New Things in the Heart Failure Toy Box

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Heart Failure Updates

- Discuss new options in heart failure medications
- Present recent updates in device therapies for heart failure

New(ish) CHF tools

Pharmacologic

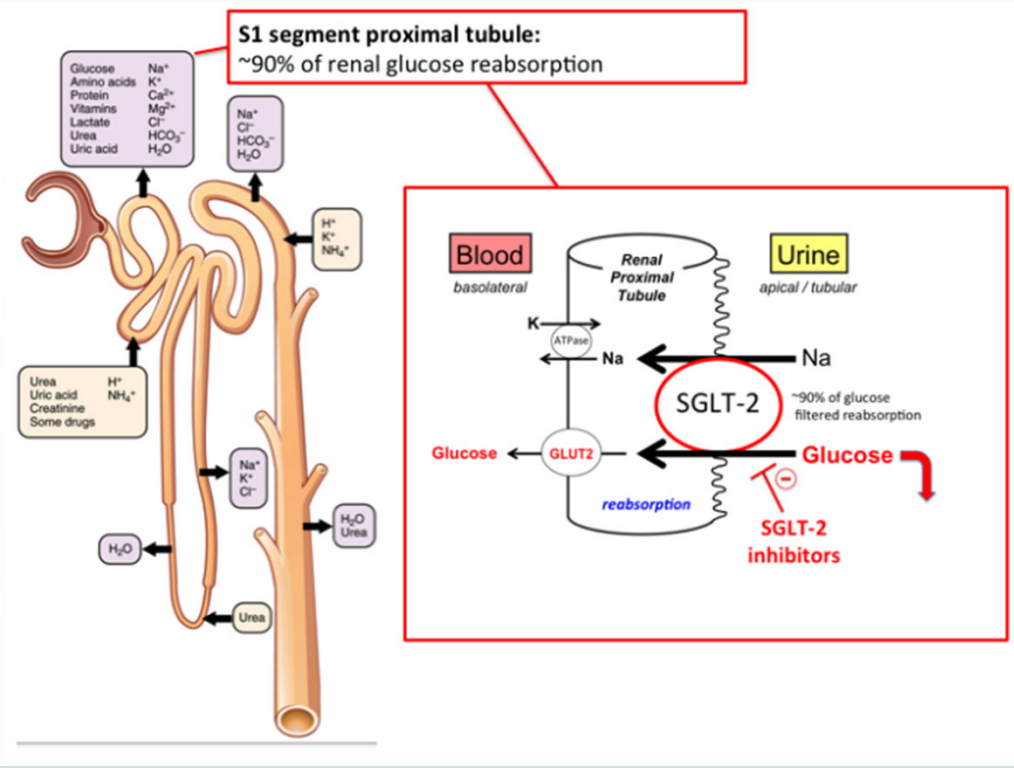
- SLGT-2 inhibitors
- GLP-1 agonists
- Vericiguat
- IV Iron

Device Therapy

- Mitraclip
- Cardiac Contractility Modulation
- Baroflex Activation Therapy
- Cardiomems

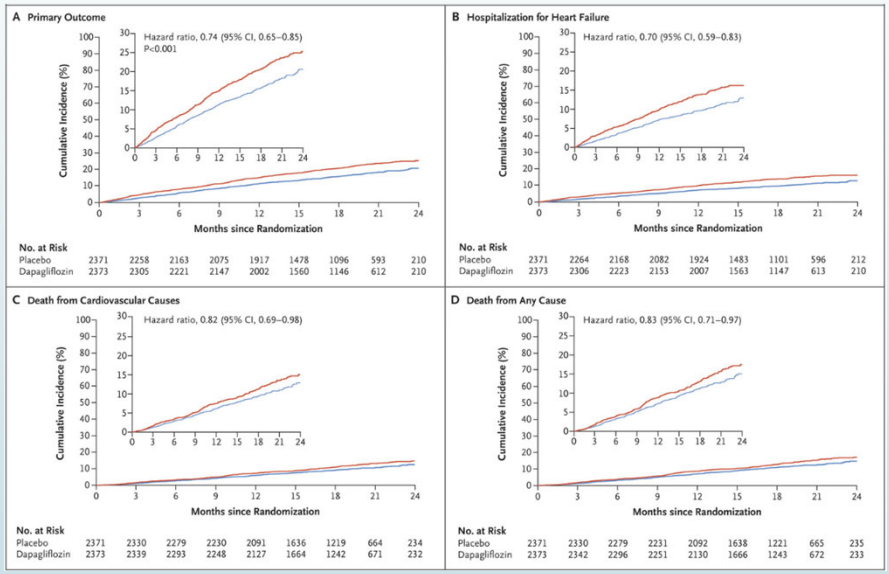
SGLT-2 (Sodium-glucose co-transporter inhibitors) -Empagliflozin (Jardiance), Dapagliflozin (Farxiga)

- Designed as diabetic treatment
  - SGLT2 receptor responsible for glomerular glucose and sodium resorption
  - Blocking resorption of glucose at SLGT2 in proximal tubule increases renal excretion of glucose
  - Modest A1c reduction
  - New diabetic meds are mandated by FDA to undergo CV safety studies after rosiglitazone issues
  - In diabetic CV safety diabetic studies, noted significant decrease in cardiovascular (CV) events
    - Analyses found almost 40% reduction in CHF hospitalizations in some studies



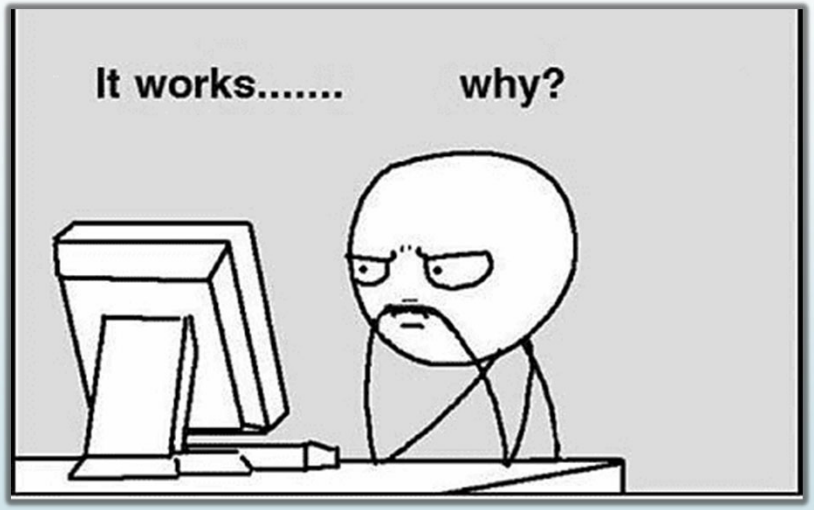
SGLT-2 (Sodium-glucose co-transporter inhibitors) -Empagliflozin (Jardiance), Dapagliflozin (Farxiga)

- Studies then transitioned from diabetics to anyone with HFREF
  - DAPA-HF (dapagliflozin)
  - EMPORER-reduced (empagliflozin)
  - Composite (CV death, hospitalizations, urgent HF visits) and individual outcomes significantly reduced
- Then to patients with HFPEF regardless of diabetic status
  - SOLOIST-WHF (sotogliflozin in worsening CHF in diabetics)
  - EMPOROR-preserved (empagliflozin)
  - DELIVER (dapagliflozin)
  - Composite (CV, hospitalizations, urgent HF visits) significantly reduced, driven mostly by hospitalization reduction
    - >20% reduction in CHF admissions



