

Contemporary Advanced Heart Failure Therapy

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Audience Response Question

40 yo male with NIDM and Class III heart failure.
Creatinine 1.0 and K 4.1. LVEF 30%. HR 90/min
Lisinopril 5 mg qd and Toprol XL 150 mg qd.

Next step should be:

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- b) Add digoxin 0.125 mg qd
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40 yo white male with NIDDM and Class III heart failure. Creatinine 1.0 and K 4.1. LVEF 30%. HR 90/min. QRS duration 170 msec. Lisinopril 40 mg qd, Toprol XL 150 mg qd, aldactone 25 mg qd.

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- c) Add corlanor (ivabradine)
- d) Add entresto (sacubitril/valsartan)
- e) Change to Lisinopril to entresto (sacubitril/valsartan)



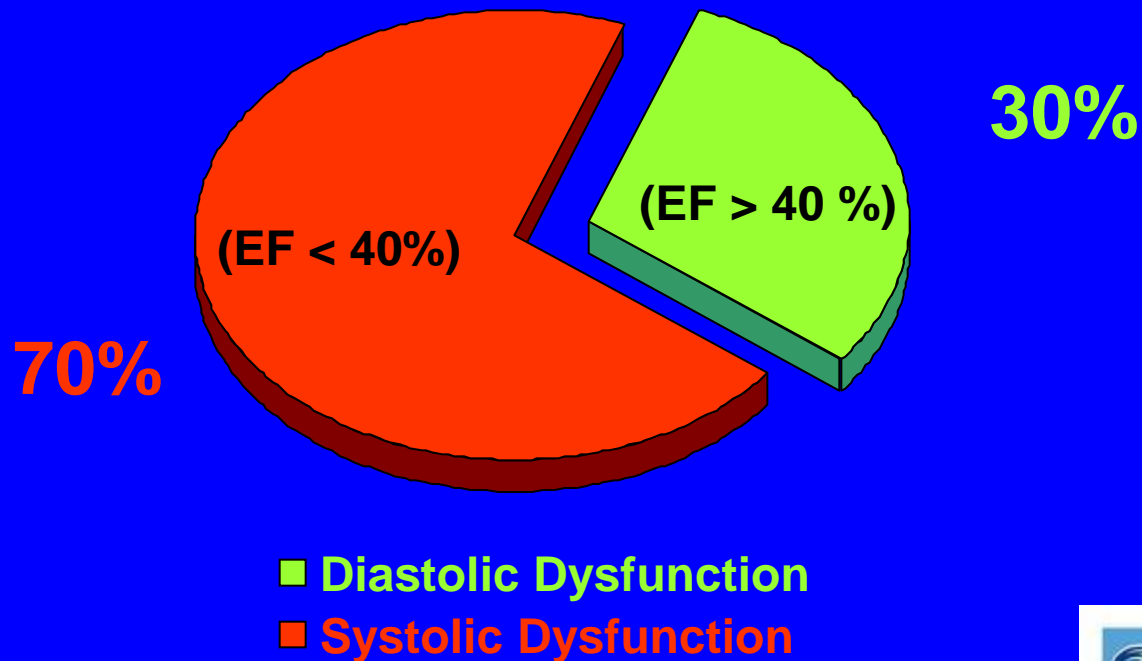
Epidemiology of Heart Failure

- Approximately 5.7 million Americans have CHF
- 670,000 new cases annually
- Five-year mortality rate as high as 50%
- Most frequent cause of hospitalization in patients older than 65 years
- Prevalence: 11.7% of population > 85 years old
- DRG 127 (Congestive Heart Failure):
 - Primary Dx 990,000 hospitalizations/yr
 - Secondary Dx 2,000,000 hospitalizations/yr
- Single largest expense for Medicare

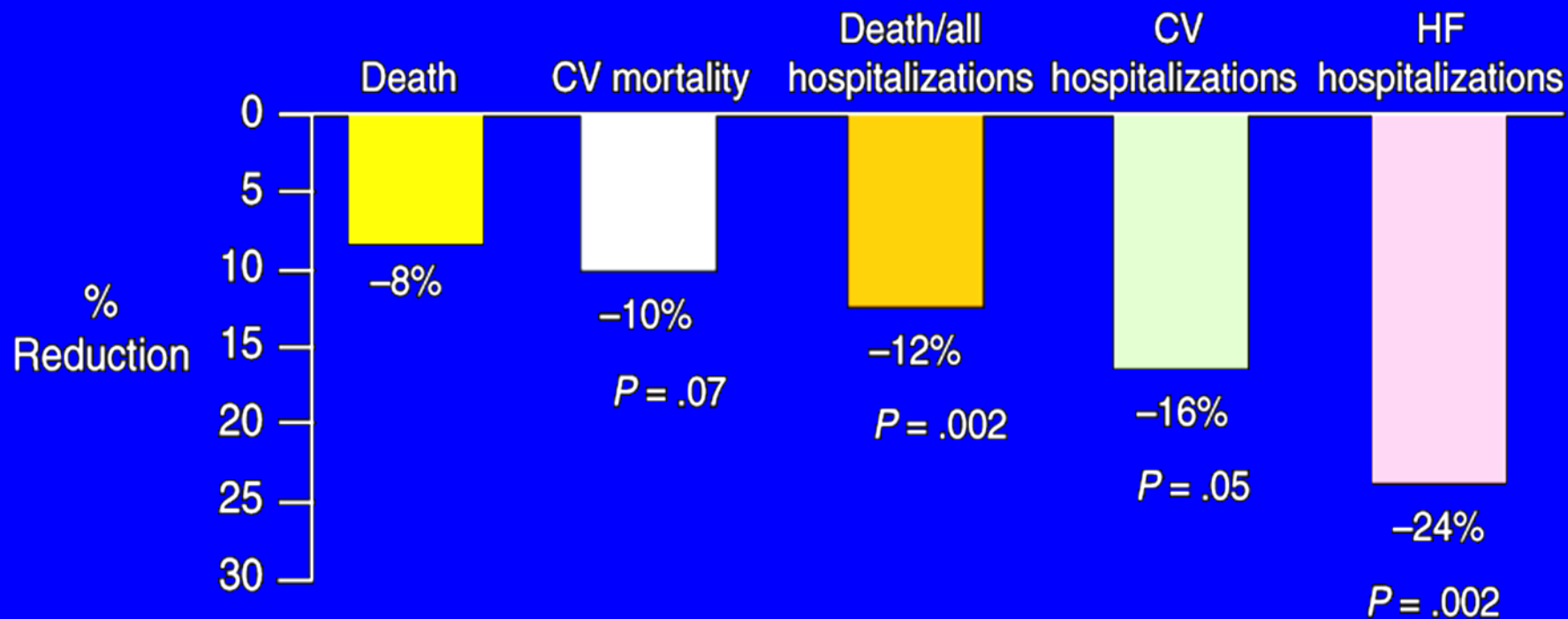


Left Ventricular Dysfunction

- **Systolic: Impaired contractility/ejection**
 - Approximately two-thirds of heart failure patients have systolic dysfunction¹
- **Diastolic: Impaired filling/relaxation**



ATLAS: High-dose ACE-I reduces adverse outcomes in heart failure



Packer M, et al. *Circulation*. 1999;100:2312-2318.

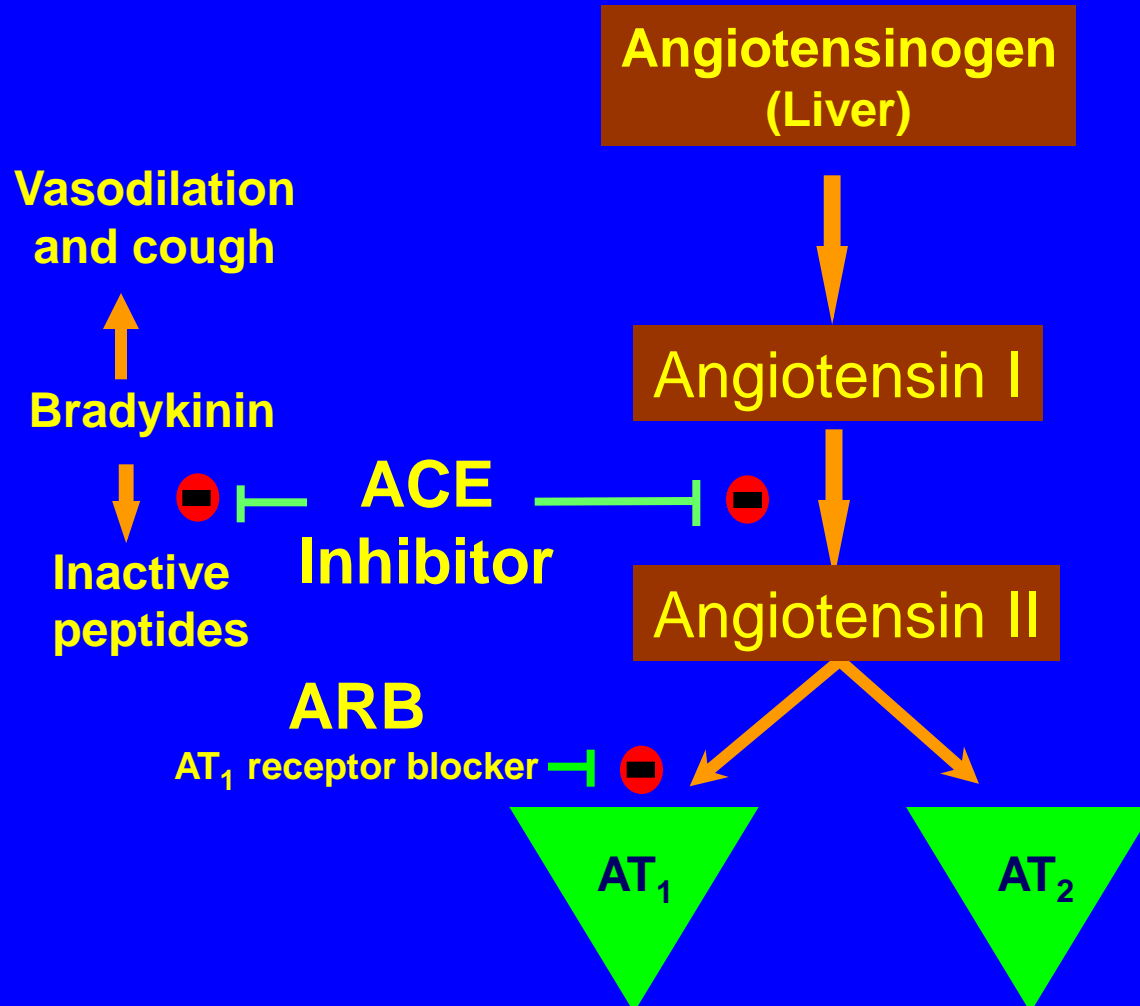
Relative Doses of ACEI

Target dose

- **Captopril** 50 mg TID
- **Enalapril** 20 mg BID
- **Lisinopril** 40 mg qd
- **Ramipril** 10 mg qd

