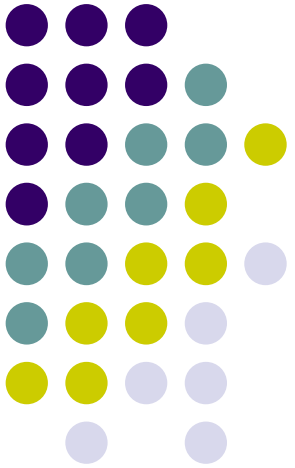
Biopolymer gel implants in heart failure

경북대학교병원 순환기내과
양 동 헌



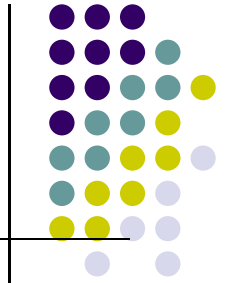
American Heart Association Scientific Sessions 2013

A Multicenter, Randomized Study Assessing the Efficacy of Left Ventricular Augmentation with Algisyl-LVR in the Treatment of Advanced Heart Failure Patients with Ischemic and Non-ischemic Cardiomyopathy: *Interim Results of the **AUGMENT-HF Study***

Douglas L Mann, Hani N Sabbah, Andy Hinson, Stefan D Anker, Andrew Coats, Randall J Lee, Gabriel Cristian, Dinu Dragomir, Enrico Pusineri, Ottavio Alfieri, Antonello Gavazzi, Benno Rensing, Maurizio Volterrani, Anthony Dart, Luca Bettari, on behalf of the AUGMENT-HF Investigators

Funded by LoneStar Heart, Inc.

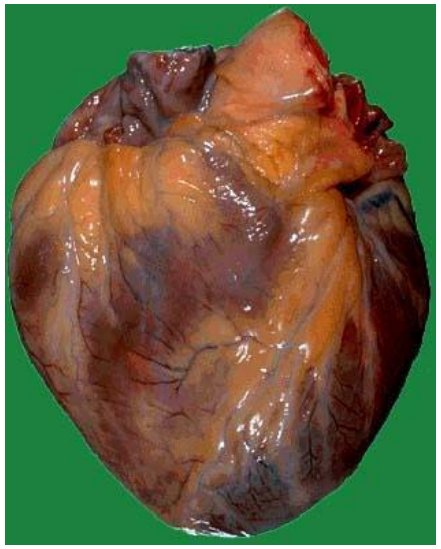
Contents



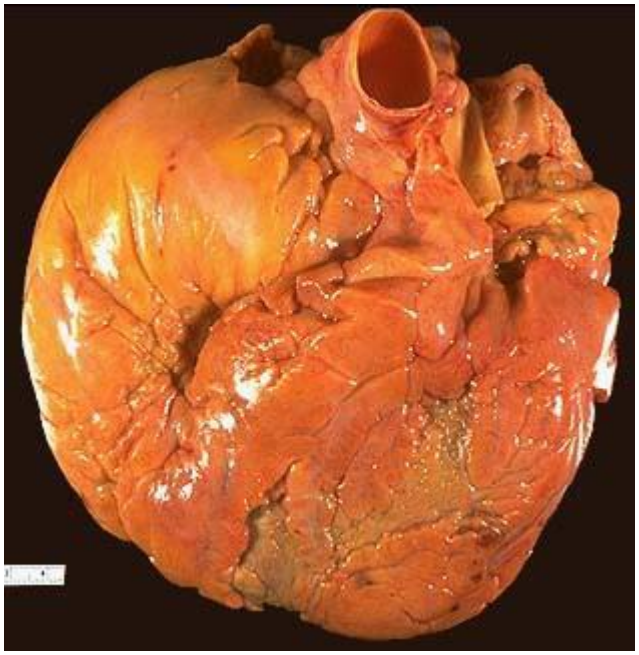
- **Remodeling**
- **Reverse remodeling**
- **Biopolymer gel implants**

Remodeling & Recovery

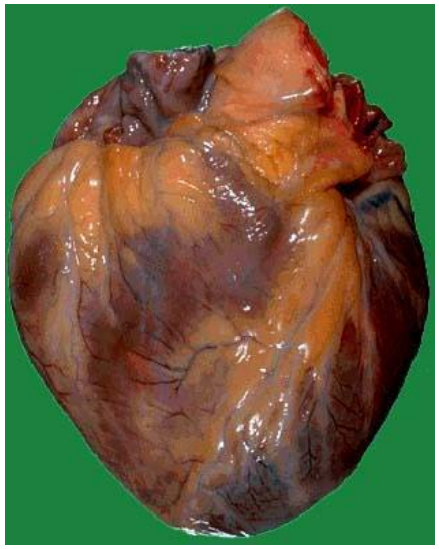
Normal



CHF Remodeled



CHF covered



Progressive LV Dilation

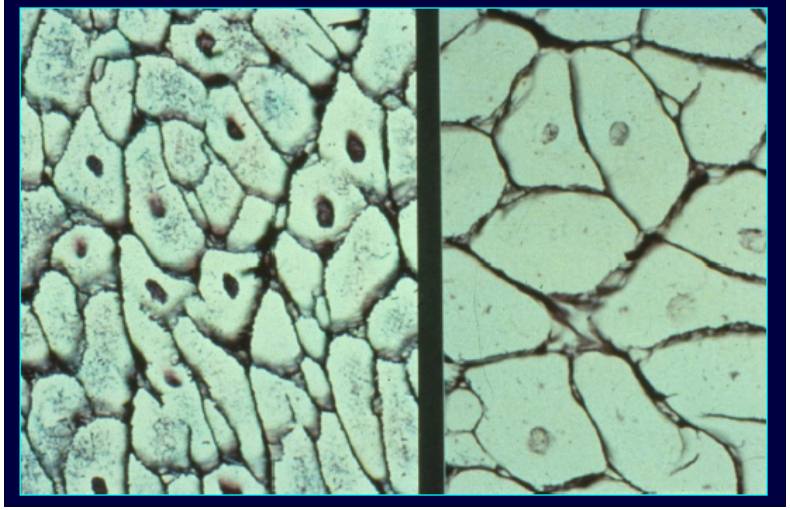
EF = 60 %
SV = 100 ml

EF = 40 %
SV = 100 ml

EF = 20 %
SV = 100 ml

Cardiomyocyte Hypertrophy

Normal CHF



Loss of Cardiomyocytes (e.g. AMI) or Generalized Cardiomyocyte Injury

Increased Workload on Residual Cardiomyocytes

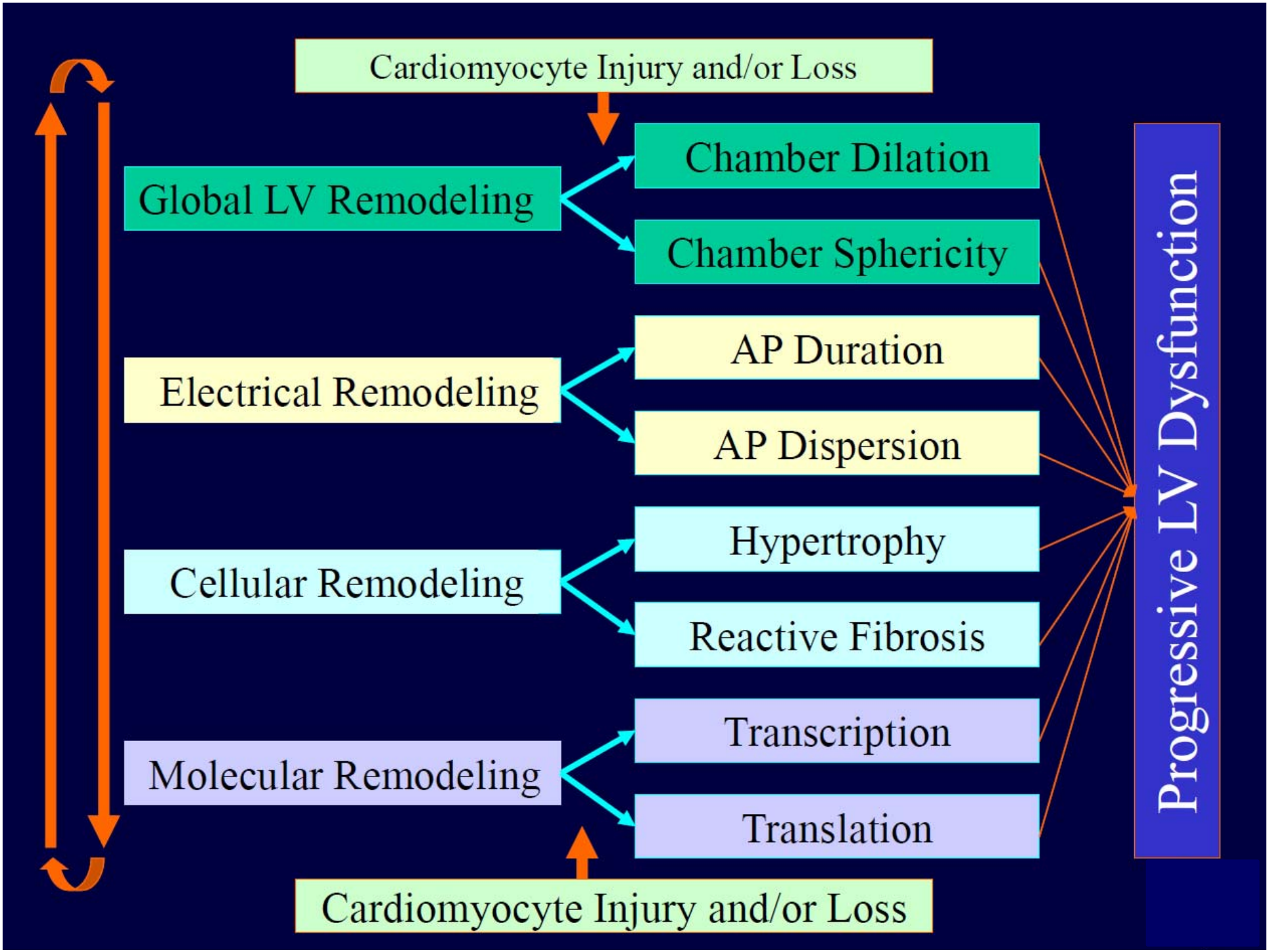
LV Dilation

LV Hypertrophy

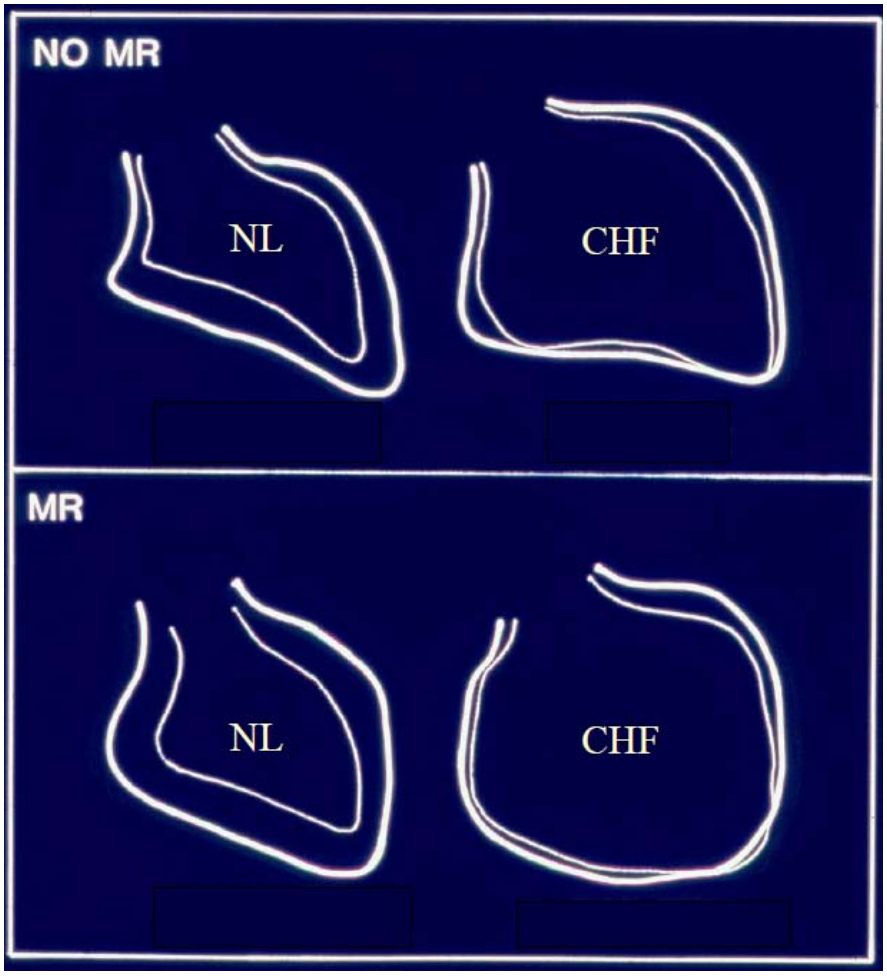
Sustained Increase LV Wall Stress

Sustained Increase MVO_2

Progressive LV Dysfunction

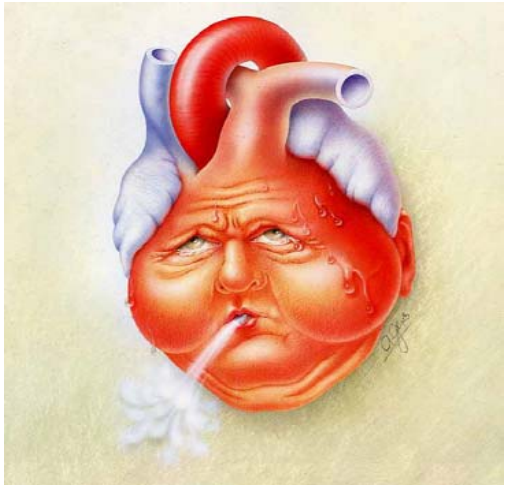

Cardiomyocyte Injury and/or Loss
Global LV Remodeling
Chamber Dilation
Chamber Sphericity
Electrical Remodeling
AP Duration
AP Dispersion
Cellular Remodeling
Hypertrophy
Reactive Fibrosis
Molecular Remodeling
Transcription
Translation
Cardiomyocyte Injury and/or Loss
Progressive LV Dysfunction

Increased LV sphericity



- **LV dilation + Sphericity**
  - **Higher wall stress**
  - **Higher MVO_2**
  - **Abnormal distribution of fiber shortening**
  - **Greater blunted response to exogenous catecholamines**
- **And associated with**
  - **Functional MR**
  - **Lower exercise capacity**
  - **Higher CHF score**
  - **Worse long-term survival**

심부전의 치료

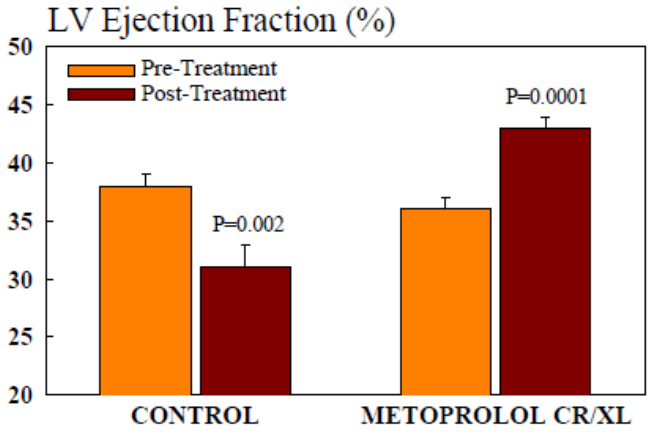


Reverse Remodeling - Recovery

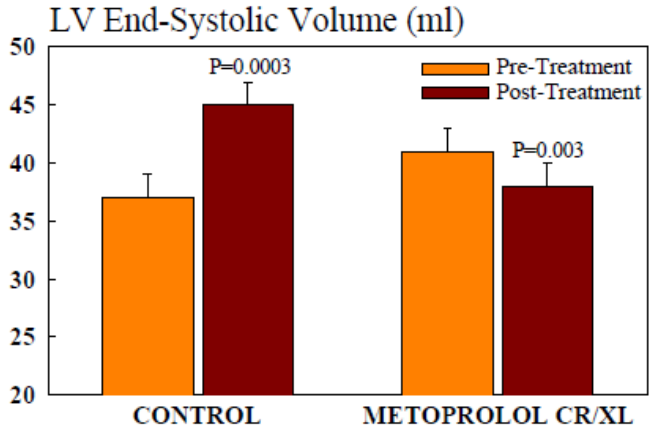
- **Anti-remodeling drugs**
- **Device**
- **LVAD**
- **Sugical**
- **Cell therapy**

Reverse Remodeling - Recovery

Metoprolol CR/XL in Dogs With Heart Failure



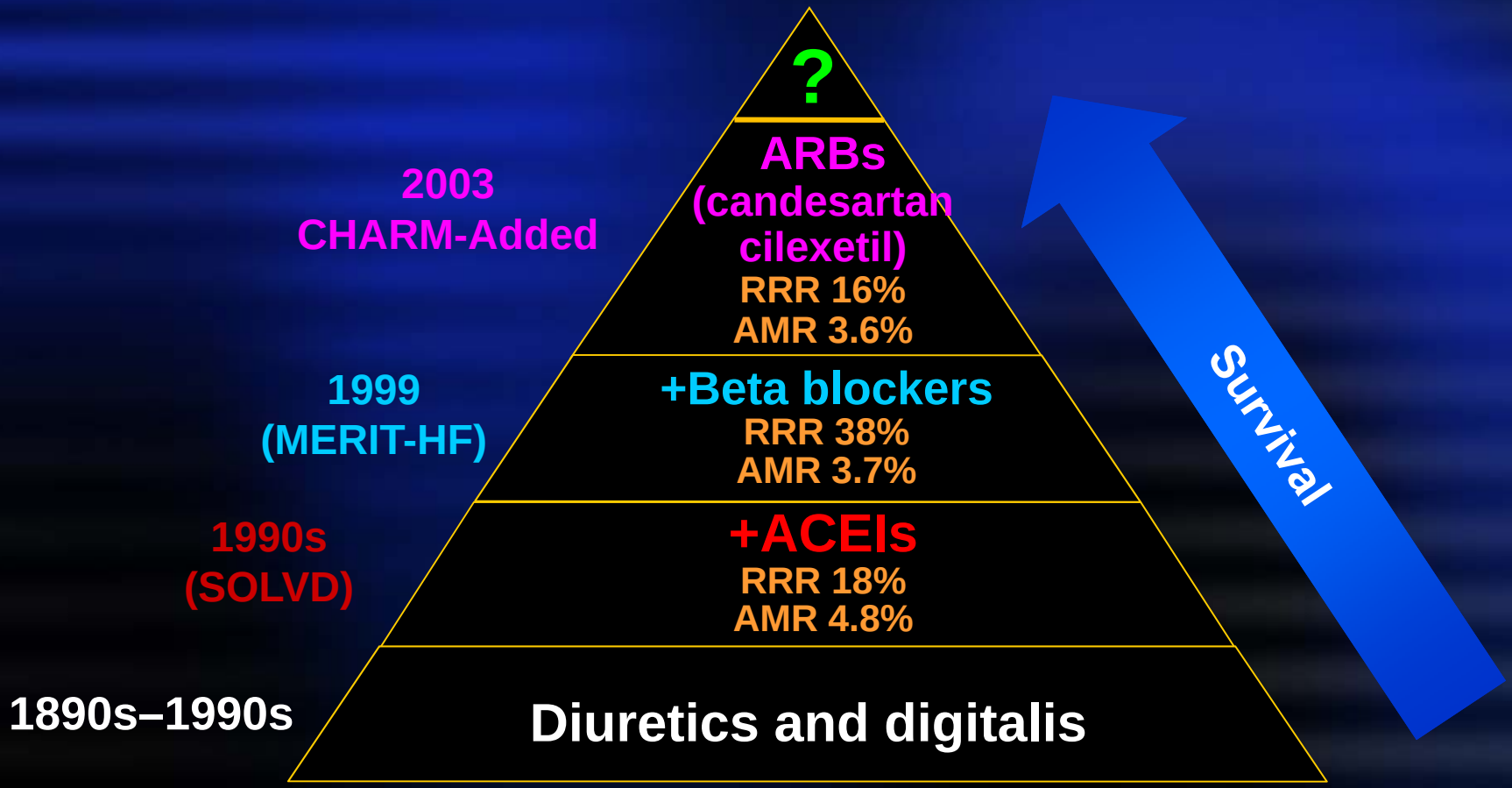
Metoprolol CR/XL in Dogs With Heart Failure



