UNIVERSITY of ROCHESTER MEDICAL CENTER

28th Annual Cardiology for Clinicians Spring Update 2015

Class of '62 Auditorium

Thursday, May 21, 2015

"Focus on Failure: Angiotensin-Neprilysin Inhibition versus Enalapril in Heart Failure"

Leway Chen, MD, MPH, FACC, FACP, FAHA

Director, Program in Heart Failure and Transplantation

Associate Professor of Medicine

Division of Cardiology

Strong Memorial Hospital - University of Rochester Medical Center

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"What's New in 2015 for Heart Failure Management?"

Leway Chen, MD, MPH, FACC, FACP, FAHA

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Disclosures

- I will discuss investigational agents/devices
- Consultant- Thoratec
- Site PI for Thoratec studies: ROADMAP and RESIST (completed)
- Site co-PI for Thoratec HeartMate III study (in process)
- Immediate Past Upstate Governor for the NY State ACC

- Leway_Chen@URMC.Rochester.edu
- Heart Failure/Transplant/MCS
  Office: 585-273-3760
- Cellular: 585-747-3303

Outline

I. **Introduction to Heart Failure**

II. **Sacubitril & valsartan (LCZ696)** – The PARADIGM-HF Study

III. **Ivabradine (Corlanor)** – The SHIFT study

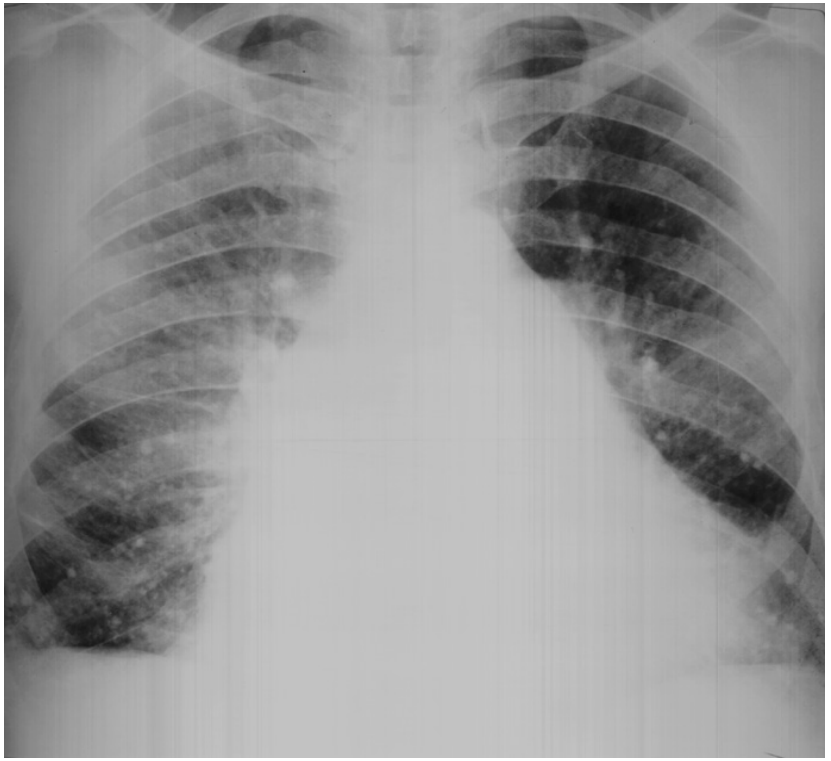
IV. **Seralaxin (Relaxin)** – ongoing RELAX-AHF studies (2-ASIA-EURO)

V. **CardioMEMS** – The CHAMPION study

VI. **HeartMate III** – ongoing HeartMate III study

GREEN = FDA approved; RED = under investigation or awaiting FDA approval

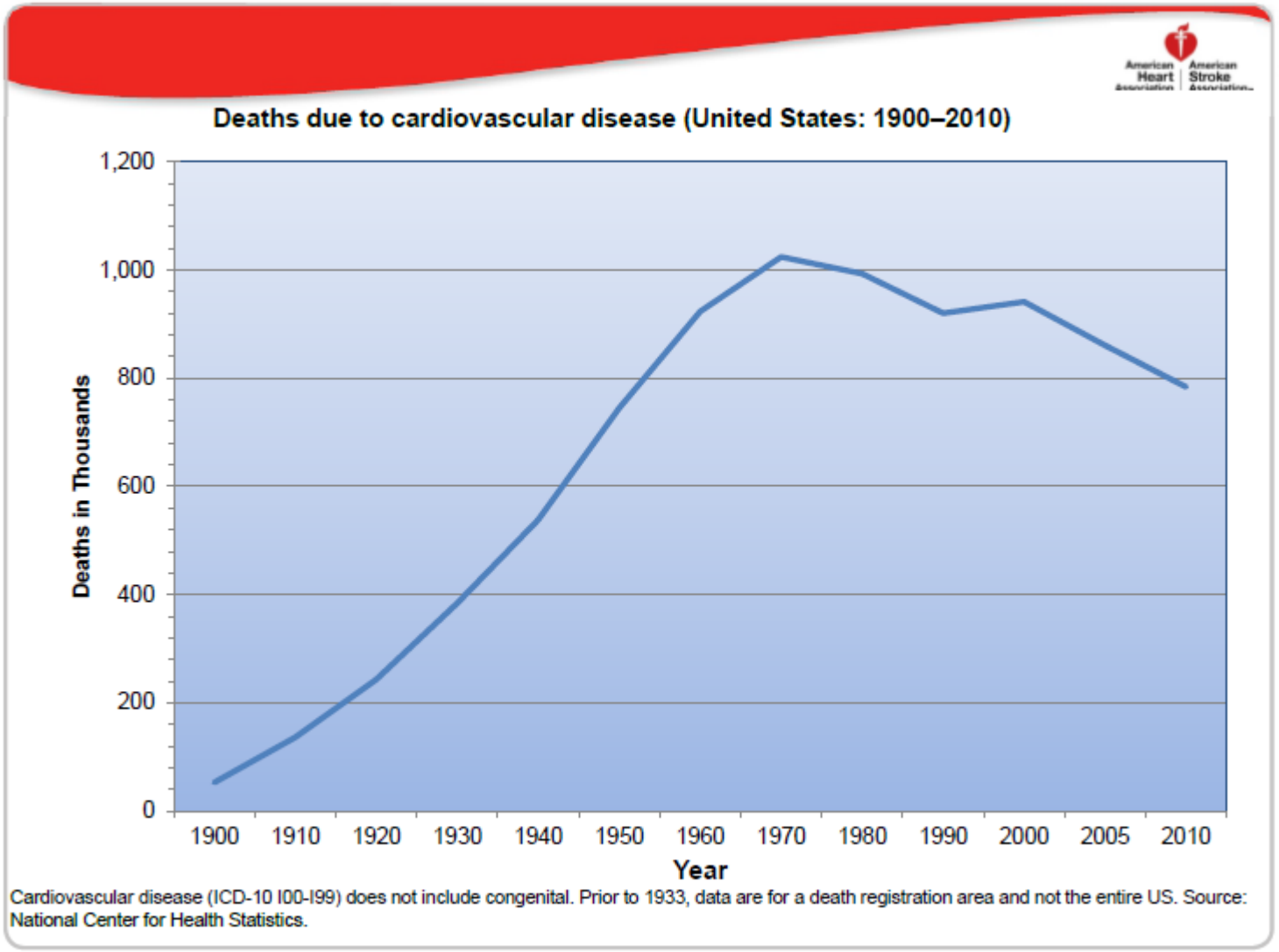
Heart Failure



"The situation when the heart is incapable of maintaining a cardiac output adequate to accommodate metabolic requirements and the venous return."

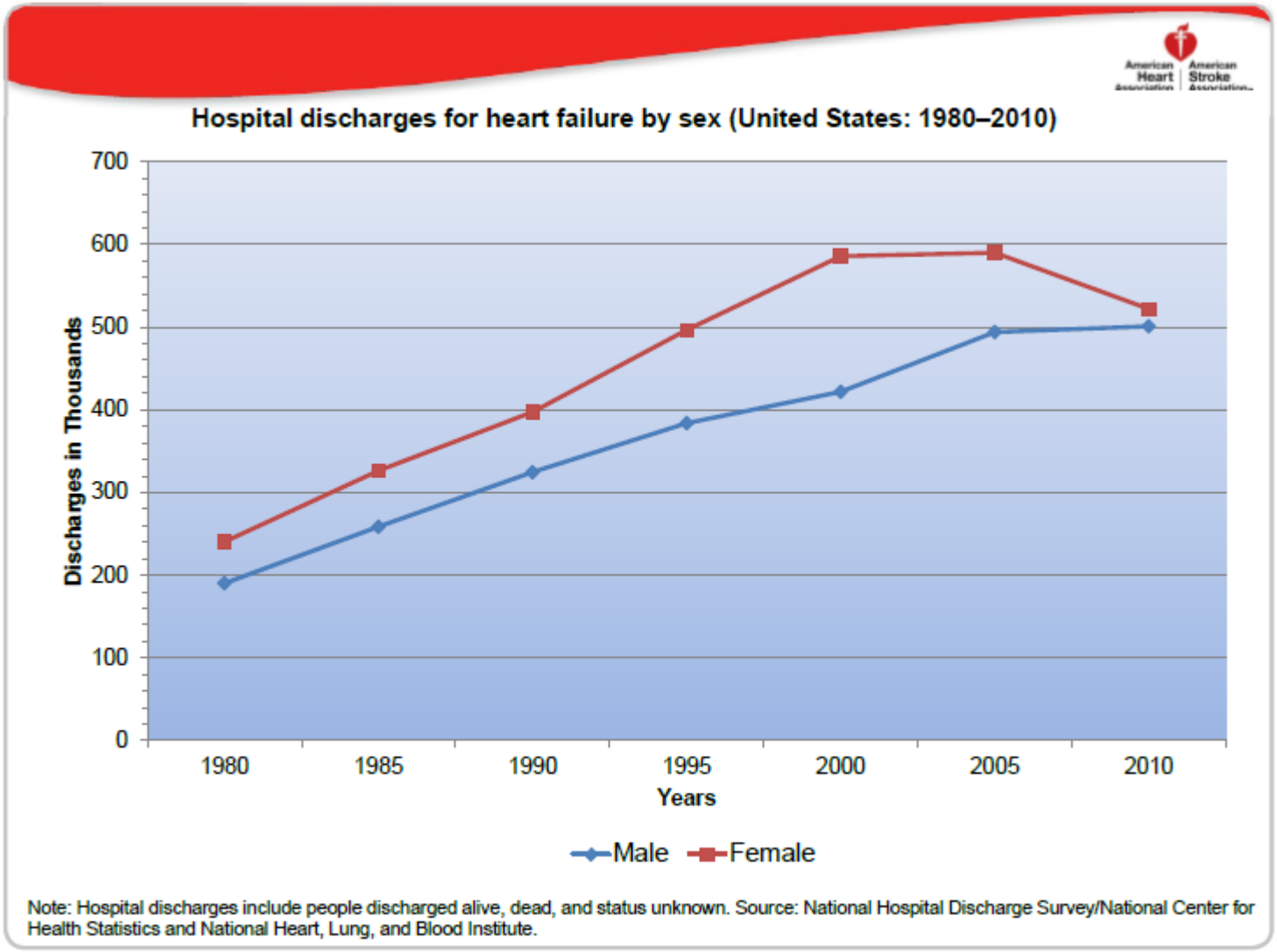
E. Braunwald

Deaths Due to Cardiovascular Disease (United States: 1900-2010)



