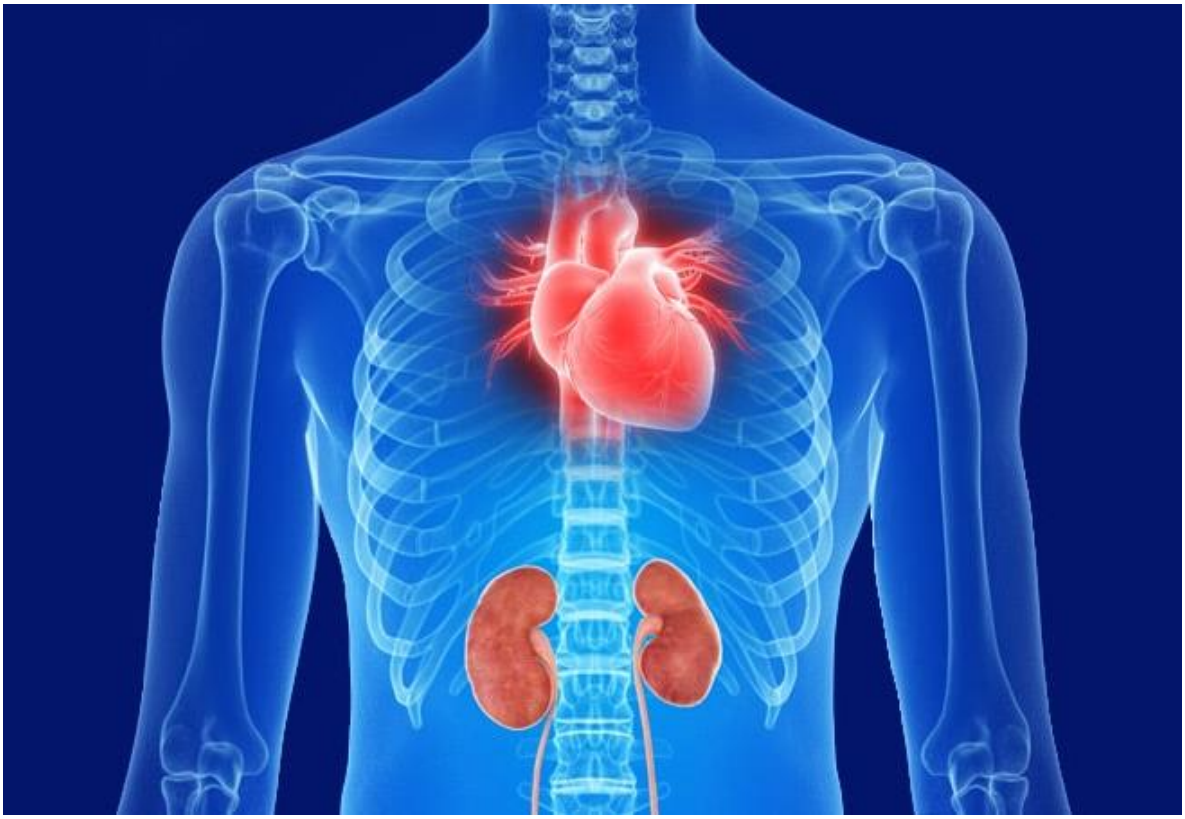
SGLT-2 Inhibitors in Chronic Kidney Disease and Heart Failure: Going with the "-Flozin"



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Learning Objectives

- Pharmacists:
  - Describe the shared pathophysiology of chronic kidney disease (CKD) and heart failure (HF).
  - Discuss the cardiovascular and renal benefits of SGLT-2 inhibition in CKD and HF.
  - Summarize the effects of SGLT-2 inhibitors on mortality, heart failure hospitalizations, and renal outcomes in patients with CKD and HF.
- Pharmacy Technicians:
  - Recall the shared pathophysiology of chronic kidney disease (CKD) and heart failure (HF).
  - List the cardiovascular and renal benefits of SGLT-2 inhibition in CKD and HF.
  - Review the effects of SGLT-2 inhibitors on mortality, heart failure hospitalizations, and renal outcomes in patients with CKD and HF.