	Normal	HF-Control	HF + Metoprolol
VFIF (%)	3.7 ± 0.1	14.2 ± 0.8*	9.7 ± 0.3†
Cap/cell	1.0 ± 0.0	0.89 ± 0.04*	1.08 ± 0.0†
ODD (μm)	8.9 ± 0.2	11.9 ± 0.2*	10.3 ± 0.3†
MCSA (μm^2)	409 ± 10	687 ± 26*	561 ± 4†

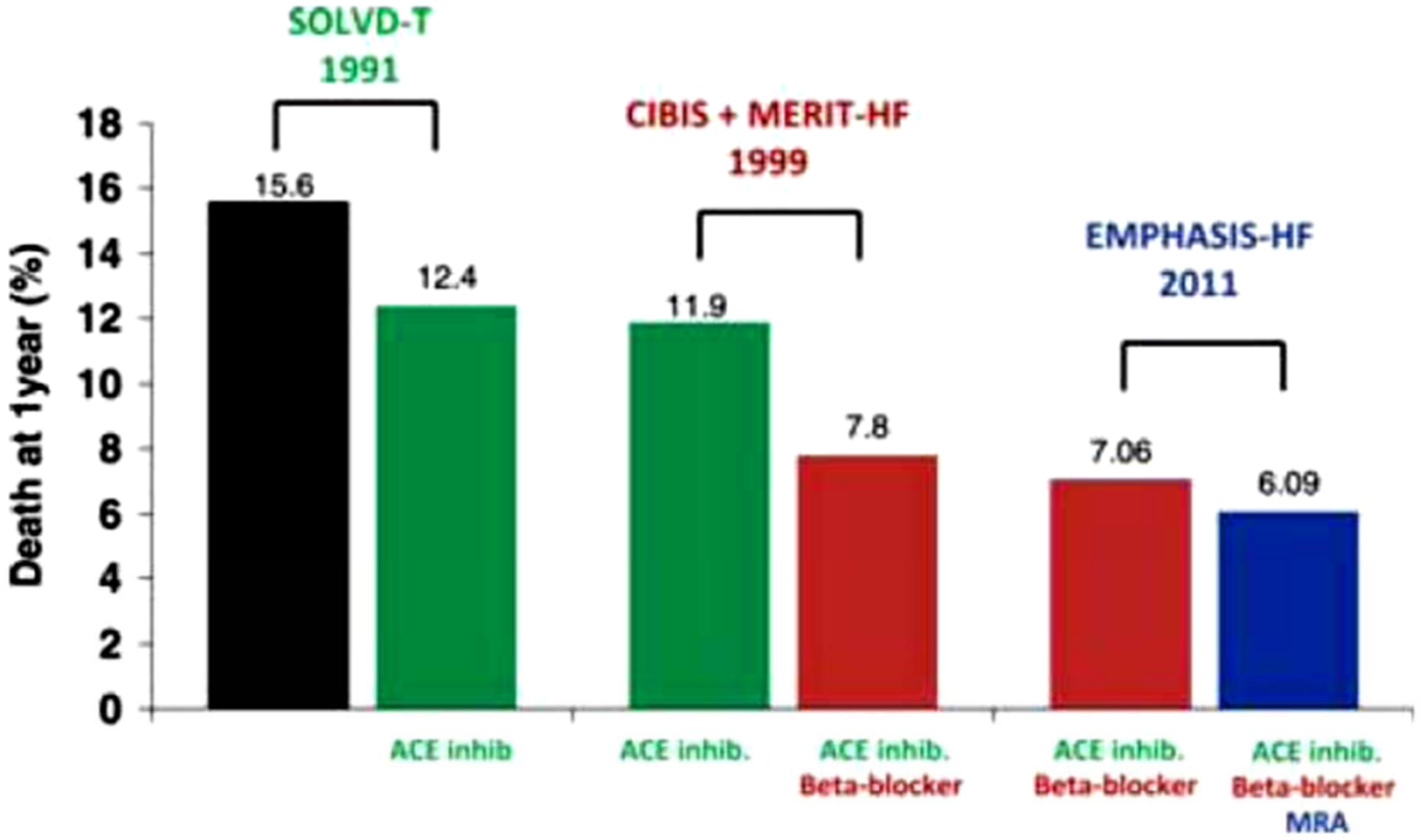
**=p<0.05 vs. Normal; †=p<0.05 vs. HF-Control*

Historical Advances in Heart Failure Treatment

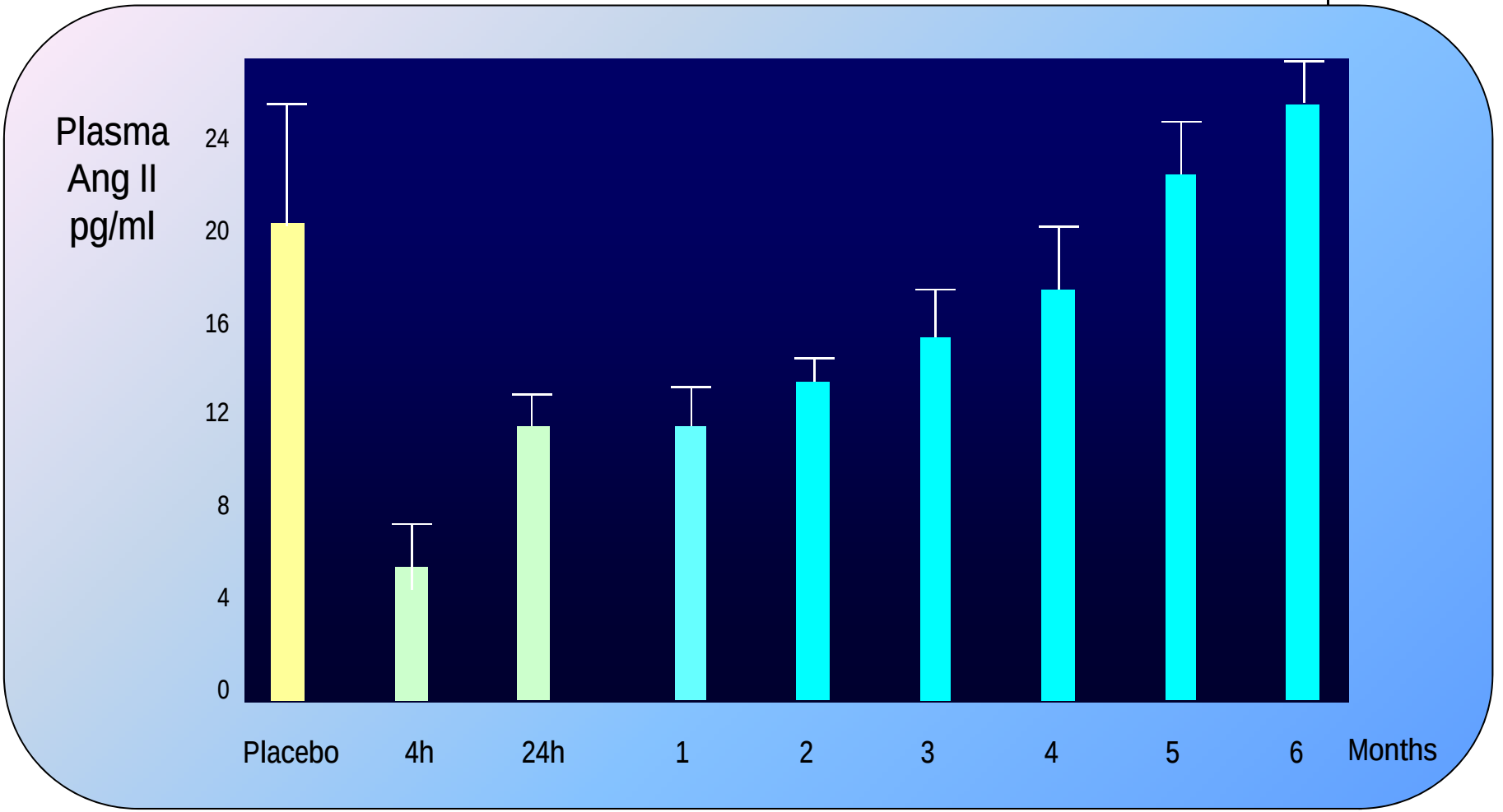


McMurray JJV. *Lancet* 2003;362 (9386):777-81
MERIT-HF Study Group. *Lancet* 1999;353(9169):2001-7
SOLVD Investigators. *N Engl J Med* 1991;325(5):293-302

Drugs for HF treatment

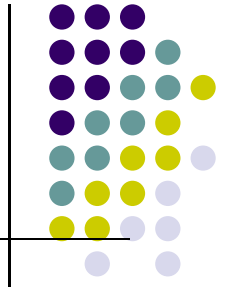


ACE escape



Biollaz et al. J Cardiovasc Pharmacol 1982:4:966

Aldosterone Breakthrough During ARB

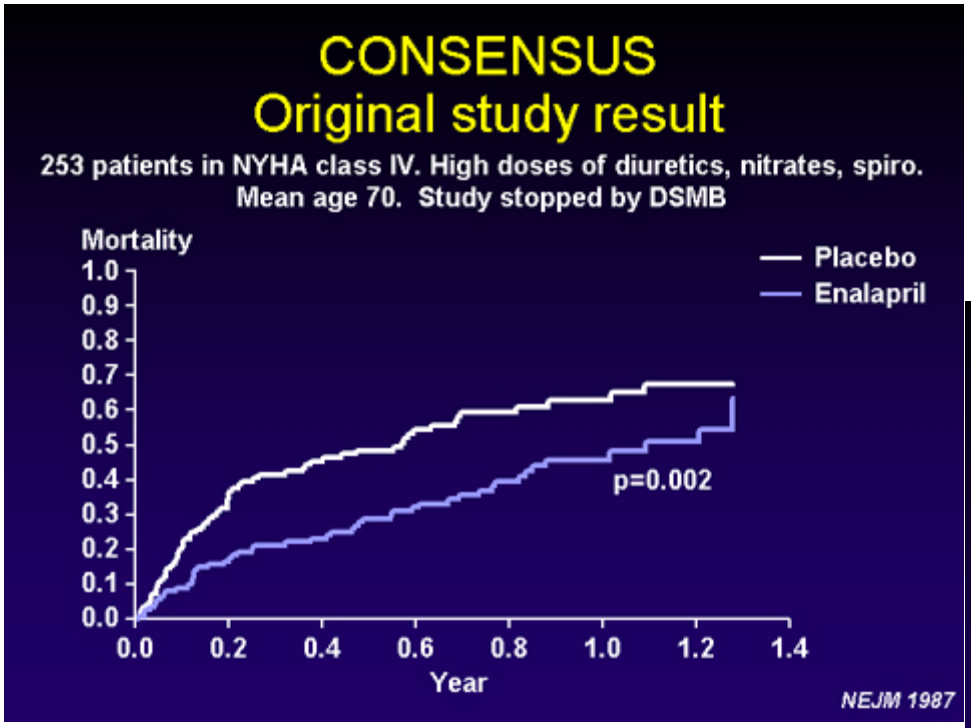


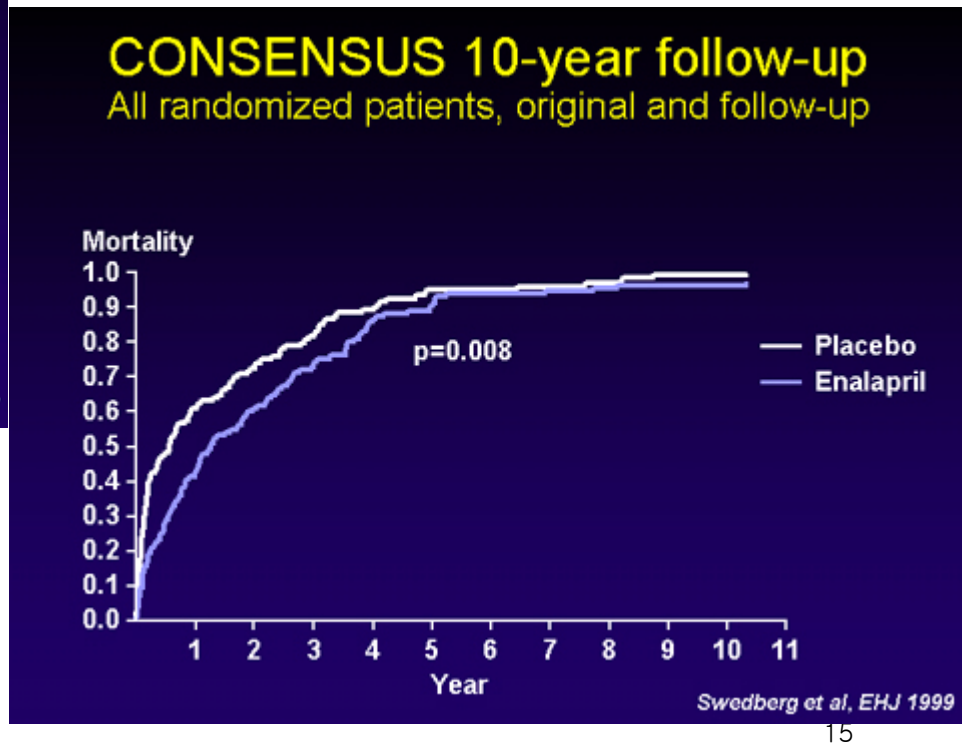
	Before	3 Months	6 Months	12 Months	15 Months
SBP (mm Hg)	163 ± 15	132 ± 13*	128 ± 12*	124 ± 11*	125 ± 11*
DBP (mm Hg)	87 ± 8	76 ± 7*	77 ± 4	73 ± 4	77 ± 6
HR (beats/min)	74 ± 5	74 ± 5	75 ± 5	73 ± 4	78 ± 4
PRA (ng/mL · h)	1.1 ± 0.4	2.5 ± 0.6*	2.5 ± 0.8*	2.8 ± 0.7*	2.6 ± 0.7*
PAC (pg/mL)	98 ± 7.8	69 ± 8.9*	72 ± 7.4*	71 ± 9.4*	80 ± 8.9*
HbA1c (%)	6.8 ± 0.7	6.6 ± 0.8	6.7 ± 0.6	6.7 ± 0.8	6.8 ± 0.6
Serum K (mEq/L)	4.5 ± 0.5	4.6 ± 0.8	4.6 ± 0.9	4.5 ± 0.7	4.6 ± 0.7

Characteristic	Breakthrough (+)	Breakthrough (−)
Number (men/women)	21 (11/10)	74 (36/38)
Age (y)	63 ± 11	61 ± 10
SBP (mm Hg)	129 ± 15	132 ± 15
DBP (mm Hg)	74 ± 6	76 ± 8
Na (mEq/L)	143 ± 1.8	142 ± 2.1
K (mEq/L)	4.5 ± 0.5	4.6 ± 0.8
BUN (mg/dL)	16 ± 2.1	17 ± 2.7
Cr (mg/dL)	1.0 ± 0.3	0.9 ± 0.3
FPG (mg/dL)	129 ± 22	131 ± 28
HbA_{1c} (%)	6.8 ± 0.5	6.9 ± 0.7
Urinary Na excretion (mEq/day)	159 ± 42	152 ± 66
Urinary K excretion (mEq/day)	43 ± 10	42 ± 15
PRA (ng/mL · h)	2.4 ± 0.9	2.6 ± 1.0
PAC (pg/mL)	111 ± 10	71 ± 7.4*
24-h Ccr	72 ± 21	78 ± 20

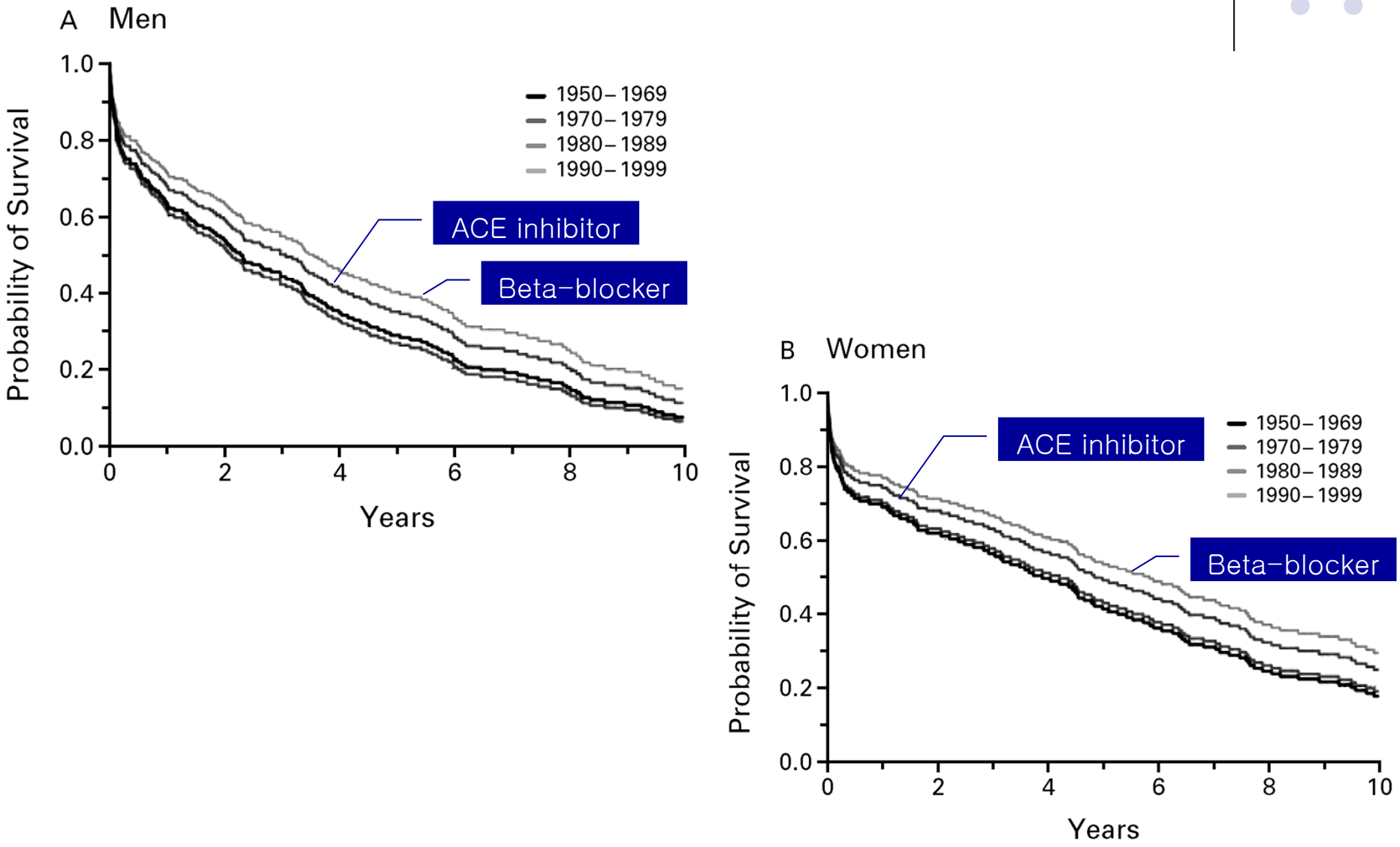
Yoneda T et al. *AJH 2007; 20:1329–1333*