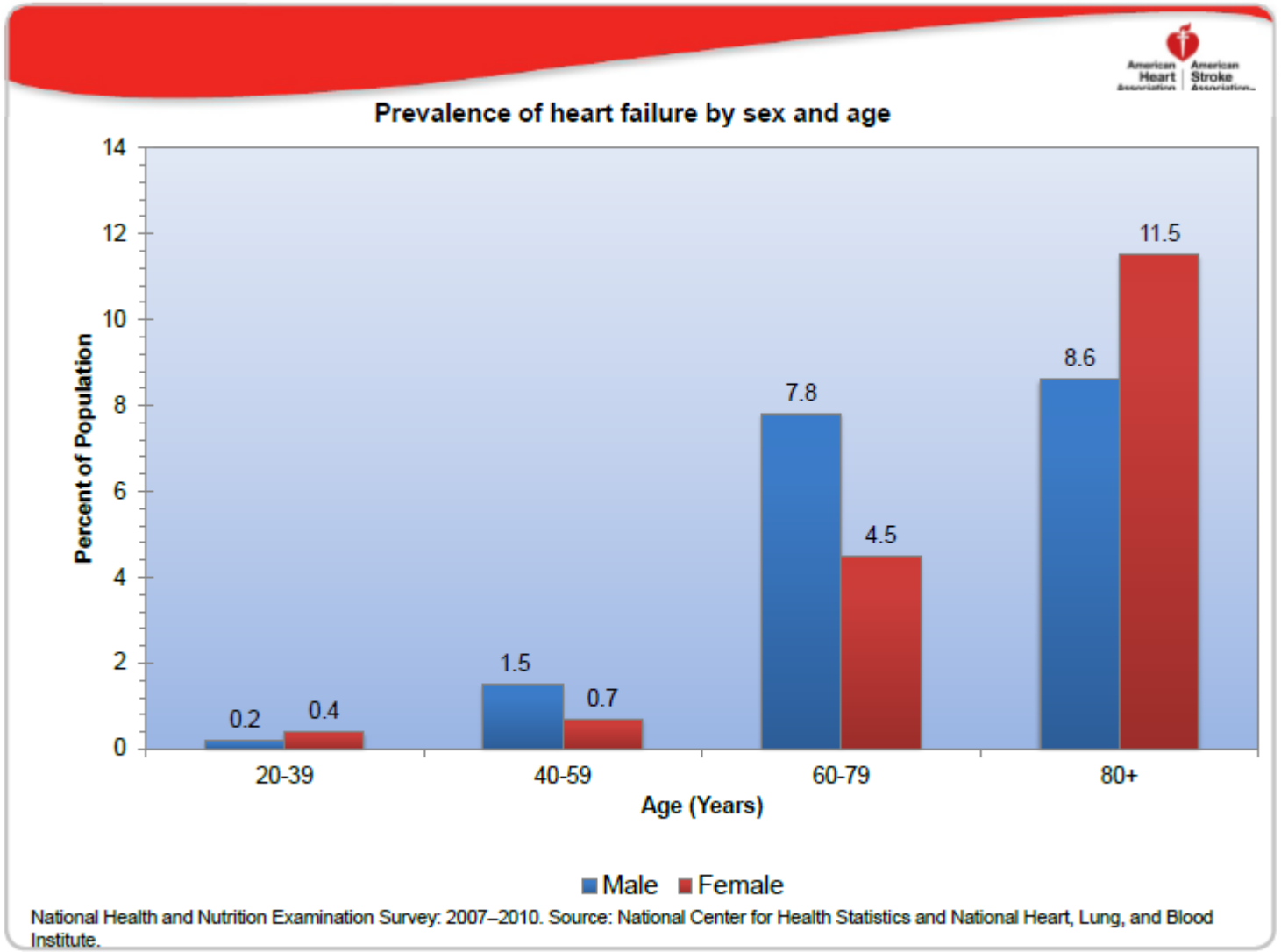
Go AS et al. Published online in *Circulation* Dec. 18, 2013

Hospital Discharges for heart failure by sex (United States: 1980-2010)



Go AS et al. Published online in *Circulation* Dec. 18, 2013

Prevalence of Heart Failure by Sex and Age



National Health and Nutrition Examination Survey: 2007–2010. Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

Go AS et al. Published online in *Circulation* Dec. 18, 2013

Cost of HF

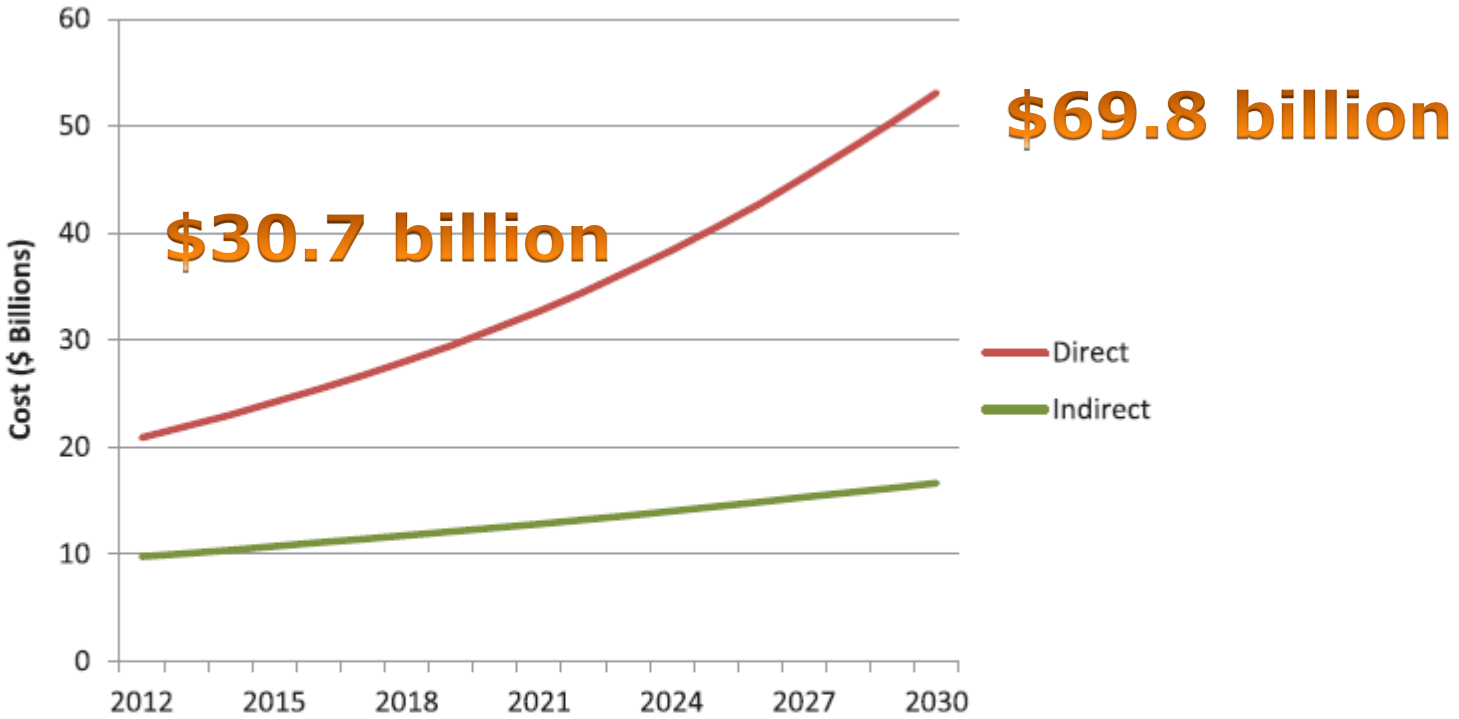


Figure 1. The projected increase in direct and indirect costs attributable to HF from 2012 to 2030 is displayed. Direct costs (cost of medical care) are expected to increase at a faster rate than indirect costs because of lost productivity and early mortality. HF indicates heart failure.

Sacubitril - Valsartan

Success?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

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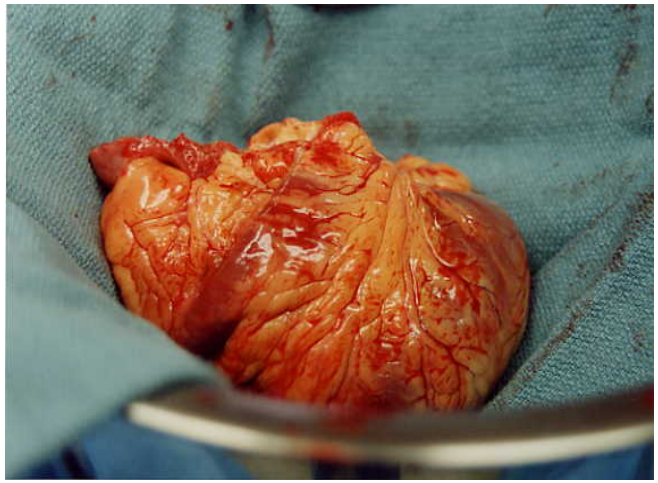
Historical Perspective on Heart Failure



Cardiorenal
Digitalis
Diuretics

Hemodynamic
Vasodilators
Inotropes

Neurohormonal
ACEI/ARB
β-Blockers
Aldosterone Antagonists

1940s 1960s 1970s 1990s and beyond

Cardiovascular Medications Useful for Treatment of Various Stages of Heart Failure (Slide 1 of 3)

Drug	Stage A	Stage B	Stage C
ACE Inhibitors			
Benazepril	H	-	-
Captopril	H, DN	Post MI	HF
Enalapril	H, DN	Asymptomatic LVSD	HF
Fosinopril	H	-	HF
Lisinopril	H, DN	Post MI	HF
Moexipril	H	-	-
Perindopril	H, CV Risk	-	-
Quinapril	H	-	HF
Ramipril	H, CV Risk	Post MI	Post MI
Trandolapril	H	Post MI	Post MI

CV Risk indicates reduction in future cardiovascular events; DN, diabetic nephropathy; H, hypertension; HF, heart failure; Asymptomatic LVSD, Asymptomatic left ventricular systolic dysfunction; Post MI, reduction in heart failure or other cardiac events following myocardial infarction.

Hunt SA et al. *J Am Coll Cardiol.* 2001;38:2101–2113.

Cardiovascular Medications Useful for Treatment of Various Stages of Heart Failure (Slide 2 of 3)

Drug	Stage A	Stage B	Stage C
Angiotensin Receptor Blockers			
Candesartan	H	-	HF
Eprosartan	H	-	-
Irbesartan	H, DN	-	-
Losartan	H, DN	CV Risk	-
Olmesartan	H	-	-
Telmisartan	H	-	-
Valsartan	H, DN	Post MI	Post MI, HF
Aldosterone Antagonists			
Eplerenone	H	Post MI	Post MI
Spironolactone	H	-	HF

CV Risk indicates reduction in future cardiovascular events; DN, diabetic nephropathy; H, hypertension; HF, heart failure; Asymptomatic LVSD, Asymptomatic left ventricular systolic dysfunction; Post MI, reduction in heart failure or other cardiac events following myocardial infarction.

Hunt SA et al. *J Am Coll Cardiol.* 2001;38:2101–2113.

Cardiovascular Medications Useful for Treatment of Various Stages of Heart Failure (Slide 3 of 3)

Drug	Stage A	Stage B	Stage C
Beta Blockers			
Acebutolol	H	-	-
Atenolol	H	Post MI	-
Betaxolol	H	-	-
Bisoprolol	H	-	HF
Carteolol	H	-	-
Carvedilol	H	Post MI	HF, Post MI
Labetalol	H	-	-
Metoprolol succinate	H	-	HF
Metoprolol tartrate	H	Post MI	-
Nadolol	H	-	-
Penbutolol	H	-	-
Pindolol	H	-	-
Propranolol	H	Post MI	-
Timolol	H	Post MI	-
Digoxin	-	-	HF

CV Risk indicates reduction in future cardiovascular events; DN, diabetic nephropathy; H, hypertension; HF, heart failure; Asymptomatic LVSD, Asymptomatic left ventricular systolic dysfunction; Post MI, reduction in heart failure or other cardiac events following myocardial infarction.

Hunt SA et al. *J Am Coll Cardiol.* 2001;38:2101–2113.

Biventricular Pacing / ICD

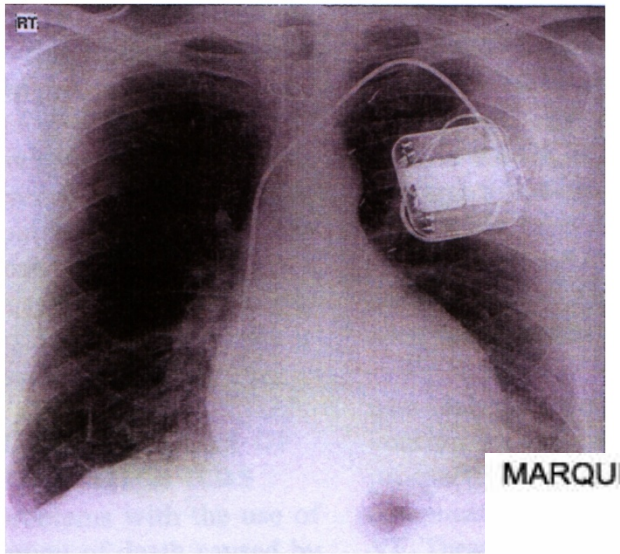


Figure 4. Chest X-ray showing sub-pectorally place chamber implantable defibrillator and lead to right apex. Note arterial clips and sternal wires of previ bypass surgery.

