2023 Howard B. Burchell Memorial Lecture

Dr. Burchell is widely recognized as one of the foremost authorities in cardiology during the 1950s and 1960s. He is considered to have set the stage, with his colleagues, for the ablation of accessory AV connections, which ultimately led to the current era of interventional cardiac electrophysiology. The annual Burchell lecture is a tradition that was created over twenty years ago as a way to honor Dr. Burchell and his contributions to the world of medicine.

Minneapolis Heart Institute Foundation | GRAND ROUNDS

1

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Minneapolis Heart Institute Foundation | GRAND ROUNDS

2

Burchell Lecture Past Presentations

- **2022: Clyde Yancy, MD** *Heart Failure; a new coming of age for an old disease*
- **2021: Mathew Maurer, MD** *Cardiac Amyloidosis: Transition from rare, underdiagnosed and untreatable to an increasingly and easily recognized and treatable disorder*
- **2019: Navin Kapur, MD** *Ventricular Unloading: State of the Art and Future Directions*
- **2018: Anne Marie Valente, MD** *The STORCC Initiative (Standardized Outcomes in Reproductive Cardiovascular Care)*
- **2017: Robert Harrington, MD** *Rethinking Randomized Clinical Trials*
- **2016: Carl Pepine, MD** *Emergence of Nonobstructive Coronary Artery Disease in Women*
- **2013: Richard Asinger, MD** *Stroke Prevention in Atrial Fibrillation: An Overview and Future Directions*
- **2012: David Holmes, Jr, MD** *Global Cardiovascular Disease*
- **2010: Bernie Gersh, MD** *The Epidemic of Cardiovascular Disease in the Developing World: Global Implications*

Minneapolis Heart Institute Foundation | GRAND ROUNDS

3

Minneapolis Heart Institute Foundation®
Cardiovascular Grand Rounds

Burchell Lecture: Heart Failure with an Improved Left Ventricular Ejection Fraction: Mechanics, Models and Management

Speaker: Douglas L. Mann

Aida L. Steininger Professor of Cardiology
Professor of Medicine, Cell Biology and Physiology
Washington University School of Medicine
St. Louis, MO

April 17, 2023 | 7:00 – 8:00 AM

Minneapolis Heart Institute Foundation | GRAND ROUNDS

4

Heart Failure with an Improved Left Ventricular Ejection Fraction: Mechanisms, Models and Management

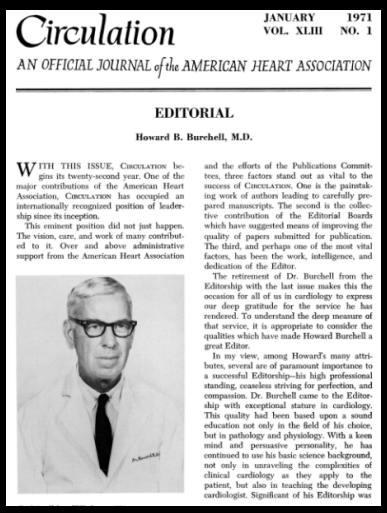
Howard B. Burchell Memorial Lecture
Minneapolis Heart Institute Foundation
April 17th, 2023

Washington University in St. Louis
School of Medicine

CENTER FOR CARDIOVASCULAR RESEARCH
DISCOVER | INNOVATE | TRANSLATE

5

Dr. Howard Bertram Burchell



Circulation
AN OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION
JANUARY 1971
VOL. XLIII NO. 1

EDITORIAL

Howard B. Burchell, M.D.

WITH THIS ISSUE, CIRCULATION begins its twenty-second year. One of the major contributions of the American Heart Association, CIRCULATION has occupied an internationally recognized position of leadership since its inception.

This eminent position did not just happen. The vision, care, and work of many contributed to it. Over and above administrative support from the American Heart Association and the efforts of the Publications Committees, three factors stand out as vital to the success of CIRCULATION. One is the painstaking work of authors leading to carefully prepared manuscripts. The second is the collective contribution of the Editorial Boards which have suggested means of improving the quality of papers submitted for publication. The third, and perhaps one of the most vital factors, has been the work, intelligence, and dedication of the Editor.

The retirement of Dr. Burchell from the Editorship with the last issue makes this the occasion for all of us in cardiology to express our deep gratitude for the service he has rendered. To understand the deep measure of that service, it is appropriate to consider the qualities which have made Howard Burchell a great Editor.

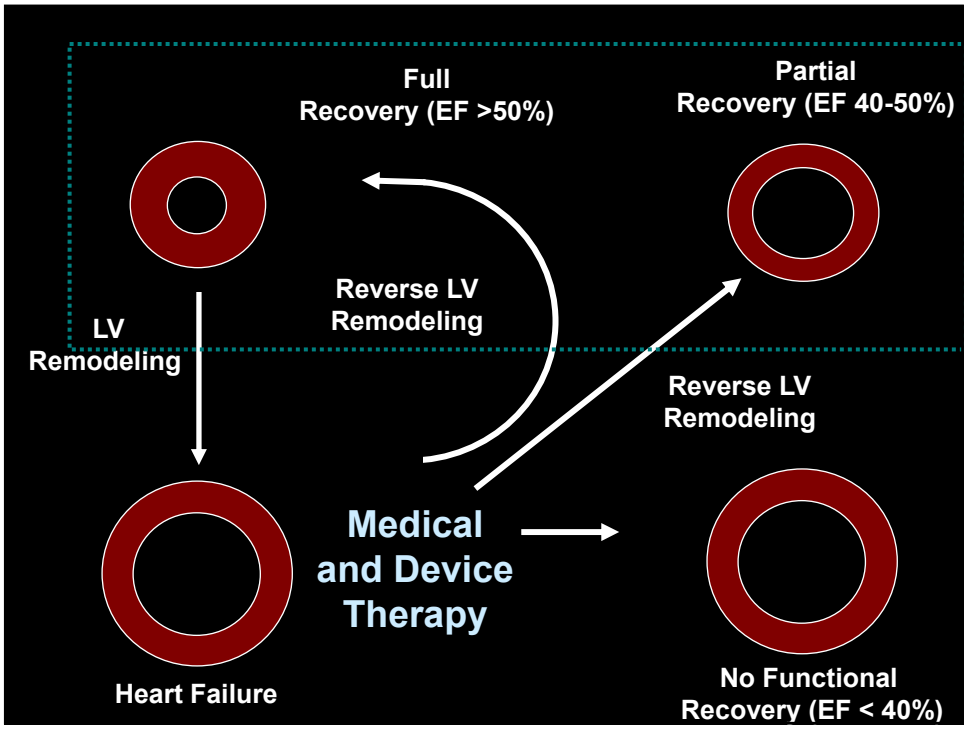
In my view, among Howard's many attributes, several are of paramount importance to a successful Editorship–his high professional standing, ceaseless striving for perfection, and compassion. Dr. Burchell came to the Editorship with exceptional stature in cardiology. This quality had been based upon a sound education not only in the field of his choice, but in pathology and physiology. With a keen mind and persuasive personality, he has continued to use his basic science background, not only in unraveling the complexities of clinical cardiology as they apply to the patient, but also in teaching the developing cardiologist. Significant of his Editorship was

Physician, Scholar, Leader

"In my view, among Howard's many attributes, several are of paramount importance to a successful Editorship-his high professional standing, ceaseless striving for perfection, and compassion…. With a keen mind and persuasive personality, he has continued to use his basic science background, not only in unraveling the complexities of clinical cardiology as they apply to the patient, but also in teaching the developing cardiologist."

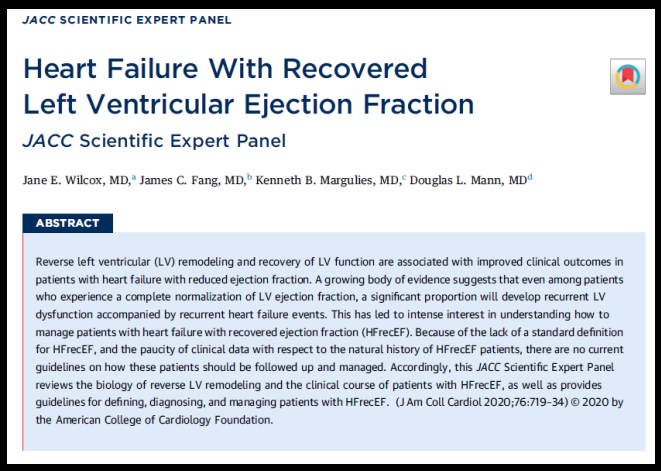
Jesse Edwards, MD

6



7

Heart Failure with a Recovered Ejection Fraction



JACC SCIENTIFIC EXPERT PANEL

Heart Failure With Recovered Left Ventricular Ejection Fraction

JACC Scientific Expert Panel

Jane E. Wilcox, MD,[a] James C. Fang, MD,[b] Kenneth B. Margulies, MD,[c] Douglas L. Mann, MD[d]

ABSTRACT

Reverse left ventricular (LV) remodeling and recovery of LV function are associated with improved clinical outcomes in patients with heart failure with reduced ejection fraction. A growing body of evidence suggests that even among patients who experience a complete normalization of LV ejection fraction, a significant proportion will develop recurrent LV dysfunction accompanied by recurrent heart failure events. This has led to intense interest in understanding how to manage patients with heart failure with recovered ejection fraction (HFrecEF). Because of the lack of a standard definition for HFrecEF, and the paucity of clinical data with respect to the natural history of HFrecEF patients, there are no current guidelines on how these patients should be followed up and managed. Accordingly, this *JACC* Scientific Expert Panel reviews the biology of reverse LV remodeling and the clinical course of patients with HFrecEF, as well as provides guidelines for defining, diagnosing, and managing patients with HFrecEF. (J Am Coll Cardiol 2020;76:719-34) © 2020 by the American College of Cardiology Foundation.