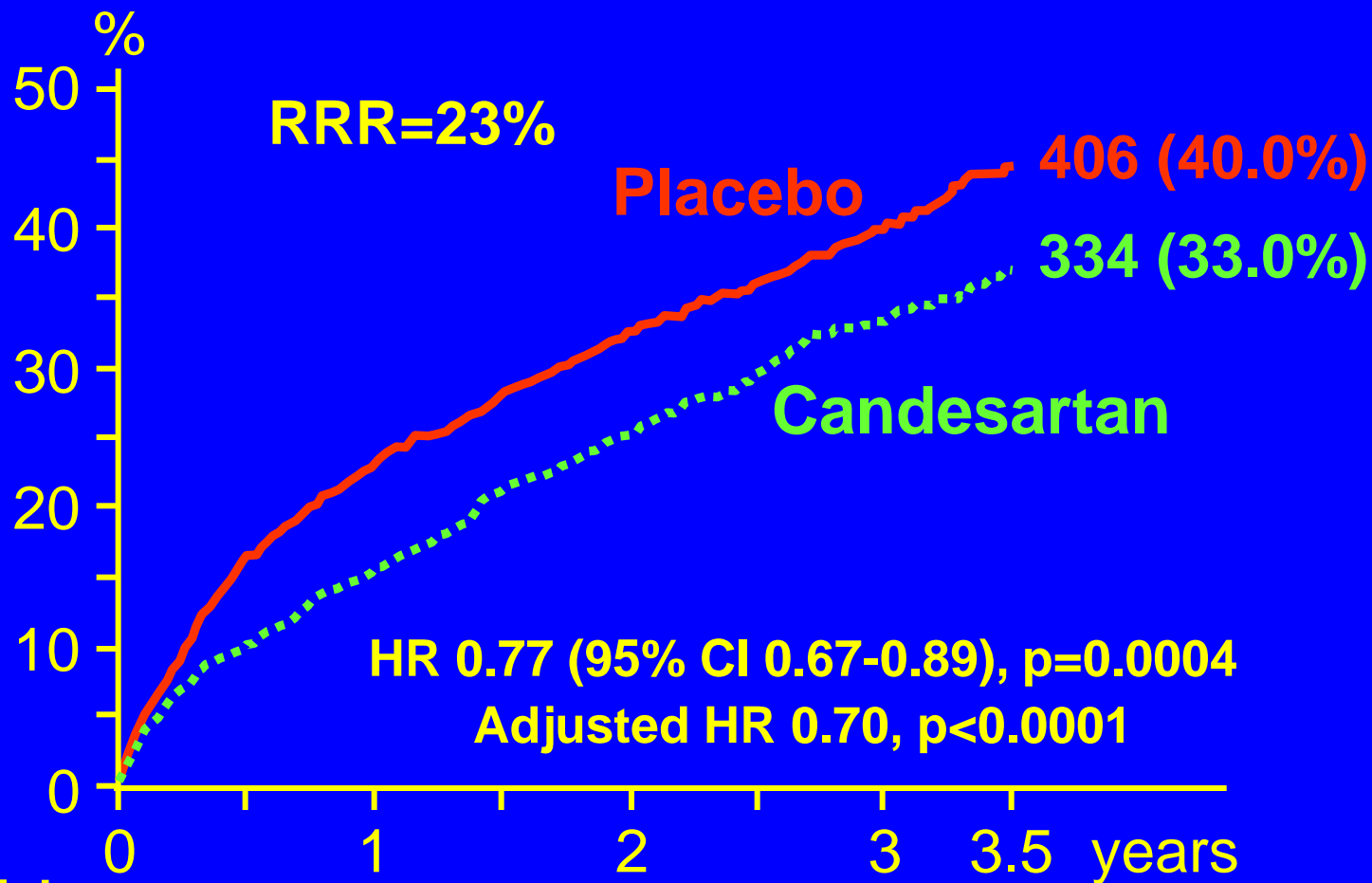


Blockade of RAAS



CHARM-Alternative: ACEI intolerant Patients

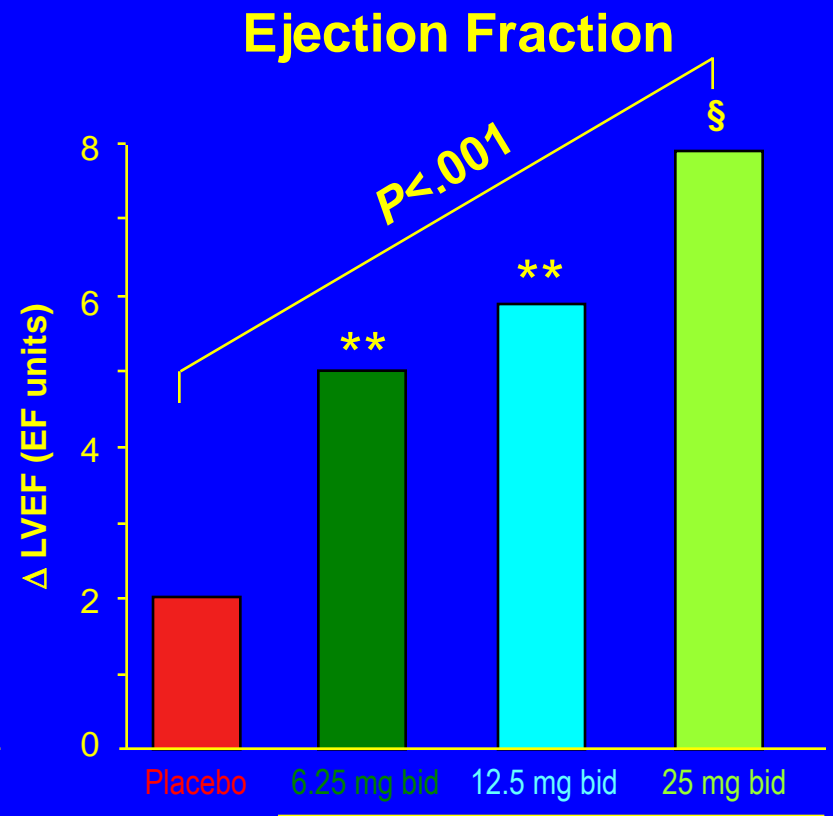
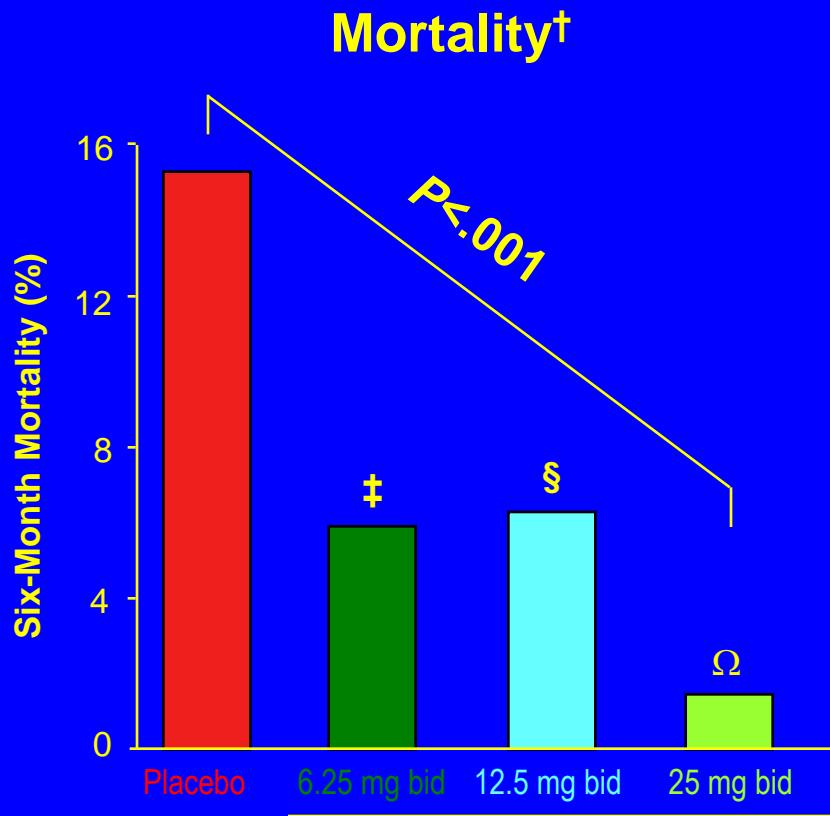
Primary outcome CV death or CHF hospitalisation



Number at risk

Candesartan	1013	929	831	434	122
Placebo	1015	887	798	427	126

MOCHA*



‡ $P < .05$ vs placebo.

§ $P = .07$ vs placebo.

Ω $P < .001$ vs placebo.

** $P < .005$ vs placebo.

§ $P < .0001$ vs placebo.

Patients receiving diuretics, ACE inhibitors, ± digoxin; follow-up 6 months; placebo (n=84), carvedilol (n=261).

*Multicenter Oral Carvedilol Heart Failure Assessment.

†Mortality was not a planned end point in this study.

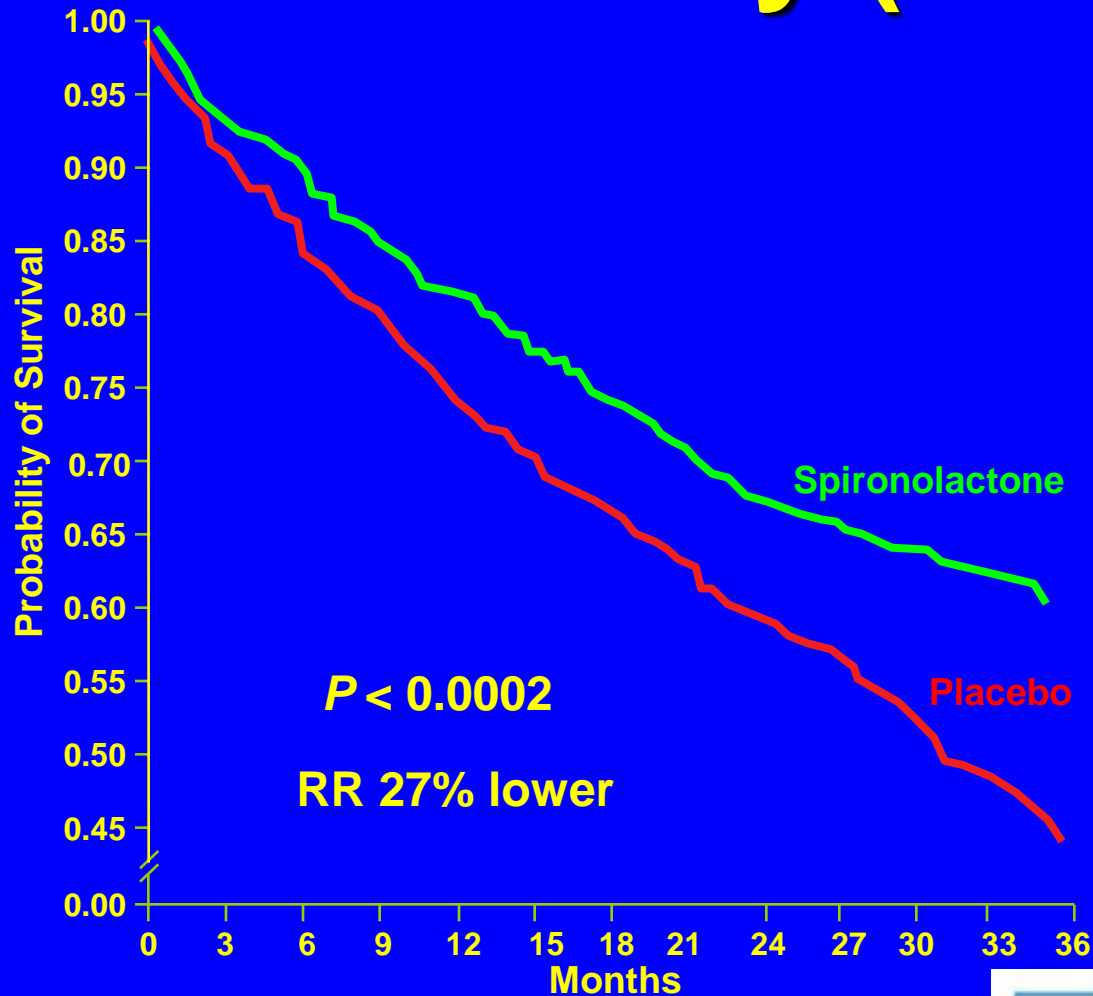
Adapted from Bristow M et al. *Circulation*. 1996; 94: 2807–2816.

Target Doses of Beta Blockers

- **Carvedilol 25 mg BID**
- **Metoprolol Succinate 150 mg qd**
- **Coreg CR 80 mg qd**



Randomized Aldactone Evaluation Study (RALES)



Inclusion Criteria
NYHA Class 3 or 4
LVEF < 35%
Cr < 2.5
K < 5.0

$P < 0.0002$

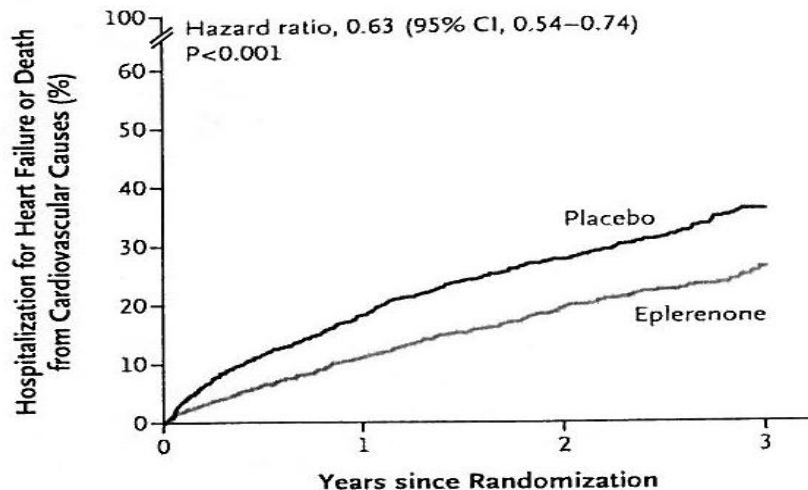
RR 27% lower



Jefferson.
University Hospitals

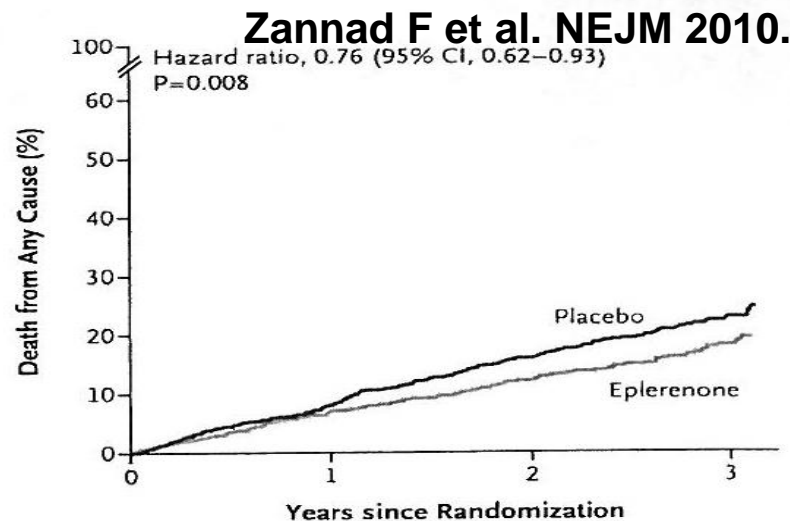
EMPHASIS-HF: Eplerenone in NYHA II

A



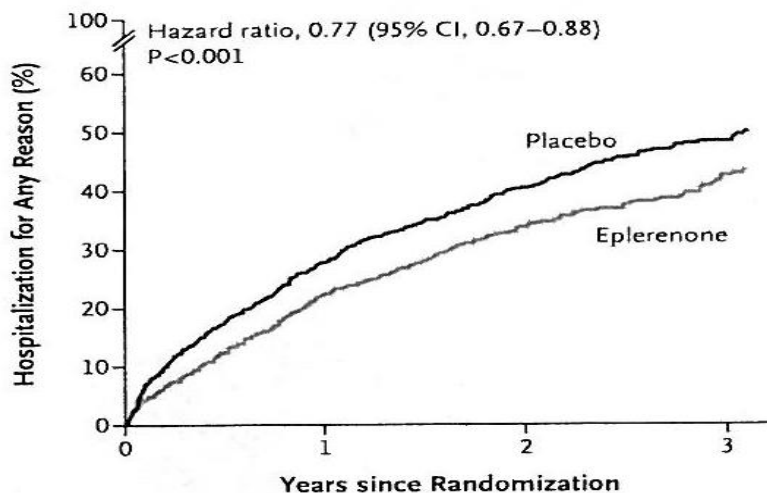
No. at Risk				
Placebo	1373	848	512	199
Eplerenone	1364	925	562	232

