Giving patients with HFpEF their heart rate back

Personalized accelerated physiologic pacing and insights from the myPACE clinical trial

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Objectives

1. **Define** heart failure with preserved ejection fraction (**HFpEF**), and how *this condition* ***differs*** *from heart failure with reduced ejection fraction* (**HFrEF**).
2. **Describe** the *hemodynamic effects of heart rate modulation* in HFpEF.
3. **Illustrate** the *basic concepts of physiological pacing* and **contrast** with more traditional right ventricular or right atrial appendage pacing.
4. **Summarize** the design, results, and key findings of the *myPACE randomized clinical trial*.
5. **Relate** the results of the myPACE trial to an *overall approach* to heart rate and therapies that modulate heart rate in HFpEF.

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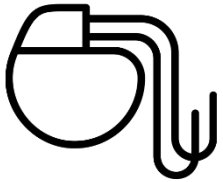
Key Points

There are few evidence-based treatments for heart failure with preserved ejection fraction (HFpEF)

No evidence that lower heart rates (and therapies that lower heart rate) are beneficial in HFpEF



Emerging evidence suggests a role for therapeutic heart rate modulation (increase in heart rate) in HFpEF

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Acknowledgements and Disclaimers

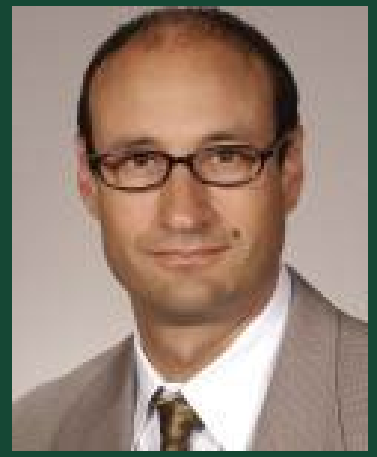
I am a general cardiologist, not an EP doc

Much of what I will be talking about was led by the brilliant people below

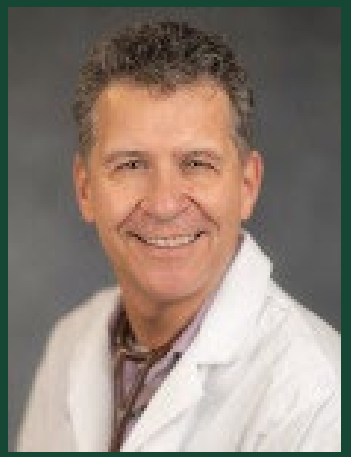
This topic is an active area of research

Margaret Infeld MD, MS

Nicole Habel MD, PhD



Dan Lustgarten MD, PhD



Markus Meyer MD, PhD

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Heart Failure with *Preserved* Ejection Fraction (HFpEF)

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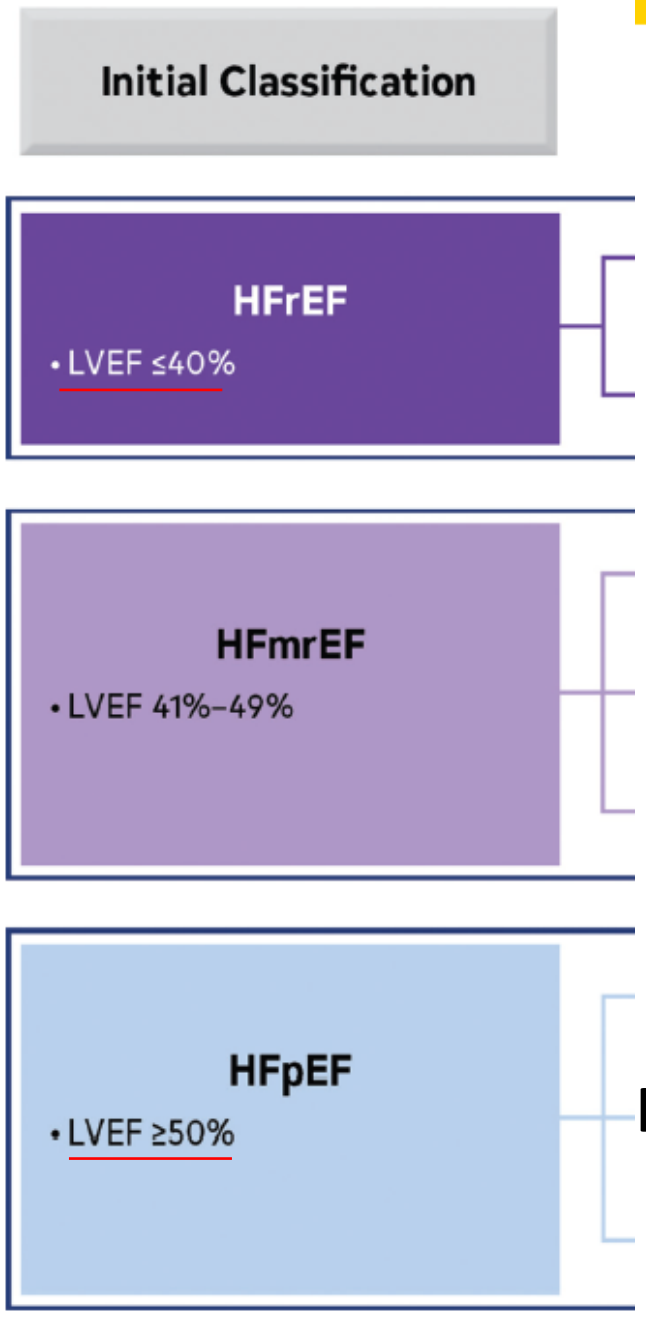
“Systolic”
heart failure



heart failure with reduced ejection fraction

heart failure with preserved ejection fraction

“Diastolic”
heart failure

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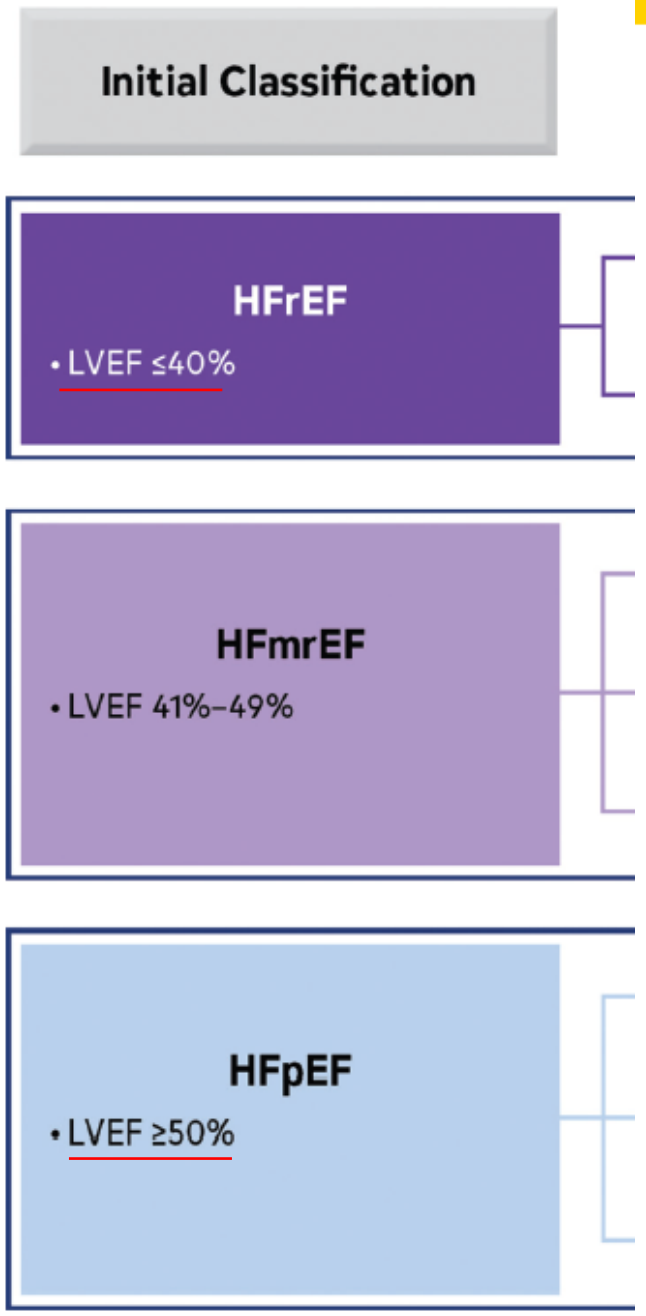
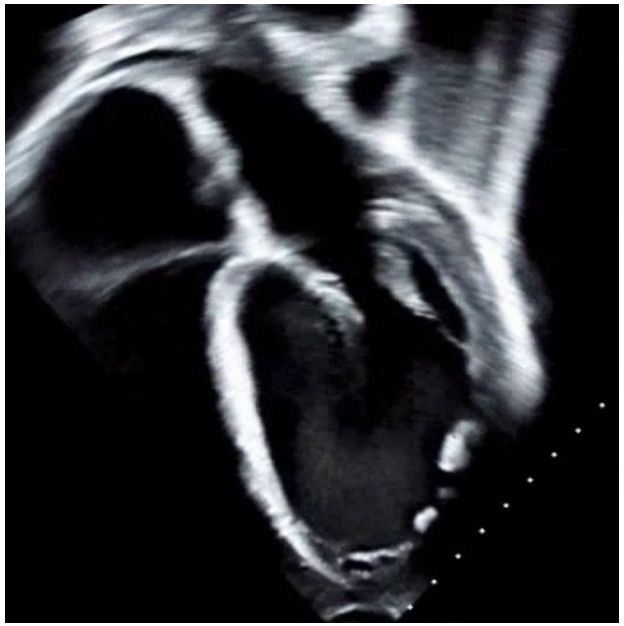
2022 AHA/AACC/HFSA Guidelines for management of heart failure

“Systolic”
heart failure

“Diastolic”
heart failure





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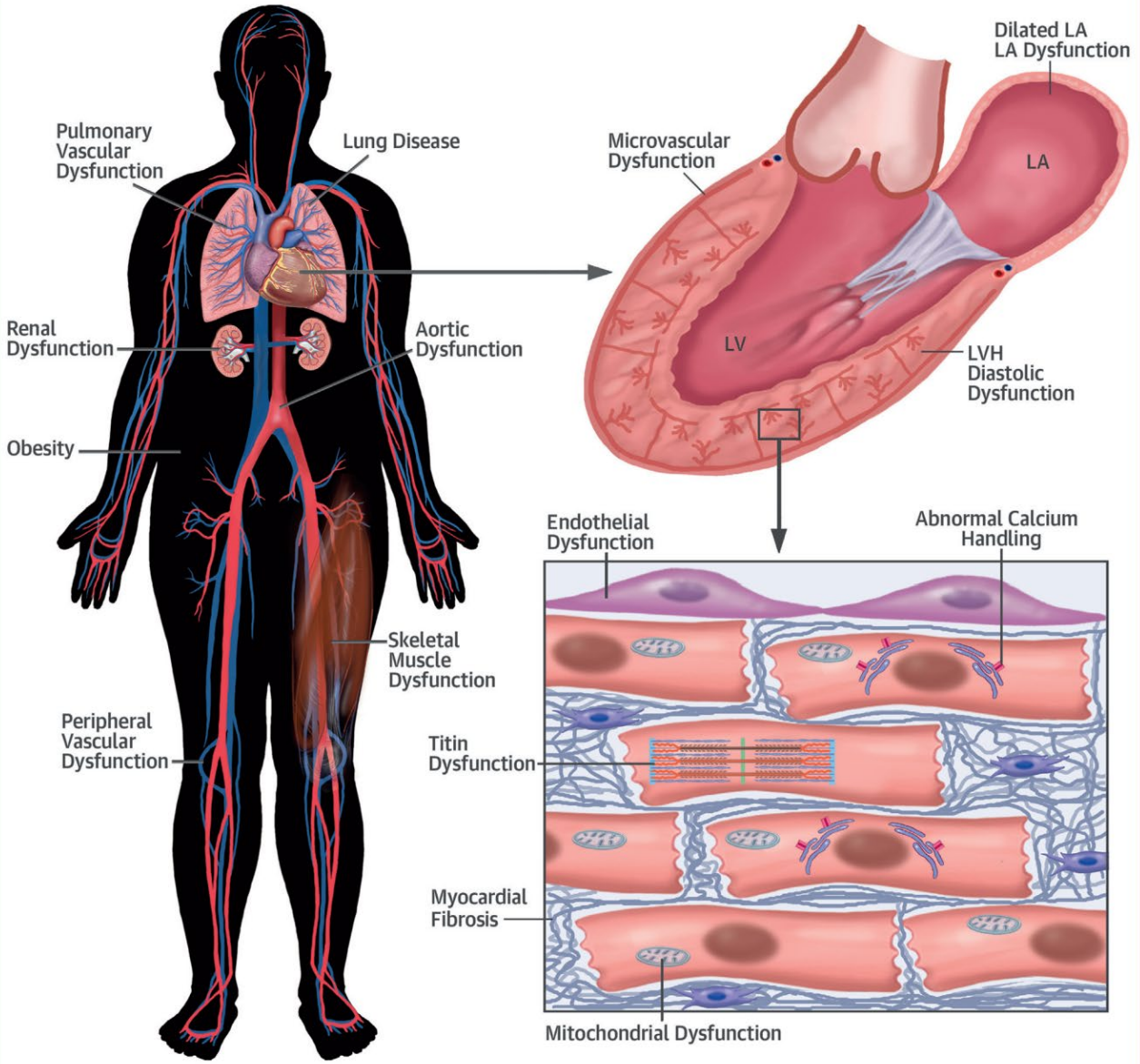
2022 AHA/AACC/HFSA Guidelines for management of heart failure

CENTRAL ILLUSTRATION Biological Phenotypes in HFpEF



Lewis, G.A. et al. J Am Coll Cardiol. 2017;70(17):2186-200.

Heart failure with preserved ejection fraction (HFpEF) is a systemic disease with multiple biological phenotypes contributing to a heterogeneous clinical syndrome, including cardiomyocyte, extracellular matrix, vascular, and comorbidity-related pathophysiological mechanisms. LA = left atrial; LV = left ventricle; LVH = left ventricular hypertrophy.

