# Heart Failure: New Drugs and Devices

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No relevant disclosures

## HFrEF- What is *old* in drug therapy?

- Beta-blockers (Carvedilol and Metoprolol xl)
- ACE-I inhibitor (Enalapril, Ramipril etc.)
- ARBs (Losartan, Candesartan, Valsartan etc.)
- MRAs (Spironolactone and Eplerenone)

## HFrEF- What is *new* in drug therapy?

1- Angiotensin Receptor Neprilysin Inhibitor (ARNI)- Sacubitril/Valsartan

2-Sodium Glucose Co-transport-2 Inhibitors (SGLT2i)- Empagliflozin and Dapagliflozin

3- Sinus node modulator (Ivabradine)

4- Soluble Guanylate Cyclase Stimulator (Vericiguat)

5- Transthyretin tetramer stabilizer (Tafamidis)

## HFrEF- What is *old* in Device therapy?

- Cardiac Resynchronization Therapy (CRT)

- for LVEF<=35% and prolonged QRS

## HFrEF- What is *new* in Device therapy?

For narrow QRS and LVEF <45%

1- Cardiac Contractility Modulation (CCM)

For narrow QRS and LVEF <35%

2- Baroreflex Activation Therapy (BAT)

For moderate-severe or severe secondary **Mitral Regurgitation**

3- Mitraclip

## HFpEF- What is *old* in drug therapy?

- MRAs (Spironolactone) COR IIb, LOE B-R, EF>=45%, elevated BNP or HF admission within 1 year, GFR>30, creatinine <2.5, K<5

## HFpEF- What is *new* in drug therapy?

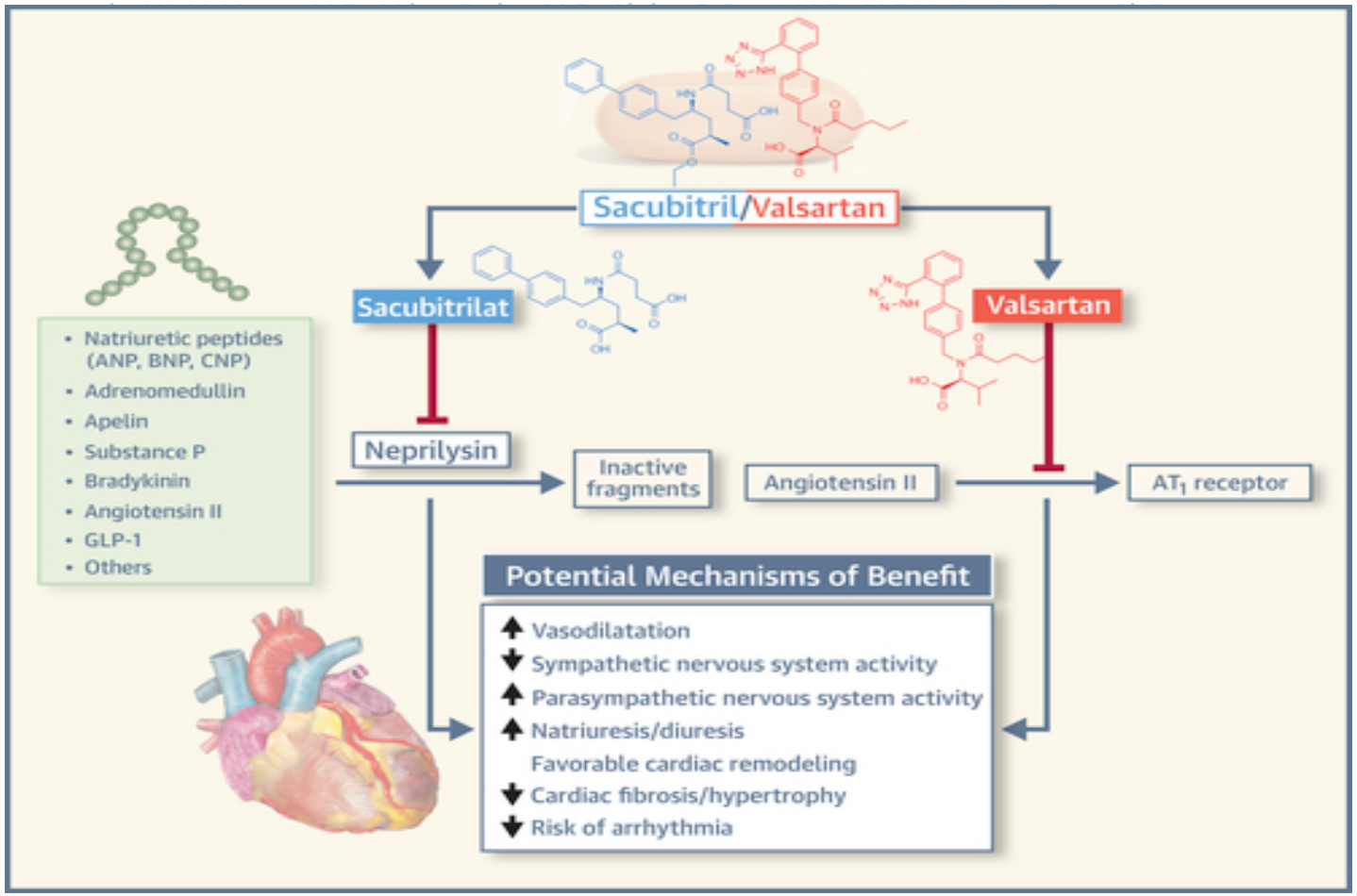
- Angiotensin Receptor Neprilysin Inhibitor (ARNI)- (Valsartan/Sacubitril), approved in 2021, EF 45-57%
- Sodium Glucose Co-transporter-2 Inhibitor (Empaglifozin)- published 8/27/2021

1- ARNI

The NEW ENGLAND JOURNAL of MEDICINE

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

# Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure




Kieran F. Docherty et al. *J Am Coll Cardiol HF* 2020; 8:800-810.

# Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

- PARADIGM HF trial 2014
- ARNI (200 mg bid) vs enalapril (10 mg bid)
- N 8442, symptomatic HF, EF<=40%, f/u 27 m
- Primary outcome – composite of CV death or HF hospitalization
- 22% vs 27% in enalapril
- ARNI was superior to enalapril in reducing the risks of death and of hospitalization for heart failure

# ARNI

- Dose - 24/26 mg bid titrate up 97/103 mg bid
- Contraindications: Pregnancy, history of angioedema, Hypotension, Severe Hepatic impairment

2- SGLT2i

# Sodium-Glucose Co-transporter-2 Inhibitors(SGLT2i)

| Study | Design | Baseline | Intervention | Outcome |
|---|---|---|---|---|
| DAPA-HF | RCT, Primary outcome-CV death or HF hosp, f/u 1.5 yrs. | N 4744, HFrEF, NYHA II-IV, EF <40% | Dapagliflozin 10 mg daily vs placebo | 16% vs 21% in placebo, 30% reduction in HF hosp |

# 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment

**Indications for Use of an SGLT2 Inhibitor**

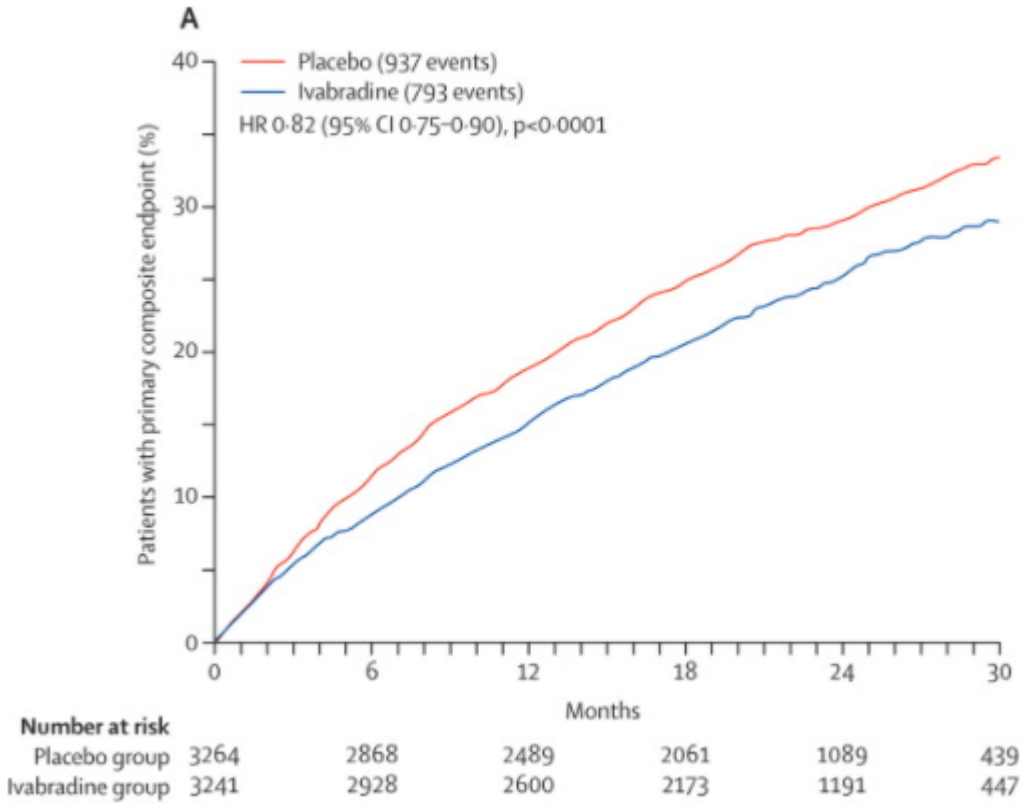
- HFrEF (EF ≤40%) with or without diabetes
- NYHA class II–IV HF
- Administered in conjunction with a background of GDMT for HF

- Dose: 10 mg po daily
- Contraindications: Type I DM, Dialysis, Lactation
- Cautions: eGFR<20 for Empa and <30 for Dapa, pregnancy, mycotic genital infection, ketoacidosis, urosepsis and pyelonephritis, Necrotizing fasciitis of perineum

3- Ivabradine

# Ivabradine: If-channel inhibitor

- Slows sinus node rate
- SHIFT trial
- Elevated resting heart rate is a risk factor for adverse outcome
- RCT, DB, PC, EF<=35%, in sinus >=70 bpm, HF hospitalization
- Ivabradine up to 7.5 mg bid vs placebo
- N 6558, f/u 23 m
- Primary endpoint CV death or HF hospitalization
- 24% vs. 29% in placebo, mostly HF hosp
- Approved in 2015



