Congestive Heart Failure Update and Management and Review of Clinical Trials

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POMA May 1, 2019

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Disclosures

- Advisory Board
  - Medtronic
- Speaker's Bureau
  - None
- Supported Clinical Trials
  - Medtronic
  - Abbott
  - Novartis

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Today's Agenda

- Background
  - We will be discussing SYSTOLIC heart failure: HFrEF
  - Evaluation for reversible causes
- Chronic systolic heart failure
  - Current therapies
  - New Therapies
    - Medical
    - Device
    - Clinical trials
  - How to tell a patient is failing despite treatment
- Acute systolic heart failure
  - Current and new therapies
  - Heart transplant and mechanical circulatory support

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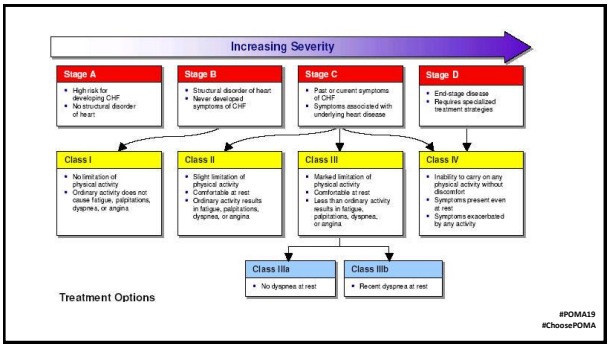
Increasing Severity
Stage A
High risk for developing CHF
No structural disorder of heart
Stage B
Structural disorder of heart
Never developed symptoms of CHF
Stage C
Past or current symptoms of CHF
Symptoms associated with underlying heart disease
Stage D
End-stage disease
Requires specialized treatment strategies
Class I
No limitation of physical activity
Ordinary activity does not cause fatigue, palpitations, dyspnea, or angina
Class II
Slight limitation of physical activity
Comfortable at rest
Ordinary activity results in fatigue, palpitations, dyspnea, or angina
Class III
Marked limitation of physical activity
Comfortable at rest
Less than ordinary activity results in fatigue, palpitations, dyspnea, or angina
Class IV
Inability to carry on any physical activity without discomfort
Symptoms present even at rest
Symptoms exacerbated by any activity
Class IIIa
No dyspnea at rest
Class IIIb
Recent dyspnea at rest
Treatment Options
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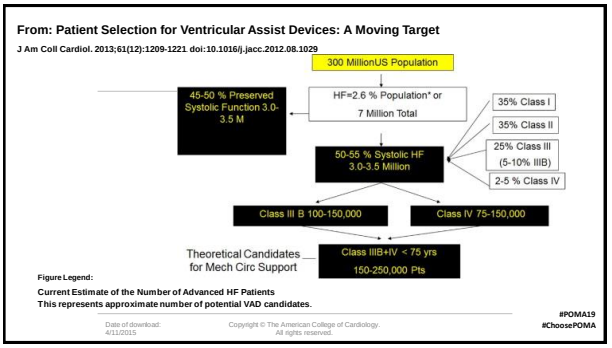
From: Patient Selection for Ventricular Assist Devices: A Moving Target
J Am Coll Cardiol. 2013;61(12):1209-1221 doi:10.1016/j.jacc.2012.08.1029
300 MillionUS Population
HF=2.6 % Population* or
7 Million Total
45-50 % Preserved Systolic Function 3.0-3.5 M
35% Class I
35% Class II
25% Class III
(5-10% IIIB)
2-5 % Class IV
50-55 % Systolic HF 3.0-3.5 Million
Class III B 100-150,000
Class IV 75-150,000
Theoretical Candidates for Mech Circ Support
Class IIIB+IV < 75 yrs
150-250,000 Pts
Figure Legend:
Current Estimate of the Number of Advanced HF Patients
This represents approximate number of potential VAD candidates.
Date of download: 4/11/2015
Copyright © The American College of Cardiology. All rights reserved.
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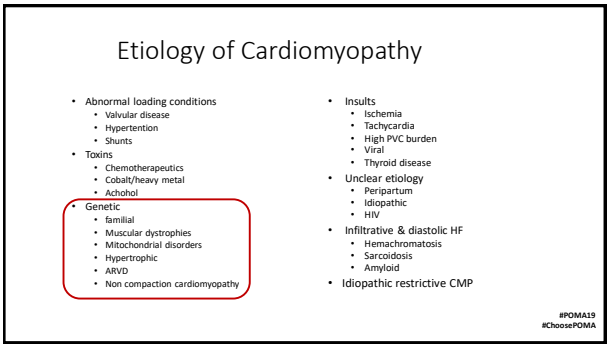
Etiology of Cardiomyopathy
Abnormal loading conditions
Valvular disease
Hypertention
Shunts
Toxins
Chemotherapeutics
Cobalt/heavy metal
Achohol
Genetic
familial
Muscular dystrophies
Mitochondrial disorders
Hypertrophic
ARVD
Non compaction cardiomyopathy
Insults
Ischemia
Tachycardia
High PVC burden
Viral
Thyroid disease
Unclear etiology
Peripartum
Idiopathic
HIV
Infiltrative & diastolic HF
Hemachromatosis
Sarcoidosis
Amyloid
Idiopathic restrictive CMP
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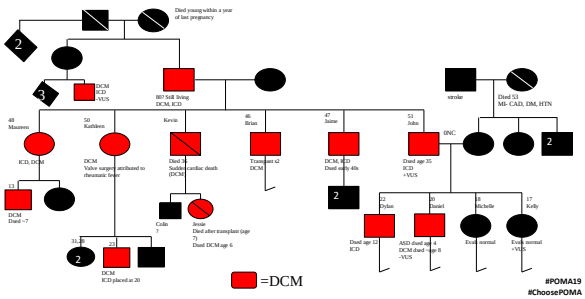
Just one family can lead to the identification of a high risk gene to help then prognosticate not only the patient, but their family members



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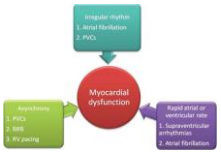
Cardiomyopathy
evaluate for reversibility

- Alcohol intake?
  - In persons who consumed 70 g of ethanol (or the equivalent of 7oz of whiskey, 20 oz of wine, or 72 oz of beer [ie, six 12-oz cans]) per day for 20 years, 36% had an abnormal ejection fraction.
- Tachycardia mediated
- Asynchrony
  - PVC-induced (≥ 10%)
  - BBB
  - RV pacing
- Ischemia
- Valvular disease
- Consider RV biopsy



Demakis JG, Proskey A, Rahimtoola SH, et al. The natural course of alcoholic cardiomyopathy. *Ann Intern Med.* Mar 1974;80(3):293-7.
Poppis E et al. Alcoholic Cardiomyopathy. Medscape 2011.
Gopinathannair R Tachycardia-mediated Cardiomyopathy:recognition and Management. *Curr Heart Fail Rep.* Dec 2009;6(4):257-64
Simantirakis E. Arrhythmia-induced cardiomyopathies:the riddle of the chicken or the egg still unanswered? *Europace*. Nov 2011

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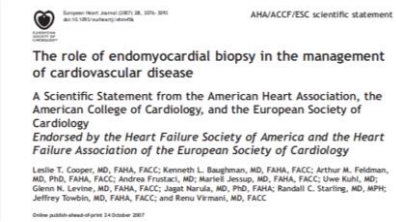
Cardiomyopathy
evaluate for reversibility