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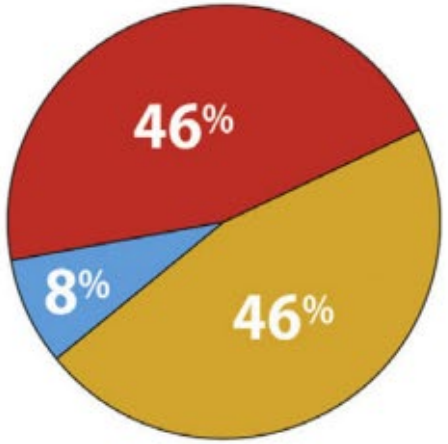
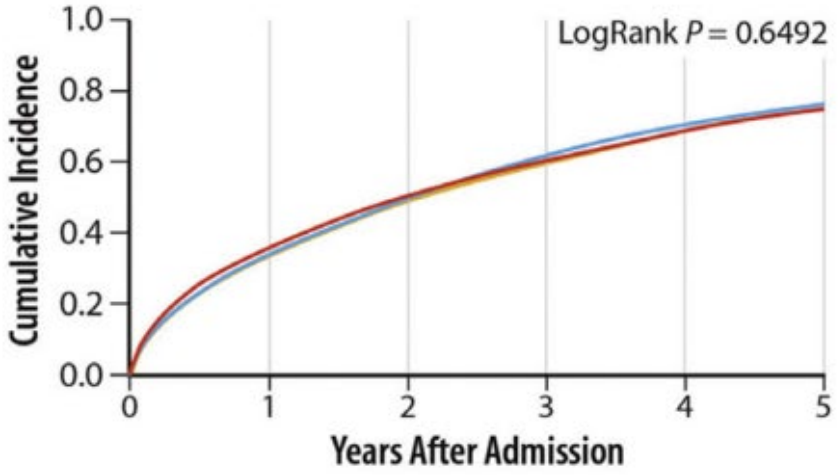
5-YEAR OUTCOMES IN PATIENTS HOSPITALIZED WITH HF WITH PRESERVED, BORDERLINE, AND REDUCED EF

Heart Failure



5-Year Mortality



HFpEF (EF ≥50%) HFbEF (EF 41-49%) HFrEF (EF ≤40%)

Outcomes: 5-Year Event Rates (%)

	Mortality	Readmission	CV Readmission	HF Readmission	Mortality/Readmission
HFrEF	75.3	82.2	63.9	48.5	96.4
HFbEF	75.7	85.7	63.3	45.2	97.2
HFpEF	75.7	84.0	58.9	40.5	97.3

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Bozkurt. Heart Failure Epidemiology and Outcomes Statistics: A Report of the Heart Failure Society of America

Medical Therapy **Saves Lives** in ***HFrEF***

"Optimal" GDMT could save *estimated* **98,000** lives annually in the US

GDMT = guideline-directed medical therapy

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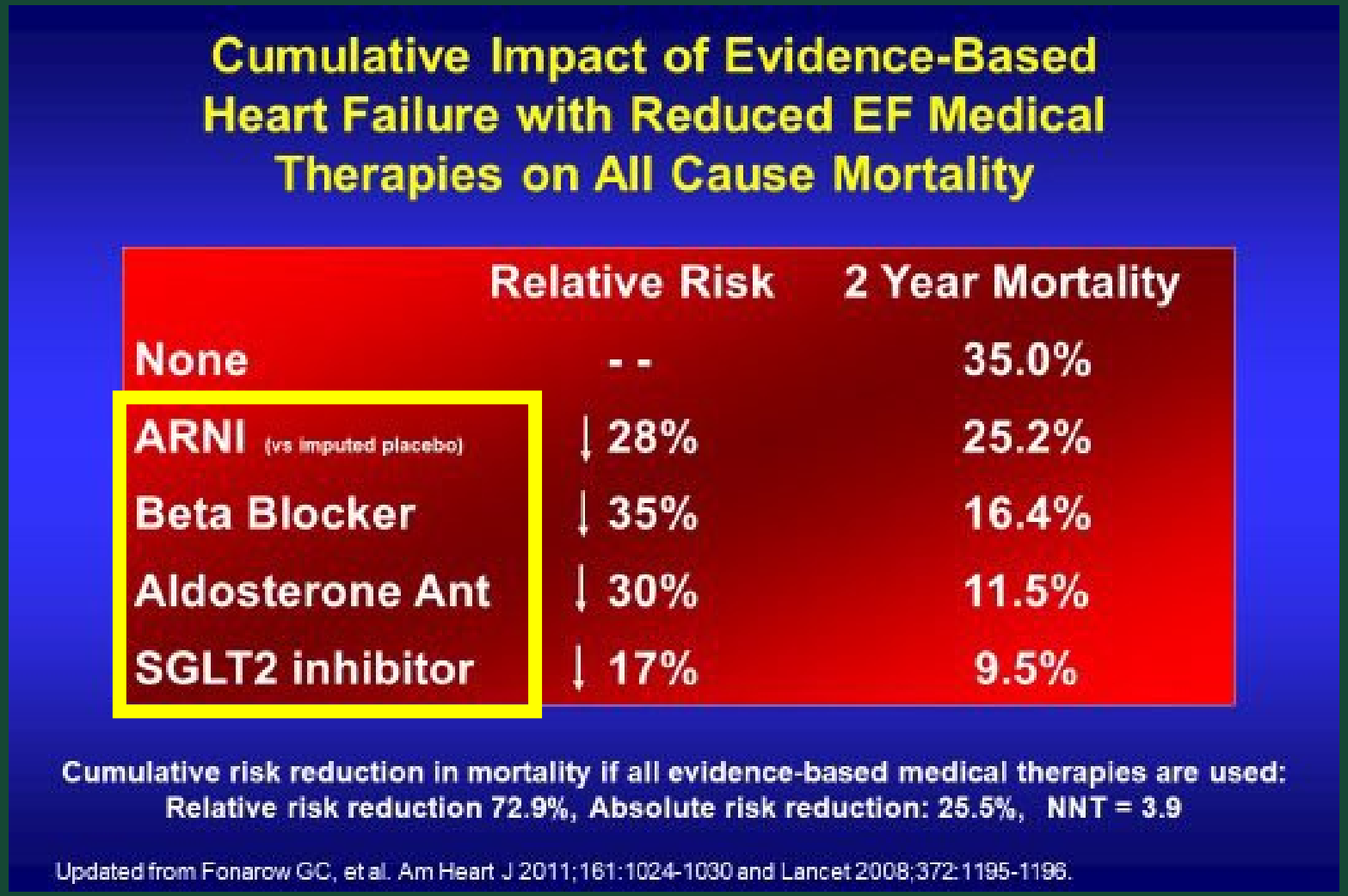
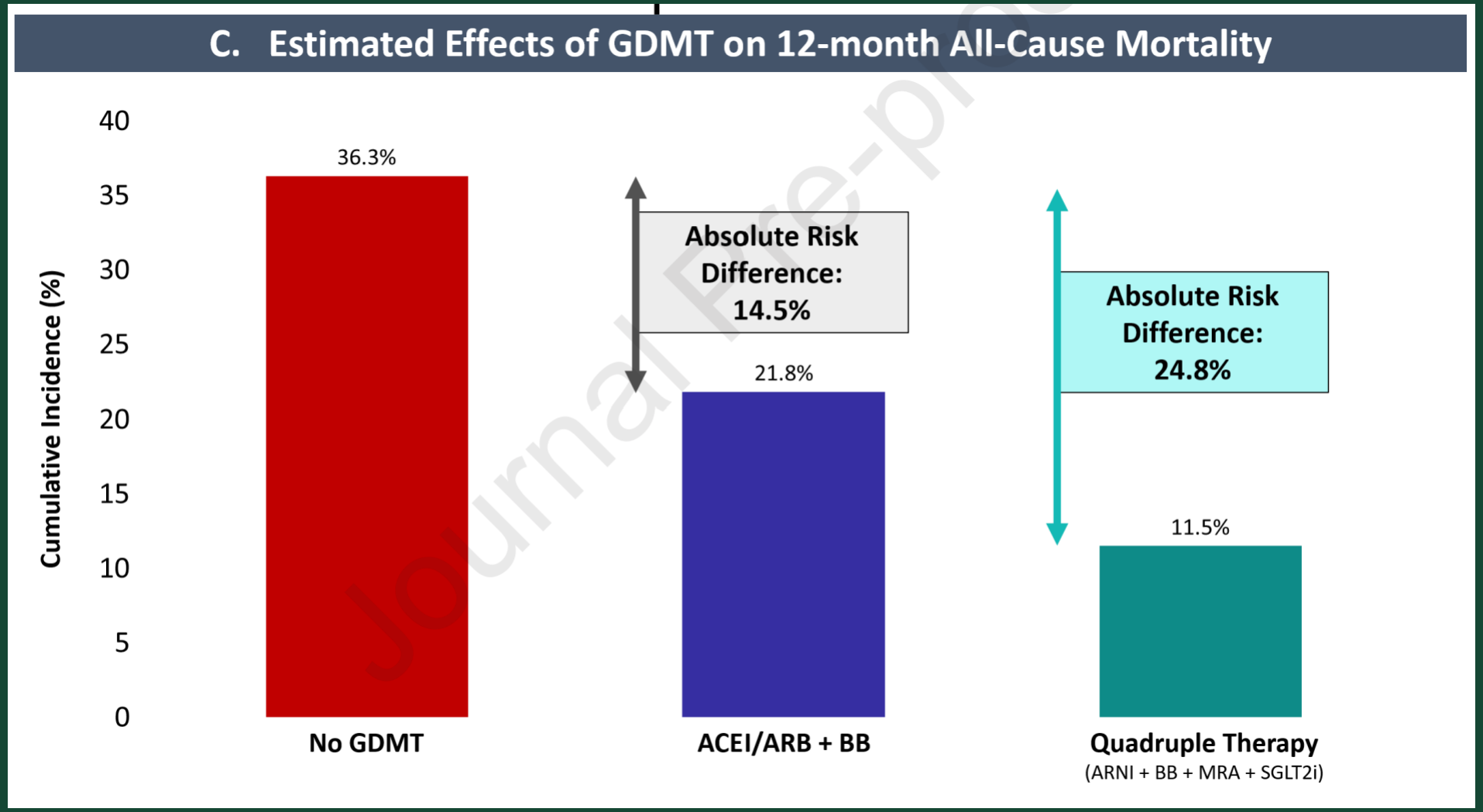


Medical Therapy **Saves Lives** in ***HFrEF***



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Greene. Eligibility and Projected Benefits of Rapid Initiation of Quadruple Medical Therapy for Newly Diagnosed Heart Failure. 2024

Medical therapy for **heart failure**

Summary of guideline recommendations

Drug	Guideline	HFrEF (EF ≤ 40%)	HFmrEF (EF 41-49%)	HFpEF (EF ≥ 50%)
ARNI	ESC 2021	I	IIb	
	ACC/AHA/HFSA 2022	I	IIb	IIb*†
BB	ESC 2021	I	IIb	
	ACC/AHA/HFSA 2022	I	IIb	
MRA	ESC 2021	I	IIb	
	ACC/AHA/HFSA 2022	I	IIb	IIb*
SGLT2i	ESC 2021	I		
	ACC/AHA/HFSA 2022	I	IIa	

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The four pillars of HFrEF therapy: is it time to treat heart failure regardless of ejection fraction? European Heart Journal Supplements, Volume 24, Issue Supplement_L, December 2022, Pages L10–L19

Many **patients** with HFpEF are prescribed **beta blockers**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 24, 2019 VOL. 381 NO. 17

Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

Table 1. (Continued.)

Characteristic	Sacubitril–Valsartan (N=2407)	Valsartan (N=2389)
Treatment — no. (%)		
Diuretic agent at randomization	2294 (95.3)	2291 (95.9)
ACE inhibitor or ARB at screening	2074 (86.2)	2065 (86.4)
Mineralocorticoid-receptor antagonist at randomization	592 (24.6)	647 (27.1)
Beta-blocker at randomization	1922 (79.9)	1899 (79.5)

Many **patients** with HFpEF are prescribed **beta blockers**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 14, 2021 VOL. 385 NO. 16

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

TABLE S2. CARDIOVASCULAR MEDICATIONS AT BASELINE

Type of medication — number (%)	**Empagliflozin** (n=2997)	**Placebo** (n=2991)
Inhibitor of renin-angiotensin system with or without neprilysin inhibitor	2428 (81.0)	2404 (80.4)
Sacubitril/valsartan	65 (2.2)	69 (2.3)
Mineralocorticoid receptor antagonist	1119 (37.3)	1125 (37.6)
Beta blocker	2598 (86.7)	2569 (85.9)
Digitalis glycosides	293 (9.8)	263 (8.8)
Aspirin	1240 (41.4)	1272 (42.5)
Statins	2042 (68.1)	2089 (69.8)

Inhibitors of the renin-angiotensin system include angiotensin converting-enzyme inhibitors and angiotensin receptor blockers.

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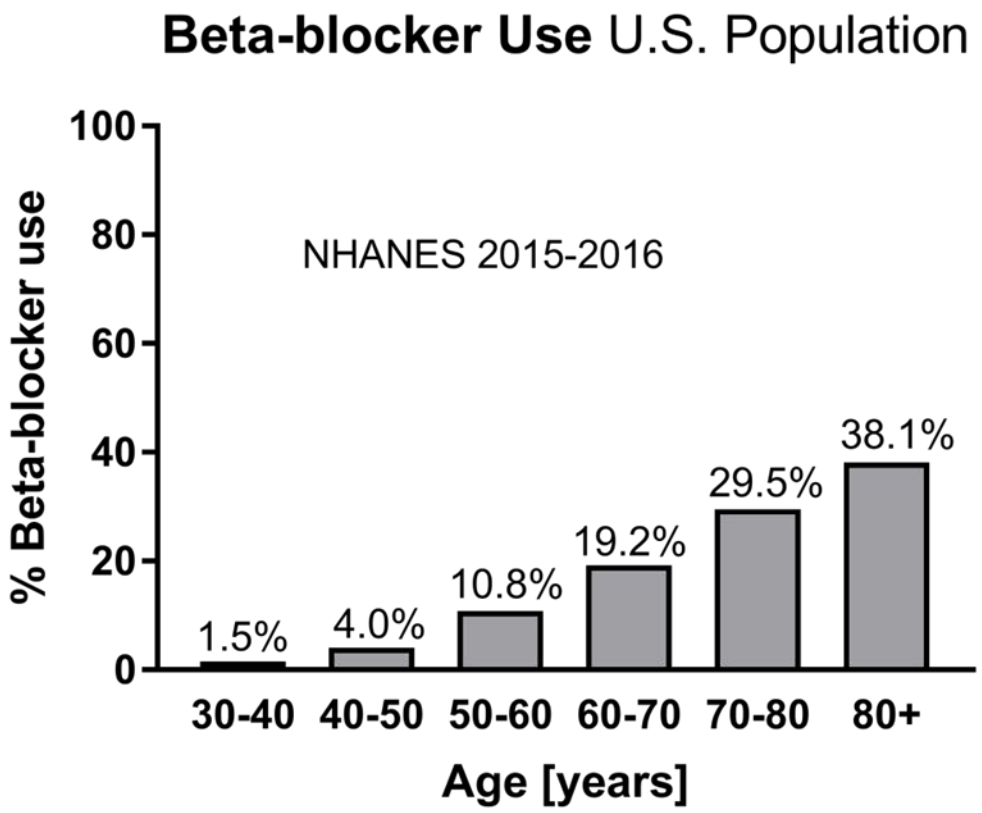
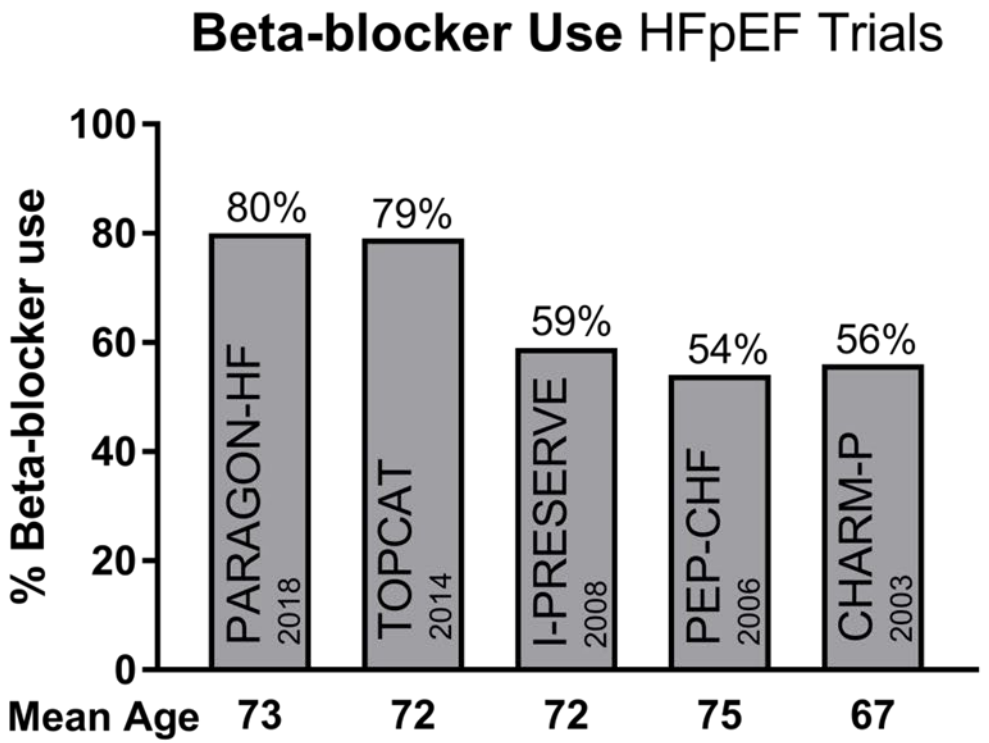
Many **patients** with HFpEF are prescribed **beta blockers**





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Lower heart rates are better right???