JACC 2020;76: 719-734

8

Heart Failure with a Recovered Ejection Fraction

- Nomenclature is messy
  - HF improved EF (HFimpEF)
  - HFpEF
  - borderline HFpEF
  - **HF recovered EF (HFrecEF)**
  - HF midrange EF (HFmrEF)
- The definition is unclear
  - LVEF increase ≥ 5%
  - **LVEF increase ≥ 10%**
  - LVEF > 50%
  - **LVEF ≥ 40%**
- Unclear clinical course
- Unclear biological substrate

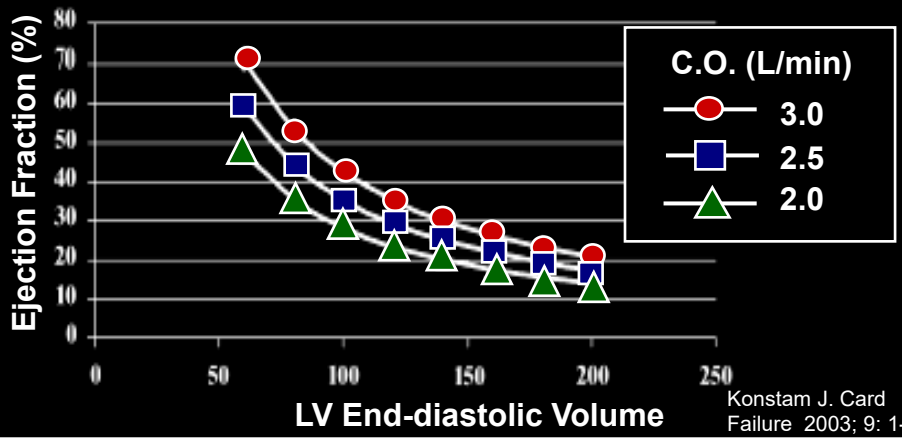
JACC 2020;76: 719-734

9

LV Ejection Fraction as a Surrogate Measure of LV Volume

EF = (EDV-ESV)/EDV
or
EF = SV/EDV

For a fixed SV a decline in EF reflects an increase in EDV



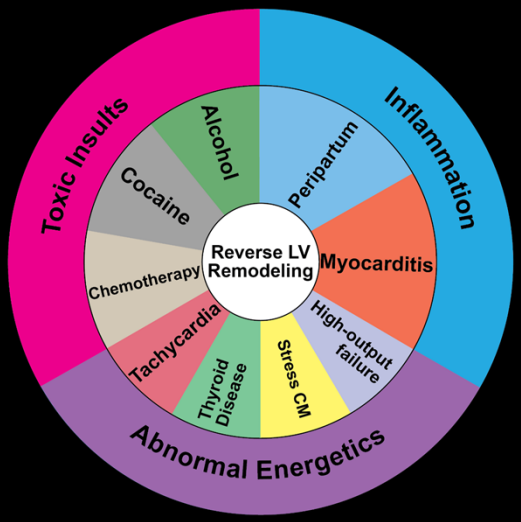
Konstam J. Card Failure 2003; 9: 1-3

10

Epidemiology of Heart Failure with a Recovered LVEF

11

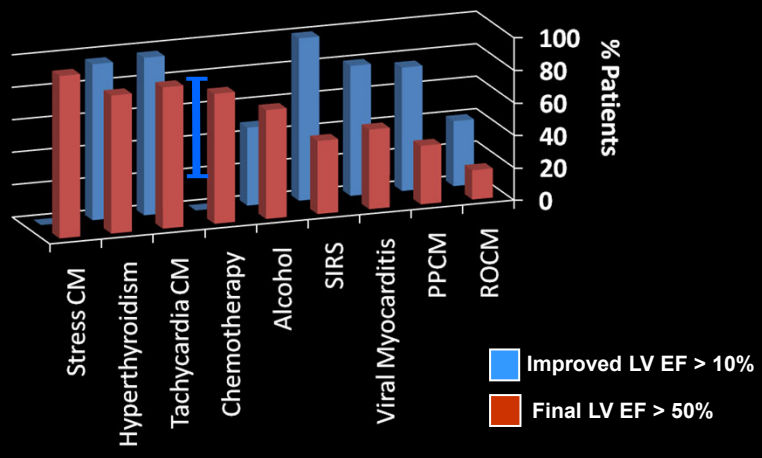
Epidemiology of Recovery of LVEF



Modified from Hellawell and Margulies Cardiovasc Ther 2012; 20: 172-181

12

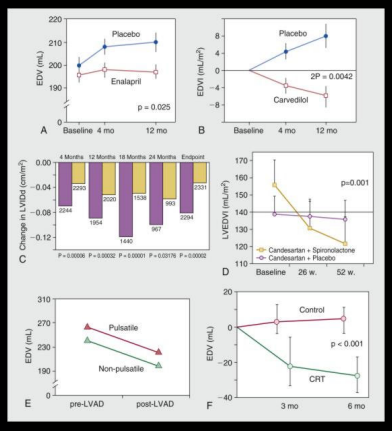
Epidemiology of Recovery of LVEF



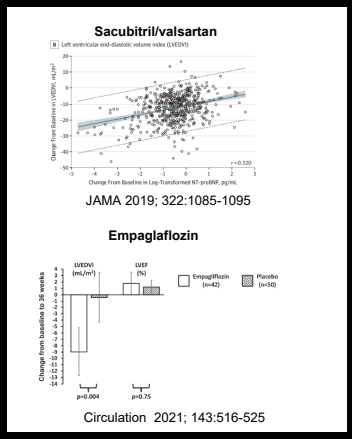
Givertz and Mann, Curr Heart Fail Report 2013; 10:321-330

13

Effect of FDA Approved Therapies on Reverse LV Remodeling



Topkara VK, Mann DL. Heart Failure: A Companion to Braunwald's Heart Disease, 2011



14

Take Home Message #1

Once the inciting event is removed, recovery of LVEF is the rule rather than the exception.

Take Home Message #2

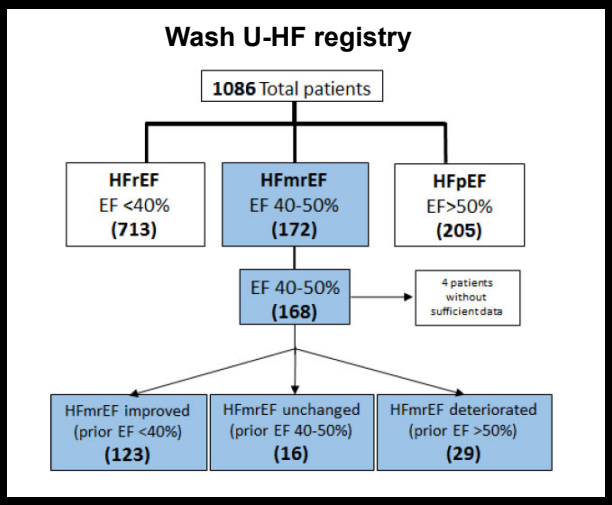
Although recovery of LVEF occurs frequently, normalization of LVEF (i.e. LVEF > 50%) varies according to the nature and duration of the inciting event.