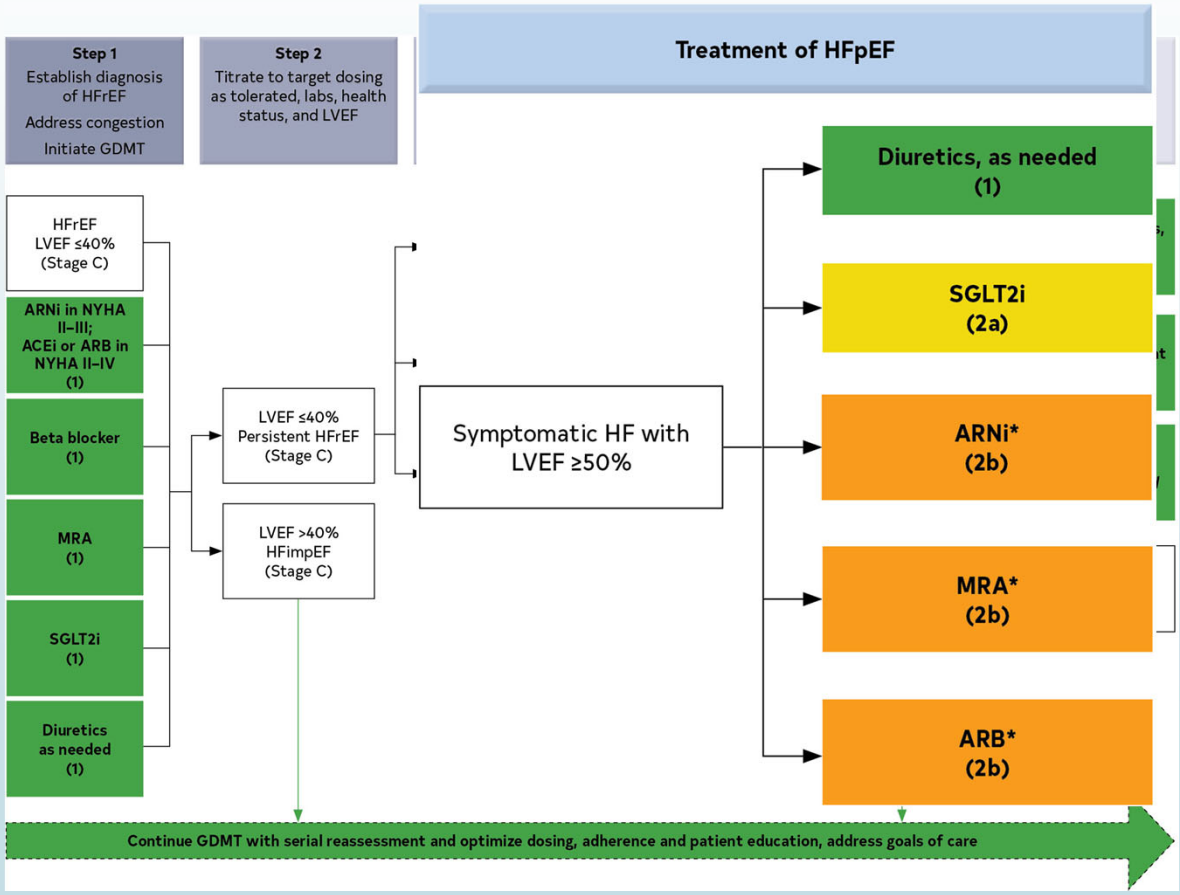
SGLT-2 (Sodium-glucose co-transporter inhibitors)
-Empagliflozin (Jardiance), Dapagliflozin (Farxiga)

- Well, how does it reduce CV events?
  - Osmotic diuresis and natriuresis?
  - Promote vasodilation?
  - Improve myocardial metabolism?
  - Increase mitochondrial calcium (through a sodium-hydrogen exchanger)?
  - Reduce cardiac fibrosis (by altering adipokines and cytokine production)?
  - **NOT** by glucose lowering effects.



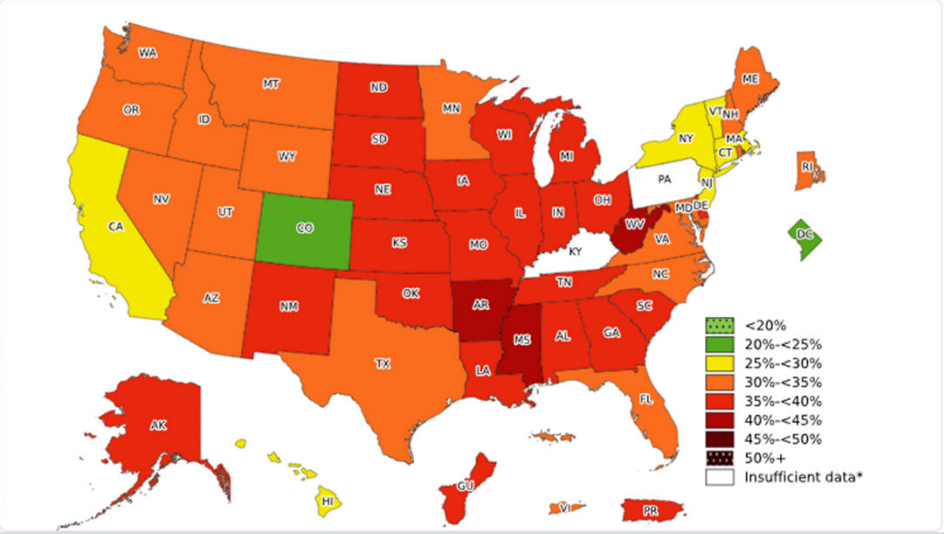
SGLT-2 (Sodium-glucose co-transporter inhibitors) -Empagliflozin (Jardiance), Dapagliflozin (Farxiga)

- Current guidelines
  - HFREF: Class 1 recommendation regardless of diabetic status
    - Beta blocker, ACE/ARB/ARNi, RAS, now SGLT
  - HFPEF: Class 2a
    - Beyond diuretics, best targeted treatment we have
  - Empagliflozin: 10 mg
  - Dapagliflozin: 10 mg



GLP-1 agonists (Glucagon-like peptide-1 analog) -Semaglutide (Ozempic/Wegovy)