B



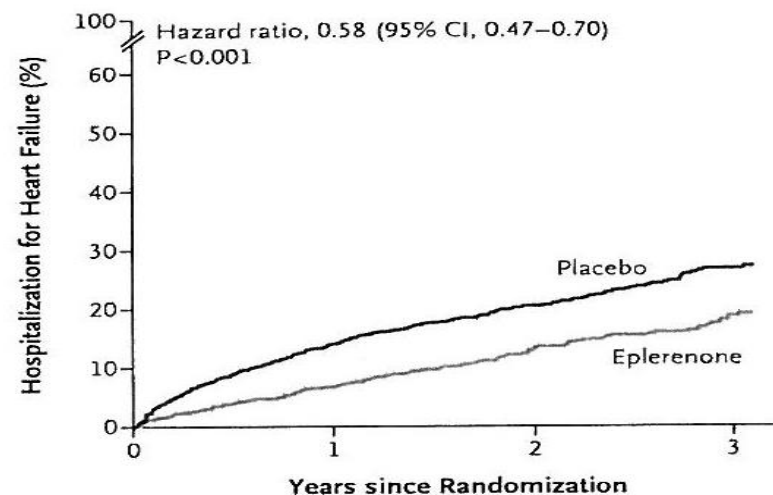
No. at Risk				
Placebo	1373	947	587	242
Eplerenone	1364	972	625	269

C



No. at Risk				
Placebo	1373	742	403	146
Eplerenone	1364	795	451	179

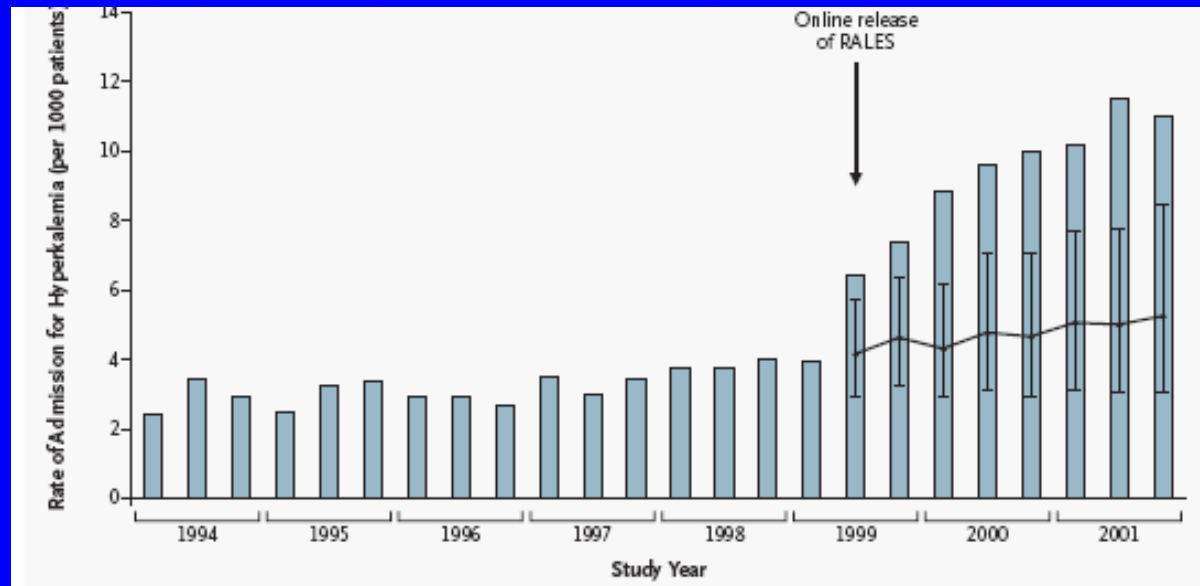
D



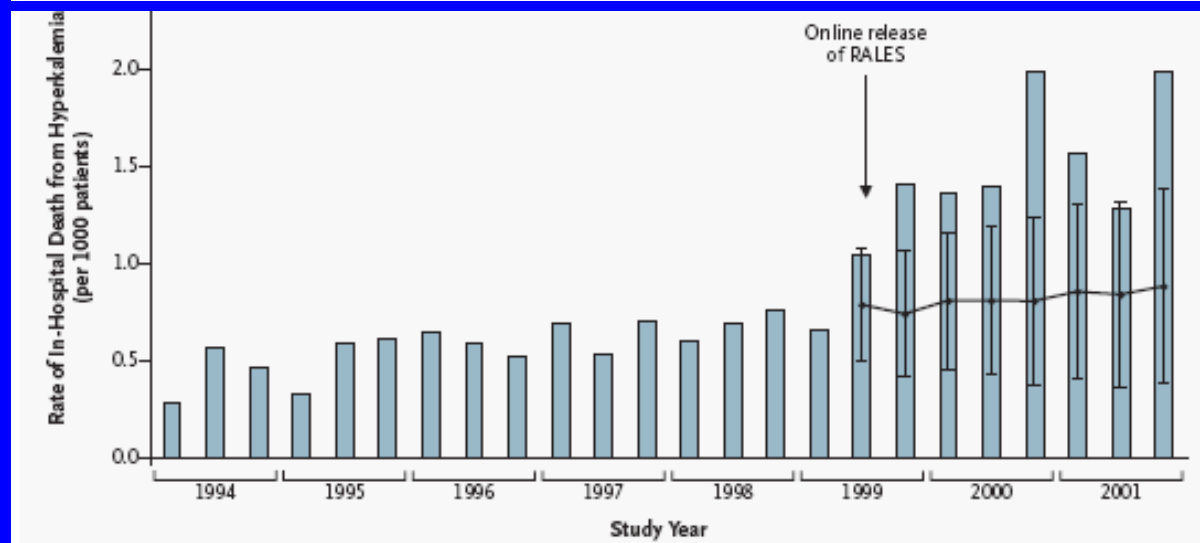
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Hyperkalemia Secondary to Spironolactone for Heart Failure