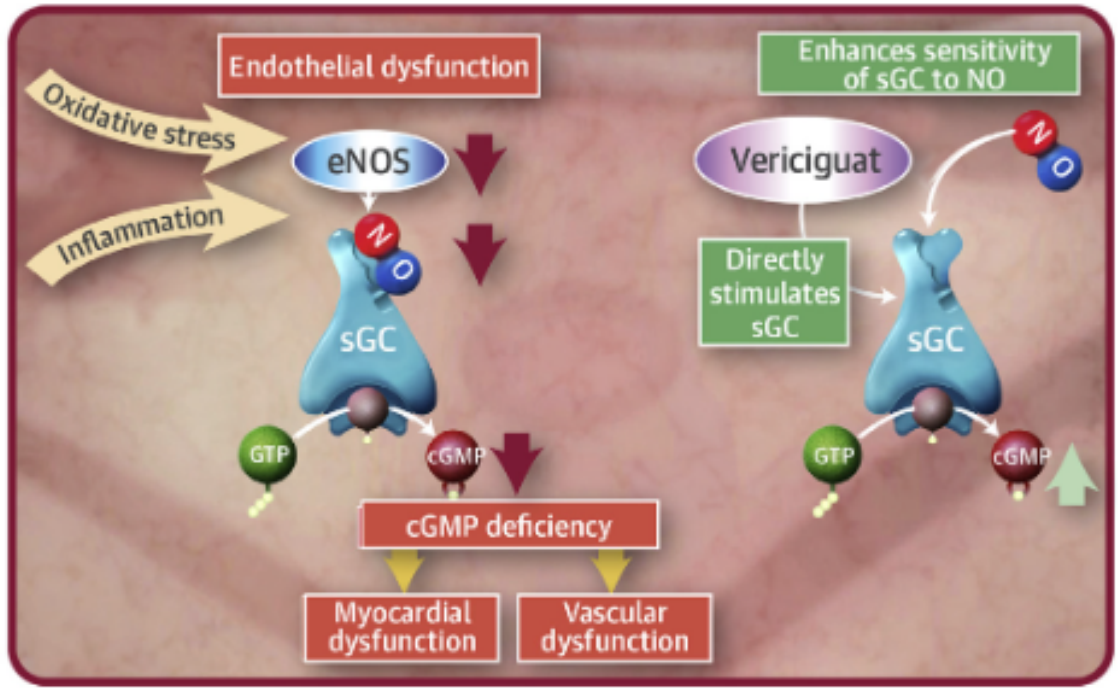

Swedberg K et al. Lancet 2010

# Ivabradine

- Starting dose 5 mg bid for 2 weeks, Max dose 7.5 mg bid (can be started as 2.5 mg bid)
- Contraindications: acute decompensated HF, BP<90, sick sinus syndrome, advanced AV block

# 4-Vericiguat

**CENTRAL ILLUSTRATION Restoration of Sufficient sGC-cGMP Signaling as Novel Target in HF**




**Armstrong, P.W. et al. J Am Coll Cardiol HF. 2018;6(2):96-104.**

Endothelial dysfunction due to oxidative stress and inflammation reduces nitric oxide bioavailability leading to insufficient activation of sGC. The resulting cGMP deficiency is associated with myocardial dysfunction and impaired endothelium-dependent vasomotor regulation **(orange)**. Vericiguat directly stimulates sGC in a NO-independent manner and by sensitizing the enzyme to endogenous NO **(green)**. cGMP = cyclic guanosine monophosphate; HF = heart failure; NO = nitric oxide; sGC = soluble guanylate cyclase.

Armstrong et al. JACC 2018

# VERICIGUAT- novel oral soluble guanylate cyclase stimulator- enhances cGMP pathway, and sensitized soluble GC to endogenous NO

- VICTORIA Trial
- Phase 3, RCT, parallel, placebo controlled, double blind, multicenter
- Primary endpoint – combination of time to CV death or HF hospitalization
- Titrated up to 10 mg daily vs matching placebo
- N = 5,050 , HFrEF, NYHA II-IV, EF<45%, Median f/u 11 months

| | Vericiguat | Placebo | Significance |
|---|---|---|---|
| Primary outcome | 36% | 39% | p=0.02 |
| HF hospitalization | 27% | 30% | p=ns |
| CV death | 16% | 18% | P=ns |

- Vericiguat (Verquvo) is indicated to reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for HF or need for outpatient IV diuretics, in adults with symptomatic chronic HF and EF<45%.