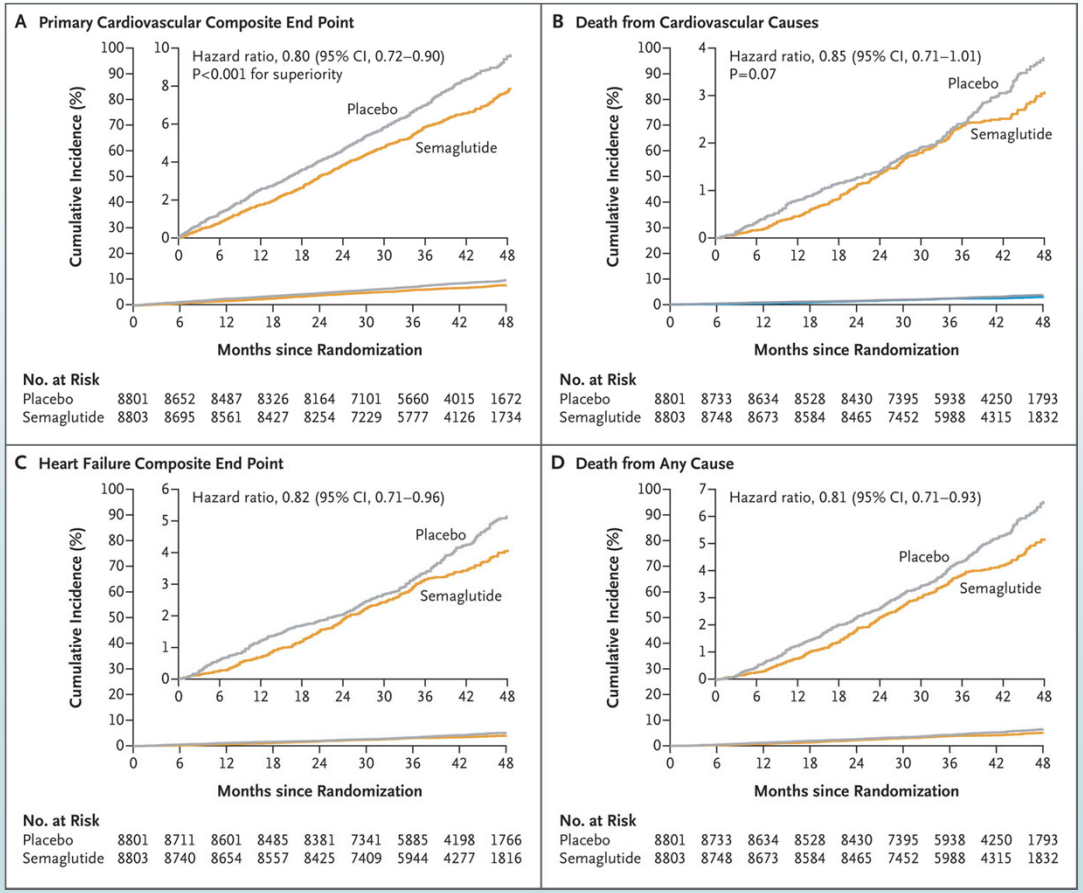
- Obesity is an endemic problem and risk factor for CHF development
  - Doubles CHF risk
    - 5-7% increased risk with each BMI point
  - 1:5 cases of atrial fibrillation associated with obesity
- GLP-1 agonists designed for diabetes
  - Increases insulin production
  - Inhibits glucagon secretion
  - Delay gastric emptying
- Significant weight loss
  - In obesity studies >50% had >15% reduction in body mass vs 4.9% in placebo



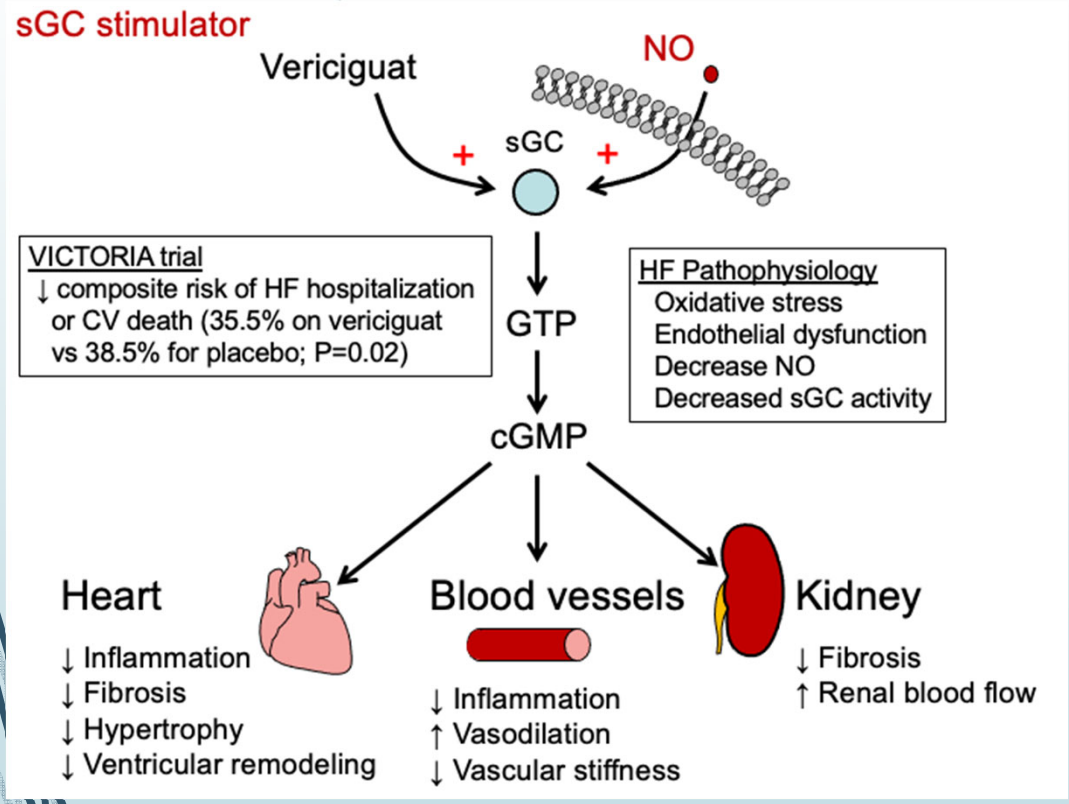
GLP-1 agonists (Glucagon-like peptide-1 analog)

-Semaglutide (Ozempic/Wegovy)

- Emerging therapy, not currently in CHF guidelines
- SELECT TRIAL (semaglutide)
  - Reduction in CV composite (6.5% vs 8.0%)
  - Reduced HF composite
  - Reduced death from any cause
- STEP-HFPEF (semaglutide)
  - Improved KCCQ score
  - Improved 6 minute walk
  - Trend towards reduced CV events (driven by reduced afib?)
- Several reviews have failed to show class benefit in CHF