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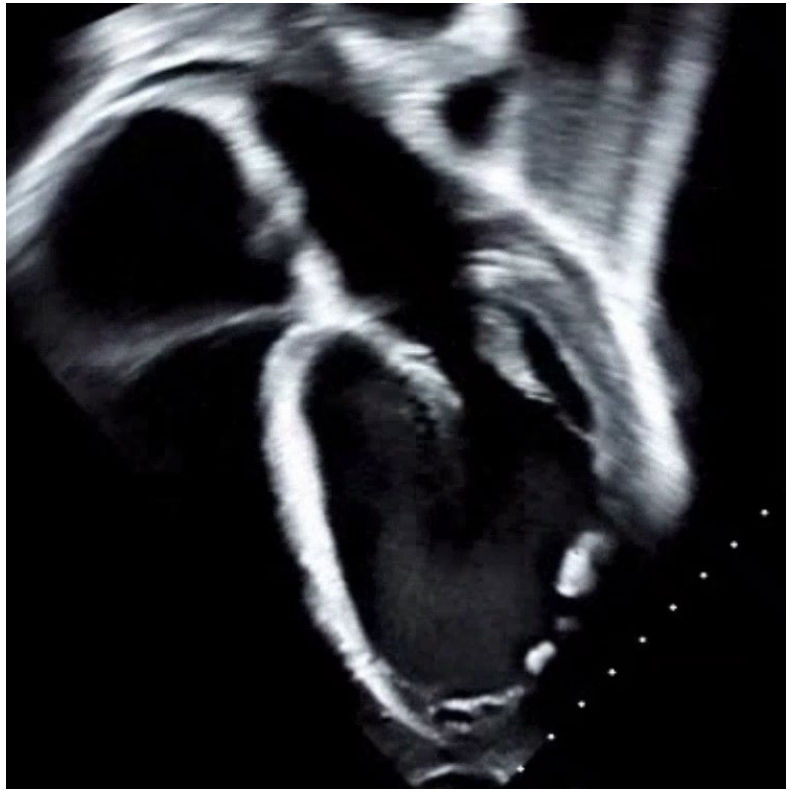
Are lower heart rates better for all?



Heart failure with reduced ejection fraction (HFrEF)

YES! ✓

Medications
(beta blockers)

Pacemakers
(if backup rate programmed 60bpm)

Normal/preserved ejection fraction

Generally, no

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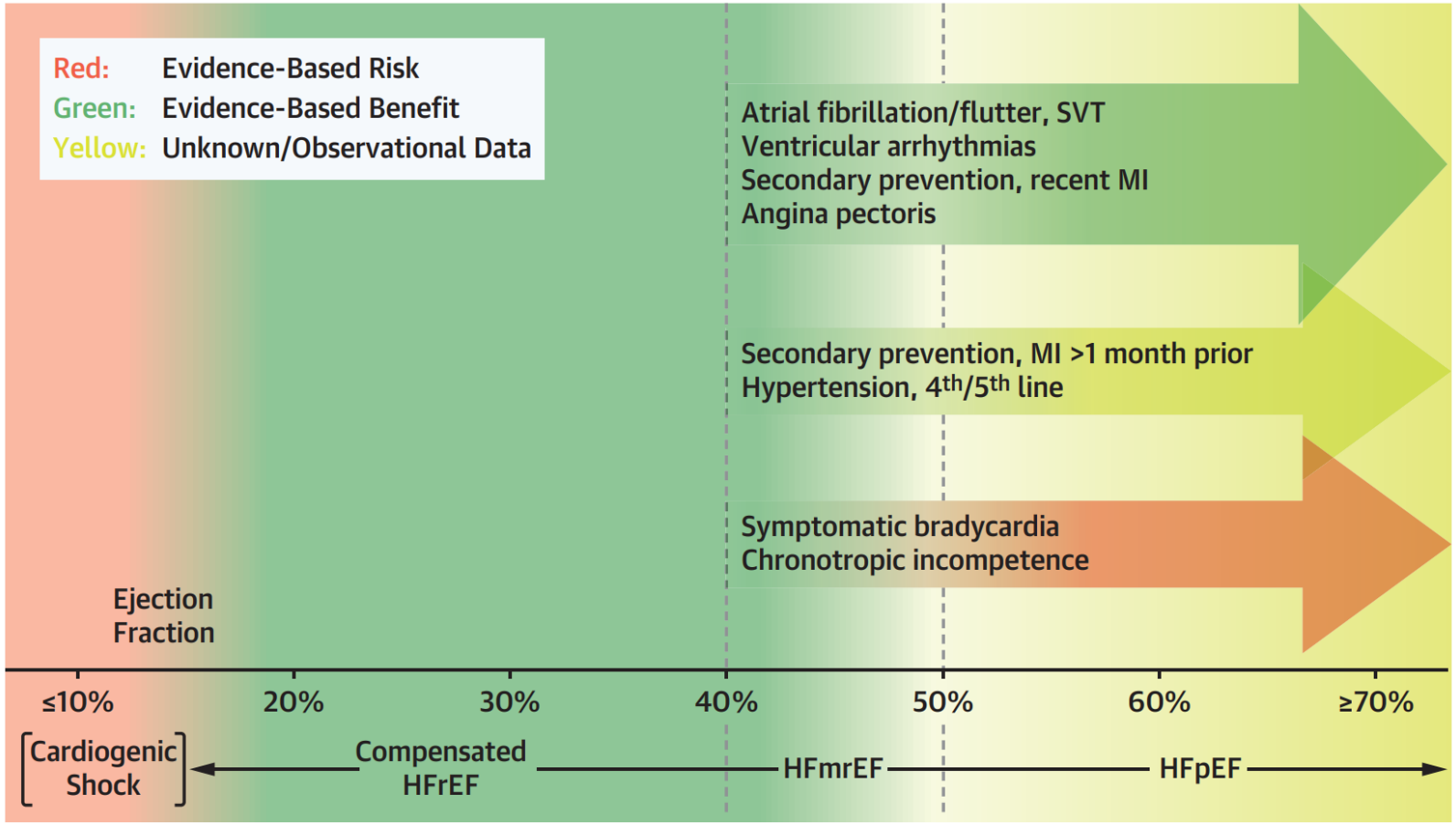
CENTRAL ILLUSTRATION **Summary of Evidence for Beta-Blocker Benefit vs Risk According to LVEF**



Arnold SV, et al. J Am Coll Cardiol HF. 2023;11(8):893-900.

HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SVT = supraventricular tachycardia.

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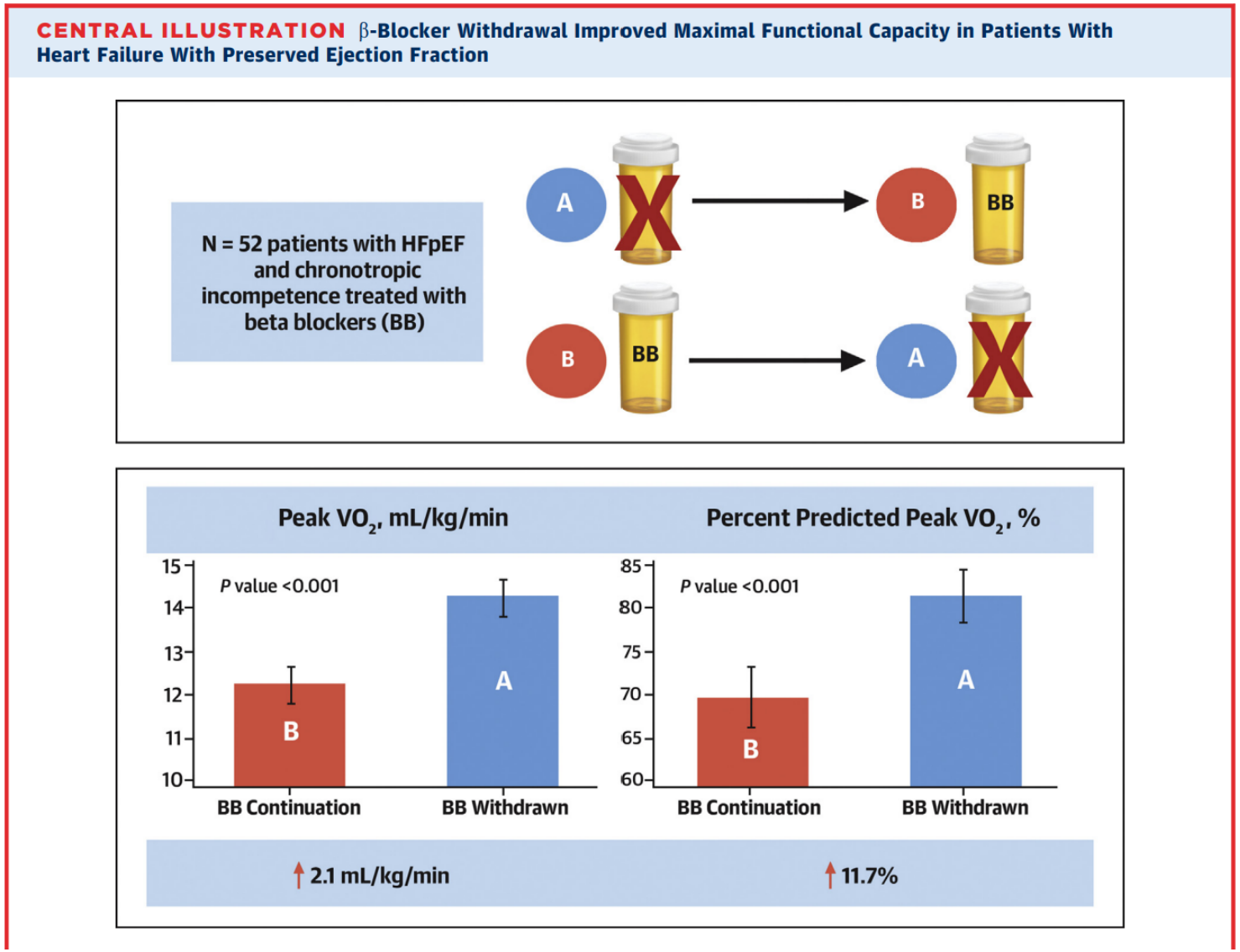
Beta blocker **withdrawal** improves functional capacity in HFpEF



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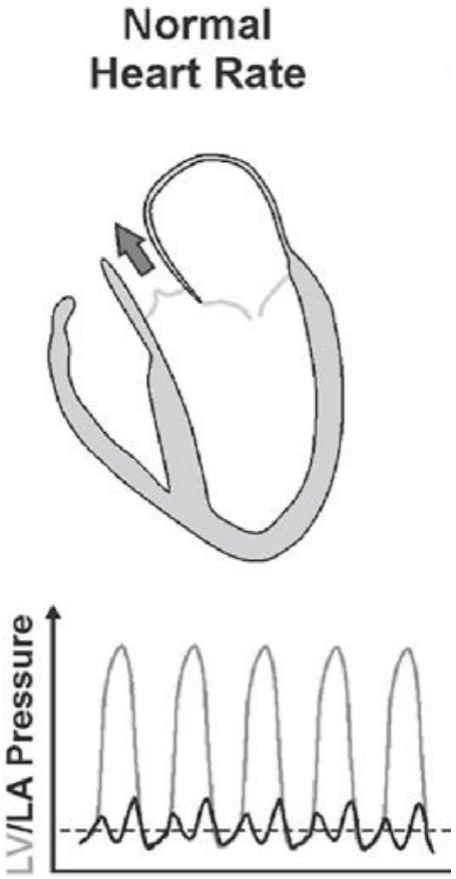
Why might **lower** heart rates be deleterious in HFpEF?



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Meyer, Infeld, Habel, Lustgarten. European Heart Journal Supplements (2023) 25 (Supplement G), G33–G43

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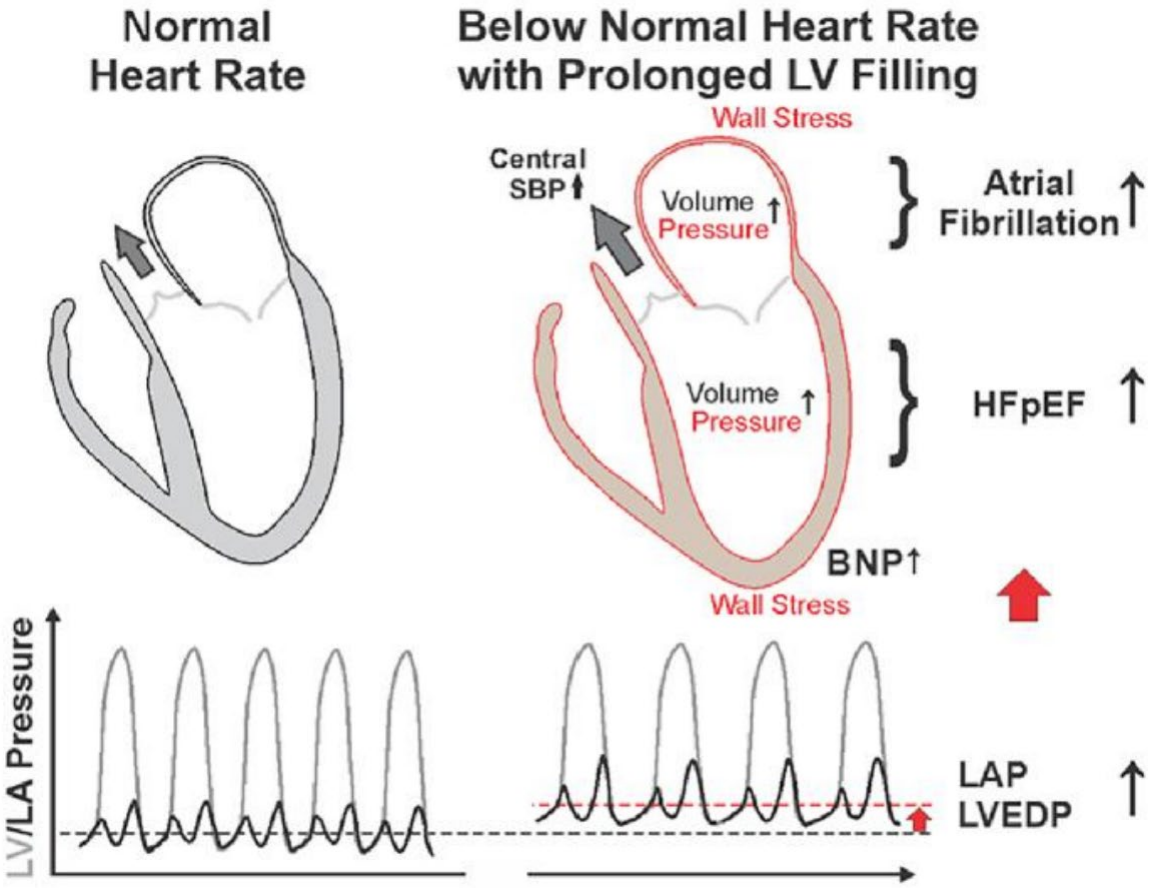

Medications and therapies that **lower** heart rate may lead to ***increased*** filling pressures and worsening heart failure symptoms in HFpEF

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Meyer, Infeld, Habel, Lustgarten. European Heart Journal Supplements (2023) 25 (Supplement G), G33–G43

What about interventions that ***increase heart rate?***

Invasive hemodynamic studies have shown that pacing at higher HR, ***lowers*** filling pressures at rest

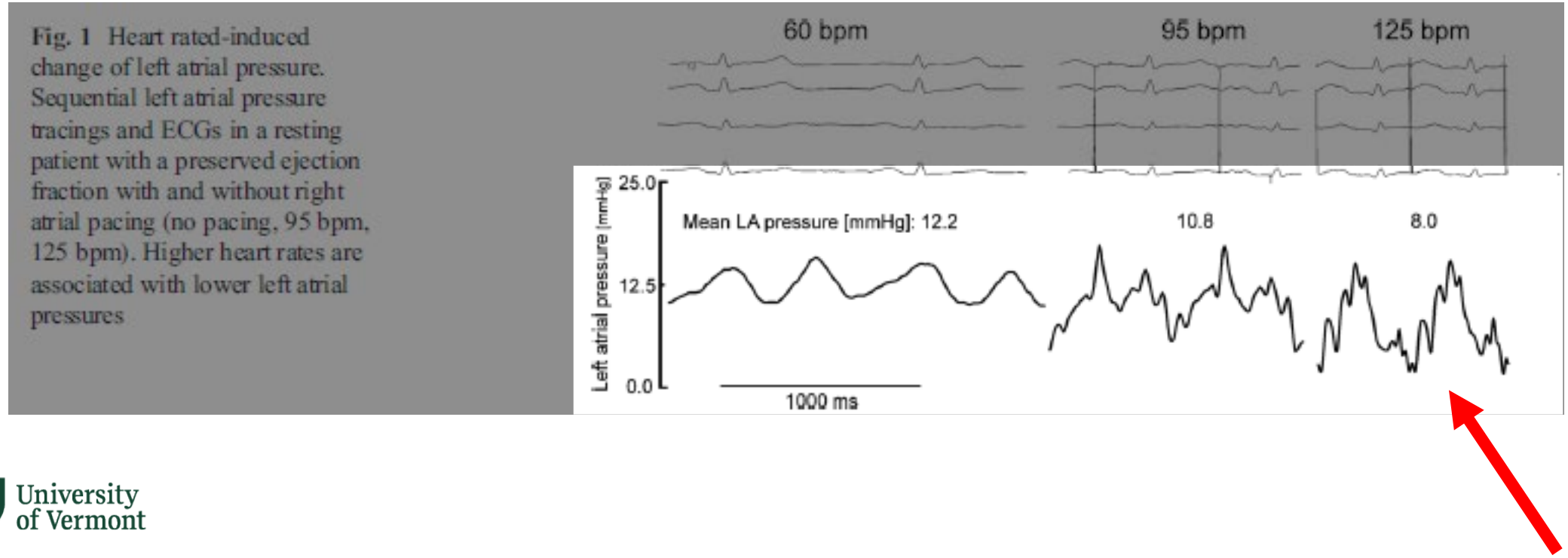

Fig. 1 Heart rated-induced change of left atrial pressure. Sequential left atrial pressure tracings and ECGs in a resting patient with a preserved ejection fraction with and without right atrial pacing (no pacing, 95 bpm, 125 bpm). Higher heart rates are associated with lower left atrial pressures