Ceiling effect of ACEI



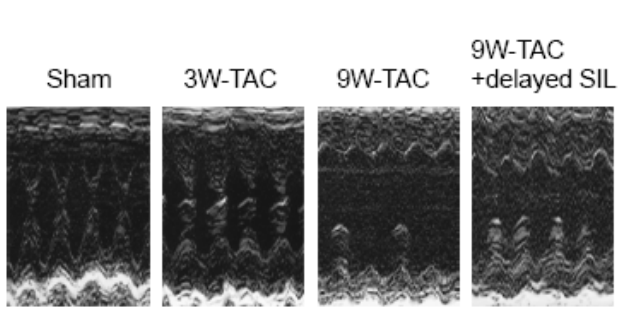


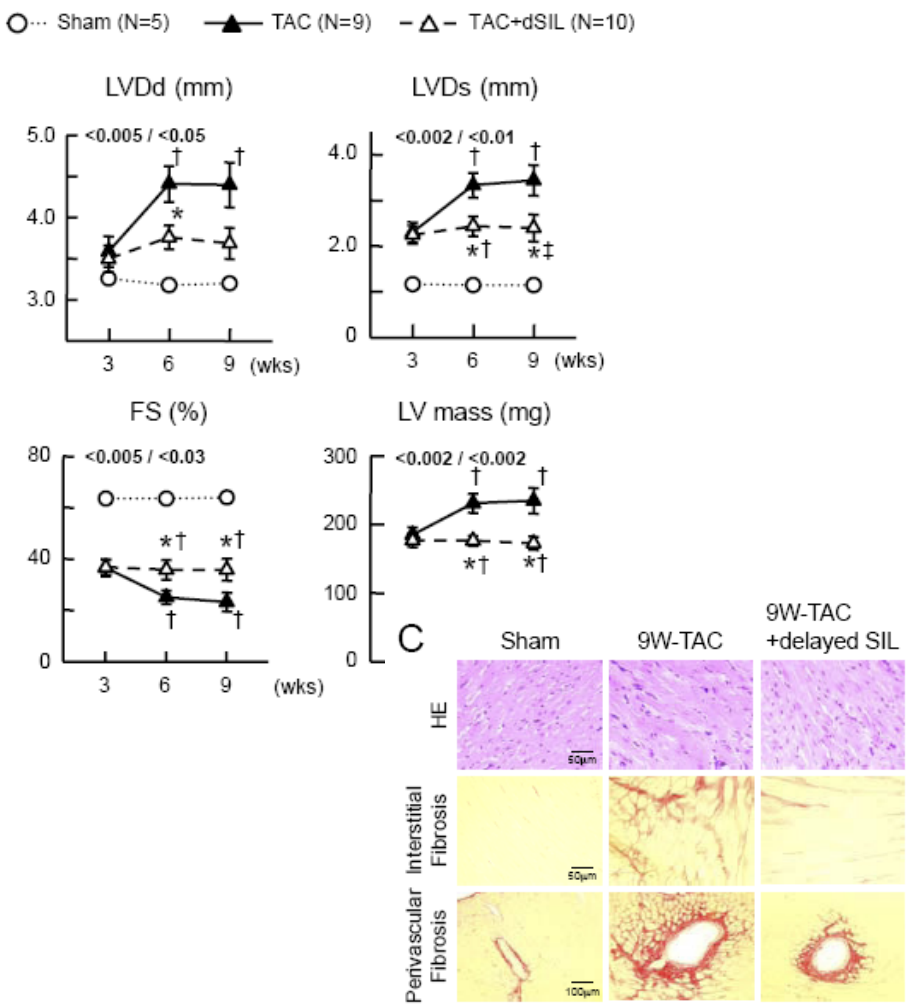
Age-adjusted survival of CHF



Drug's trials

- **phosphodiesterase type 5A (PDE5A) inhibition**
- **recombinant human relaxin-2**

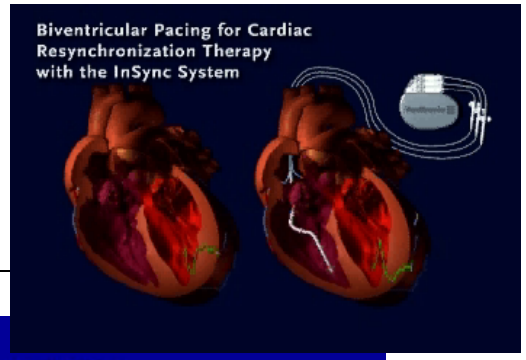


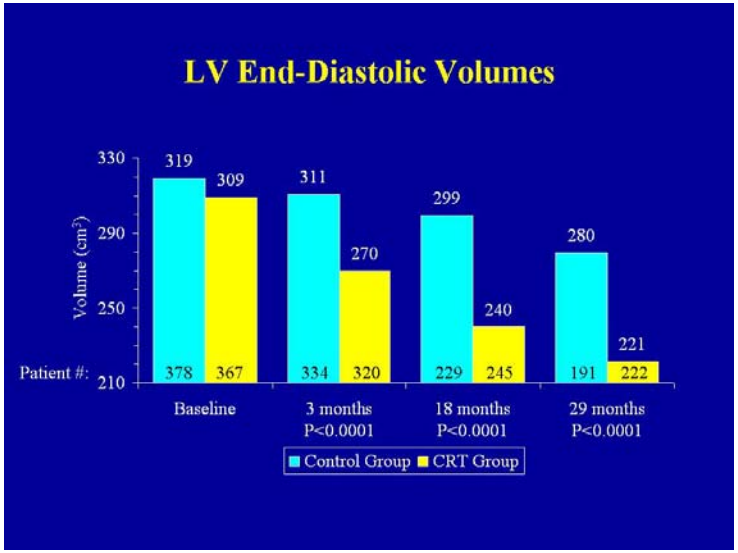


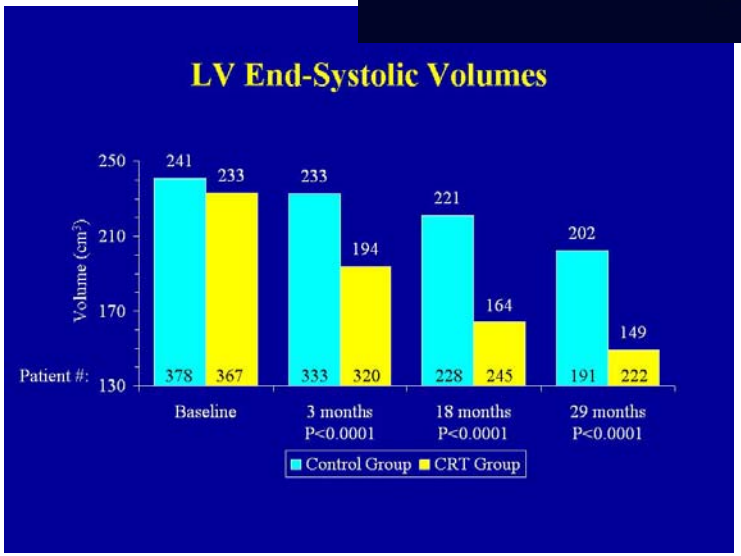
Reverse Remodeling - Recovery

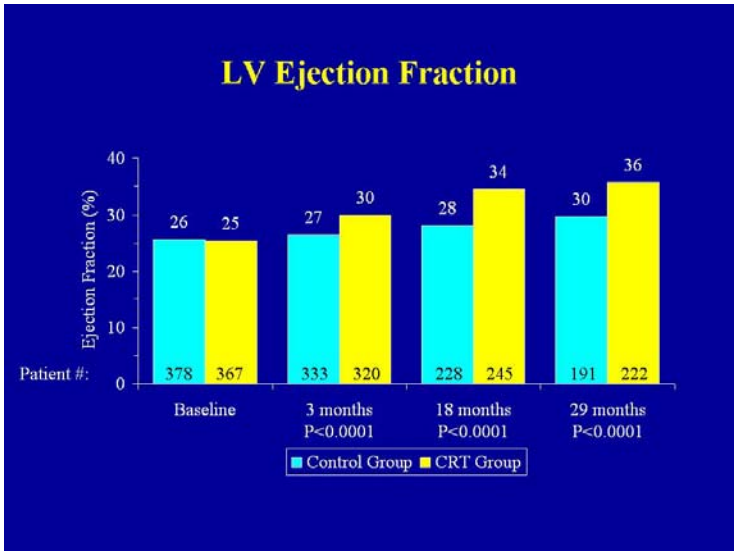
- **Anti-remodeling drugs**
- **Device**
- **LVAD**
- **Sugical**
- **Cell therapy**