AHA/ACCF/ESC scientific statement

The role of endomyocardial biopsy in the management of cardiovascular disease

A Scientific Statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology
Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology

Leslie T. Cooper, MD, FAHA, FACC; Kenneth L. Baughman, MD, FAHA, FACC; Arthur M. Feldman, MD, PhD, FAHA, FACC; Andrea Frustaci, MD; Marielli Jessup, MD, FAHA, FACC; Uwe Kuhl, MD; Glenn N. Levine, MD, FAHA, FACC; Jagat Narula, MD, PhD, FAHA; Randall C. Starling, MD, MPH; Jeffrey Towbin, MD, FAHA, FACC; and Renu Virmani, MD, FACC

Online publish-ahead-of-print 24 October 2007

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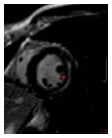
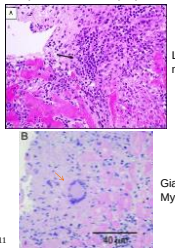
Cardiomyopathy
evaluate for reversibility

- When to perform endomyocardial biopsy



Think about myocarditis with arrhythmias, + troponin



Lymphocytic myocarditis

Giant Cell Myocarditis

Yeglee N et al *Value of MRI in patients with a clinical suspicion of acute myocarditis*.EUR RAD 2007;17;2211

Gotsman & Keren *Fulminant lymphocytic myocarditis vs giant cell myocarditis*. ESCARDIO.org Oct 2008

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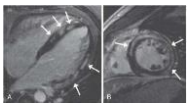
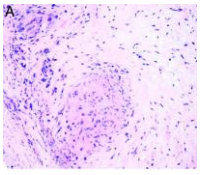
Cardiomyopathy
evaluate for reversibility

- When to perform endomyocardial biopsy



Think Sarcoid with CHB, arrhythmias



Kandolin R et al. Circ Arrhythm Electrophysiol 2011;4:303-309

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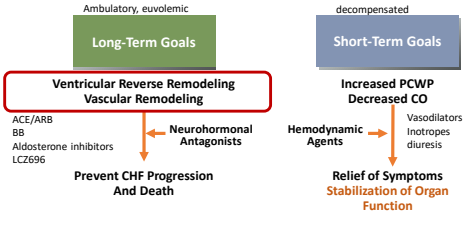
Goals of Therapy:
Chronic Versus Acute HF



PCWP = pulmonary capillary wedge pressure.

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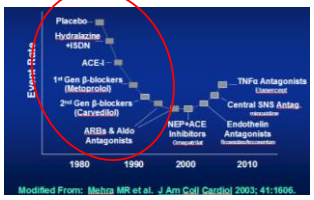
Therapy For Chronic Systolic Heart Failuare

Diminishing Returns with Vasodilators & Neurohumoral Antagonists in HF



Modified From: Mehra MR et al. J Am Coll Cardiol 2003; 41:1606.

And Hijacked from Dr. Ken Margulies and then further modified

EVEREST
Tolvaptan vasspressin antagonist

Protect
Rolofylline:Adenosine antagonist

TRIDENT-1
Tonapofylline-adenosine antag

Pre-RELAX-AHF
Relaxin:vasodilator

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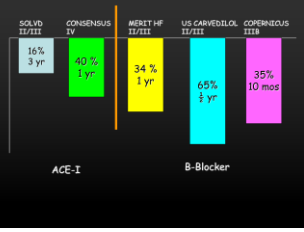
Reduction in Mortality with ACE-I & B-Blocker therapy



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First-line therapy
B blocker

- Effects
  - Inhibit the adverse effects of sympathetic system
  - ***Delay and reverse remodeling***
  - Improve survival, morbidity
- Clinical use: systolic and diastolic heart failure
  - Given to all patients with systolic HF in absence of fluid overload
- Adverse effects
  - Hypotension, bradycardia, worsening HF
- Lingering questions
  - Class effect?
- Target heart rate?
- Target dose?

Good review:
Bristow M. Beta adrenergic blockade in chronic heart failure. Circulation 2000;101:558-69

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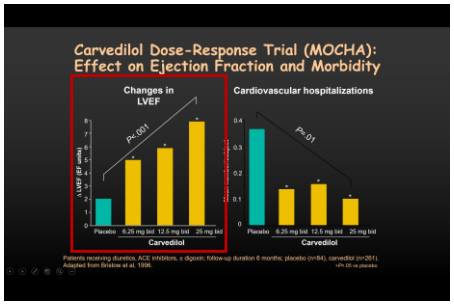

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BB Dose Matters: almost 20 years later!!!!!!
Presented at HFSA 10/2015

	BB dose (carvedilol equivalent) Low= < 25 mg daily *Hi= >25 mg daily	
Baseline Heart Rate Low = < 70bpm Hi= > 70 bpm	LL	*HL
	LH	*HH

LH- low dose, high HR
13 % higher risk of bad outcome: All cause death, all cause hosp
The beneficial effect is beyond the HR effect, even if HR is already low

Fiuzat Mona. Heart Rate or Beta-blocker Dose? Association with Outcomes in Ambulatory Heart Failure Patients with Systolic Dysfunction: Results from the HF-ACTION Trial, *JACC: Heart Failure* (2015), doi: 10.1016/j.jchf.2015.09.002.

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Secondary aldosteronism in CHF

- Two pathophysiologic mechanisms
  - increased production by adrenals
  - decreased hepatic clearance
    - Effects of aldosterone:
      Sodium retention
    - Potassium and magnesium loss
    - Myocardial and vascular fibrosis
    - Baroreceptor dysfunction
    - Impairs arterial compliance
    - Decreased myocardial norepinephrine uptake

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Aldosterone Inhibitors

- RALES Trial
  - 1663 NYHA III-IV
  - 25 mg Aldactone vs Placebo
- 30% reduction in death*
  - Progressive HF
  - SCD
- 35%reduction in hospitalization
- Significant improvement in NYHA functional class

Pitt et al. NEJM 1999;341:709

- EPHESUS Trial
  - 6632 pts 3-14 d after AMI, EF < 40%
    - And sign of HF
    - Or DM with or without signs of HF
  - 50 mgQD Eplerenone vs placebo
- Significant reduction in:
  - Death 14 % v 17%
  - CVd/hosp 27% v 30%
  - SCD 4.9% vs 6%

Pitt NEJM 2003;348:1309

EMPHASIS Trial:
N= 2737 with mild HF EF ≤ 35%
Improvement with Epleranone

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Zannad NEJM 2011;364:11

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A-HeFT: Design

Inclusion Criteria

- Self-identified African American, symptomatically stable NYHA class III-IV on standard HF treatment; b-blockers for at least 3 months
- LVEF ≤35% or LVEF <45% and a resting LVIDD >2.9 cm/m² or >6.5 cm (by Echo)

Exclusion Criteria

- Women of childbearing age who were pregnant, nursing, or not using contraception
- MI, ACS, CVA, cardiac surgery, PCI within 3 months
- Valvular disease, HOCM, restrictive CMY, myocarditis
- Ventricular arrhythmias unless ICD
- Requirement for inotropes or OHTx

Hydralazine
(target dose: 100 mg three times a day)

Isosorbide mononitrate
(target dose: 40 mg three times a day)

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Taylor AL, et al. NEJM 2004;351:2049-57