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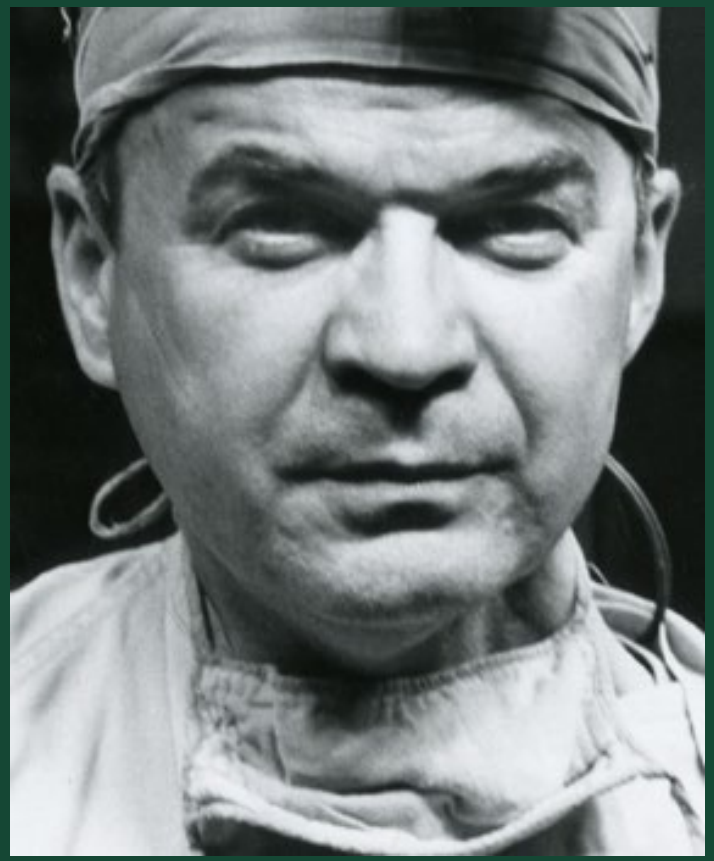
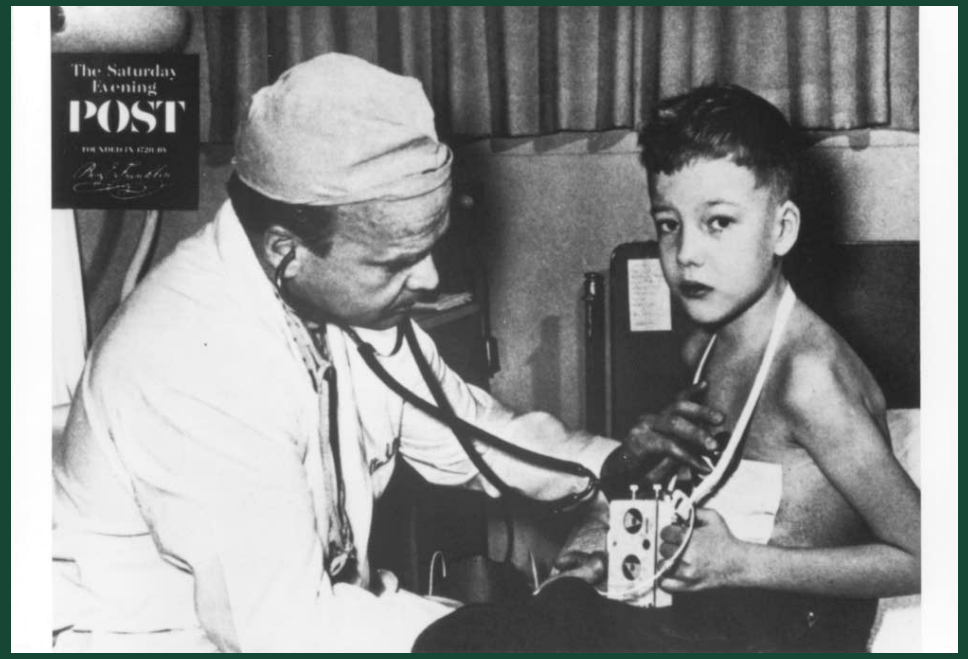
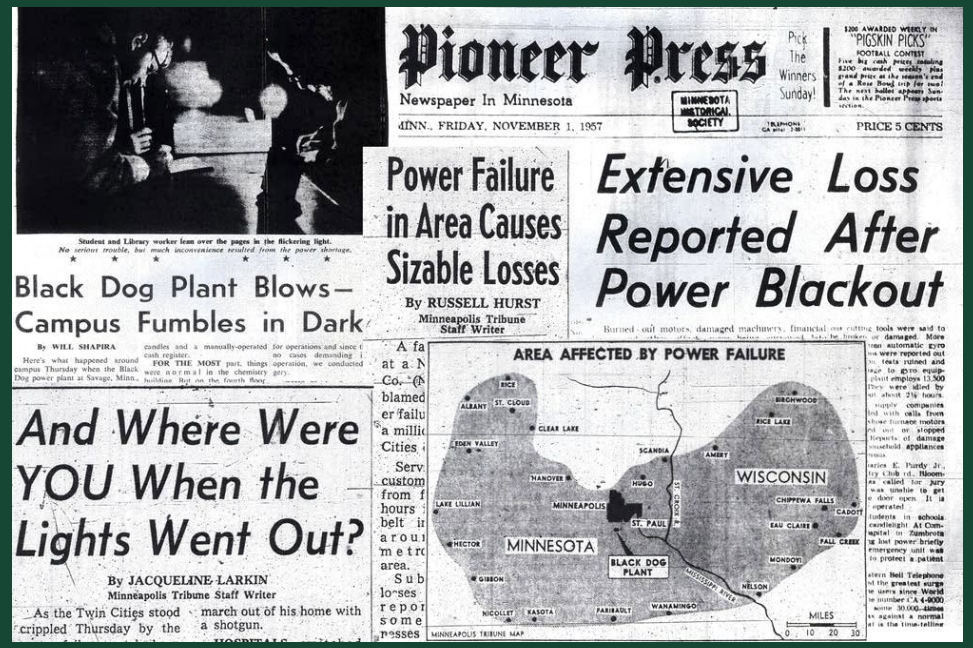
Meyer, Infeld, Habel, Lustgarten. European Heart Journal Supplements (2023) 25 (Supplement G), G33–G43

A little history







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https://www.mprnews.org/story/2007/10/29/batterypacemaker

A little history

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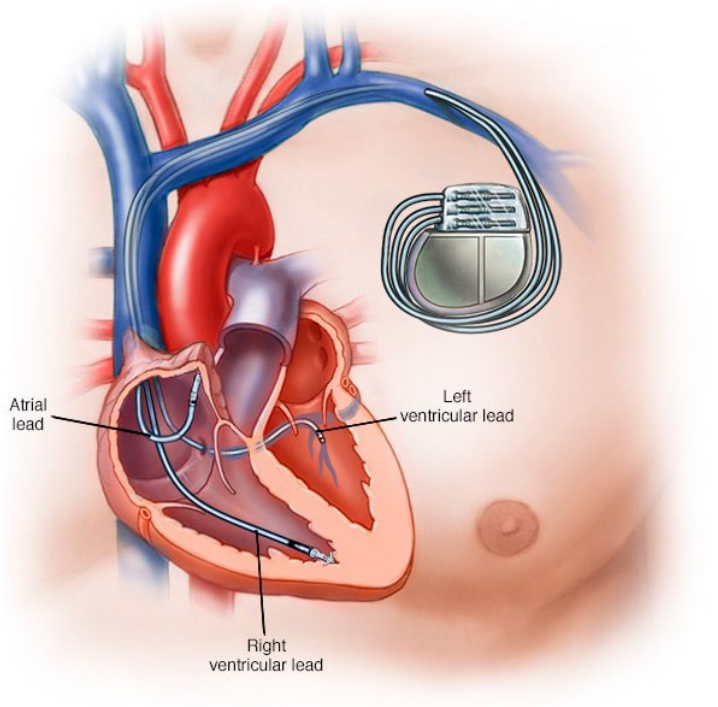
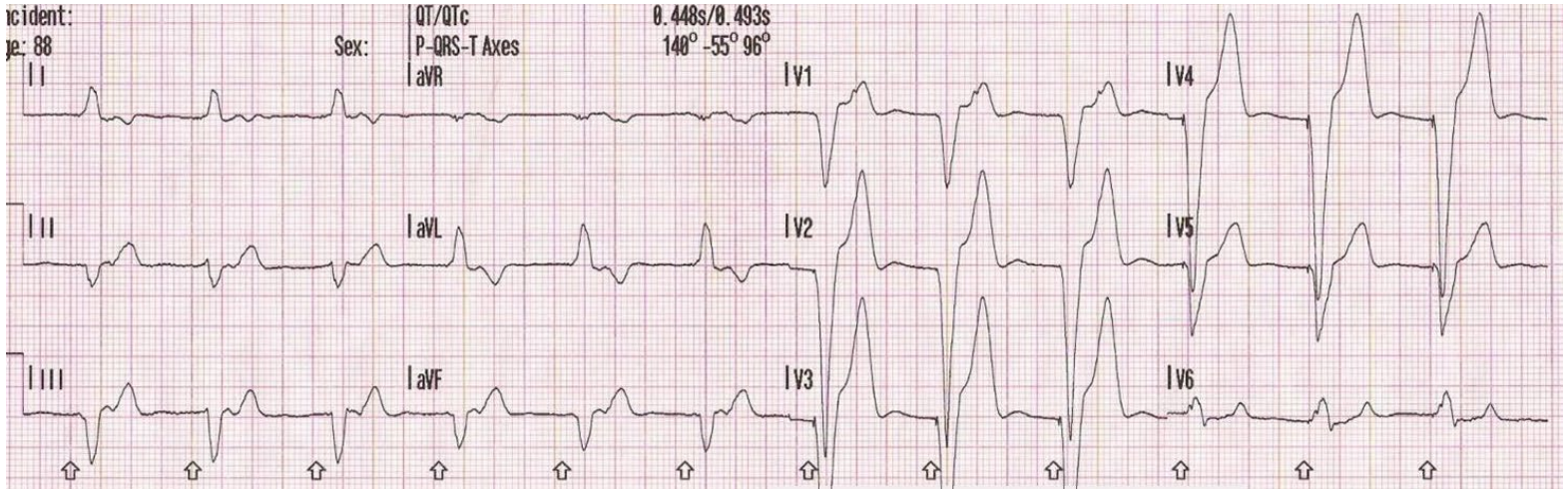
Pacemakers – lead ***location*** matters





Traditional pacing from the right ventricle apex produces **wide QRS complexes**, similar to left bundle branch block

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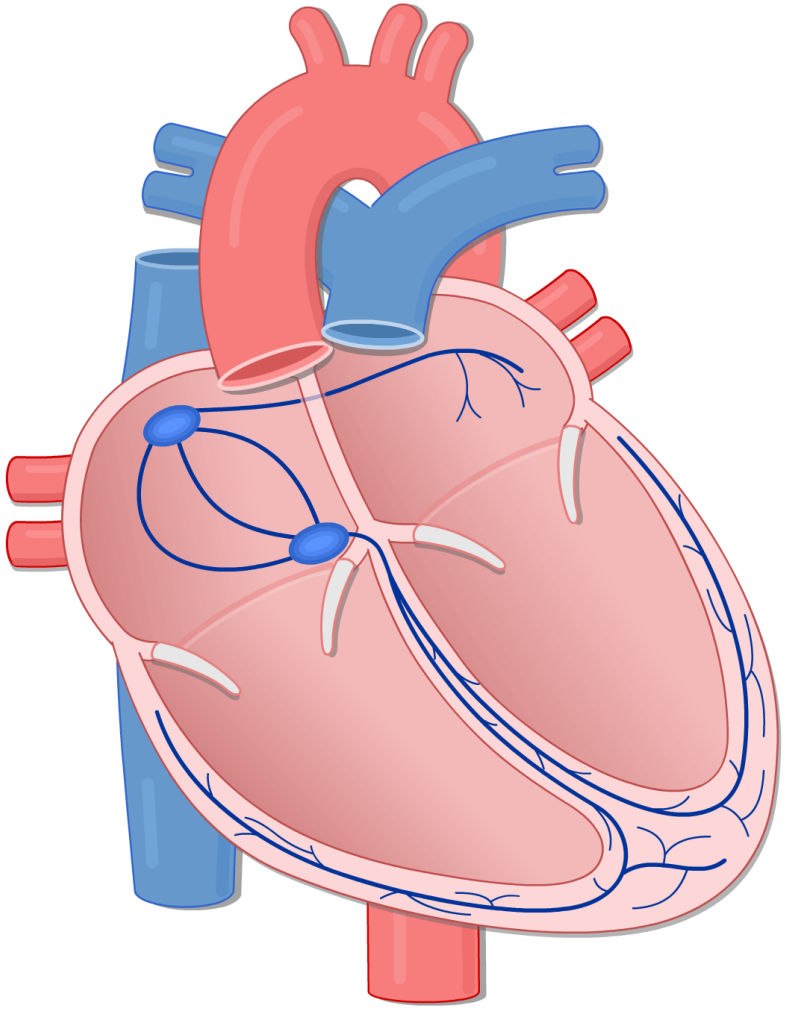
Pacemakers – lead ***location*** matters