15

Durability of Partial Recovery of LV Fucntion (LV EF 40-50%)

16

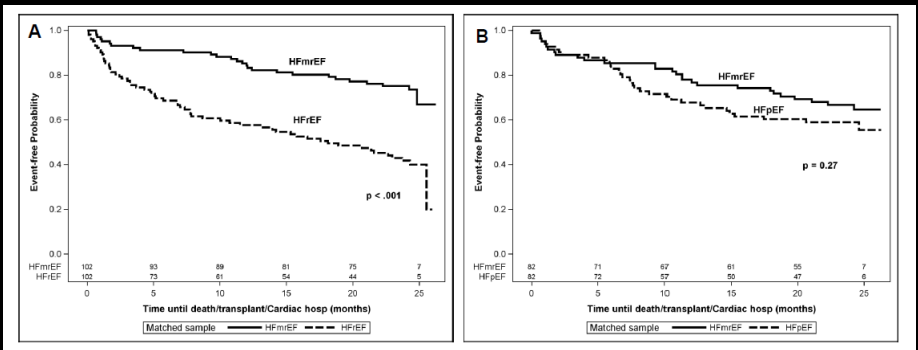
Natural History of Functional Responders with a Mid-Range LVEF (HFmrEF)



Rastogi et al; Eur J Heart Fail 2017; 19: 1597-1605

17

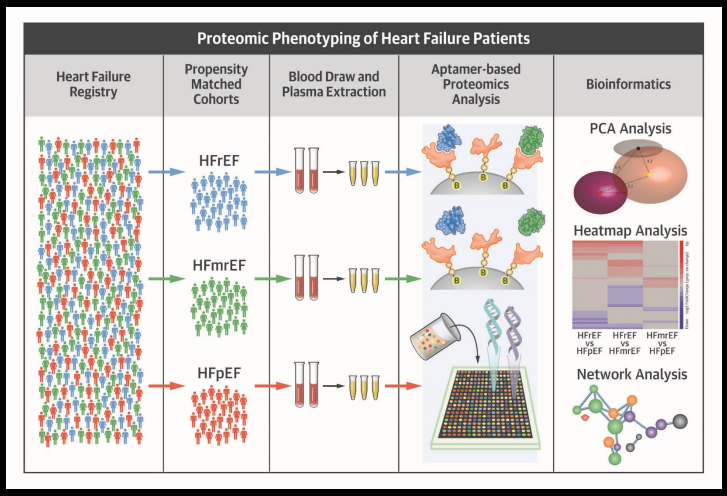
Natural History of Functional Responders with a Mid-Range LVEF (HFmrEF)



Rastogi et al; Eur J Heart Fail 2017; 19: 1597-1605

18

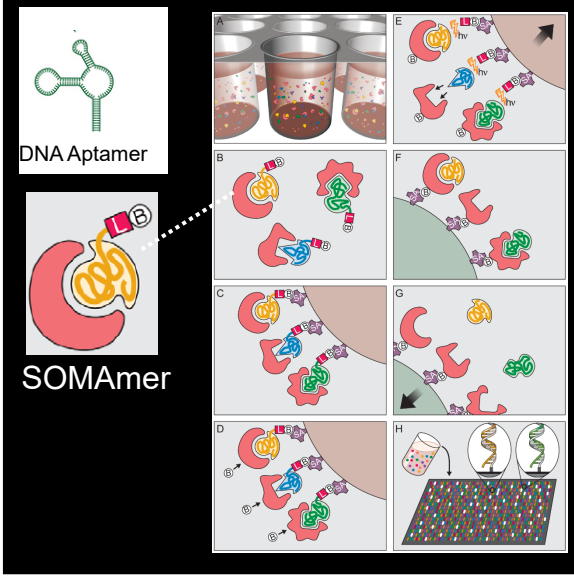
Proteomic Signatures of Heart Failure in Relation to LVEF



Adamo…Mann, *JACC 2020; 76: 1982-1994*

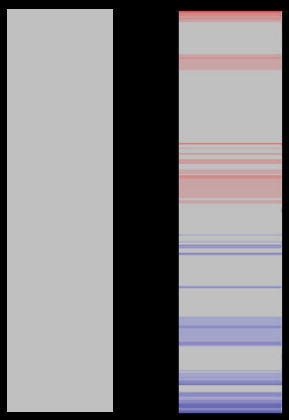
19

Serum Protein Profiling Using DNA Aptamers (SomaLogic 1.3K)



Profile will be gray if no differences exist

Profile will Have red and blue bars if differences exist



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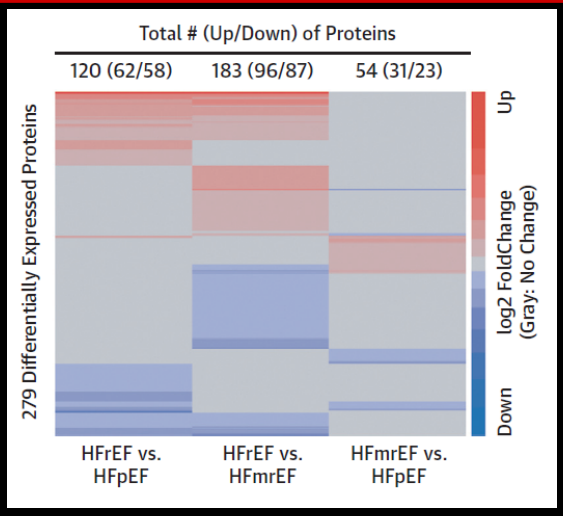
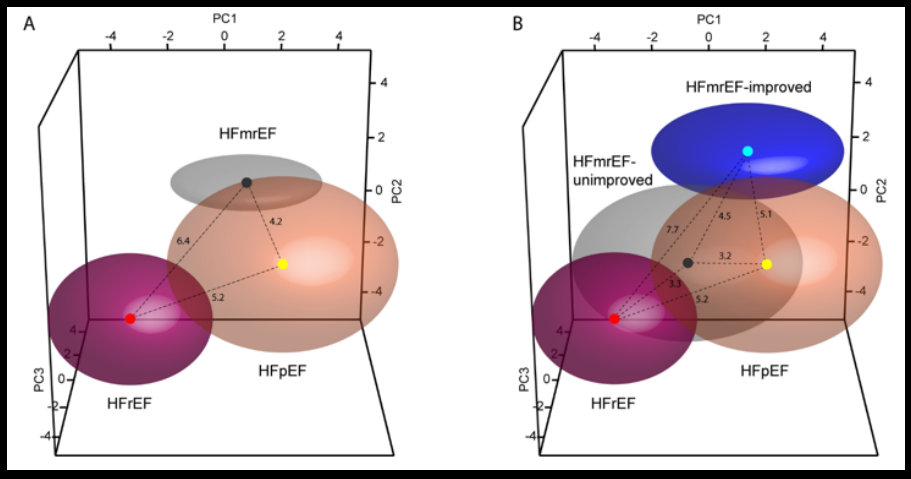
Proteomic Signatures of Heart Failure in Relation to LVEF



Adamo…Mann, *JACC 2020; 76: 1982-1994*

21

PCA Analysis Serum Protein Profiles



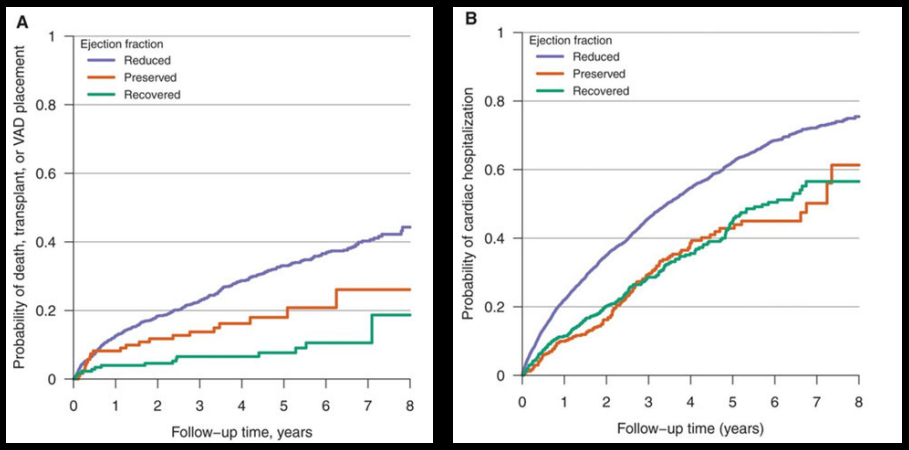
Adamo…Mann, *JACC 2020; 76: 1982-1994*

22

Durability of Complete LVEF Recovery (EF > 50%) in Patients with Heart Failure

23

Natural History of Heart Failure with a Recovered Ejection Fraction



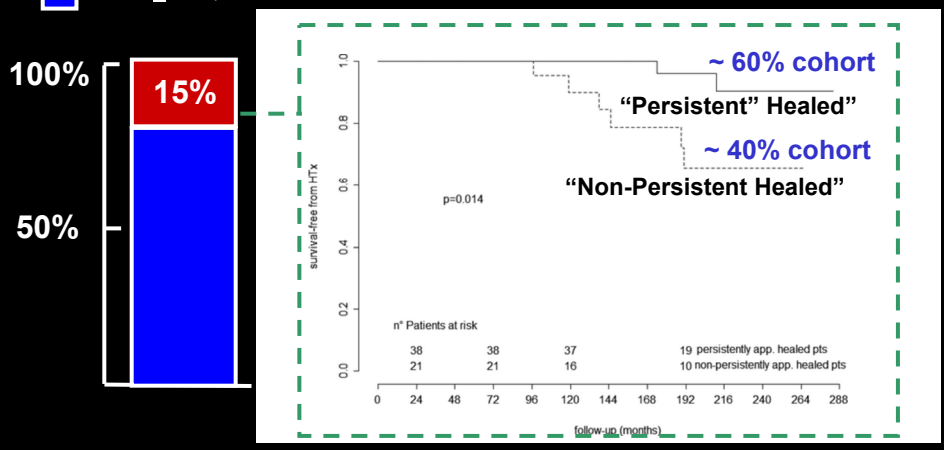
Basuray et al Circulation 2016; 129:2380-2387

