New Innovations in Heart Failure

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MedNet21

Disclosure

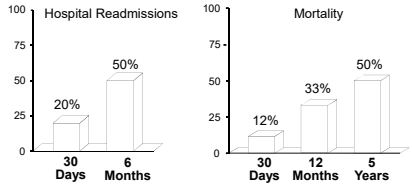
- **Ajay Vallakati – None related to current topic**
- **Indra Bole – None related to current topic**

Objectives

- **Discuss pharmacological management of heart failure**
- **Recognize new heart failure therapies, focusing on ivabradine, sacubitril-valsartan, and SGLT2i.**
- **Provide understanding to the benefit and guidance to use of new therapies in treating heart failure**

The Problem….

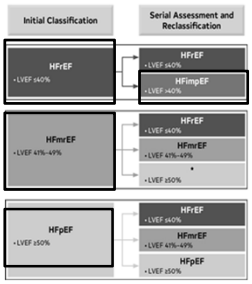
At age 40, lifetime risk of heart failure is 1 in 5



With each HF hospitalization, survival goes down

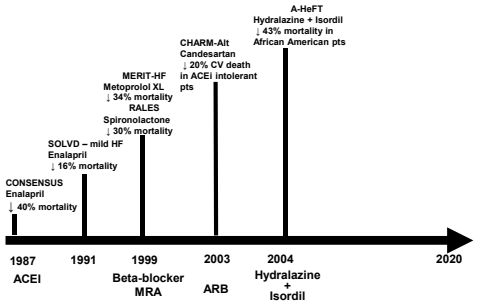
Aghababian RV. Rev Cardiovasc Med 2002; 3:S3
Jong P et al. Arch Intern Med 2002; 162:1689
Benjamin, et al. Circulation 2017.
AHA Statistics 2011

Classification of HF based on LVEF



Paul A. Heidenreich et al. Circulation 2022.

Management of Heart Failure



Beta-blockers

COR	LOE	Recommendation
1	A	1. In patients with HFrEF, with current or previous symptoms, use of 1 of the 3 beta blockers proven to reduce mortality (eg, bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations.[1–3]
Value Statement: High Value (A)		2. In patients with HFrEF, with current or previous symptoms, beta-blocker therapy provides high economic value.[4–8]

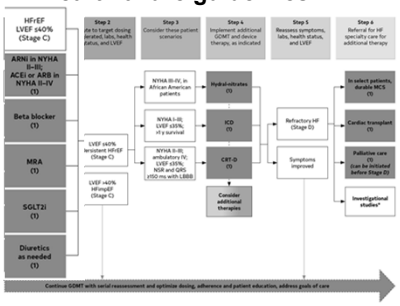
Paul A. Heidenreich et al. Circulation 2022.

Aldosterone Antagonists

COR	LOE	Recommendations
1	A	1. In patients with HFrEF and NYHA class II to IV symptoms, an MRA (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m² and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely monitored thereafter to minimize risk of hyperkalemia and renal insufficiency.[1–3]
Value Statement: High Value (A)		2. In patients with HFrEF and NYHA class II to IV symptoms, MRA therapy provides high economic value.[4–7]
3: Harm	**B-NR**	3. In patients taking MRA whose serum potassium cannot be maintained at <5.5 mEq/L, MRA should be discontinued to avoid life-threatening hyperkalemia.[8,9]

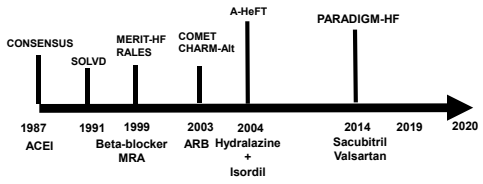
Paul A. Heidenreich et al. Circulation 2022.

Heart Failure guidelines

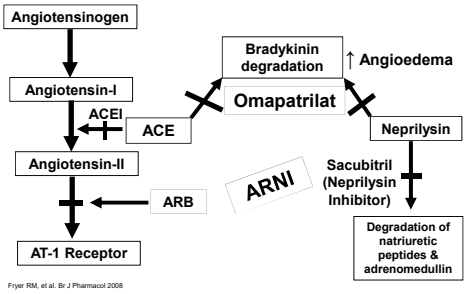


Paul A. Heidenreich et al. Circulation 2022.