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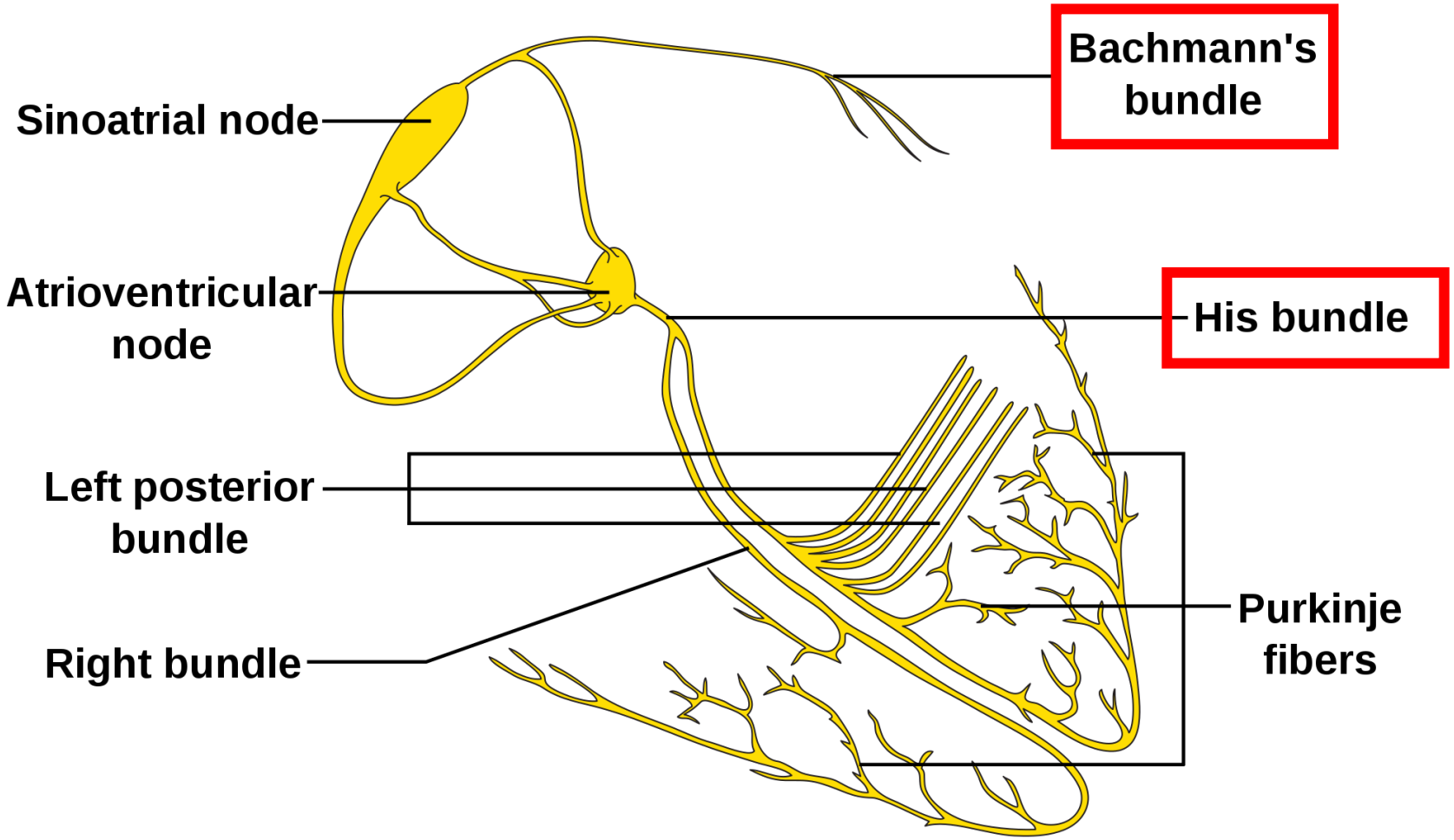
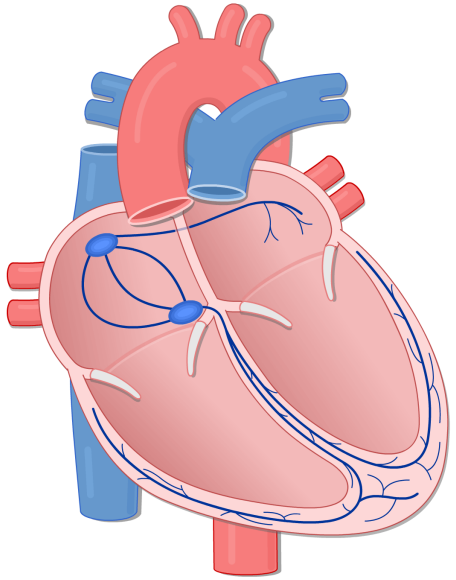
Pacemakers – lead ***location*** matters





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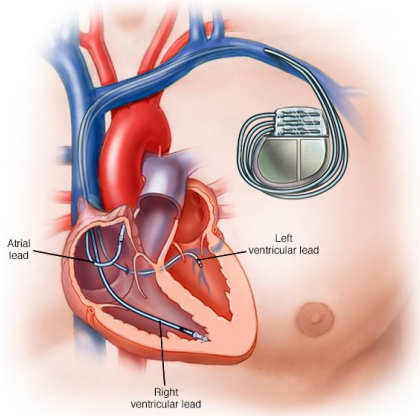
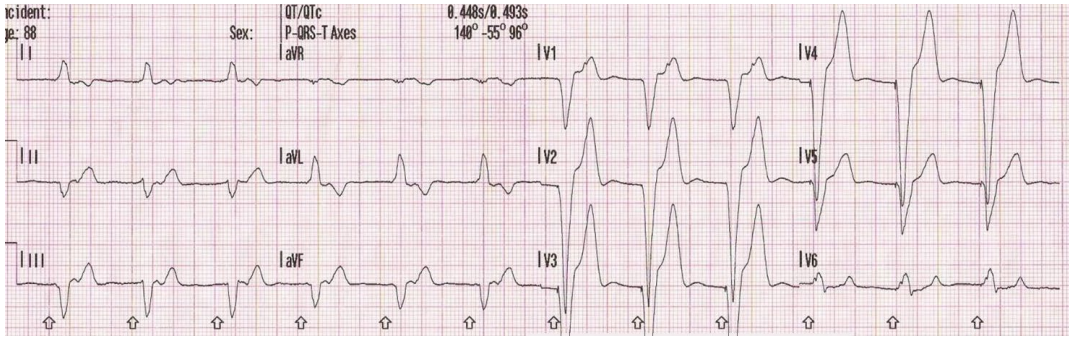
Pacemakers – lead ***location*** matters





Traditional pacing from the right ventricle apex produces **wide QRS complexes**, similar to left bundle branch block. This causes ventricular **dyssynchrony** and can lead to the development of cardiomyopathy and HFrEF

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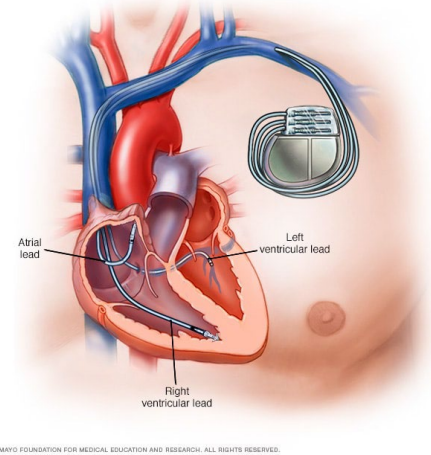
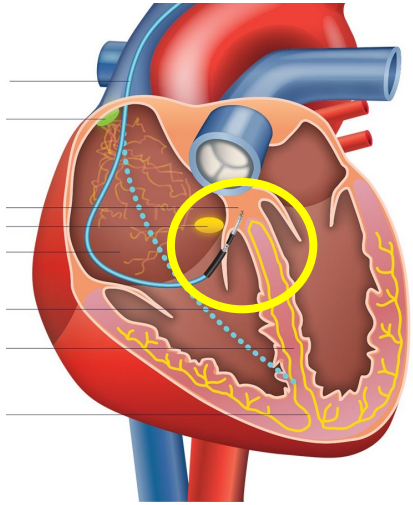
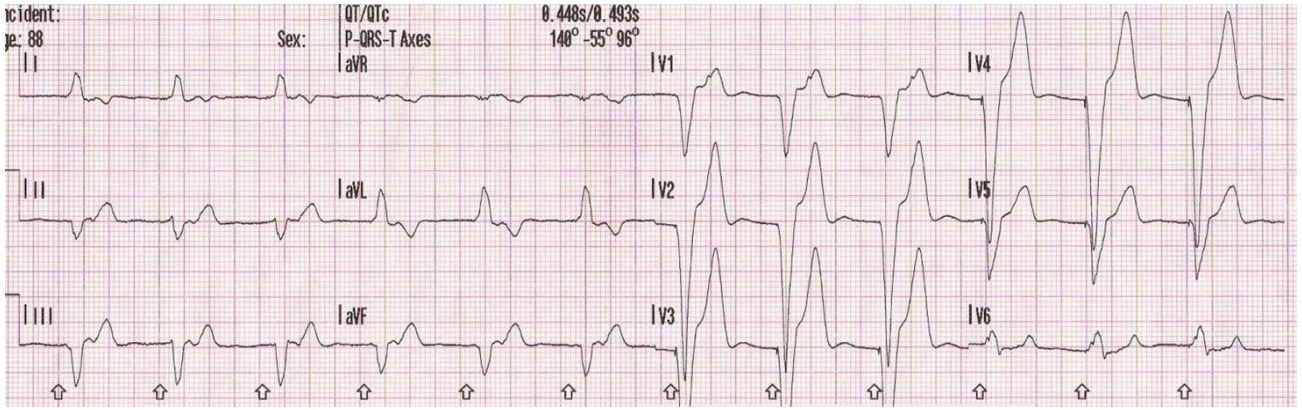
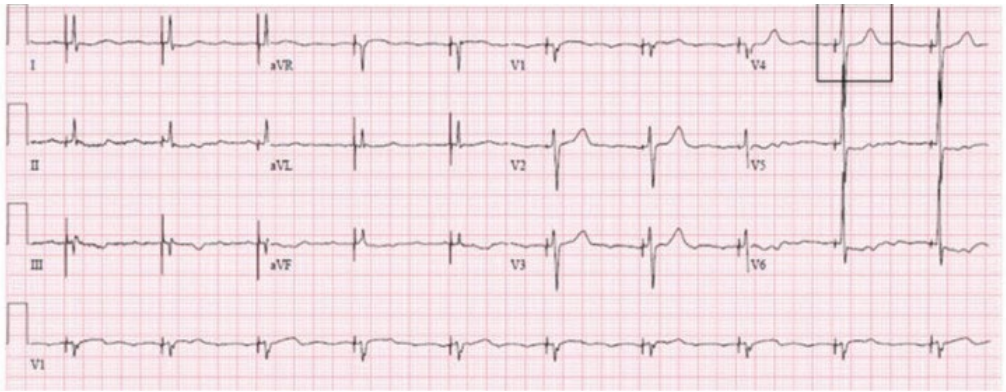
Pacemakers – lead ***location*** matters







Traditional RV pacing – **wide QRS**



"Physiologic" pacing from the His bundle – **Narrow QRS**, using the bodies natural conduction system

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Bringing this all together

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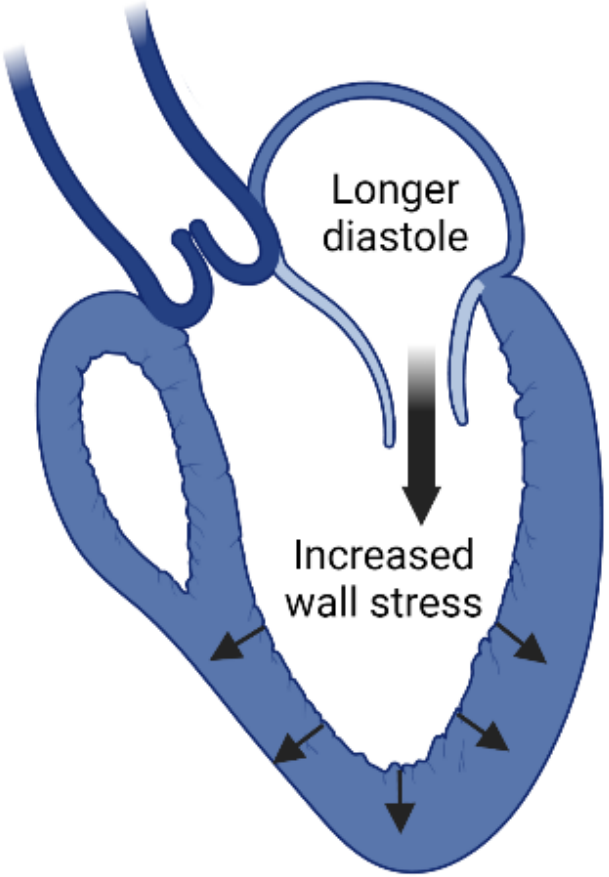
Adult Resting Heart Rates

- Average adult resting HR 71-79bpm, but the pacemaker backup rate is typically at the factory setting of 60bpm

- For patients with HFpEF, a backup rate of 60bpm may not be ideal



Lower rate 60bpm

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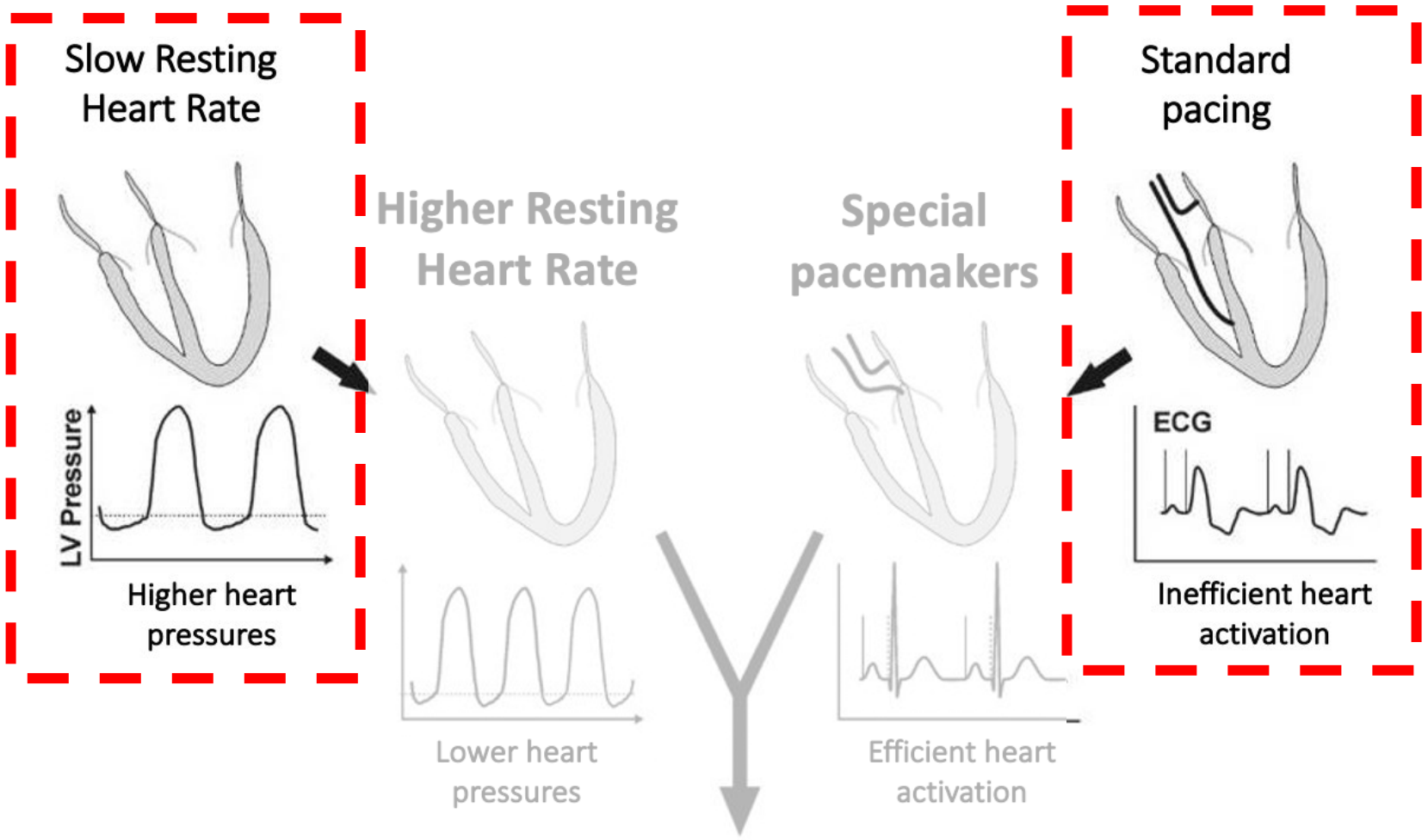
Infeld M, Avram R, Wahlberg K, Silverman DN, Habel N, Lustgarten DL, Pletcher MJ, Olgin JE, Marcus GM, Meyer M. *Heart Rhythm O2*. 2020

The myPACE Randomized Clinical Trial



Higher heart rates decrease heart pressures in patients with stiff hearts and specialized pacemakers

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Infeld M, Wahlberg K, Cicero J, Meagher S, Habel N, Muthu Krishnan A, Silverman D, Lustgarten D, Meyer M. *Heart Rhythm O2*. 2021

