Management of Heart Failure - A Continuing Update

Richard Clarens, PharmD
UND School of Medicine & Health Sciences
Big Sky NDAFP Conference
January, 2022

1

RESOURCES

- 2013 ACCF/AHA Guideline for the Management of Heart Failure
  - Circulation 13;128:e240-e327
- 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for Management of HF
  - Circ 17;136:e137-e61
- 2021 Update to 2017 ACC Expert Consensus Decision Pathway for Optimization of HF Treatment
  - J Am Coll Cardiol Online Jan 11, 2021

2

RECENT CASE

- 36 y/o African American male with SOB, DOE, malaise, fatigue, n/v, cough
  - Worsening DOE over several days
  - Bilateral LE edema
- PMH: HTN
- Med Reconciliation
  - Lisinopril 20 mg/d – not taking
  - Meloxicam – not taking

3

- BP 210s/120s, 71, 180 kg
- Cr 1.4, BNP 1,463
- EKG: NSR, no ischemic changes
- Labetalol 20 mg IV + Lisinopril 20 mg po + Furosemide 40 mg IV
- ECHO
  - LV severely dilated
  - EF 25-30%
  - LV severe global hypokinesis

4

- Cards assessment
  - Biventricular HF with EF 25-30%
  - Mod to severe LVH
  - Long-standing uncontrolled HTN
  - Acute on CKD
  - Need at least 3 antihypertensives
  - Carvedilol, Lisinopril, Amlodopine consistent with GDMD in setting of HFrEF
    - Can use nitrates and hydralazine if necessary

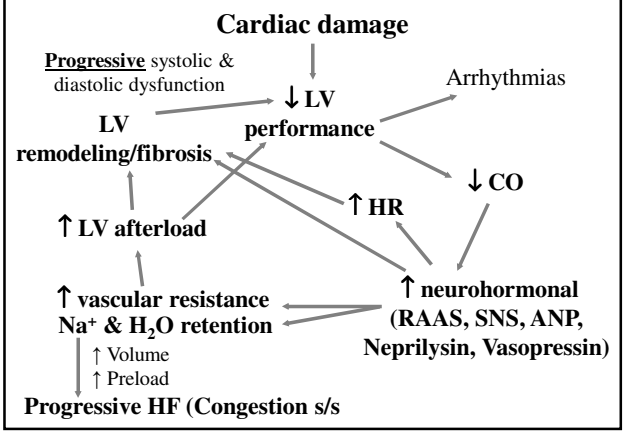
5

HF STATISTICS

- Affects ~6 million US residents
  - > 8M by 2030 – 46% increase from 2012
  - Survival ~ 50% at 5 y in symptomatic
  - Mortality after hospitalization ~20-25% at 1y
- Impact on health care resources
  - > 1M hospitalizations/y
  - Up to 50% readmitted within 6 mon of discharge
  - Projected 2030 cost $~70B (2012 ~$31B)

AHA Heart Disease & Stroke Stats – 2021 Circ 18;137:e67-492
HF Clin 19;15:371–75.
ACC/AHA Key Data Elements & Definitions for HF: ACC/AHA Statement 4/2021

6

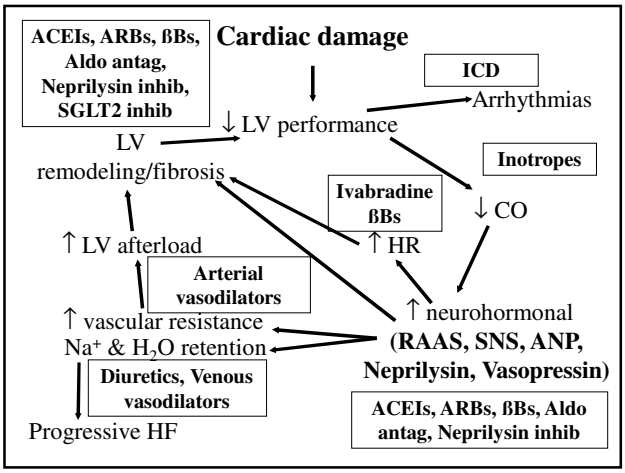


7

HEART FAILURE (HFrEF)