Management of Heart Failure



Renin-Angiotensin Pathway



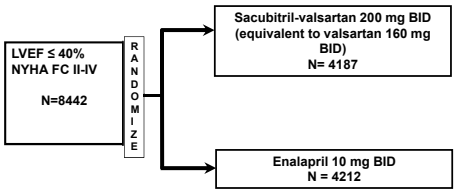
Fryer RM, et al. Br J Pharmacol 2008

Angiotensin Receptor Neprilysin Inhibitor (ARNI)

- **Combination of Sacubitril and Valsartan**
- **Sacubitril inhibits the degradation of natriuretic peptides, adrenomedullin, substance P**
- **Valsartan is angiotensin receptor blocker**
- **This combination leads to vasodilation, decreased SNS activity, increased PNS activity, natriuresis.**
- **This combination also decreases cardiac fibrosis and risk of arrhythmia.**

Pascual-Figal D, et al Front Cardiovas Med. 2021

PARADIGM-HF



Primary endpoint: **Composite CV death or first HFH**

McMurray J, et al. NEJM 2014

PARADIGM-HF: Baseline Characteristics

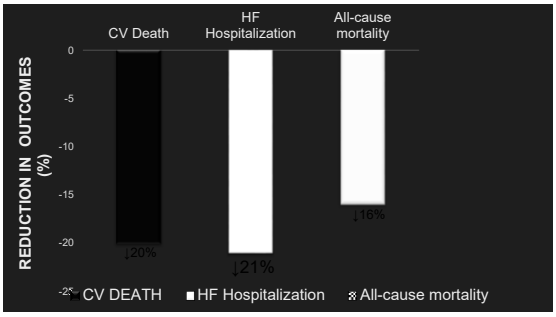
	LCZ 696 N=4187	Enalapril N=4212
Mean age, years	63.8	63.8
Women, %	21	22.6
ICM, %	59.9	60.1
Mean LVEF, %	29.6	29.4
NYHA FC II/III, %	71.1/23.1	69.4/29.4
SBP, mm Hg	122	121
Mean HR, bpm	72	73
NT-pro BNP, pg/ml	1631	1594
BNP, pg/ml	255	251
Beta-blockers, %	93.1	92.9

PARADIGM-HF: Results

- **Stopped early (median follow up 27 months) because of the overwhelming benefit seen in interim analysis**
- **Sacubitril-valsartan reduced primary endpoint by 20%**
  - **HR:0.80, p<0.001**
  - **NNT = 21**

McMurray J, et al. NEJM 2014

PARADIGM-HF Results



Sacubitril-Valsartan: Contraindications

- History of angioedema with ACEi or ARB
- Pregnancy
- No concurrent administration with ACEi
- Avoid using with another ARB
- Hold for 36 hours after switching from ACEi

Sacubitril-Valsartan: Dosing

- High dose ACE ~ equivalent > 10 mg/day enalapril
- High dose ARB > 160 mg/day valsartan
  - Starting dose 49/51 mg BID

Sacubitril-Valsartan: Dosing

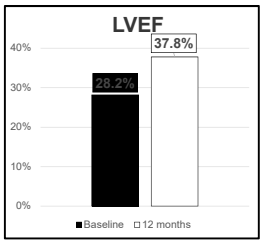
- Low or medium dose ACE ~ ≤ 10 mg/day enalapril
- Low or medium ARB ~ ≤ 160 mg/day valsartan
- De novo ARNI
- ACE/ARB naïve
- Elderly (age ≥ 75 years)
  - Starting dose 24/26 mg BID
  - Double dose (as tolerated) q 2-4 weeks to target 97/103 mg BID

PROVE-HF

- Initiation of sacubitril-valsartan in 794 HFrEF pts
  - De novo HF
  - ACE or ARB naïve
  - Low NT-pro BNP (median 816 pg/ml)
- Followed for 12 months