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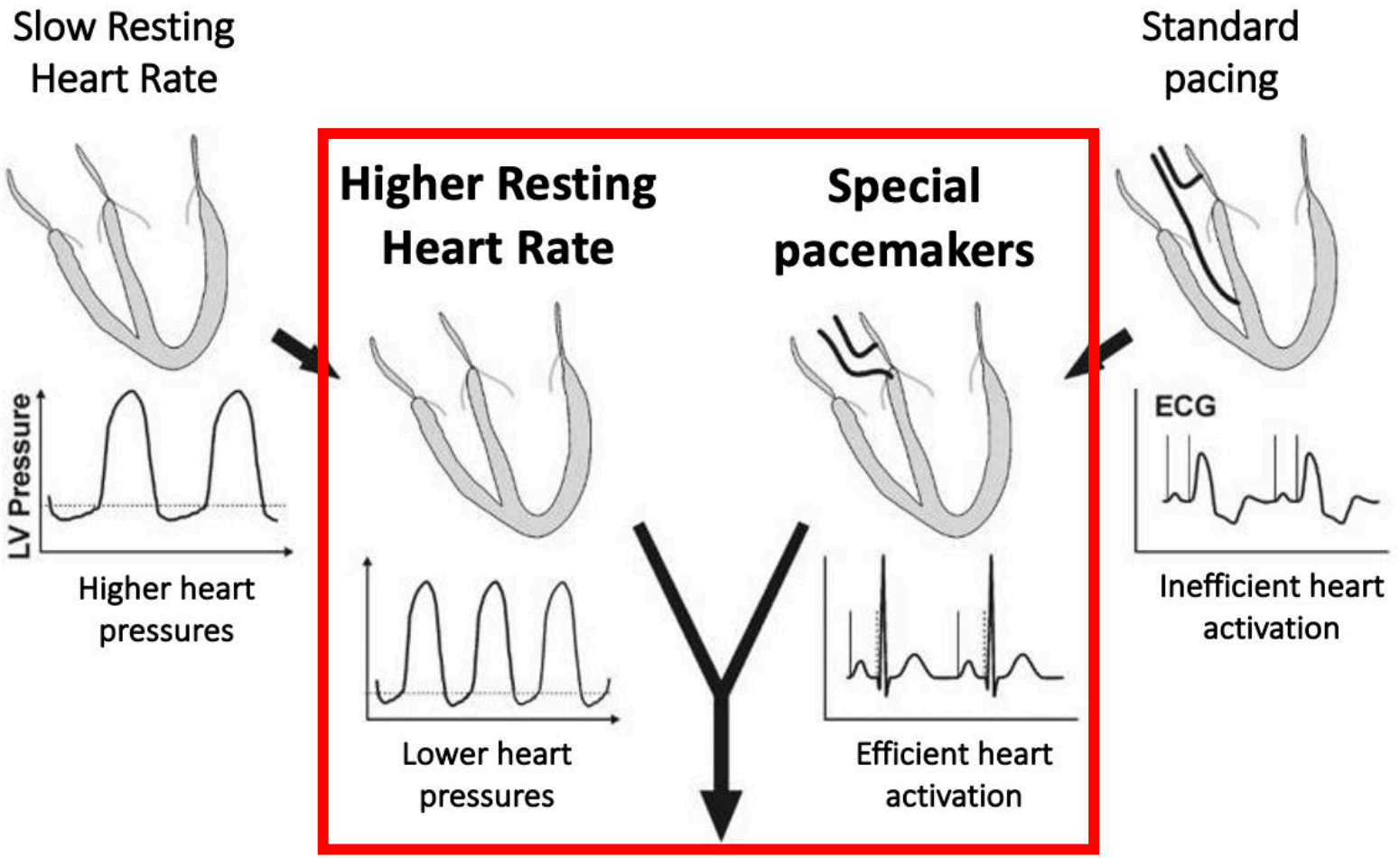

Higher heart rates decrease heart pressures in patients with stiff hearts and specialized pacemakers

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Infeld M, Wahlberg K, Cicero J, Meagher S, Habel N, Muthu Krishnan A, Silverman D, Lustgarten D, Meyer M. *Heart Rhythm O2*. 2021

JAMA Cardiology | Original Investigation

Effect of Personalized Accelerated Pacing on Quality of Life, Physical Activity, and Atrial Fibrillation in Patients With Preclinical and Overt Heart Failure With Preserved Ejection Fraction

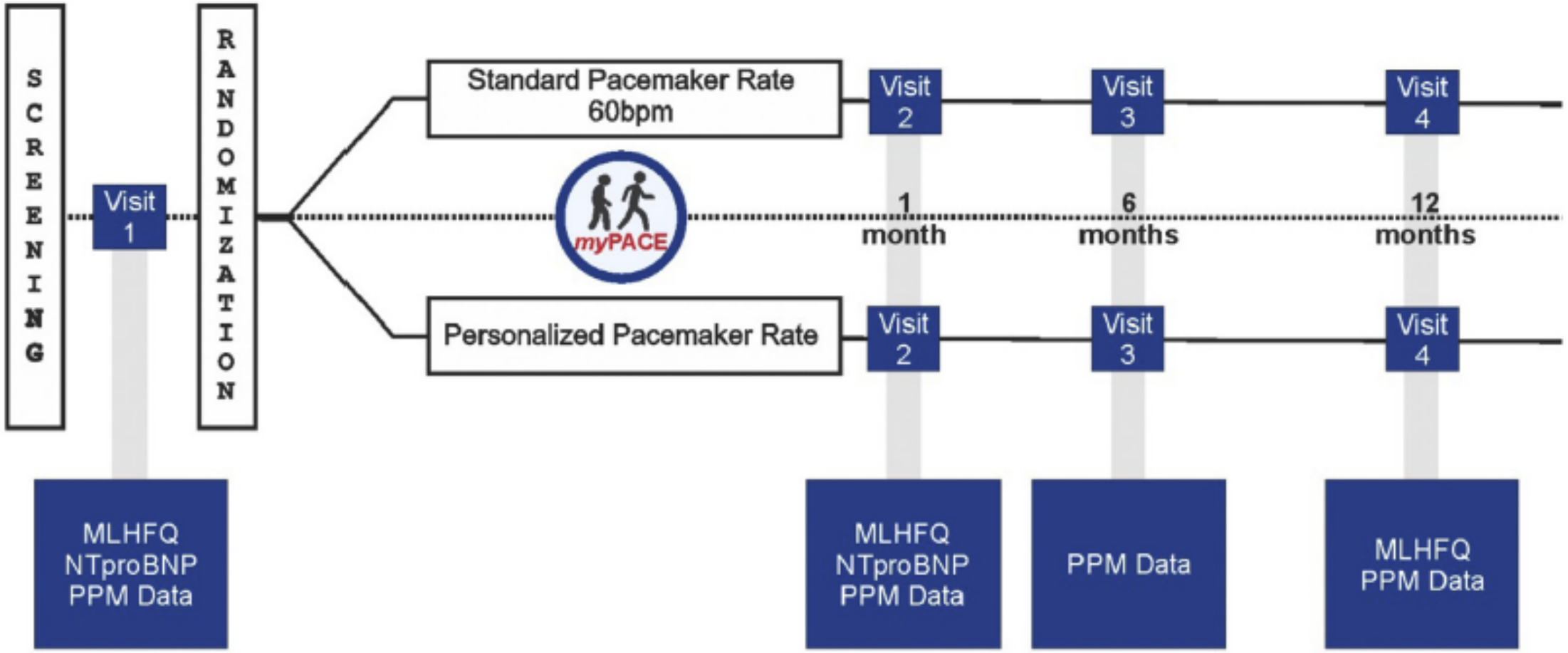
The myPACE Randomized Clinical Trial

Margaret Infeld, MD, MS; Kramer Wahlberg, MD; Jillian Cicero, BS; Timothy B. Plante, MD, MHS; Sean Meagher, MD; Alexandra Novelli, BS; Nicole Habel, MD, PhD; Anand Muthu Krishnan, MD; Daniel N. Silverman, MD; Martin M. LeWinter, MD; Daniel L. Lustgarten, MD, PhD; Markus Meyer, MD, PhD

Margaret Infeld MD, MS

University of Vermont

myPACE Randomized Clinical Trial - Design



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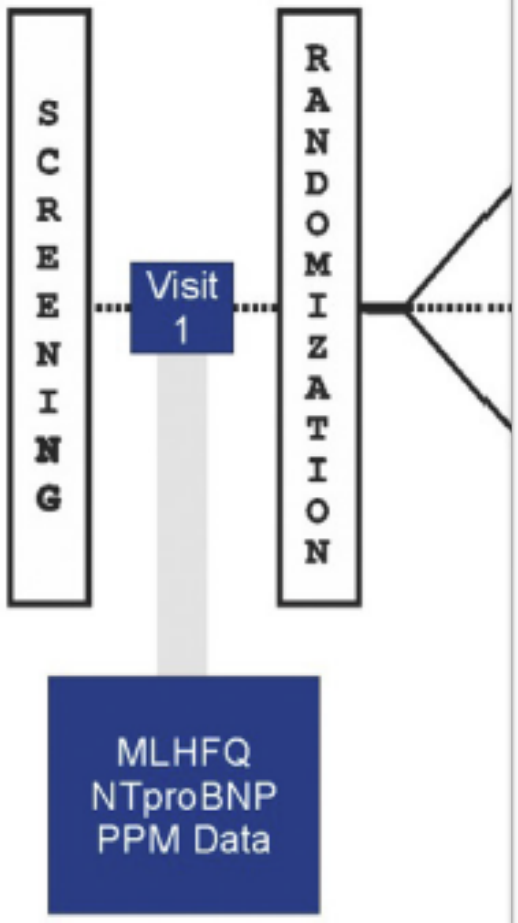
Infeld M, Wahlberg K, Cicero J, Meagher S, Habel N, Muthu Krishnan A, Silverman D, Lustgarten D, Meyer M. *Heart Rhythm O2*. 2021

myPACE Rando

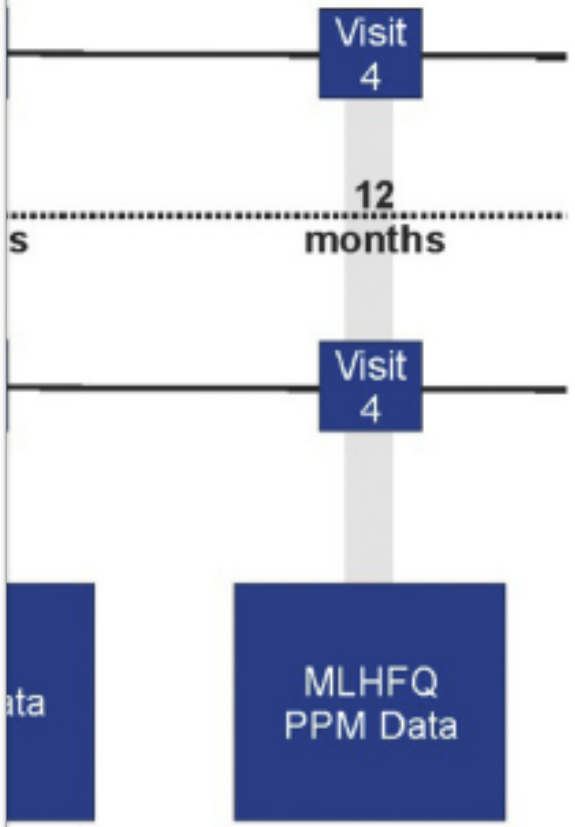


MINNESOTA LIVING WITH HEART FAILURE® QUESTIONNAIRE

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -	No					Very Much
		Very Little				
1. causing swelling in your ankles or legs?	0	1	2	3	4	5
2. making you sit or lie down to rest during the day?	0	1	2	3	4	5
3. making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4. making your working around the house or yard difficult?	0	1	2	3	4	5
5. making your going places away from home difficult?	0	1	2	3	4	5
6. making your sleeping well at night difficult?	0	1	2	3	4	5
7. making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8. making your working to earn a living difficult?	0	1	2	3	4	5
9. making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the foods you like?	0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5
13. making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14. making you stay in a hospital?	0	1	2	3	4	5
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side effects from treatments?	0	1	2	3	4	5
17. making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18. making you feel a loss of self-control in your life?	0	1	2	3	4	5
19. making you worry?	0	1	2	3	4	5
20. making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21. making you feel depressed?	0	1	2	3	4	5

11/10/04



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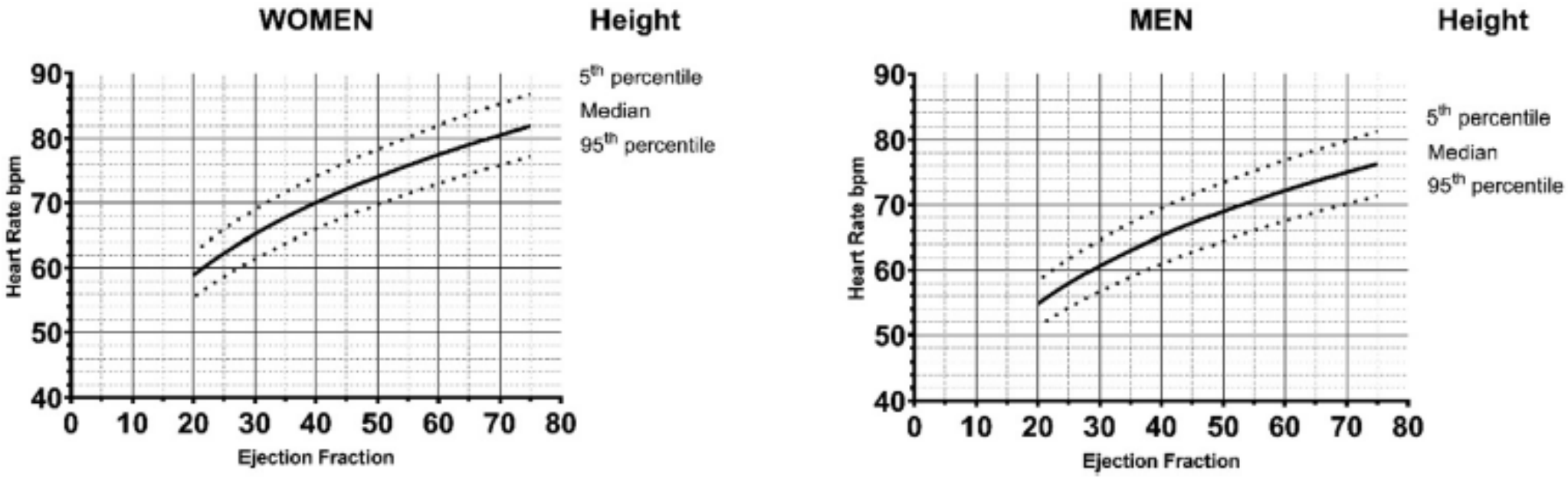
Infeld M, Wahlberg K, Cicero J, Meagher S, I *Rhythm O2*. 2021

The “myPACE” resting heart rate



Algorithm calculated resting heart rate by **height** and **ejection fraction**

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Infeld M, Wahlberg K, Cicero J, Meagher S, Habel N, Muthu Krishnan A, Silverman D, Lustgarten D, Meyer M. *Heart Rhythm O2*. 2021

myPACE Randomized Clinical Trial - Results

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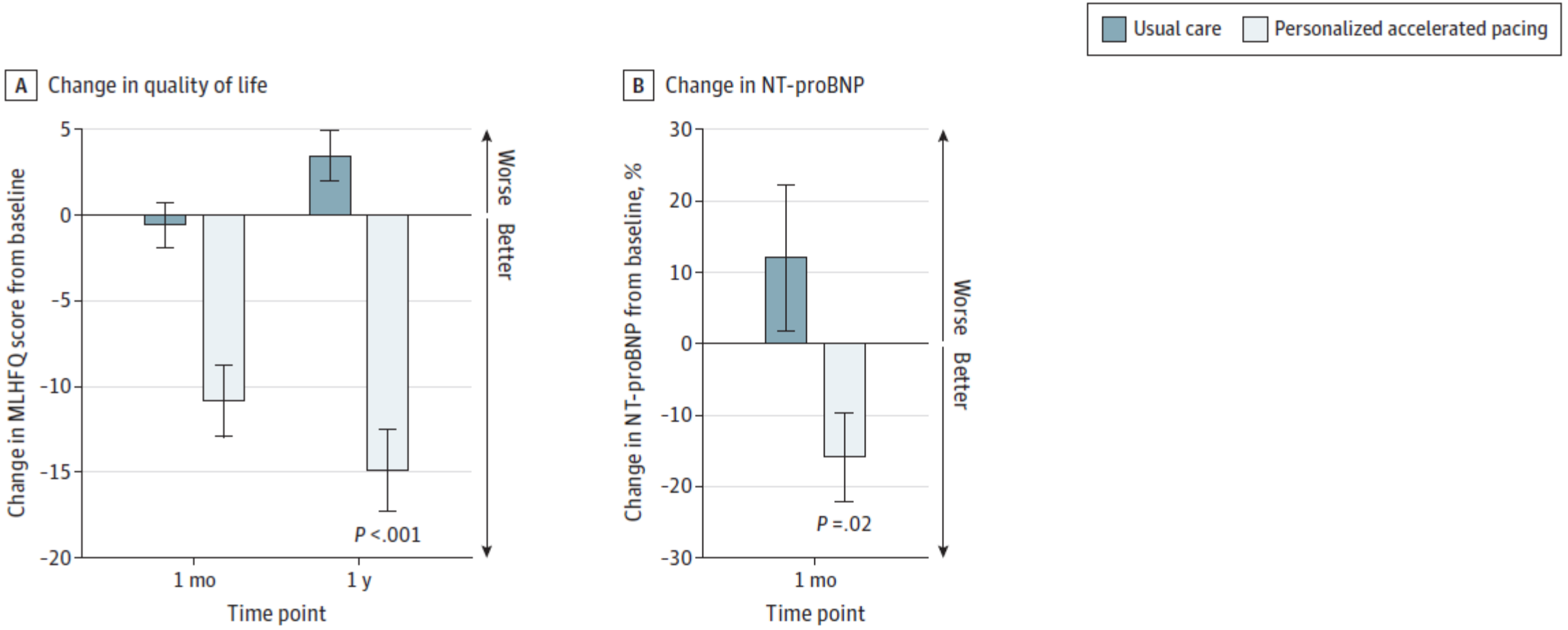
Infeld, Wahlberg…Lustgarten, Meyer. JAMA Cardiology. 2023