- Conventional therapy – relief of symptoms
  - Diuretics, digoxin
- Reduction in morbidity & mortality therapy
  - Hydralazine/Isosorbide (early 1980s)
  - ACEIs (late 1980s)
  - ß-blockers (mid 1990s)
  - Mineralocorticoid receptor antagonists (MRAs) (late 1990s)
  - ARBs (early 2000s)
  - ARB-neprilysin inhibitor (ARNI) (2015)
  - Ivabradine (2015)
  - SGLT2 inhibitors (2020)
  - Guanylyl cyclase stimulator (2021)

8



9

ß BLOCKERS AND CHF

- Historically were contraindicated
  - Negative inotropic activity & slow HR
- **Inhibit negative actions of chronic increased sympathetic stimulation on failing heart**
- **Metoprolol succinate, carvedilol, bisoprolol**
  - **FDA-approved agents that show mortality benefit**
  - "unlike ACEIs, there is **no class effect**"

Med Clin N Am 11;95:439-61
ACC/AHA Guidelines 2013
Treatment Guidelines from Medical Letter 03;1:53-6
J Am Coll Cardiol 19;74:672–82

10

ß BLOCKERS BENEFITS

- **Improve symptoms (only with long term use)**
- **Improve survival – RRR ~34% within 1 y**
- **Reverse/reduce remodeling/progression of LV dysfunction – increase in EF in many patients**
- **Reduce hospitalization**
- **Reduce sudden cardiac deaths (30-35%)**
- **Use in eligible patients is suboptimal**
  - <10% ßB at right dose JACC 18;72:351-66

CIBIS-II Lancet 99;353:9-13 MERIT-HF JAMA 00;283:1295-1302 CHARM Lancet 03;362:767-71
COPERNICUS Circ 02;106:2194-99 J Am Coll Cardiol 19;74:672–82
2020 ACC/AHA HF Measures. Circ Cardiovasc Qual Outcomes. 20;13:919-56

11

ACEI/ARB CLINICAL EFFECTS

- Most believe that all ACEIs & ARBs are effective for treatment of HF

Treatment Guidelines from Medical Letter 03;1:53-6 JAMA 12;307:1506-12

- **Improve symptoms**
  - ↓ preload and afterload and ↑ CO
- Modify progression of chronic CHF
  - **↑ Survival – RRR ~28%, NNT 7-22 over 41 mon**
  - **↓ Hospitalizations – RRR ~26%**

CONSENSUS NEJM 87;316:1429-35 SOLVD NEJM 91;325:293-302

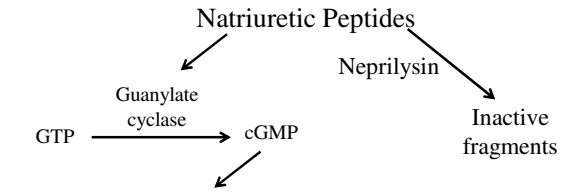
12

Sacubitril/Valsartan (Entresto)

- **Angiotensin Receptor Neprilysin Inhibitor (ARNI)**
- **Neprilysin degrades vasoactive peptides**
  - Natriuretic peptides, bradykinin, adrenomedulin
  - Neprilysin may be increased in HF (part of pathophys maladaptation in HF)
- **Sacubitril is a neprilysin inhibitor**
- **Valsartan is an ARB**

Pharmacist's Letter/Prescriber's Letter. September 2015.
Lancet. Published online December 2, 2016 http://dx.doi.org/10.1016/S0140-6736(16)30969-2
Circulation 16;133:1115-24 Med Lett Drugs Ther. 2021 Jun 14;63(1626):89-96

13



Vasodilation	↑ Bradykinin
↓ BP, SVR	↓ V. Hypertrophy
↓ SNS tone	↓ Cardiac fibrosis
↓ Vasopressin	↑ Natriuresis
↓ Aldosterone	↑ Diuresis
↓ RAAS	

Novel Approach to Medical Management of HFrEF. Can J Card 21;37:632-43

14

PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in HF)

- 8442 with NYHA II to IV with EF ≤ 40%
  - 72% Class II
  - BNP ≥ 150 (or NT-proBNP ≥ 600) or hospitalized within 1 y and BNP ≥ 100
  - Sacubitril/Valsartan 97/103 mg 2xd vs. Enalapril 10 mg 2xd
    - Most were also on recommended HF therapy
- The primary outcome a composite of death from CV causes and HF hospitalization

NEJM 14;371:993-1004

15

PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in HF)