Background

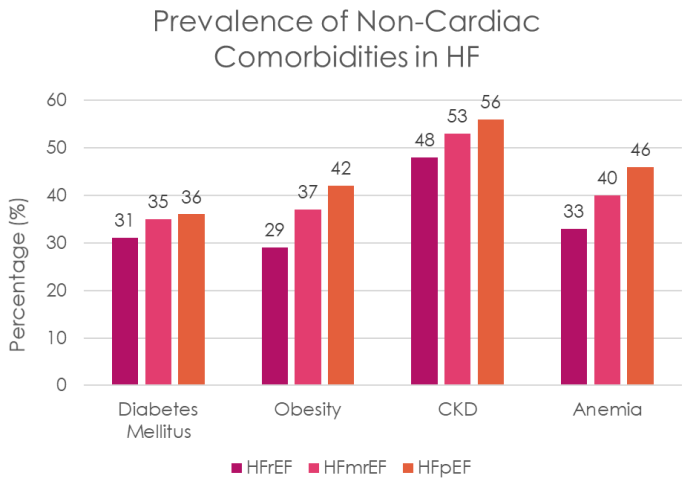
- Definition[1,2]
  - Heart Failure (HF)
    - Defined by abnormal structural and/or functional cardiac function which leads to decreased cardiac output with or without increased intracardiac pressure at rest or in periods of stress (2016 ESC HF Guidelines)
    - Classified based on ejection fraction: reduced ejection fraction <40% (HFrEF), preserved ejection fraction (HFpEF), and midrange ejection fraction 40-49% (HFmrEF)
  - Chronic Kidney Disease (CKD)
    - Defined by estimated glomerular filtration rate (eGFR < 60mL/min/1.73 m^2) or at least 1 marker of kidney dysfunction for > 3 months
      - Markers include:
        - Albuminuria
        - Urine sediment abnormalities
        - Histological abnormalities
        - Structural abnormalities

Table 1. CKD Stages per Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines[2]

Stage	Description	eGFR (mL/min/1.73m^2)
1	Normal or high	≥90
2	Mildly decreased	60-89
3a	Mildly to moderately decreased	45-59
3b	Moderately to severely decreased	30-44
4	Severely decreased	15-29
5	Kidney Failure	<15 (or dialysis)

- Epidemiology[1-4]
  - In patients with HF:
    - Expected to affect greater than 8 million people in the United States
      - 1 million HF hospitalizations per year
    - Estimated 55% of patients with HFrEF and HFpEF have CKD G3a or higher

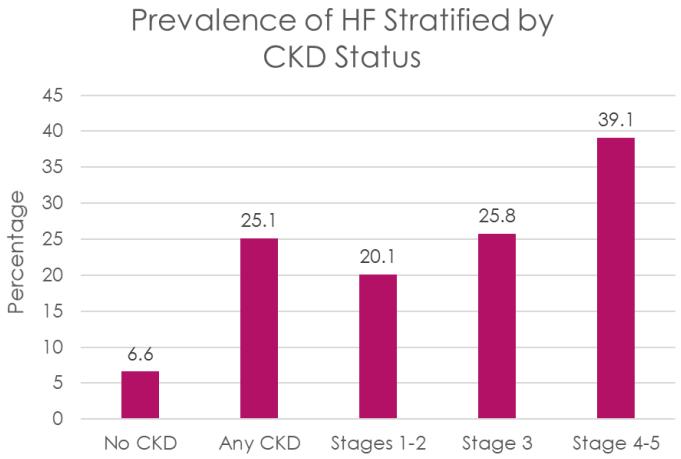
Figure 1. Prevalence of Non-Cardiac Comorbidities in HF[4]



  - In patients with CKD:
    - About 500 million people in the United States report CKD Stage 3 or higher
    - Estimated risk of developing new onset HF in known CKD: 17-21%

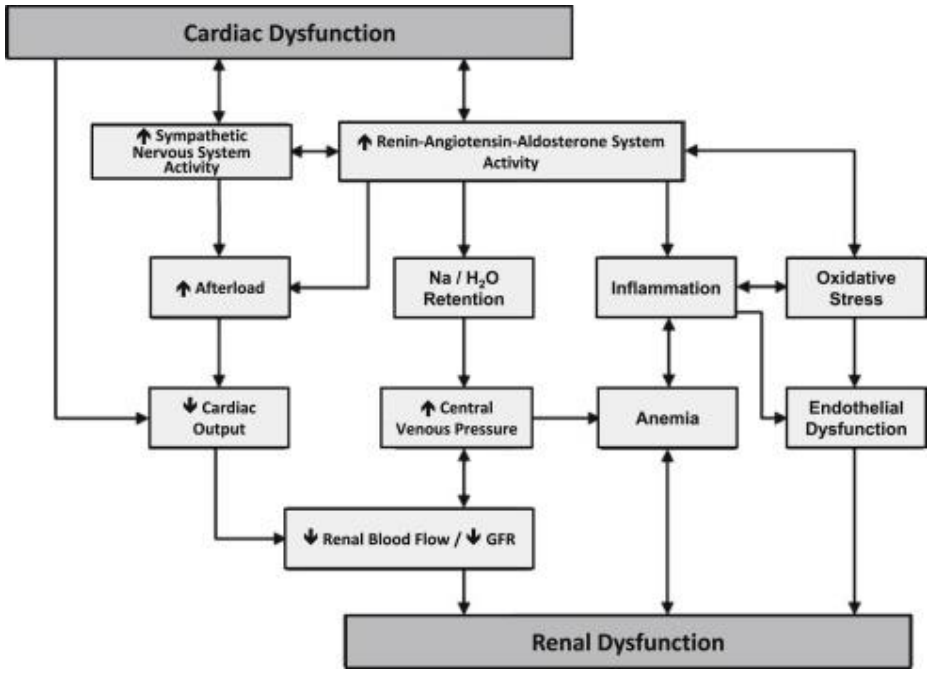
- Probability of developing HF increases as CKD progresses
- HF was ~4x more common in patients with CKD versus without CKD