ICD

MADIT

SCD-HeFT

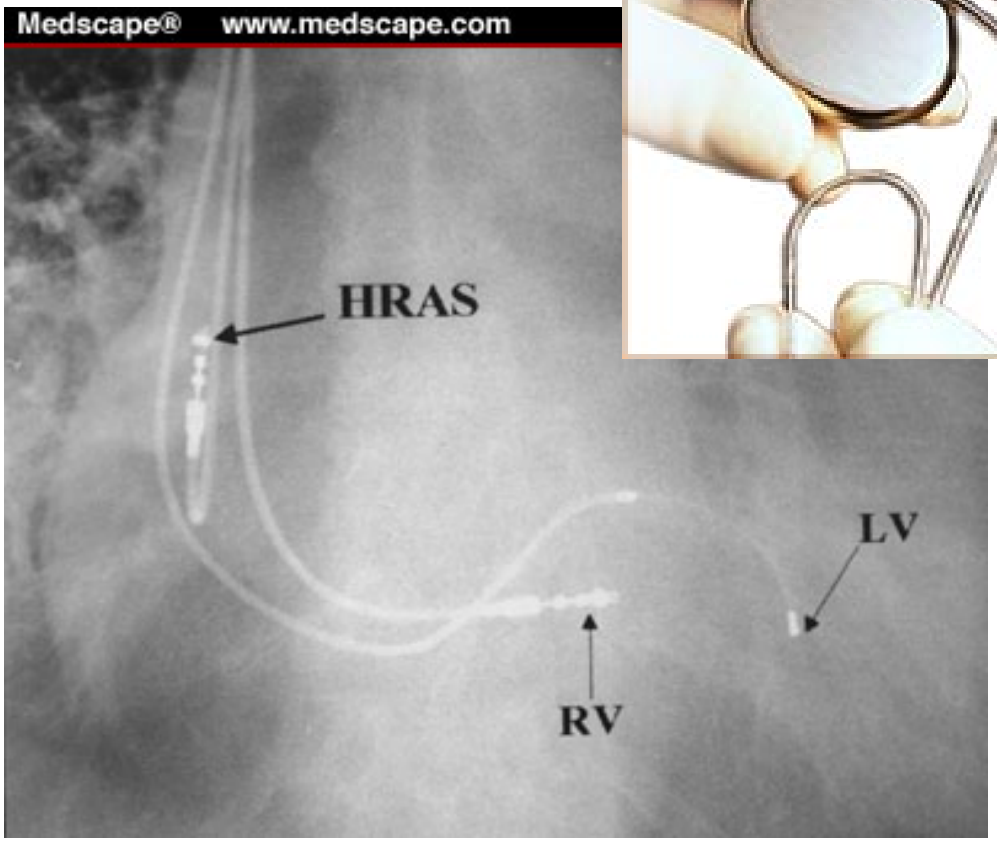
MADIT II

CRT

CARE-HF

Companion

MADIT CRT



http://www.chfpatients.com/implants/pacemakers.htm

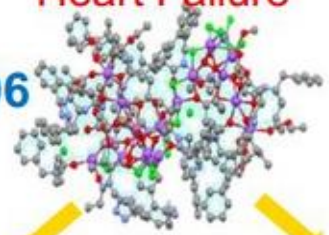
LCZ696 – A first-in-class Angiotensin Receptor Neprilysin Inhibitor

Heart Failure

Vasoactive Peptide System

Renin Angiotensin System

LCZ696



pro-BNP

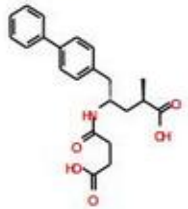
NT-pro BNP

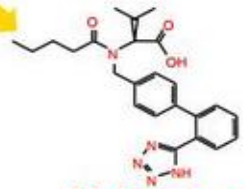
ANP BNP CNP

Adrenomedullin
Bradykinin
Substance P
(angiotensin II)

Sacubitril (AHU377)

LBQ657





Valsartan

Neprilysin

Inactive fragments

Angiotensinogen (liver secretion)

Angiotensin I

Angiotensin II

AT_1 receptor

Vasodilation
- ↓ blood pressure
- ↓ sympathetic tone
- ↓aldosterone levels
- ↓ fibrosis
- ↓ hypertrophy

Natriuresis/Diuresis

LCZ696 is a novel crystalline complex consisting of the molecular moieties of valsartan and sacubitril in an equimolar ratio

Vasoconstriction
- ↑ blood pressure
- ↑ sympathetic tone
- ↑ aldosterone
- ↑ fibrosis
- ↑ hypertrophy

Provided by M.D. Scott Solomon

PARADIGM-HF: presented at European Society of Cardiology Meeting August 30, 2014

Dec 2009 – March 2014, 1043 centers 47 countries

8442 Patients EF <40, class II-IV

LCZ696 200mg BID (Sacubitril + Valsartan 160mg BID) or enalapril 10mg BID

Primary endpoint: Combined CV mortality and hospitalization for HF

Secondary endpoint: Overall mortality, Kansas City Cardiomyopathy Questionnaire

EARLY TERMINATION: At 27 months, when the primary outcome had occurred in 914 (21.8%) in the LCZ696 group and 1117 (26.5%) in the enalapril group. NNT 21

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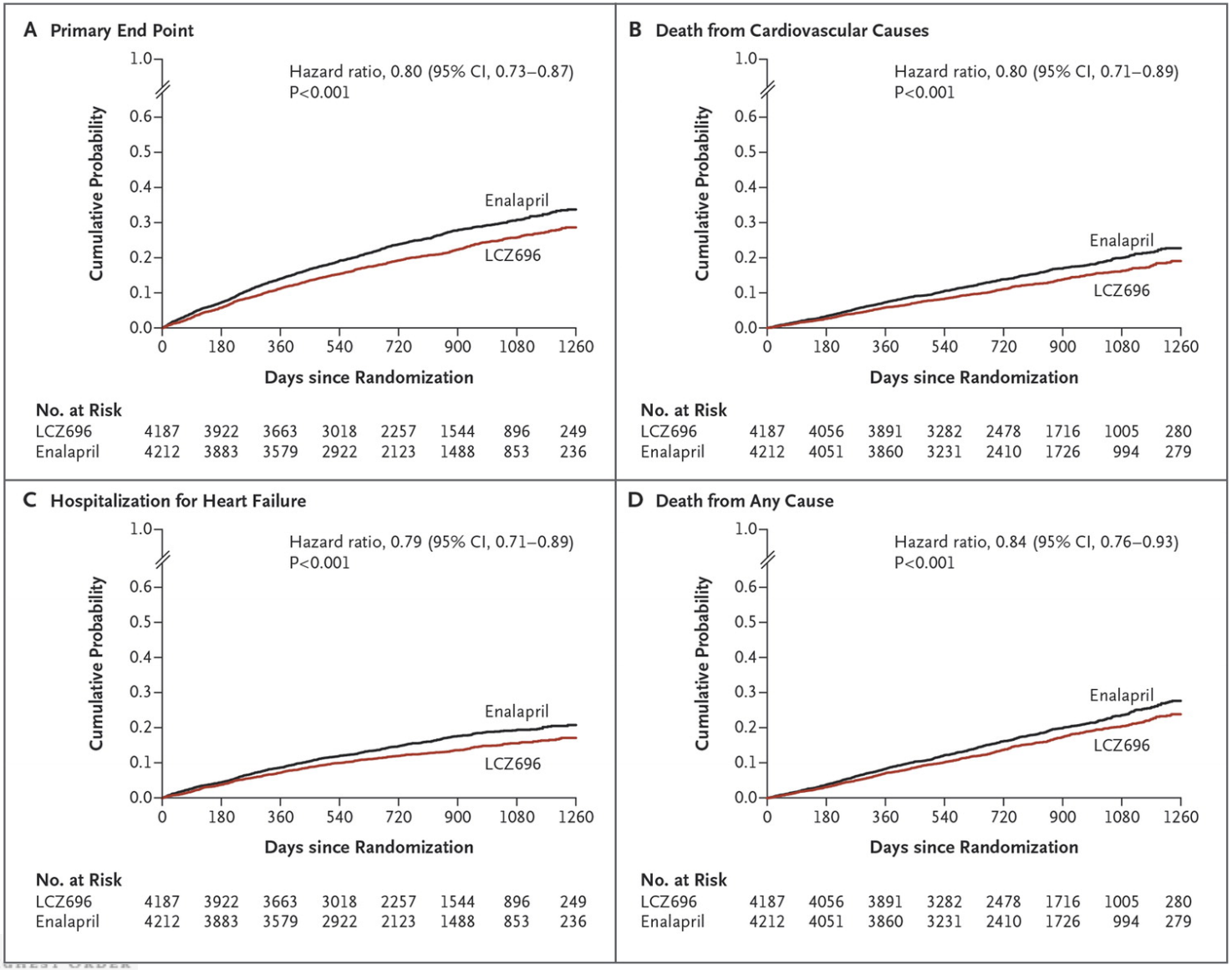
RESULTS



Results

Table 2. Primary and Secondary Outcomes.*

Outcome	LCZ696 (N=4187)	Enalapril (N=4212)	Hazard Ratio or Difference (95% CI)	P Value
Primary composite outcome — no. (%)				
Death from cardiovascular causes or first hospitalization for worsening heart failure	914 (21.8)	1117 (26.5)	0.80 (0.73–0.87)	<0.001
Death from cardiovascular causes	558 (13.3)	693 (16.5)	0.80 (0.71–0.89)	<0.001
First hospitalization for worsening heart failure	537 (12.8)	658 (15.6)	0.79 (0.71–0.89)	<0.001
Secondary outcomes — no. (%)				
Death from any cause	711 (17.0)	835 (19.8)	0.84 (0.76–0.93)	<0.001
Change in KCCQ clinical summary score at 8 mo†	−2.99±0.36	−4.63±0.36	1.64 (0.63–2.65)	0.001
New-onset atrial fibrillation‡	84 (3.1)	83 (3.1)	0.97 (0.72–1.31)	0.83
Decline in renal function§	94 (2.2)	108 (2.6)	0.86 (0.65–1.13)	0.28

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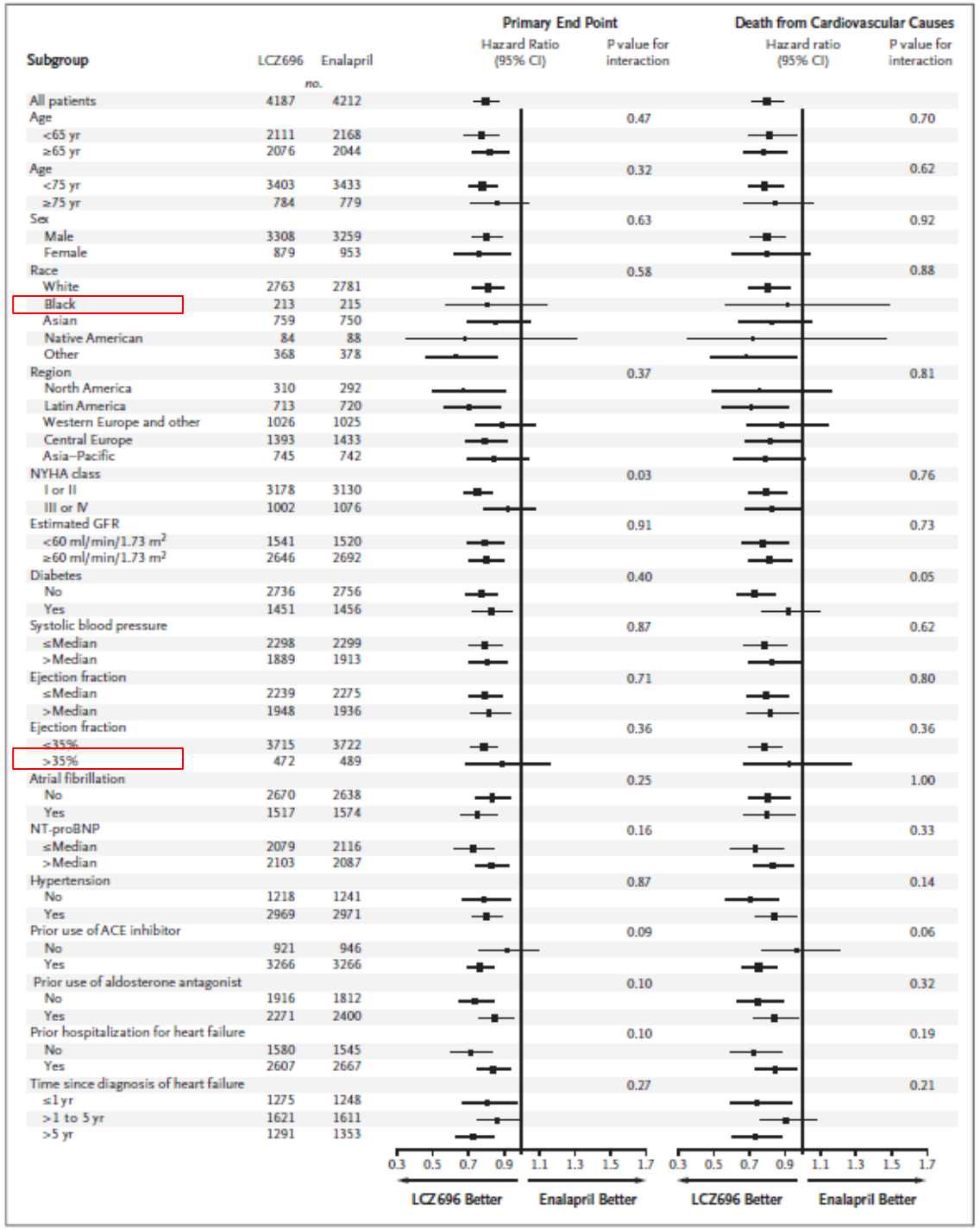

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Adverse Events

Table 3. Adverse Events during Randomized Treatment.*

Event	LCZ696 (N=4187)	Enalapril (N=4212)	P Value
	no. (%)		
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90 mm Hg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dl	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dl	63 (1.5)	83 (2.0)	0.10
Elevated serum potassium			
>5.5 mmol/liter	674 (16.1)	727 (17.3)	0.15
>6.0 mmol/liter	181 (4.3)	236 (5.6)	0.007
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema†			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Use of catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	0.52
Hospitalization without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	—

* Shown are results of the analyses of prespecified safety events at any time after randomization. The numbers of patients who permanently discontinued a study drug were as follows: for hypotension, 36 (0.9%) in the LCZ696 group and 29 (0.7%) in the enalapril group (P=0.38); for renal impairment, 29 (0.7%) and 59 (1.4%), respectively (P=0.002); and for hyperkalemia, 11 (0.3%) and 15 (0.4%), respectively (P=0.56).