- Stopped early at median of 27 months due to overwhelming benefit
- **Death/hospitalization**
  - **Sacubitril/Valsartan 21.8% vs Enalapril 26.5%** (HR 0.80; p=<0.001) – NNT 21 over ~ 2 years
- CV Mortality 13.3% vs. 16.5% (HR 0.80, p<0.001)
- **Superior to inhibition of RAAS alone**

NEJM 14;371:993-1004

16

Sacubitril/Valsartan (Entresto)

- **Adverse effects**
  - **Hypotension, hyperkalemia, cough, dizziness, angioedema and renal failure**
- **Contraindicated**
  - **h/o angioedema with previous ACEI/ARB**
  - **Concomitant with ACEI – ↑ risk angioedema**
- Precautions
  - Monitor for s/s angioedema/ hypotension
  - SCr & serum K should be monitored periodically

Pharmacist's Letter/Prescriber's Letter. September 2015
Med Lett Drugs Ther. 2021 Jun 14;63(1626):89-96

17

Sacubitril/Valsartan (Entresto)

- **FDA-approved indication**
  - **Reduce risk of CV death & hospitalization in NYHA Class II-IV HFrEF with EF ≤40%**
  - **New wording as of 2/16/21**
    - **Reduce risk of CV death & hospitalization for HF in chronic HF. Benefits most evident with EF below normal. EF variable measure use clinical judgement.**
- **Added to GDMT in place of an ACEI or ARB**

2021 ACC DECISION PATHWAY. J Am Coll Cardiol Online Jan 11, 2021

- **~$585/mon**

Med Lett Drugs Ther. 2021 Jun 14;63(1626):89-96

18

MINERALOCORTICOID/ALDOSTERONE RECEPTOR ANTAGONISTS – MRAs

- **Spironolactone**
  - **NOT FDA**-approved for HF
  - **RALES** study – Recent or current class IV HF
    - 12.5-50 mg/d vs. placebo – stopped early after 2 y
    - **30% decrease death, 35% decrease hospitalization**

    NEJM 99;341:709-17
- **Eplerenone** (Inspra) **FDA-approved**
  - **Improve survival** of stable patients with **LVSD (EF < 40%) & clinical evidence of CHF after acute MI**
  - Selective aldosterone blocker
    - May be better tolerated than spironolactone

19

Minimizing Risk of Hyperkalemia With Aldosterone Antagonists

- **Caution if creatinine ≥ 2.5 or CrCl < 30**
- **Do not use if baseline serum K ≥ 5 mEq/L**
- **Use with ACEIs or ARBs increases risk of hyperkalemia (monitor)**
- Avoid NSAIDs and COXIBs
- Stop (or reduce if needed) K+ supplements
- Monitor serum K+ & renal function frequently

. Pharmacotherapy 12;00:00 Online First ACC/AHA Guidelines 2021

20

BUT WAIT

THERE'S MORE TO THE STORY ON HF MEDS!!!

21

SGLT2 INHIBITORS

- Canagliflozin (Invokana), with metformin (Invokamet)
- **Dapagliflozin** (Farxiga), with metformin (Xigduo XR, with saxagliptin (Qtern), with saxagliptin and metformin (Qternmet XR)
- **Empagliflozin** (Jardiance), with linagliptin (Glyxambi), with metformin (Synjardy)
- Ertugliflozin (Steglatro), with metformin (Segluromet), with sitagliptin (Steglujan)

22

SGLT2i EFFECTS

- **Weight loss** of ~2-4.7 kg
- **Reduces FPG and PPG**
- **Reduces pre-load and afterload – HF effects**
- **Osmotic diuresis – HF effects**
- **Reduces total body Na – HF and BP lowering**
- **Decreases SBP ~2-10 mmHg & DBP ~1.3-1**
- **Reduces angiotensinogen**

JACC 18;72:1845-55 Diabetologia 18;61:2134–9
Med Lett Drugs Ther 2020 Nov 16;62(1611):e184-8
Med Clin N Am 21;105:955-66

23

SGLT2i EFFECTS

- **Reduces serum uric acid**
- **Reduces epicardial adipose tissue**
- **Improves mitochondrial efficiency**
- **Reduces steatosis – fatty liver**
- **Nephroprotective**
  - **Reduces progressive decline** in CKD
  - Reduces albuminuria