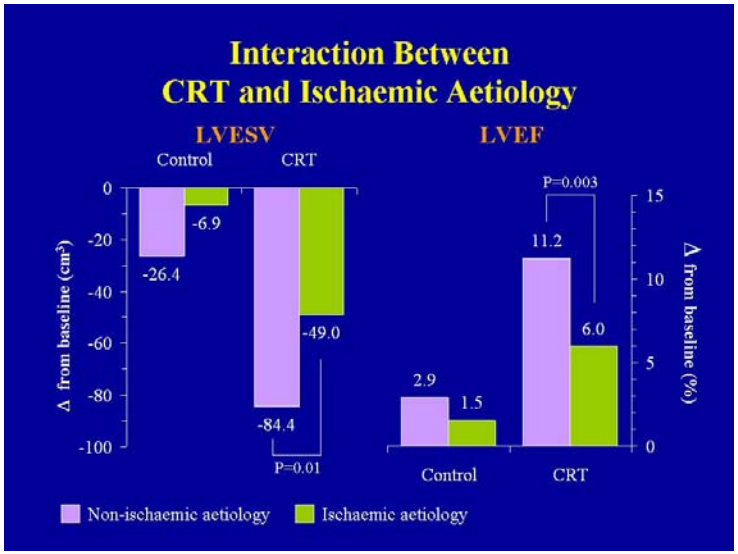
Reverse remodeling effects of CRT



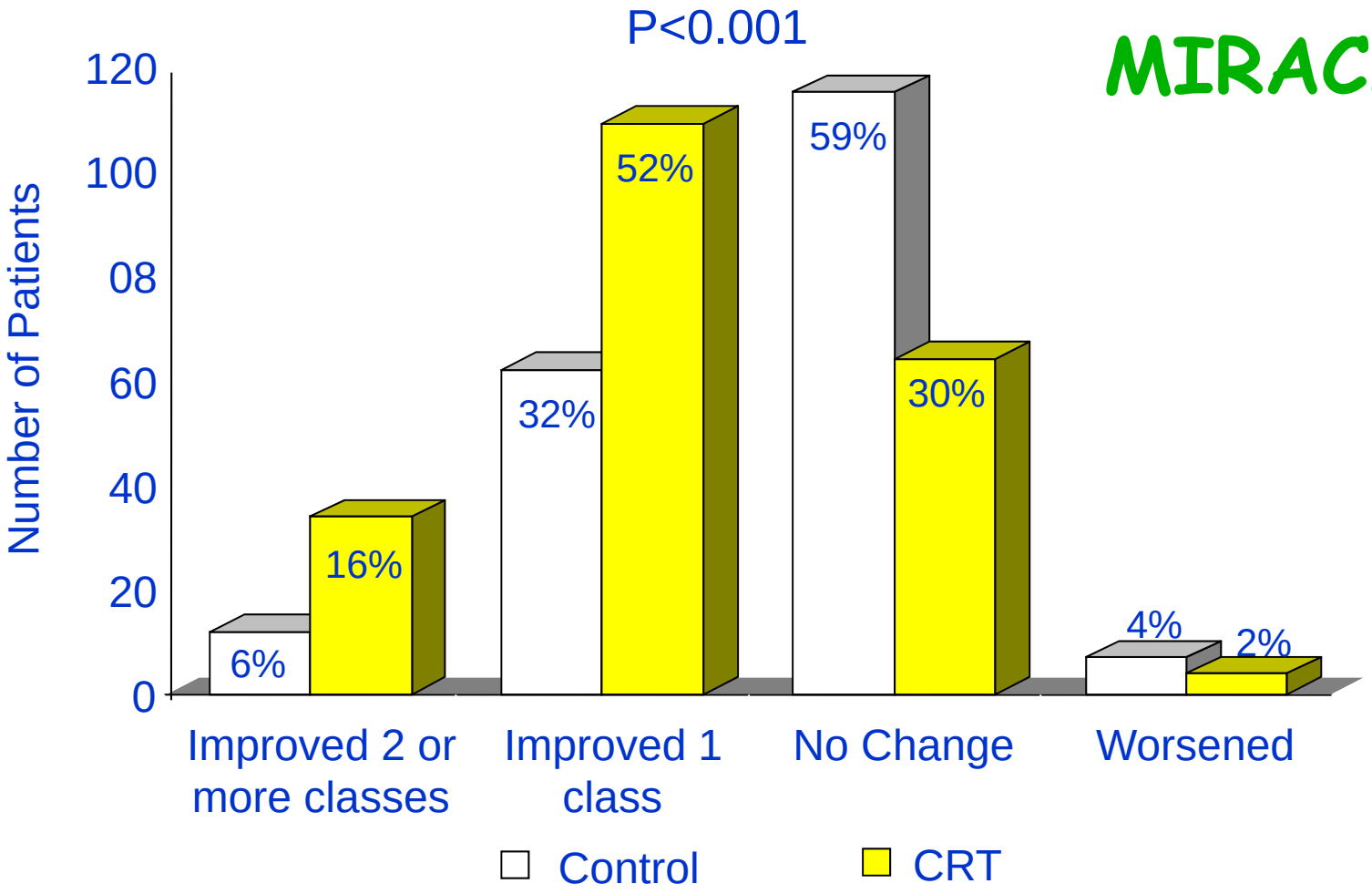






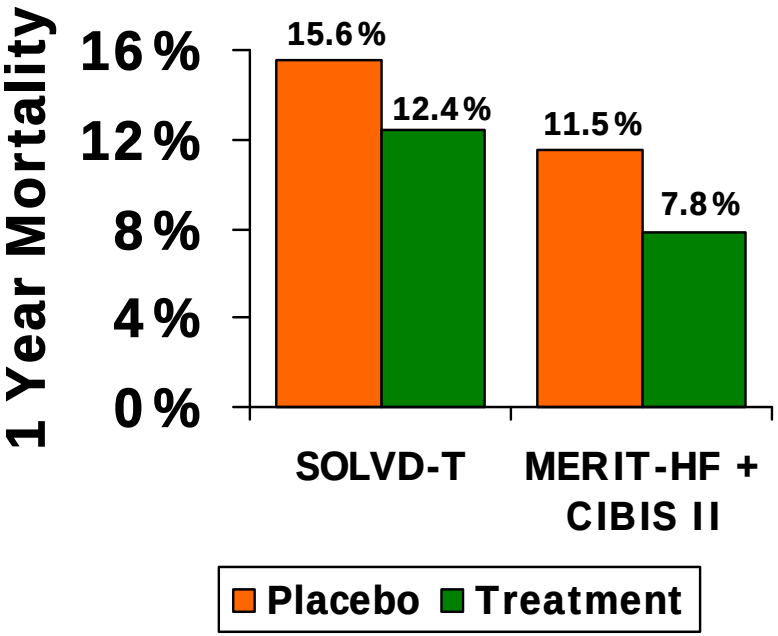


Clinical Responders to CRT

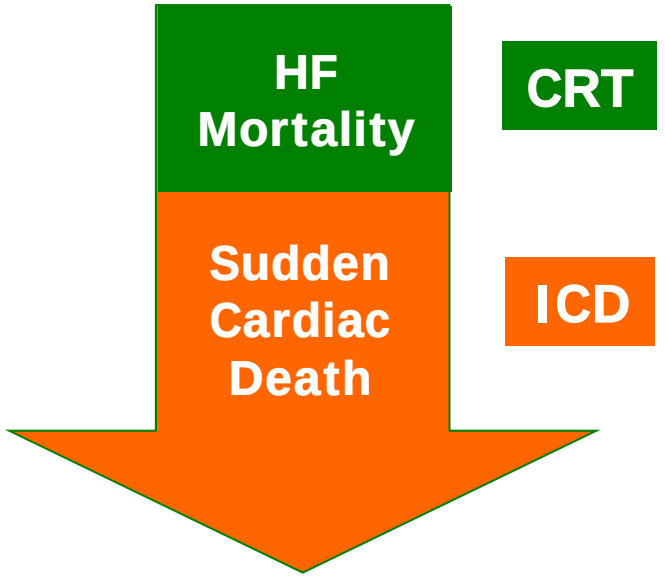


Reduced Mortality in HF

ACE-I & Beta Blockade Reduce Mortality

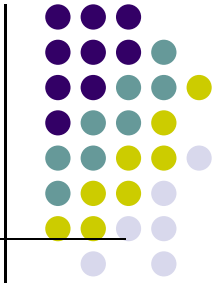


Further Reduction with CRT + ICD for Higher Risk Patients



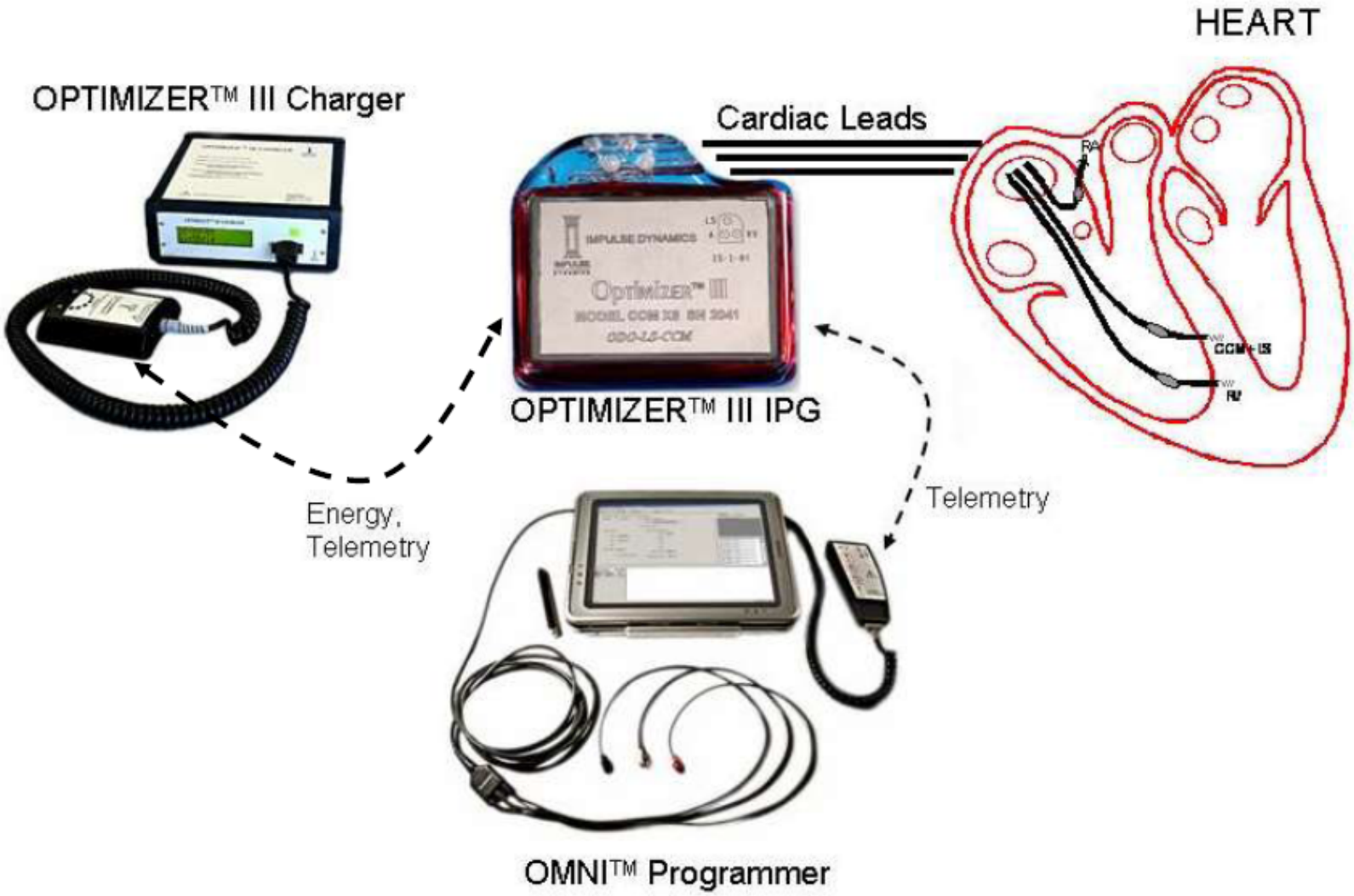
Patient selection criteria

Devices for HF management



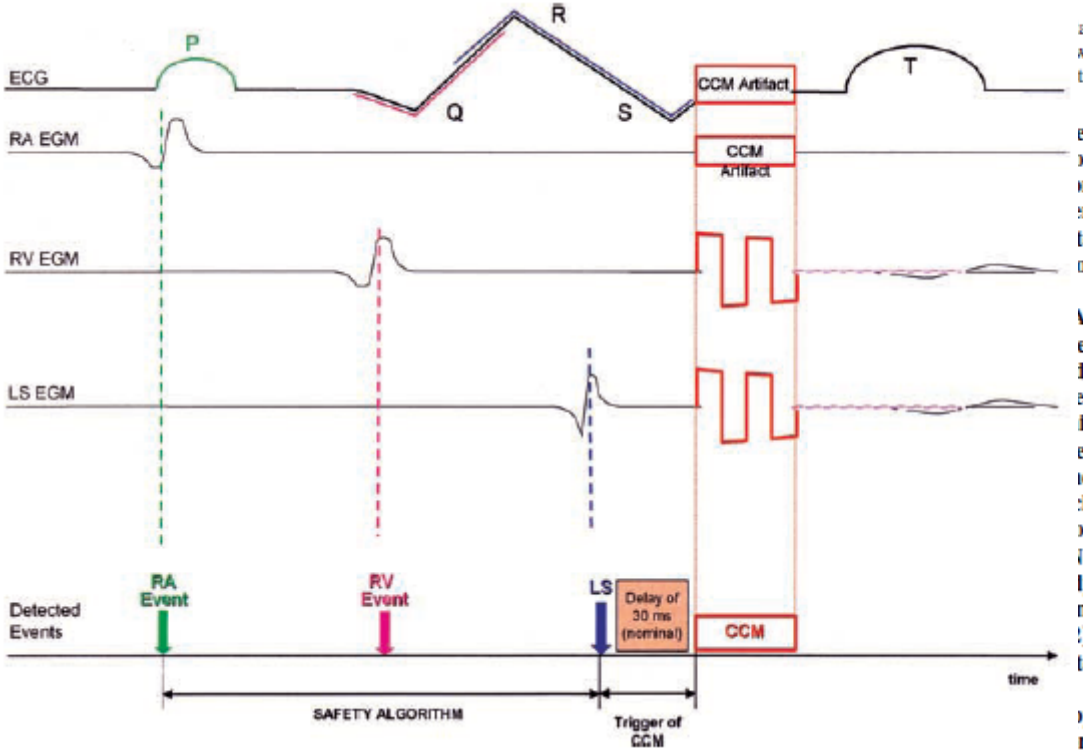
- Monitoring device
  - Implantable hemodynamic monitor (IHM)
  - Pulmonary artery pressure monitoring device
  - LA pressure monitoring
- **Therapeutic device**
  - Implantable cardiac defibrillator (ICD)
  - Cardiac resynchronization therapy (CRT)
  - **Cardiac contractility modulation (CCM)**
  - **Vagal nerve stimulation**
  - **Transvenous phrenic nerve stimulation for CSA**
  - Mechanical circulatory support (MCS)
    - Ventricular assist device (VAD)
    - Total artificial heart (TAH)

CCM : Optimizer III system



First Human Chronic Experience with Cardiac Contractility Modulation by Nonexcitatory Electrical Currents for Treating Systolic Heart Failure: Mid-Term Safety and Efficacy Results from a Multicenter Study

CARLO PAPPONE, M.D., PH.D., GIUSEPPE AUGELLO, M.D.,
SALVATORE ROSANIO, M.D., PH.D., GABRIELE VICEDOMINI, M.D.,
VINCENZO SANTINELLI, M.D., MASSIMO ROMANO, M.D., EUSTACHIO AGRICOLA, M.D.,
FRANCESCO MAGGI, D.SC., GERHARD BUCHMAYR, D.SC.,‡ GIOVANNI MORETTI,‡
YUVAL MIKA, D.SC.,* SHLOMO A. BEN-HAIM, M.D., PH.D.,† MICHAEL WOLZT, M.D.,‡
GUENTER STIX, M.D.,‡ and HERWIG SCHMIDINGER, M.D.‡

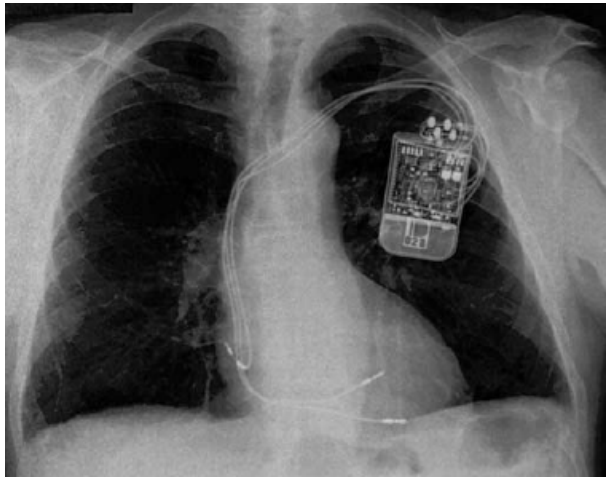


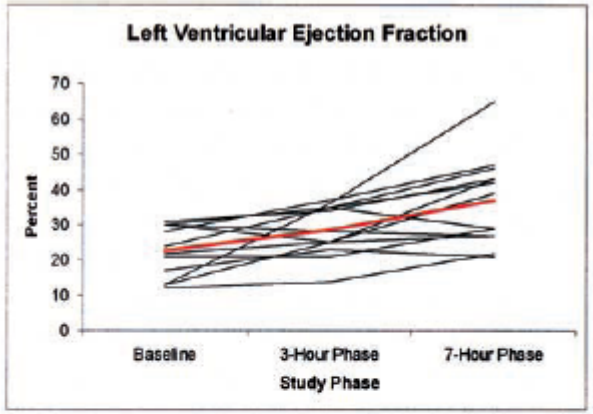
mance, symptoms, and functional status. CCM therapy for 7 hours per day is associated with greater dispersion near the mean, emphasizing the need to individually tailor CCM delivery duration. The technique appears to be attractive as an additive treatment for severe HF. Controlled randomized studies are needed to validate this novel concept. *(J Cardiovasc Electrophysiol, Vol. 15, pp. 418-427, April 2004)*

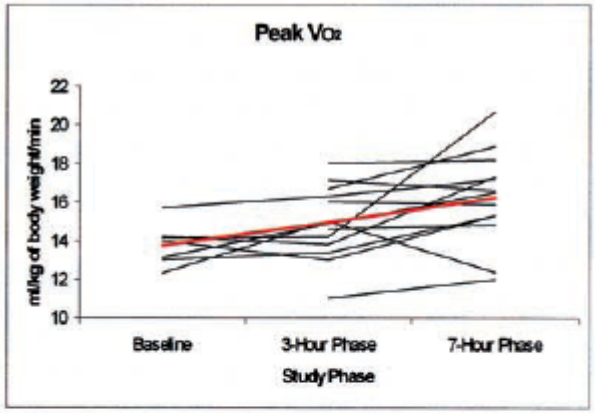
n=13
NYHA FC III
LVEF 23%
Peak VO2 13.8
QRSD <140 ms
Optimal Tx >3 months

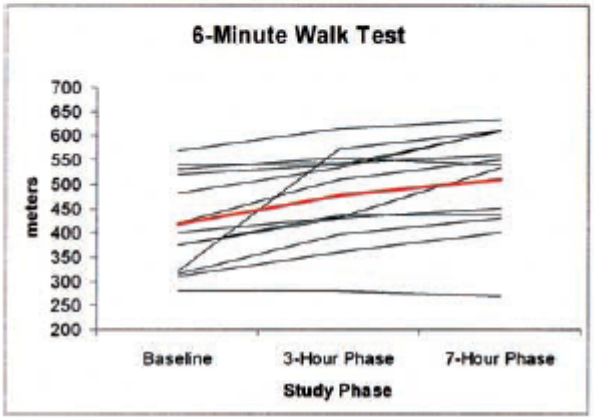
3 hr daily over 8 weeks
7 hr daily over 24weejs

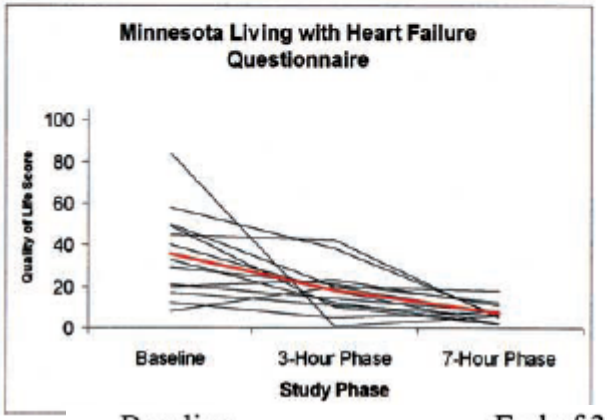
5.8 – 7.7 V

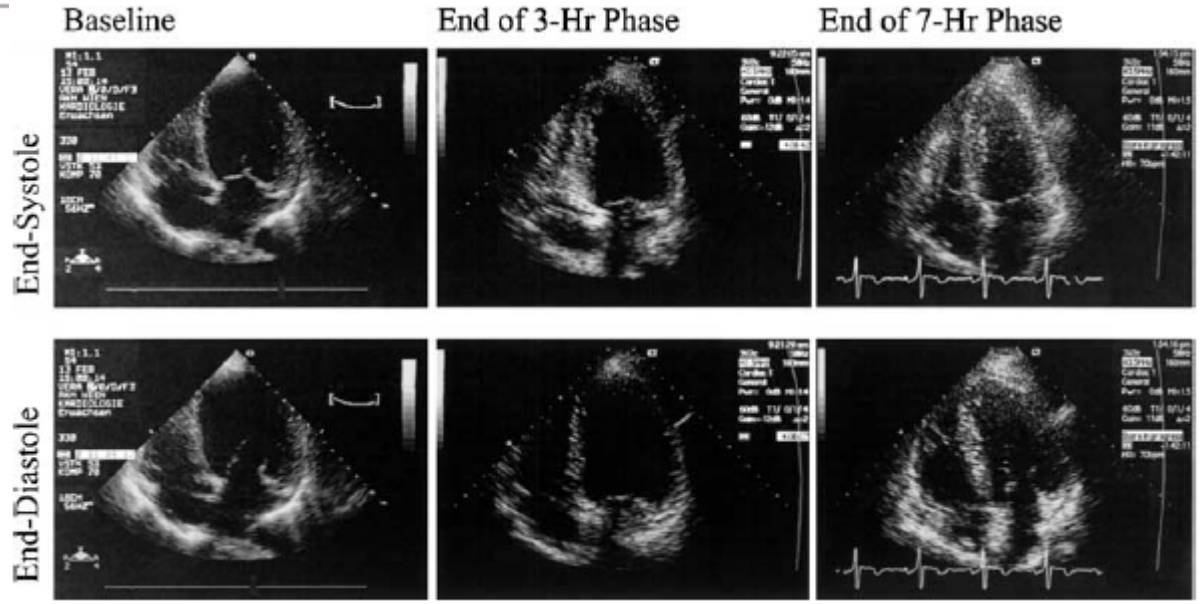



Left Ventricular Ejection Fraction
Percent
70
60
50
40
30
20
10
0
Baseline
3-Hour Phase
7-Hour Phase
Study Phase

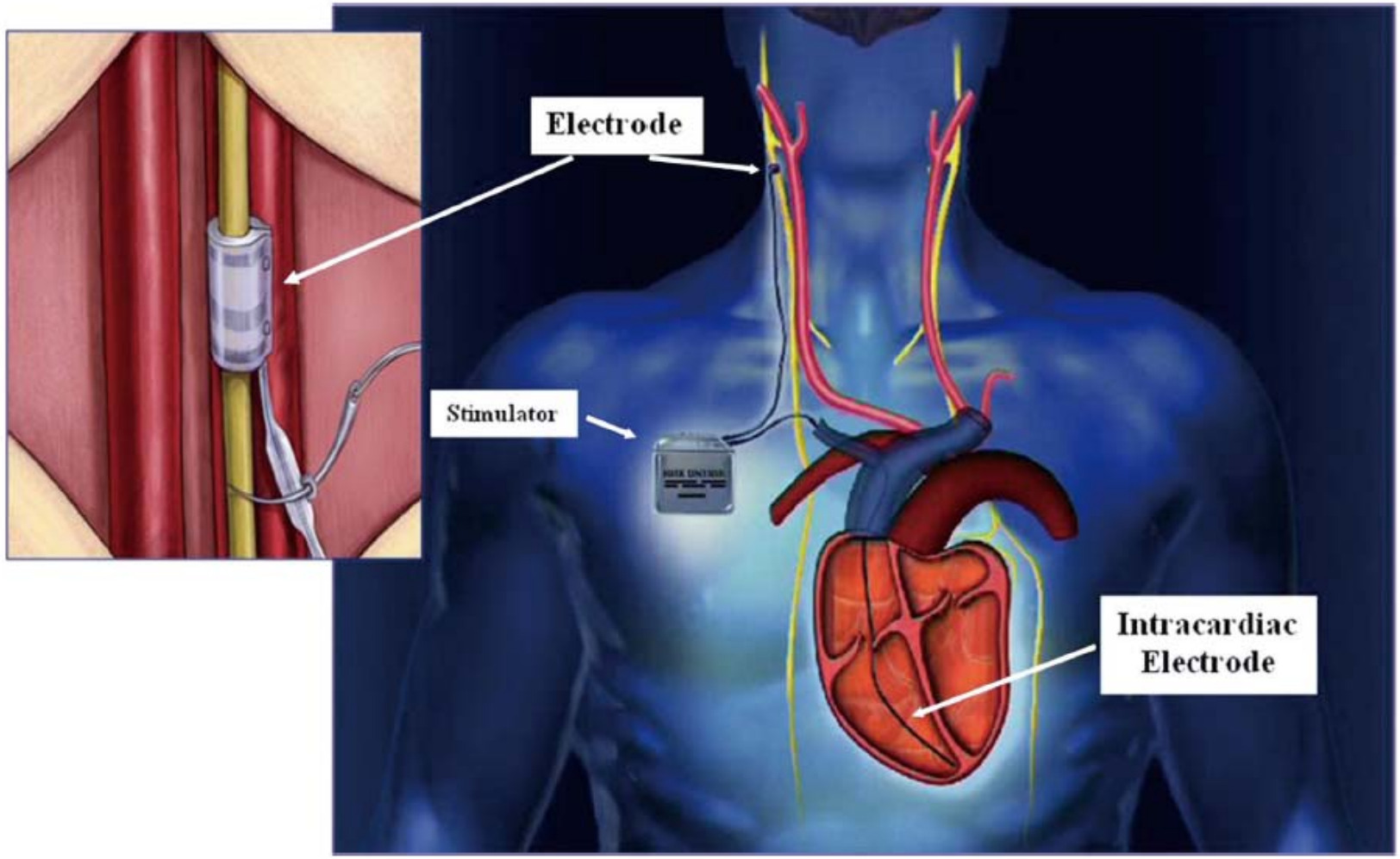

Peak Vo2
ml/kg of body weight/min
22
20
18
16
14
12
10
Baseline
3-Hour Phase
7-Hour Phase
Study Phase


6-Minute Walk Test
meters
700
650
600
550
500
450
400
350
300
250
200
Baseline
3-Hour Phase
7-Hour Phase
Study Phase