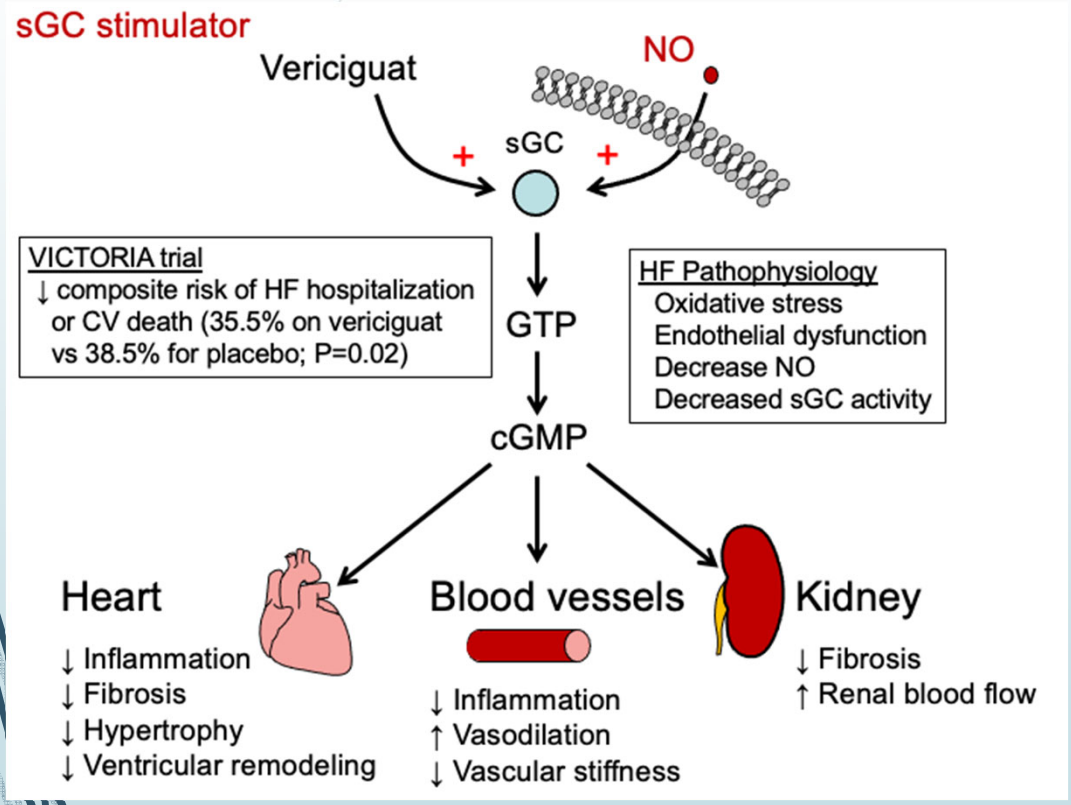


Vericiguat (Verquvo)



- Guanylate cyclase stimulator
  - Enhances cyclic guanosine monophosphate pathway (GMP)
  - Sensitizes soluble guanylate cyclase to nitric oxide (NO)
  - Restores cyclic GMP under low NO conditions and oxidative stress
  - Huh?

Vericiguat (Verquvo)



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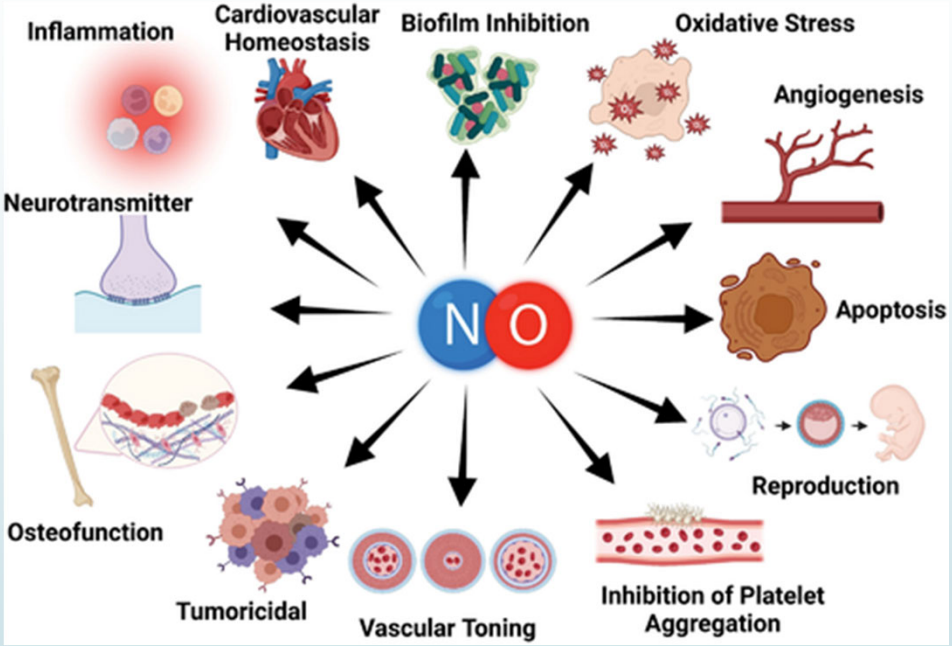
Nitric Oxide

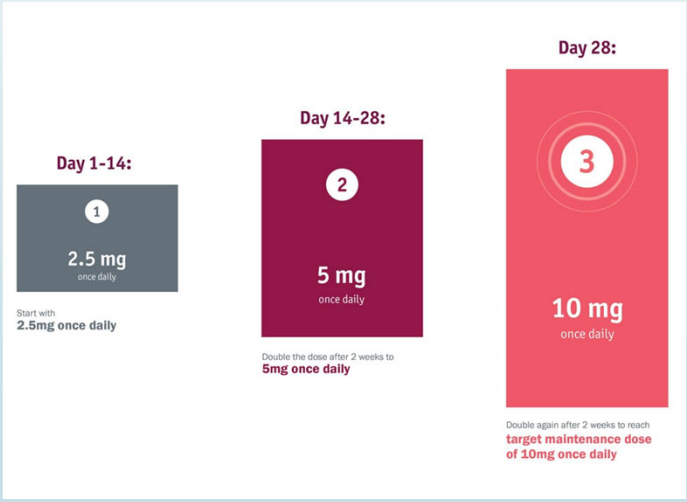
- Important in a host of physiologic functions
  - Immunologic response
  - Neurotransmission
  - Inflammation
  - Gastrointestinal smooth muscle
  - Erectile tissue
  - Inhibits vascular smooth muscle contraction and growth
  - Inhibits platelet aggregation
  - **Vasodilation**
  - **Cardiac contractility**



Vericiguat (Verquvo)

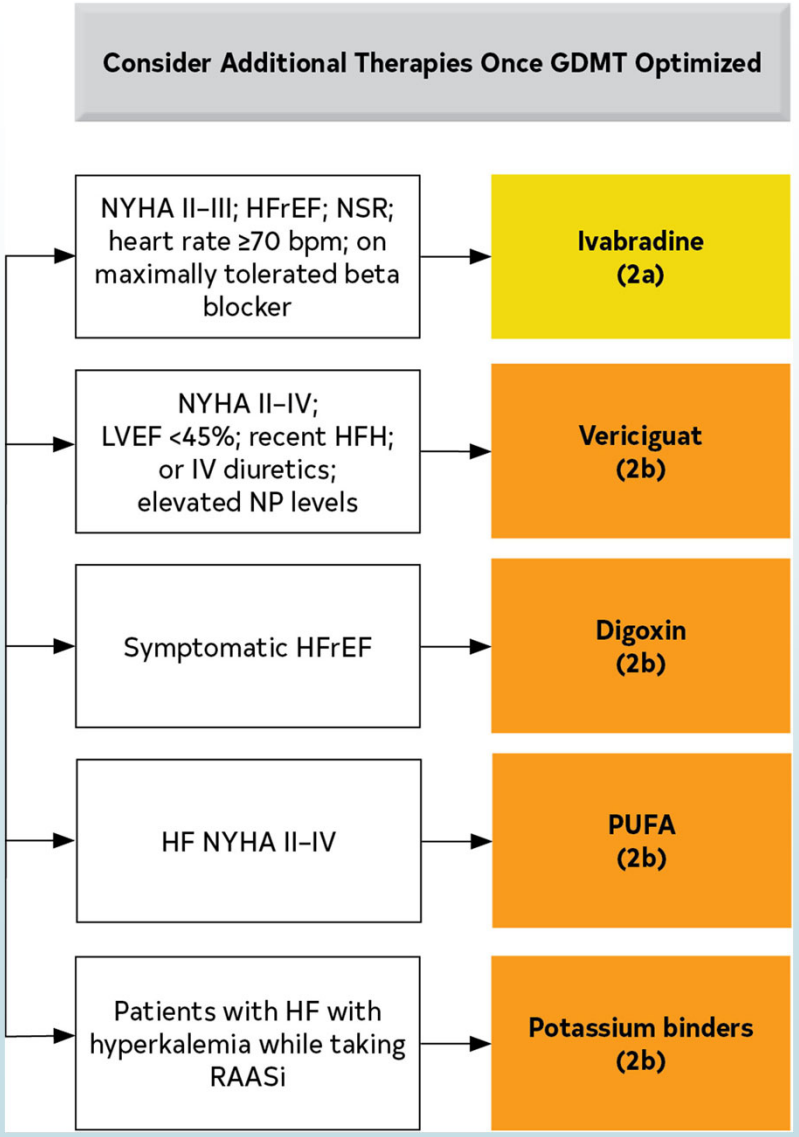
- In heart failure, there is increased NO dysregulation
- Biggest limitation in NO therapeutics has been development of tolerance
  - Upregulation of NO degradation
- Vericiguat increases nitric oxide (NO) sensitivity in the heart
  - As opposed to increased NO production