JACC 18;72:1845-55 Diabetologia 18;61:2134–9 Med Lett Drugs Ther 20;62:e184-8
Med Clin N Am 21;105:955-66 Lancet Diabetes Endocrinol 17;5:610-21
Circulation 18;137:119-29 Clin J Am Soc Nephrol 18;13:318-20 JACC 18;72:1845-55

24

SGLT2i ADVERSE EFFECTS

- **Polyuria, frequency,** volume depletion
- **Genital yeast infections** ~3-8%
- **UTIs** – ~0.3-2%
- **Renal don't use if eGFR <30-60**
  - eGFR cutoff varies with agent
  - Some associated with AKI
- **Hyperkalemia – DDI with ACEIs/ARBs, K-sparing diuretics and renal dysfunction**

J Diabetes Its Complications 13;27:280-6 Med Clin N Am 15;99:131-43 JACC 18;72:1845-55
Med Lett Drugs Ther 2020 Nov 16;62(1611):e184-8
2021 ACC Update. J Am Coll Cardiol Online Jan 11, 2021 Med Clin N Am 21;105:955-66

25

SGLT2i ADVERSE EFFECTS

- Hypermagnesemia, hyperphosphatemia
- Increase risk of fracture
- Ketoacidosis with low PG < 250 – rare
- Rare Fournier's gangrene
- Canagliflozin may increase risk of amputations
  - FDA removed boxed warning on 8/26/20
  - Still low risk – precaution

https://www.fda.gov/drugs/drug-safety-and-availability/fda-removes-boxed-warning-about-risk-leg-and-foot-amputations-diabetes-medicine-canagliflozin
FDA Drug Safety. 9/10/15 http://www.fda.gov/Drugs/DrugSafety/ucm461449.htm
2021 ACC Update. J Am Coll Cardiol Online Jan 11, 2021 Med Clin N Am 21;105:955-66

26

SGLT2i in HFrEF: Meta-analysis of EMPEROR-Reduced & DAPA-HF trials

- Confirms role of empagliflozin or dapagliflozin
- ~25% ↓ CV death, hospitalization worsening HF
- ~28% reduced hospitalizations
- Slows progression of renal disease
- Suggests reduction in mortality
  - **Those with T2DM and not with T2 DM**
  - **Those on ARNI and not on ARNI**

Lancet 20;396:819-29 Med Lett Drugs Ther 2020 Nov 16;62(1611):177-8

27

Totality of evidence in trials of SGLT2 inhibitors in HFrEF: implications for clinical practice

- Benefits are attained regardless of DM, MRAs and/or ARNIs
- Benefits
  - Once daily dosing, no uptitration
  - Little or no hypotension, bradycardia, hyperkalaemia, or azotaemia seen with other drugs
- Dapagliflozin and empagliflozin
  - **New standard of care** for patients with HFrEF

Butler J, Zannad F, Filippatos G, Anker SD, Packer M. opinion. ESC on line 9/15/20.

28

FDA-APPROVED INDICATIONS

- Canagliflozin (Invokana)
  - T2DM – 2013
  - CV: ↓ risk of major adverse **CV events in T2DM** & established CVD – Oct 30, 2018
  - CV & Renal: ↓ risk of end-stage kidney disease, doubling of SCr, hospitalization for **HF & CV death in T2DM and nephropathy with albuminuria** – Sept 30, 2019
- Ertugliflozin (Steglatro)
  - T2DM – 2017

29

FDA-APPROVED INDICATIONS

- Dapagliflozin (Farxiga)
  - T2DM – 2014
  - CV: **↓ T2DM HF hospitalization in T2DM** & established CVD or multiple CVD risk factors – Oct 21, 2019
  - CV: ↓ risk of CV death & hospitalization in **HFrEF ± DM** – May 6, 2020
  - CV & Renal: ↓ risk of sustained eGFR decline, ESRD, CV death, & **HF hospitalization in CKD at risk of progression ± DM** – Apr 30, 2021

30

FDA-APPROVED INDICATIONS

- Empagliflozin (Jardiance)
  - T2DM – 2014
  - CV: ↓ CV death **in T2DM** with established CVD – Dec 2, 2016
  - CV: ↓ risk of CV death & HF hospitalization in **HFrEF ± DM** – Aug 18, 2021

31

BUT WAIT

AGAIN, THERE'S MORE TO THE STORY ON HF MEDS!!!

