:1482-87

Acute HFrEF Rx: Reproducing History of Medicine

- Diuretics [1962], ACEi [1980], Beta Blocker [1990]

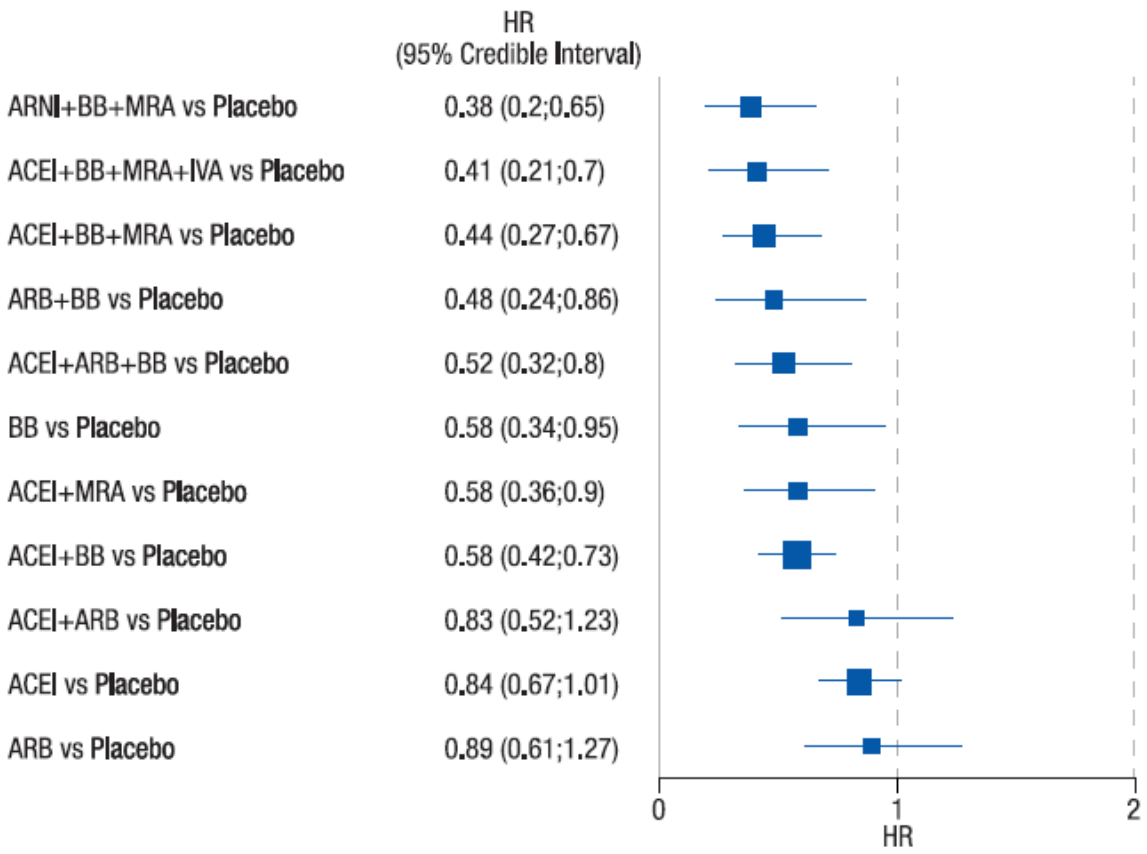
"Any family history of cancer, heart disease, diabetes, extinction..."