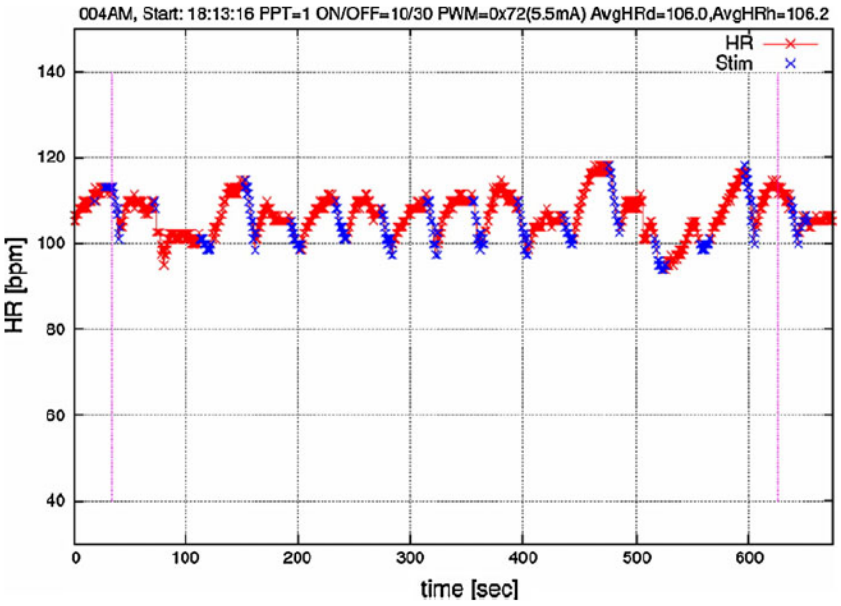

Minnesota Living with Heart Failure Questionnaire
Quality of Life Score
100
80
60
40
20
0
Baseline
3-Hour Phase
7-Hour Phase
Study Phase

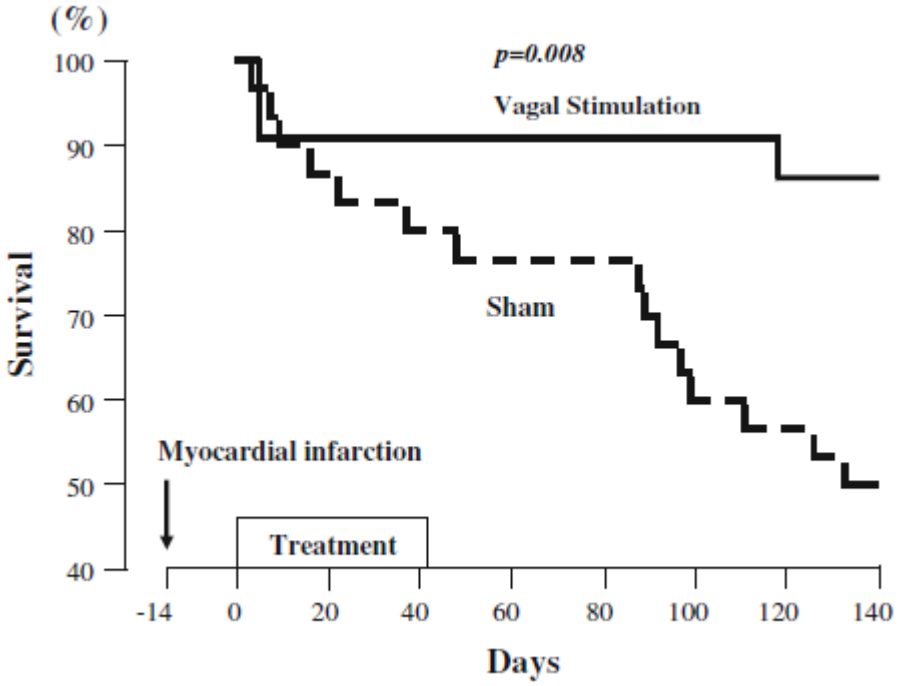

Baseline
End of 3-Hr Phase
End of 7-Hr Phase
End-Systole
End-Diastole

Vagal nerve stimulation

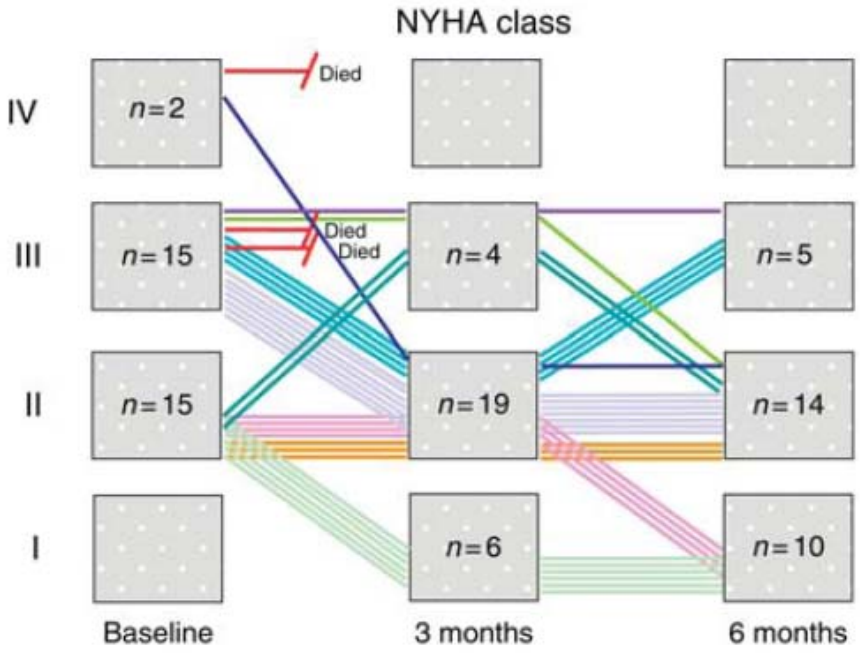


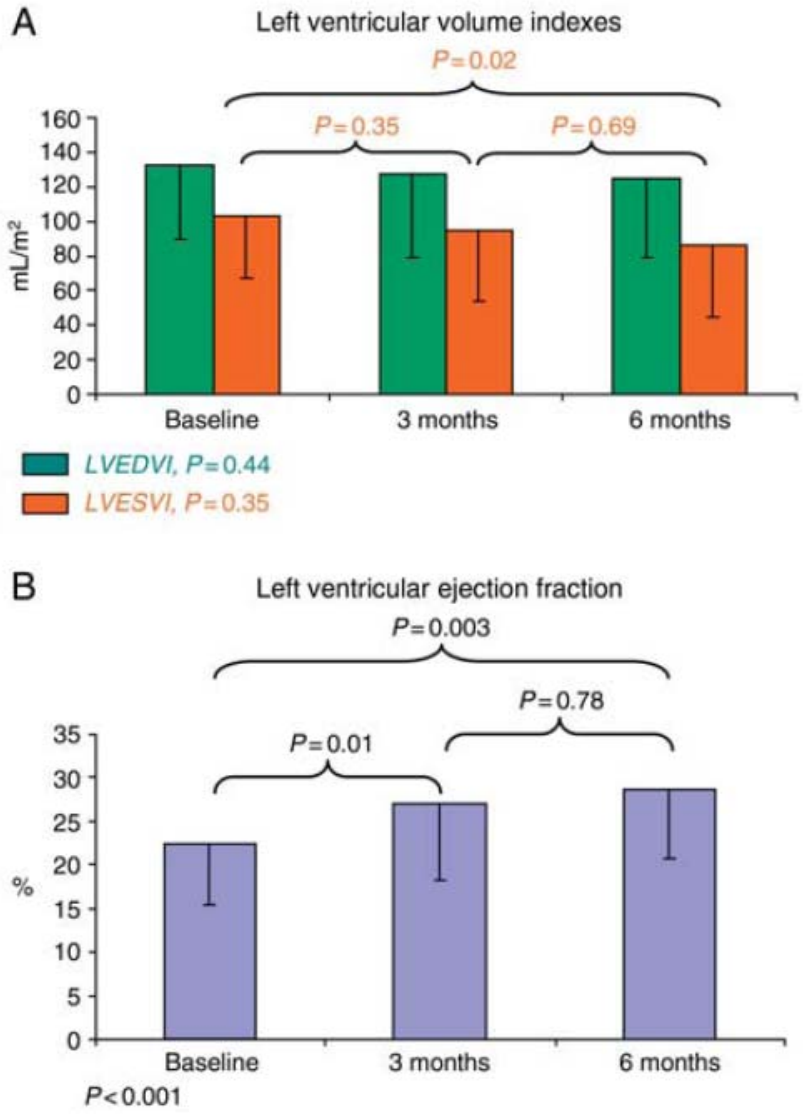
Vagal nerve stimulation



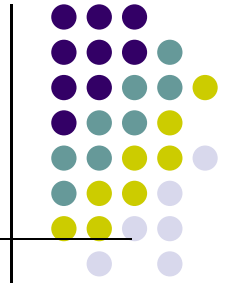


Vagal nerve stimulation





Effects of VBS



- **HR ↓**
- **Rate-independent effects**
  - **Anti-apoptotic**
  - **NO ↑**
  - **Ischemia/reperfusion injury ↓**
  - **Anti-inflammatory**
  - **Anti-arrhythmic**

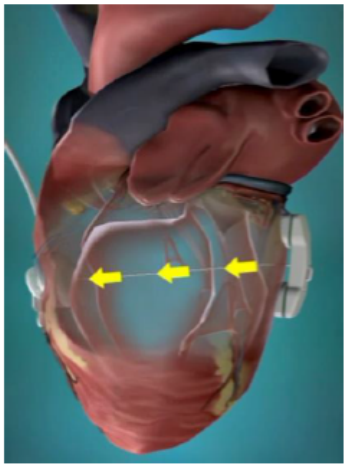
Annular & Ventricular Remodeling

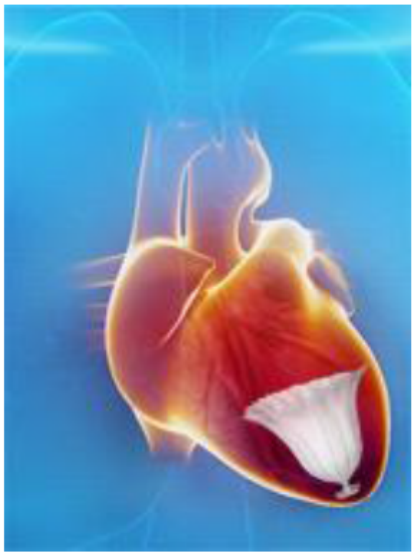
Direct Annuloplasty

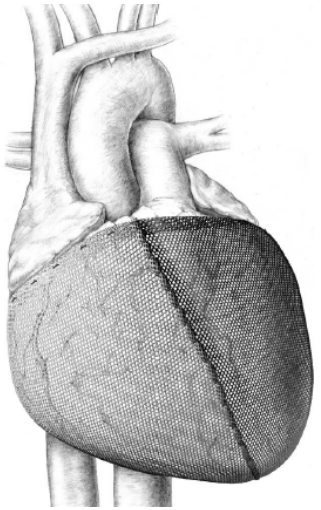
- Mitralign
- ValtechCardio
- GDS

LV remodeling

- i-Coapsys
- Bioventrix
- Parachute
- GDS

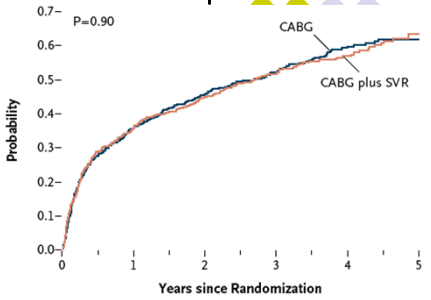


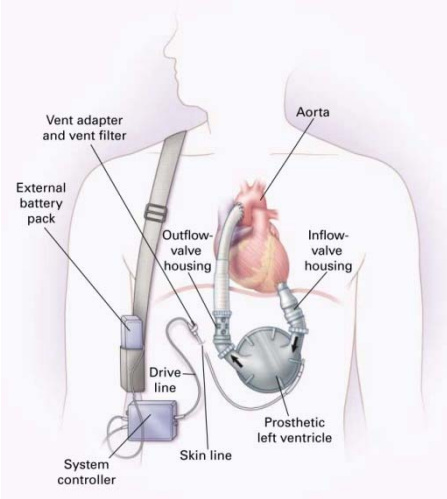


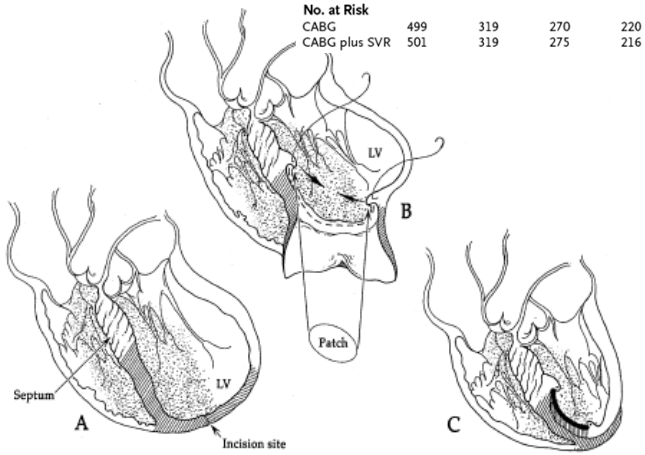


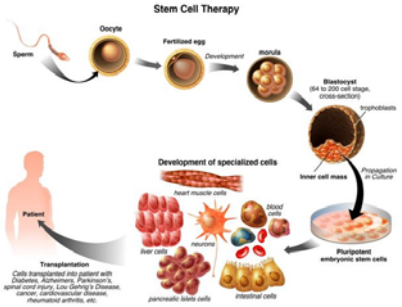
Reverse Remodeling - Recovery

- **Anti-remodeling drugs**
- **Device**
- **LVAD**
- **Sugical ventricular restoration**
- **Cell therapy**

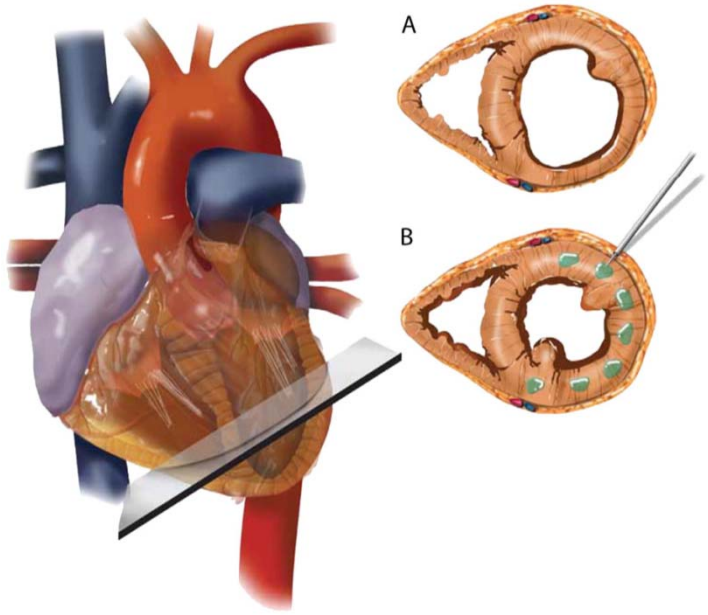








Biopolymer gel implants



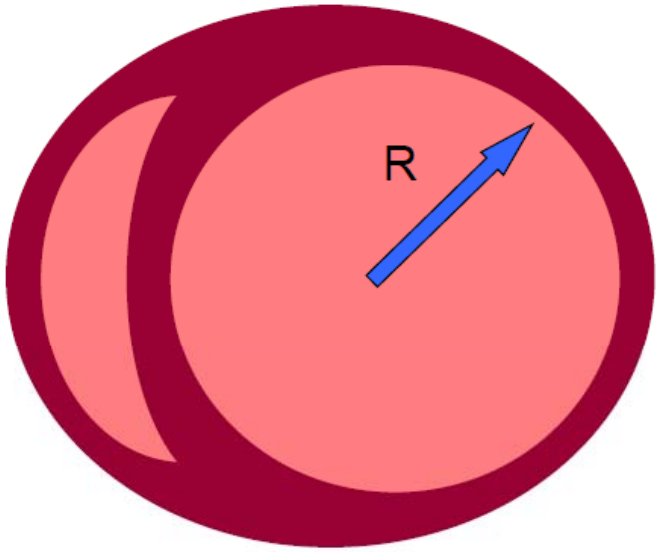
American Heart Association Scientific Sessions 2013

A Multicenter, Randomized Study Assessing the Efficacy of Left Ventricular Augmentation with Algisyl-LVR in the Treatment of Advanced Heart Failure Patients with Ischemic and Non-ischemic Cardiomyopathy: *Interim Results of the **AUGMENT-HF Study***

Douglas L Mann, Hani N Sabbah, Andy Hinson, Stefan D Anker, Andrew Coats, Randall J Lee, Gabriel Cristian, Dinu Dragomir, Enrico Pusineri, Ottavio Alfieri, Antonello Gavazzi, Benno Rensing, Maurizio Volterrani, Anthony Dart, Luca Bettari, on behalf of the AUGMENT-HF Investigators

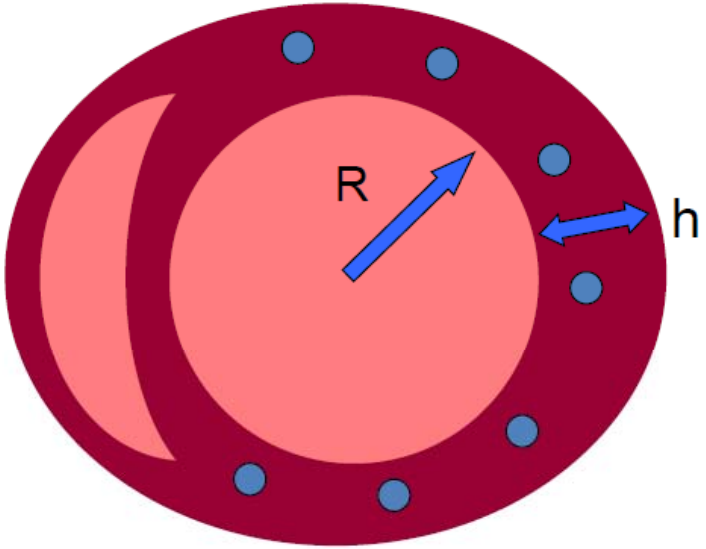
Funded by LoneStar Heart, Inc.