32

HF AND HR

- Heart rate independently predicts outcomes in HFrEF
- ßB trials suggest that HR lowering is directly related to improved outcomes
  - The higher the dose, the better the outcome
- Some on optimal ßB doses continue to have resting HR > 70
  - Some do not tolerate up-titration of ßB to target dose and have an elevated heart rate

2021 ACC Update. J Am Coll Cardiol Online Jan 11, 2021

33

IVABRADINE (CORLANOR)

- Slows HR by inhibiting SA node I(f) (funny current)
  - Does not reduce contractility or BP
- Indication – Reduces composite of HF death or HF hospitalization with EF < 35% who are in NSR & resting HR >70 & on max doses of ßBs or a contraindication to ßB
  - Does NOT ↓ CV death

Med Lett Drugs Ther. 19;61:49-54 Card Electrophysiol Clin 19;11:21-37
2021 ACC Update. J Am Coll Cardiol Online Jan 11, 2021

34

IVABRADINE

- Adverse effects
  - Bradycardia, hypertension, AF, transient visual increases in brightness
- Drug interactions
  - Use with strong CYP3A4 inhibitors is contraindicated
  - Use with 3A4 inducers should be avoided

Med Lett Drugs Ther. 19;61:49-54

35

VERICIGUAT (VERQUVO)

- FDA-approved Jan 20, 2021
  - Reduce risk CV death & HF hosp following a HF hosp or need for outpatient IV diuretics in symptomatic chronic HF & < 45%

https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=214377

- Soluble guanylyl cyclase stimulator
  - Augments (sensitizes) guanylyl cyclase activation by NO by stabilizing NO to binding site
  - May also increase formation of cGMP
  - No tolerance unlike nitrates

NEJM 20;382:1952-3

36

2013 ACCF/AHA Guideline for the Management of Heart Failure

by Clyde W. Yancy, Mariell Jessup, Biykem Bozkurt, Javed Butler, Donald E. Casey, Mark H. Drazner, Gregg C. Fonarow, Stephen A. Geraci, Tamara Horwich, James L. Januzzi, Maryl R. Johnson, Edward K. Kasper, Wayne C. Levy, Frederick A. Masoudi, Patrick E. McBride, John J.V. McMurray, Judith E. Mitchell, Pamela N. Peterson, Barbara Riegel, Flora Sam, Lynne W. Stevenson, W.H. Wilson Tang, Emily J. Tsai, and Bruce L. Wilkoff

Circulation
Volume 128(16):e240-e327
October 15, 2013

American Heart Association
Learn and Live

37

ACC/AHA HF 2013 – Stage C HFrEF Class I

- **All with reduced EF with HF s/s**
  - **ACEIs** (or ARBs if intolerant) to prevent symptomatic HF and reduce mortality
  - Evidence-based **ßBs** to reduce mortality
- MRAs recommended to reduce mortality
  - NYHA II-IV and EF ≤ 35% unless contraindicated
  - After acute MI and EF ≤ 40% with HF s/s or have DMHF

38

Circulation
Volume 136, Issue 6, 8 August 2017. Pages e137-e161
https://doi.org/10.1161/CIR.0000000000000509

CLINICAL STATEMENTS AND GUIDELINES - ACC/AHA/HFSA FOCUSED UPDATEACC/AHA/HFSA FOCUSED UPDATE

2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

Clyde W. Yancy, MD, MSc, MACC, FAHA, FHFSA, Chair, Mariell Jessup, MD, FACC, FAHA, Vice Chair, Biykem Bozkurt, MD, PhD, FACC, FAHA, Javed Butler, MD, MBA, MPH, FACC, FAHA, Donald E. Casey, Jr, MD, MPH, MBA, FACC, Monica M. Colvin, MD, FAHA, Mark H. Drazner, MD, MSc, FACC, FAHA, FHFSA, Gerasimos S. Filippatos, MD, Gregg C. Fonarow, MD, FACC, FAHA, FHFSA, Michael M. Givertz, MD, FACC, FHFSA, Steven M. Hollenberg, MD, FACC, JoAnn Lindenfeld, MD, FACC, FAHA, FHFSA, Frederick A. Masoudi, MD, MSPH, FACC, Patrick E. McBride, MD, MPH, FACC, Pamela N. Peterson, MD, FACC, FAHA, Lynne Warner Stevenson, MD, FACC, and Cheryl Westlake, PhD, RN, ACNS-BC, FAHA, FHFSA