† Angioedema was adjudicated in a blinded fashion by an expert committee.

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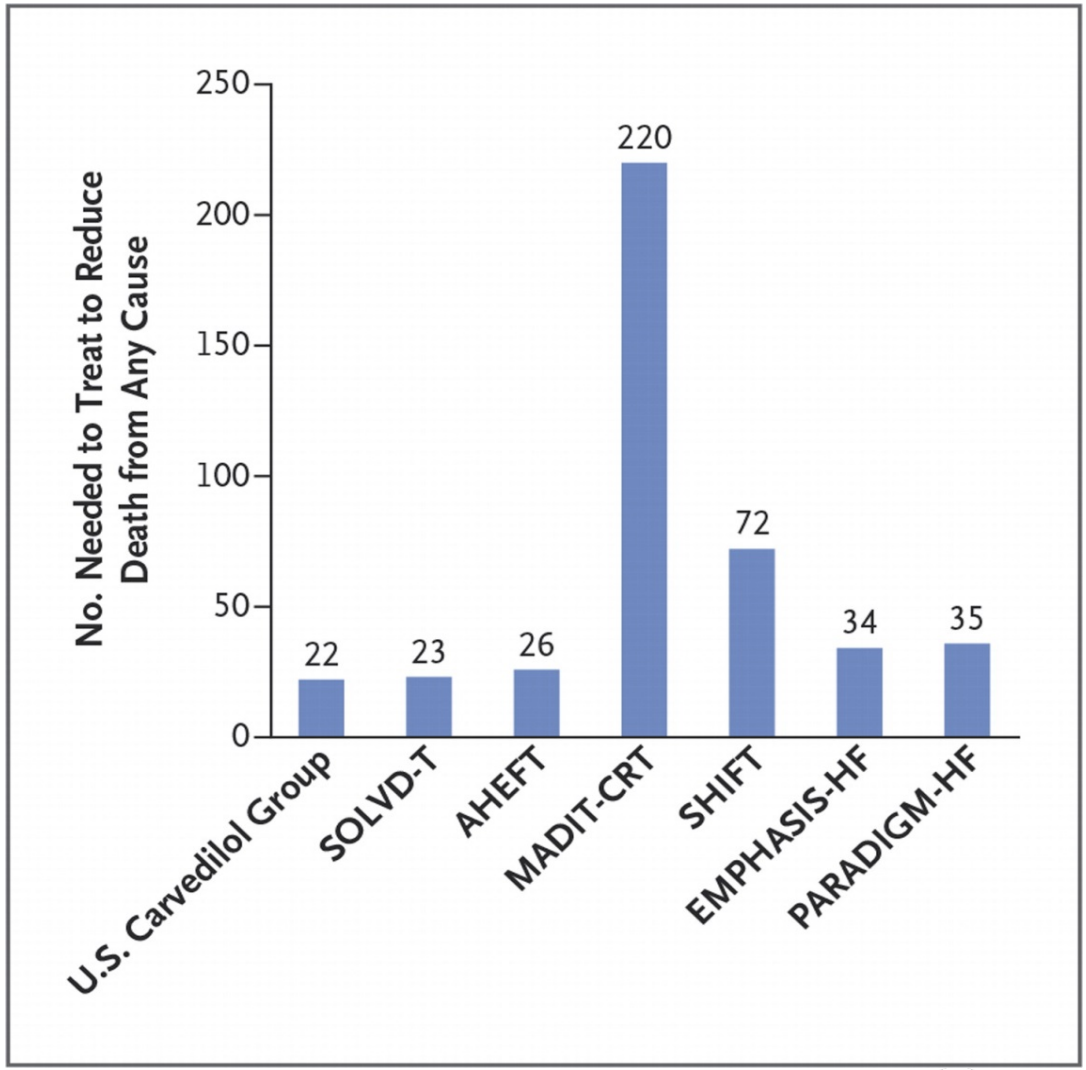
Numbers of Patients with Heart Failure Who Would Need to Be Treated to Reduce Any-Cause Mortality in Seven Clinical Trials.



Jessup M. N Engl J Med 2014;371:1062-1064.

Status?

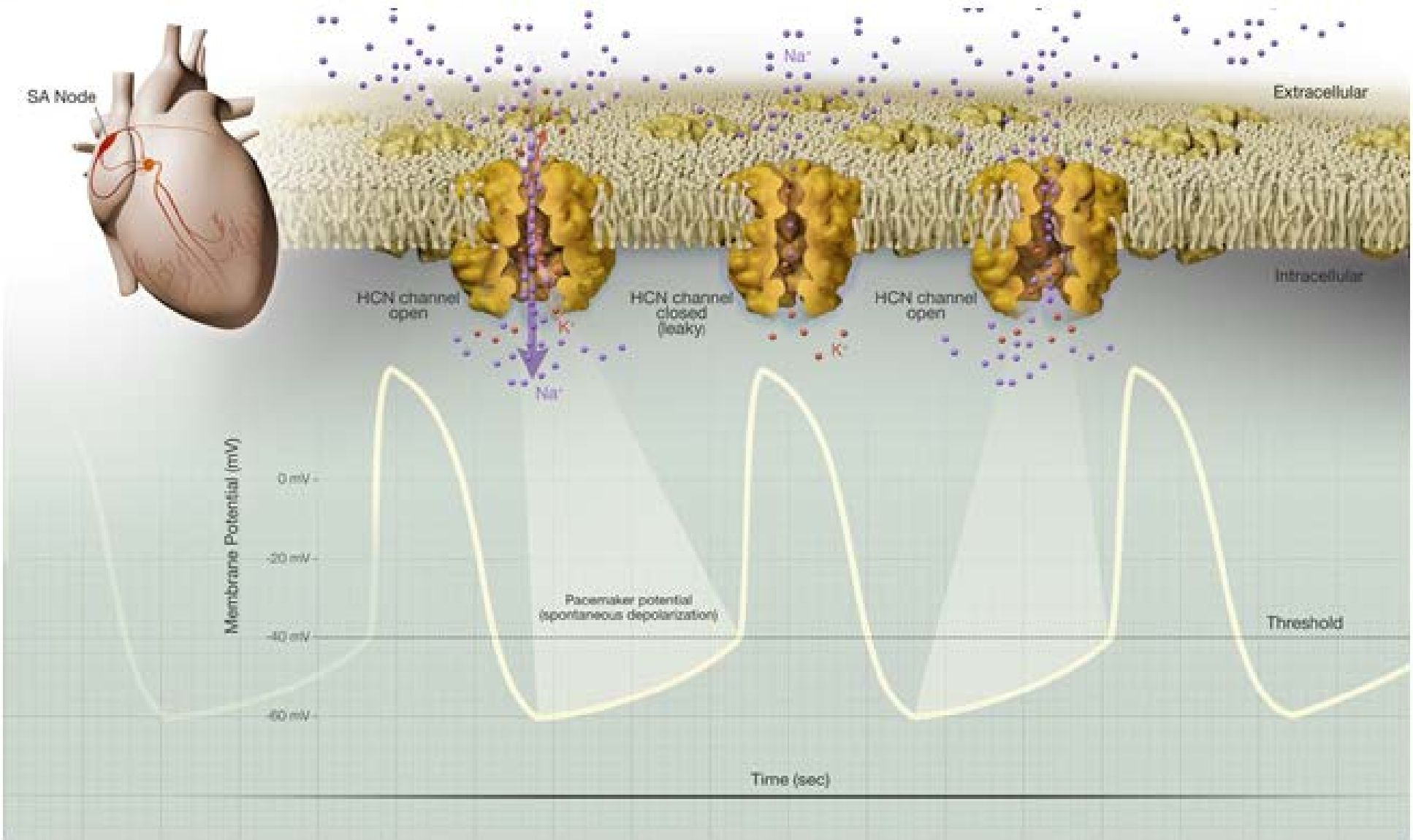
FDA granted priority review in February 2015

Likely decision to be made August 2015

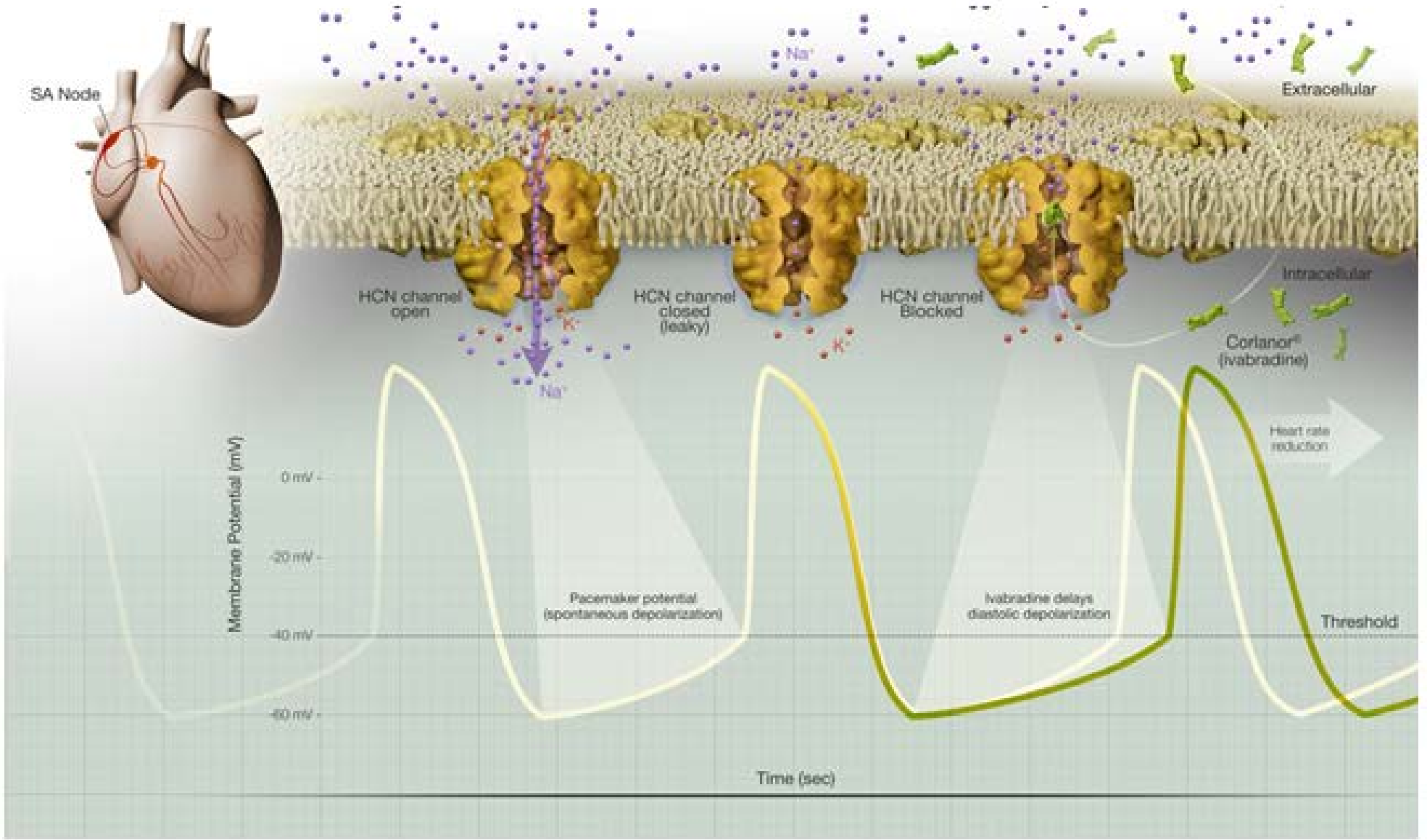
Ivabradine

Success?