- Increase in cardiac output
  - Increase in cardiac contractility
  - Decrease in systemic vascular resistance



Vericiguat (Verquvo)

- VICTORIA Trial
  - Vericiguat added to typical GDMT
  - Targeted worsening CHF
    - EF <45%
    - Elevated BNP >300, NT-proBNP>1000
    - Decompensation with hospitalization or IV diuretics in past 6 months
- Composite of CHF hospitalization and CV death reduced over 11 months
  - 37.9% vericiguat vs 40.9% placebo (p 0.02)
  - Individual target points nonsignificant
  - Decreased BNP
  - NNT 24

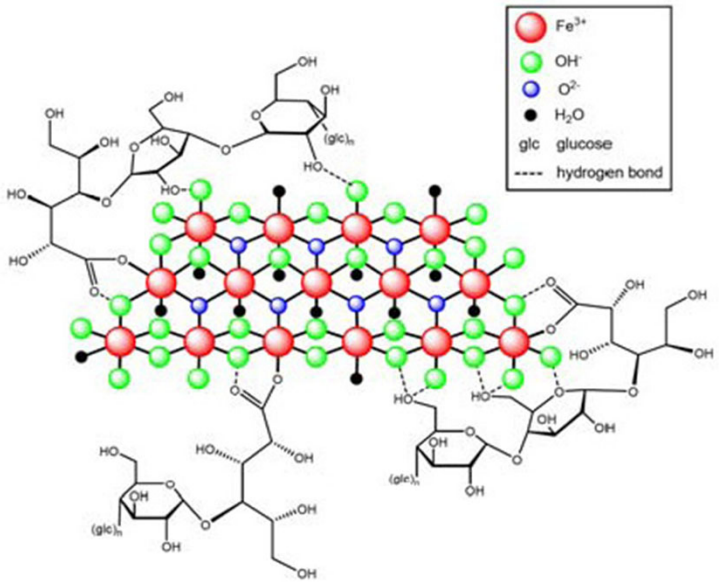


IV Iron

- Iron Deficiency
  - Prevalence may be >50% in CHF patients
  - Independent risk factor for functional capacity and survival
    - Regardless of anemia
  - Ferritin <100 ug/L or ferritin 100-200 ug/L with transferrin sat <20%
  - Risk factors include females, advanced CHF, elevated CRP, high BNP levels

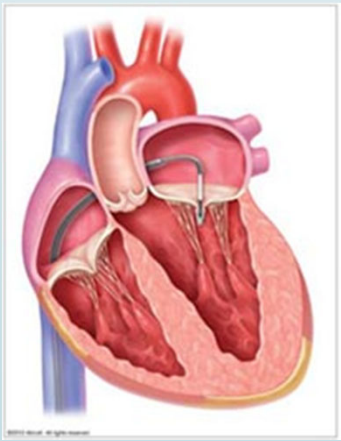
IV Iron

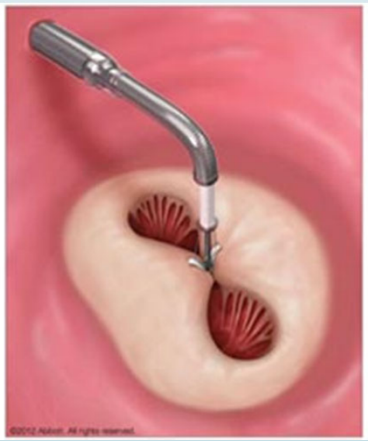
- 2 meta-analyses showed reduced risk in all-cause mortality and cardiovascular hospitalization
  - EF <45%, NYHA II-III symptoms
  - Individual trials showed improvement in patient reported outcomes and functional capacity
- Most Studies have used iron sucrose (200 mg/dose) or ferric carboxymaltose (up to 1000 mg/week)
  - Re-evaluate in 3-6 months
- European Guidelines IIa recommendation for symptoms and quality of life
- US guidelines recommendation IIb
- No data to support oral iron supplementation
  - Higher adverse events
  - Poor absorption in general worse in CHF patients
- No data currently showing benefit in HFPEF (Studies ongoing)

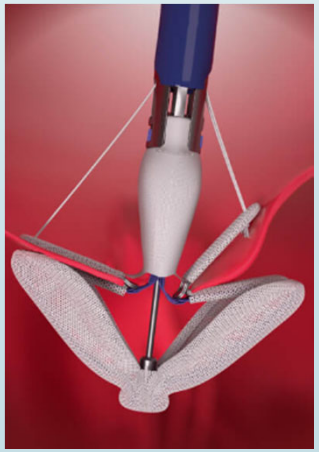


Transcatheter edge-to-edge mitral repair (MitraClip, PASCAL)

- Nonsurgical option for mitral valve regurgitation
- Transcatheter procedure based on Alfieri mitral repair
  - Suturing together middle segments of anterior and posterior mitral leaflets
  - Creates a "double orifice" valve
- Transcatheter mitral devices can be attached centrally or laterally

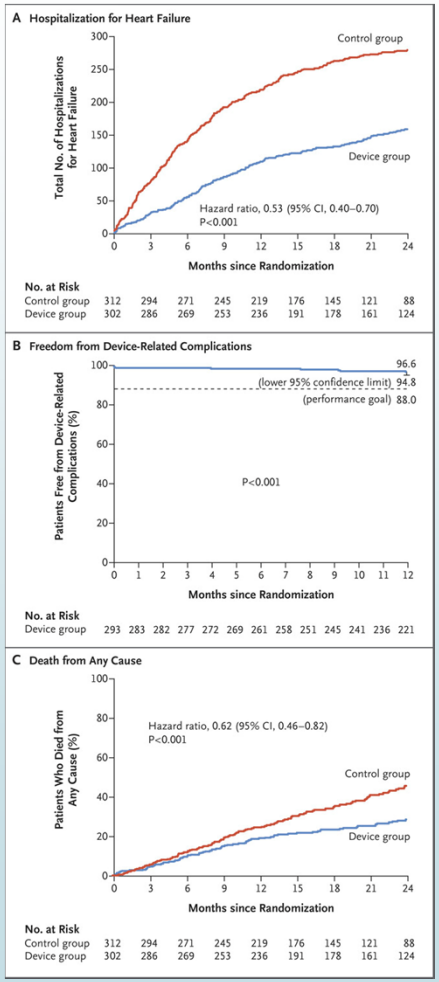






Transcatheter edge-to-edge mitral repair (MitraClip, PASCAL)