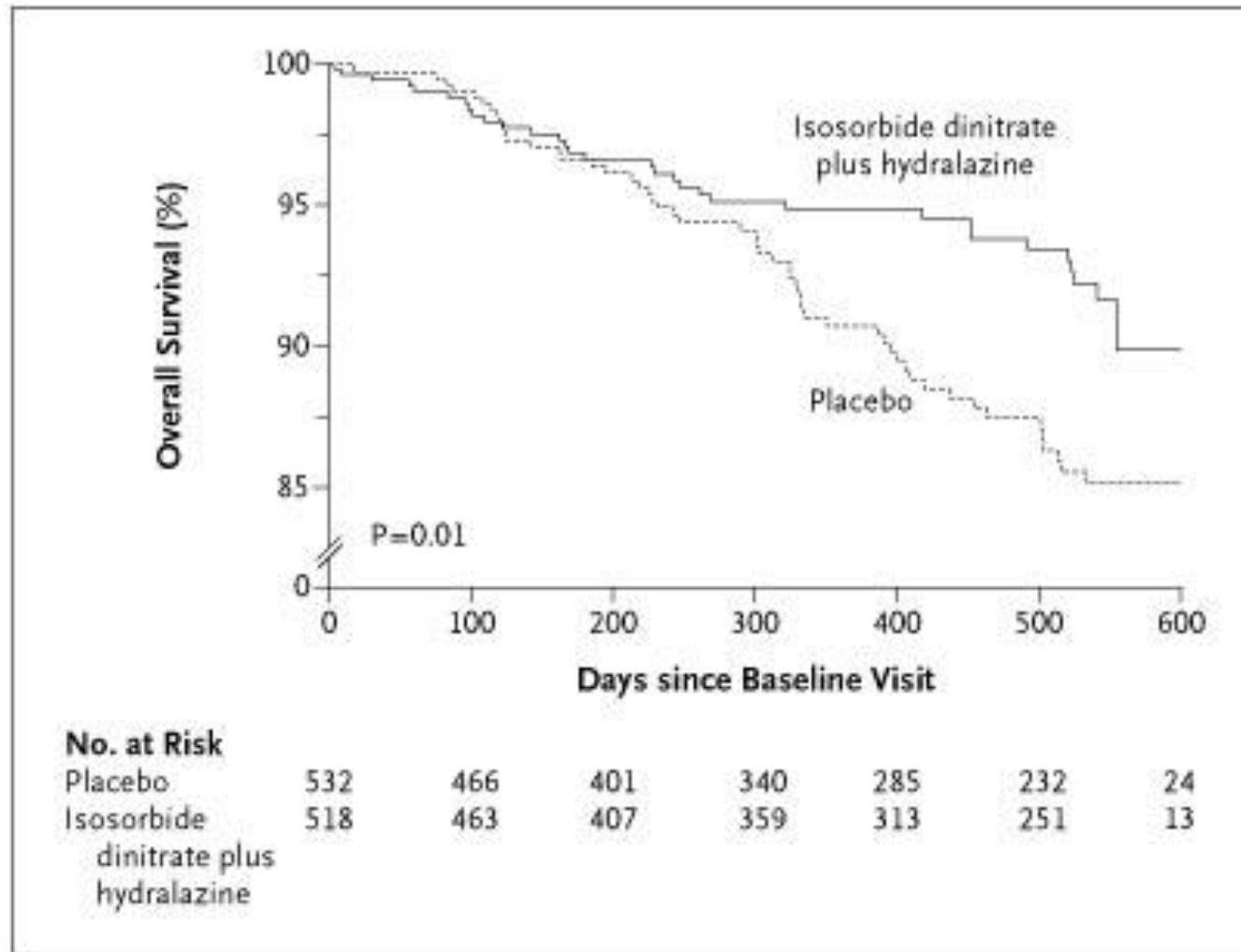
Admission Rate For Hyperkalemia



Mortality from Hyperkalemia



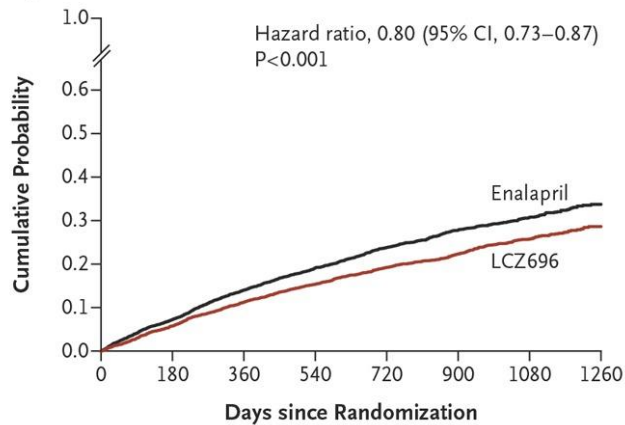
AHeFT: Overall Survival



- NYHA III and IV
- Full medical therapy
- AA only

PARADIGM-HF: Sacubitril/Valsartan

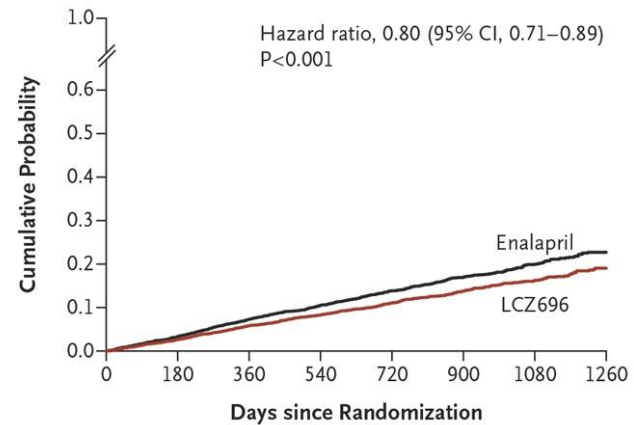
A Primary End Point



No. at Risk

LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

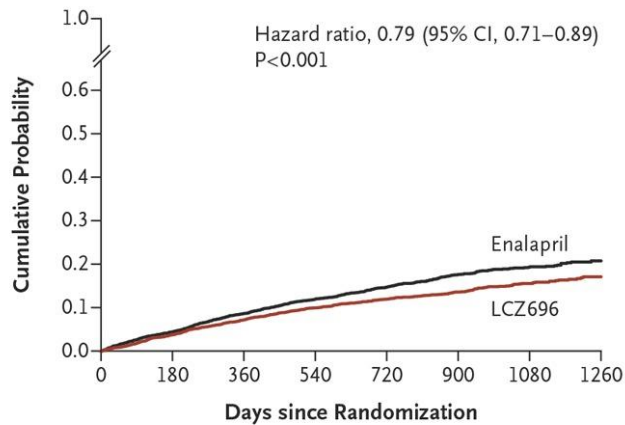
B Death from Cardiovascular Causes



No. at Risk

LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

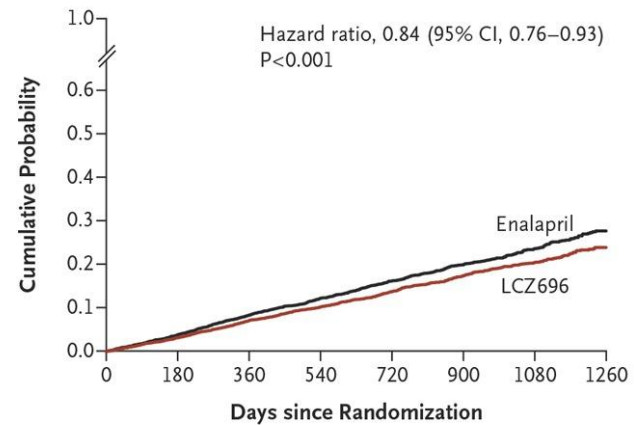
C Hospitalization for Heart Failure



No. at Risk

LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

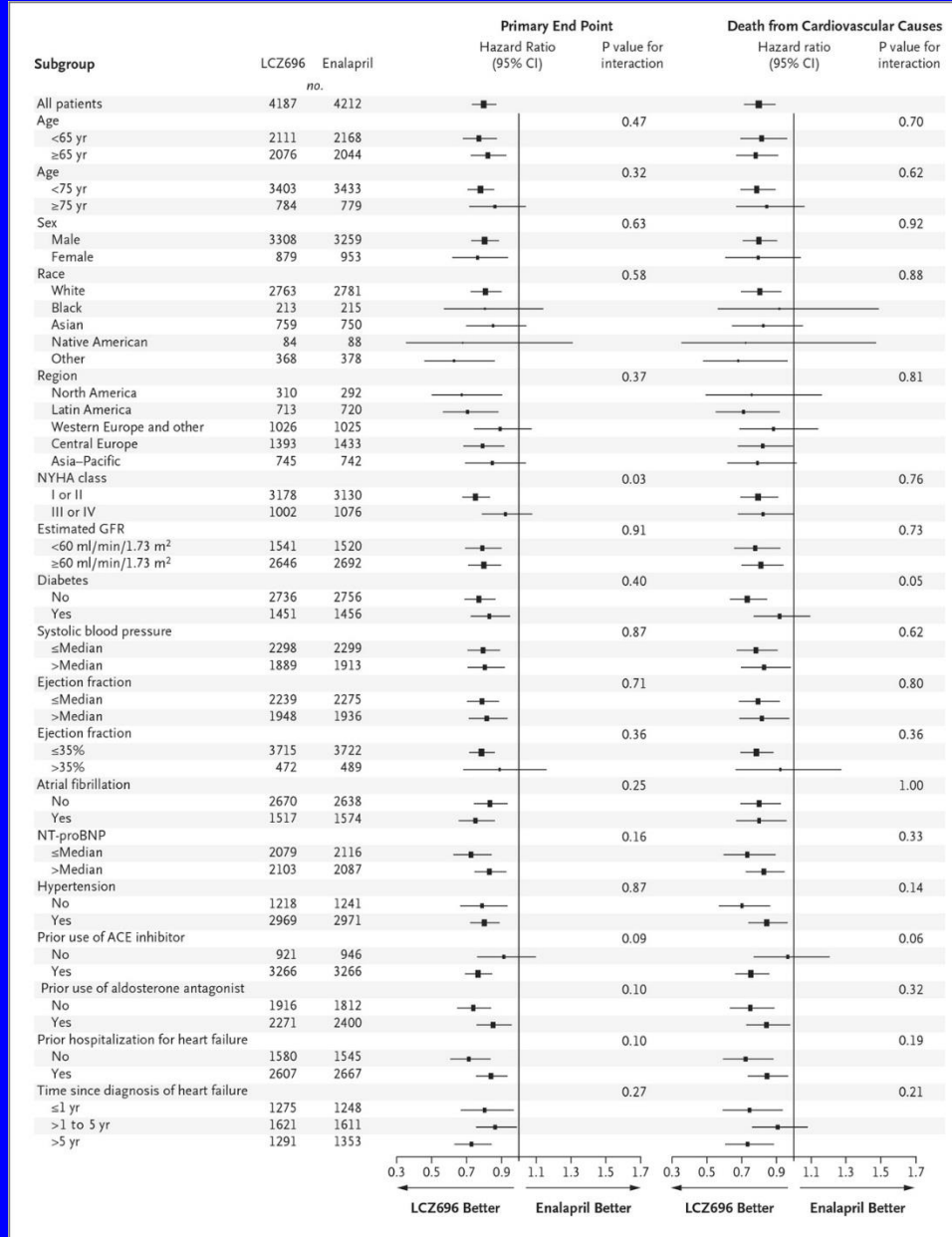
D Death from Any Cause



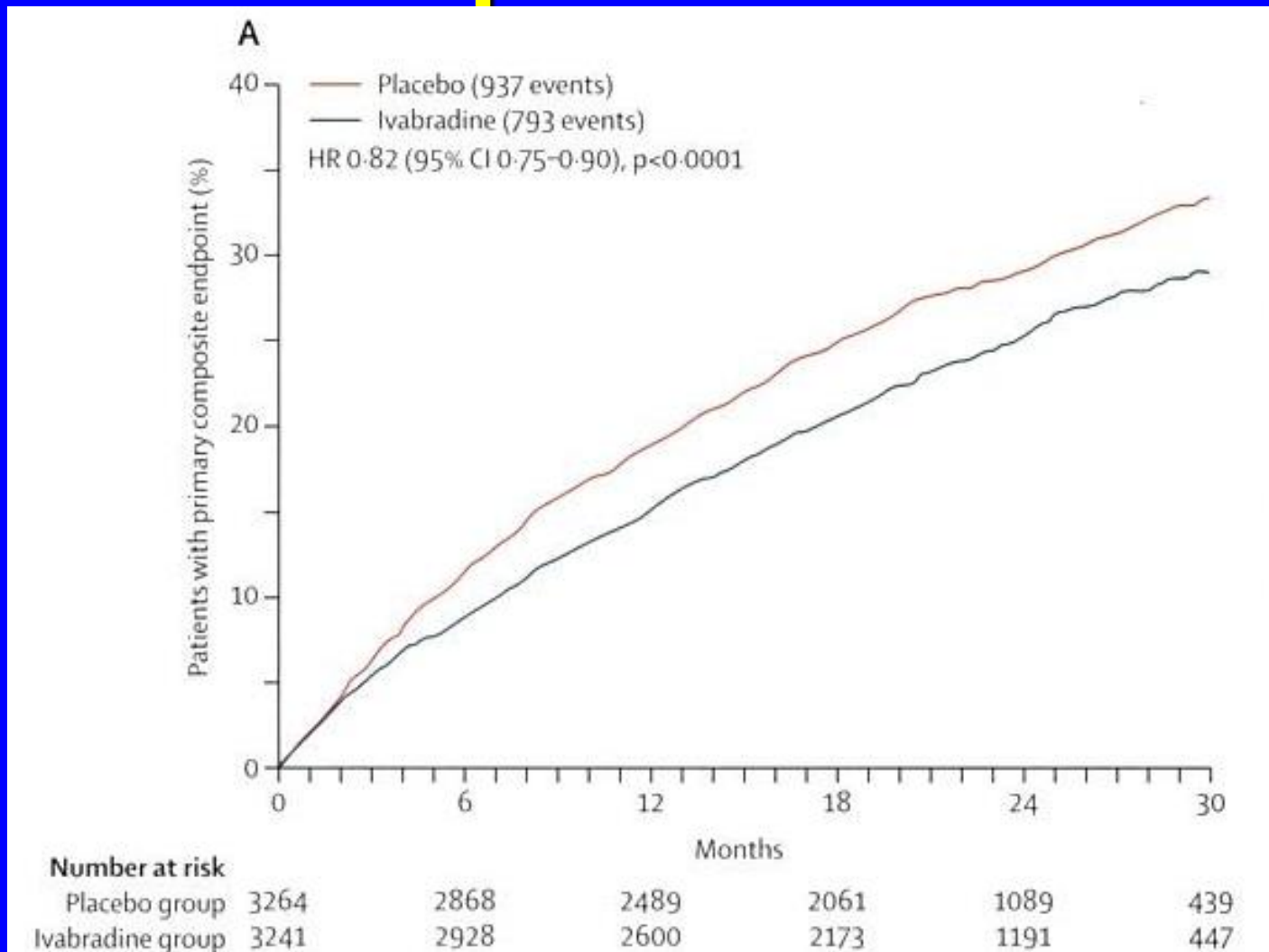
No. at Risk

LCZ696	4187	4056	3891	3282	2478	1716	1005	280
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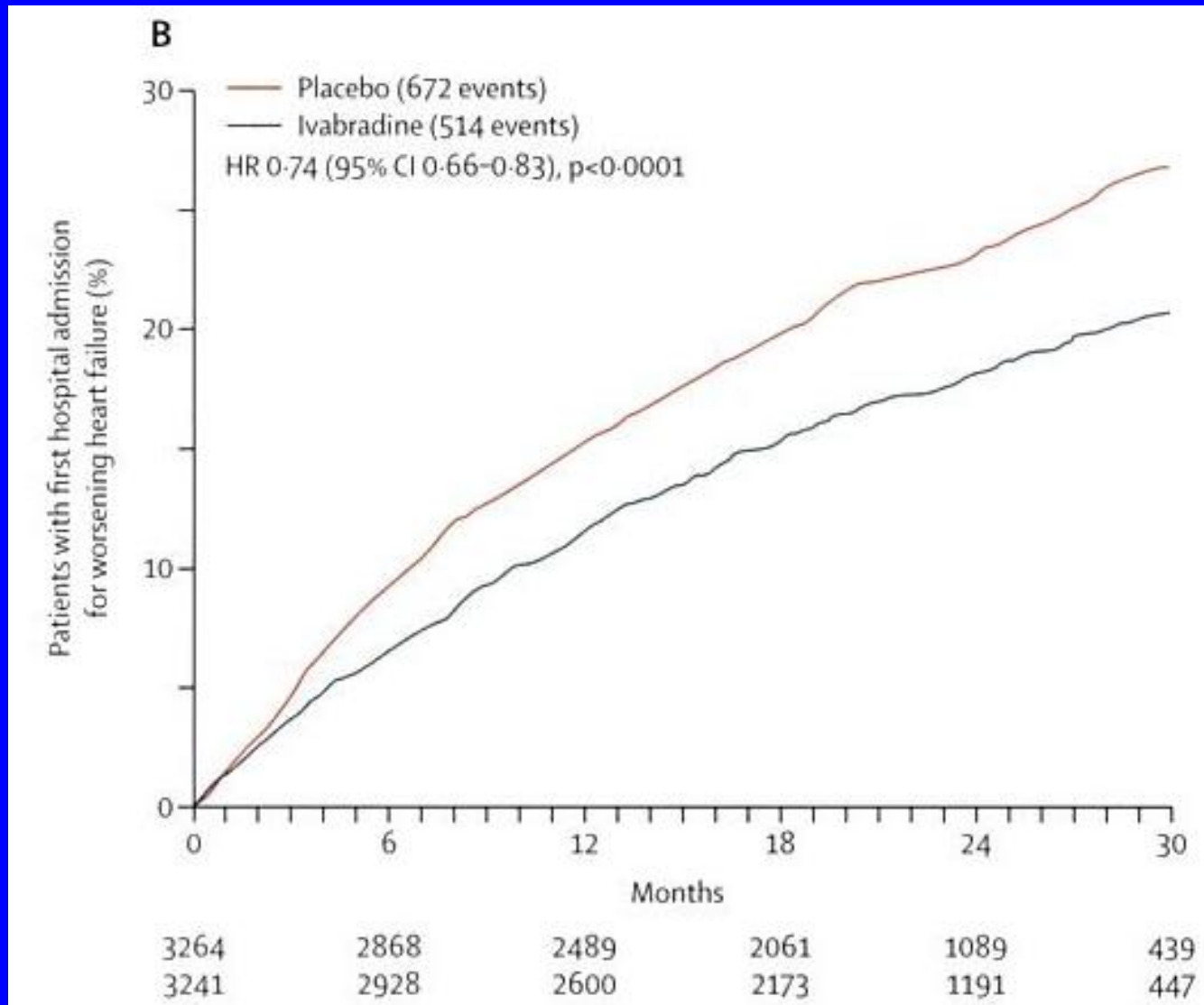
PARADIGM-HF: Sacubitril/Valsartan



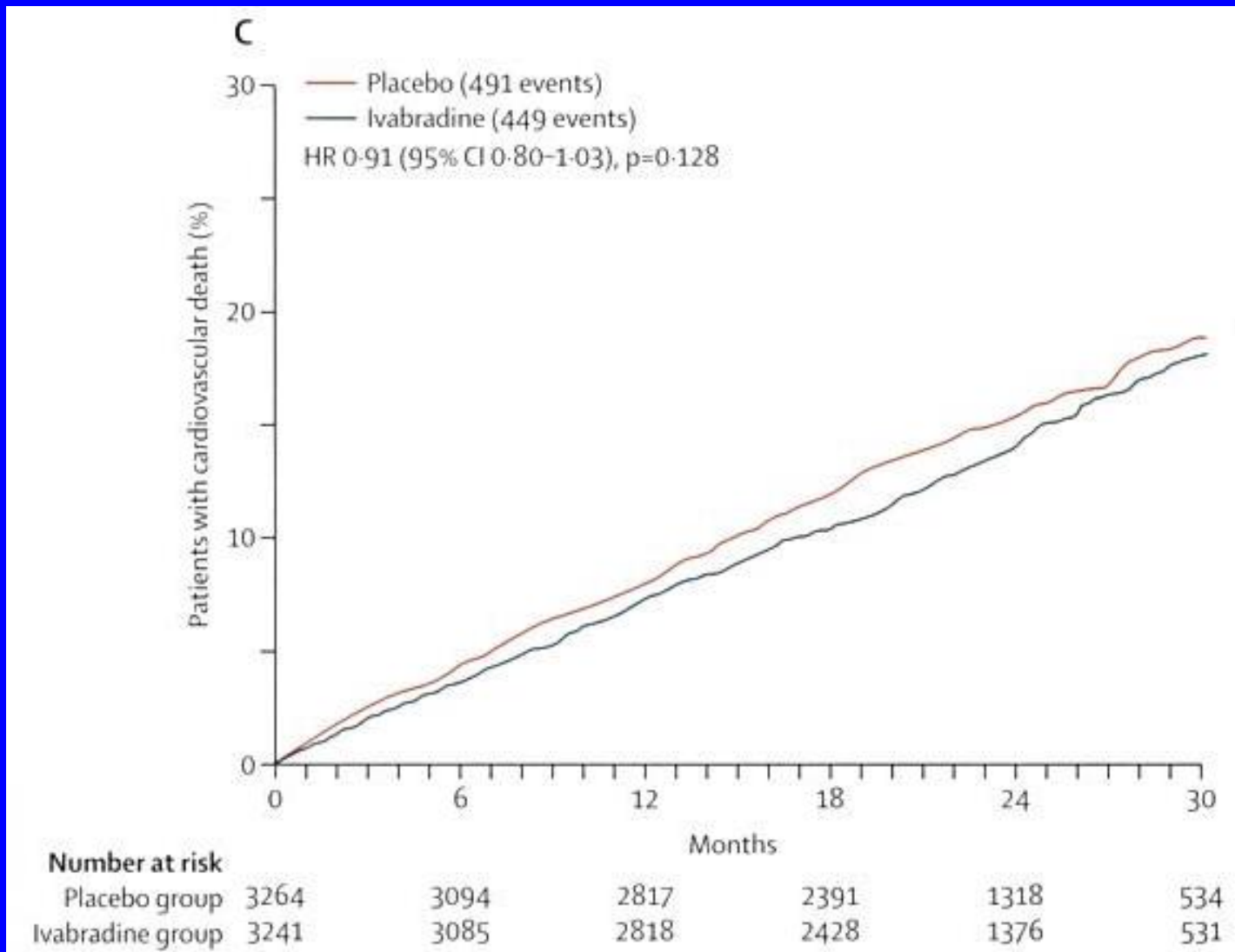
Ivabradine: CV death or HF Hospitalization