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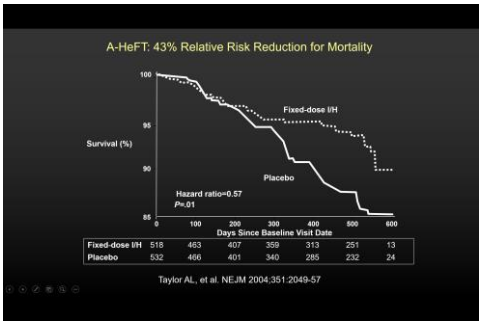

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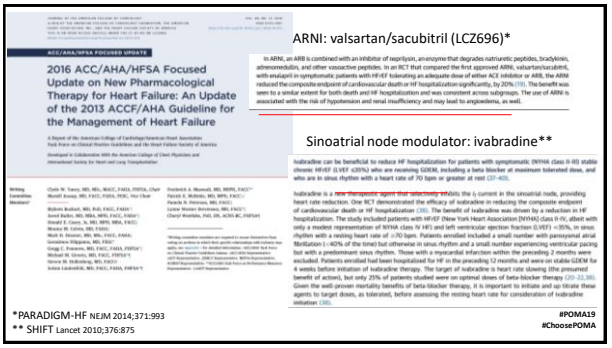
ACC/AHA/HFSA FOCUSED UPDATE
2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure
ARNI: valsartan/sacubitril (LCZ696)*
Sinoatrial node modulator: ivabradine**
*PARADIGM-HF NEJM 2014;371:993
** SHIFT Lancet 2010;376:875
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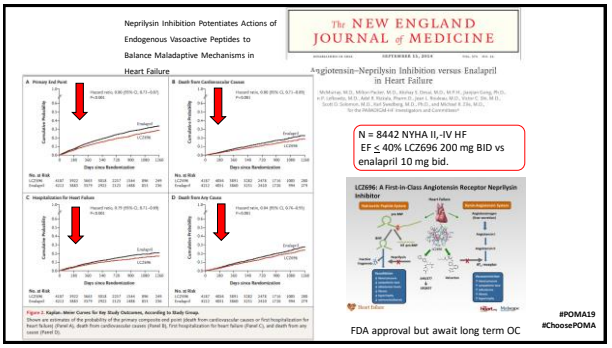
Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides to Balance Maladaptive Mechanisms in Heart Failure
The NEW ENGLAND JOURNAL of MEDICINE
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure
N = 8442 NYHA II, IV HF
EF ≤ 40% LCZ696 200 mg BID vs enalapril 10 mg bid.
LCZ696: A First-in-Class Angiotensin Receptor Neprilysin Inhibitor
FDA approval but await long term OC
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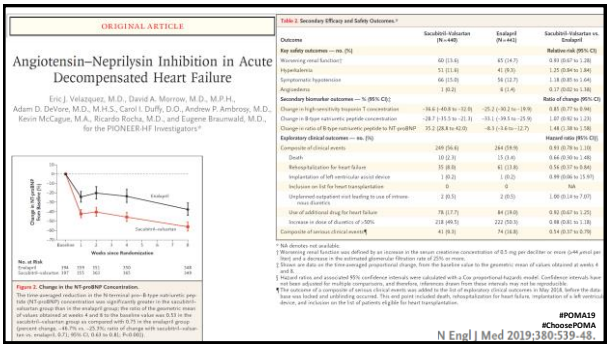
ORIGINAL ARTICLE
Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure
N Engl J Med 2019;380:539-48.
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Incorporating Sacubitril/Valsartan into practice

- PARADIGM-HF Trial enrolled mostly NYHA Class II and some Class III ambulatory patients
- May be limited by blood pressure in patients with more advanced disease
- Incorporated in lieu of an ACE or ARB for Stage C with NYHA Class 2 or 3 symptoms without significant renal insufficiency or hyperkalemia
- PIONEER-HF suggests that Sacubitril/Valsartan can be started during acute heart failure hospitalization without harm, and biomarker evidence of improving BNP (short term study- 8 weeks)
- *WATCH RENAL FUNCTION CAREFULLY*

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PARAGON-HF Trial (*honorable mention*)

- Randomized, double-blind, parallel group, active-controlled, event-driven trial comparing the long-term efficacy and safety of valsartan and sacubitril/valsartan in patients with chronic HFpEF (left ventricular ejection fraction ≥45%)
- NYHA II to IV symptoms
- Elevated natriuretic peptides and evidence of structural heart disease.
- Sequential single-blind run-in periods to ensure tolerability of both drugs at half the target doses
- The primary outcome is the composite of cardiovascular death and total (first and recurrent) HF hospitalizations.

Enrollment is complete – 4882 patients randomized
Mean age 72.7±8.4 years
Female 52%
Mean left ventricular ejection fraction 57.5%,
New York Heart Association class II 72%
38% had ≥1 hospitalizations for heart failure w/I 9 months

Results due late 2019 or 2020

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JACC Heart Fail. 2017 Jul;5(7):471-482

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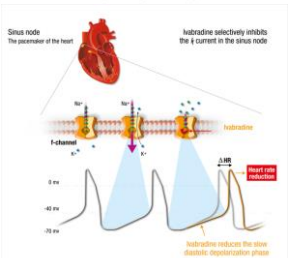
Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

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

N-6558 ivabradine 7.5 mg bid Vs placebo (OMM)

Ivabradine selectively inhibits the sinus node thereby decreasing myocardial oxygen demand without effecting inotropy or bloodpressure.



Swedberg Lancet 2010;376:875

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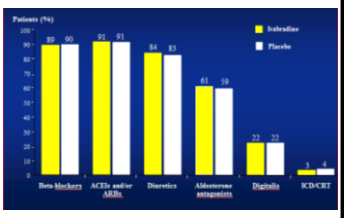
Inclusion Criteria Background Tx

- >18 years
- Class II to IV NYHA heart failure
- Ischaemic/non-ischaemic aetiology
- LV systolic dysfunction (EF ≤35%)
- Heart rate >70 bpm
- Sinus rhythm
- Documented hospital admission for worsening heart failure <12 months



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Conclusions

Ivabradine significantly reduces major risks associated with heart failure (f/u up to 23 months):

- 18% reduction in CV death or hospital admission for worsening HF
- 26% reduction in hospital admission for worsening heart failure
- No benefit for all cause or CV mortality alone

Benefits are apparent early (within 3 months), are consistent in predefined subgroups, and have been demonstrated on top of recommended therapy
Treatment is well tolerated

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

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FDA

- On April 15, 2015 the FDA approved Ivabradine in the US
  - ***"To reduce the risk of heart failure hospitalization"***
  - LVEF less than 35%
  - Heart rate above 70 BPM (sinus) on maximally tolerated beta blockade

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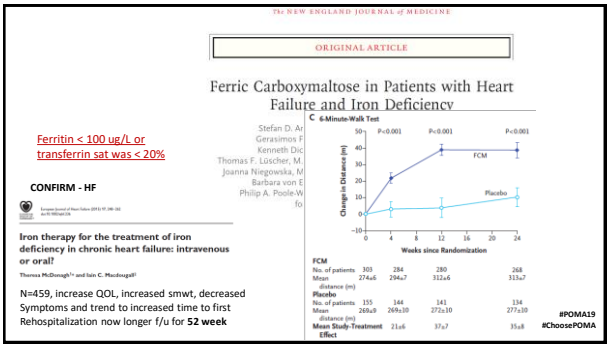

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Take Away Points: ambulatory HFrEF patients