LV Restoration & Laplace's Law
The mechanism of the Algisyl-LVR™



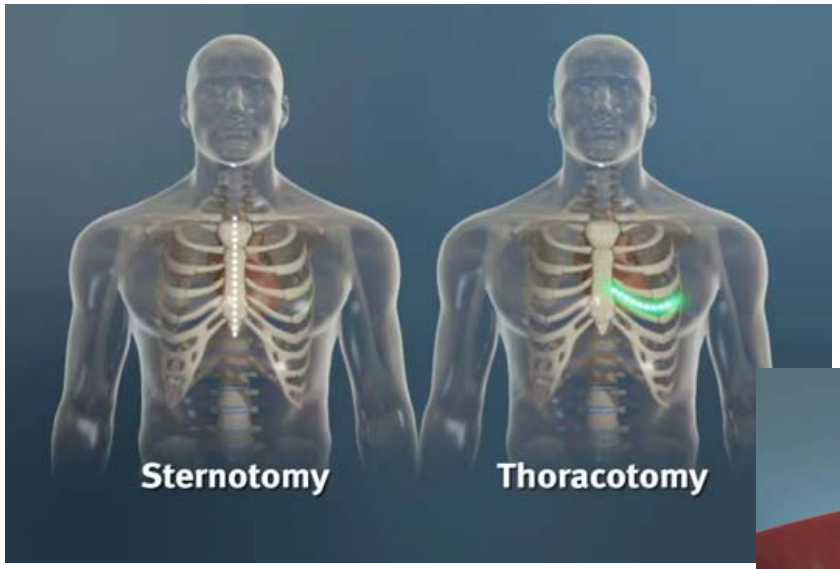
Dilated

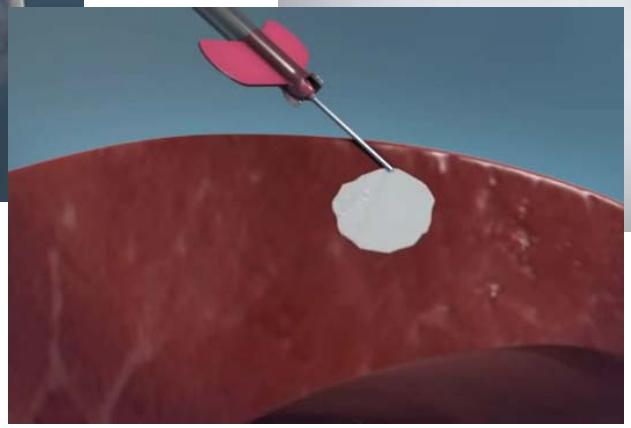
$$\sigma = \frac{P \times R}{2h}$$

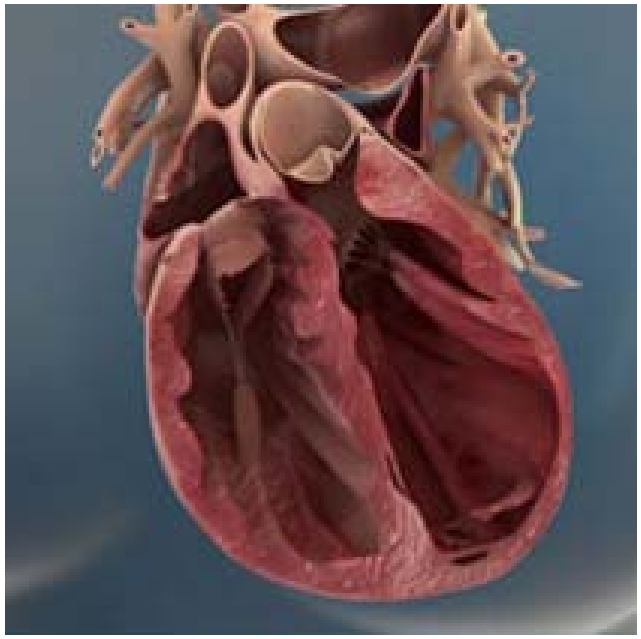


Modified (LVR)

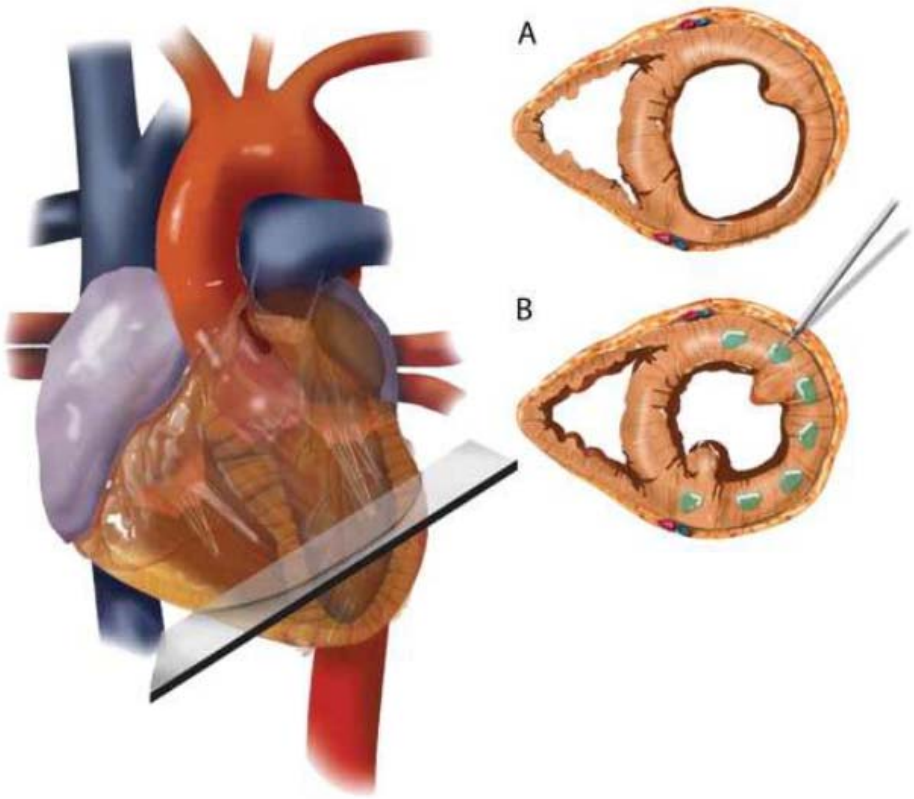
$$\sigma = \frac{P \times R}{2h}$$

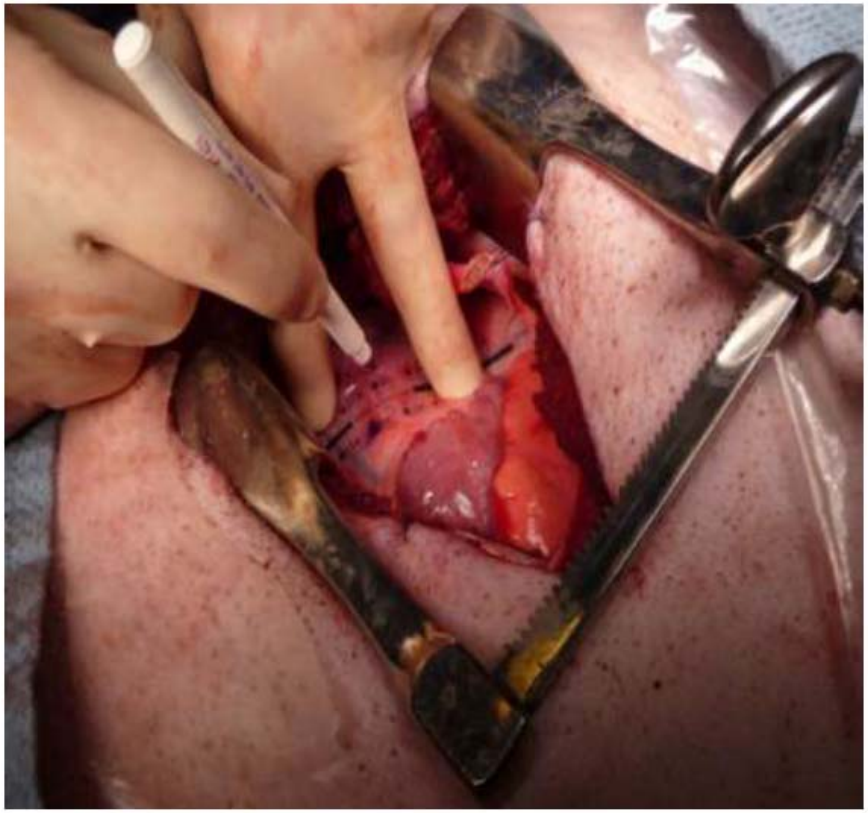

Sternotomy
Thoracotomy



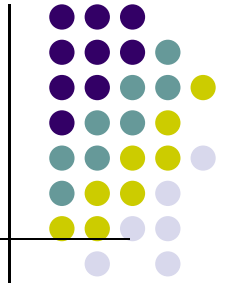


LV Restoration with Algisyl- LVR™
Placement of Alginate Hydrogel



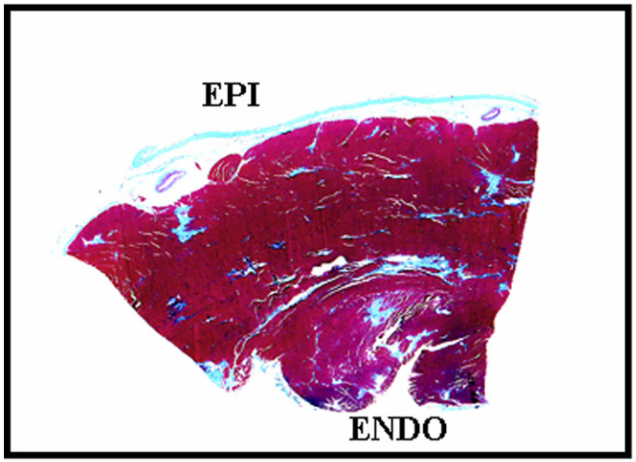


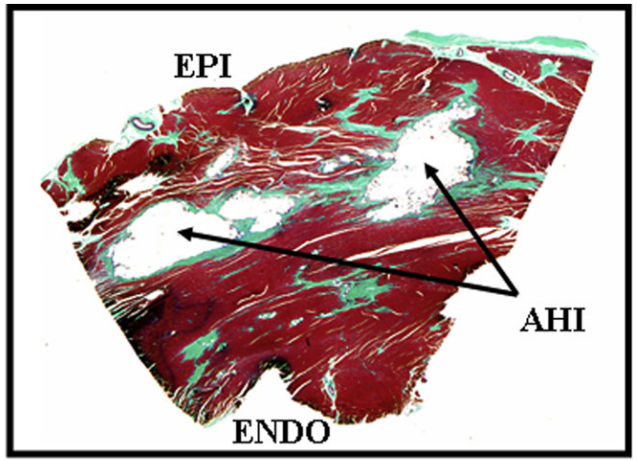
Novelty of the approach

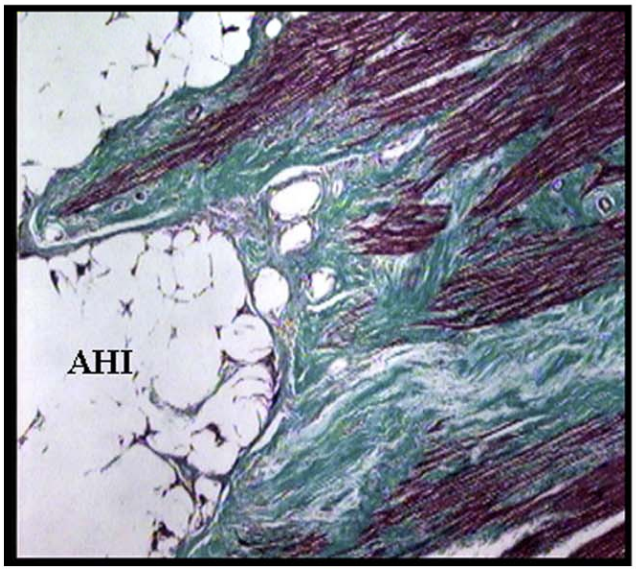


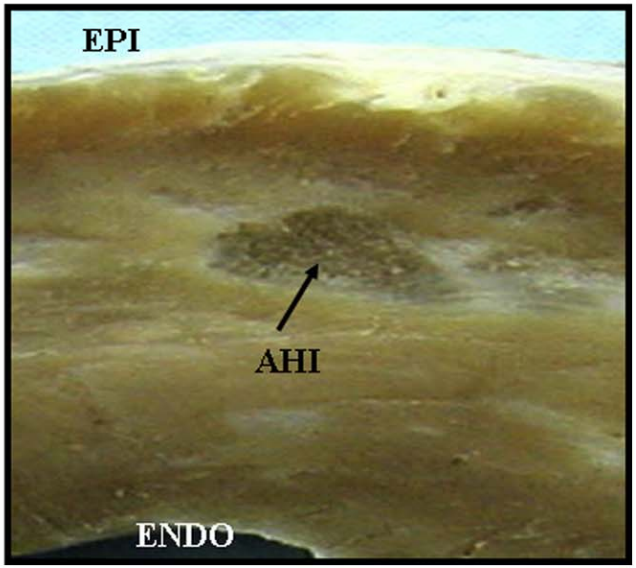
- **Alginates as new biomaterials in tissue engineering**
  - **Natural, polysaccharides found in brown seaweed**
  - **Biocompatible and inert**
  - **Injectable biomaterial during heart surgery**
  - **transition into hydrogel that will remain as cardiac implants**

Histology









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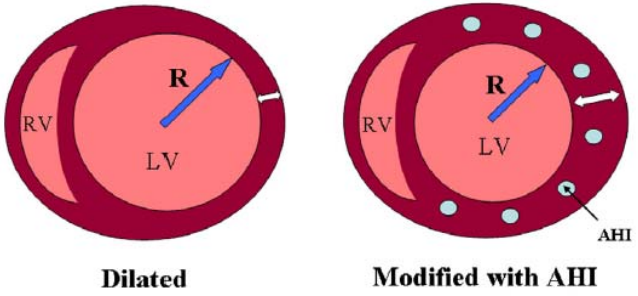
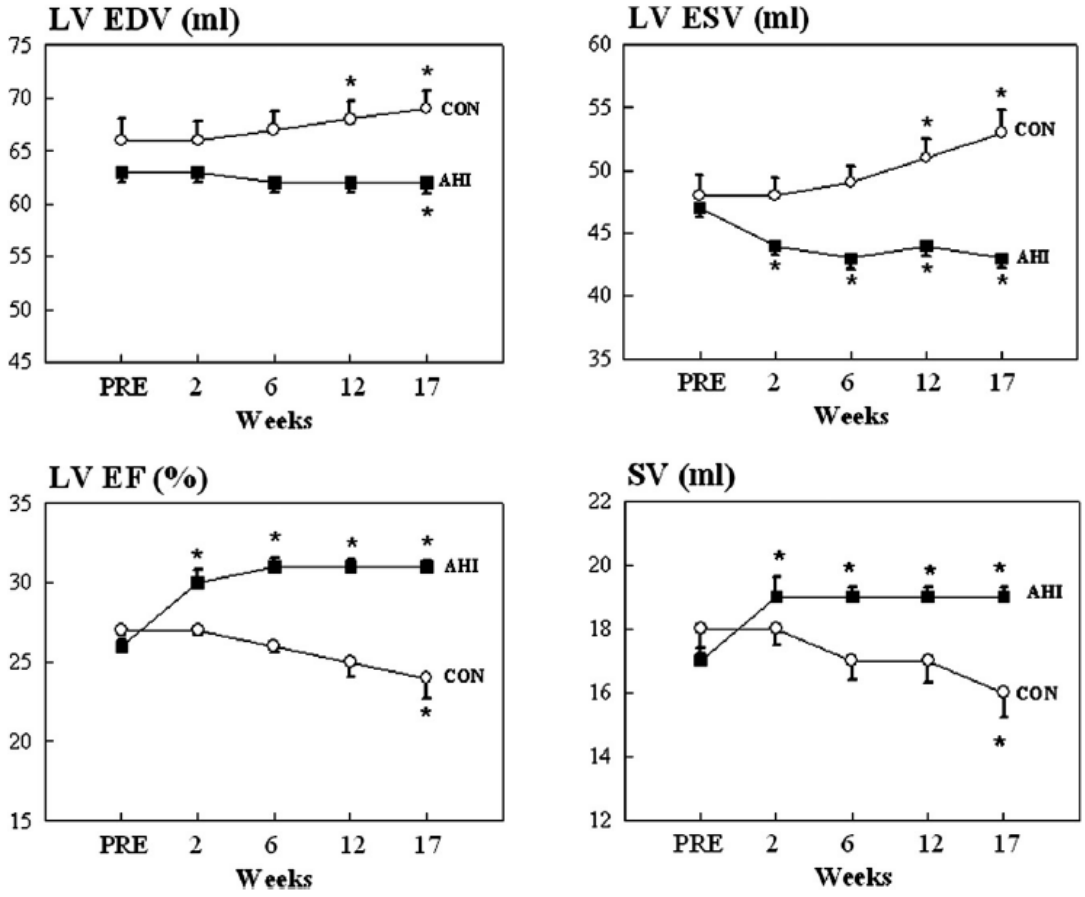
Augmentation of Left Ventricular Wall Thickness With Alginate Hydrogel Implants Improves Left Ventricular Function and Prevents Progressive Remodeling in Dogs With Chronic Heart Failure

Hani N. Sabbah, PHD,* Mengju
Itamar Ilsar, DVM,* Michael S.
Randall J. Lee, MD, PHD‡
Detroit, Michigan; and Laguna H

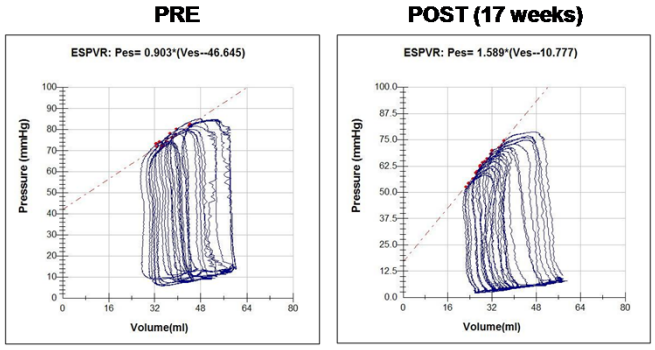




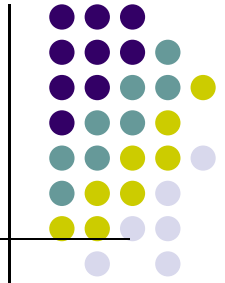
Effects of alginate hydrogel implants

- Increased wall thickness
- Greater radial deformation
- Small end-systolic volume
- Partially reversed maladaptive LV sphericity
- Reduced severity of functional MR
- Pre-Vol loops

FIGURE 1



Effects of alginate hydrogel implants



- **Reduced cardiomyocyte cross-sectional area (reduced hypertrophy)**
- **Reduction of interstitial fibrosis**
- **Reduction of O_2 diffusion distance**
- **Increase of capillary density**

- **Lack of AHI degradation for 2 yr**
- **No inflammatory reaction**
- **No arrhythmic events**

First-in-Man Experience

Cell Transplantation, Vol. 22, pp. 529–533, 2013

0963-6897/13 $90.00 + .00
DOI: http://dx.doi.org/10.3727/096368911X637461
E-ISSN 1555-3892
www.cognizantcommunication.com

Polymer-Based Restoration of Left Ventricular Mechanics

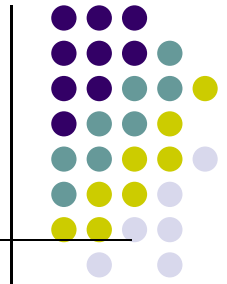
Randall J. Lee,*†‡ Andy Hinson,§ Sam Helgerson,§ Robert Bauernschmitt,¶ and Hani N. Sabbah#

*Cardiovascular Research Institute, University of California-San Francisco, San Francisco, CA, USA
†Department of Medicine, University of California-San Francisco, San Francisco, CA, USA
‡Institute for Regeneration Medicine, University of California-San Francisco, San Francisco, CA, USA
§LoneStar Heart, Inc., Laguna Hills, CA, USA
¶Isar Heart Center, IsarKliniken, Munich, Germany
#Department of Medicine, Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, MI, USA

Heart failure continues to be a major health care concern with relatively few options for severely advanced heart failure patients. The hallmark of heart failure is the progressive dilatation of the left ventricle, thinning of the left ventricular wall leading to increased wall stress and increased myocardial oxygen consumption. Applying Laplace's law to the failing dilated ventricle, left ventricular augmentation utilizes a tissue engineering strategy to increase wall thickness and reduce chamber diameter, resulting in a decrease in wall stress and improved left ventricular function. A review of the rationale for an in situ tissue engineering approach for this treatment of heart failure and early clinical results of the Algisyl-LVR™ program are presented.