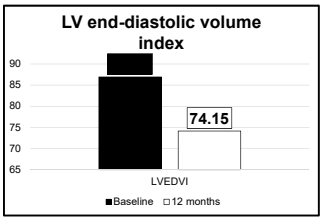
Januzzi, et al. JAMA 2019

PROVE-HF



Januzzi, et al. JAMA 2019

PROVE-HF



↓ LV systolic volume index and left atrial size at 12 months

Januzzi, et al. JAMA 2019

PIONEER-HF

- Initiation of sacubitril-valsartan in ADHF hospitalized pts
- 881 patients randomized: sacubitril-valsartan or enalapril
  - LVEF ≤ 40%
  - NT pro-BNP ≥1600 pg/mL or BNP ≥400 pg/mL
  - Enrolled within 24 hrs-10 days of presentation
  - Hemodynamically stable (no increase in diuretics or use of inotropes)
- Primary outcome: Change in the NT-proBNP concentration from baseline through weeks 4 and 8

Velazquez EJ, et al. NEJM 2019

PIONEER-HF

- Greater BNP reduction in sacubitril-valsartan group
  - % change: −46.7% vs. −25.3%
  - Ratio of change with sacubitril–valsartan vs. enalapril 0.71; 95% CI, 0.63 to 0.81; P<0.001
  - Reduction evident as early as 1 week

Velazquez EJ, et al. NEJM 2019

PIONEER-HF: Safety Outcomes

- Rates of worsening renal function, hyperK, and symptomatic hypotension did not differ significantly between groups
- 1 angioedema in sacubitril-valsartan vs 6 in enalapril group (all in African American pts)
- Rate of drug discontinuation d/t adverse events did not differ

LIFE Trial

- Initiation of sacubitril-valsartan in advanced HF
- 335 patients randomized: sacubitril-valsartan or valsartan
  - LVEF ≤ 35%
  - NT pro-BNP ≥800 pg/mL or BNP ≥250 pg/mL
  - Current inotropic Tx or in the last 6 months
  - NYHA FC IV
- Primary outcome: AUC for proportional change in ratio of NT pro-BNP compared to baseline through 24 weeks

Mann DL, et al. JAMA Cardiol. 2022

LIFE Trial

- No statistically significant difference with respect to reduction in NT pro-BNP levels
  - NT pro-BNP AUC for valsartan – 1.19 vs. sacubitril–valsartan – 1.08
  - Ratio of change with sacubitril–valsartan vs. valsartan 0.95; 95% CI, 0.84-1.08; P=0.45

LIFE Trial

Secondary outcomes for sacubitril/valsartan vs. valsartan:

- Days alive, out of hospital, or free from HF events: 103.2 vs. 111.2 days (p = 0.45)
- CV death or HF hospitalization: HR 1.32, 95% CI 0.86-2.03 (p = 0.20)
- Hypotension: 17% vs. 12% (p = 0.16)
- Hyperkalemia: 17% vs. 9% (p = 0.035)

PRIME Study

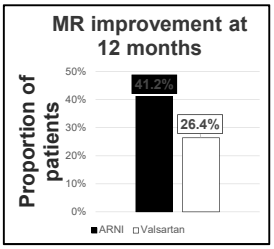
- 118 pts with chronic functional MR
- Randomized to sacubitril/valsartan or valsartan (in addition to standard GDMT)
- Primary endpoint: change in effective regurgitant orifice area at 12 months

Kang DH, et al. Circulation 2019

PRIME Study

Results:

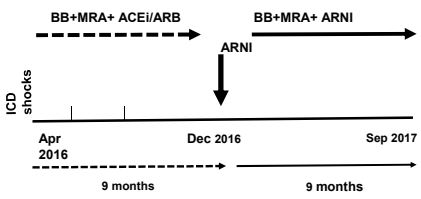
- EROA -0.058 in sacubitril/valsartan vs -0.018 in valsartan (P=0.032)
- Regurg volume decreased (mean difference -7.3 mL, P=0.009)



Kang DH, et al. Circulation 2019

Sacubitril-Valsartan

- Effect on ventricular arrhythmias
- 120 patients, NYHA II-IV, EF ≤ 40%, remote monitoring