# AMYLOID CARDIOMYOPATHY

5- Tafamidis

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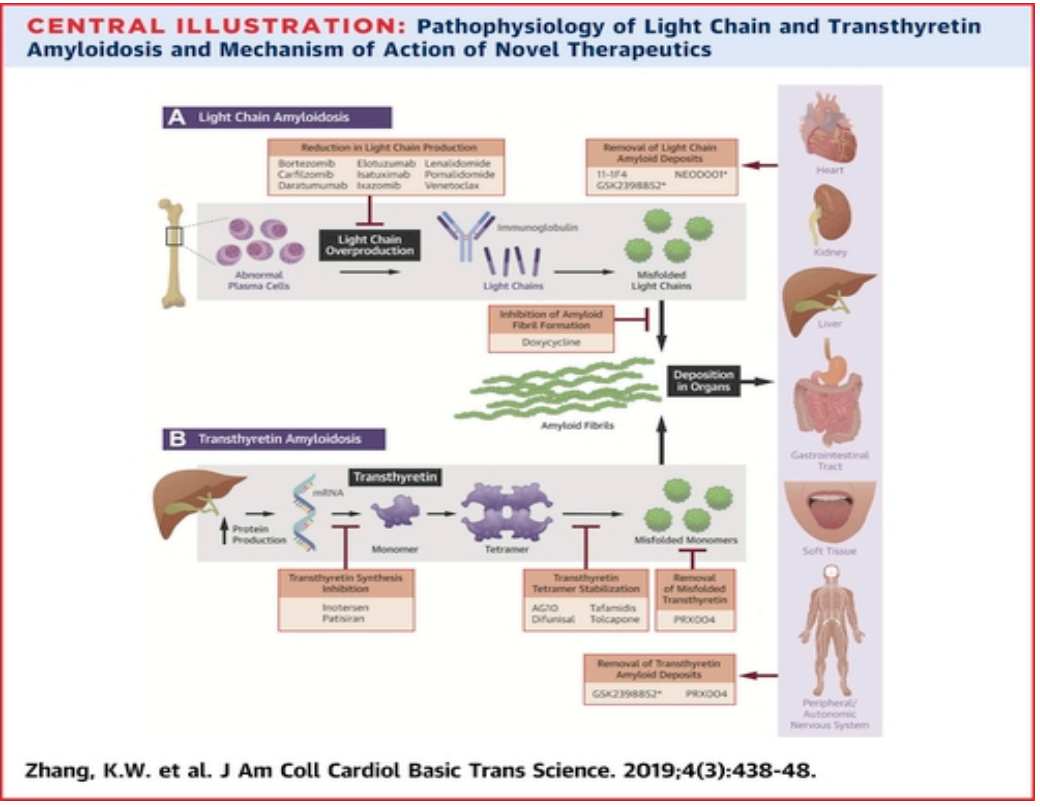
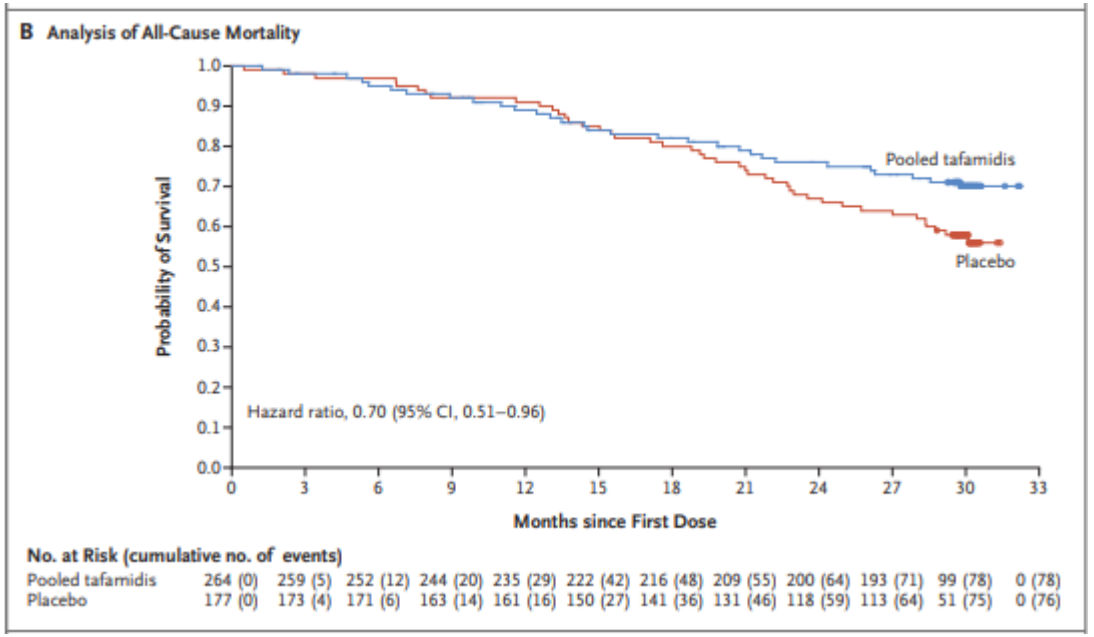
ESTABLISHED IN 1812 SEPTEMBER 13, 2018 VOL. 379 NO. 11

## Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

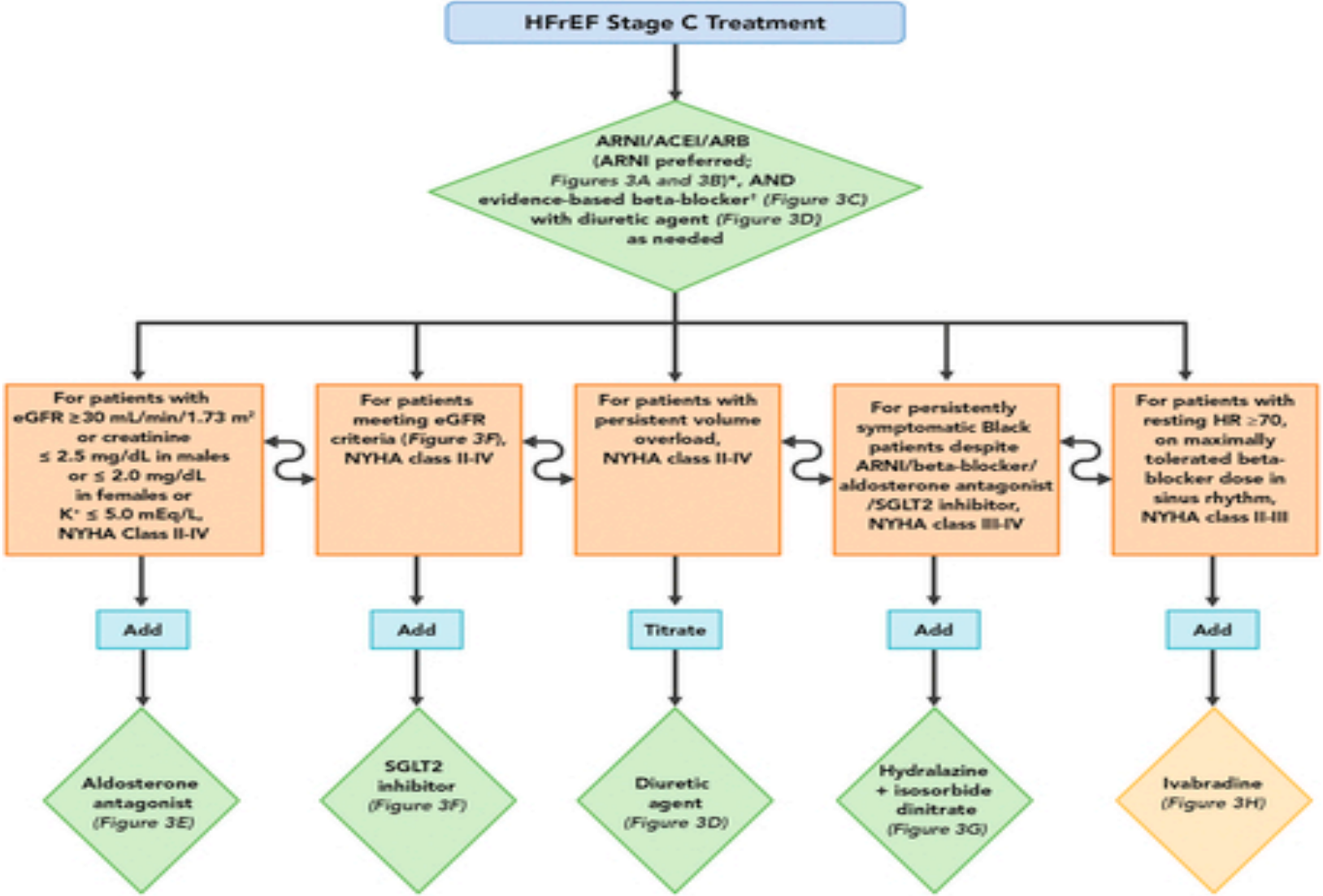
Mathew S. Maurer, M.D., Jeffrey H. Schwartz, Ph.D., Balarama Gundapaneni, M.S., Perry M. Elliott, M.D., Giampaolo Merlini, M.D., Ph.D., Marcia Waddington-Cruz, M.D., Arnt V. Kristen, M.D., Martha Grogan, M.D., Ronald Witteles, M.D., Thibaud Damy, M.D., Ph.D., Brian M. Drachman, M.D., Sanjiv J. Shah, M.D., Mazen Hanna, M.D., Daniel P. Judge, M.D., Alexandra I. Barsdorf, Ph.D., Peter Huber, R.Ph., Terrell A. Patterson, Ph.D., Steven Riley, Pharm.D., Ph.D., Jennifer Schumacher, Ph.D., Michelle Stewart, Ph.D., Marla B. Sultan, M.D., M.B.A., and Claudio Rapezzi, M.D., for the ATTR-ACT Study Investigators*




Zhang, K.W. et al. J Am Coll Cardiol Basic Trans Science. 2019;4(3):438-48.




Indicated for the treatment of the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.




*ACEI/ARB should only be considered in patients with contraindications, intolerance or inaccessibility to ARNI. In those instances, please consult Figure 3 and text for guidance on initiation.

†Carvedilol, metoprolol succinate, or bisoprolol.

ACEI = angiotensin-converting enzyme inhibitors; ARNI = angiotensin receptor-neprilysin inhibitors; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; K⁺ = potassium; NYHA = New York Heart Association; SGLT2 = sodium-glucose cotransporter-2.

Thomas M. Maddox et al. *J Am Coll Cardiol* 2021; 77:772-810.