Key words: Congestive heart failure (HF); Left ventricular (LV) mechanics; Tissue engineering; Alginate hydrogel

First-in-Man Experience



- **Ischemic (n=4) / nonischemic (n=2)**
- **CABG / Valve procedure**
- **LVEF ≤40%, LVEDDi 30-40 mm/m^2**
- **0.25-0.35 ml intramyocardial injection**
- **10-15 points at LV midventricular level**

Table 1. First-in-Man Experience With Left Ventricular Restoration in Patients With Systolic Heart Failure

	Presurgery	Post 3 Days	Post 8 Days	Post 3 Months
LVEF (%)	28.7±8.5	37.6±11.2	36.5±16.0	36.0±13.5
LVEDV (ml)	139.5±20.6	122.5±13.9	123.5±45.0	123.6±18.6
LVESV (ml)	99.8±25.8	79.5±22.8	87.2±46.0	77.2±29.5
KCCQ score	39.4±28.0	n/a	53.4±19.9	74.0±25.0*
No. of patients in NYHA class III/IV	6	n/a	1	1

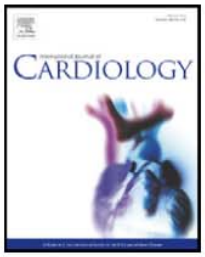
Cardiac MRI study

International Journal of Cardiology 168 (2013) 2022–2028

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



Algisyl-LVR™ with coronary artery bypass grafting reduces left ventricular wall stress and improves function in the failing human heart☆,☆☆

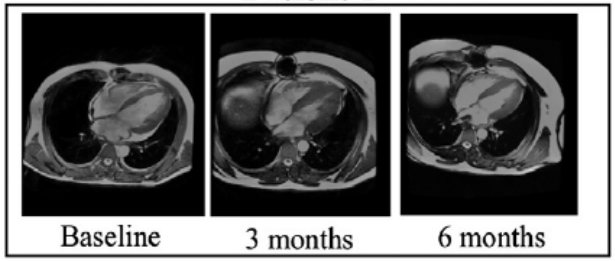
Lik Chuan Lee [a,b,1], Samuel T. Wall [d,1], Doron Klepach [a,b,1], Liang Ge [a,b,1], Zhihong Zhang [a,1], Randall J. Lee [b,c,1], Andy Hinson [e,1], Joseph H. Gorman III [f,1], Robert C. Gorman [f,1], Julius M. Guccione [a,b,*,1]

[a] *Department of Surgery, University of California, San Francisco, CA, USA*
[b] *Department of Bioengineering, University of California, San Francisco, CA, USA*
[c] *Department of Medicine, University of California, San Francisco, CA, USA*
[d] *Simula Research Laboratory, Oslo, Norway*
[e] *Lonestar Heart Inc, USA*
[f] *Glenolden Research Laboratory, Gorman Cardiovascular Research Group, University of Pennsylvania, Philadelphia, USA*

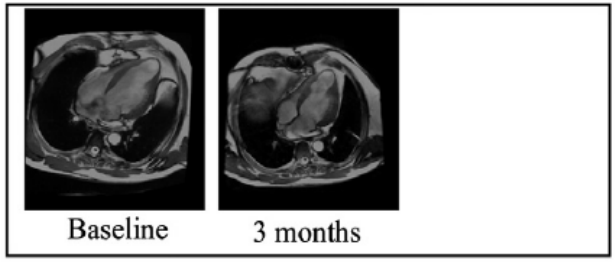
Cardiac MRI study

End-systole

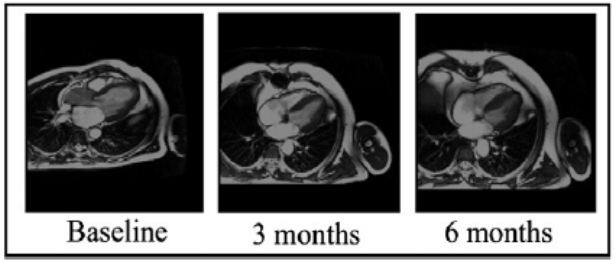
Patient 1



Patient 2

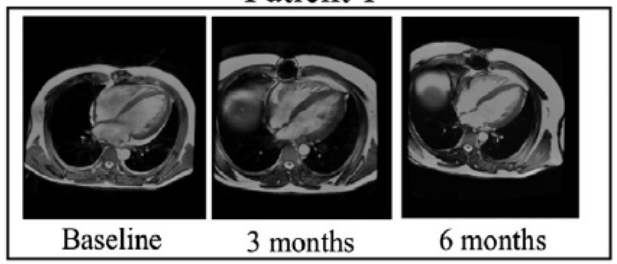


Patient 3

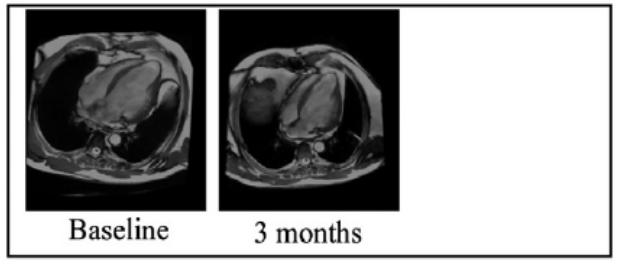


End-diastole

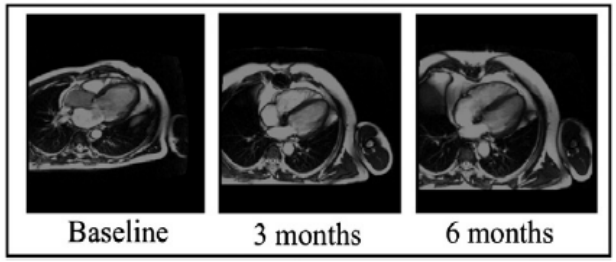
Patient 1



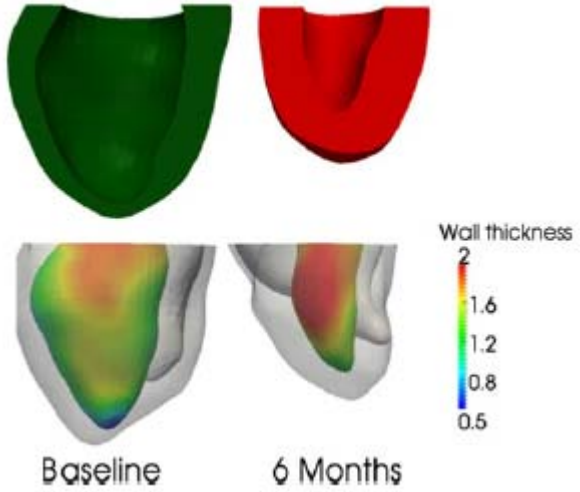
Patient 2



Patient 3



Wall thickness

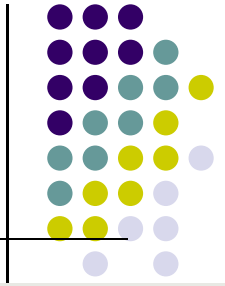


Cardiac MRI study

Table 1
Summary on the effects of Algiysl-LVR™ + CABG at different time points.

	Patient 1			Patient 2			Patient 3		
	Baseline	3 months	6 months	Baseline	3 months	6 months	Baseline	3 months	6 months
EDV (ml)	197.4	98.2	98.2	367.6	244.7	–	228.2	94.6	93.8
ESV (ml)	122.4	34.0	23.7	280.4	173.3	–	148.1	50.1	35.7
SV (ml)	75.0	64.2	74.5	87.2	71.4	–	80.1	44.5	58.1
EF (%)	40	65.4	75.9	23.7	29.2	–	35.1	47.0	61.9
Sphericity index	0.74	0.61	0.56	0.72	0.7	–	0.77	0.73	0.67
Average thickness (cm)	1.12	1.52	1.65	0.83	1.02	–	1.24	1.35	1.58
Average ED stress (kPa)	5.6	3.1	3.1	8.7	6.4	–	5.4	3.6	2.8
Average ES stress (kPa)	29.6	12.7	9.4	52.4	37.4	–	29.4	19.3	12.8
Peak ES stress (kPa)	61.9	27.2	24.5	178.2	109.6	–	69.4	48.2	35.2

AUGMENT-HF



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

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Text Size

A Randomized, Controlled Study to Evaluate Algisyl-LVR™ as a Method of Left Ventricular Augmentation for Heart Failure (AUGMENT-HF)

This study is currently recruiting participants.
Verified January 2014 by LoneStar Heart, Inc.

Sponsor:
LoneStar Heart, Inc.

Information provided by (Responsible Party):
LoneStar Heart, Inc.

ClinicalTrials.gov Identifier:
NCT01311791

First received: March 8, 2011
Last updated: January 8, 2014
Last verified: January 2014
History of Changes

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

Purpose

This is a pilot study to evaluate the safety and efficacy of the Algisyl-LVR™ device. The purpose of this study is to investigate Algisyl-LVR™ employed as a method of left ventricular augmentation and restoration in patients with dilated cardiomyopathy. Algisyl-LVR™ will be injected into the myocardium under direct visualization during the surgical procedure.

This study will evaluate the concept that direct mid left ventricular (LV) intramyocardial injections of Alginate hydrogel implants into the free wall of the failing LV will reduce LV size, restore LV shape, lower LV wall stress and improve global LV function.

The Primary Efficacy Endpoint of the study is the change in Peak VO2 (maximum oxygen uptake) from baseline to 6 months of follow-up. The Primary Safety Endpoint of the study is to estimate the 30 day mortality associated with the implantation of the Algisyl-LVR device

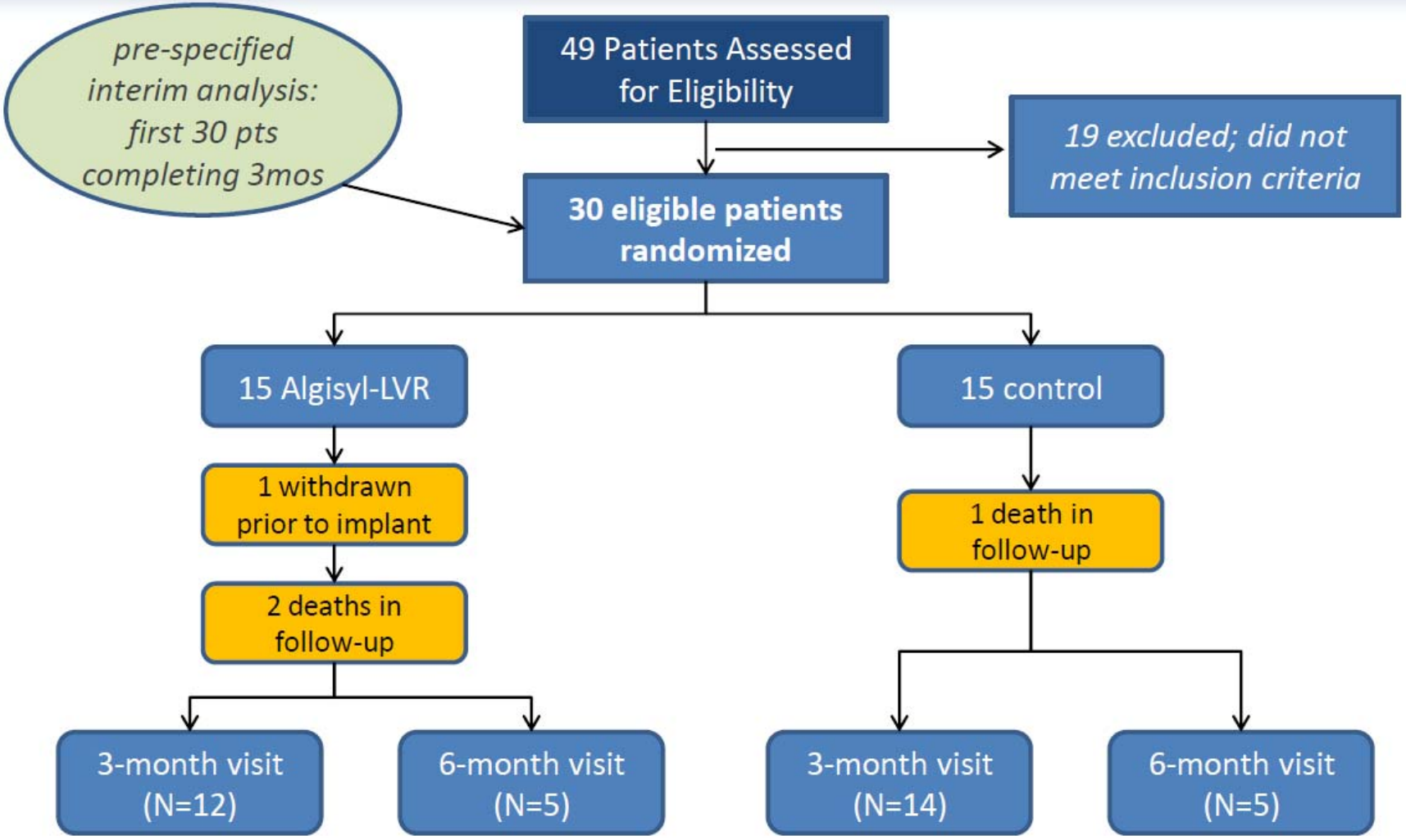
The hypothesis of the study is that there is a statistically significant difference in change in Peak VO2 from baseline to 6 month follow-up when the medically managed arm is compared to the Algisyl-LVR arm, i.e. the Algisyl LVR arm is superior to medical management.

Condition	Intervention	Phase
Heart Failure Dilated Cardiomyopathy	Device: Algisyl-LVR Drug: Standard medical therapy	Phase 2 Phase 3

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Single Blind (Outcomes Assessor)
Primary Purpose: Treatment

Official Title: A Randomized, Controlled Study to Evaluate the Safety and Cardiovascular Effects of Algisyl-LVR™ as a Method of Left Ventricular Augmentation in Patients With Dilated Cardiomyopathy (AUGMENT-HF)

AUGMENT-HF Interim Analysis



AUGMENT-HF Interim Dataset

Baseline Demographics (ITT)

	ALL (n=30)	Algisyl-LVR (n=15)	Control (n=15)	*P*
Age (years)	63.3 (9.1)	63.1	62.3	*N.S.*
Male	24 (80%)	10 (67%)	14 (93%)	*N.S*
Ethnicity (white)	30 (100%)	15 (100%)	15 (100%)	*N.S.*
NYHA class II/III/IV	(3)(23)(4)	(0)(13)(2)	(3)(10)(2)	-
Ischemic HF	20 (67%)	10 (67%)	10 (67%)	*N.S.*
Non-Ischemic HF	10 (33%)	5 (33%)	5 (33%)	*N.S.*
CRT	13 (43%)	6 (40%)	7 (47%)	*N.S.*
LVEF (%)	25.7	25.0	26.7	*N.S.*
LVEDD (cm)	6.24	6.11	6.37	*N.S.*
Peak VO2 (ml/min/kg)	12.2	12.3	12.0	*N.S.*
6 MWT (m)	270	235	305	***.013****

AUGMENT-HF Interim Dataset

Concomitant Medications

	Algisyl-LVR (N=15)	Usual Care (N=15)
Anti-thrombotics / Anti-platelet agents	14 (93.3%)	14 (93.3%)
Anti-platelet aggregation agents	12 (80.0%)	10 (66.7%)
Diuretics	14 (93.3%)	13 (86.7%)
Aldosterone antagonists	11 (73.3%)	5 (33.3%)
Beta-blockers	13 (86.7%)	12 (80.0%)
ARB/ ACE	10 (66.7%)	11 (73.3%)
Lipid-lowering	10 (66.7%)	11 (73.3%)

Primary Safety End Point
Estimate of Algisyl-LVR device 30 day mortality

30 day mortality

Algisyl-LVR (N=14)	Total # of events	# Pts with event (% of Pts)
30 day mortality	0	0 (0.0%)
30 day morbidity - Serious adverse events within 30 days of the surgical implant procedure	5	3 (21.4%)

Overall mortality in the interim data set

- Algisyl-LVR Group: 2 patients died > 30 days post-operatively
  - Drug resistant Klebsiella Pneumonia – 66 days post-procedure
  - Critical illness 2° to Sepsis – 49 days post-procedure
- Usual Care Group: 1 patient
  - Worsening Heart Failure – 39 days post-randomization