24

Natural History of Functional Responders with DCM

LVEF ≥ 50%, LVEDDi < 33 mm/m²

LVEF ≤ 50%, LVEDDi > 33 mm/m²



Merlo et al JAHA 2015; 4:e001504

25

The observation that heart failure recurs in patients whose LV structure and function completely normalized, was irreconcilable with everything that I (thought) knew about heart failure biology.

26

Consensus Statement on Cardiac Remodeling

Cardiac Remodeling—Concepts and Clinical Implications: A Consensus Paper From an International Forum on Cardiac Remodeling

Jay N. Cohn, MD,* Roberto Ferrari, MD,† Norman Sharpe, MD,‡ on Behalf of an International Forum on Cardiac Remodeling

Minneapolis, Minnesota; Ferrara, Italy; and Auckland, New Zealand

JACC 2000; 35:569-82

Consensus Statement Four

"Although remodeling is generally accepted as a determinant of the clinical course of HF, slowing or reverse remodeling has not, until recently, been a recognized goal of HF therapy. "

27

Leading Textbooks in the Field Indicated that Reverse LV Remodeling Was Synonymous with Resolution of HF

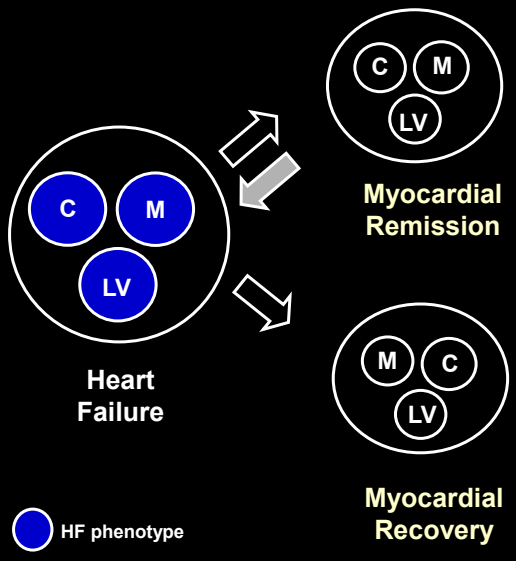
28

Take Home Message #3

Try not to avoid drinking too much of your own Kool-Aid, it can leave you confused and hung over.

29

Clinical Outcomes of Recovery of LV Function



Yes !!

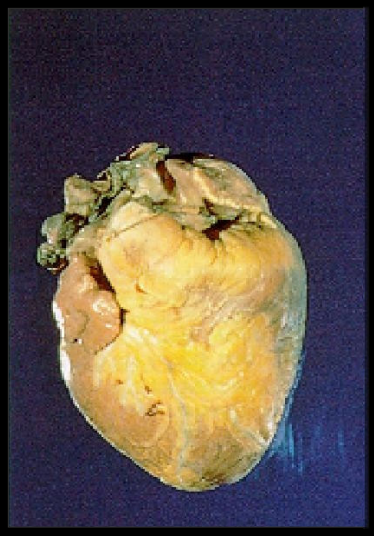
Mann et al. JACC 2012; 60: 2465-2472

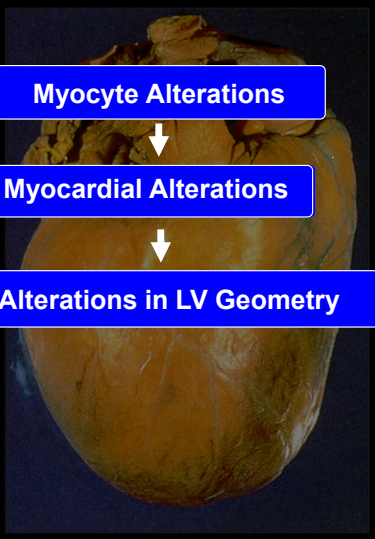
30

So What Are the Biological Determinants of Myocardial Remission ?

31

The Biology of Reverse LV Remodeling and Recovered LVEF



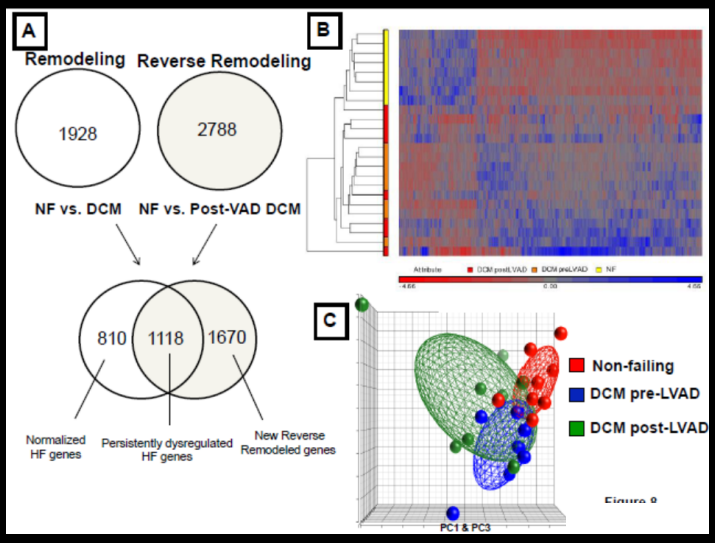


32

The Slinky Hypothesis™

33

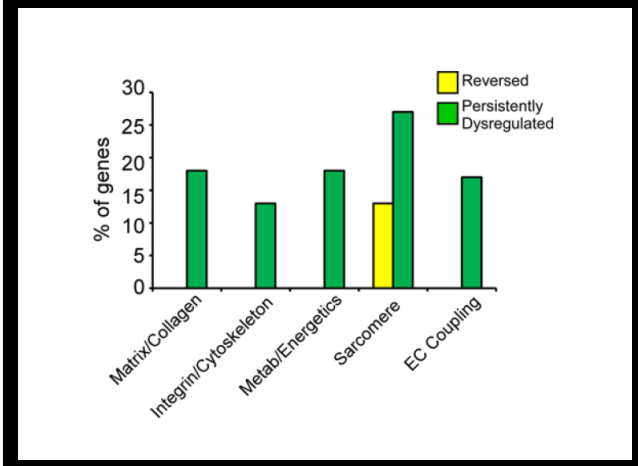
Transcriptional Profiling of Human DCM pre- and post-VAD

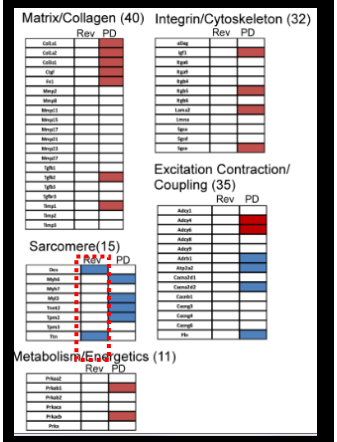


Topkara et al JCI Insight 2016; 1:e86038

34

Transcriptional Profiling of Human DCM pre- and post-VAD

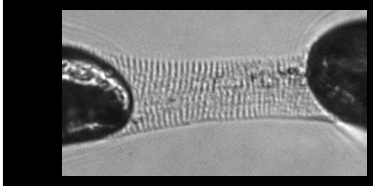


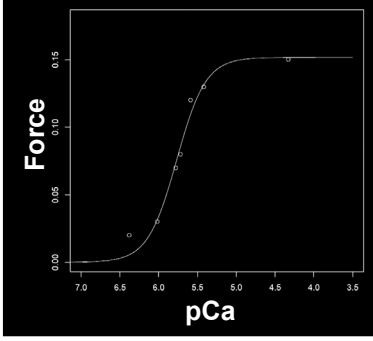


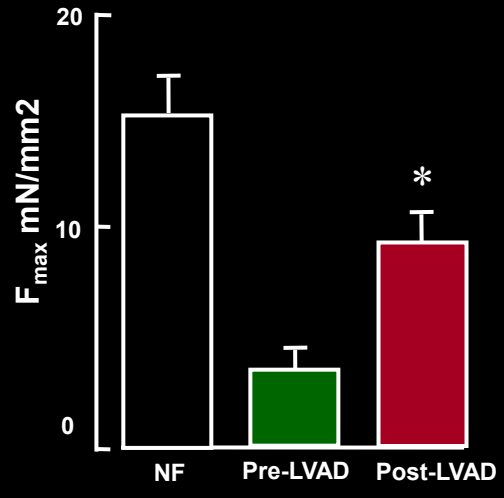
Topkara et al JCI Insight 2016; 1:e86038