De Diego, et al. Heart Rhythm 2018

Sacubitril-Valsartan - Arrhythmias

Compared to ACE/ARB, ARNI

- ↓ NSVT (5.4 ± 0.5 vs 15 ± 1.7 in ACE/ARB; *P* <.002)
- ↓ sustained VT and ICD shocks (0.8% vs 6.7% in ACE/ARB; *P* <.02)
- ↓ PVCs/hr (33 ± 12 vs 78 ± 15 in ACE/ARB; *P* <.0003)
- ↑ biventricular pacing (95%±6% to 98.8%±1.3%; *P* <.02)

De Diego, et al. Heart Rhythm 2018

PARAGON-HF

- 4822 patients randomized: sacubitril-valsartan or valsartan
  - EF > 45%
  - NYHA II-IV
  - NT-proBNP > 300 pg/mL (> 900 pg/mL if A-Fib)
- Primary Outcome
  - Composite of total HFH and CV death

Solomon SD, et al. Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med*. 2019.

PARAGON-HF - Results

- No benefit with ARNI in terms of composite of HF hospitalizations and CV death (RR 0.87, 0.75 -1.01)
- Trend towards benefit for HF hospitalizations alone (RR 0.85, 0.72 -1.00)
- ↓ in primary event in patients with EF <57%
- Benefit in females compared to males

Solomon SD, et al. Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med*. 2019.

Heart Failure	Sacubitril/Valsartan
Outpatient	Yes
Inpatient	Yes
Advanced HF/Stage D	+/-
ACE/ARB Naive	Yes
Functional MR	Yes
HFpEF	No

Ivabradine

- Selective inhibitor of sinoatrial pacemaker modulating "f-current" (If)
- Slows sinus HR
- Unlike β-blockers, does not modify myocardial contractility and intracardiac conduction
- Mechanism of ivabradine in HFrEF likely d/t HR reduction

Dobre D, et al. Eur J Heart Fail 2014

SHIFT Trial

- **6558 patients**
- **LVEF ≤ 35%, NYHA FC II-III**
- **Sinus rhythm and resting HR ≥ 70 bpm**
- **Randomized to ivabradine or placebo**
- **Primary endpoint: composite CV death or HF hospitalization**
- **Median follow-up 23 months**

Swedberg K, et al. Lancet 2010

SHIFT Trial: Baseline Characteristics

	Ivabradine N=3241	Placebo N=3264
Mean age, years	60.7	60.1
Male, %	76	77
BMI, kg/m^2	28	28
Mean HF duration, years	3.5	3.5
HF, ischemic cause, %	68	67
NYHA Class III, %	50	51
NYHA Class IV, %	2	2
Mean LVEF, %	29.0	29.0
Mean HR, bpm	79.7	80.1

SHIFT Trial: Baseline Characteristics

GDMT	Ivabradine N=3241	Placebo N=3264
β-blocker, %*	**89**	**90**
At least ½ target dose	55	56
At target dose	26	26
ACEi / ARB, %	**93**	**92**
Diuretics, %	**84**	**83**
Aldosterone antagonists, %	**61**	**59**

*Most common reasons for not reaching target dose: Hypotension (44%), fatigue (32%), dyspnea (14%), and dizziness (13%).

SHIFT Trial: Results

- **↓ 18% in primary end-point in ivabradine group**
- **Results largely d/t ↓ HF hospitalization (HR 0.74, 95% CI 0.66-0.83) and ↓ HF death (HR 0.74, 95% CI 0.58-0.94)**
- **Significant benefit if resting HR ≥ 77 bpm, but not with lower HR**
- **Highlights importance of HR control in HF**

Swedberg K, et al. Lancet 2010

Ivabradine

- Approved by the FDA on April 15, 2015
- "Corlanor"
- Stable HF with LVEF ≤ 35%
- Sinus rhythm with resting HR ≥ 70 bpm
- Either on max tolerated dose of β-blocker or have contraindication to β-blockers
- Not a full or partial substitute for β-blockade