The HCN Channel Responsible for the Cardiac Pacemaker I_f Current Regulates Heart Rate



Corlanor® (ivabradine) Blocks the HCN Channel in the Sinus Node which Reduces Heart Rate



History

SHIFT study

Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial

Swedberg K, *Lancet.* 2010; 376(9744):875-885.

February 2012

- European Medicine Agency granted indication of ivabradine in chronic heart failure (NYHA Class II-IV, SR, Heart rate ≥75 bpm)

May 2012

- ESC guidelines for the diagnosis and management of heart failure included ivabradine in the algorithm for the treatment of chronic heart failure (NYHA Class II-IV, SR, heart rate ≥ 70 bpm)

Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

*Karl Swedberg, Michel Komajda, Michael Böhm, Jeffrey S Borer, Ian Ford, Ariane Dubost-Brama, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators**

Summary

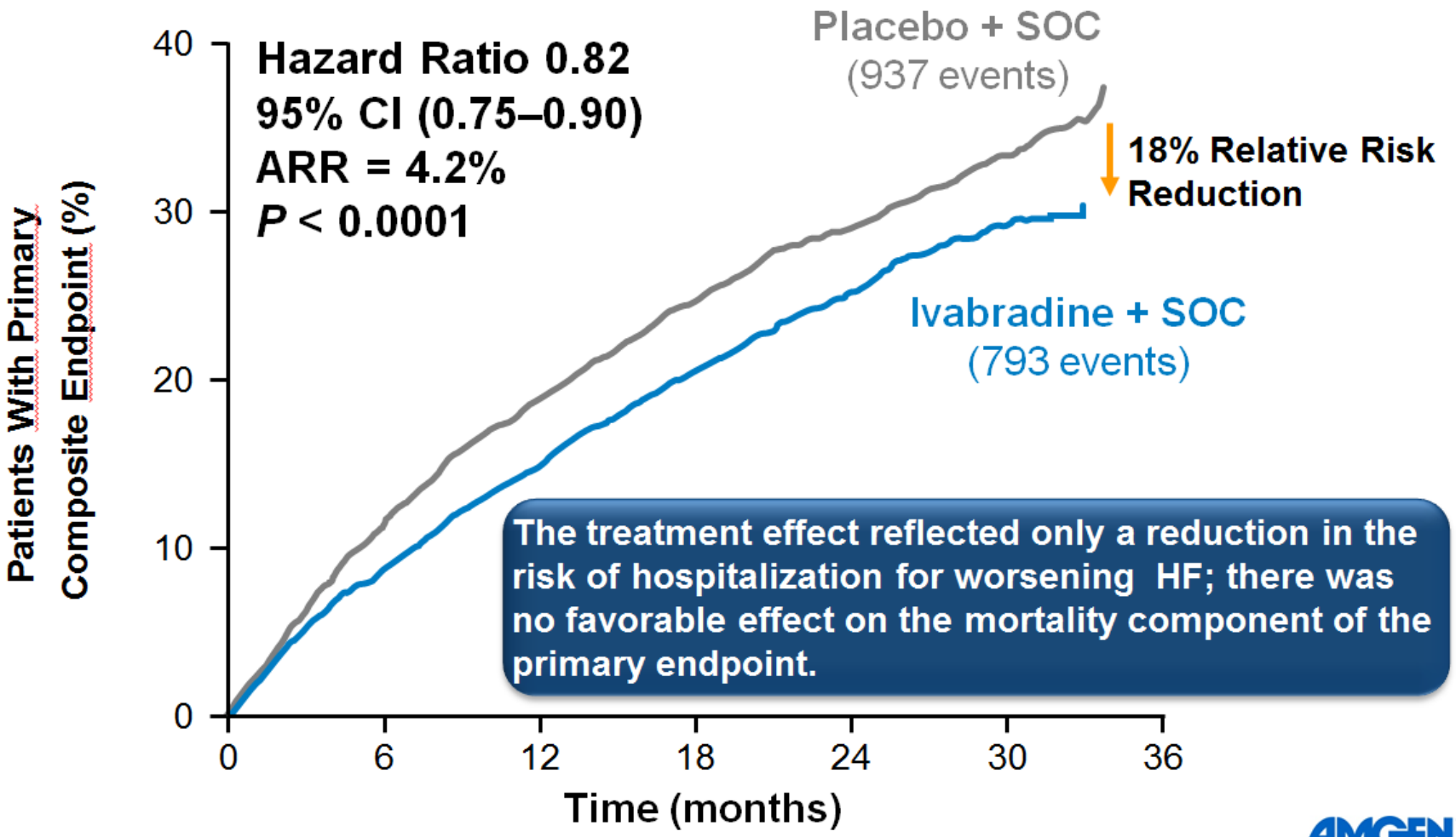
Background Chronic heart failure is associated with high mortality and morbidity. Raised resting heart rate is a risk factor for adverse outcomes. We aimed to assess the effect of heart-rate reduction by the selective sinus-node inhibitor ivabradine on outcomes in heart failure.

Methods Patients were eligible for participation in this randomised, double-blind, placebo-controlled, parallel-group study if they had symptomatic heart failure and a left-ventricular ejection fraction of 35% or lower, were in sinus rhythm with heart rate 70 beats per min or higher, had been admitted to hospital for heart failure within the previous year, and were on stable background treatment including a β blocker if tolerated. Patients were randomly assigned by computer-generated allocation schedule to ivabradine titrated to a maximum of 7·5 mg twice daily or matching placebo. Patients and investigators were masked to treatment allocation. The primary endpoint was the composite of cardiovascular death or hospital admission for worsening heart failure. Analysis was by intention to treat. This trial is registered, number ISRCTN70429960.

Findings 6558 patients were randomly assigned to treatment groups (3268 ivabradine, 3290 placebo). Data were available for analysis for 3241 patients in the ivabradine group and 3264 patients allocated placebo. Median follow-up was 22·9 (IQR 18–28) months. 793 (24%) patients in the ivabradine group and 937 (29%) of those taking placebo had a primary endpoint event (HR 0·82, 95% CI 0·75–0·90, p<0·0001). The effects were driven mainly by hospital admissions for worsening heart failure (672 [21%] placebo *vs* 514 [16%] ivabradine; HR 0·74, 0·66–0·83; p<0·0001) and deaths due to heart failure (151 [5%] *vs* 113 [3%]; HR 0·74, 0·58–0·94, p=0·014). Fewer serious adverse events occurred in the ivabradine group (3388 events) than in the placebo group (3847; p=0·025). 150 (5%) of ivabradine patients had symptomatic bradycardia compared with 32 (1%) of the placebo group (p<0·0001). Visual side-effects (phosphenes) were reported by 89 (3%) of patients on ivabradine and 17 (1%) on placebo (p<0·0001).

Interpretation Our results support the importance of heart-rate reduction with ivabradine for improvement of clinical outcomes in heart failure and confirm the important role of heart rate in the pathophysiology of this disorder.

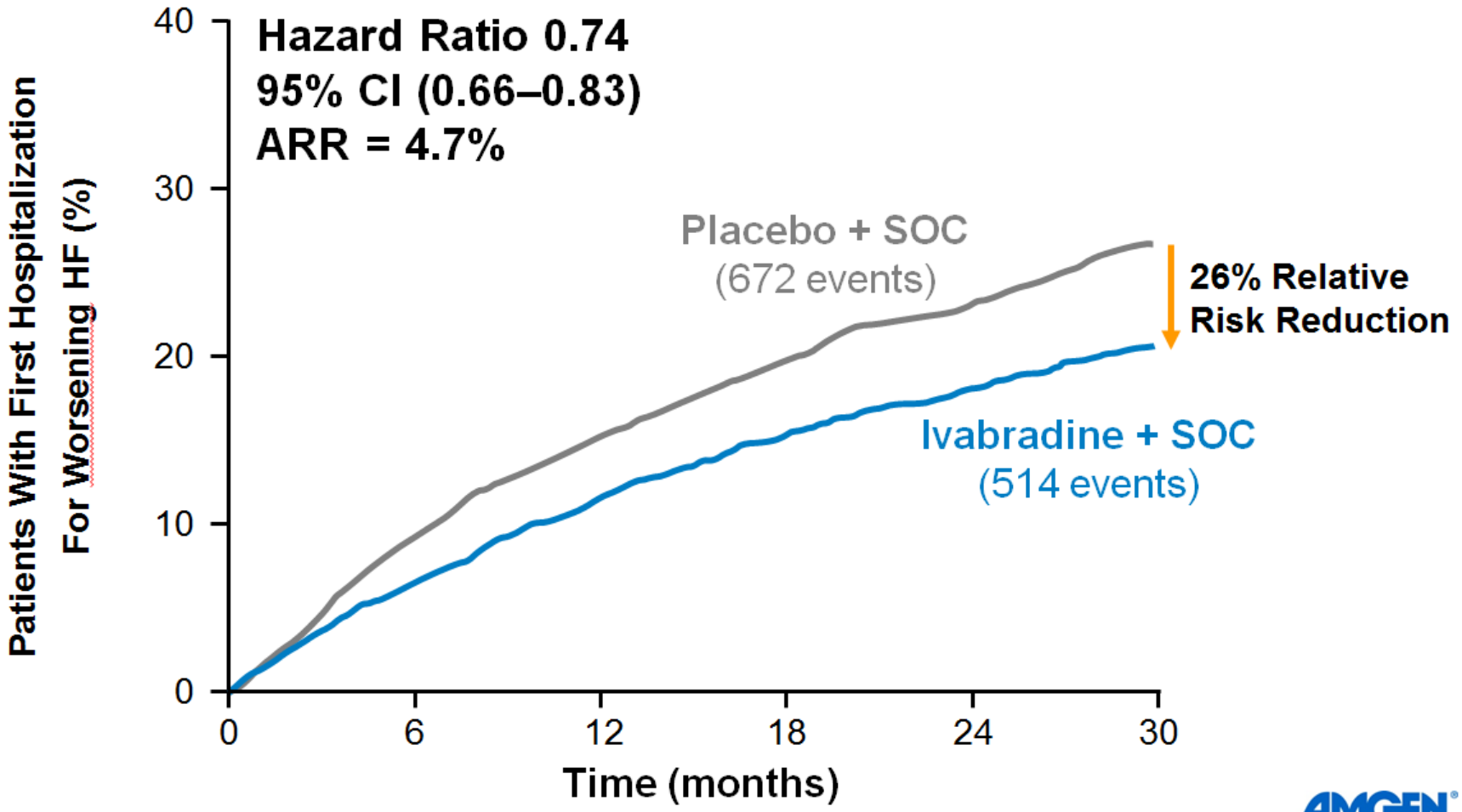
Time to First Event of Hospitalization for Worsening HF or CV Death



Primary Composite Endpoint: Time to CV Death or First Hospitalization for Worsening HF.
ARR, absolute risk reduction; CI, confidence interval; SOC, standard of care.
Corlanor® (ivabradine) Prescribing Information, Amgen.
Swedberg K, et al. *Lancet*. 2010;376:875-885

AMGEN®
Cardiovascular

Hospitalization for Worsening HF at Any Time



AMGEN
Cardiovascular

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

FDA News Release

FDA approves Corlanor to treat heart failure

For Immediate Release April 15, 2015

Release

Español

The U.S. Food and Drug Administration today approved Corlanor (ivabradine) to reduce hospitalization from worsening heart failure.

Inquiries

Media

Sandy Walsh
301-796-4669

Consumers

888-INFO-FDA

Share

Considerations

NYHA Class I-IV

LVEF ≤ 35%

Prior HF hospitalization in previous 12 months

Heart rate sinus rhythm ≥ 70 bpm (resting ECG)

On standard HF agents

Not for acute decompensated HF

Increased risk of atrial fibrillation?

Coverage?

Not on inpatient formularies at this time

Serelaxin

Success?