- Indications
  - Chronic Secondary (LV or LA dilation)
    - COAPT trial
      - Moderate-severe MR, NYHA II-IV, EF 20-50%, on maximal medical therapy
      - Reduced CHF admissions after just 30 days
      - Reduced mortality at 1, 2 & 5 years
    - Limited and poor surgical data and outcomes
  - Chronic Primary (leaflet, chordae, papillary abnormality)
    - Surgery is management of choice
    - Prohibitive Risk: **Porcelain aorta, Frailty, Hostile chest, Severe liver disease/cirrhosis, Severe pulmonary hypertension, other comorbidities**
    - EVEREST II: Similar outcomes surgery vs TEER except for high transition to surgery in TEER group over 5 years
    - Success defined as moderate or less MR with Mean Gradient <10 mmHg
      - Patients with mild or less MR and Mean Gradient <5 mmHg had best mortality, CHF outcomes in registries
- Contraindications
  - Endocarditis, Rheumatic mitral disease, Intracardiac thrombus, Nickel allergy

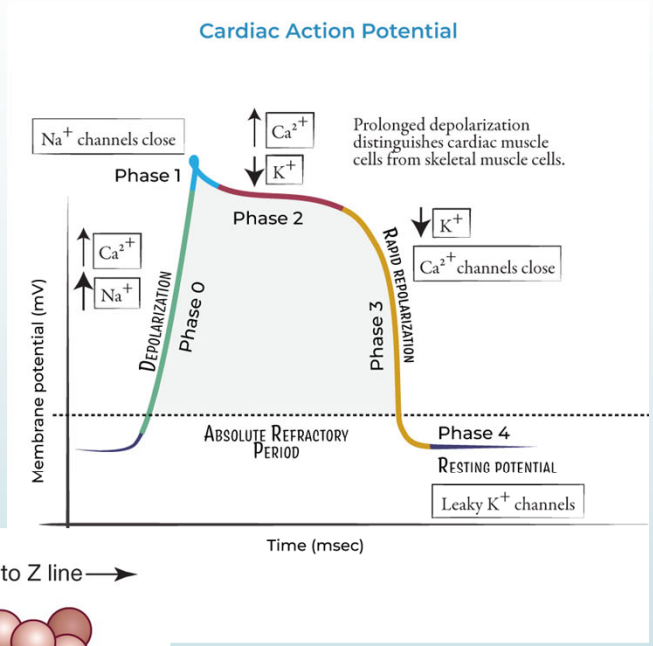


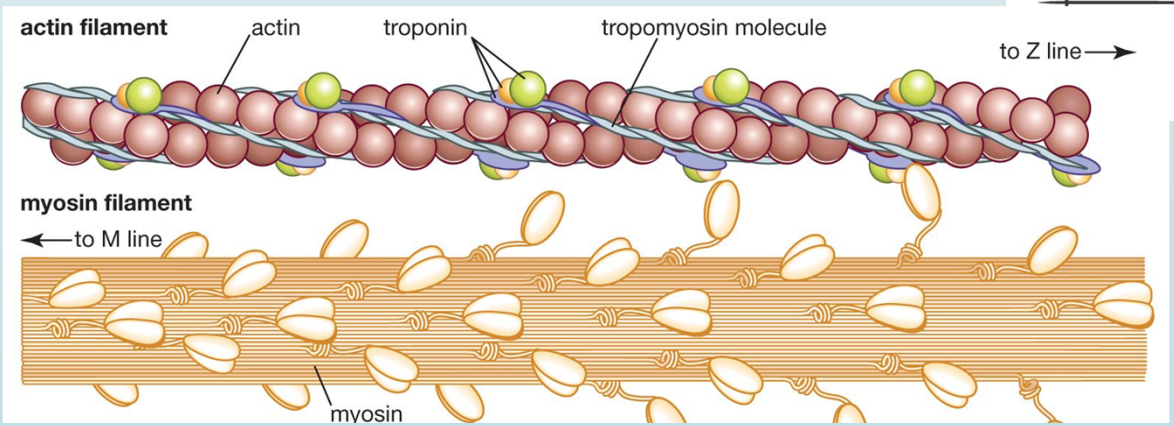
Transcatheter edge-to-edge mitral repair (MitraClip, PASCAL)

- Quantification of regurgitation (meet at least 3)
  - Color flow jet may be central and large (>6 cm^2 or >30 percent of left atrial area) or smaller if eccentric, encircling the left atrium
  - Pulmonary vein flow may show systolic blunting or systolic flow reversal
  - Vena contracta width ≥0.5 cm measured in the parasternal long-axis view
  - Regurgitant volume of ≥45 mL/beat
  - Regurgitant fraction ≥40 percent
  - Regurgitant orifice area ≥0.30 cm^2
- Anatomic Requirements
  - Planimetered mitral valve area (in parasternal short-axis view at tips of the mitral valve) ≥4.0 cm^2.
  - Minimum leaflet length of 6 mm for MitraClip NT, 8 mm for PASCAL (ACE and standard) devices, and 9 mm for MitraClip XT devices.
  - Flail segment <15 mm and flail gap of <10 mm.
  - Minimal mitral leaflet calcification in the grasping area.
  - No pathologic mitral leaflet cleft causing the regurgitation
  - No vegetations and perforations.

Cardiac Contractility Modulation (CCM)

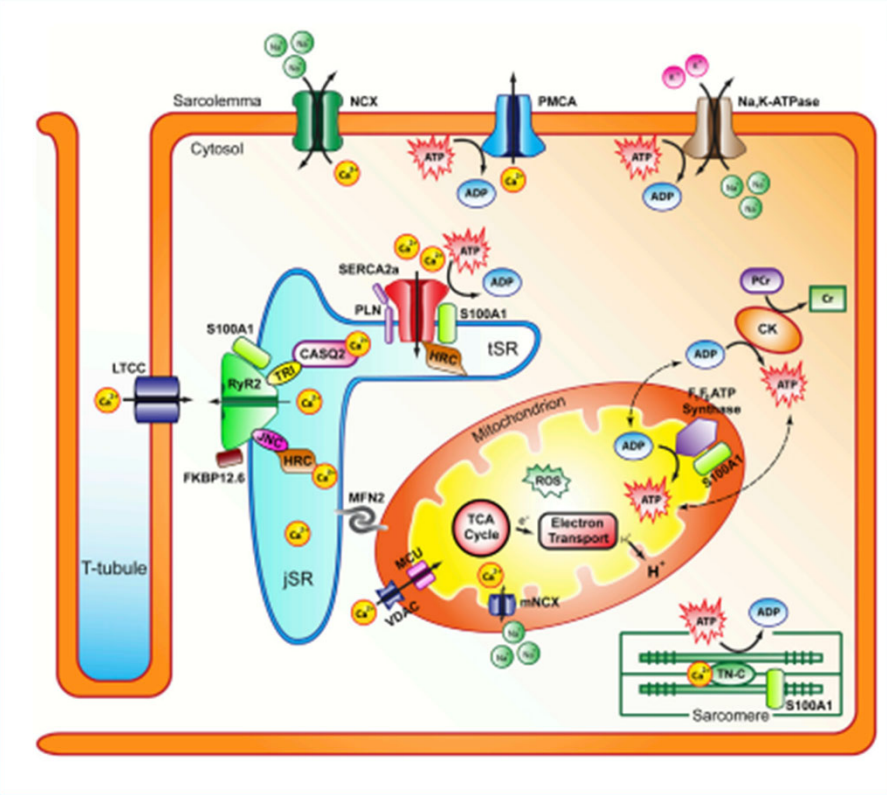
- Myocardial contraction
  - Plasma membrane depolarization
  - Flux of calcium into cytosol from both intra and extra cellular sources
  - Calcium binds to troponin
  - Sliding of actin and myosin fibers across each other resulting in contraction
  - The magnitude and duration of calcium flux intracellularly is a major regulator of the force of myocardial contraction