- ACE-Inhibitors are still first line therapy (high dose if BB intolerant)
- ARBs is as effective if ACE intolerant, the addition of ARB to ACE therapy may be done without harm, maybe some benefit, but close watch of potassium and renal function
- Beta Blockers: dose matters, try and achieve target doses, even at the cost of vasodilator dose
  - Carvedilol 25 mg bid (US carvedilol Trial)
  - Metoprolol Succinate 150 mg daily (MERIT HF Trial)
  - Bisoprilol 7.5 mg daily (CIBIS Trial)
- We are using aldosterone inhibitors earlier, they are becoming also part of the mainstay of therapy
  - Caveat: compliance, Scr ≤ 2.5 and K ≤ 5
- Hydralazine/ISDN: better than nothing, consider in AA if unresponsive to ACE/ARB/BB
- LCZ696: Entresto: great outcomes II-IV
  - Ongoing trials for HFpEF patients as well evaluating neurologic consequences
- Ivabradine: decreases hospitalizations in pts with HR > 70, NSR despite GDT
  - *Be careful of fixed SV patients- ie restrictives and infiltratives, they may need HR to maintain CO*
- IV iron: should be considered in HF patients who remain symptomatic despite OMM regardless if anemic or not, ongoing chronic IV iron may also be beneficial (benefits seen up to a year out)
  - Ferritin < 100 ug/L or transferrin sat was < 20%

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What's new in Device therapy for Chronic HF?

- **NECTAR-HF**
  - Chronic vagal stimulation
- **CUPID**
  - Intracoronary infusion of SRCA 2a
- **FIX-HF**
  - CCM: cardiac contractility modulation

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FASTTRACK ESC HOT LINE
Heart failure/cardiomyopathy

Chronic vagal stimulation for the treatment of low ejection fraction heart failure: results of the NEural Cardiac TherApy foR Heart Failure (-HF) randomized controlled trial

ietano M. De Ferrari[2], Anton E. Tuinenburg[3], David Wright[4], ıristian Butter[4], Helmut Klein[7], Craig Stolen[8], Scott Meyer[8], Agnes Ramuzat[9], Bernd Schubert[9], Doug Daum[8], Petr Neuzil[10], , Maria Angeles Castel[5], Antonio D'Onofrio[11], Scott D. Solomon[13], id Stephen B. Ruble[8]

N=96 2:1 randomization
6 month follow up
Although no change in LV end syst diam
Significantly improved quality of life
Need larger trials

Multiple device based therapies to suppress the sympathetic nervous system or stimulate the vagal system

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Clinical/Translational Research

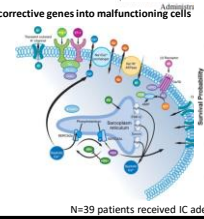
Long-Term Effects of AAV1/SERCA2a Gene Transfer in Patients With Severe Heart Failure

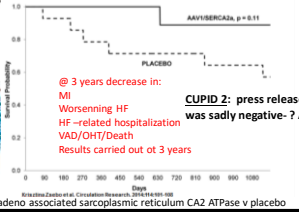
Analysis of Recurrent Cardiovascular Events and Mortality

Krisztina | Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease phase 2 survival curve for all-cause mortality in high dose recombinant adeno-associated viral vector (AAV) containing human sarcoplasmic reticulum Ca2+ ATPase2a (SERCA2a) gene (AAV1/SERCA2a) group versus placebo.

Administers

nsert corrective genes into malfunctioning cells





@ 3 years decrease in:
MI
Worsenning HF
HF –related hospitalization
VAD/OHT/Death
Results carried out ot 3 years

CUPID 2: press release 4/26/2015 was sadly negative- ? AAV1 vs AAV9

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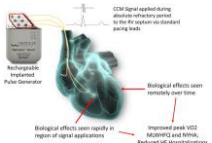
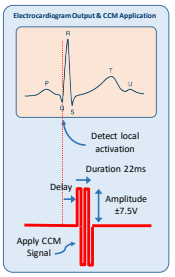
N=39 patients received IC adeno associated sarcoplasmic reticulum CA2 ATPase v placebo

35

Cardiac Contractility Modulation

- Pacemaker like device
- Delivers energy to the myocardium during the absolute refractory period – no contraction with stimulation
- Causes changes that lead to increased intracellular calcium and therefore increased contractility





J Am Coll Cardiol HF 2018

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Clinical Trials Program for CCM

- FIX-HF-4 study - (168 patients) conducted in European Union - showed that 3 months of CCM treatment improved exercise tolerance and quality of life.
- Fix HF-5 randomized 428 patients followed up for 1 year
  - Did NOT achieve primary end-point - analysis of anaerobic threshold measured on cardiopulmonary stress test
  - Showed significant improvements in the secondary end points:
    - Peak Vo_2
    - Minnesota Living With Heart Failure Questionnaire score
    - First to show that patients with an LVEF between 35% and 45% benefited the most, whereas those with EF <25% derived inadequate benefit.

Circulation. 2018;138:2738–2740

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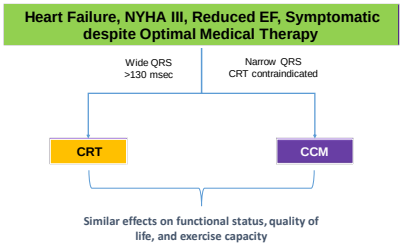
Potential Role of CCM



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Take Away Points

- Vagal nerve stimulation did not improve markers of remodeling, but did improve symptoms, more to come
- Intracoronary infusion of AAV1/SERCA2a in patients with advanced heart failure, positive signals of cardiovascular events which persist for years.
  - No safety concerns were noted during the 3-year follow-up.
  - *Larger scale CUPID 2 was negative:*
    - *?correct carrier AAV1 VS AAV9*
    - *?correct molecule to effect cell function? S100A1 (includes effect on cell energetics: ? MYK491003 (myosin activator)*
- Cardiac Contractility Modulation
  - May have a beneficial effect in patient swith EF 25-40% anc continued symptoms despite GDMT and not CRT candidates.

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Today's Agenda

- Background
  - Evaluation for reversible causes
  - How to tell a patient is failing
- Chronic systolic heart failure
  - Current therapies
  - New Therapies
    - Medical
    - Device
    - Clinical trials
- Acute systolic heart failure
  - Current and new therapies
  - Heart transplant and mechanical circulatory support

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How to know your patient may need advanced therapies:

Early warning signs that an adult HF patient is starting to fail.