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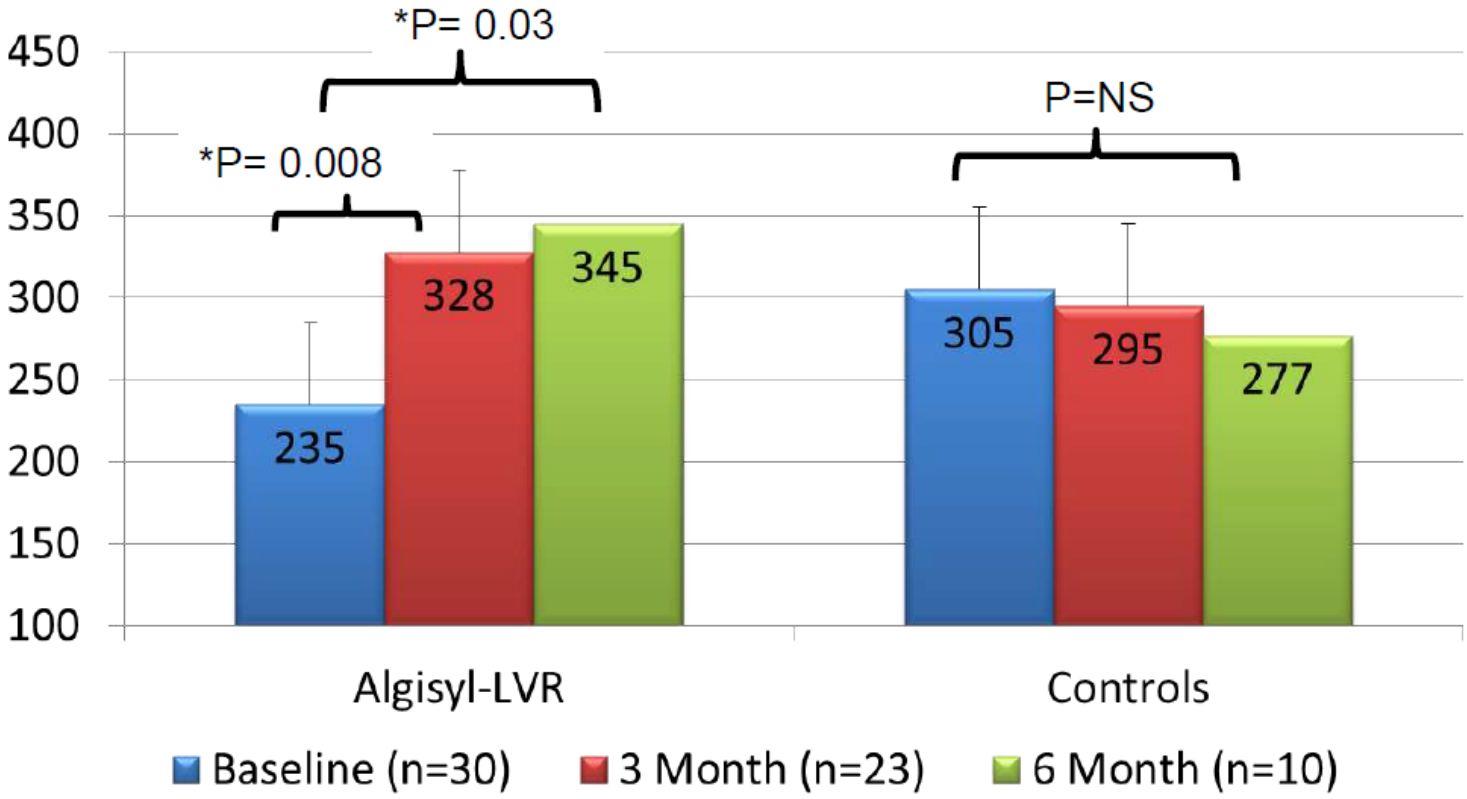
Six Minute Walk Distance by Visit



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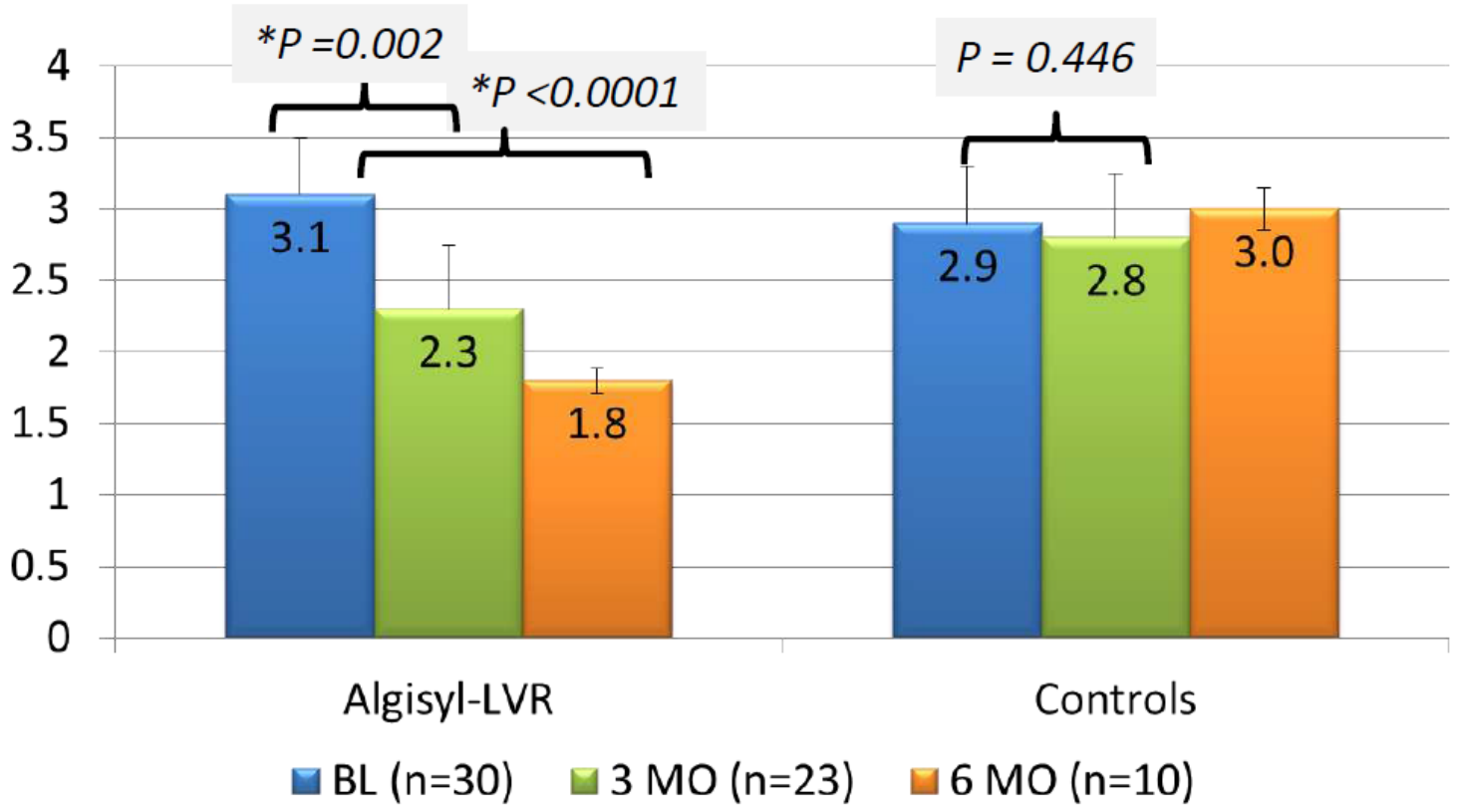
NYHA Functional Class by Visit



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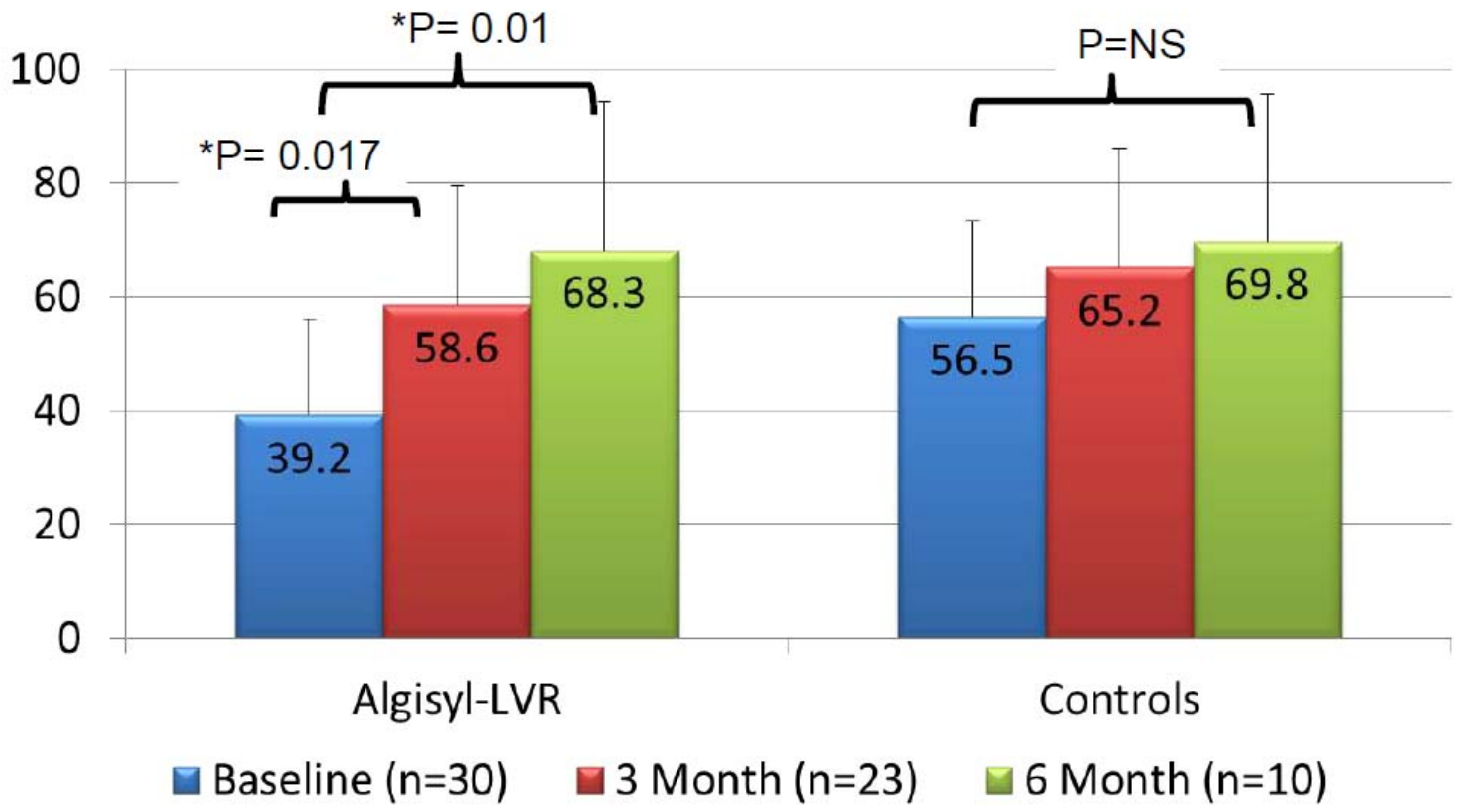
KCCQ Overall Summary Score



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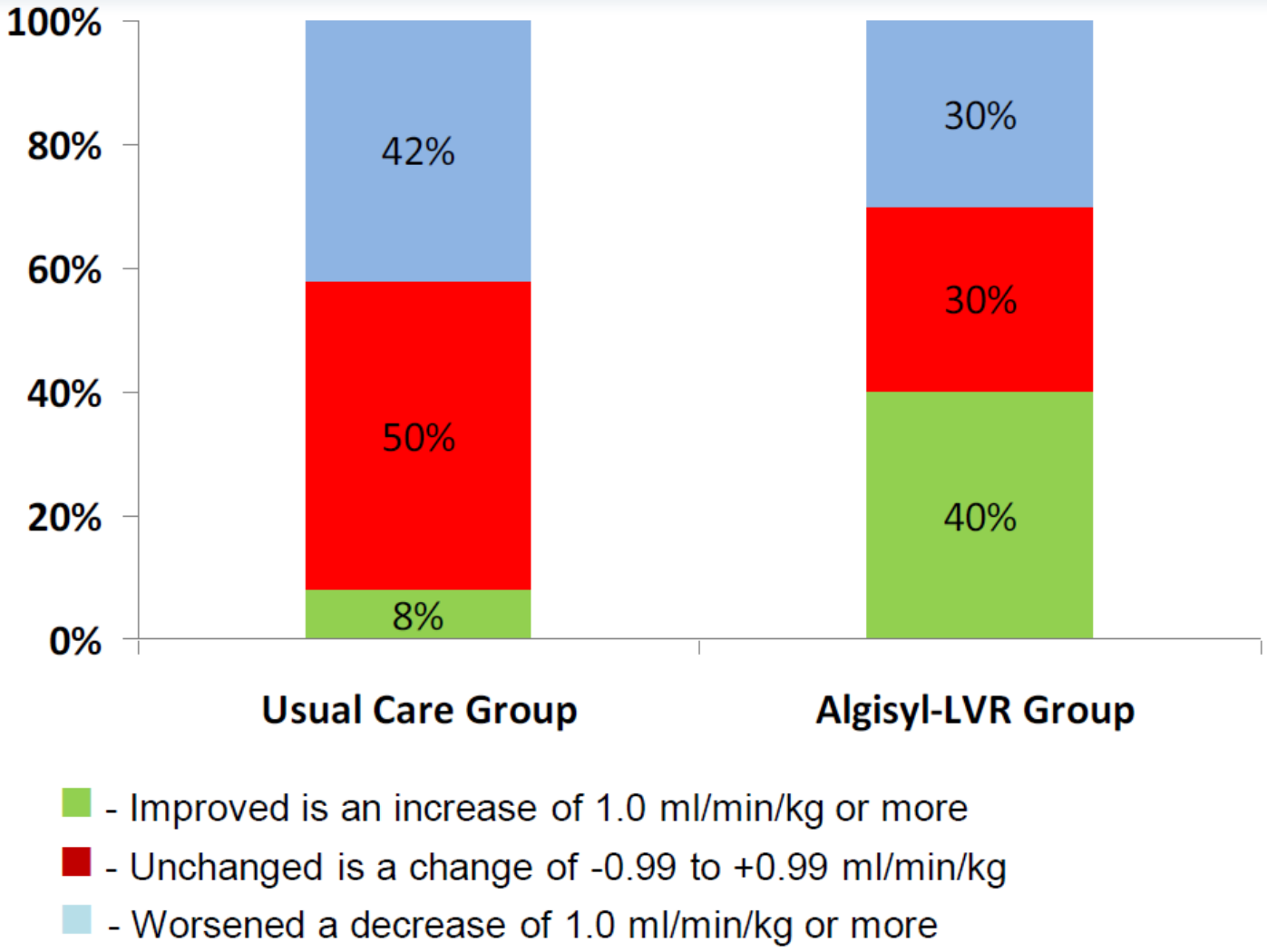
Clinical Composite of Peak VO2 at 3 Months



AUGMENT-HF Interim Analysis

Conclusions

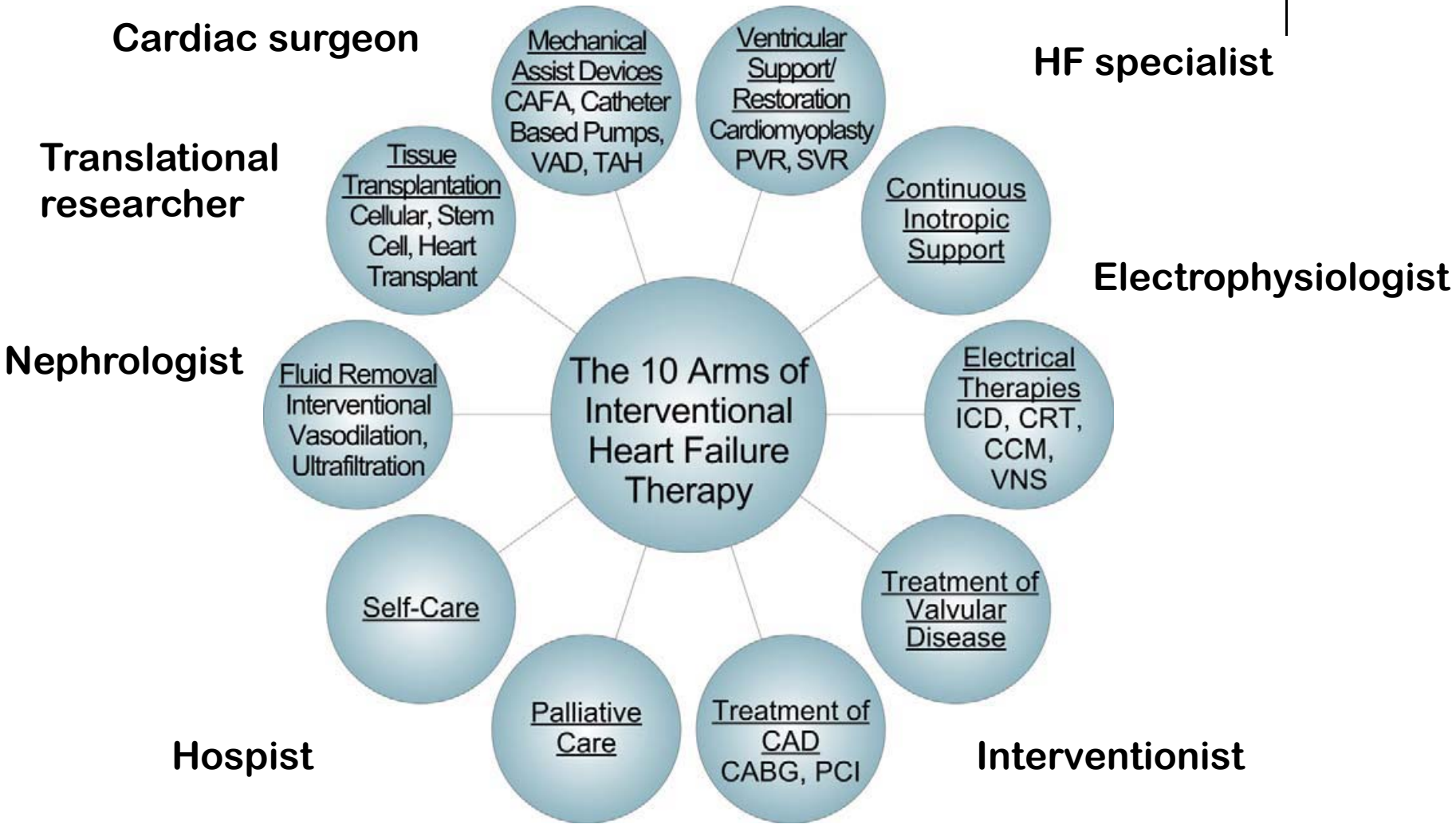
- Interim results of the AUGMENT-HF trial show that Algisyl-LVR™ is safe, with an acceptable 30 day post-operative morbidity and mortality
- The interim efficacy analysis suggests that the Algisyl-LVR ™ leads to improvements in quality of life and functional capacity in comparison to patients who are treated with optimal medical management alone
- These interim results should be viewed as provisional given the small number of patients and the short follow-up time
- These studies provide proof-of-concept for LV reconstruction with Algisyl-LVR ™ as a potential novel new therapy for patients with advanced heart failure

Solving problems

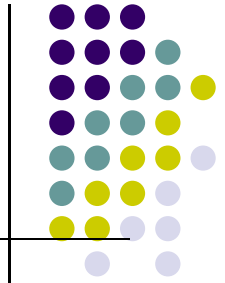
- **Long-term safety and effects ?**
- **Larger number study**
- **Blinded trial (vs open trial design)**
- **Risk of arrhythmia ?**
- **Survival benefits ?**

- **Percutaneous approach ?**

HF managements



Summary



- **Diverse designs and trials for reverse remodeling**
- **Biopolymer gel implants**
  - **One of promising novel approach**
  - **Less invasive**
  - **Short-term safety**
  - **Early effects of reverse remodeling at the levels of histology, hemodynamics and LV structures**
  - **Needs for long-term safety and effects**
  - **Needs for blinded trial with larger number**

경청해 주셔서 감사합니다.