Figure 2. Prevalence of HF Stratified by CKD Status[5]



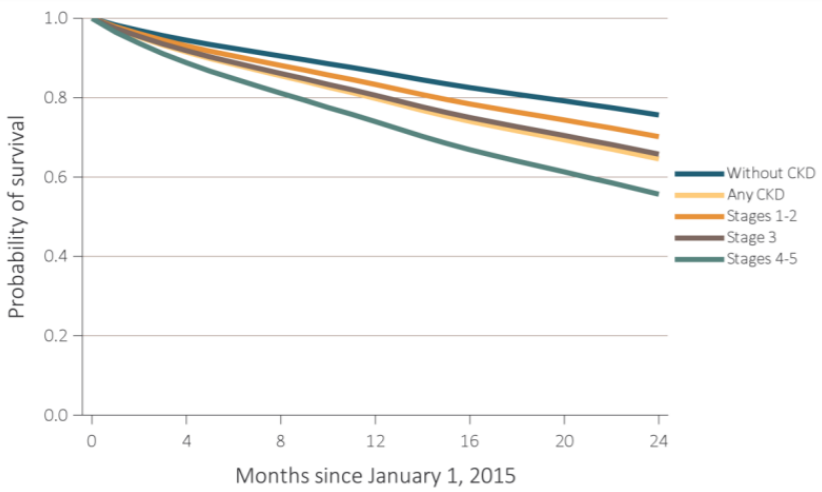
- Shared Pathophysiology of CKD and HF[6]
  - CKD and HF share risk factors and comorbidities that each contribute to their development.
    - Cardiac dysfunction leads to increased activation of sympathetic nervous system and RAAS activity which results in sodium and water retention, inflammation, and increased afterload.
    - Decreased cardiac output and increased central venous pressure (increased preload) leads to decreased renal blood flow and renal dysfunction.
    - Comorbidities such as coronary artery disease, myocardial infarction, infiltrative processes, atrial fibrillation, and mitral/aortic valvular disease contribute to cardiac dysfunction and progressive volume overload. (House)
    - Additionally, T2DM, obesity, and anemia can contribute to chronic pressure overload leading to progressive volume overload. (House)

Figure 3. Pathophysiology of CKD and HF[6]



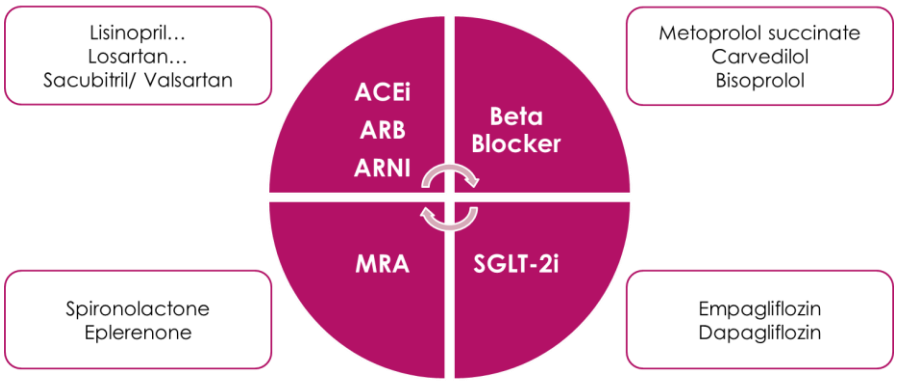
- Risk of Concomitant CKD and HF[7-10]
  - Increased risk of all cause mortality, CV mortality, and HF hospitalization in patients with CKD and HF including HFpEF, HFrEF, and HFmrEF.[6,7]
  - In patients with end stage renal disease, one study found that the likelihood of death increases by 3-, 4-, and 6- fold with each successive HF hospitalization.[8]
  - Increased risk of mortality with each successive stage of CKD.[9]

Figure 4. Probability of Survival of HF Patients by CKD Status[11]



- Guideline Directed Medical Therapy (GDMT)[12]
  - Treatment of HFrEF traditionally included RAAS inhibitors (ACEi, ARB, ARNIs), beta blockers and MRAs that are proven to reduce morbidity and mortality.
  - SGLT-2 inhibitors are the newest members of GDMT that have been shown to significantly reduce mortality, HF hospitalizations, and improve quality of life when added to the current standard drugs in patients with HFrEF.
  - Notably, ACEi/ARBs are also first line medications in CKD because of the prevent adverse renal outcomes (decline in eGFR, progression to dialysis), decrease risk of cardiovascular death and decrease all cause mortality.