myPACE Randomized Clinical Trial - Results



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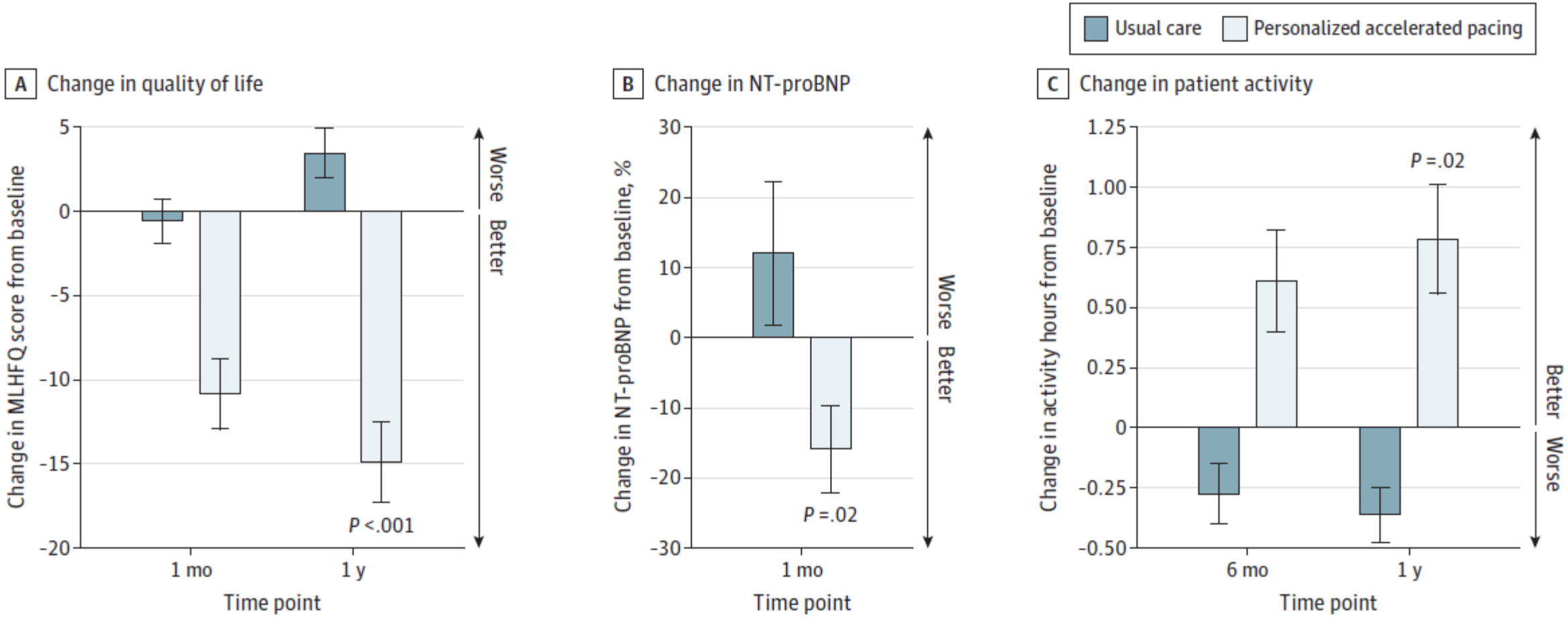
Infeld, Wahlberg…Lustgarten, Meyer. JAMA Cardiology. 2023

myPACE Randomized Clinical Trial - Results



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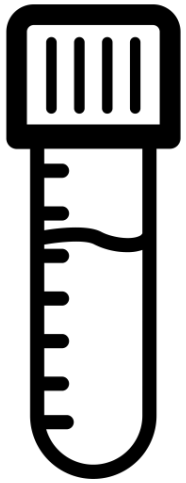
Infeld, Wahlberg…Lustgarten, Meyer. JAMA Cardiology. 2023

myPACE in HFpEF led to improvements in

Heart Failure Symptoms

MLHFQ Score
myPACE +15 (15.5)
Usual care -3.5 (10.6)
p < 0.001



NT-proBNP

myPACE -109 (458) pg/dL
Usual care 128 (537) pg/dL
p = 0.02

Activity

myPACE +47 (67) min
Usual care -22 (35) min
p < 0.001

Atrial Fibrillation

myPACE 27% relative risk reduction
p = 0.04

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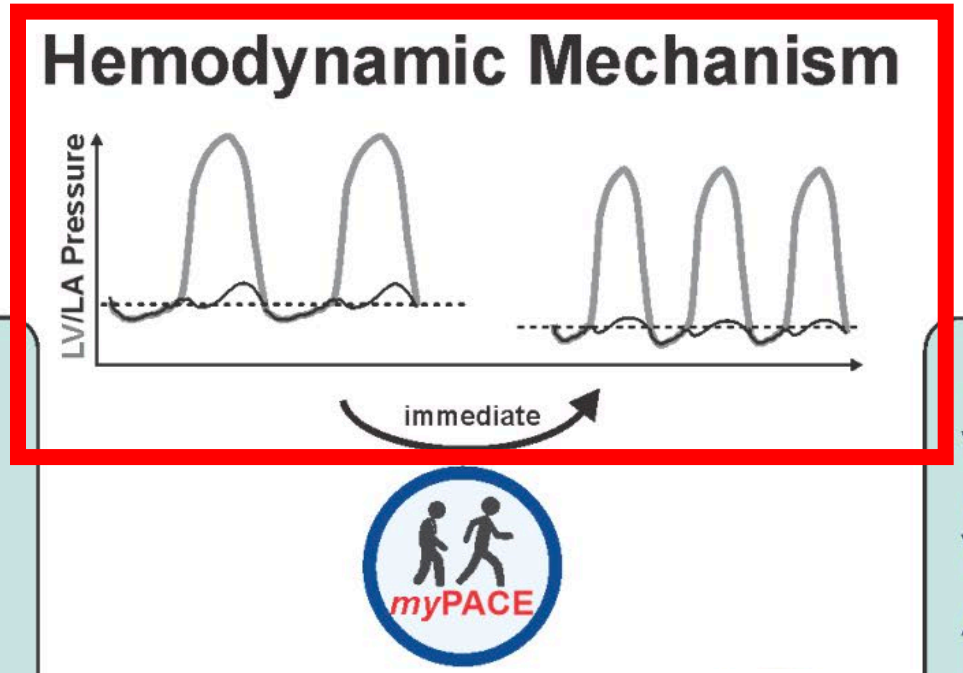
Infeld, Wahlberg…Lustgarten, Meyer. JAMA Cardiology. 2023

Why does myPACE work?

Personalized Accelerated Pacing in HFpEF



- ↓ HF Symptoms
- ↓ NT-proBNP
- ↑ Physical Activity
- ↓ Atrial Fibrillation

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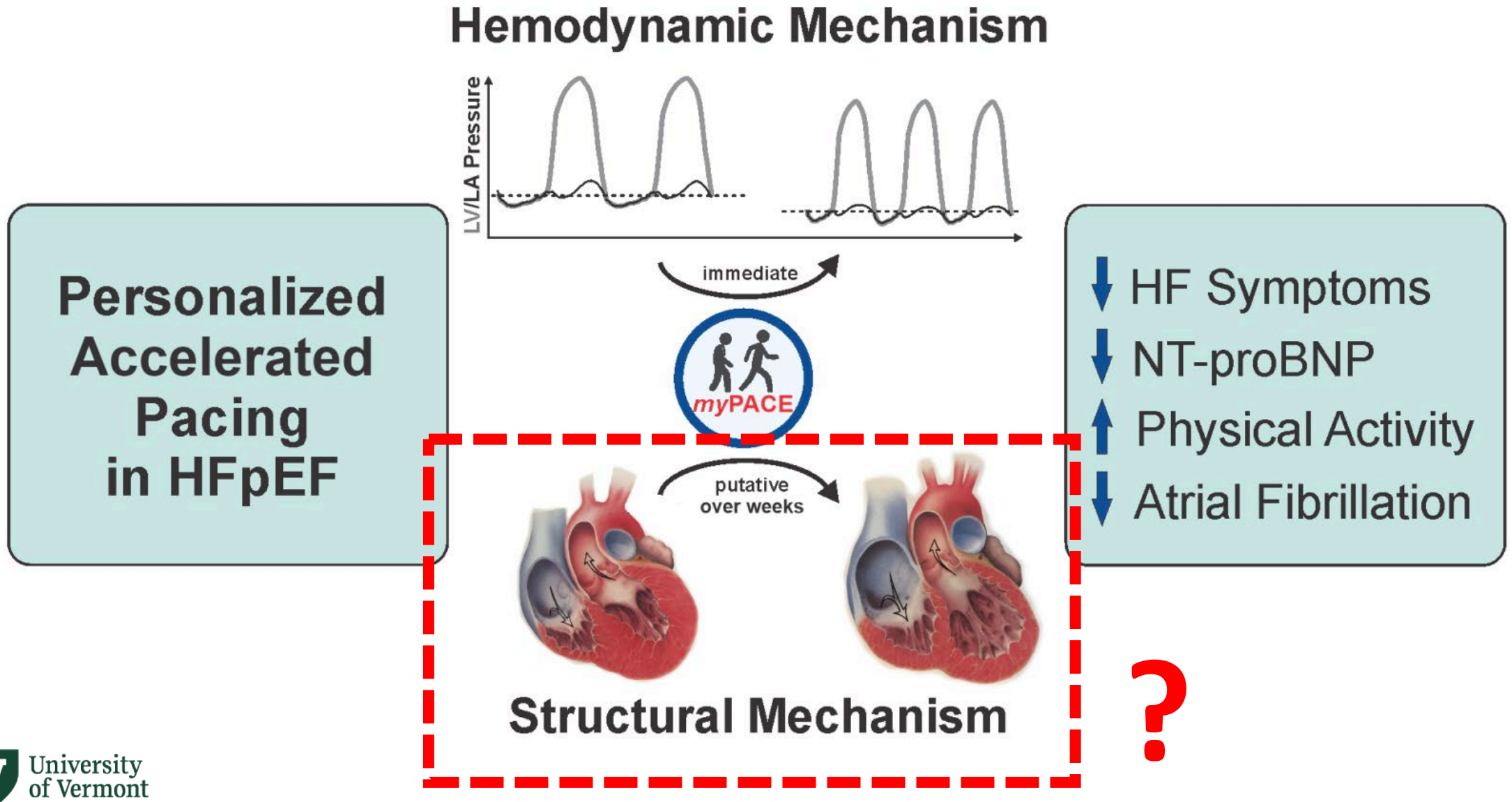
Infeld, Wahlberg…Lustgarten, Meyer. JAMA Cardiology. 2023

Why does myPACE work?



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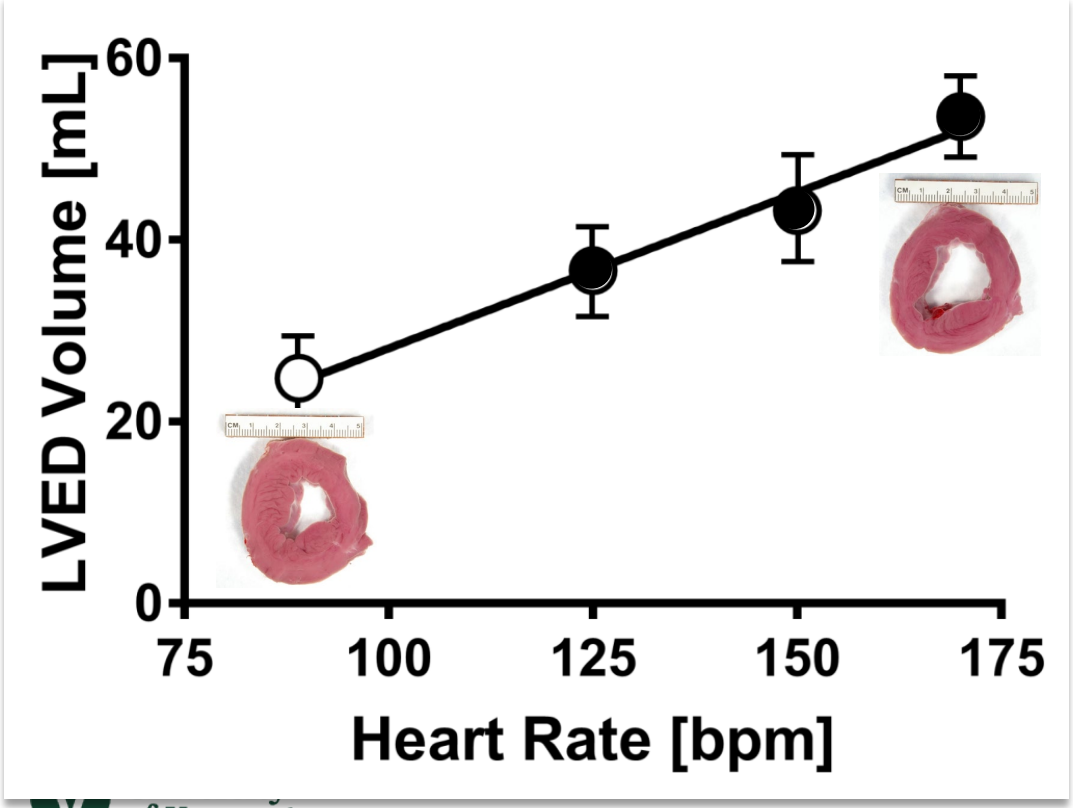
Infeld, Wahlberg…Lustgarten, Meyer. JAMA Cardiology. 2023

Basis for therapeutic heart rate modulation: preclinical animal model

The potential for remodeling

Pig model of LVH exposed to accelerated pacing for 2 weeks

Pig 170bpm ~ Human 125bpm



The pacing intervention:

- reduced wall thickness
- normalized LV chamber volumes
- improving LV mass-to-volume ratios without reducing LVEF

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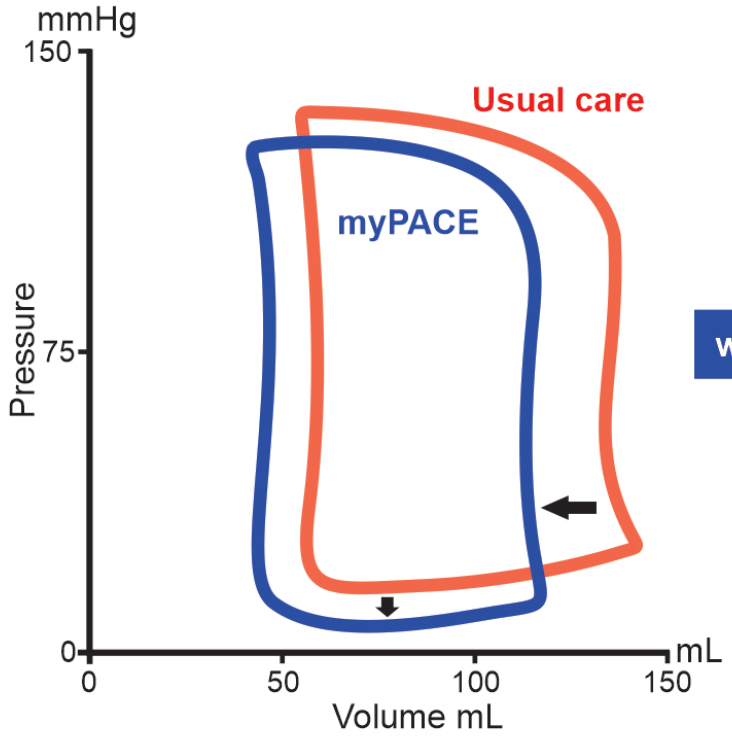
Klein FJ et al Heart rate-induced modifications of concentric left ventricular hypertrophy: exploration of a novel therapeutic concept. Am J Physiol. 2016

The myPACE echo study

Usual care

my*PACE *(personalized accelerated pacing)