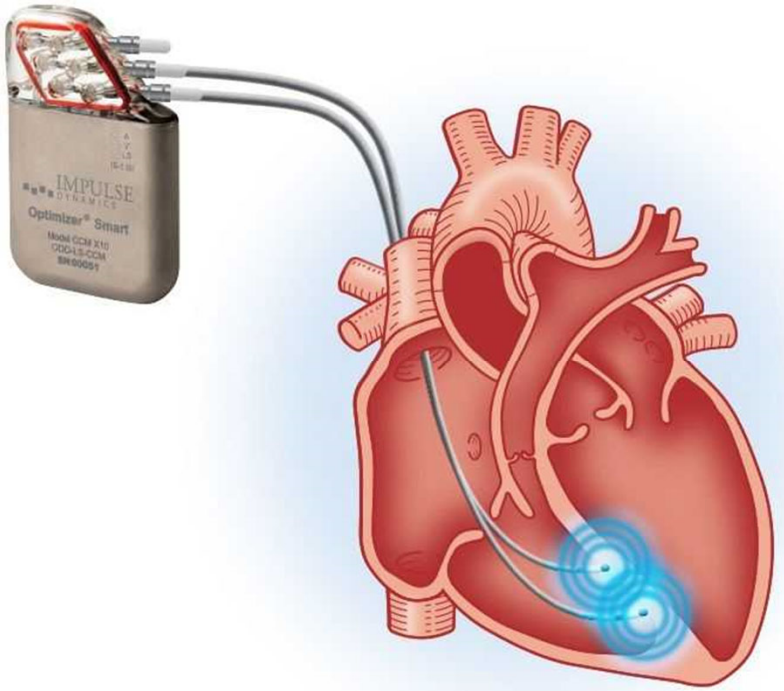
Cardiac Contractility Modulation (CCM)

- In Heart Failure calcium mishandling impairs cellular flux for multiple reasons
  - Downregulation of genes related to calcium cycling
  - Upregulation of myocardial fetal and stretch response genes
  - Reduced L-type calcium channel (LTCC) activity
  - Decreased sarcoplasmic reticulum calcium uptake and release
  - Enhanced clearance of calcium by the sodium-calcium exchange protein



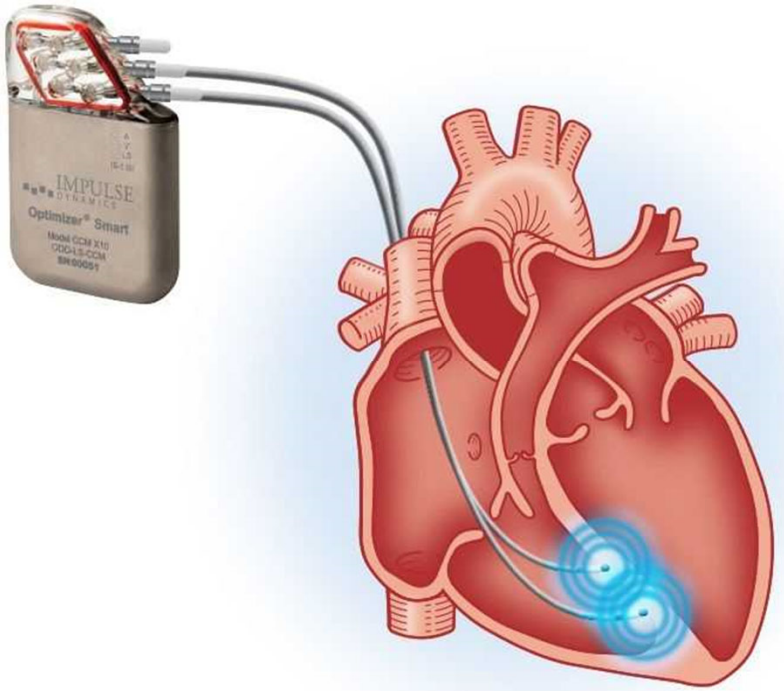
Cardiac Contractility Modulation (CCM)

- Apply relatively high-voltage (≈7.5 V), long-duration (≈20 milliseconds), biphasic electric signals in right ventricle septal wall during the absolute myocardial refractory period
- Electrical pulses delivered for 5-7 hours/day
- One-hour treatments separated by regular intervals
- Patient charges the device one hour per week using an external wireless charger
- 20+ year battery with newest system



Cardiac Contractility Modulation (CCM)

- Clinical benefits
  - Reduced LV systolic volume
  - Improvement in EF
  - Improved myocardial contraction by 3D ECHO
  - Gene upregulation and reverse remodeling for calcium cycling
  - Improved survival against predicted survival
  - Not consistent, but majority of studies have shown improvement in CHF metrics (NYHA scores, CHF scores, QoL scores, peak VO2)
- Indications (meet all criteria)
  - LVEF 25-45%
  - NYHA III
  - On GDMT
  - NO indication for CRT
- Future directions
  - HFPEF studies ongoing
  - CCM/ICD combination systems



Baroflex Activation Therapy (BAT)

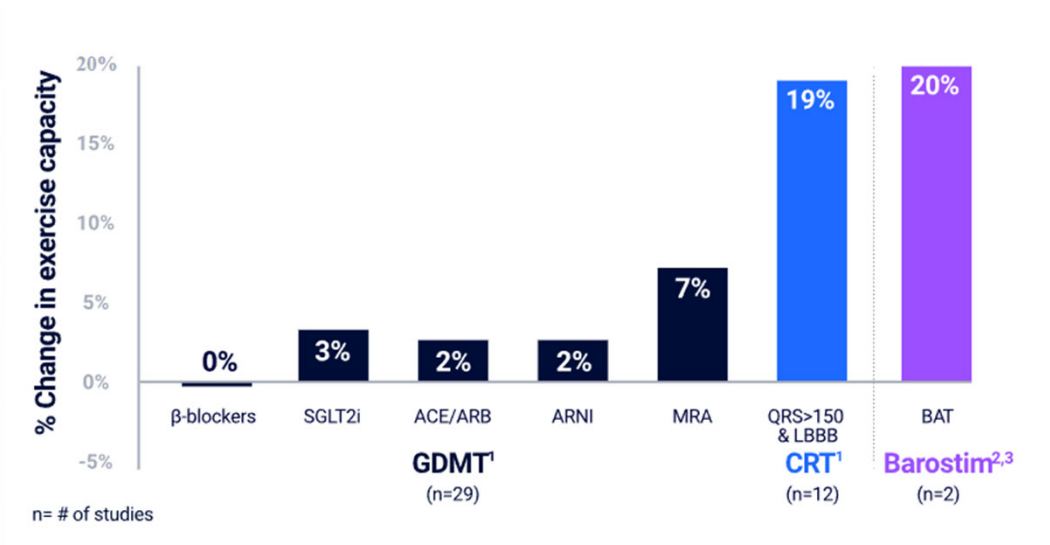
- Sympathetic overactivation from autonomic dysfunction is one of several pathways leading to progression of CV diseases
  - Resistant HTN
  - CHF
- Baroreflex dysregulation is part of this process
- Theory behind BAT is that device-based electrical stimulation of baroflex system at carotid sinus can decrease autonomic dysfunction by increasing parasympathetic outflow and inhibit sympathetic overactivity

Baroflex Activation Therapy (BAT)