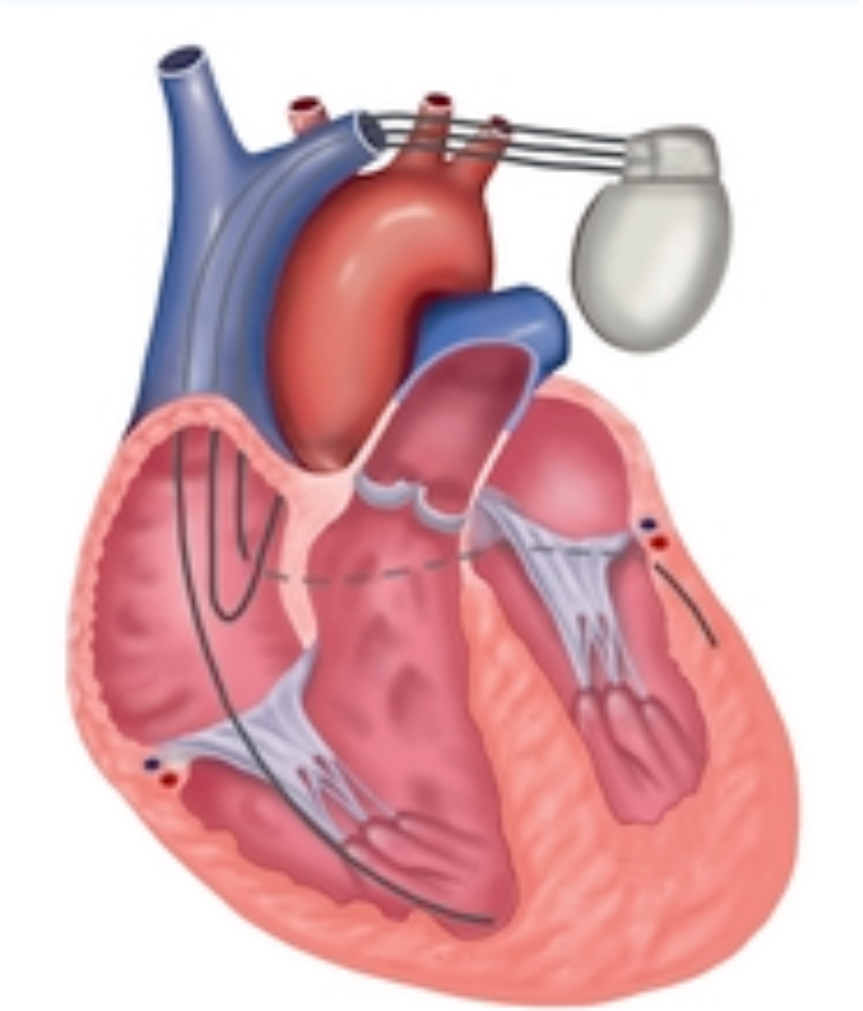
# Therapy for HFpEF

| Drug | Study | Design | Intervention | Primary Outcome | Results |
|---|---|---|---|---|---|
| Spironolactone | TOPCAT trial 2014 | RCT, N 3445, symptomatic HF, EF>=45% | Spironolactone 15-45mg daily vs placebo, f/u 3.3 yrs | CV death, aborted arrest, HF hosp | 18.6 % vs 20% in placebo (nonsig), But HF hosp (sig) |
| ARNI | PARAGON-HF 2019 | RCT, N 4822, symptomatic HF, EF>=45% | Sacubitril-valsartan 97/103 mg bid vs valsartan 160 mg bid | CV death and HF hosp | 37% vs 42% (nonsig) |
| SGLT2i | EMPEROR-Preserved 2021 | RCT, N 5988, symptomatic HF, EF>=40%, f/u 26 m | Empagliflozin 10 mg daily vs placebo | CV death or HF hosp | 13% vs 17% (p<0.001) Mainly HF hosp |

# Cardiac Resynchronization Therapy

OLD

FDA approval in 2002
For LVEF <=35%
Prolonged QRS >120-130 ms
NYHA functional class I-IV

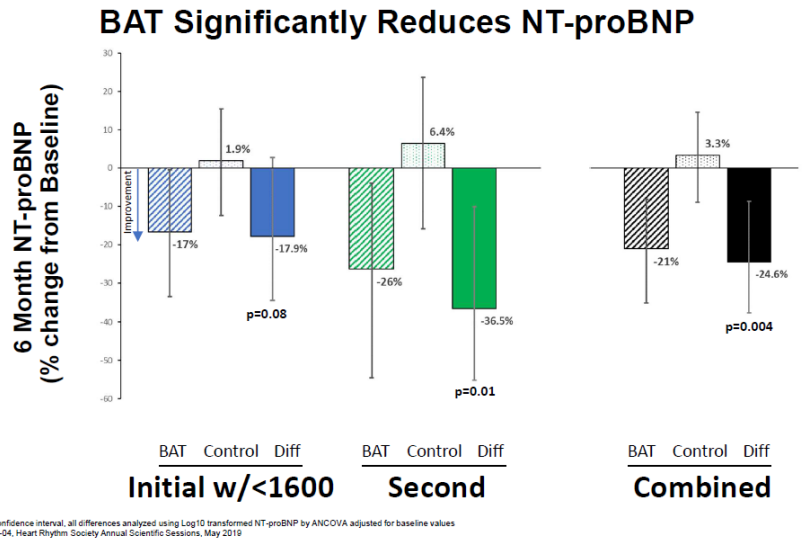


Contraindicated
1- NYHA I, QRS<=150 ms, non-LBBB
2- NYHA II, QRS<=150 ms, non-LBBB

Nemer, D.M. et al. J Am Coll Cardiol EP. 2021;7(1):62-72.