Figure 5. Guideline Directed Medical Therapy (GDMT)[12]



- Limitations of GDMT in HFrEF and CKD[13,14]
  - Increased risk of ADRs including hyperkalemia, acute kidney injury, hypotension, and bradycardia
  - Limited evidence in advance CKD (stage 4 and 5)
  - Leads to:

- ↓ACEi or ARB use approaching dialysis
- ↓prescription rates of GDMT compared to non-CKD patients

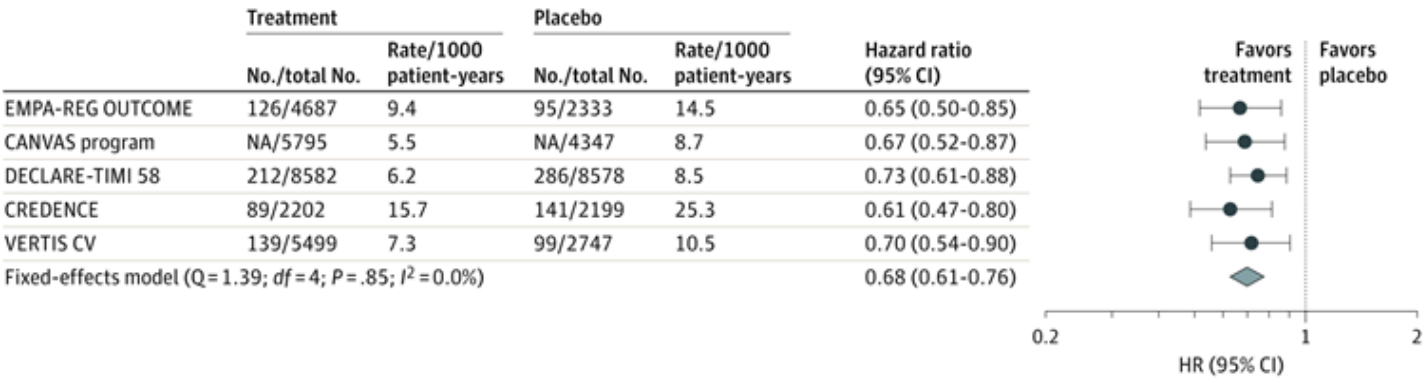
Table 2. Heart Failure Studies with Renal Cutoffs[13]

Trial, yr	Age and Diabetes	<Creatinine (mean) or >eGFR
Angiotensin-converting enzyme inhibitors		
SAVE 1992	59 yr, 29%	<2.5 mg/dl
Angiotensin receptor blockers		
CHARM 2003	66 yr, 28%	<3 mg/dl
***β*-Blockers**		
CIBIS II 1999	61 yr, 12%	<3.4 mg/dl
MERIT HF 1999	63 yr, 25%	—
Mineralocorticoid receptor antagonists		
RALES 1999	65 yr, NA	<2.5 mg/dl
EPHESUS 2003	64 yr, 32%	<2.5 mg/dl (1.1 mg/dl)
Angiotensin receptor neprilysin inhibitors		
PARADIGM HF 2014	64 yr, 35%	>30 ml/min (1.1 mg/dl)

Role of SGLT-2i in HFrEF and CKD

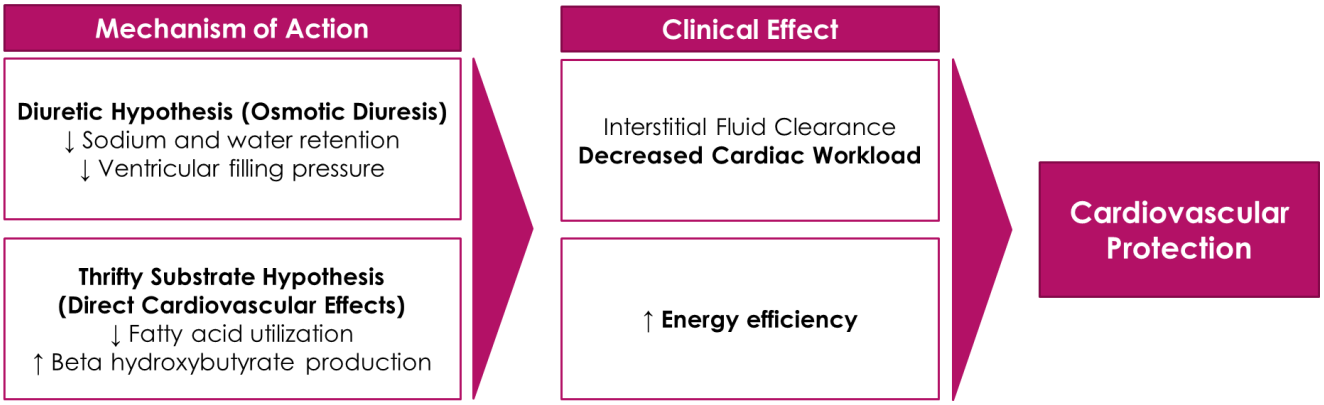
- What are SGLT-2 inhibitors?[15-17]
  - Mechanism of Action: Inhibits sodium glucose cotransporter 2 (SGLT-2) in proximal renal tubules → decreased glucose reabsorption and lowered renal threshold for reabsorption → increased urinary excretion of glucose; decreased plasma glucose concentrations
    - SGLT-2 protein → reabsorbs 90% of filtered glucose
    - SGLT-1 protein → reabsorbs 10% of filtered glucose
- SGLT2i in T2DM
  - SGLT-2i significantly reduce the risk of CV death and HF hospitalizations patients with T2DM including those with or without HF.
  - CREDENCE provided specific results for patients with CKD and T2DM and found that canagliflozin significantly reduced the risk of CKD progression and renal outcomes like ESRD and doubling of creatinine.