35

Incomplete Recovery of Myocyte Function Following LVAD Support



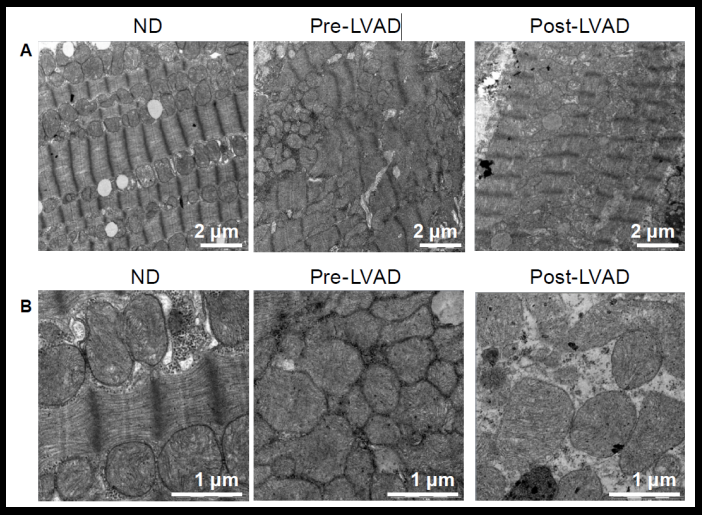




Ambardekar et al Circ Heart Fail 2011:4; 425-432

36

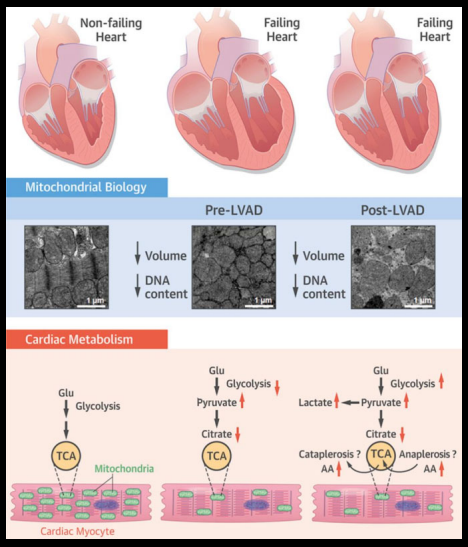
Persistent Ultrastructural Changes Following Reverse Remodeling



Diakos et al. JACC Basic Transl Sci 2016; 1: 432-444

37

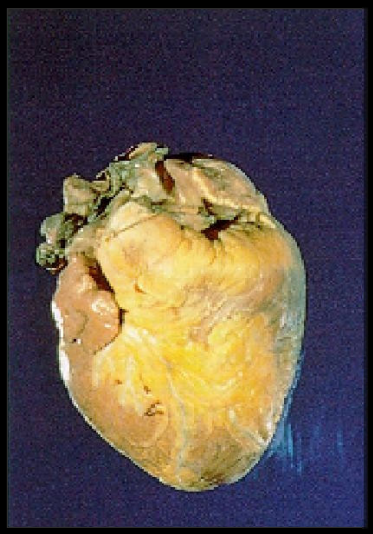
Changes in Myocardial Metabolism Following LVAD support