NT-proBNP Levels During & Post Discharge for ADHF

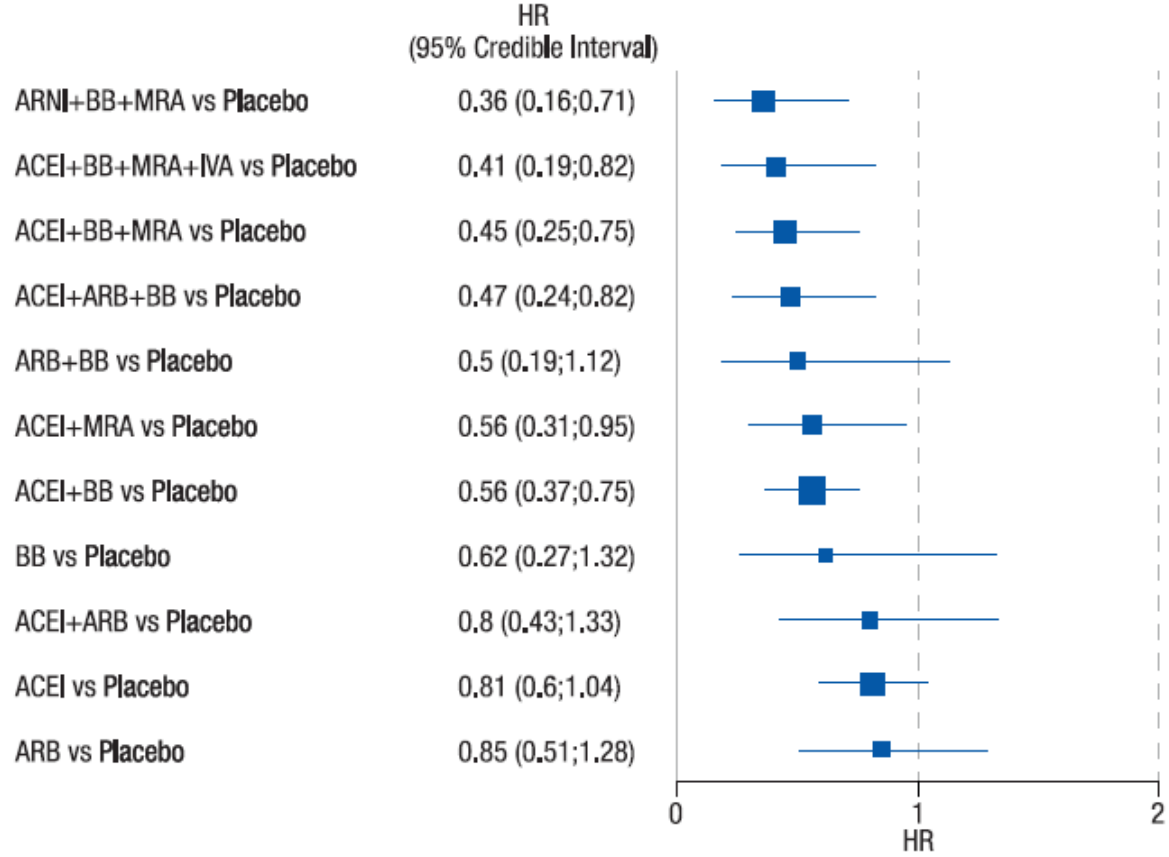


Benefits of Combinatorial Rx for HFrEF

All-cause Mortality

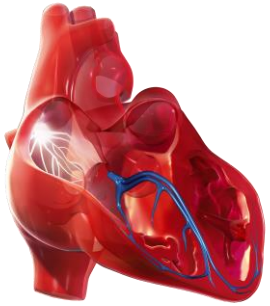


Cardiovascular Mortality



- *Komajda M, et al. Eur J Heart Fail 2018*

Complementarity Between the HF Treatments Neurohormonal + Physiological, Rapid + Chronic



Direct determinant of **heart function**

Decline in systolic function

Activation of three major neurohormonal systems

Natriuretic peptide system

Renin angiotensin aldosterone system

Sympathetic nervous system

Heart rate

NEUROHOMONAL
CHRONIC

PHYSOLOGICAL
RAPID + CHRONIC

Time for a Disruption in HF Treatment: Cluster Titration (CT) for HFrEF

Cluster A: Diuretic & SGLTi	Cluster B: ARNi & MRA	Cluster C: BB & SNI
Encounter 1		
Start 1st Med Cluster A	Start 1st med Cluster B	Start 1st med Cluster C
Encounter 2 (whenever feasible)		
Start 2nd med Cluster A	Start 2nd med Cluster B	Start 2nd med Cluster B
Encounter 3 & ongoing (whenever feasible)		
Diuretic titration	Easiest cluster B titration	Alternate Cluster C titration

Ivabradine in Hospitalized HF Patients

- Effect of ivabradine on stroke volume in failing heart is immediate
- Effect of ivabradine on the failing heart in HFrEF is sustained:
  - Decreases LV volumes
  - Improves LV ejection fraction
  - Reduces NTproBNP over time
  - Reduces mortality
- Combines well with other treatment “clusters” in HFrEF

For the Patient Admitted with HFrEF

- Rapid symptom relief and volume optimization
- Assess patient risk for rehospitalization
- Hold ACEi and consider sacubitril/valsartan if no contraindication (BP, Creatinine)
- If HR>77/minute, consider adding ivabradine to beta blockade
- Patient education, community/family support
- Timely follow-up as outpatient

Question 5: What statement best describes your understanding of initiation of in-hospital therapies for HFrEF (assume eligible for all therapies)?

1) Triple therapy should be optimized prior to initiation of any 'new' therapies such as ARNi or SNI

2) Patients should be started on ARNi while in hospital but not SNI

3) Patients should be started on both ARNi and SNI while in hospital

4) New therapies should only be started in outpatient population

Thank you!

Please remember to complete the online evaluation.