Figure 6. Risk of HF Hospitalization with SGLT-2i use in T2DM[17]



- Mechanism of Cardiovascular Benefits[18]
    - Diuretic Hypothesis: Osmotic Diuresis and Natriuresis
        - SGLT-2 inhibitors reduce sodium and water retention resulting in osmotic diuresis. This action decreases ventricular filling pressure which decreases cardiac workload.
            - This may be connected to activation of tubuloglomerular feedback which does not occur with other diuretics such as loop and thiazide diuretics.
            - SGLT-2 inhibitors are associated with higher interstitial fluid clearance from circulation which could relieve congestion without significantly impacting BP, arterial filling or lead to neurohumoral activation.
    - Thrifty Substrate Hypothesis: Direct Cardiovascular Effects
        - Type 2 diabetes results in a shift in metabolism from glucose utilization to oxidation of fatty acids due to increased insulin resistance.
            - Fatty acid oxygenation is less energy efficient and also results in decreased cardiac function (increased oxidative stress and lipotoxicity).
            - SGLT-2 inhibitors increase beta-hydroxybutyrate by stimulating hepatic synthesis and preventing the excretion of ketones. Beta-hydroxybutyrate is able to be used as energy over fatty acids and glucose in the heart and kidney resulting in improved energy efficiency.

Figure 7. Mechanism of Action of SGLT-2 Inhibitors: Cardiovascular[18]



- Mechanism of Renal Benefits[19]
    - Reduction in Intraglomerular Pressure (Restoration of Tubuloglomerular Feedback)
        - SGLT-2 inhibitors decrease sodium absorption in proximal tubule and increase delivery of sodium to distal tubules. This results in reversal of afferent arteriole vasodilation and efferent arteriole vasoconstriction which relieves glomerular hypertension.
    - Neurohormonal Improvement
        - Decreased intrarenal RAAS activity and SNS activity which can contribute to fibrogenesis and arterial stiffness.
    - Decreased Inflammation/ Fibrosis
        - Chronic inflammation may contribute to kidney disease progression. Chronic hypoxia, hyperglycemia and RAAS activation may lead to fibrogenesis. SGLT-2 inhibitors reduce markers of inflammation and fibrogenesis. Anti-fibrotic action appears to be mediated through mTORC1 inhibition.
    - Improved Renal Metabolism
        - SGLT-2 inhibitors decrease the amount of sodium and glucose load on the tubules resulting in improved oxygenation and tubule protection.

Figure 8. Mechanism of Action of SGLT-2 Inhibitors: Renal[19]

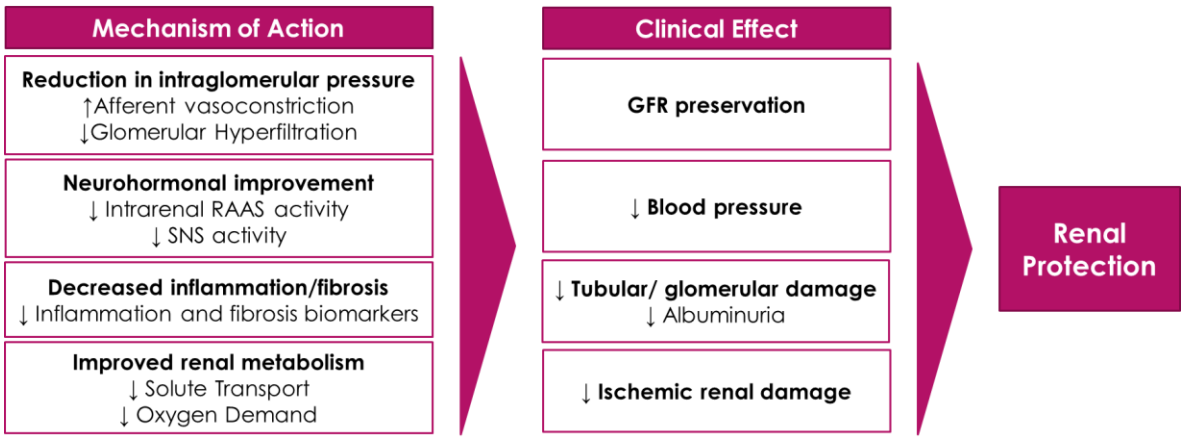
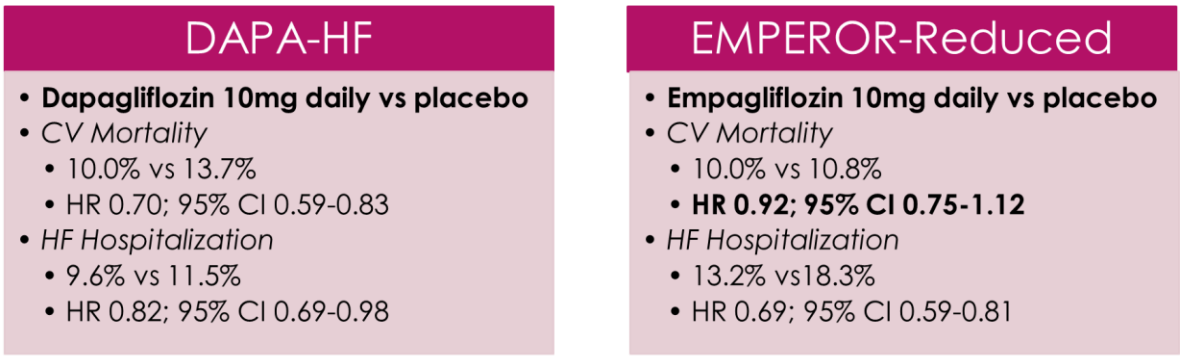