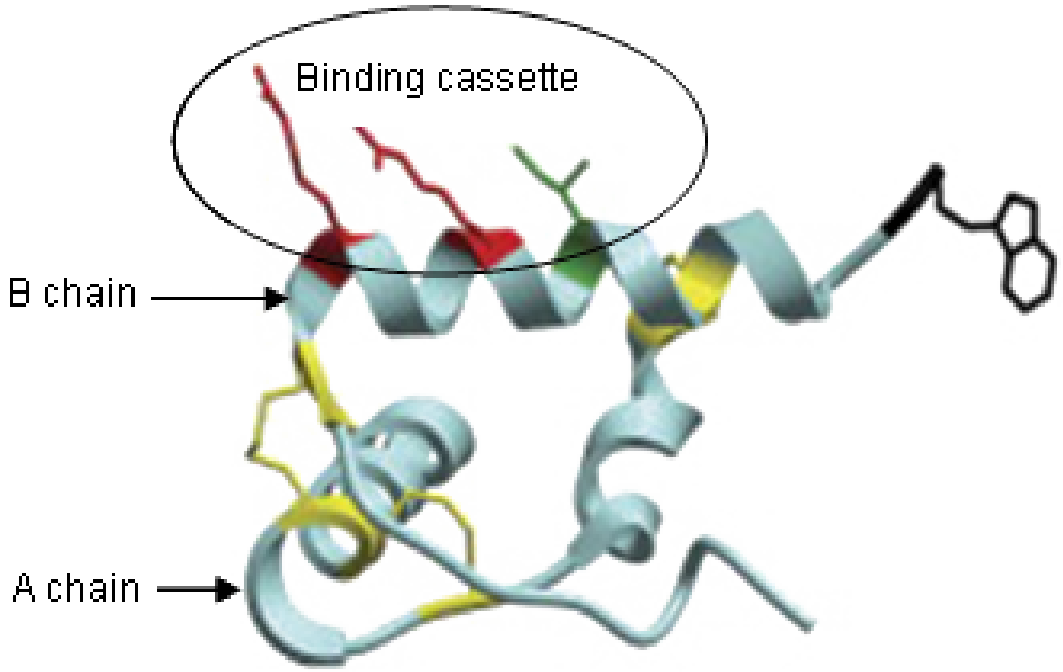
Relaxin

Classified as a protein hormone

- Belongs to the insulin-superfamily

Produced:

- Women
  - Ovary (Corpus luteum)
  - Breast
  - Placenta
- Men
  - Prostate and in prostatic fluid



Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial

John R Teerlink, Gad Cotter, Beth A Davison, G Michael Felker, Gerasimos Filippatos, Barry H Greenberg, Piotr Ponikowski, Elaine Unemori, Adriaan A Voors, Kirkwood F Adams Jr, Maria I Dorobantu, Liliana R Grinfeld, Guillaume Jondeau, Alon Marmor, Josep Masip, Peter S Pang, Karl Werdan, Sam L Teichman, Angelo Trapani, Christopher A Bush, Rajnish Saini, Christoph Schumacher, Thomas M Severin, Marco Metra, for the RELAXin in Acute Heart Failure (RELAX-AHF) Investigators

Lancet 2013; 381: 29–39

Published Online
November 7, 2012
http://dx.doi.org/10.1016/
S0140-6736(12)61855-8

RELAX-AHF Conclusions

- **Significant reduction in primary endpoint: Dyspnea -19%**
  - And other acute HF signs/symptoms
- **Reduced length of stay**
- No reduction in 60-day hospital readmission
- No reduction in combined hospital readmission and cardiovascular death, BUT

  Reduced Cardiovascular Death at 180 days with an Absolute Risk Reduction of 3.5%

- Not powered to look at mortality…

RELAX-AHF-2

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Angeles"
Search for studies: Search
Advanced Search | Help | Studies by Topic | Glossary

Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home > Find Studies > Search Results > Study Record Detail Text Size

Trial record **1 of 1** for: relax-ahf-2
Previous Study | Return to List | Next Study

Efficacy, Safety and Tolerability of Serelaxin When Added to Standard Therapy in AHF (RELAX-AHF-2)

This study is currently recruiting participants. (see Contacts and Locations)

Verified March 2015 by Novartis

Sponsor:
Novartis Pharmaceuticals

Information provided by (Responsible Party):
Novartis (Novartis Pharmaceuticals)

ClinicalTrials.gov Identifier:
NCT01870778

First received: June 3, 2013
Last updated: March 23, 2015
Last verified: March 2015
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

URMC

We are a site for RELAX-AHF-2

Screening since March 2015

1200 screened; one consented; no enrollment yet

Study will be powered to look at mortality

CardioMEMS

Success?

Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial

William T Abraham, Philip B Adamson, Robert C Bourge, Mark F Aaron, Maria Rosa Costanzo, Lynne W Stevenson, Warren Strickland, Suresh Neelagaru, Nirav Raval, Steven Krueger, Stanislav Weiner, David Shavelle, Bradley Jeffries, Jay S Yadav, for the CHAMPION Trial Study Group*

Summary

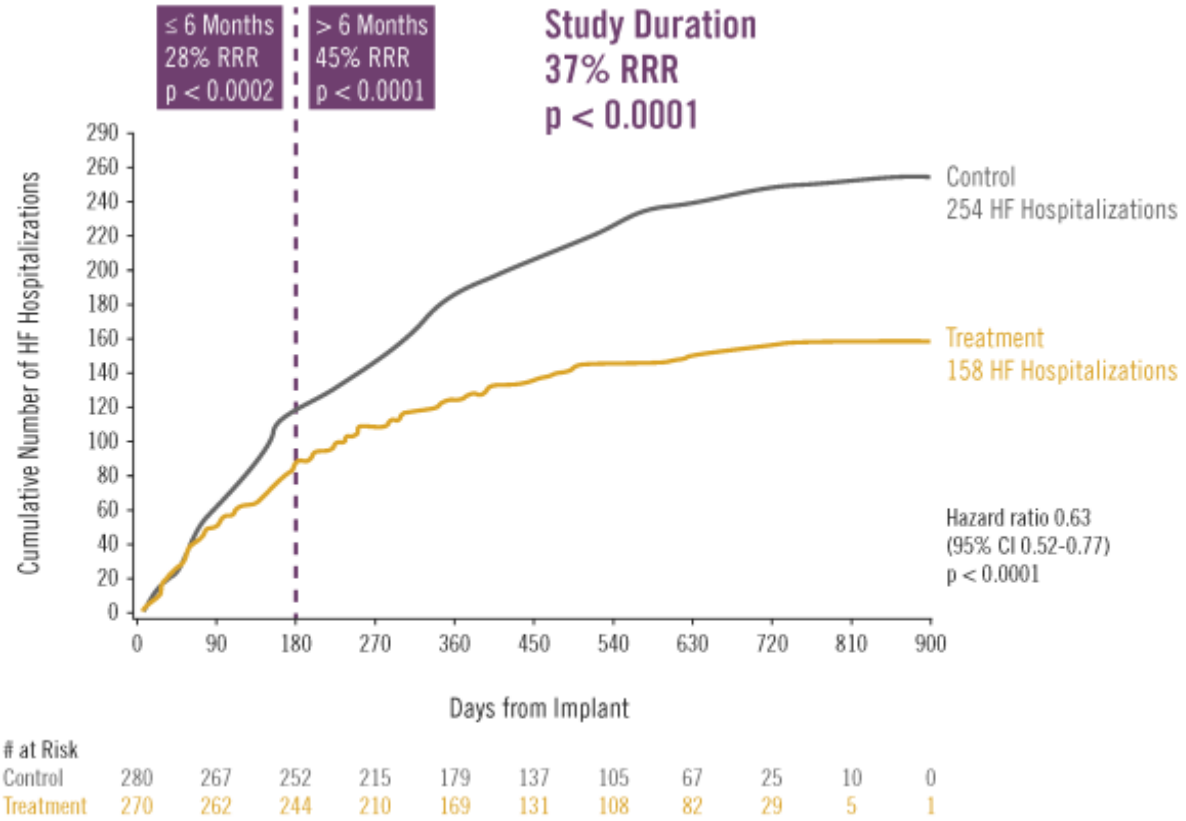
Background Results of previous studies support the hypothesis that implantable haemodynamic monitoring systems might reduce rates of hospitalisation in patients with heart failure. We undertook a single-blind trial to assess this approach.

Methods Patients with New York Heart Association (NYHA) class III heart failure, irrespective of the left ventricular ejection fraction, and a previous hospital admission for heart failure were enrolled in 64 centres in the USA. They were randomly assigned by use of a centralised electronic system to management with a wireless implantable haemodynamic monitoring (W-IHM) system (treatment group) or to a control group for at least 6 months. Only patients were masked to their assignment group. In the treatment group, clinicians used daily measurement of pulmonary artery pressures in addition to standard of care versus standard of care alone in the control group. The primary efficacy endpoint was the rate of heart-failure-related hospitalisations at 6 months. The safety endpoints assessed at 6 months were freedom from device-related or system-related complications (DSRC) and freedom from pressure-sensor failures. All analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00531661.

Findings In 6 months, 83 heart-failure-related hospitalisations were reported in the treatment group (n=270) compared with 120 in the control group (n=280; rate 0·31 *vs* 0·44, hazard ratio [HR] 0·70, 95% CI 0·60–0·84, p<0·0001). During the entire follow-up (mean 15 months [SD 7]), the treatment group had a 39% reduction in heart-failure-related hospitalisation compared with the control group (153 *vs* 253, HR 0·64, 95% CI 0·55–0·75; p<0·0001). Eight patients had DSRC and overall freedom from DSRC was 98·6% (97·3–99·4) compared with a prespecified performance criterion of 80% (p<0·0001); and overall freedom from pressure-sensor failures was 100% (99·3–100·0).

Interpretation Our results are consistent with, and extend, previous findings by definitively showing a significant and large reduction in hospitalisation for patients with NYHA class III heart failure who were managed with a wireless implantable haemodynamic monitoring system. The addition of information about pulmonary artery pressure to clinical signs and symptoms allows for improved heart failure management.

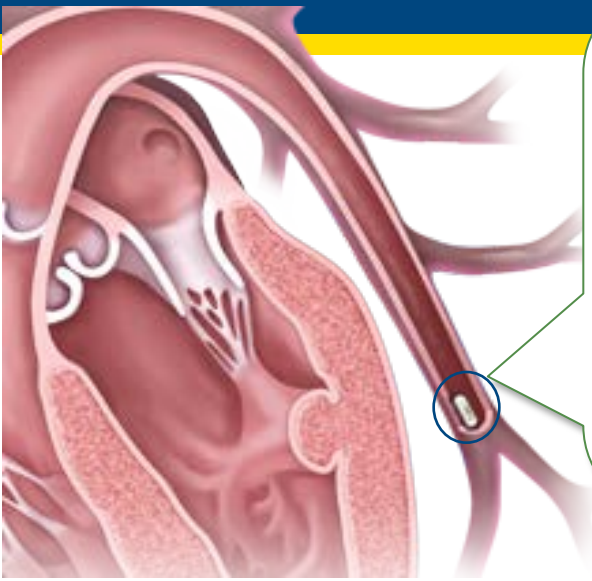
CHAMPION Clinical Trial: PA Pressure-guided Therapy Reduces HF Hospitalizations



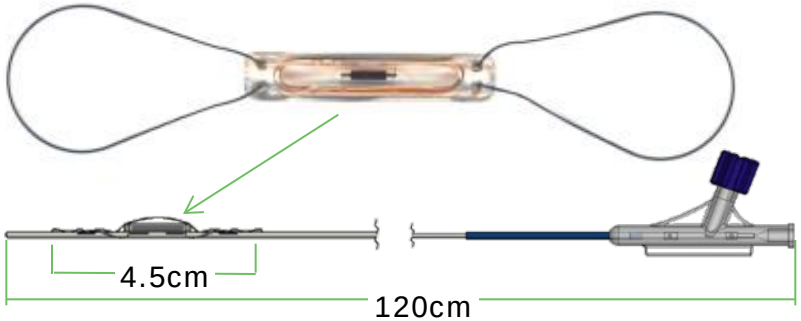
Patients managed with PA pressure data had **significantly fewer HF hospitalizations** as compared to the control group.