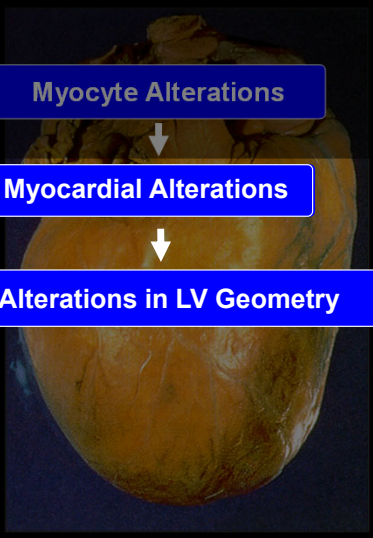


Diakos et al. JACC Basic Transl Sci 2016; 1: 432-444

38

The Biology of Reverse Cardiac Remodeling





Myocyte Alterations

↓

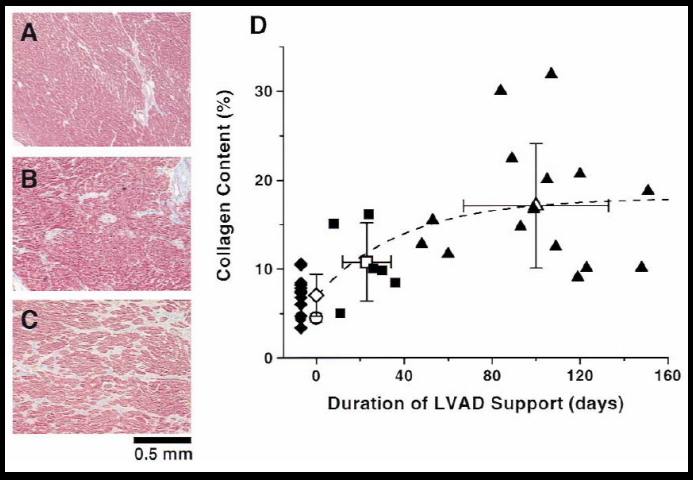
Myocardial Alterations

↓

Alterations in LV Geometry

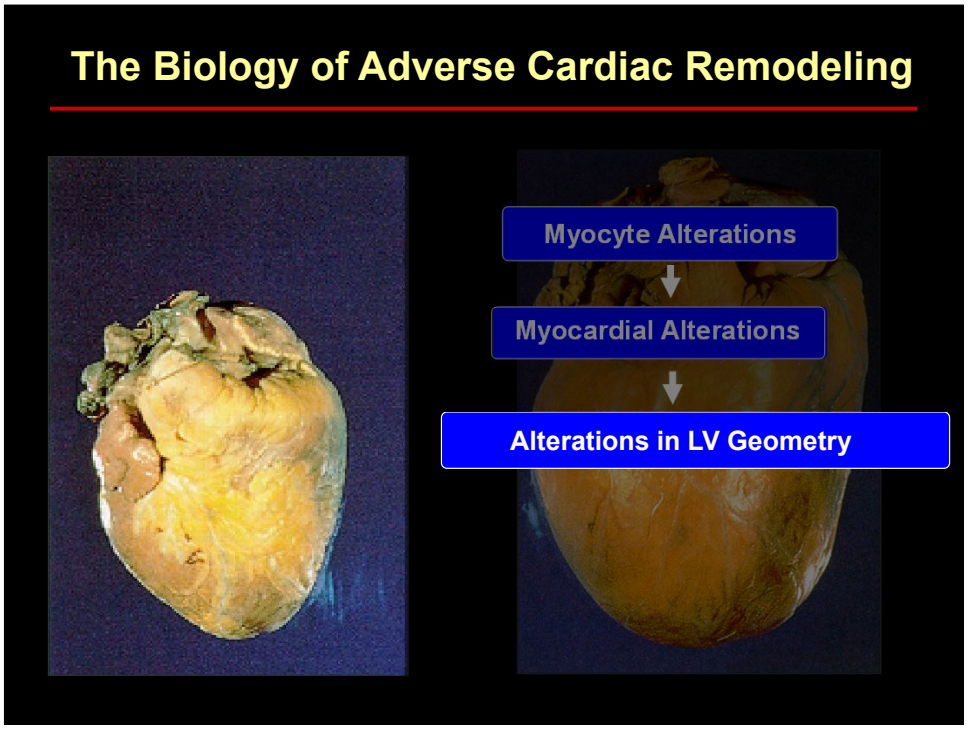
39

Persistent Changes in ECM Following Reverse Remodeling

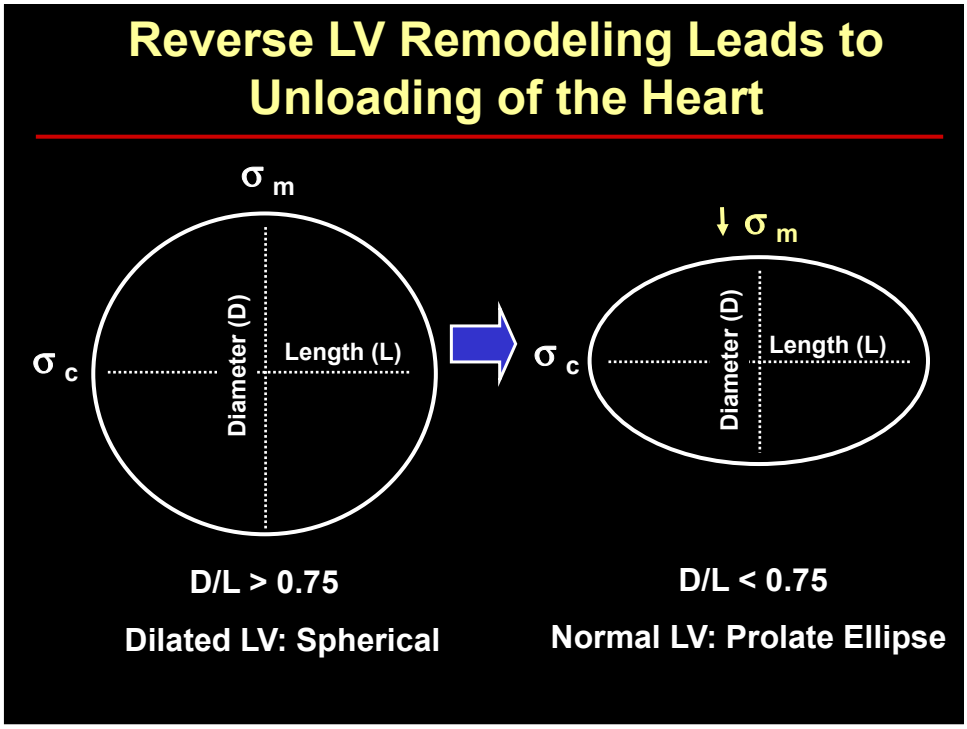


Madigan et al J Thorac Cardiovasc Surg. 2001 May;121:902-8

40

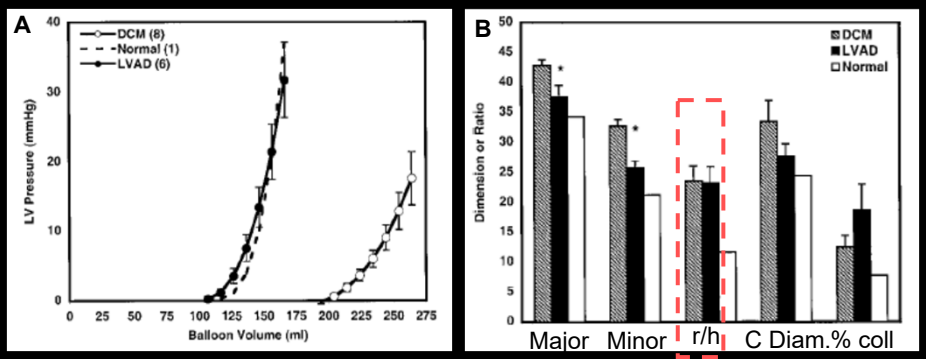

The Biology of Adverse Cardiac Remodeling
Myocyte Alterations
Myocardial Alterations
Alterations in LV Geometry

41


Reverse LV Remodeling Leads to Unloading of the Heart
σ m
σ c
Diameter (D)
Length (L)
↓ σ m
σ c
Diameter (D)
Length (L)
D/L > 0.75
Dilated LV: Spherical
D/L < 0.75
Normal LV: Prolate Ellipse

42

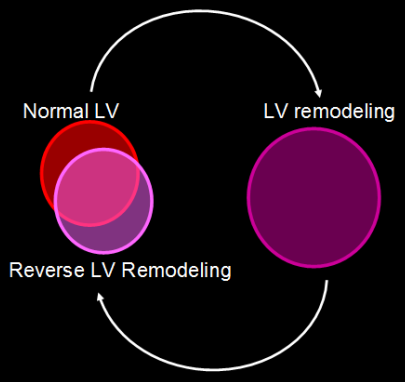
Abnormal LV Structure Following Reverse Remodeling



From Barbone Circ 2001: 101[Suppl I]; I-229-I232

43

Take Home Message # 4

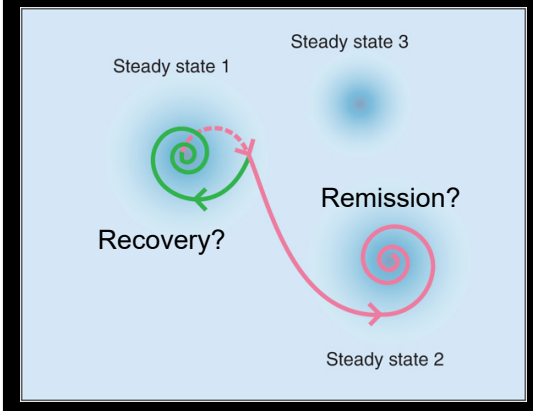


Reverse LV remodeling is not a mirror image of the molecular and cellular pathways that become dysregulated during adverse LV remodeling, but rather reverse LV remodeling represents a coordinated multilevel process that allows the heart to adopt a new, less pathologic steady state that is associated with improved pump function and improved clinical prognosis.

Many of the multilevel molecular changes that occur during forward LV remodeling remain dysregulated in reverse remodeled hearts, despite improvements in structural and functional abnormalities

44

Biological Robustness



- A perturbation may drive the state of the system toward the boundary of its steady state
- When the state of the system returns to its original state, it is called 'stability' and 'homeostasis'. When it transits to steady state 2, the system regains its stability in a new steady state.
- If the system's functions are still intact, such a transition is considered to be a biologically robust response regardless of whether it is in steady state 1 or 2.

Kitano Mol Syst Biol 2007: 137; 1-7

45

Frankly, we also are becoming a little concerned that he has no intention of making this talk clinically relevant

46

Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial

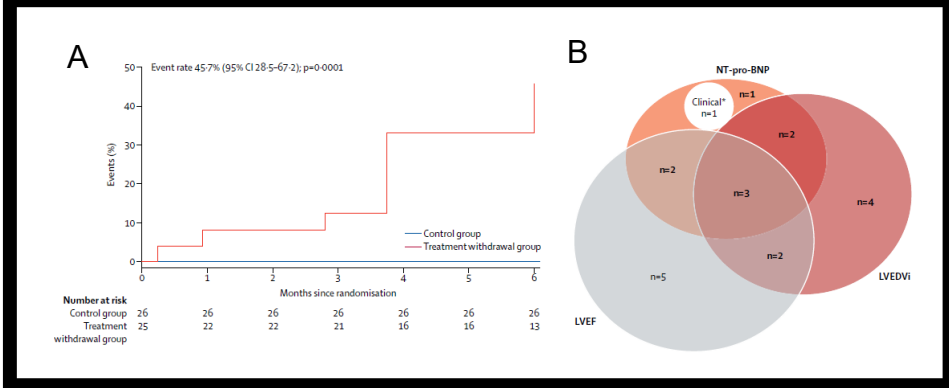
Brian P Halliday, Rebecca Wassall, Amrit S Lota, Zohya Khalique, John Gregson, Simon Newsome, Robert Jackson, Tsveta Rahneva, Rick Wage, Gillian Smith, Lucia Venneri, Upasana Tayal, Dominique Auger, William Midwinter, Nicola Whiffin, Ronak Rajani, Jason N Dungu, Antonis Pantazis, Stuart A Cook, James S Ware, A John Baksi, Dudley J Pennell, Stuart D Rosen, Martin R Cowie, John G F Cleland, Sanjay K Prasad

- Recovered LVEF from < 40% to > 50%
- Normalized LVEDV
- NT-proBNP < 250 mg/ml
- Randomly assigned 1:1 to phased withdrawal of GDMT
- Primary end point relapse of DCM in 6 mos
  - Decrease in LVEF by > 10% and LVEF < 50%
  - Increase in LVEDV by > 10%
  - 2x rise in NT-proBNP

Halliday et al Lancet 2018

47

TRED-HF: Primary End Point



"This finding suggests that, for many patients, improvement in cardiac function following treatment does not reflect full and sustained recovery but rather reflects remission, which requires at least some treatment to be maintained."