Ivabradine: Hospitalization for HF

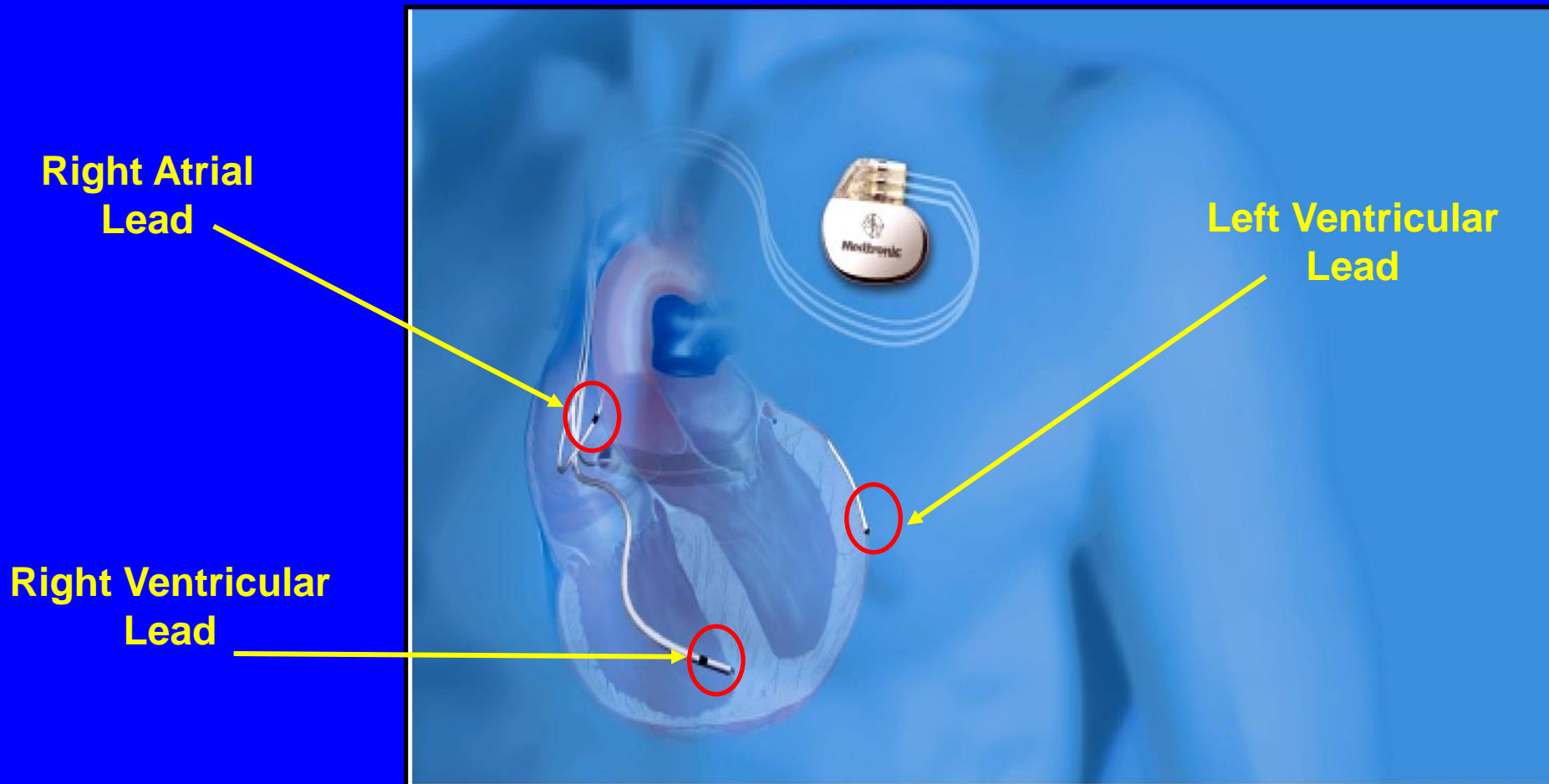


Ivabradine: CV death



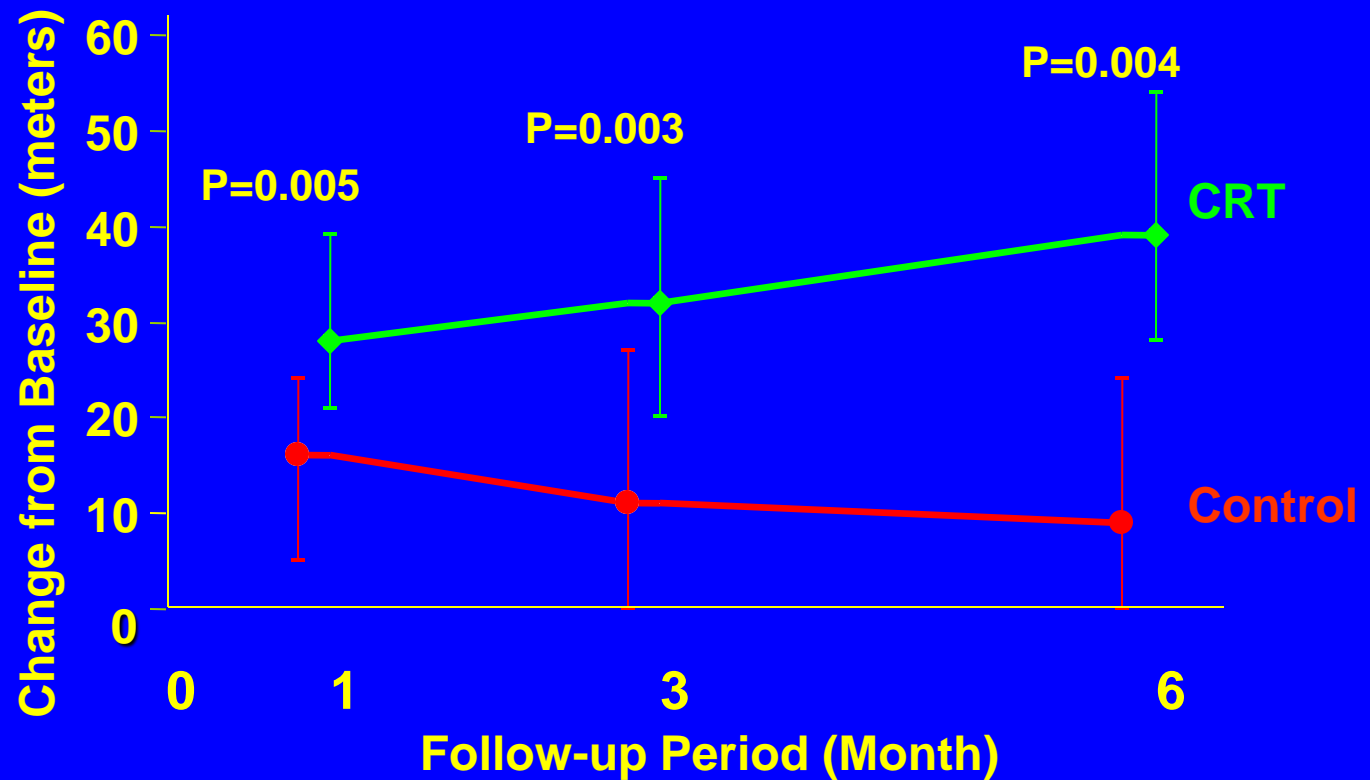
Achieving Cardiac Resynchronization

**Mechanical Goal: Atrially-synchronized
biventricular pacing**



CRT Improves Submaximal Exercise

Distance Walked in 6 Minutes



Baseline (meters)

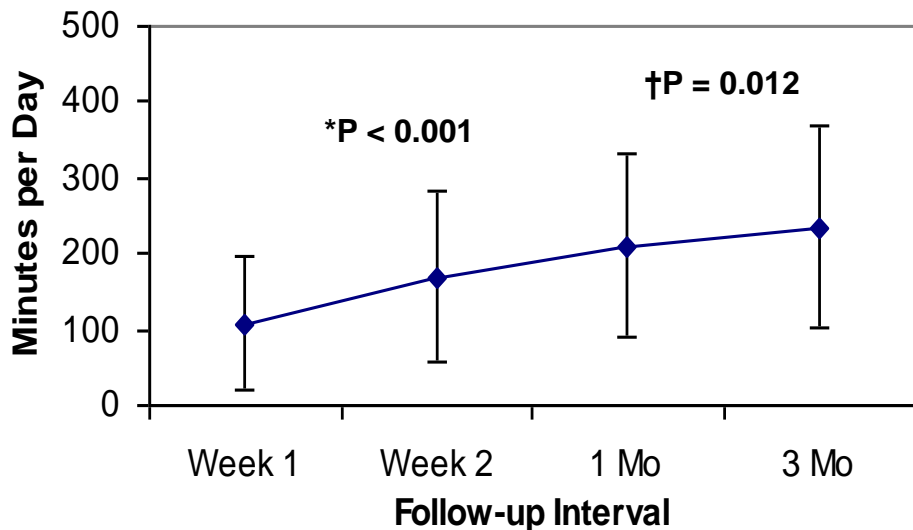
291 ± 101

305 ± 85



Patient Activity Improved Over Time in Patients with CRT

Daily Physical Activity Measured by the InSync III



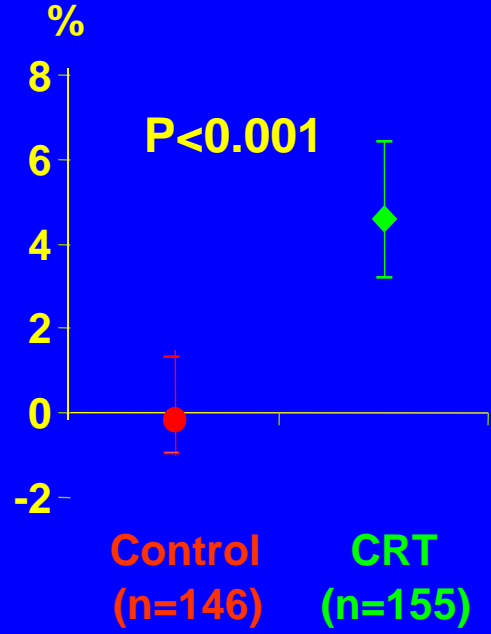
*week 2 compared to week 1

†3 months Compared to 1 month

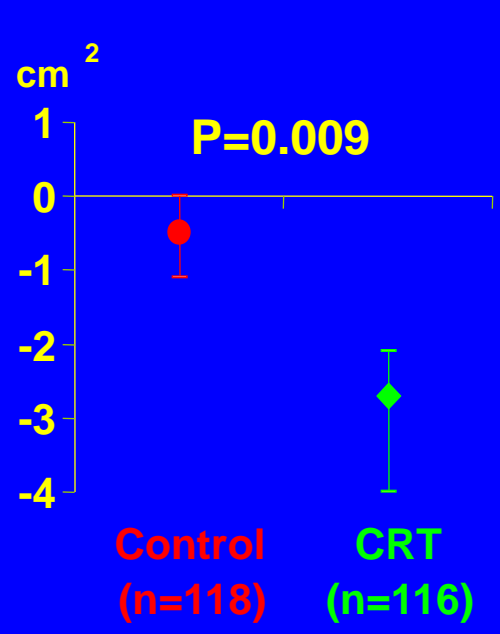
- 56 InSync III patients monitored minutes of daily patient activity
- 7-day means were compared from 1st week after implant at 2 weeks, 1 month, and 3 months.

CRT Improves Cardiac Function and Structure

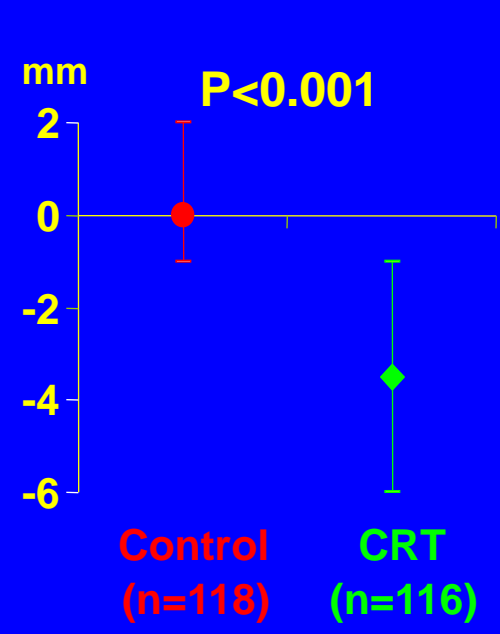
Absolute Change in LVEF



Change in MR Jet Area



Change in LVEDD



Paired median change from baseline at 6 months. Error bars are 95% CI.