Figure 9. Results of DAPA-HF and EMPEROR-Reduced Trials[20,21]



- 2021 Updates in HFrEF Treatment[12]
  - Sodium-glucose cotransporter 2 (SGLT-2) inhibitors
    - First line guideline directed medical therapy based on results from DAPA-HF and EMPEROR-Reduced trials
    - Agents of Choice
      - Dapagliflozin 10mg once daily
      - Empagliflozin 10mg once daily
    - SGLT-2 inhibitor not recommended if:
      - eGFR < 30ml/min/1.73m^2 for dapagliflozin
      - eGFR < 20ml/min/1.73m^2 for empagliflozin
      - Dialysis
- Concerns of Using SGLT-2i in CKD[16]
  - Acute Kidney Injury
    - Post marketing reports of AKI requiring hospitalization and dialysis
    - Risk Factors
      - Hypovolemia
      - Chronic Renal Insufficiency
      - Congestive Heart Failure
      - Concomitant Medications (diuretics, ACEi, ARBs, NSAIDs)

Clinical Controversy

- Are the cardiac and renal benefits of SGLT-2 inhibitors consistent across the spectrum of kidney function in patients with CKD and HF?

Literature Review

<table>
<tr><th colspan="3">Jhund PS, Solomon SD, Docherty KF, et al. Efficacy of Dapagliflozin on Renal Function and Outcomes in Patients With Heart Failure With Reduced Ejection Fraction: Results of DAPA-HF. Circulation. 2021; 143(4): 298–309.[22]</th></tr>
<tr><td>Objective</td><td colspan="2">To determine if dapagliflozin reduces CV mortality and heart failure hospitalizations in patients with heart failure with reduced ejection fraction (HFrEF) regardless of baseline renal function.</td></tr>
<tr><td colspan="3">Methods</td></tr>
<tr><td>Study Design</td><td colspan="2">Multicenter, double-blind, randomized, placebo-controlled trial
• Conducted in 410 centers in 20 countries</td></tr>
<tr><td>Population</td><td>Inclusion Criteria
• Age at least 18 years
• Ejection fraction ≤ 40%
• NYHA Class II, III, or IV
• Plasma NT-proBNP level
≥ 600pg/mL OR
≥ 400pg/mL if hospitalization for HF within previous 12 months OR
≥ 900 pg/mL if patient had atrial fibrillation/ flutter</td><td>Exclusion Criteria
• Unacceptable side effects from SGLT-2 inhibitor
• Type 1 diabetes
• Hypotension/ SBP < 95mmHg
• eGFR ≤ 30mL/min/ 1.73 m2
• “Unstable or rapidly progressing renal disease”
• Current HF decompensation or HF hospitalization within 4 weeks
• MI, unstable angina, stroke, or TIA within 3 months</td></tr>
<tr><td>Intervention</td><td colspan="2">Intervention (n=2,373): Dapagliflozin 10mg once daily
Control (n=2,371): Placebo
• Required to receive standard guideline directed medical therapy including an ACEi/ARB/ARNI and beta blocker unless not tolerated or contraindicated.
• Encouraged to use an MRA.</td></tr>
<tr><td>Outcomes</td><td colspan="2">Primary Outcome:
• Composite (HF Hospitalization and Cardiovascular Death)
Secondary Outcomes:
• Individual components of primary outcome (HF hospitalization, Cardiovascular Death)
• HF Hospitalizations (first and recurrent)
• All-cause death
• Renal composite: ≥ 50% decline in eGFR, ESRD or renal death</td></tr>
<tr><td>Statistical Analysis</td><td colspan="2">Estimated 844 primary outcome events needed to provide a power of 90% to detect a hazard ratio of 0.80 assuming an annual event incidence of 11% in the placebo group
Estimated 4500 patients needed to provide an adequate number of primary outcome events
Alpha level of 0.0499 used
Used intention to treat analysis
Used Kaplan Meier estimate and Cox proportional-hazards models in post hoc analysis</td></tr>
<tr><td colspan="3">Results</td></tr>
<tr><td>Baseline Characteristics</td><td colspan="2">
<table>
<tr><th>Characteristic</th><th>eGFR < 60mL/min/ 1.73m2 (n=1926)</th><th>eGFR ≥ 60mL/min/ 1.73m2 (n=2816)</th><th>P-value</th></tr>
<tr><td>Age, mean, yr</td><td>70.9±9.0</td><td>63.2±11.0</td><td><0.001</td></tr>
<tr><td>Male, n (%)</td><td>1392 (72.3)</td><td>2241 (79.6)</td><td><0.001</td></tr>
<tr><td>Body mass index, median (IQR), kg/m^2</td><td>28.4±5.8</td><td>28.0±6.0</td><td>0.009</td></tr>
<tr><td>eGFR, mL/min/1.73 m^2, mean</td><td>47.0±8.0</td><td>78.7±13.5</td><td>-</td></tr>
<tr><td>Ejection Fraction, %</td><td>31.3±6.6</td><td>30.9±6.9</td><td>0.069</td></tr>
<tr><td>NYHA Class
II
III
IV</td><td>
1267 (65.8)
645 (33.5)
14 (0.7)</td><td>
1934 (68.7)
853 (30.3)
29 (1.0)</td><td>0.043</td></tr>
<tr><td>Medical History, n (%)
T2DM
Atrial Fibrillation</td><td>
982 (51.0)
880 (45.7)</td><td>
1157 (41.1)
938 (33.3)</td><td>
<0.001
<0.001</td></tr>
<tr><td>Ischemic Cause of HF</td><td>1174 (61.0)</td><td>1498 (53.2)</td><td><0.001</td></tr>
</table>
</td></tr>
</table>