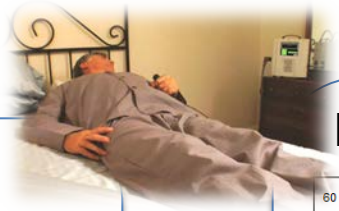
Lancet; February 19, 2011. 377:658-665

CardioMEMS™ HF System



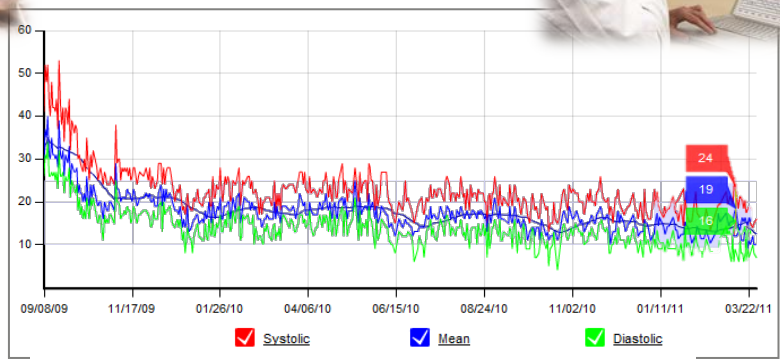
PA Pressure Sensor on
Catheter Delivery System





Hospital and Patient Home
Electronics Unit

PA Pressure Database



Physician Access Via Secure Website

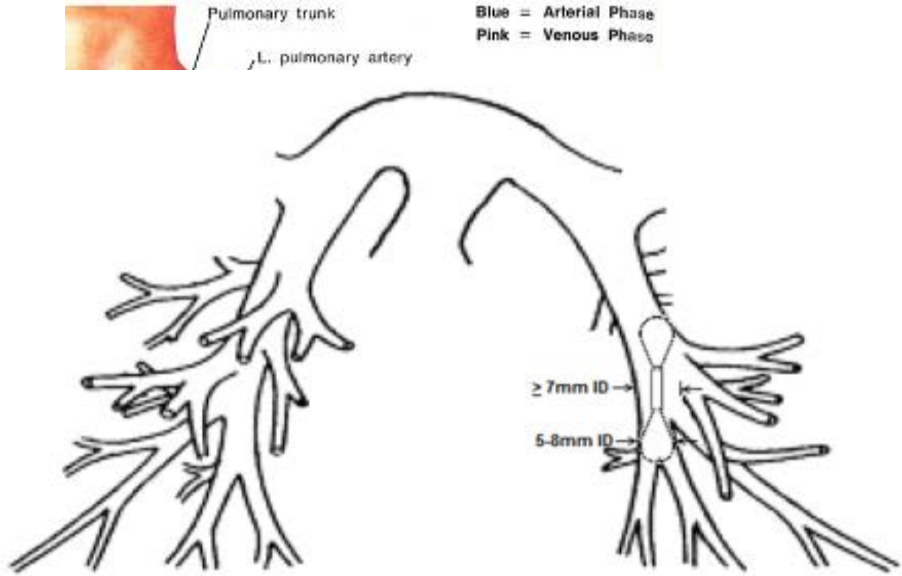
Pulmonary Artery Sensor Implant

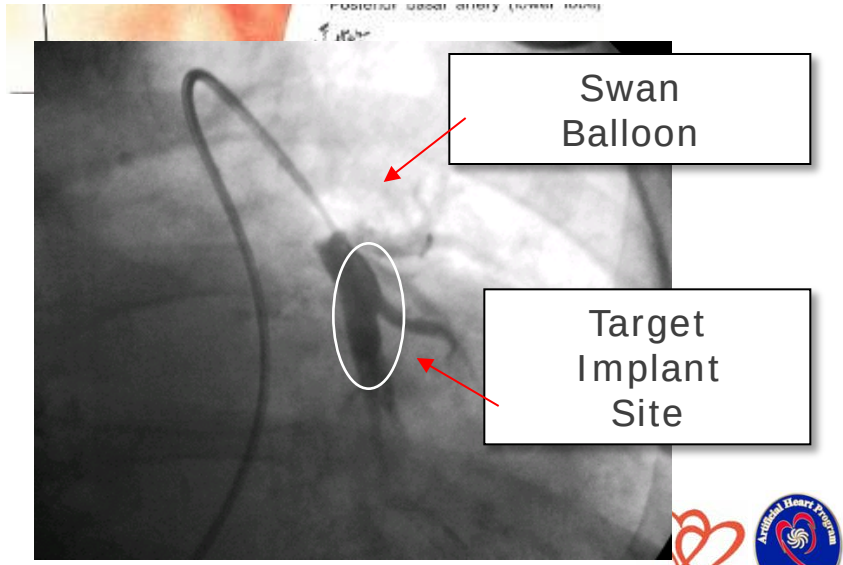
RHC with selective pulmonary angiogram (limited ~ 5cc)

Right or left PA branch, basal (lower) lobe, descending branch, pre-bifurcation

Vessel Lumen ID: 7-15mm

The Sensor and nitinol anchoring loop sizes have been carefully optimized to allow placement in the pulmonary artery in a distal location and not injure artery





CardioMEMS™ HF System
Indications for Use

The CardioMEMS HF System is indicated for wirelessly measuring and monitoring pulmonary artery (PA) pressure and heart rate in New York Heart Association (NYHA) Class III heart failure patients who have been hospitalized for heart failure in the previous year. The hemodynamic data are used by physicians for heart failure management and with the goal of reducing heart failure hospitalizations.

Major Inclusion Criteria

- NYHA Class III HF
- Reduced EF Patients had to be on stable heart failure therapy per ACC/AHA guidelines
  - ACE/ARB, Beta Blocker and CRT therapy if indicated
- HF Hospitalization within the last 12 months
- Anatomical criteria
  - PA branch diameter $\geq$ 7mm

HeartMate III

Success?

At a Glance

Heart	Lung	Heart / Lung
4,138	1,648	38

people r… (total w… …ary 2015

78,200 people are active waiting list candidates. Totals as of today 10:56am

as of 04/03/2015

as of 04/03/2015

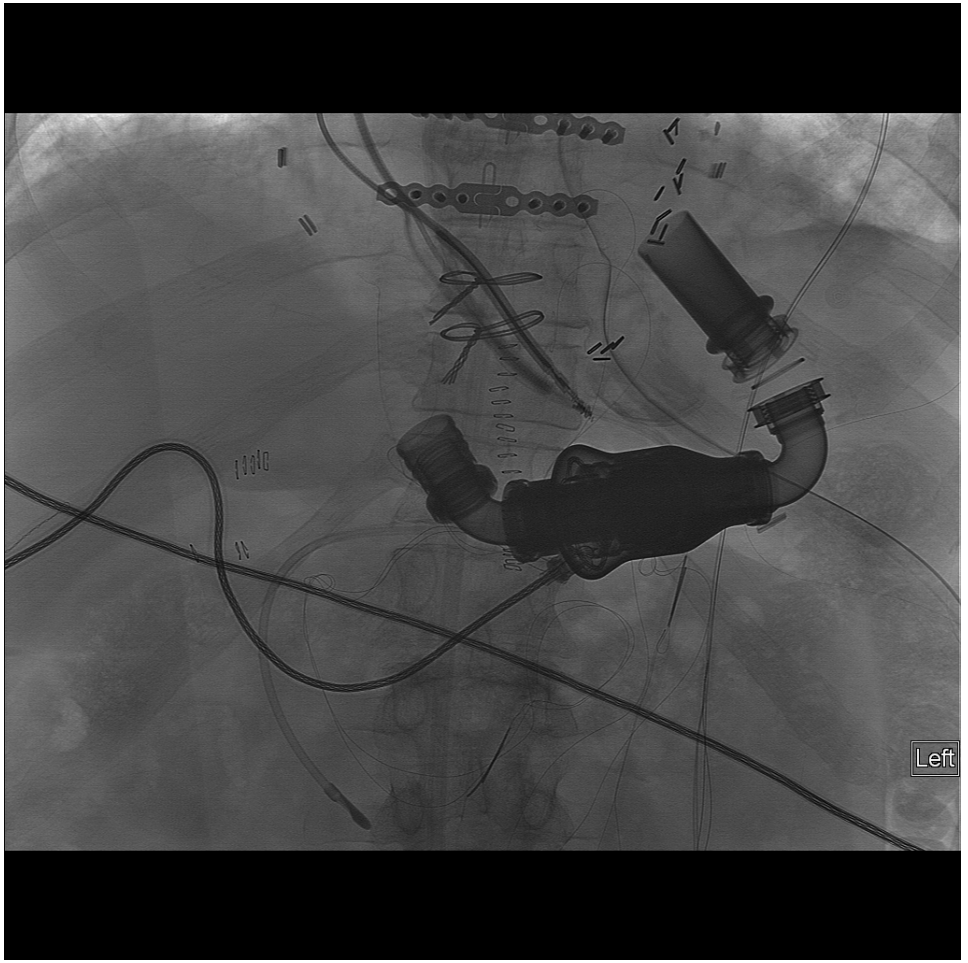
Organ donation and transplantation can save lives

Every ten minutes, someone is added to the national transplant waiting list.

On average, 21 people die each day while waiting for a transplant.

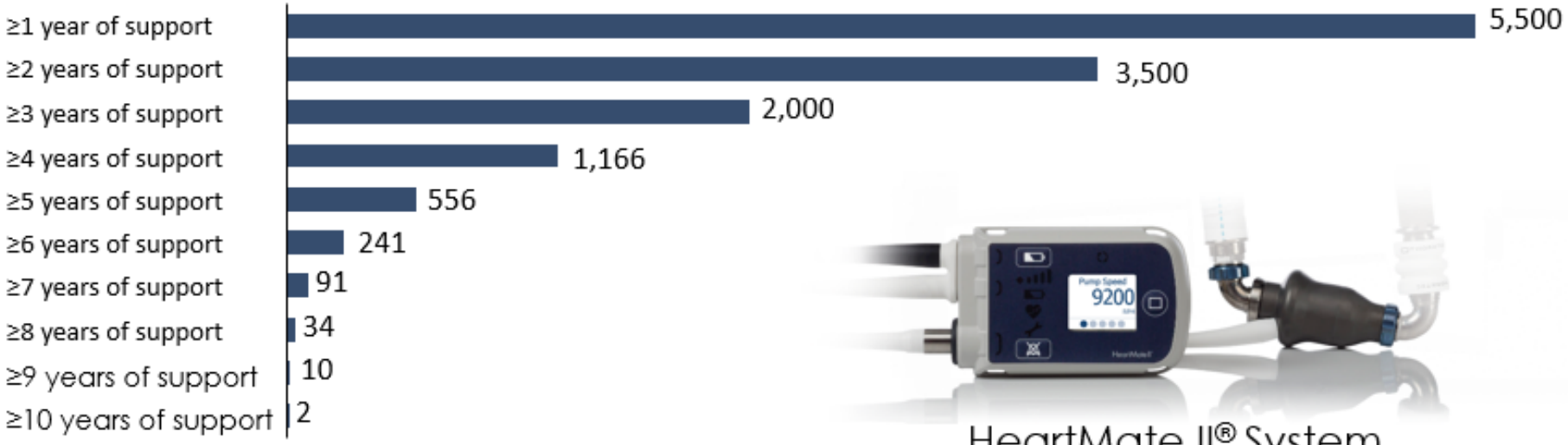
One organ donor can save eight lives. Sign up to be a donor in your state.

URMC = 152 patients on HeartMate II support



Worldwide, over **21,000** patients have now been implanted with the HeartMate II LVAS*

Over 8,000 patients on ongoing support*



HeartMate II® System

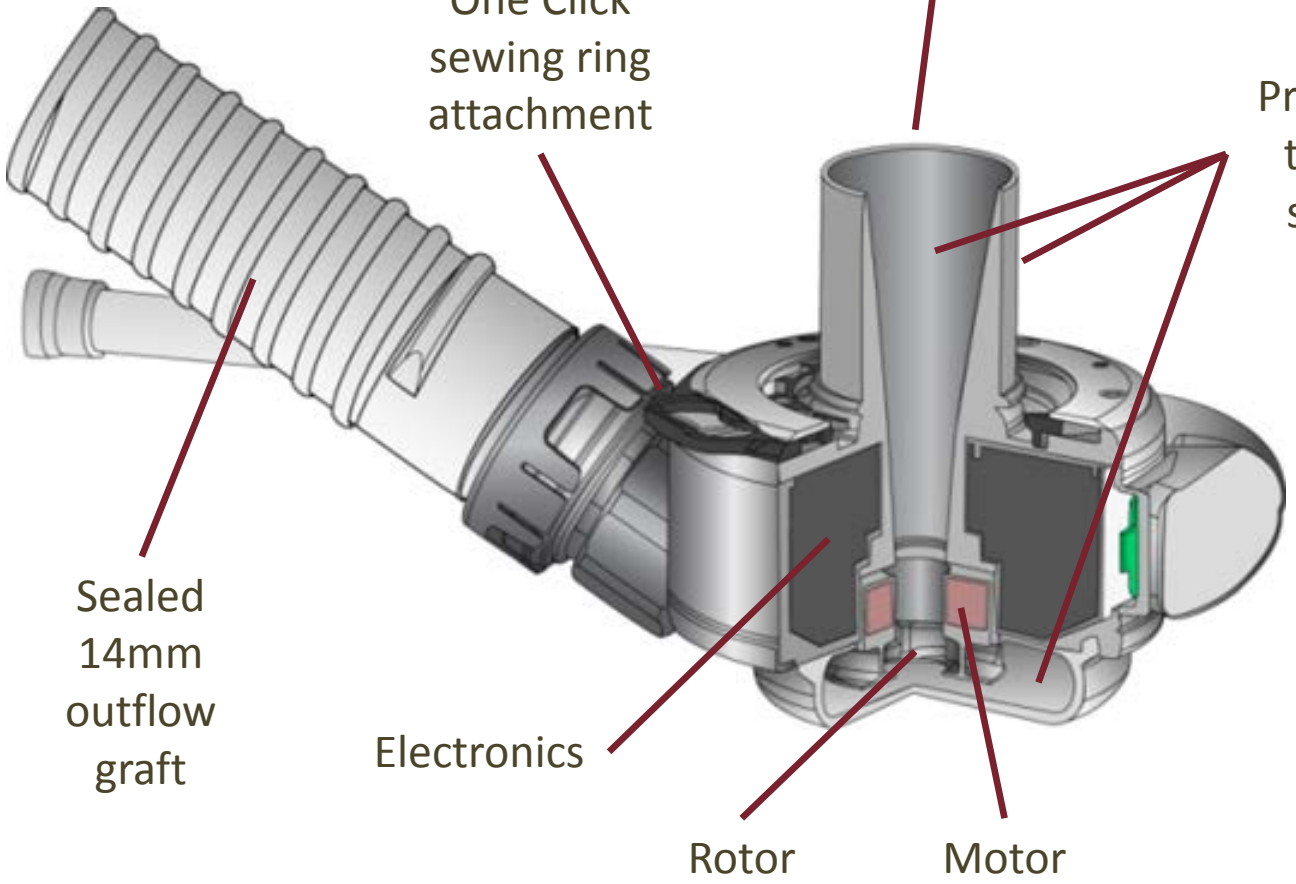
Over **12 million days** of HeartMate II support.