# BAROREFLEX ACTIVATION THERAPY

# Findings from BEAT-HF Trial

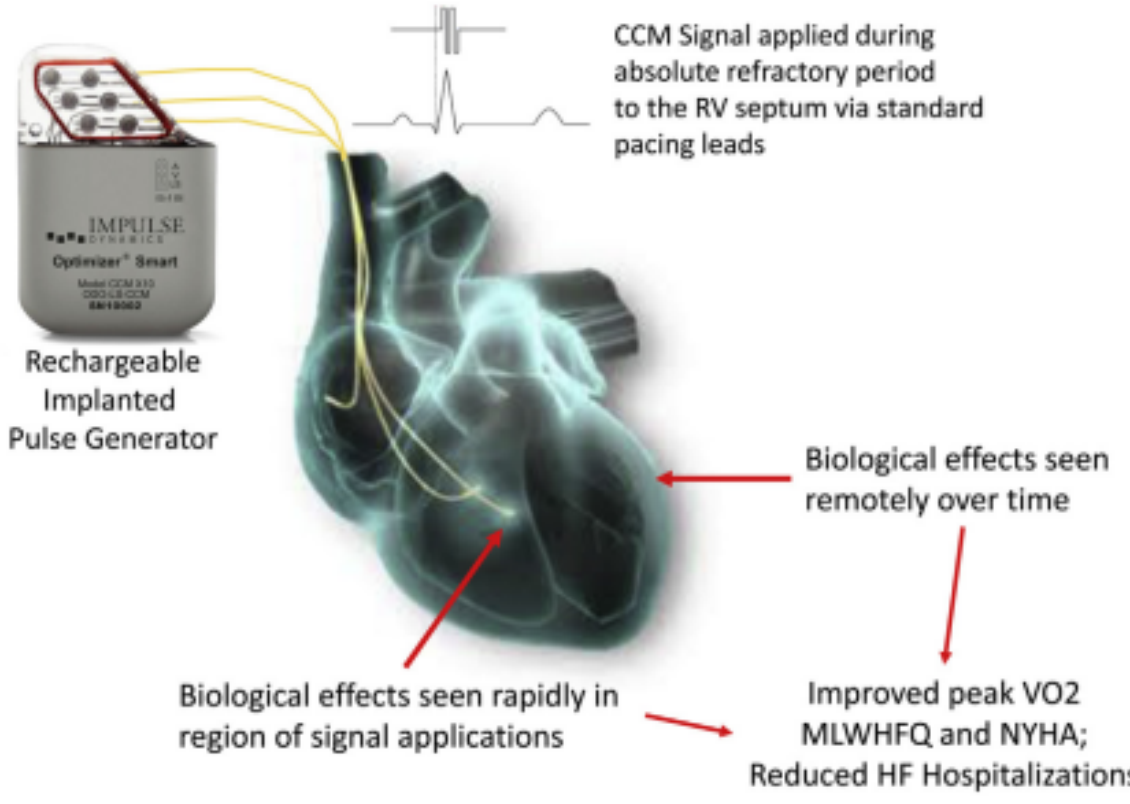



a = Mean ± 95% confidence interval, all differences analyzed using Log10 transformed NT-proBNP by ANCOVA adjusted for baseline values
MR, et al. LBCT01-04, Heart Rhythm Society Annual Scientific Sessions, May 2019

**FDA approval for**
**-NYHA II-III + LVEF <=35%**
**-NT-proBNP <1600 pg/ml**

# Cardiac Contractility Modulation (CCM)

**FIGURE 1 Clinical Implementation of CCM Treatment**




CCM signals are delivered from an implanted pulse generator connected to the heart via one atrial lead (for p-wave sensing) and two ventricular leads (for sensing timing of local electrical activation and for delivering CCM signals). CCM signal are biphasic pulses delivered during the absolute refractory period. CCM signals impact the biology of the failing muscle local and, over time, distal to the site of signal delivery. These myocardial effects ultimately contribute to favorable clinical effects. CCM = cardiac contractility modulation; MLWHFQ = Minnesota Living With Heart Failure questionnaire; NYHA = New York Heart Association.

# A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation

William T. Abraham, MD,[a] Karl-Heinz Kuck, MD,[b] Rochelle L. Goldsmith, PhD,[c] JoAnn Lindenfeld, MD,[d] Vivek Y. Reddy, MD,[e] Peter E. Carson, MD,[f] Douglas L. Mann, MD,[g] Benjamin Saville, PhD,[h] Helen Parise, ScD,[i] Rodrigo Chan, MD,[j] Phi Wiegn, MD,[k] Jeffrey L. Hastings, MD,[k] Andrew J. Kaplan, MD,[l] Frank Edelmann, MD,[m] Lars Luthje, MD,[m] Rami Kahwash, MD,[n] Gery F. Tomassoni, MD,[o] David D. Gutterman, MD,[p] Angela Stagg, BS,[q] Daniel Burkhoff, MD, PhD,[r] Gerd Hasenfuß, MD[s]

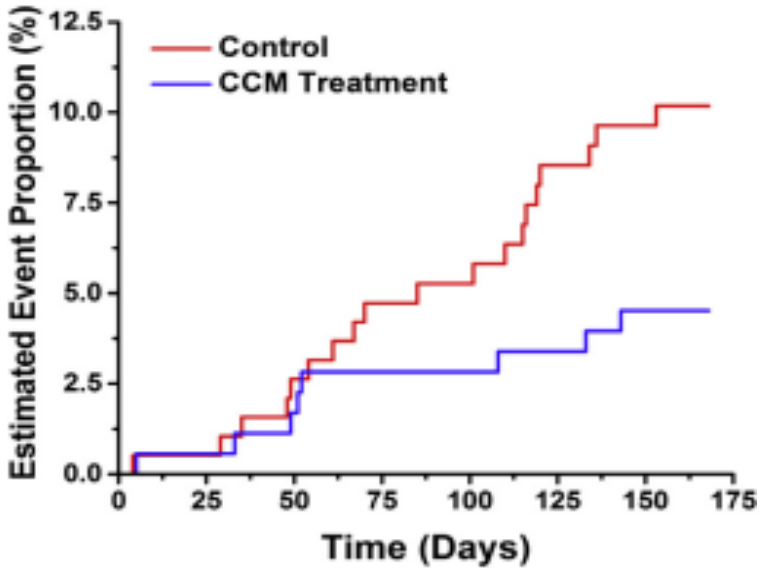
- FIX-HF-5C trial
- NYHA III-IV
- QRS <130 m, NSR, on GDMT, not indicated for CRT
- EF>=25% -<=45%
- RCT, N 160, F/U 24 wks
- Improvement in VO2, QOL, NYHA functional class and 6MHWT