Ivabradine: Contraindications

- Acute decompensated heart failure
- Hypotension (BP < 90/50)
- Sick sinus syndrome, sinoatrial block, or 3rd degree AV block
- Patients who are pacemaker dependent
- Severe hepatic impairment
- Persistent AF or flutter
- HFpEF

New Innovations in Heart Failure

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MedNet21
Center for Continuing Medical Education

The Ohio State University Wexner Medical Center

The Birth of SGLT2 inhibition

- Phlorizin was isolated from the bark of the apple tree in 1835
- Phlorizin was later found to inhibit glucose reabsorption in the PCT of the nephron
- Synthetic oral derivatives found to lower to HbA1c without hypoglycemia

Braunwald E. Gliflozins in the management of cardiovascular disease. Longo DL, ed. *N Engl J Med.* 2022;386(21):2024-2034.

SGLT2i Cardiovascular Outcome Trials

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373(22):2117-2128.

SGLT2i CVOT: EMPA-REG

- **Population:**
  - **~7,000 patients with high CV risk (known CAD, CVA, PAD) and DMT2 followed for 3.1 years**
  - **Randomized to empagliflozin or placebo**

Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373(22):2117-2128.

SGLT2i CVOT: EMPA-REG

Primary outcome: MACE (CV death, MI, CVA)

- **Empagliflozin: 10.5%**
- **Placebo: 12.1%**
- **HR 0.86 (95% CI 0.74-0.99); P=0.04 demonstrating superiority of empagliflozin**

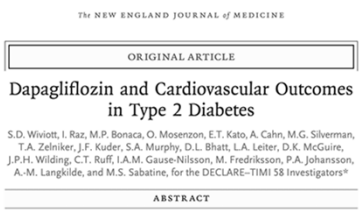
Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373(22):2117-2128.

SGLT2i CVOT: EMPA-REG

- **Benefit of empagliflozin on primary outcome driven by CV death**
  - **ARR 2.2%, RRR 38%**
- **Significant reduction in heart failure hospitalization was observed (ARR 1.4%, RRR 35%)**

Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373(22):2117-2128.

SGLT2i Cardiovascular Outcome Trials



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*

ABSTRACT

Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357.

SGLT2i CVOT: DECLARE-TIMI 58

- **Population:**
  - **~17,000 patients with high CV and DMT2 followed for 4.2 years**
  - **Randomized to dapagliflozin or placebo**

Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357.

SGLT2i CVOT: DECLARE-TIMI 58

Primary efficacy outcomes:
- **MACE (CV death, MI, CVA)**
- **CV death + HF hospitalization**

Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357.

SGLT2i CVOT: DECLARE-TIMI 58

- **Primary efficacy outcomes:**
  - **MACE (CV death, MI, CVA)**
    - **Not significant for superiority**
    - **HR 0.93 (95% CI 0.84-1.03)**
    - **Lower risk population than EMPA-REG**

Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357.

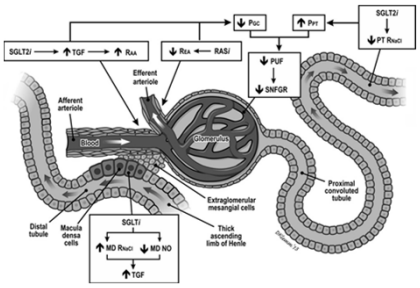
SGLT2i CVOT: DECLARE-TIMI 58

CV death + HF hospitalization

- **Reduced with dapagliflozin (4.9% vs. 5.8%)**
- **HR 0.83 (95% CI 0.73-0.95), P = 0.005**
- **Driven by reduced HF hospitalization**

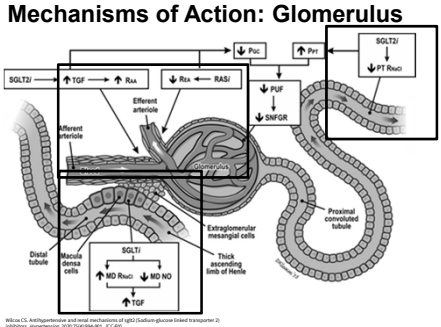
Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357.