Baseline (%)
22 ± 6
22 ± 6

Baseline (cm²)
7.2 ± 4.9
7.6 ± 6.4

Baseline (mm)
69 ± 10
70 ± 10

Indications for the Cardiac Resynchronization-ICD System

A CRT-ICD system is indicated for the reduction of HF symptoms in patients that meet the following criteria:

- Moderate to severe heart failure (NYHA Class II-IV)
- QRS \geq 120 msec (although substantially greater efficacy if $>$ 150 msec)
- LV ejection fraction \leq 35%
- Symptomatic despite maximized medical therapy



CRT for NYHA Class IV Heart Failure

2 Year Mortality with CRT/CRT-D in NYHA Class IV Patients

TABLE 3. Mode of Death at 2 Years

Mode of Death	OPT (n/N=55/253)	CRT (n/N=79/538)	CRT-D (n/N=83/512)
All death			
NYHA class IV	29 (62)	34 (45)	34 (55)
NYHA class III	46 (26)	92 (23)	68 (20)
HF			
NYHA class IV	14 (29)	17 (28)	21 (41)
NYHA class III	18 (10)	34 (10)	29 (8)
Sudden cardiac death			
NYHA class IV	8 (25)	11 (16)	4 (9)
NYHA class III	10 (5)	36 (9)	13 (5)
Other			
NYHA class IV	7 (28)	6 (12)	9 (18)
NYHA class III	18 (14)	22 (6)	26 (8)

Values are expressed as n (%).



COMPANION NYHA Class IV Patients

TABLE 4. Functional Capacity in NYHA Class IV Patients: Change From Baseline to 6 Months

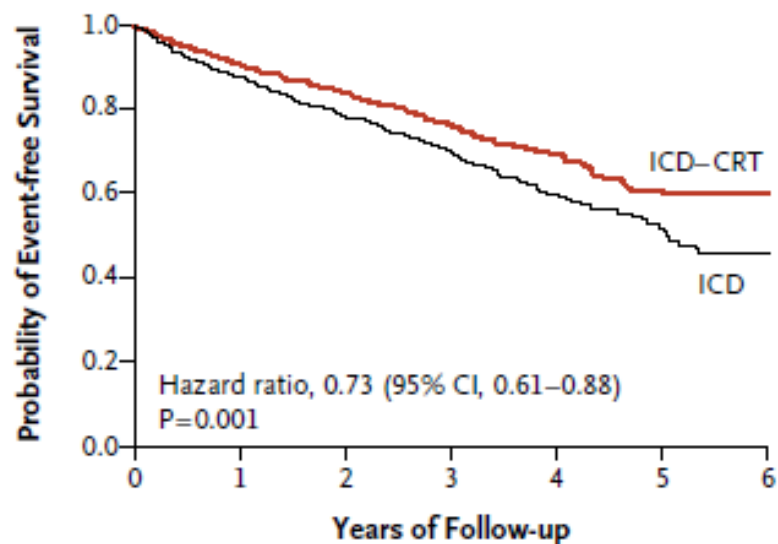
Indicator	Number	Median (Q1, Q3)	% Improved	<i>P</i>
6-Minute walk				
CRT/CRT-D	69	45.6 (−15.2, 106.4)	...	0.55
OPT	12	45.6 (−22.3, 60.9)
Quality of life				
CRT/CRT-D	109	−25.0 (−44.0, −8.0)	...	<0.01
OPT	29	−4.0 (−20, 9.0)
NYHA				
CRT/CRT-D	119	...	78	<0.01
OPT	27	...	52	...

Q indicates quartile.



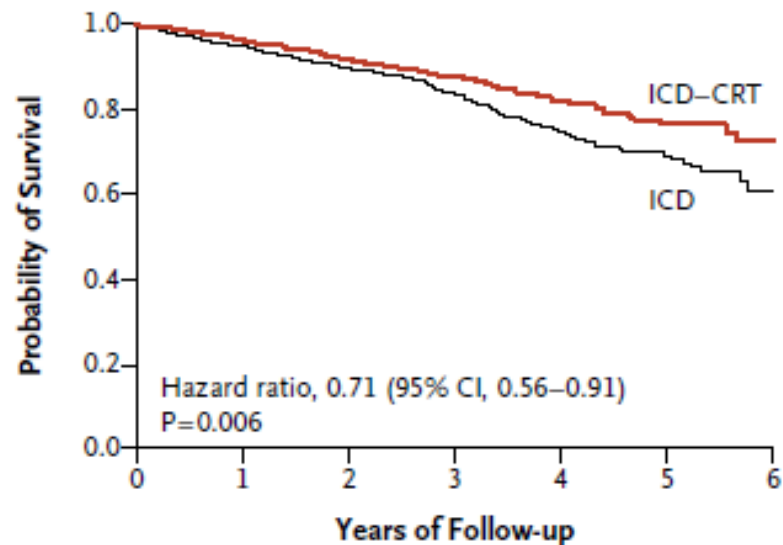
RAFT: CRT-D in NYHA Class II

A NYHA Class II, Death or Hospitalization for Heart Failure



No. at Risk	0	1	2	3	4	5	6
ICD-CRT	708	640	488	315	181	70	15
ICD	730	638	465	299	146	57	6

C NYHA Class II, Death

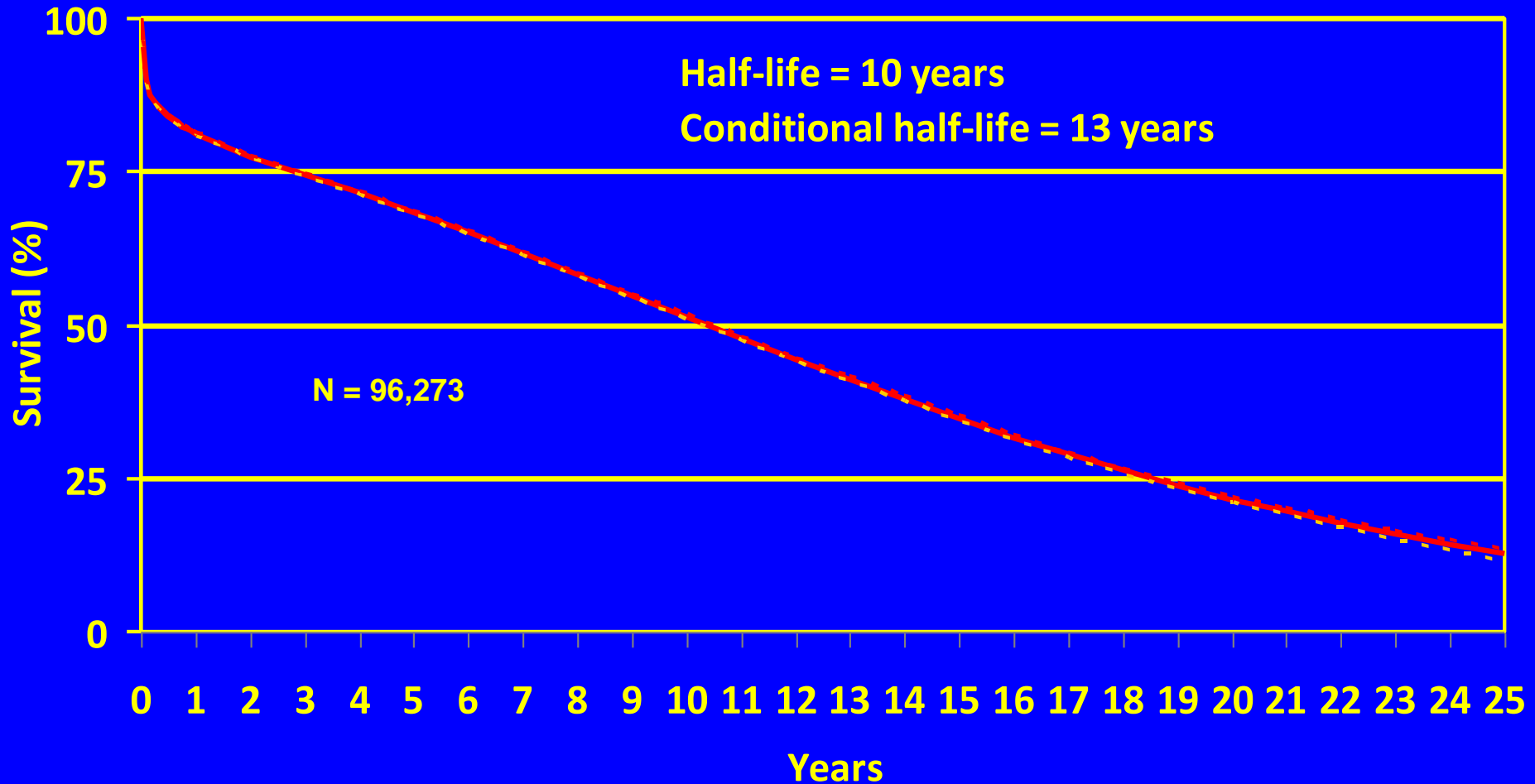


No. at Risk	0	1	2	3	4	5	6
ICD-CRT	708	679	530	361	206	89	20
ICD	730	687	533	366	189	83	13

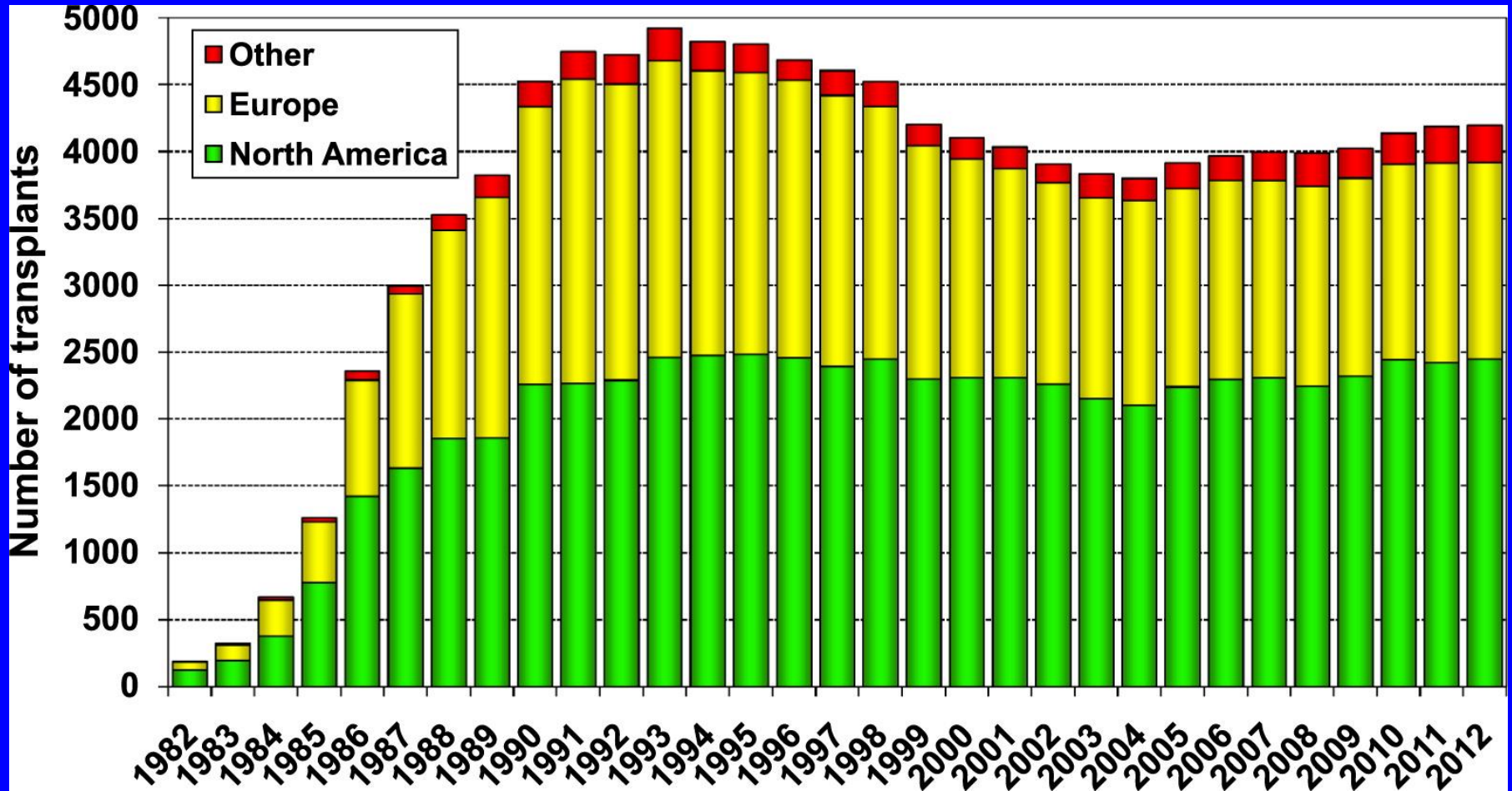
HEART TRANSPLANTS

Kaplan-Meier Survival

(Transplants: January 1982 - June 2010)