FDA approval in 2019-

NYHA class III + LVEF 25-45%

-Improves 6MHW, QOL and functional status of NYHA

**FIGURE 5 Heart Failure and Mortality Events**



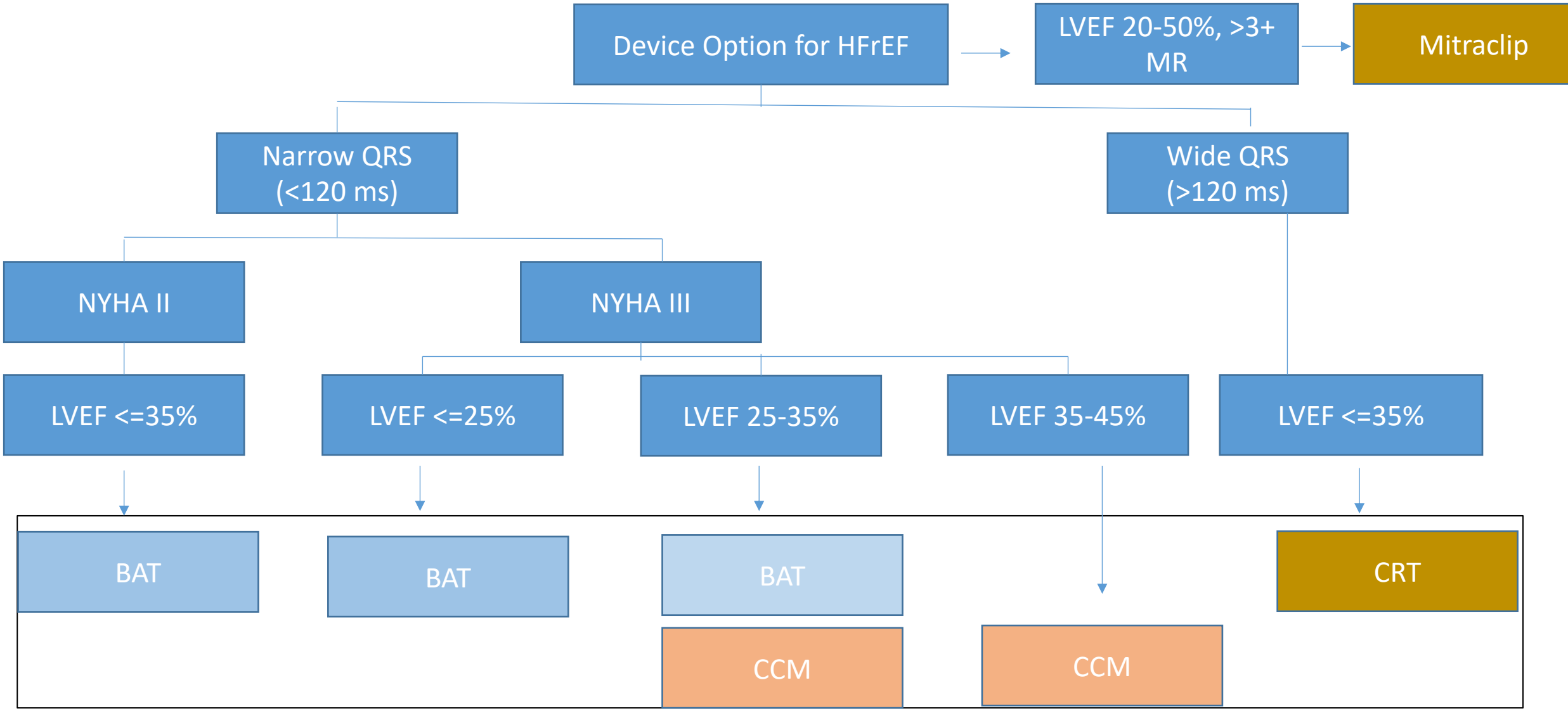

Comparison of estimated event proportions of the composite of cardiac death and heart failure hospitalizations between Control and Treatment; p = 0.042 by log-rank test and p = 0.036 when comparing 24 weeks using Greenwood's formula for the variance. Further details in Online Table 6. CCM = cardiac contractility modulation.

Abraham WT, et al. JACC Heart Failure 2018;6:874-883

RCT, multicenter,
Mod-severe or severe secondary MR
Symptomatic HF despite GDMT
EF 20%-50%, LVESD <=7 cm, exclude
RVSP >70 mm Hg
Endpoint – HF hospitalization
N 614, f/u 24 m
36% vs 68% in medical therapy

Divergent result in MITRA-FR; need for GDMT prior to referral

# Device Therapy to improve Heart Failure Symptoms



# Summary: what is new (since 2016)?

- SGLT2i, Vericiguat and Tafadimis
- Adoption of SGLT2i and Vericiguat in ESC guidelines
- Devices for narrow QRS (BAT and CCM)
- Mitraclip for severe secondary MR