Mechanisms of Action: Glomerulus



Wilcox CS. Antihypertensive and renal mechanisms of sglt2 (Sodium-glucose linked transporter 2) inhibitors. *Hypertension*. 2020;75(4):894-901. (CC-BY)

Mechanisms of Action: Glomerulus



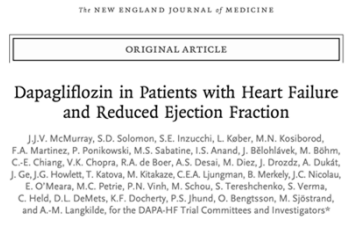
Wilcox CS. Antihypertensive and renal mechanisms of sglt2 (Sodium-glucose linked transporter 2) inhibitors. *Hypertension*. 2020;75(4):894-901. (CC-BY)

Early Reduction in GFR after SGLT2i

- **SGLT2i use associated with a 3 mL·min^{-1}·1.73 m^{-2} decrease in eGFR after 14 days of treatment**
- **12.6% of patients had > 20% decrease in eGFR after starting SGLT2i**
- **The benefit of SGLT2i was concentrated in patients with an initial eGFR "dip".**

Adamson C, Docherty KF, Heerspink HJL, et al. Initial decline (Dip) in estimated glomerular filtration rate after initiation of dapagliflozin in patients with heart failure and reduced ejection fraction: insights from dapa-hf. *Circulation*. 2022;146(6):438-449.

DAPA-HF: The First Trial in HF Patients



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2019;381(21):1995-2008.

DAPA-HF: Patient Population

- **Major Inclusion Criteria:**
  - **EF ≤ 40%**
  - **NYHA II-IV**
  - **NT-proBNP ≥ 600 pg/mL (≥ 400 if HFH <12 mo)**
- **Major Exclusion Criteria:**
  - **SBP ≤ 95 mmHg**
  - **eGFR ≤ 30 mL/min**
  - **DM type I**

McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2019;381(21):1995-2008.

DAPA-HF: Patient Population

- **Key Baseline Characteristics**
  - **23% Female sex**
  - **70% White, 23% Asian, 5% Black**
  - **67% NYHA II, 32% NYHA III**
  - **Median NT-proBNP 1450 pg/mL**
  - **42% with DMT2**
  - **Low use of ARNI**

McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2019;381(21):1995-2008.

DAPA-HF: Outcomes

- **Primary Outcome**
  - **Composite of CV death or worsening HF**
    - **Worsening HF: HFH or urgent visit w/ IV diuretic**

McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2019;381(21):1995-2008.

DAPA-HF: Outcomes

- **Secondary Outcomes**
  - **Composite of HFH + CV death**
  - **Total HFH**
  - **KCCQ change from baseline at 8 months**
  - **Worsening renal function**
    - **eGFR decline ≥ 50%, ESRD**
- **Major Safety Outcomes: DKA, renal events, hypoglycemia, volume depletion, amputations**

McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2019;381(21):1995-2008.

DAPA-HF: Outcomes

- **Primary Outcome: CV death or worsening HF**
  - **Dapagliflozin arm: 16.3 %**
  - **Placebo arm: 21.2 %**
  - **HR 0.74 (95% CI 0.65 – 0.85)**
- **No difference in primary outcome based on diabetes status of patient**

McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2019;381(21):1995-2008.

DAPA-HF: Outcomes

- **Key secondary outcomes**
  - **Improvement in HF symptom burden (KCCQ)**
  - **Cardiovascular death significantly reduced**
- **No significant adverse safety signal**
  - **Serious adverse events higher in placebo arm**
  - **No signal for increased renal events**

McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2019;381(21):1995-2008.

EMPEROR-Reduced

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez Juanatey, S. Kaul, H.-P. Brunner-La Rocca, B. Merkely, S.J. Nicholls, S. Perrone, I. Pina, P. Ponikowski, N. Sattar, M. Senni, M.-F. Seronde, J. Spinar, I. Squire, S. Taddei, C. Wanner, and F. Zannad, for the EMPEROR-Reduced Trial Investigators*

Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med.* 2020;383(15):1413-1424.