- Severely reduced cardiac function
  - EF <30%
- Poor functional status
  - NYHA IIIb-IV
  - Six minute walk: < 400 meters
  - Cardiopumonary testing revealing poor cardiac reserve
    - VO2 <14 cc/kg/min
      - Cardiac limitation
      - Maximal medical therapy

- Intolerance of NHB
  - Kittleson et al. JACC 2003;41:2029
- recurrent hospitalizations
  - Setoguchi et al Am Heart J 2007
- Need for inotropes
  - Kittleson et al. JACC 2003;41:2029
- Hyponatremia
- Renal insufficiency
  - Hillege HL et al. Circulation. 2000;102:203.
- Increasing diuretic need
  - Levy ESC HF 2003
- Living in a smaller and smaller space
  - Circulation 1991;83:778-786
- Electrical instability
  - Afib or ventricular arrhythmias

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Severe Heart Failure

Recognizing the "Walking Wounded"

- Underperfused
  - Walk in, drive in, fly in
  - Obvious
    - Malignant arrhythmias
    - Low BP
  - Less Obvious (3T's)
    - End organ underpersion despite a normal BP
      - Talk: lethargic, breathless at the end of a sentence
      - Touch: cool, pulses are low, lips/ears turn blue when they lay back for exam
      - Testing:
        - Lactate
        - Tbili/LFTs
        - Scr/BUN

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Acute Decompensated heart failure vs SHOCK

- ADHF::: congestion, possibly low output, quickly responsive to medical intervention
  - Medical therapy
- SHOCK::: unstable hemodynamics, end organ underperfusion
  - Device therapy
    - Ischemic shock AMI
    - Hemodyanmic shock
    - Arrhythmic shock

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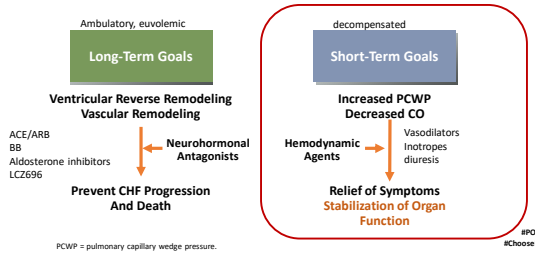
Goals of Therapy: *Chronic Versus Acute HF*



PCWP = pulmonary capillary wedge pressure.

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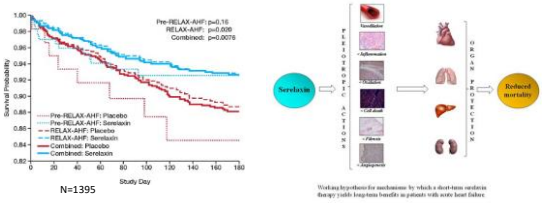
RELAX-AHF and Pre RELAX-AHF Trials



N=1395

Concl: N= 1395decreased 180 day mortality, markers of end organ damage (scr, transaminases) and markers of decongestion (BNP) were improved in the seralaxin groups. Unfortunately
*RELAX-AHF2: approx 6800 pts; completed 1/26/17;ClinicalTrials.gov Identifier:NCT01870778: no benefit

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*EUR J Heart Fail 2017, april 28

Metra JACC 2013: 61;196-206

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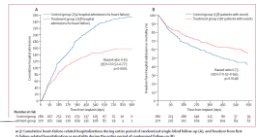
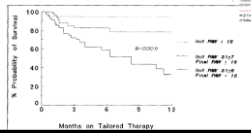
More About Congestion

PCWP after tailored therapy
Predicted outcomes

The CHAMPION Trial Abraham LANCET 2011



LWS AJC 1990



Protocol: if PAP ressures elevated:
first: increase diuretics
second: increase vasodilators

Target Pressures:
sPAP :15-35
dPAP: 8-20
mPAP: 10-25

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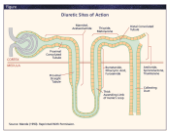
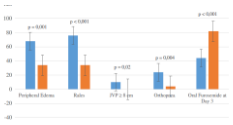
Congestion: what's new with diuresis?



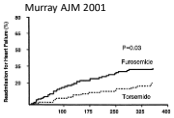
Combination of Loop Diuretics With Thiazide-Type Diuretics in Heart Failure

may be more effective, but use with caution: must watch Na, Potassium and magnesium!

Ferreira EJIM 2014



Murray AJM 2001



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Congestion: what's new with diuresis?

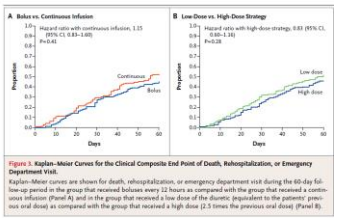

Figure 3. Kaplan–Meier Curves for the Clinical Composite End Point of Death, Rehospitalization, or Emergency Department Visit.

Kaplan–Meier curves are shown for death, rehospitalization, or emergency department visit during the 60-day follow-up period in the group that received boluses every 12 hours as compared with the group that received a continuous infusion (Panel A) and in the group that received a low dose of the diuretic (equivalent to the patients' previous oral dose) as compared with the group that received a high dose (2.5 times the previous oral dose) (Panel B).

Trend towards more weight loss in the high dose strategy and decreased DOE, it was at the cost of trend towards higher Scr (that did not last) out to 60 days.
Also, the low dose group did require an increase in dose

The DOSE Trial Felker NEJM 2011

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Mechanical Fluid Removal

Journal of Cardiac Failure Vol. 16 No. 4 2010

Clinical Trial

Journal of Cardiac Failure Vol. 18 No. 3 2012

...s Associated With Fewer Rehospitalizations than ...uretic Infusion in Patients With Decompensated ...art Failure: Results From UNLOAD

Clinical Trial: Methods and Design

Cardiorenal Rescue Study in Acute Decompensated Heart Failure: Rationale and Design of CARRESS-HF, for the Heart Failure Clinical Research Network

UF lead to worse renal function and no decrease in hospitalizations

Do Any Patients with Acute Decompensated Heart Failure and Acute Cardio-Renal Syndrome Benefit from Ultrafiltration?

Jeffrey M. Turner* and Jeffrey M. Testani*†

*Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut, and †Program of Applied Translational Research, Yale University School of Medicine, New Haven, Connecticut

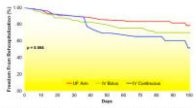

Fig. 3. Freedom from heart failure rehospitalization. Kaplan-Meier estimate of freedom from rehospitalization for heart failure within 90 days after discharge in the ultrafiltration (red line), intravenous (IV) bolus diuretic (green line), and IV continuous diuretic (blue line) groups.

Testani Sem in Dialysis 2014;27(3):231

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Inotropic Therapy
in Patients With ADHF

- Routine use not indicated in short- or long-term setting (despite low EF)
- Rather, inotropes should only be used in patients with:
  - Cardiogenic shock ie: signs of end organ underperfusion
  - Decompensated patients refractory to diuretics
  - Short-term bridge to definitive treatment such as revascularization or cardiac transplantation
  - To optimize vasodilator therapy or add BB therapy

Felker GM, et al. *Am Heart J*. 2001;142:393-401.

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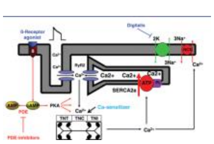
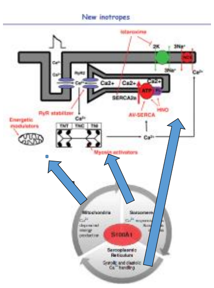
Inotropes





Digoxin: improved QOL
Dobutamine: beta agonist
Milirnone: PDE inhibitor
CLR325 trial: ongoing trial (apeline peptide)
BMS study: BMS-986231 (nitroxyl)
MYK491003: myosin activator

Hasenfuss & Teerlink *EHJ* 2011

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Cardiogenic Shock definition

Hemodynamic Definition
- MAP 30 mmHG below baseline
  - MAP ≤ 60
- CI < 1.8 without support
- CI < 2.0 with support
- LVEDp > 18 mmHg
- RVEDp > 10-15 mm Hg

Clinical signs
- Depressed MS
- Decreased UO
- Liver insufficiency
- Elevated lactate

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New York Heart Association (NYHA) Classification of Heart Failure

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea).
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea).
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea) are present at rest. If any physical activity is undertaken, discomfort increases.