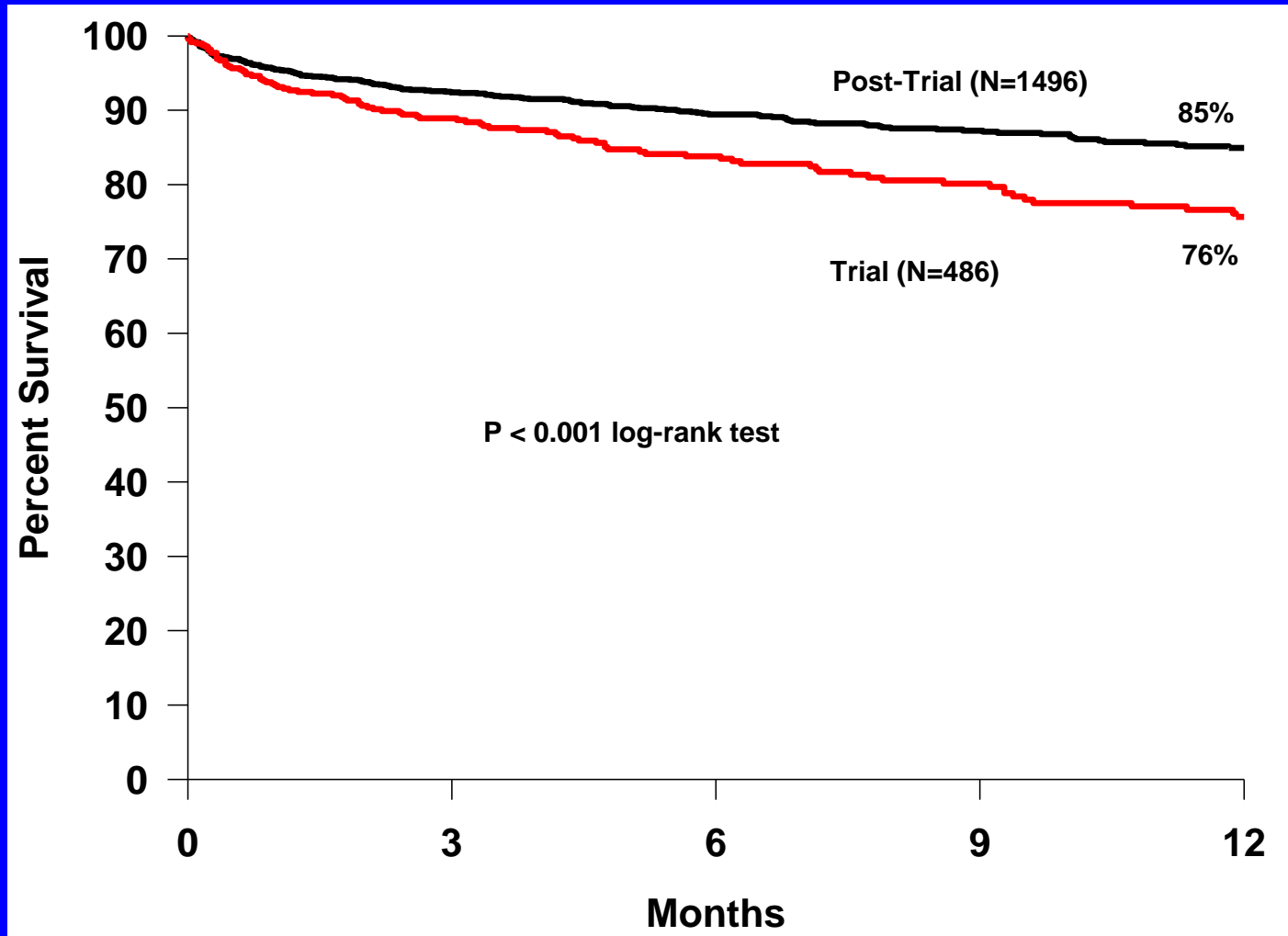


Heart Transplantation Volume

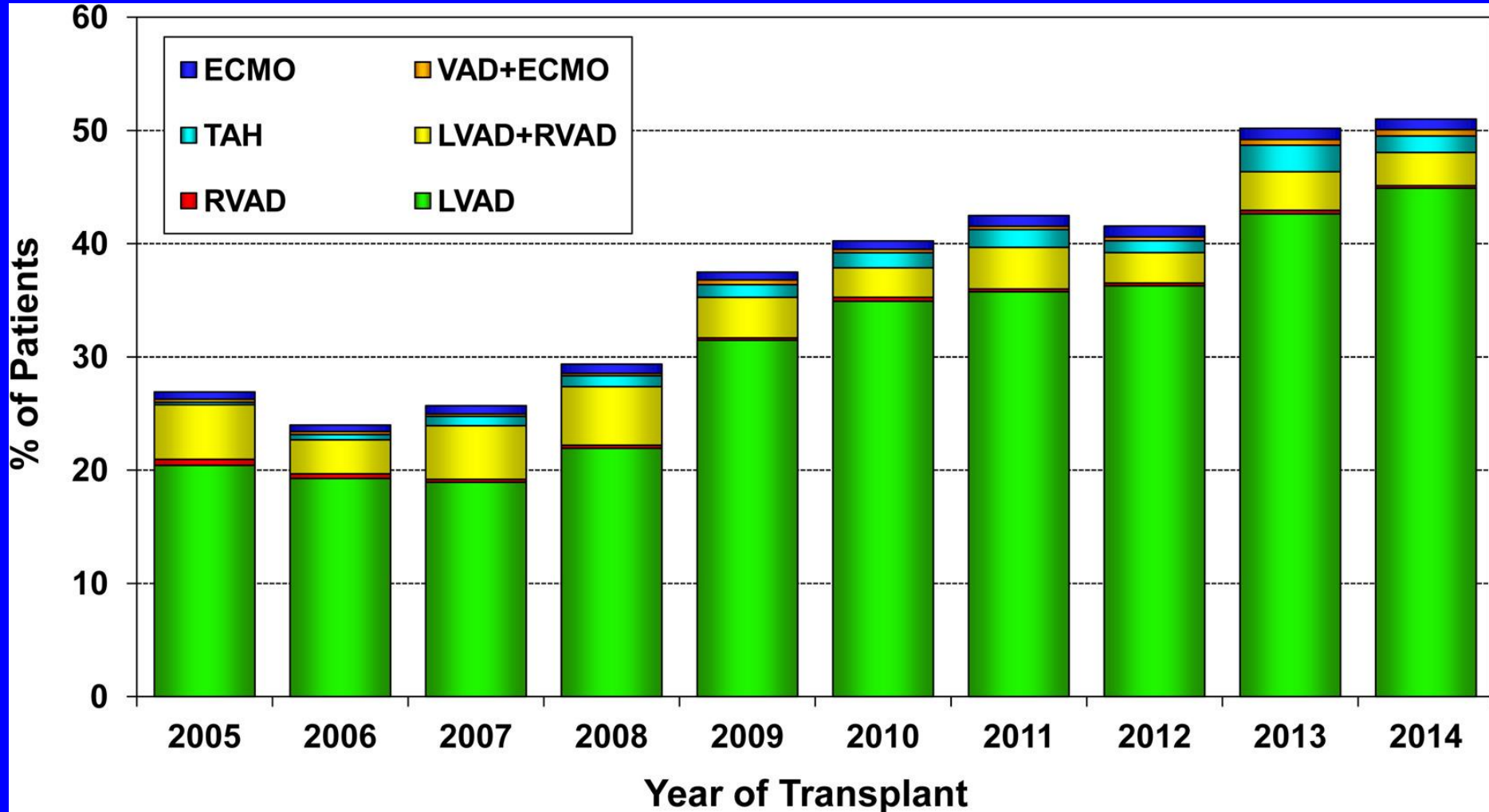


Mechanical Circulatory Support

HeartMate II Improvements in BTT Survival from Clinical Trial to Commercial Use

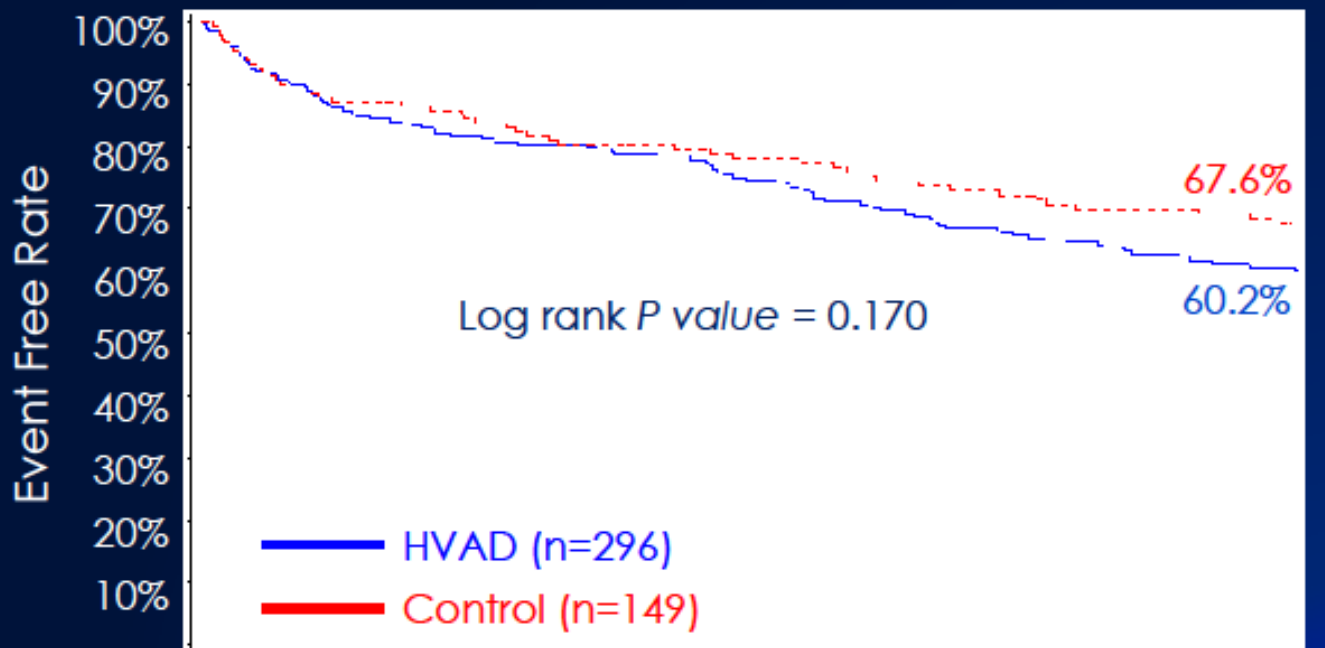


MCS Prior to Cardiac Transplantation



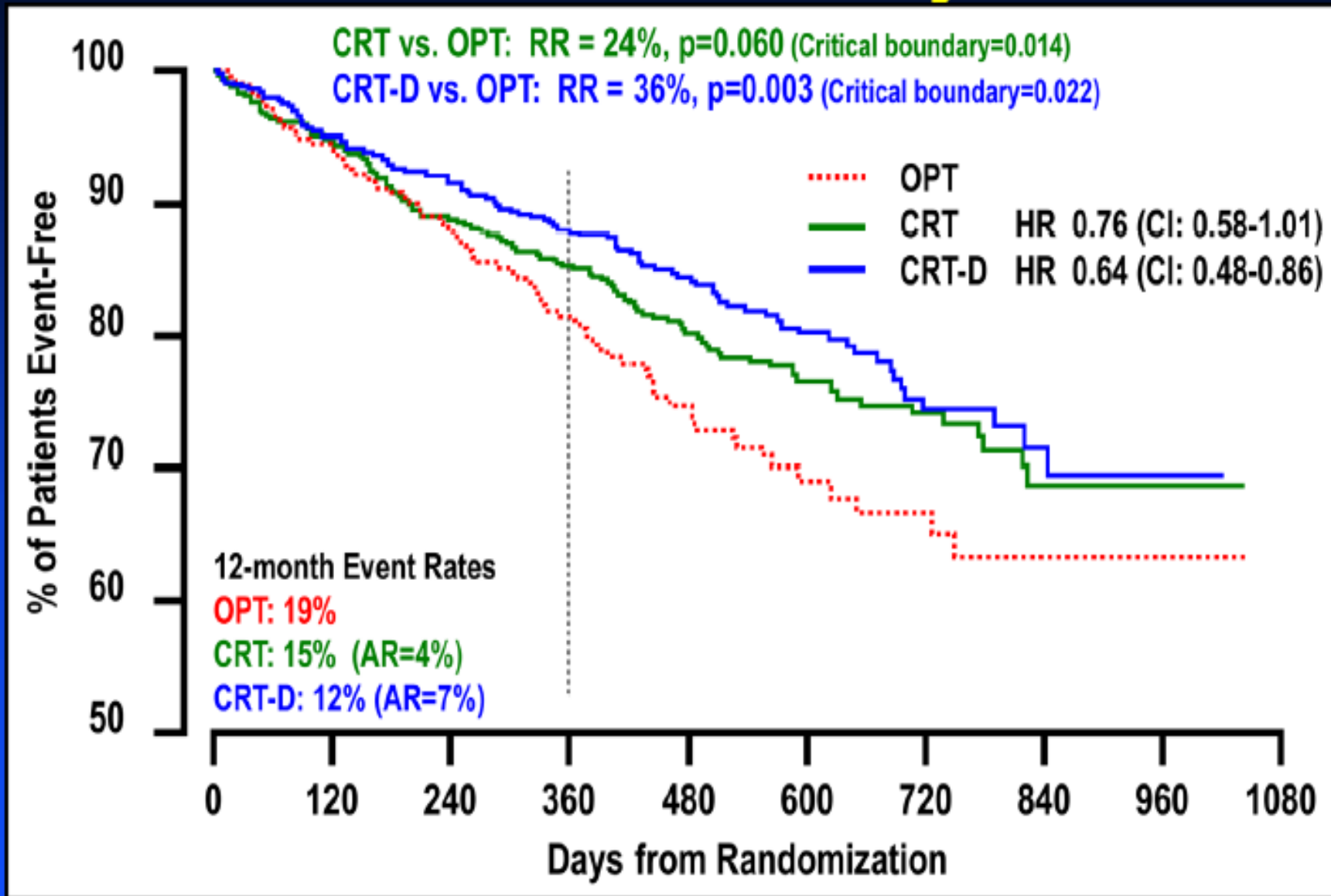
ENDURANCE Trial: DT Survival

Kaplan-Meier Survival Overall HVAD Compared to Control



Days	0	365	730
HVAD	296	212	158
Control	149	108	86

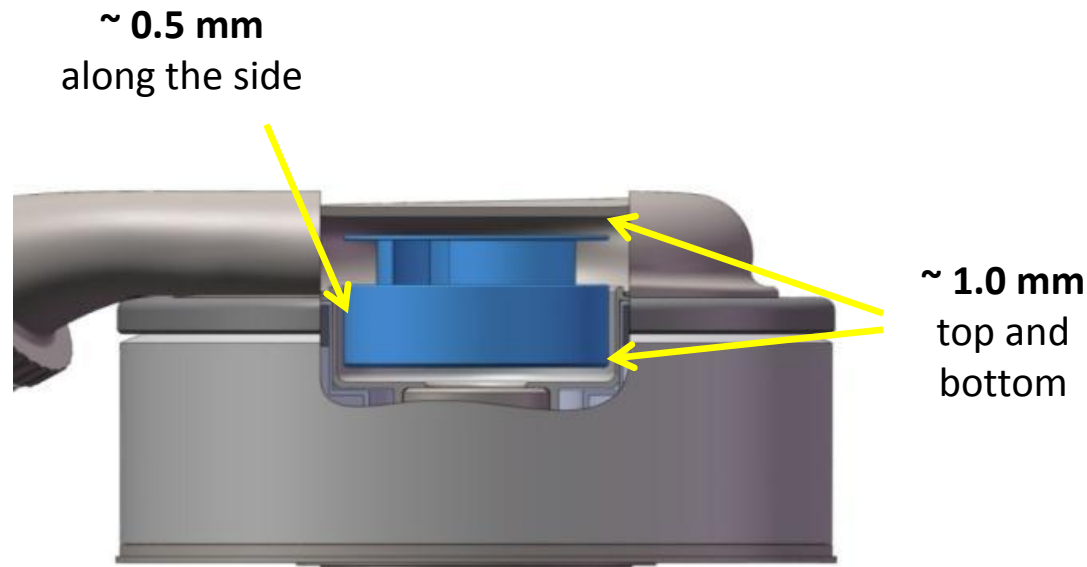
COMPANION: Secondary Endpoint of All-Cause Mortality