EMPEROR-Reduced: Patient Population

- Similar inclusion criteria to DAPA-HF, though with higher minimum natriuretic peptide levels
- Key Baseline Characteristics
  - 24% Female sex
  - 70% White, 18% Asian, 7% Black
  - 75% NYHA II, 25% NYHA III
  - Median NT-proBNP 1900 pg/mL (1450 in DAPA-HF)
  - 50% with DMT2
  - Higher ARNI use compared to DAPA-HF

Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med.* 2020;383(15):1413-1424.

EMPEROR-Reduced: Outcomes

- **Primary Outcome:** CV death or first HFH
  - Empagliflozin arm: 19.4%
  - Placebo arm: 24.7%
  - HR 0.75 (95% CI 0.65 – 0.86)
  - Consistent effect independent of diabetes

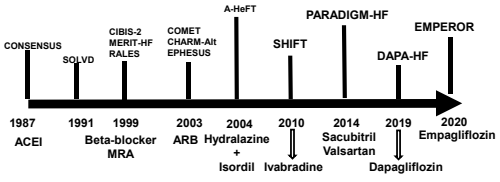
Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med.* 2020;383(15):1413-1424.

EMPEROR-Reduced: Outcomes

- **Secondary Outcomes:**
  - Total HFHs: 30% reduced in SGLT2i arm
  - Rate of eGFR decline: 2 ml/min/1.73 m^2 improved

Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med.* 2020;383(15):1413-1424.

Management of Systolic Heart Failure



SGLT2i Benefiting Populations

- Established ASCVD (CAD, PAD, CVA) in DMT2
- High risk for CAD in DMT2
- Heart failure with reduced ejection fraction
  - With or without DMT2
- CKD patients
  - With or without DMT2
- What's left??
  - HFpEF

EMPEROR-Preserved

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

S.D. Anker, J. Butler, G. Filippatos, J.P. Ferreira, E. Bocchi, M. Böhm, H.-P. Brunner–La Rocca, D.-J. Choi, V. Chopra, E. Chuquiure-Valenzuela, N. Giannetti, J.E. Gomez-Mesa, S. Janssens, J.L. Januzzi, J.R. Gonzalez-Juanatey, B. Merkely, S.J. Nicholls, S.V. Perrone, I.L. Piña, P. Ponikowski, M. Senni, D. Sim, J. Spinar, I. Squire, S. Taddei, H. Tsutsui, S. Verma, D. Vinereanu, J. Zhang, P. Carson, C.S.P. Lam, N. Marx, C. Zeller, N. Sattar, W. Jamal, S. Schnaidt, J.M. Schnee, M. Brueckmann, S.J. Pocock, F. Zannad, and M. Packer, for the EMPEROR-Preserved Trial Investigators*

Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385(16):1451-1461.

EMPEROR-Preserved: Patient Population

- Major Inclusion Criteria:
  - EF > 40%
  - NYHA II-IV
  - NT-proBNP > 300 pg/mL (> 900 pg/mL if A-Fib)

Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385(16):1451-1461.

EMPEROR-Preserved: Patient Population

- Key Baseline Characteristics
  - 45% Female sex
  - 76% White, 14% Asian, 4% Black
  - 82% NYHA II, 18% NYHA III
  - Median NT-proBNP 950 pg/mL
  - 49% with DMT2

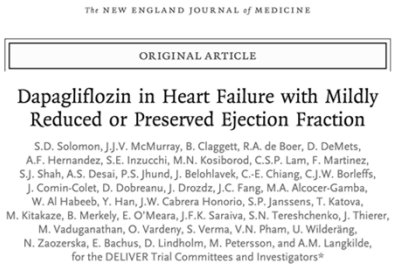
Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385(16):1451-1461.

EMPEROR-Preserved: Outcomes

- **Primary Outcome: CV death or First HFH**
  - **Empagliflozin arm: 13.8%**
  - **Placebo arm: 17.1%**
  - **HR 0.79 (95% CI 0.69 – 0.90)**
  - **Effect driven by reduction in time to first HFH**
  - **Consistent across DMT2 status**
- **Secondary Outcomes:**
  - **Total HFHs: 27% lower in SGLT2i arm**
  - **Rate of eGFR decline: 1.5 ml/min/1.73m^2 better**

Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med.* 2021;385(16):1451-1461.