INTERMACS Registry: Patient Profiles

Interagency Registry for Mechanically Assisted Circulatory Support

Profile 1: "Crashing and burning" – critical cardiogenic shock

Profile 2: "Progressive decline" – inotrope dependence with continuing deterioration

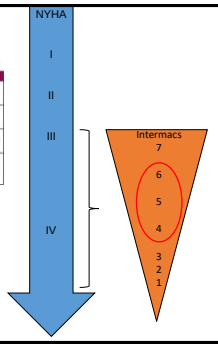
Profile 3: "Stable but inotrope dependent" – describes clinical stability on mild-moderate doses of intravenous inotropes

Profile 4: "Recurrent advanced heart failure" – "recurrent" rather than "refractory" decompensation

Profile 5: "Exertion intolerant" – describes patients who are comfortable at rest but are exercise intolerant

Profile 6: "Exertion limited" – a patient who is able to do some mild activity, but fatigue recurs within a few minutes or any meaningful physical exertion

Profile 7: "Advanced NYHA III" – describes patients who are clinically stable with a reasonable level of comfortable activity, despite history of previous decompensation that is not recent



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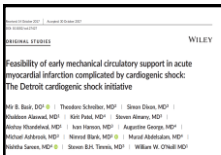

ORIGINAL STUDIES — WILEY

Feasibility of early mechanical circulatory support in acute myocardial infarction complicated by cardiogenic shock: The Detroit cardiogenic shock initiative

Mir B. Basir, DO | Theodore Schreiber, MD | Simon Dixon, MD | Khaldoon Alaswad, MD | Kirti Patel, MD | Steven Almany, MD | Alishia Rhinehland, MD | Ivan Hanson, MD | Augustine George, MD | Michael Ashbrook, MD | Nimrod Blank, MD | Murad Abdelsalam, MD | Nishtha Sanon, MD | Steven B.H. Timmis, MD | William W. O'Neill MD

N= 41 pts w AMICS encouraged HD monitoring and early MCS.
93% on ino/pressors
15% out of hosp arrest
27% in hosp cardiac arrest
17% active CPR while MCS deployment
Door to support time:
avg 83 minutes
71% had ino/pressors decreased within 24 h of index procedure
66% had MCS deployed before PCI

Basir MB Catheter Cardiovasc Interv 2018:91:454

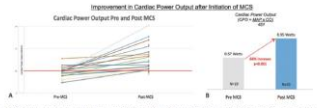

FIGURE 3 Cardiac power output measurements recorded on available patients, including overall increase in cardiac power output preprocedure and postprocedure [Color figure can be viewed at wileyonlinelibrary.com]

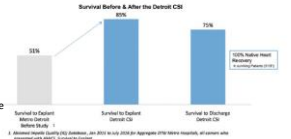

FIGURE 4 Bar graph depicting the improvement in survival to explant of patients included in the Detroit Cardiogenic Shock Initiative compared with institutional historical controls, including overall survival to hospital discharge [Color figure can be viewed at wileyonlinelibrary.com]