As of May 2015.
*Based on clinical trial and device tracking data.

HeartMateIII™ Trial

HeartMate III

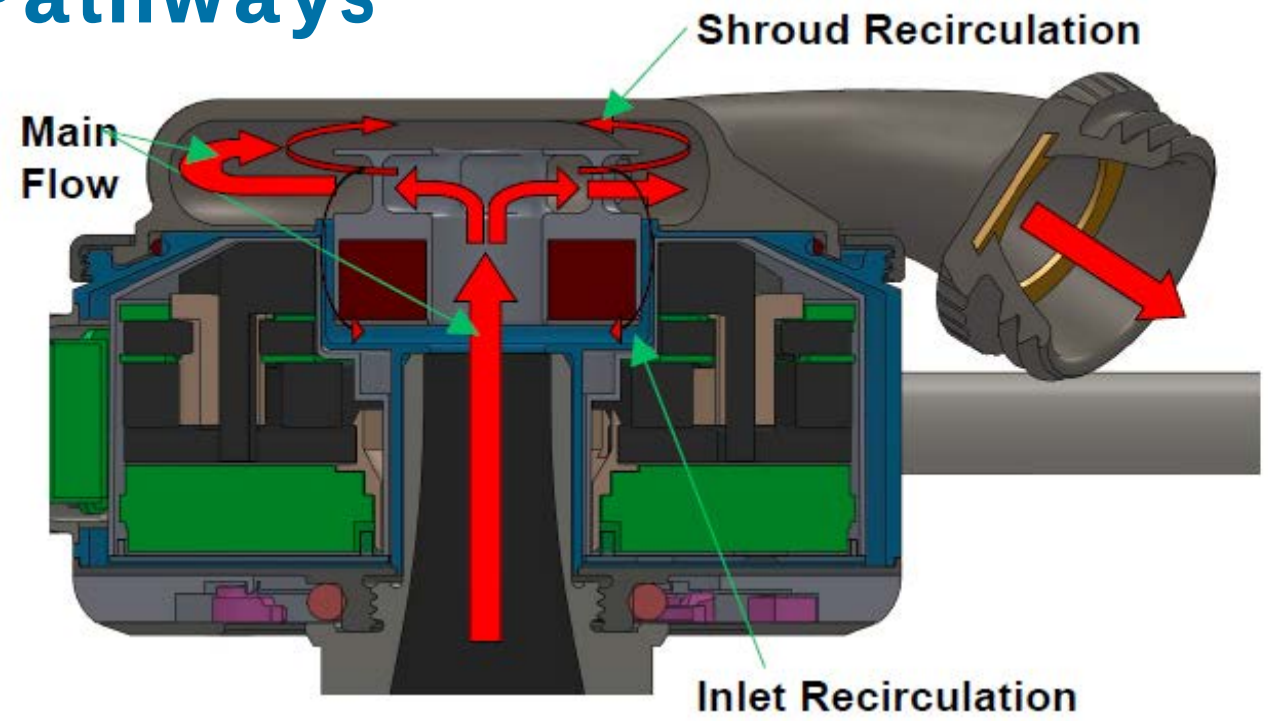
Device components



Exclusively for clinical investigations. CAUTION - Investigational device. Limited by US Federal law to investigational use.

THORATEC CORPORATION for Life

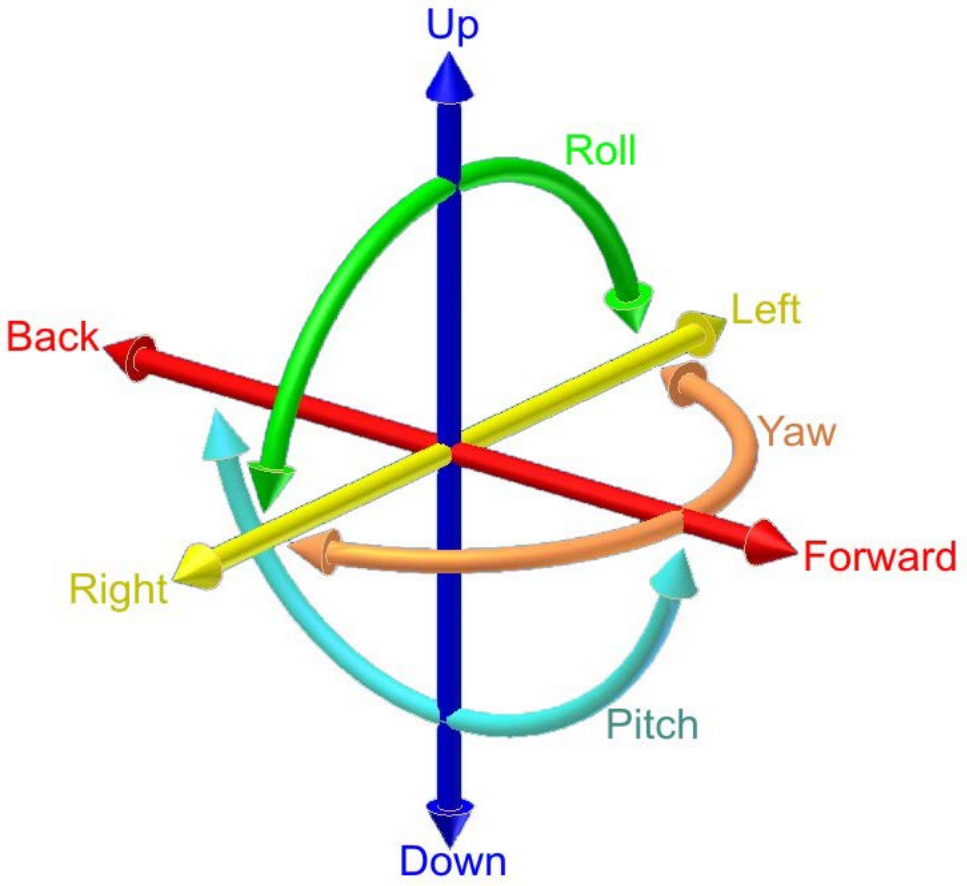
Flow Pathways



THORATEC CORPORATION for Life

Controlling the Rotor

Key Design Decision

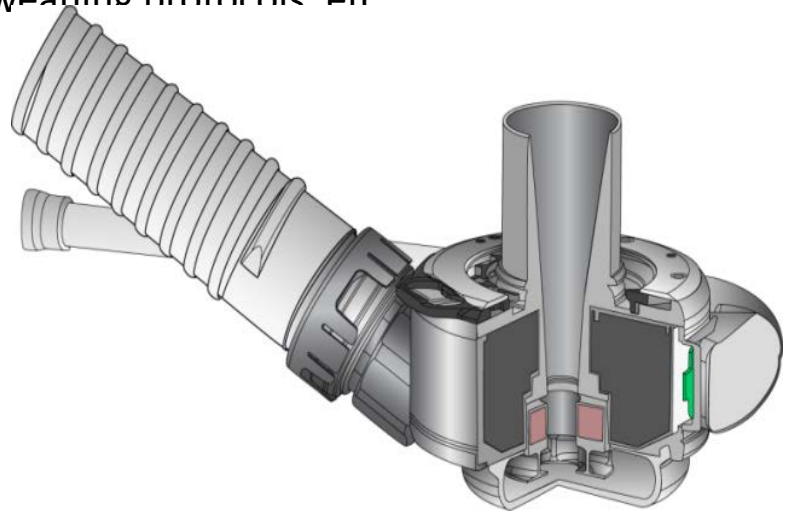


The rotor can potentially move with 6-degrees of freedom

HeartMate III: Full MagLev Technology

Key Design Feature: ***Wide Range of Operation***

- **HeartMate III rotor levitation is independent of rotor speed**; levitation is maintained at any rotor speed, even zero.
  - Conversely, for a hydrodynamic bearing the rotor scrapes the housing surface until it comes up to speed and entrains a thin layer of blood to produce lift; a certain critical speed must be maintained to avoid rotor/housing contact.
- **Rotor speed independence permits flexibility in operating speeds**, which could in the future enable use in low-speed conditions, e.g., pulmonary circulation, weaning protocols, etc.



10L/Min

Wide Range of Operation

2.5L/Min

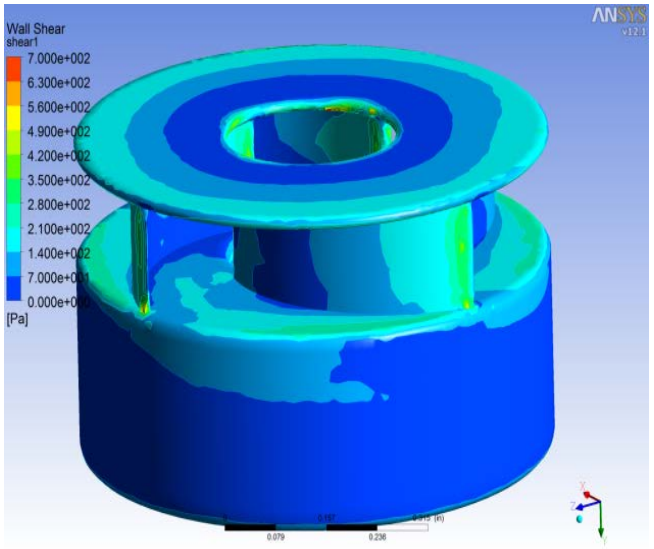
*Caution: Investigational device. Limited to investigational use only.

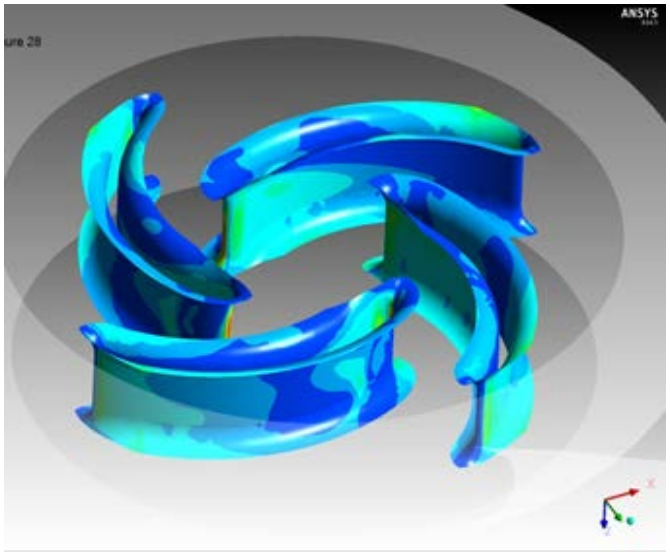
THORATEC CORPORATION for Life

HeartMate III: Full MagLev Technology

Key Design Feature: ***Rotor Design (Minimize Shear Stress and Activation of Blood Components)***

- The HeartMate III rotor and inflow have been designed to **minimize shear and avoid stasis over the entire range of operation (2.5 to 10 L/min).**
- Impressively **low hemolysis** has been demonstrated in both *in vitro* and *in vivo* (plasma-free hemoglobin always <10 mg/dL) studies.





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