DELIVER Trial



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, B. Claggett, R.A. de Boer, D. DeMets, A.F. Hernandez, S.E. Inzucchi, M.N. Kosiborod, C.S.P. Lam, F. Martinez, S.J. Shah, A.S. Desai, P.S. Jhund, J. Belohlavek, C.-E. Chiang, C.J.W. Borleffs, J. Comin-Colet, D. Dobreanu, J. Drozdz, J.C. Fang, M.A. Alcocer-Gamba, W. Al Habeeb, Y. Han, J.W. Cabrera Honorio, S.P. Janssens, T. Katova, M. Kitakaze, B. Merkely, E. O'Meara, J.F.K. Saraiva, S.N. Tereshchenko, J. Thierer, M. Vaduganathan, O. Vardeny, S. Verma, V.N. Pham, U. Wilderäng, N. Zaozerska, E. Bachus, D. Lindholm, M. Petersson, and A.M. Langkilde, for the DELIVER Trial Committees and Investigators*

DELIVER: Patient Population

- **Major Inclusion Criteria:**
  - **EF > 40%**
  - **Structural heart disease (LVH, left atrial enlargement)**
  - **NYHA II-IV**
  - **NT-proBNP > 300 pg/mL (> 600 pg/mL if A-Fib)**
  - **eGFR ≥ 25 mL/min/1.73 m2**

Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med.* 2021;385(16):1451-1461.

DELIVER: Patient Population

- **Key Baseline Characteristics**
  - **44% Female sex**
  - **71% White, 20% Asian, 3% Black**
  - **75% NYHA II, 25% NYHA III**
  - **Median NT-proBNP 1400 pg/mL**
  - **45% with DMT2**

Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med.* 2021;385(16):1451-1461.

Deliver: Outcomes

- **Primary Outcome: CV death or Worsening HF**
  - **Dapagliflozin arm: 16.4%**
  - **Placebo arm: 19.5%**
  - **HR 0.82 (95% CI 0.73 – 0.92), P < 0.001**
  - **Effect largely driven by reduction in worsening HF**
  - **Consistent across DMT2 status**
  - **Results similar above and below LVEF of 60%**

Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med.* 2021;385(16):1451-1461.

Other Benefits of SGLT2i

- **Reduced risk of serious ventricular arrhythmia**
- **Reduced risk of atrial fibrillation**
- **Reduced risk of hyperkalemia with concurrent GDMT use**
- **Improved diuresis effect for patients hospitalized with acute heart failure**

Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med.* 2021;385(16):1451-1461.

Other Novel HF Therapies: Vericiguat

- **An oral soluble guanylyl cyclase stimulator**
- **The VICTORIA trial studied vericiguat in HFrEF**
  - **High risk cohort: Recent HFH or IV diuretic**
  - **Outcomes:**
    - **Positive for primary outcome: composite CV death and HFH, driven by HFH**
    - **10% ARR in primary outcome was considered underwhelming in a high-risk cohort**
    - **Subgroup analysis suggested less benefit with highest quartile of NT-proBNP (>5300 pg/mL)**

Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2020;382(20):1883-1893.

Other Novel HF Therapies: Omecamtiv mecarbil

- **An oral selective myosin activator**
- **The GALACTIC-HF trial studied omecamtiv mecarbil (OM) in HFrEF (LVEF ≤35%)**
  - **Outcomes:**
    - **Positive for primary outcome: composite CV death and HFH, driven by HFH (2% ARR)**
    - **Subgroups suggest possible heterogeneity with improved outcomes if LVEF < 28% and SBP < 100 mmHg**
- **In COSMIC-HF, OM improved KCCQ**

Teerlink JR, Diaz R, Felker GM, et al. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. *N Engl J Med.* 2021;384(2):105-116.; Felker GM, Solomon SD, McMurray JJV, et al. Effects of omecamtiv mecarbil on symptoms and health-related quality of life in patients with chronic heart failure: results from the cosmic-hf study. *Circ: Heart Failure.* 2020;13(12):e007814.