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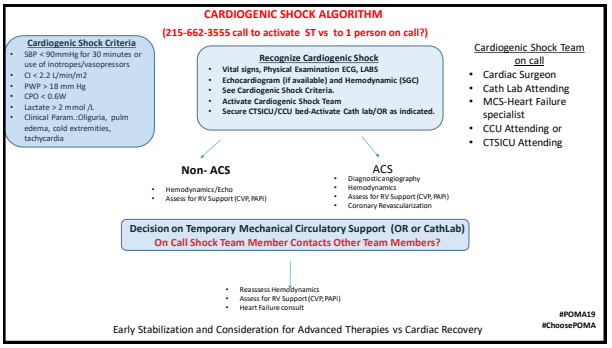
CARDIOGENIC SHOCK ALGORITHM
(215-662-3555 call to activate ST vs to 1 person on call?)
Cardiogenic Shock Criteria
SBP < 90mmHg for 30 minutes or use of inotropes/vasopressors
CI < 2.2 L/min/m2
PWP > 18 mm Hg
CPO < 0.6W
Lactate > 2 mmol /L
Clinical Param..Oliguria, pulm edema, cold extremities, tachycardia
Recognize Cardiogenic Shock
Vital signs, Physical Examination ECG, LABS
Echocardiogram (if available) and Hemodynamic (SGC)
See Cardiogenic Shock Criteria.
Activate Cardiogenic Shock Team
Secure CTSICU/CCU bed-Activate Cath lab/OR as indicated.
Cardiogenic Shock Team on call
Cardiac Surgeon
Cath Lab Attending
MCS-Heart Failure specialist
CCU Attending or
CTSICU Attending
Non- ACS
Hemodynamics/Echo
Assess for RV Support (CVP, PAPi)
ACS
Diagnostic angiography
Hemodynamics
Assess for RV Support (CVP, PAPi)
Coronary Revascularization
Decision on Temporary Mechanical Circulatory Support (OR or CathLab)
On Call Shock Team Member Contacts Other Team Members?
Reassess Hemodynamics
Assess for RV Support (CVP, PAPi)
Heart Failure consult
Early Stabilization and Consideration for Advanced Therapies vs Cardiac Recovery
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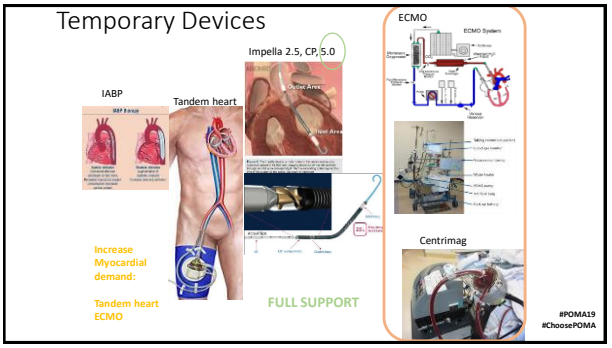
Temporary Devices
IABP
Tandem heart
Impella 2.5, CP, 5.0
ECMO
Centrimag
Increase Myocardial demand:
Tandem heart
ECMO
FULL SUPPORT
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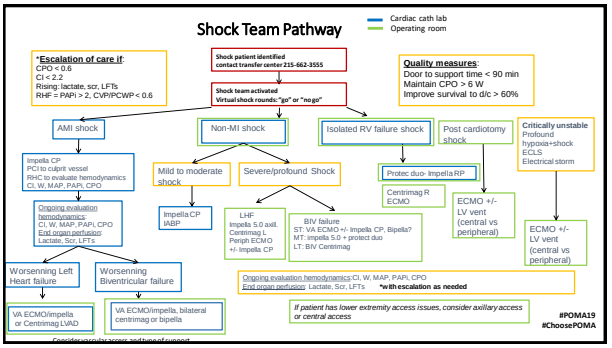
Shock Team Pathway
Cardiac cath lab
Operating room
*Escalation of care if:
CPO < 0.6
CI < 2.2
Rising: lactate, scr, LFTs
RHF = PAPi > 2, CVP/PCWP < 0.6
Shock patient identified
contact transfer center 215-662-3555
Shock team activated
Virtual shock rounds: "go" or "no go"
Quality measures:
Door to support time < 90 min
Maintain CPO > 6 W
Improve survival to d/c > 60%
AMI shock
Non-MI shock
Isolated RV failure shock
Post cardiotomy shock
Critically unstable
Profound hypoxia+shock
ECLS
Electrical storm
Impella CP
PCI to culprit vessel
RHC to evaluate hemodynamics
CI, W, MAP, PAPI, CPO
Mild to moderate shock
Severe/profound Shock
Protec duo- Impella RP
Centrimag R ECMO
ECMO +/- LV vent (central vs peripheral)
Ongoing evaluation hemodynamics:
CI, W, MAP, PAPI, CPO
End organ perfusion:
Lactate, Scr, LFTs
Impella CP IABP
LHF
Impella 5.0 axill.
Centrimag L
Periph ECMO
+/- Impella CP
BIV failure
ST: VA ECMO +/- Impella CP, Bipella?
MT: impella 5.0 + protect duo
LT: BiV Centrimag
Worsenning Left Heart failure
Worsenning Biventricular failure
Ongoing evaluation hemodynamics: CI, W, MAP, PAPI, CPO
End organ perfusion: Lactate, Scr, LFTs
*with escalation as needed
VA ECMO/impella or Centrimag LVAD
VA ECMO/impella, bilateral centrimag or bipella
If patient has lower extremity access issues, consider axillary access or central access
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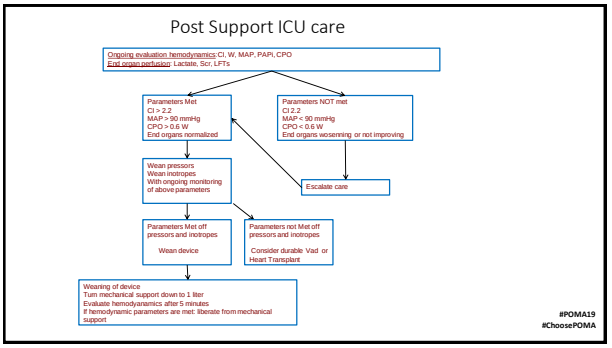
Post Support ICU care
Ongoing evaluation hemodynamics: CI, W, MAP, PAPI, CPO
End organ perfusion: Lactate, Scr, LFTs
Parameters Met
CI > 2.2
MAP > 90 mmHg
CPO > 0.6 W
End organs normalized
Parameters NOT met
CI 2.2
MAP < 90 mmHg
CPO < 0.6 W
End organs wosenning or not improving
Escalate care
Wean pressors
Wean inotropes
With ongoing monitoring
of above parameters
Parameters Met off pressors and inotropes
Wean device
Parameters not Met off pressors and inotropes
Consider durable Vad or Heart Transplant
Weaning of device
Turn mechanical support down to 1 liter
Evaluate hemodyanamics after 5 minutes
If hemodynamic parameters are met: liberate from mechanical support
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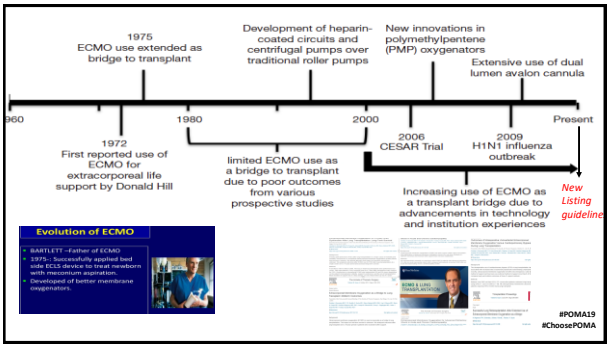
1975
ECMO use extended as bridge to transplant
Development of heparin-coated circuits and centrifugal pumps over traditional roller pumps
New innovations in polymethylpentene (PMP) oxygenators
Extensive use of dual lumen avalon cannula
960
1980
2000
Present
1972
First reported use of ECMO for extracorporeal life support by Donald Hill
limited ECMO use as a bridge to transplant due to poor outcomes from various prospective studies
2006
CESAR Trial
2009
H1N1 influenza outbreak
Increasing use of ECMO as a transplant bridge due to advancements in technology and institution experiences
New Listing guideline
Evolution of ECMO
BARTLETT –Father of ECMO
1975 – Successfully applied bed side ECLS device to treat newborn with meconium aspiration.
Developed of better membrane oxygenators.
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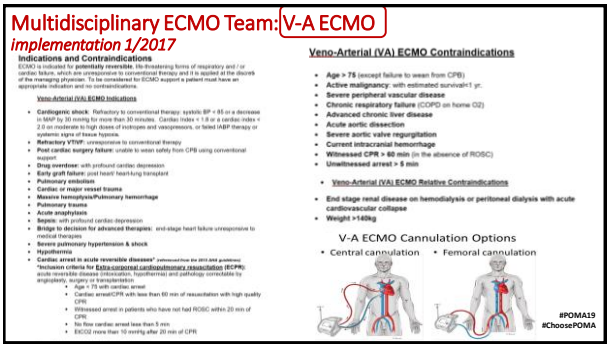
Multidisciplinary ECMO Team: V-A ECMO
implementation 1/2017
Indications and Contraindications
Veno-Arterial (VA) ECMO Indications
Cardiogenic shock: Refractory to conventional therapy: systolic BP < 85 or a decrease in MAP by 30 mmHg for more than 30 minutes. Cardiac index < 1.8 or a cardiac index < 2.0 on moderate to high doses of inotropes and vasopressors, or failed IABP therapy or systemic signs of tissue hypoxia.
Refractory VT/VF: unresponsive to conventional therapy
Post cardiac surgery failure: unable to wean safely from CPB using conventional support
Drug overdose: with profound cardiac depression
Early graft failure: post heart/ heart-lung transplant
Pulmonary embolism
Cardiac or major vessel trauma
Massive hemoptysis/Pulmonary hemorrhage
Pulmonary trauma
Acute anaphylaxis
Sepsis: with profound cardiac depression
Bridge to decision for advanced therapies: end-stage heart failure unresponsive to medical therapies
Severe pulmonary hypertension & shock
Hypothermia
Cardiac arrest in acute reversible diseases*
*Inclusion criteria for Extra-corporeal cardiopulmonary resuscitation (ECPR):
Age < 75 with cardiac arrest
Cardiac arrest/CPR with less than 60 min of resuscitation with high quality CPR
Witnessed arrest in patients who have not had ROSC within 20 min of CPR
No flow cardiac arrest less than 5 min
EtCO2 more than 10 mmHg after 20 min of CPR
Veno-Arterial (VA) ECMO Contraindications
Age > 75 (except failure to wean from CPB)
Active malignancy: with estimated survival<1 yr.
Severe peripheral vascular disease
Chronic respiratory failure (COPD on home O2)
Advanced chronic liver disease
Acute aortic dissection
Severe aortic valve regurgitation
Current intracranial hemorrhage
Witnessed CPR > 60 min (in the absence of ROSC)
Unwitnessed arrest > 5 min
Veno-Arterial (VA) ECMO Relative Contraindications
End stage renal disease on hemodialysis or peritoneal dialysis with acute cardiovascular collapse
Weight >140kg
V-A ECMO Cannulation Options
Central cannulation
Femoral cannulation
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Advanced Surgical Therapies:
Heart Transplant or VAD Therapy

Are they sick enough For Transplant/VAD?	Any other organs That limit life span?	Are they healthy Enough to undergo Surgery?
Inotropes	Cancer	Malnourished
Poor cardiac reserve VO2 < 14	Diabetes	Too deconditioned
Despite OMM	Lung disease pulmonary HTN	Liver failure
Limitations are only Cardiac	Liver disease	**Do they have Social Support?**
Intractable arrhythmias	Renal disease	

Relative age cut off for heart transplant is 65 yo
Age cut off for Heart Lung is 55 yo
Age cut of for heart liver or heart kidney is 60 yo

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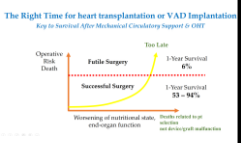
Heart Transplant vs LVAD/DT
How to Choose?