- Procedure involves placement of generator similar to a pacemaker
- Electrical lead attached to device then surgically sewn externally to carotid sinus
- Studied in HFREF patients who were
  - On GDMT
  - NOT a candidate for CRT therapy
  - NYHA III or NYHA II (recently labeled NYHA III)
  - EF <35%
  - NTproBNP <1600

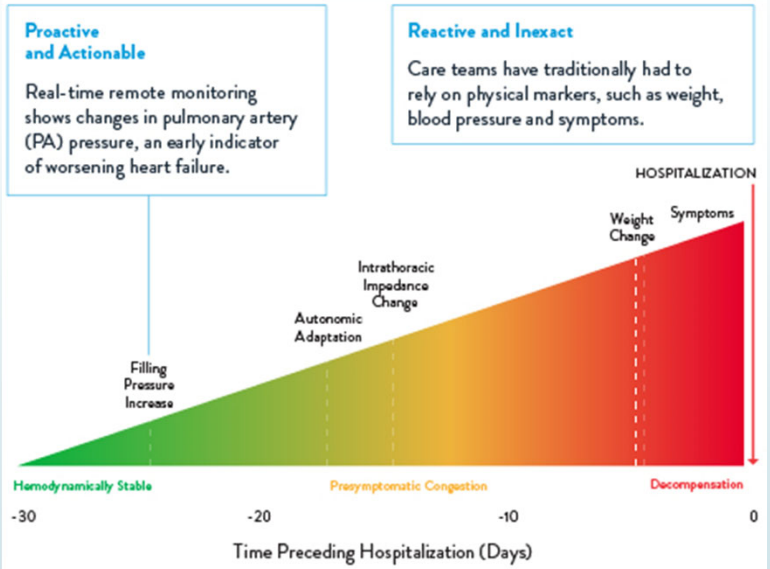
Baroflex Activation Therapy

- Barostim device (BEAT-HF trial)
  - Improved functional status
  - Improved 6 minute walk
  - Improved Quality of Life scores
  - Nonsignificant trend towards reduced CV mortality/LVAD/transplant



Cardiomems

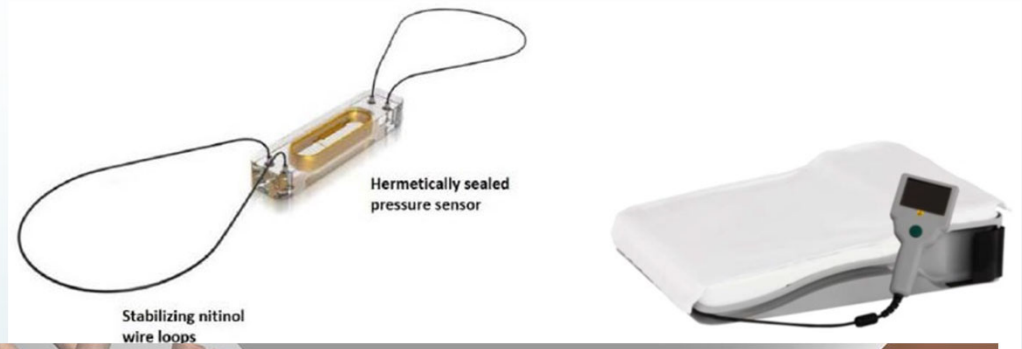
- Pulmonary artery pressure increases are early indicator of worsening CHF and fluid retention
- Occurs typically before
  - Weight change (Patient monitored)
  - Intrathoracic impedance changes (pacemaker monitored)

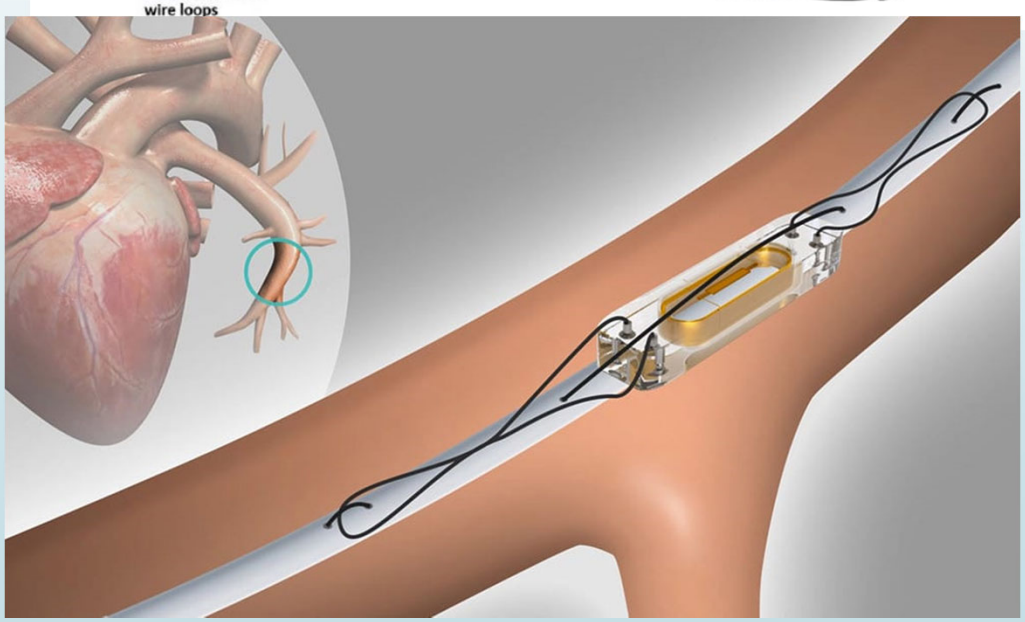


Graph adapted from Adamson PB. Pathophysiology of the transition from chronic compensated and acute decompensated heart failure: new insights from continuous monitoring devices. Current Heart Failure Reports. 2009;6:287-292.

Cardiomems

- Pulmonary artery pressure sensor
- Placed via Right Heart Cath
- Monitored telemetrically
  - Follow trends in pulmonary artery pressures
  - Early interventions with diuretics or lifestyle changes
- Does NOT need battery or parts exchange





Cardiomems

- In studies
  - 33-54% reduction in CHF hospitalizations
  - Increased survival in some studies
  - Improved Quality of Life scores
- Indicated for
  - NYHA Class II or Class III heart failure
  - One heart failure hospitalization in the past 12 months
  - Elevated natriuretic peptides

Study	Design	N	Reduce HFH	Reduce PAP	HFpEF BENEFIT	Safety	Increase QoL	Adherence	Elevated BNP
CHAMPION Pivotal Study[4] – Abraham	RCT	550	✓	✓	✓	✓	✓		
Proven Management in HFpEF Patients[5] – Adamson	RCT Subgroup	119	✓	✓	✓				
First 2000 Commercial Implants[8] – Heywood	Retrospective	2,000		✓	✓			✓	
Propensity-Matched Cohort[2] – Abraham	Retrospective Database	2,174	✓						
MEMS-HF European Study[7] – Angermann	Single-arm	234	✓	✓	✓	✓	✓	✓	
US Post-Approval Study[6] – Shavelle	Single-arm	1,200	✓	✓	✓	✓		✓	
GUIDE-HF Study[1] – Lindenfeld	RCT	1,000	✓	✓	✓	✓		✓	✓
GUIDE-HF Single Arm[11] – Mehra	Single-arm	1,001	✓	✓			✓		✓
MONITOR-HF[12] – Brugts	RCT	348	✓	✓	✓	✓	✓	✓	✓

QUESTIONS?

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