39

AHA 2017 Stage C HFrEF Recommendations – **Class I**

- **Clinical strategy of inhibition of RAAS with:**
  - **ACEIs (LOE A) OR**
  - **ARBs (LOE A) OR**
  - **ARNI (LOE B-R)**
  - **If tolerate ACEI/ARB, replacement by ARNI recommended**
- **IN CONJUNCTION WITH**
  - **Evidence-based BBs AND**
  - **Aldosterone antagonists in selected patients**

Circulation. Ahead of print May 20, 2016

40

ARTICLE IN PRESS

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2021 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. ■, NO. ■, 2021

EXPERT CONSENSUS DECISION PATHWAY

2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction

A Report of the American College of Cardiology Solution Set Oversight Committee

41

AHA 2021 Stage C HFrEF Recommendations – Class I

- ARNI or ACEI or ARB
  - ARNI preferred
  - ACEI or ARB considered only if contraindications, intolerance or inaccessibility to ARNI
- Evidence-based ßB
- MRA in NYHA II-IV if no contraindications
- SGLT2i if no contraindications

42

PRINCIPLES OF HF THERAPY
Guideline Directed Medical Therapy

- **GDMT is foundation of HF care**, and the GDMT with the highest expected benefit should be prioritized based on large RCTs
  - 1st-line meds: ARNIs (or ACEIs or ARBs), evidence-based ßBs, aldosterone antagonists, and SGLT2 inhibitors
  - HYD/ISDN is 1st-line for self-identified African Americans
  - Ivabradine is a 2nd-line med for select populations

2021 ACC Update. J Am Coll Cardiol Online Jan 11, 2021

43

	Relative Risk Reduction (%)	Iterative 2-Year Mortality (%)
None	—	35
ACEi or ARB	23	27
Beta-blocker	35	18
Aldosterone antagonists	30	13
ARNI (replacing ACEi or ARB)	16	10.9
SGLT2i	17	9.1
CRT-D (EF ≤35%; QRS duration ≥120 ms)	36	5.8

Cumulative risk reduction if all evidence-based medical therapies are used: relative risk reduction, 83.4%; absolute risk reduction, 29.2%; number needed to treat, 3.4.

Abbreviations: CRT-D, cardiac resynchronization therapy; EF, ejection fraction; SGLT2i, sodium-glucose cotransporter-2 inhibitors.

Data from Fonarow GC, Yancy CW, Hernandez AF, et al. Potential impact of optimal implementation of evidence-based heart failure therapies on mortality. Am Heart J 2011;161(6):1024-1030; and Fonarow GC. Statins and n-3 fatty acid supplementation in heart failure. Lancet 2008;372(9645):1195-1196.

Med Clin N Am 20;104:601-14

Guideline directed medical therapy (GDMT) may improve LVEF in 10-40%, including LVEF >40-50%.

J Am Coll Cardiol 20;76:719–34

44

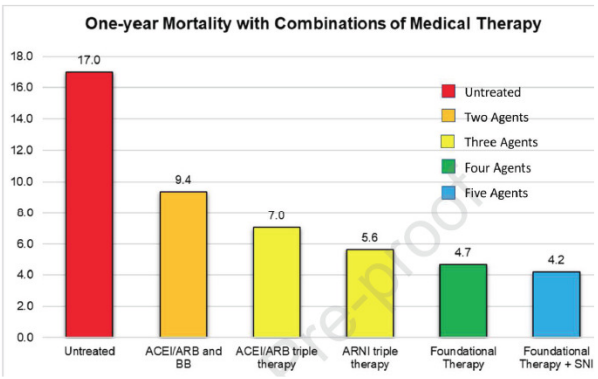
COMBINATION DRUG BENEFITS

- ARNI, ßB, MRA and SGLT2i
- Could prolong survival by 6.3 y in a 55 y/o vs. ACEI or ARB and ßB alone

Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in HFrEF. Lancet 20;396:121-8