HFpEF → **Improved Hemodynamics** → **Remodeling**



weeks

Changes in cardiac *structure* with exposure to pacing

Septal wall thickness

Usual care **increased** [1.17cm → 1.23cm], **p=0.038**
myPACE **decreased** [1.12cm → 1.07cm, p=0.089], **p-interaction=0.008**

LV mass to end-systolic volume ratio

Usual care **increased** [6.4 g/mL→ 6.8 g/mL], p=0.384
myPACE **decreased** [5.9 g/mL→ 4.8 g/mL, **p=0.045**], **p-interaction=0.038**

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Changes in cardiac *structure* with exposure to pacing

Septal wall thickness

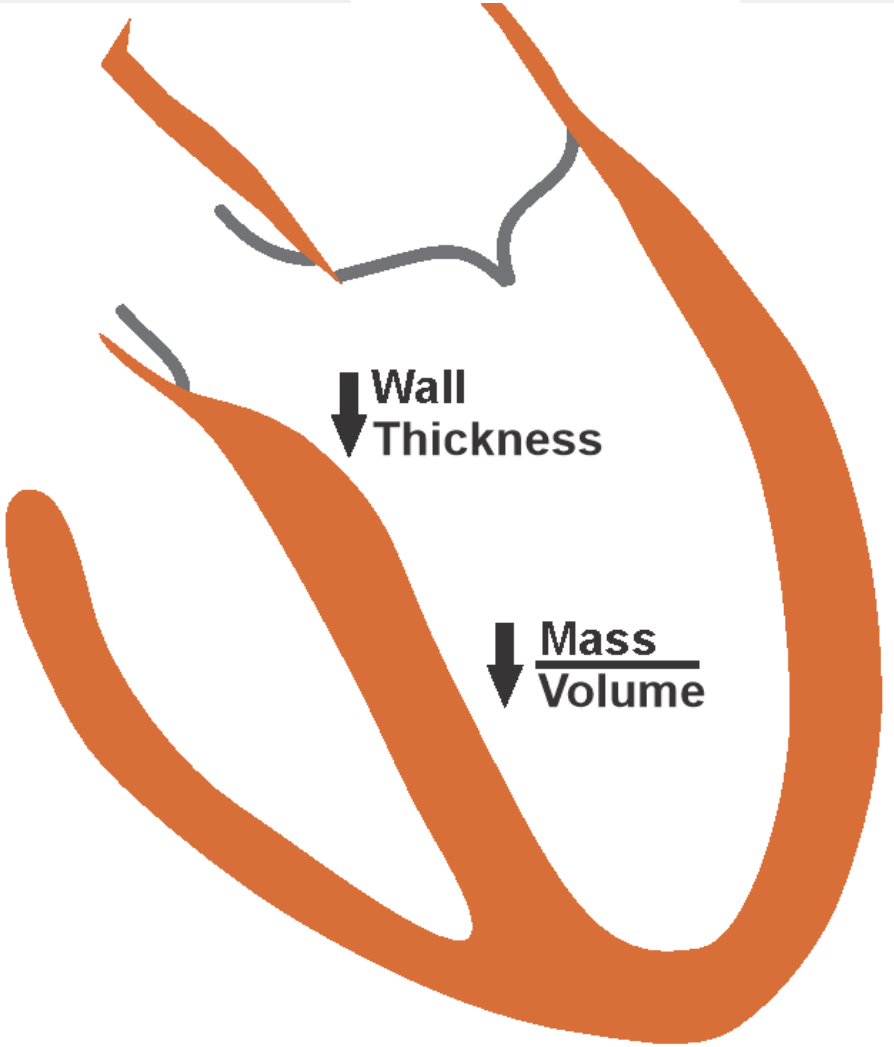
Usual care **increased** [1.17 cm → 1.23 cm], **p=0.038**

myPACE **decreased** [1.12 cm → 1.07 cm, p=0.089], **p**

LV mass to end-systolic volume ratio

Usual care **increased** [6.4 g/mL → 6.8 g/mL], p=0.38

myPACE **decreased** [5.9 g/mL → 4.8 g/mL, **p=0.045**],



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Changes in cardiac *structure* with exposure to pacing

LV ejection fraction

Usual care **unchanged** [60.0%→ 60.0%, p=0.99]

myPACE **decreased** [58.6% → 55.3%, **p=0.001**], **p-interaction=0.015**

There were no significant changes in diastolic parameters

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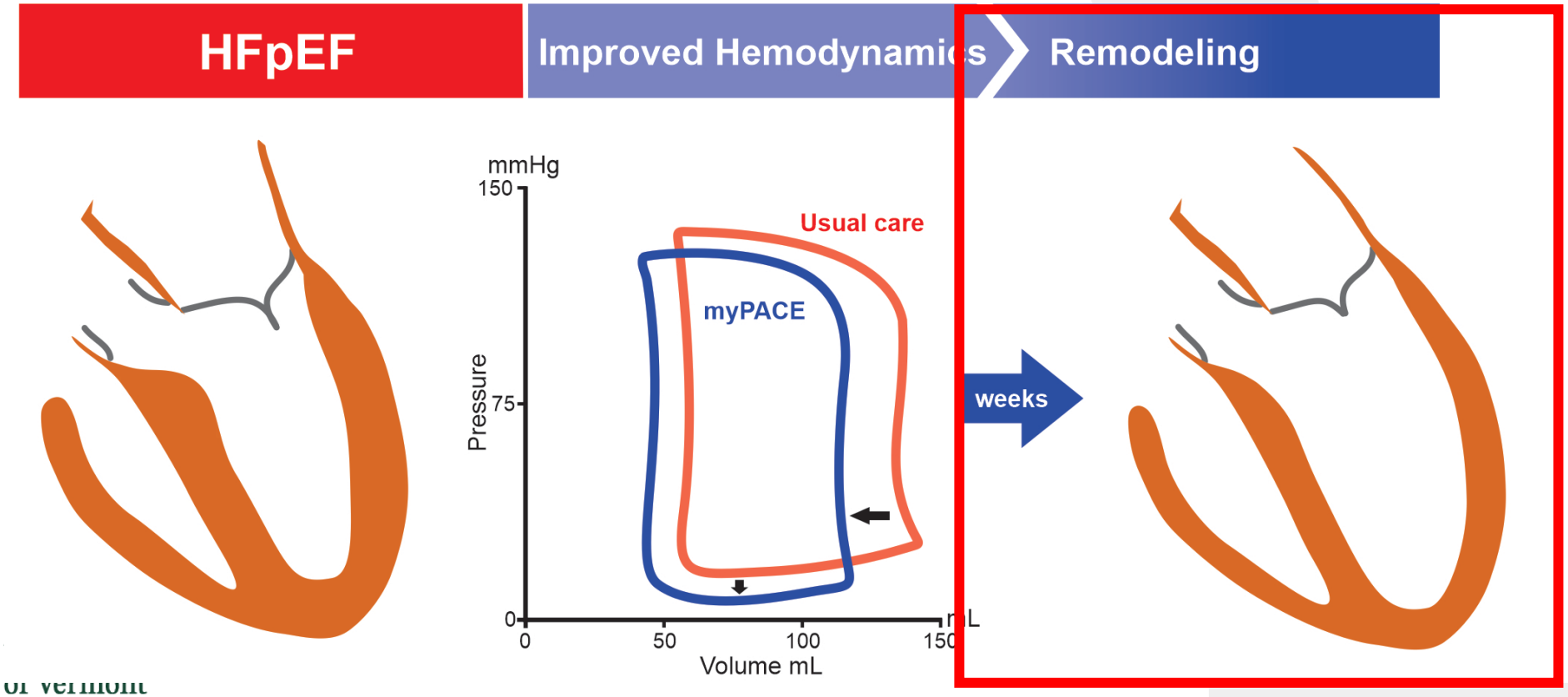
Changes in cardiac *structure* with exposure to pacing

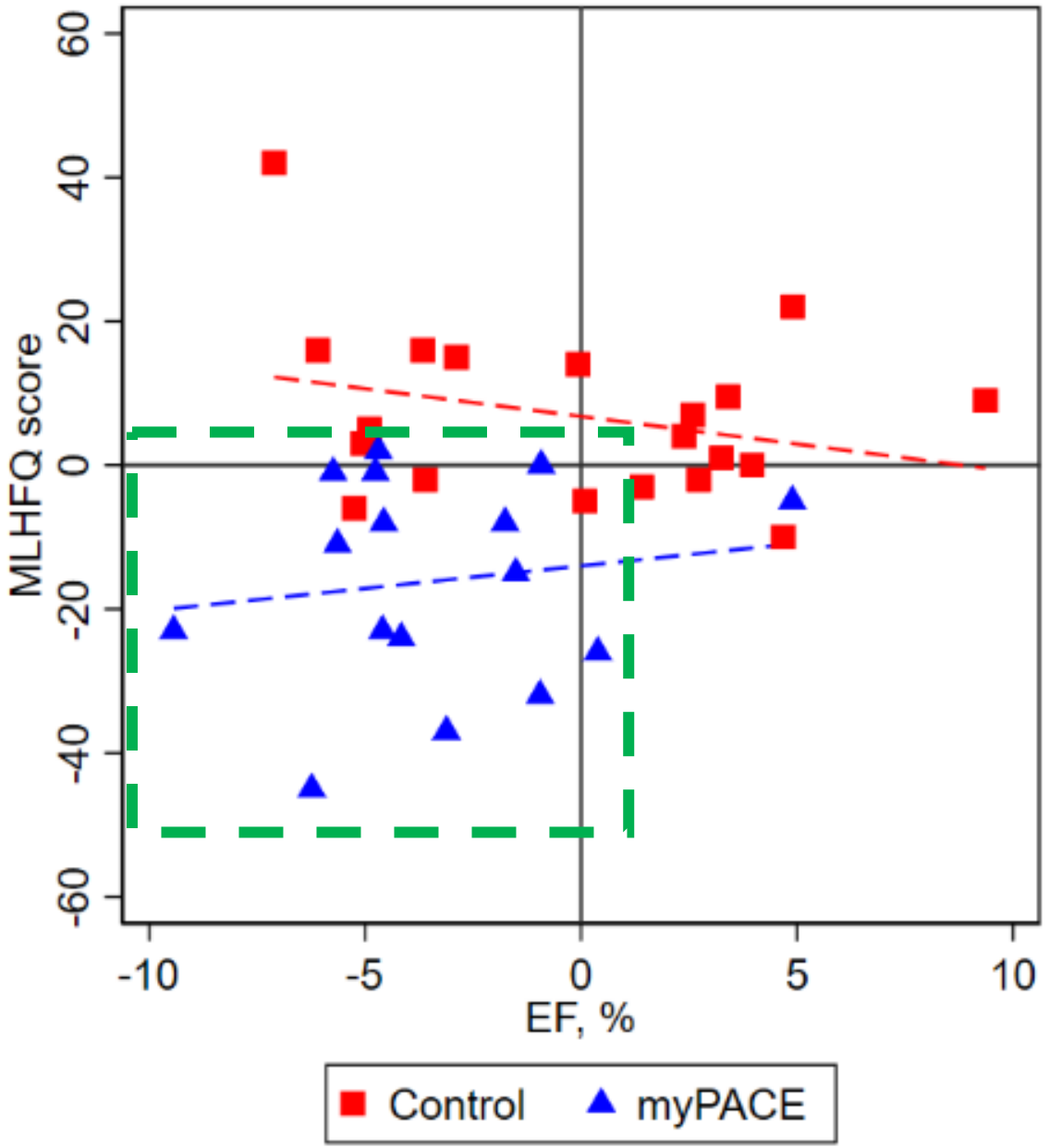
LV ejection fraction

Usual care **unchanged** [60.0%→ 60.0%, p=0.99]

myPACE **decreased** [58.6% → 55.3%, p=0.001], p-interaction=0.015



Change in LVEF associated with changes in Quality of Life



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Is the small drop in LV ejection fraction ***bad***?

The decrease in LV ejection fraction was **small** and remained in the **normal range**

No patients developed LV ejection fraction <50%

These data support the hypothesis that a small reduction in ejection fraction may be ***part of the therapeutic approach***

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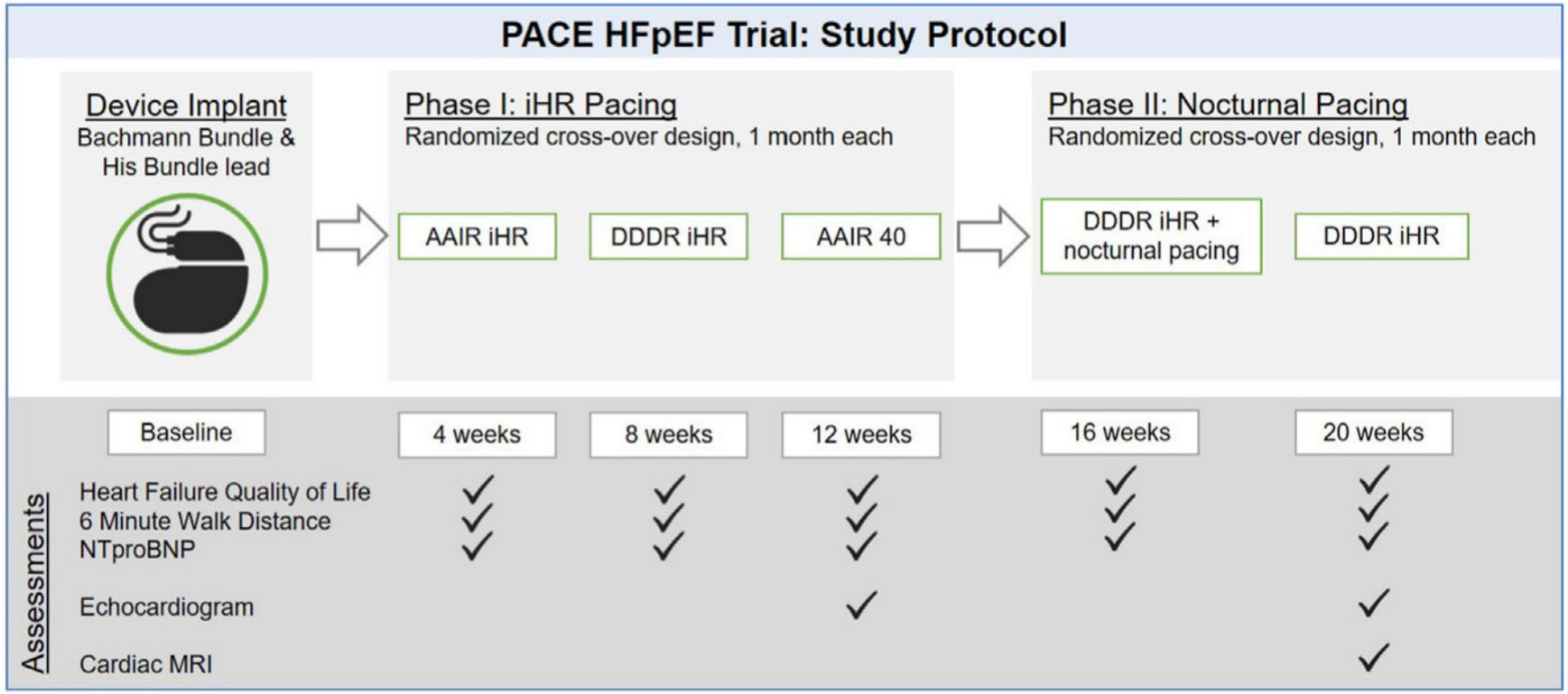
Ongoing Research: The PACE-HFpEF study

The PACE HFpEF trial is designed to determine the **safety** and **feasibility** of **continuous accelerated physiological pacing** in HFpEF patients ***without*** a standard pacemaker indication



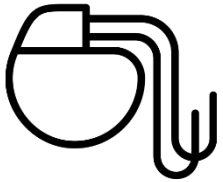
Nicole Habel MD, PhD

University of Vermont

Key Points

There are few evidence-based treatments for heart failure with preserved ejection fraction (HFpEF)

No evidence that lower heart rates (and therapies that lower heart rate) are beneficial in HFpEF



Emerging evidence suggests a role for therapeutic heart rate modulation (increase in heart rate) in HFpEF

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How does this impact current clinical practice?

- **Most** patients with HFpEF do not benefit/need beta blockers, and **de-escalation** of therapies that lower heart rate like beta blockers **should be considered**

- Among patients with HFpEF and pre-existing pacemakers that limit dyssynchrony, a backup pacing rate of 60bpm is probably *too slow*

- **Therapeutic heart rate modulation** may be an opportunity to improve symptoms, hemodynamics, and structural changes in HFpEF though ***physiologic pacing*** from the *conduction system*

Thank You!

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