Halliday et al Lancet 2018

48

Diagnosis and Management of HF Patients with a ~~Recovered~~ Improved LVEF

CLINICAL PRACTICE GUIDELINE: EXECUTIVE SUMMARY

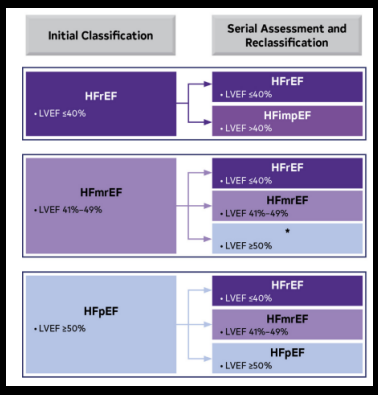
2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary

- Nomenclature
  - HF with improved EF (HFimpEF)
- Working Definition
  - Documentation of LVEF ≤ 40%
  - Follow-up LVEF > 40%
  - Assessment of LVEF trajectory is important

J Am Coll Cardiol. 2022 Mar 24. pii: S0735-1097(21)08394 7. doi: 10.1016/j.jacc.2021.12.011

49

Diagnosis and Management of HF Patients with an Improved LVEF



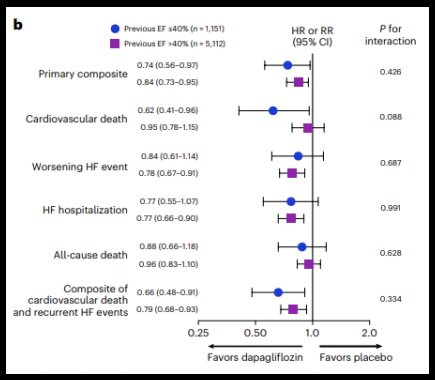
Recommendation for HF With Improved EF (HFimpEF)
Referenced studies that support the recommendation are summarized in the Online Data Supplements.

COR	LOE	RECOMMENDATION
1	B-R	1. In patients with HFimpEF after treatment, GDMT should be continued to prevent relapse of HF and left ventricular dysfunction, even in patients who may become asymptomatic (36).

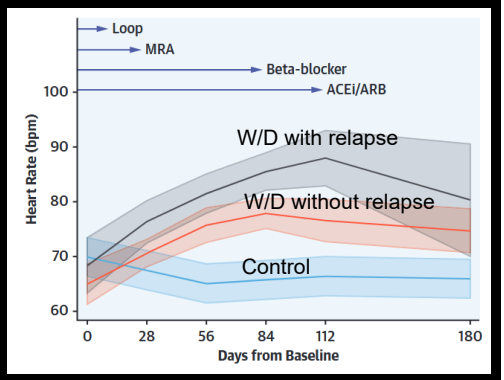
50

Which of the GDMT Drugs are Important for Treating Patients with HFimpEF ?

We don't' really know…..



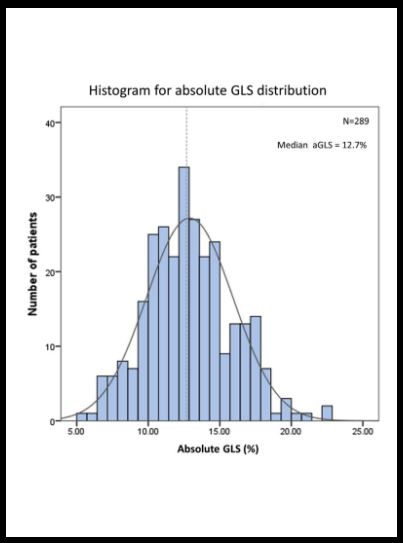
Vardeny et al, Nat Med 2022; 28: 2504-2511

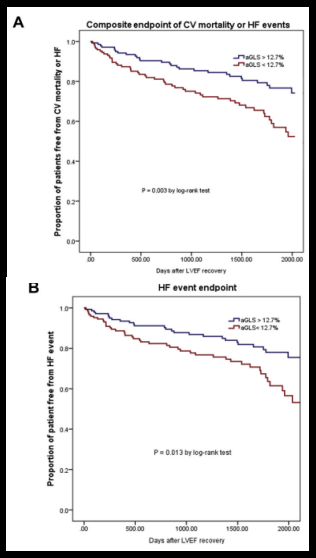


Halliday et al, JACC: Heart Failure 2022; 9: 509-517

51

HFimpEF Patients are Extremely Heterogeneous





Janwanishstaporn…Greenberg JACC:Heart Failure 2022; 10:27-37

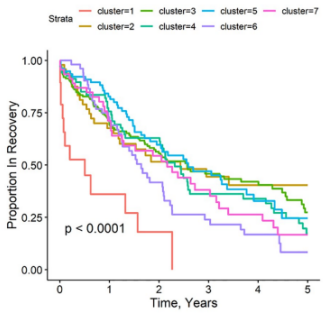
52

HFimpEF Patients are Heterogeneous

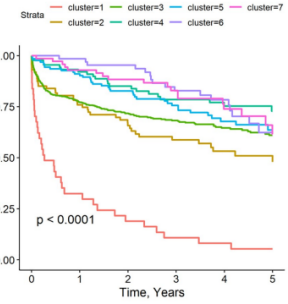
RESEARCH ARTICLE

Unsupervised cluster analysis of patients with recovered left ventricular ejection fraction identifies unique clinical phenotypes

Probability of maintaining an LVEF > 50% during follow-up



Kaplan Meier Analysis of Mortality Across Clusters



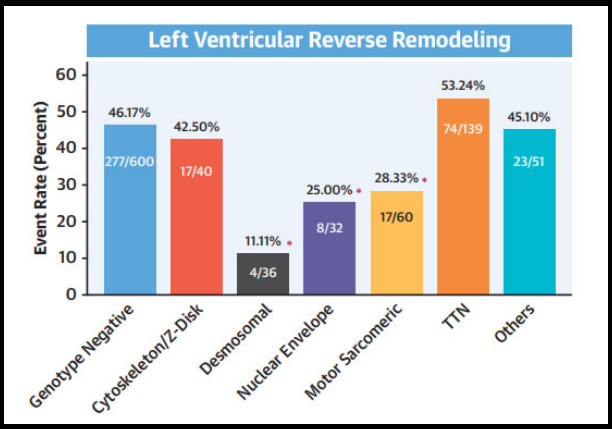
Perry...Mann PLOS ONE 2021 (doi.org/10.1371/journal.pone.o24837)

53

HFimpEF Patients are Heterogeneous

Effect of Genetic Variations

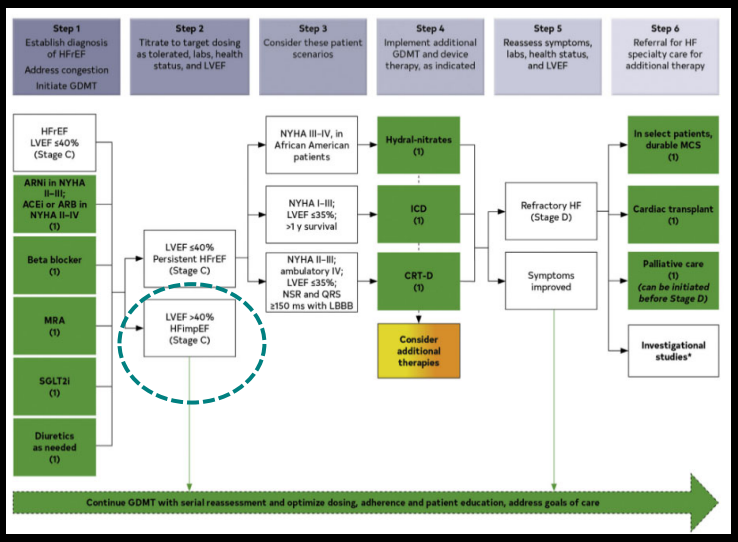
- Baseline and longitudinal data from 1,005 genotyped DCM probands from 20 centers in Spain
- Patients treated with GDMT (no SGLT2i)
- Median follow-up of 4.04 years
- Reverse LV remodeling occurred in 46.2% genotype negative patients and 39.6% of genotype positive patients



Escobar-Lopez JACC 2021: 78; 1682-1699

54

Treatment of HFrEF (Stages C and D)



J Am Coll Cardiol. 2022 Mar 24. pii: S0735-1097(21)08394 7. doi: 10.1016/j.jacc.2021.12.011