45

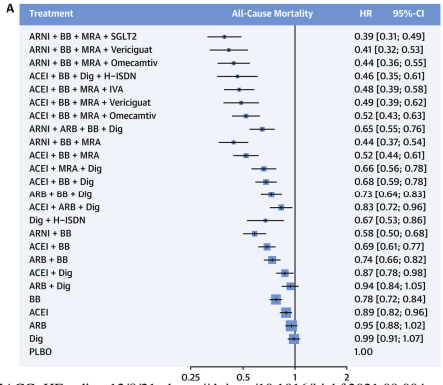
ire 3. One-year Outpatient Mortality with Combinations of Medical Therapy



Novel Approach to Medical Management of HFrEF. Can J Card. Online Jan 2021. https://doi.org/10.1016/j.cjca.2020.12.028. SNI (Sinus node inhibitor)

46

Systematic Review & Network-Meta-Analysis of Pharmacological Treatment of HFrEF



JACC: HF online 12/8/21 https://doi.org/10.1016/j.jchf.2021.09.004

47

ARNI, ßB, MRA, & SGLT2i

- Proposed foundational therapy
- "There are incremental benefits of treating patients with HFrEF with **all 4** agents impacting"
  - Angiotensin II, Aldosterone, Noradrenaline, Neprilysin, SGLT2
- "This approach should be considered the standard of care"

Butler J. Nature Reviews Card 20;17:455

48

ARNI, ßB, MRA, & SGLT2i

- Clear CV outcome benefits
- Start in eligible patients
- Patient phenotypes should guide patient-individualization
  - HR, BP, renal function
- Assess tolerability, patient wishes & cost
- Start as soon as possible
- Up-titrate to target dose or max tolerated dose

JACC: HF 21;9:775-83 Eur J Heart Fail 21;23:882-94

49

TARGET DOSES

- Associated with best outcomes
  - Attempt to achieve target dose for all recommended therapies if no contraindications &/or intolerance
  - **Titration should occur even if the patient appears stable or their symptoms &/or EF improve**

2021 ACC Update. J Am Coll Cardiol Online Jan 11, 2021

50

TARGET DOSES

- Most studies show better cardiac outcomes with higher doses vs lower doses
  - Increases risk of hypotension, hyperkalemia & worsening renal function
  - **Risk vs benefit in patient selection of up-titration**

JACC: HF 21;9:775-83

51

	Starting Dose	Target Dose
Beta-Blockers		
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25 mg twice daily for weight <85 kg and 50 m twice daily for weight ≥85 kg
Metoprolol succinate	12.5–25 mg daily	200 mg daily
ARNIs		
Sacubitril/valsartan	24/26 mg–49/51 mg twice daily	97/103 mg twice daily
ACEIs		
Captopril	6.25 mg 3× daily	50 mg 3× daily
Enalapril	2.5 mg twice daily	10–20 mg twice daily
Lisinopril	2.5–5 mg daily	20–40 mg daily
Ramipril	1.25 mg daily	10 mg daily
ARBs		
Candesartan	4–8 mg daily	32 mg daily
Losartan	25–50 mg daily	150 mg daily
Valsartan	40 mg twice daily	160 mg twice daily
Aldosterone antagonists		
Eplerenone	25 mg daily	50 mg daily
Spironolactone	12.5–25 mg daily	25–50 mg daily

2021 ACC Update. J Am Coll Cardiol Online Jan 11, 2021

52

REAL-WORLD UTILIZATION

- Recent therapies are infrequently used in patients eligible without contraindication or documented intolerance
- MRAs use 33.7–35.7%
- ARNI use 13.6-19.8%
- "These gaps in evidence-based medical therapies have been implicated in relatively stagnant mortality trajectories of patients living with HFrEF."

Lancet 20;396:819-29

53

Adherence to Evidence-Based Therapies in Heart Failure

- Evolving HFrEF regimens "has the unintended consequence of increasing the pill burden"
- Comorbidities in HF patients have guideline and evidence-based therapies
  - Add to patient pill burden

JACC: HF 21;9:887-9. edit

54

POLYPHARMACY

- "Essentially, all optimized HFrEF patients in 2020 … meet the polypharmacy criteria"

HF Reviews. Online 7/2/21. https://doi.org/10.1007/s10741-021-10135-4

- Usually refers to **≥ 5 meds**
  - A threshold definition is not always useful
- Useful to determine if appropriate or inappropriate polypharmacy

Steinman MA. JAMA Intern Med 16;176:482-3

Qato DM, Wilder J, et al. JAMA Intern Med 16;176:475-82

Levy HB. Clin Geriatr Med. Online 3/1/17
http://dx.doi.org/10.1016/j.cger.2017.01.007