Are they sick enough
For Transplant/VAD?
Inotropes
Poor cardiac reserve
VO2 < 14
Despite OMM
Limitations are only
Cardiac
Intractable
arrhythmias

DT:
Age over 65
Concern for worsenning co morbidities
with immunosuppression
DM
Need to test compliance
recent smoking
recent non compliance
Need to test social support
Malignancy < 5 years (treated
with a good prognosis

BTT:
Listed but failing intropes



BTT: bridge to transplant DT: destination therapy BTD: bridge to decision BTI: intent #POMA19 #ChoosePOMA

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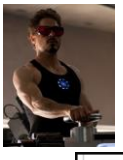
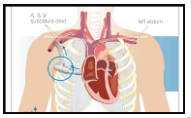
Available VAD Devices

- HeartMate II
- HeartMate 3
- HeartWare
- TAH
- MCS clinical Trials:
  - *MOMENTUM*
    - HM 3 vs HM II
  - *STEM CELL Trial*
    - VAD + endomyocardial stem cell injection
  - *RESTAGE HF*
    - VAD to recovery
- Future Devices:
  - MVAD
  - Circulite





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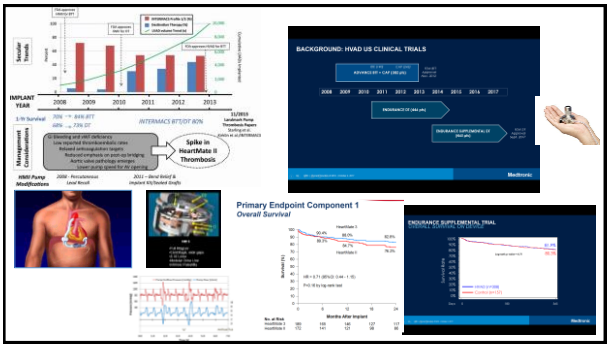

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Heart Failure Studies: *understanding the failed heart*

- **Human Heart Tissue Protocol** (Kenneth Margulies, MD)
  - To study heart tissue specimens in human heart failure. All patients listed for transplant or VAD are asked to participate.
  - As well as non failing hearts that are not suitable for heart transplant
    - 3 types of hearts:
      - Failed (evaluated at time of OHT)
      - Failed but rested (after LVAD support)
      - Non failing heart
  - *Dr. Margulies has assembled the largest biorepositories of human heart samples in the world*
- Samples
  - Processed for study
    - With clinical data
  - Banked for future study

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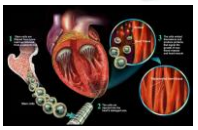
Heart Failure Studies

- observations
  - Failed myocyte
    - Down regulation of B receptors
    - Deplete of SRCA 2a
- Recovery Plan
  - Promoting growth of new cells?
  - Improving function of existing cells?
  - VAD as a platform



K Margulies, Biorepository, Unniversity of Pennsylvania

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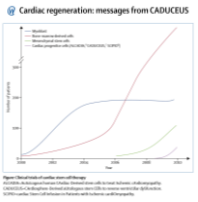
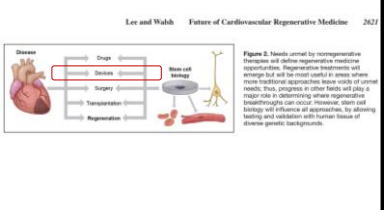
What is the best method to recover a failing ventricle?





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RESTAGE-HF Trial

early results

- 5 sites, HM II
- BTT or DT
- Mean age 36 yo
- HF ≤5 years, NICMP
- Primary end point: recovery to explant and freedom from HF recurrence at one year (requirement for OHT/VAD)
- Data of first 22 patients of 40 enrolled
  - 2 died post implant
    - Day #14 and #106
- 5 of 20 reached predefined end point
  - 1 committed suicide
- Support duration 222 d (14-445)
- Mean age 45 yo (42-55)
- 3 BTT
- To date median 138 days post explant (14-383) of the remaining 4 patients

E Birks…JE Rame. JHLTx 2015;34:S40

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Recovery at Penn *(CF era Eddie Rame, Wald, Atluri, Acker and Bermudez)*

- Study Protocol
  - De novo
    - Gene therapy — CUPID Study
    - Stem cell therapy — STOP-HF Study
  - LVAD platform
    - Clenbuterol — JB: vo2 43, 8 y/o
    - Stem cell Ph1 — NK, JY, RM, WG, JC
    - Stem cell Ph 2 — JN, CC, AH,RM, JF, WA,CS, SA, AL RH, JS
    - OMM — RESTAGE-HF
      - EM, MK,MB, EC, KD, PP, AG, EB, LQR, BS
- Planned
  - Short duration of HF* — WH*: 50%, 1y (stopped meds); TP, DJ, MD
  - Reversible insult — KW: (cobalt toxicity)
- Surprise — TJ*,CJ, LD, DB*, KC, SJ*, MG, MA, MA
- Forced to Explant — MM, GS, JM

*Not in clinical trial *(Red indicates explant)* *Recrudescence with non compliance

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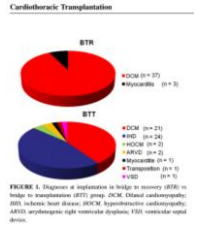
Outcomes
BTR vs BTT



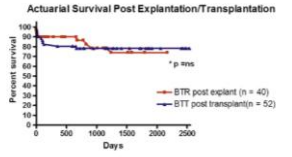


FIGURE 2. Actuarial survival of explanted (n = 40) compared with transplanted (n = 52) groups. *BTR*, Bridge to recovery; *BTT*, bridge to transplant.

Birks et al. J Thorac Cardiovasc Surg 2012;144:190-6

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Conclusions

- Chronic heart failure
  - Ambulatory patients on medical therapy
    - BB therapy is important and dose matters
    - Aldosterone inhibitors are becoming a mainstay of therapy
    - Consider IV iron for symptomatic HF pts who are iron deficient
    - Ivabradine (if HR > 70 despite OMM) improved outcomes
      - FDA approved, to decrease hospitalizations
    - LCZ696: angiotensin neprilysin inhibitor: ambulatory and ADHF
    - Targeting congestion is important to patient outcomes
      - cardiomems PA monitoring
    - Target recovery: besides aggressive medical therapy,
      - cell therapy, gene therapy, mechanical support
  - There are new devices on the horizon that may make an impact
    - Cardiac Contractility Modulation

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Conclusions (cont'd)

- Acute decompensated heart failure
  - IV diuresis bolus = continuous, high dose better
  - Seralaxin may have a benefit RELAX-AHF 2 is underway
- Advanced heart failure
  - End organ under perfusion or severe symptoms despite maximal therapy
  - Acutely ill, refractory to medical therapy
    - Temporary devices
      - IABP
      - Impella 2.5, CP, 5.0
      - Tandom heart, RP
      - ECMO
    - Permanent Platforms: better outcome with earlier tx
      - Heart transplant
      - Durable VADs (Mechanical Circulatory Support)- think of RECOVERY
        - HM II
        - Heart ware
        - with exciting new, smaller, fully implantable devices on the horizon

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Thank you!!!!

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