55

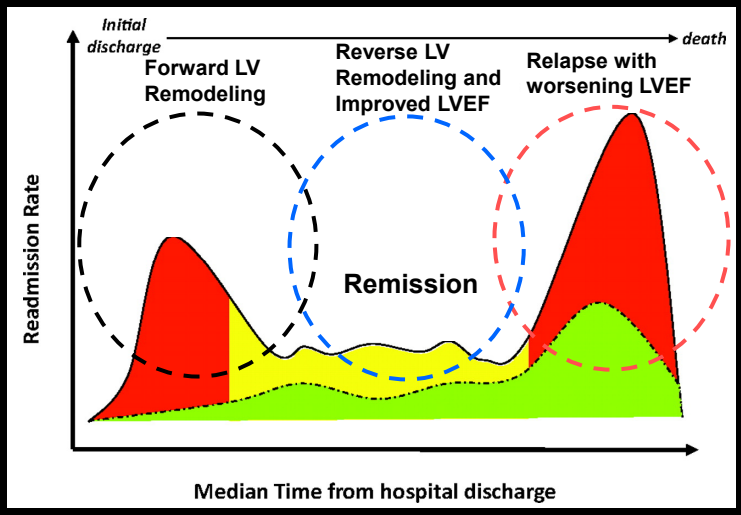
Medical Management of HFimpEF

- HFimpEF patients are very heterogeneous
  - Clinical approach should take into account the etiology of LV dysfunction
- We understand very little about which medications patients are required and which medications can be withdrawn
  - The DELVER trial demonstrated that Dapigliflozin improved outcomes in patients with HFimpEF
- Based on the results of the TRED-HF study (n=51) the 2022 ACC/HFSA/HFSA HF guidelines recommend to continue GDMT in all patients
  - Relapse of HF is associated with recurring myocyte injury
- Cessation of diuretic therapy can be considered
  - If HF recurs after stopping diuretics, uptitrating GDMT should be considered

Wilcox…Mann JACC 2020;76: 719-734

56

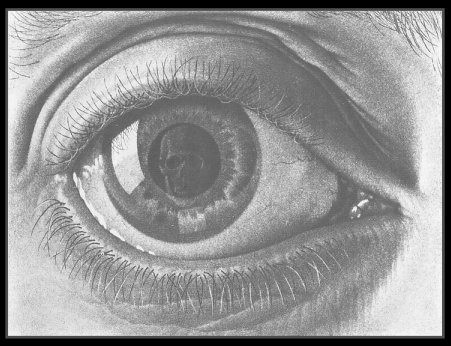
We Have Always Known About Myocardial Remission…



Desai A S , Stevenson L W Circulation 2012;126:501-506

57

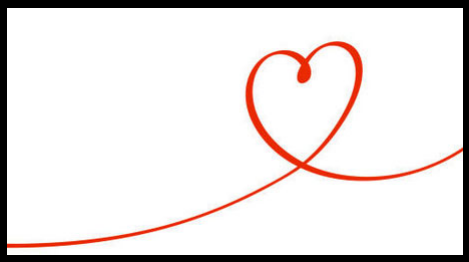
Why We All Need to Care About This Stuff….



"Does it score?"

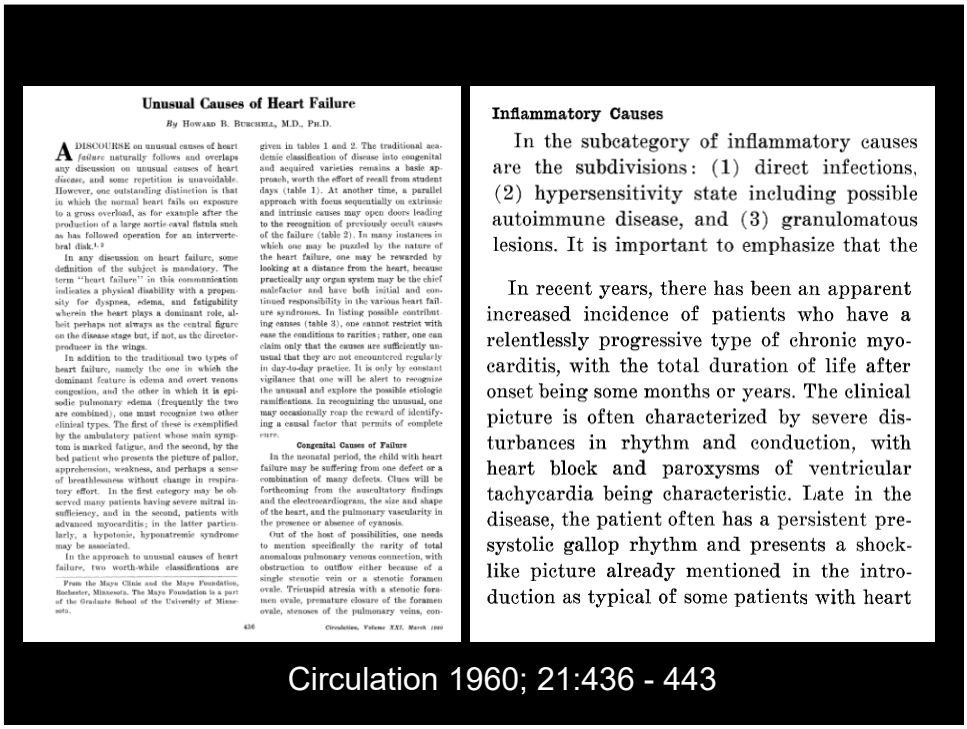
58

Thank you for giving me the opportunity to present the 2023 Burchell Lecture!



59

60



Unusual Causes of Heart Failure

By Howard B. Burchell, M.D., Ph.D.

A DISCOURSE on unusual causes of heart *failure* naturally follows and overlaps any discussion on unusual causes of heart *disease*, and some repetition is unavoidable. However, one outstanding distinction is that in which the normal heart fails on exposure to a gross overload, as for example after the production of a large aortic-caval fistula such as has followed operation for an intervertebral disk.[1,2]

In any discussion on heart failure, some definition of the subject is mandatory. The term "heart failure" in this communication indicates a physical disability with a propensity for dyspnea, edema, and fatigability wherein the heart plays a dominant role, albeit perhaps not always as the central figure on the disease stage but, if not, as the director-producer in the wings.

In addition to the traditional two types of heart failure, namely the one in which the dominant feature is edema and overt venous congestion, and the other in which it is episodic pulmonary edema (frequently the two are combined), one must recognize two other clinical types. The first of these is exemplified by the ambulatory patient whose main symptom is marked fatigue, and the second, by the bed patient who presents the picture of pallor, apprehension, weakness, and perhaps a sense of breathlessness without change in respiratory effort. In the first category may be observed many patients having severe mitral insufficiency, and in the second, patients with advanced myocarditis; in the latter particularly, a hypotonic, hyponatremic syndrome may be associated.

In the approach to unusual causes of heart failure, two worth-while classifications are given in tables 1 and 2. The traditional academic classification of disease into congenital and acquired varieties remains a basic approach, worth the effort of recall from student days (table 1). At another time, a parallel approach with focus sequentially on extrinsic and intrinsic causes may open doors leading to the recognition of previously occult causes of the failure (table 2). In many instances in which one may be puzzled by the nature of the heart failure, one may be rewarded by looking at a distance from the heart, because practically any organ system may be the chief malefactor and have both initial and continued responsibility in the various heart failure syndromes. In listing possible contributing causes (table 3), one cannot restrict with ease the conditions to rarities; rather, one can claim only that the causes are sufficiently unusual that they are not encountered regularly in day-to-day practice. It is only by constant vigilance that one will be alert to recognize the unusual and explore the possible etiologic ramifications. In recognizing the unusual, one may occasionally reap the reward of identifying a causal factor that permits of complete cure.

Congenital Causes of Failure

In the neonatal period, the child with heart failure may be suffering from one defect or a combination of many defects. Clues will be forthcoming from the auscultatory findings and the electrocardiogram, the size and shape of the heart, and the pulmonary vascularity in the presence or absence of cyanosis.

Out of the host of possibilities, one needs to mention specifically the rarity of total anomalous pulmonary venous connection, with obstruction to outflow either because of a single stenotic vein or a stenotic foramen ovale. Tricuspid atresia with a stenotic foramen ovale, premature closure of the foramen ovale, stenoses of the pulmonary veins, con-

From the Mayo Clinic and the Mayo Foundation, Rochester, Minnesota. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

436 Circulation, Volume XXI, March 1960

Inflammatory Causes

In the subcategory of inflammatory causes are the subdivisions: (1) direct infections, (2) hypersensitivity state including possible autoimmune disease, and (3) granulomatous lesions. It is important to emphasize that the

In recent years, there has been an apparent increased incidence of patients who have a relentlessly progressive type of chronic myocarditis, with the total duration of life after onset being some months or years. The clinical picture is often characterized by severe disturbances in rhythm and conduction, with heart block and paroxysms of ventricular tachycardia being characteristic. Late in the disease, the patient often has a persistent presystolic gallop rhythm and presents a shock-like picture already mentioned in the introduction as typical of some patients with heart

Circulation 1960; 21:436 - 443

61