55

POLYPHARMACY

- Reduce inappropriate polypharmacy
  - Irrational prescribing of too many meds
- Ensure appropriate polypharmacy
  - Rational Rx'ing meds medically indicated and considering individual patient factors and context
  - For instance in a patient with HF, T2DM & CAD
  - Polymedicine or Polytherapy

World Health Organization (2019) Medication Safety in Polypharmacy (WHO/UHC/SDS/2019.11). https ://apps.who.int/iris/bitst ream/handl e/10665 /32545 4/WHO-UHC-SDS-2019.11-eng.pdf?ua=1.

56

COST OF DRUGS FOR HF

- ACEIs – Lisinopril 40 mg/d ~$4/mon
- ARBs – Valsartan 160 mg 2xd ~$40/mon
- ßBs – Carvedilol 25 mg 2xd ~$6/mon; Metoprolol succinate 200 mg/d ~$25/mon
- **ARNI – Sacubitril/valsartan 97/103 mg 2xd ~$585/mon**
- MRAs – Spironolactone 25 mg/d ~$15/mon
- **SGLT2i – Dapagliflozin 10 mg/d ~$535/mon; Empagliflozin 10 mg/d ~$550/mon**
- Digoxin 0.125 mg/d ~$37/mon
- **Isosorbide/hydralazine 40/75 mg 3xd ~$690/mon**
- **Ivabradine 7.5 mg 2xd ~$490/mon**
- **Vericiguat 10 mg/d ~$585/mon**

Med Lett Drugs Ther. 2021 Jun 14;63(1626):89-96

57

PREFERRED FOUNDATIONAL THERAPY FOR HFrEF

- An ARNI is now preferred over an ACEI or an ARB in NYHA II-IV HFrEF
- In addition to an ARNI, ACEI, or ARB, all patients with ACC/AHA Stage C HFrEF should take, unless contraindicated, an evidence-based ßB, a MRA, and a SGLT2i
- Reduce risk of HF hospitalization & death

2017 ACC/AHA/HFSA HF Update. Circ 17;136:e137

2021 ACC HF Update. JACC 21;77:772

2021 ESC HF Guidelines. Europ Heart J 21;42:3599-3726

Med Lett Drugs Ther. 2021 Jun 14;63(1626):89-96

58

HFpEF MANAGEMENT

- No therapy has been shown to reduce mortality – unlike HFrEF
- Treatment for symptom relief
- Prognosis is affected by comorbidities
- Treatment of comorbidities
  - Might be important
  - Screen

Amer J Med 17;130:510-16 Cardiol Clin 17;35:261-71

Clin Res Card. On line 3/31/20 https://doi.org/10.1007/s00392-020-01633-w

Clin Card 20;43:145-55 NEJM 19;381:1675-6

59

Empagliflozin in HFpEF EMPEROR-Preserved Trial

- RCT of 5988 with NYHA II-IV HF and EF >40% to <60%
  - Empagliflozin 10 mg/d vs placebo for median of ~26 months
- Multicenter – 622 centers in 23 countries
  - Screened 11,583
  - ~50% DM, ~50% eGFR <60
  - ~66% EF ≥ 50% – median 54%
  - AF ~50%, HTN 90%

NEJM 21;385:1451-61

60

Empagliflozin in HFpEF EMPEROR-Preserved Trial

- Composite of CV death or HF hospitalization – Primary endpoint
  - Empagliflozin 13.8% vs. Placebo 17.1% (HR 0.79; p<0.001)
  - Mostly from lower hospitalization
  - Similar with/without DM

NEJM 21;385:1451-61

61

SGLT2 Inhibition in HFpEF – A Win against a Formidable Foe

- EMPEROR-Preserved trial is first phase 3 clinical trial that exclusively enrolled patients with HF and EF >40%
- "Major win against a medical condition that had previously proved formidable"
- "should contribute to a change in clinical practice"

Drazner, MH. Edit. NEJM 21;385:1522-4

62

EMPAGLIFLOZIN HFpEF FDA ACTIONS

- Breaththrough Therapy Designation. Investigational treatment in HFpEF – Priority review – Sept 9, 2021
  - EMPEROR Preserved study positive CV outcomes in HFpEF with or without DM – NEJM online 8/27//21

63