HeartMate III: Full MagLev™ Technology

Key Design Features: Large and Consistent Gaps

- HeartMate III secondary flow paths are **~0.5 mm** along the side, and **~1.0 mm** pump above and below the rotor.
 - Conversely, hydrodynamic bearings are typically operated with much smaller gaps, **0.05 of a millimeter** or so.
- HeartMate III pump surfaces are flat and flow is undisturbed, wedging surfaces and other features required for hydrodynamic bearings are not required.



Comparison of Blood Flow Pathway Sizes

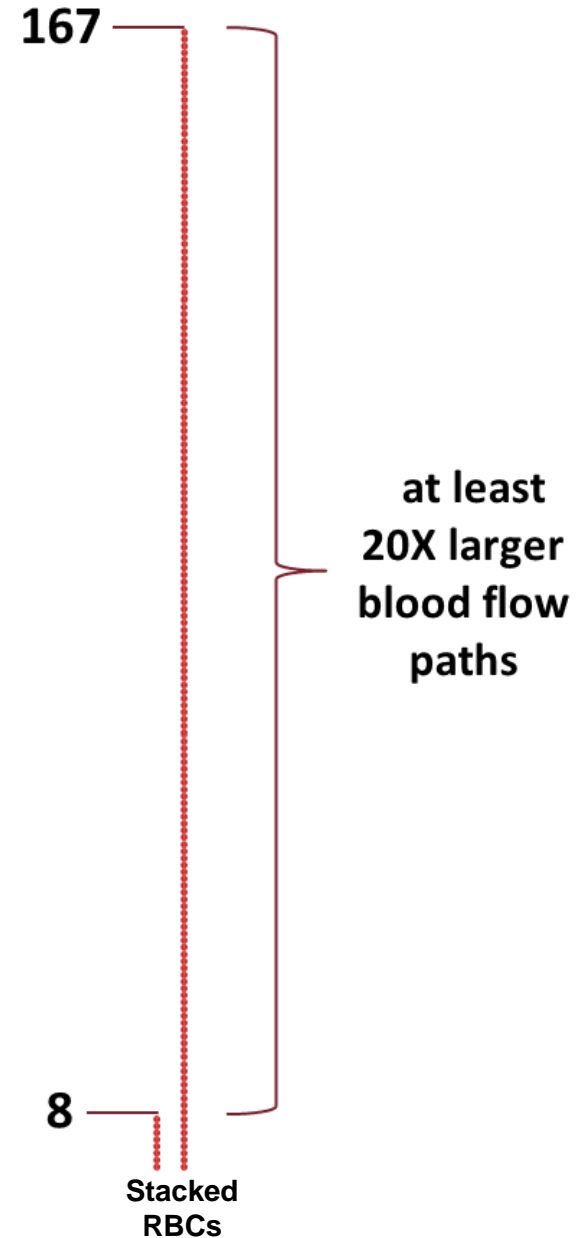
Using a Red Blood Cell for Scale



6-8 μm

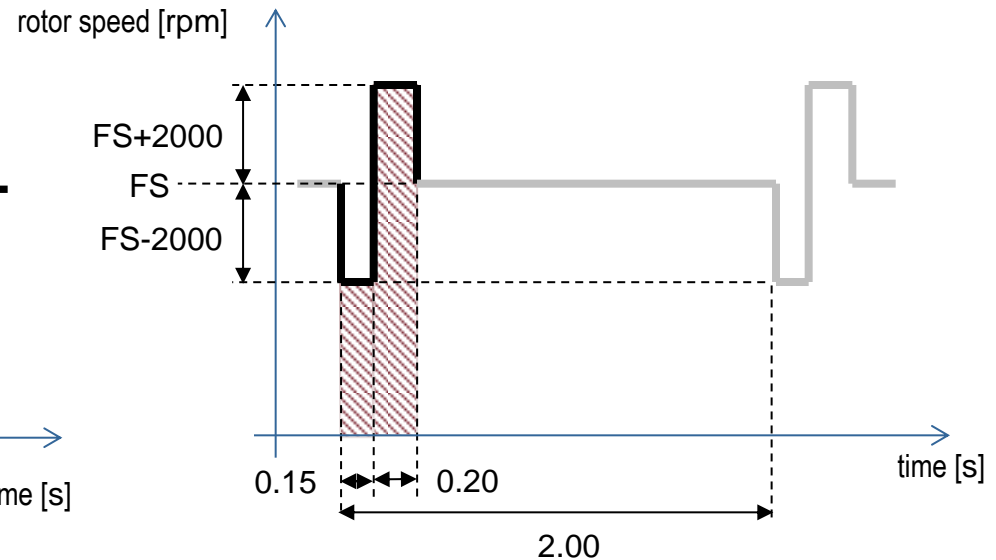
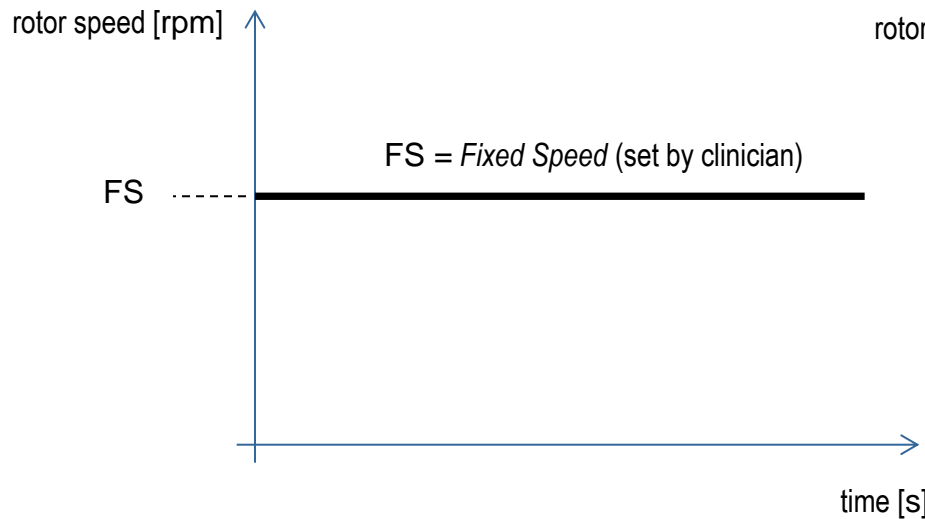
	Gap Size	# of Red Blood Cells
Full MagLev	1,000 μm	167
Hydrodynamic Bearing	50 μm	8

Note: The use of a red blood cell as a measuring unit is for illustration purposes and is not meant to imply actual blood flow quantities during operation.



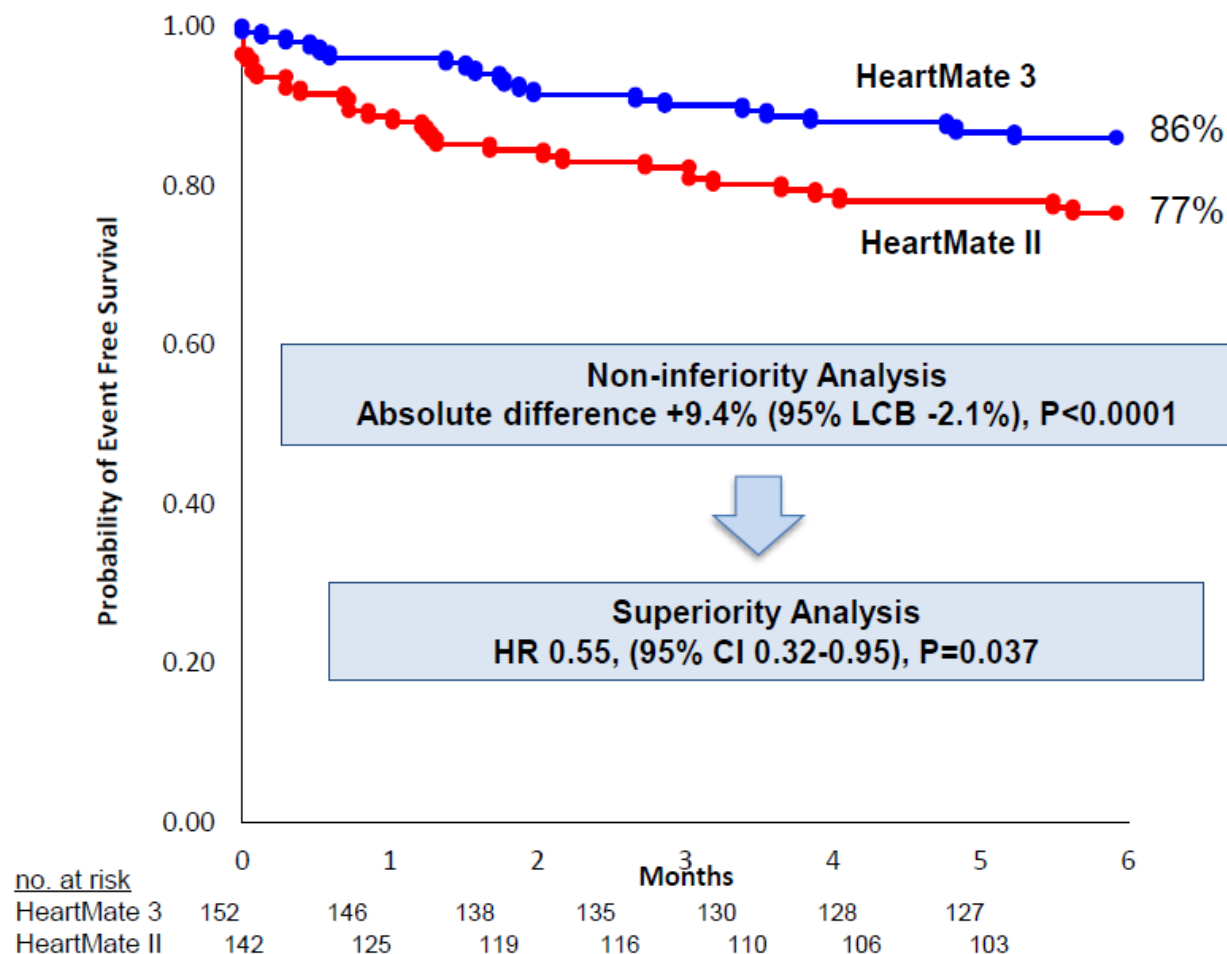
Artificial Pulse Overview

- The HM III with full magnetic levitation and wide gaps is intrinsically capable of very sharp speed changes, enabling an **“artificial pulse”** feature that has so far in pre-clinical studies proved to contribute negligible hemolysis and require low incremental power consumption.
- While unproven, augmenting the pulsatility that is generally diminished in rotary pump patients may have **benefit for some patients** or **in certain circumstances**, perhaps in part addressing adverse events such as; aortic insufficiency, bleeding and thrombogenesis



Primary End Point Analysis (ITT)

Survival at 6 months free of disabling stroke or reoperation to replace or remove the pump



LCB, lower confidence boundary, HR, hazard ratio, and CI, confidence interval

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Creatinine 1.0 and K 4.1. LVEF 30%. HR 90/min
Lisinopril 5 mg qd and Toprol XL 150 mg qd.

Next step should be:

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Audience Response Question

40 yo white male with NIDDM and Class III heart failure. Creatinine 1.0 and K 4.1. LVEF 30%. HR 90/min. QRS duration 170 msec. Lisinopril 40 mg qd, Toprol XL 150 mg qd, aldactone 25 mg qd.

Next step should be:

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- c) Add corlanor (ivabradine)
- d) Add entresto (sacubitril/valsartan)
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Conclusions

- ACEI/ARB/beta blocker doses should be maximized
- Aldosterone receptor antagonist for symptomatic patients
- Hydralazine/nitrates for symptomatic African Americans
- Consider Entresto (Sacubitril/Valsartan) as an alternative to ACEI/ARB in symptomatic LV systolic dysfunction
- Consider Corlanor (Ivabradine) in symptomatic patients with elevated HR
- CRT-D in patients who remain symptomatic, particularly NYHA Class II and III, and have prolonged QRS duration
- CRT of questionable benefit in NYHA Class IV patients
- MCS improves quality of life and functional capacity with a trade off of adverse events