Medications				
ACEi/ARB		1542 (80.1)	2408 (85.5)	<0.001
ARNI		221 (11.5)	287 (10.2)	0.16
Beta Blocker		1838 (95.4)	2718 (96.5)	0.058
MRA		1296 (67.3)	2074 (73.7)	< 0.001
Diuretic		1835 (95.3)	2597(92.2)	<0.001

Outcomes

Cardiovascular Outcomes	eGFR < 60mL/min/1.73m2		eGFR ≥ 60mL/min/1.73m2		P value
	Dapagliflozin (n=962)	Placebo (n=964)	Dapagliflozin (n=1410)	Placebo (n=1406)	
Cardiovascular death or HF hospitalization	191 (19.9)	254 (26.4)	195 (13.9)	248 (17.6)	0.54
	HR 0.72 (0.59-0.86)		HR 0.76 (0.63-0.92)		
Cardiovascular Death	119 (12.4)	134 (13.9)	108 (7.7)	139 (9.9)	0.44
	HR 0.88 (0.69-1.13)		HR 0.76 (0.59-0.98)		
HF Hospitalization	120 (12.5)	173 (18.0)	117 (8.3)	153 (10.9)	0.39
	HR 0.66 (0.52-0.83)		HR 0.75 (0.59-0.95)		
Renal Composite	18 (1.9)	19 (2.0)	10 (0.7)	20 (1.4)	0.19
	HR 0.95 (0.50-1.82)		HR 0.49 (0.23-1.06)		

Renal Outcomes	Dapagliflozin (n=2372)	Placebo (n=2370)	HR (95% CI)	P value
Composite	28 (1.2)	39 (1.6)	0.71 (0.44-1.16)	0.17
• ≥50% decline in eGFR	14 (0.6)	23 (1.0)	0.60 (0.31-1.16)	0.13
• ESRD	16 (0.7)	16 (0.7)	1.00 (0.50-1.99)	0.99
• Renal Death	0	1 (0.04)	-	-

- Rate of eGFR Decline: Dapagliflozin was associated with a slope of -1.09 compared to -2.85 with placebo after the first 2 weeks of treatment (p<0.001).

Safety Outcomes (eGFR <60ml/min/1.73m^2 only)	Dapagliflozin (n=960)	Placebo (n=962)	P value
Serious adverse event	417 (43.4)	482 (50.1)	0.003
Renal related adverse event	97 (10.1)	115 (12.0)	0.22
Volume depletion	97 (10.1)	86 (8.9)	0.39
Major hypoglycemia	3 (0.3)	0 (0.0)	0.12

Author's Conclusion

"In DAPA-HF, the benefits of dapagliflozin on the primary and secondary cardiovascular outcomes were consistent in patients with and without low eGFR, with greater absolute risk reductions in patients with lower eGFR."

Critique

Strengths
- Based off large patient population from randomized controlled trial
- Encouraged to use GDMT to compare against standard of care (including ACEi, ARB, ARNI, BB, and MRA)
- Included patients without diabetes

Limitations
- Post Hoc analysis
- Excluded patients with stage 4 CKD (eGFR < 30mL/min/1.73m^2)
- Low event rate in renal outcomes may have led to Type II error
- Unable to assess effect of dapagliflozin on urinary albumin: creatinine ratio

Take Home Points

Dapagliflozin is safe and efficacious in patients with HF regardless of baseline renal function and should be used to decrease the risk of HF hospitalizations and cardiovascular death. Dapagliflozin slowed the progression of renal dysfunction, however, renal clinical outcomes were not statistically different.

Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med.* 2020;383(15):1436-1446.[23]

Objective	Determine the safety and efficacy of dapagliflozin in CKD patients with or without diabetes.	
Methods		
Study Design	Multicenter, double-blind, randomized, placebo-controlled trial • Conducted in 386 sites in 21 countries from February 2017 to June 2020	
Population	**Inclusion Criteria** • eGFR ≥25 and ≤75 mL/min/1.73 m^2 • Urine ACR ≥200 and ≤5,000 mg/g • Receiving maximum daily dose of ACE inhibitor or ARB for ≥ 4 weeks (patients who were unable to take ACE inhibitors or ARBs were allowed to participate)	**Exclusion Criteria** • Type 1 diabetes • Certain kidney diseases (Polycystic kidney disease, Lupus nephritis, ANCA vasculitis) • Received immunotherapy for primary or secondary kidney disease within 6 months • NYHA Class IV HF • History of organ transplantation • MI, unstable angina, stroke, or TIA within 12 weeks • PCI, CABG, or valvular repair within 12 weeks • Active malignancy requiring treatment • AST/ALT > 3x ULN or total bilirubin > 2x ULN
Intervention	**Intervention (n=2152):** Dapagliflozin 10mg PO once daily **Control (n=2152):** Placebo • Randomized 1:1 to receive intervention or placebo. Stratified according to diagnosis of T2DM or UACR (≤1000 or > 1000) • Study drug was only discontinued if patient developed diabetic ketoacidosis, became pregnant or developed an ADR that was considered to be a contraindication by the investigators. • Per protocol, the study did **not** require discontinuation at a particular eGFR cut off and participants were allowed to continue the medication unless the above criteria were met.	
Outcomes	**Primary Outcome:** • Composite of sustained decline in eGFR ≥ 50%, end-stage kidney disease (maintenance dialysis for ≥28 days, kidney transplantation, or eGFR< 15mL/min), or death from renal or cardiovascular causes **Secondary Outcomes:** • Composite kidney outcome of sustained decline in eGFR ≥ 50%, end-stage kidney disease (as defined above), death from renal causes • Composite heart failure hospitalization or cardiovascular death • Death from any cause	
Statistical Analysis	Estimated 681 primary outcome events needed to detect a 22% lower risk with dapagliflozin with 90% power using alpha level of 0.05 (assumed annual event rate of 7.5%) Used Cox proportional hazards regression model to stratify according to type 2 diabetes and urinary albumin-to-creatinine ratio Used intention to treat analysis	
Results		
Baseline Characteristics		

Characteristic	Dapagliflozin (n=2152)	Placebo (n=2152)
Age, median (IQR), yr	61.8 ± 12.1	61.9 ± 12.1
Female, n (%)	709 (32.9)	716 (33.3)
Body mass index, median (IQR), kg/m^2	29.4 ± 6.0	29.6 ± 6.3
eGFR, mL/min/1.73 m^2, mean, n (%)	43.2 ± 12.3	43.0 ± 12.4
≥ 60	234 (10.9)	220 (10.2)
45-60	646 (30.0)	682 (31.7)
30-45	979 (45.5)	919 (42.7)
<30	293 (13.6)	331 (15.4)

Urine Albumin-to-creatinine ratio, median, mg/g	965 (472-1903)	934 (482-1868)
Medical History, n (%)		
T2DM	1455 (67.6)	1451 (67.4)
HF	235 (10.9)	233 (10.8)
Cardiovascular Disease	813 (37.8)	797 (37.0)
Medications		
ACEi	673 (31.3)	681 (31.6)
ARB	1444 (67.1)	1426 (66.3)
Diuretic	928 (43.1)	954 (44.3)
Statin	1395 (64.8)	1399 (65.0)

Outcomes

Efficacy Outcomes	Dapagliflozin (n=2152)	Placebo (n=2152)	Treatment Effect (95% CI)	P value	NNT
Primary Endpoint					
Primary Composite Endpoint	197 (9.2)	312 (14.5)	0.61 (0.51-0.72)	<0.001	19
Decline in estimated GFR of ≥50%	112 (5.2)	201 (9.3)	0.53 (0.42-0.67)	-	-
End-stage kidney disease	109 (5.1)	161 (7.5)	0.64 (0.50-0.82)	-	-
Death from renal causes	2 (<0.1)	6 (0.3)	-	-	-
Death from cardiovascular causes	65 (3.0)	80 (3.7)	0.81 (0.58-1.12)	-	-
Secondary Endpoint					
Composite of decline in estimated GFR of ≥50%, end-stage kidney disease, or death from renal causes	142 (6.6)	243 (11.3)	0.56 (0.45-0.68)	<0.001	22
Composite of death from cardiovascular causes or hospitalization for heart failure	100 (4.6)	138 (6.4)	0.71 (0.55-0.92)	0.009	56

Safety Outcomes	Dapagliflozin (n=2149)	Placebo (n=2149)	P value
Serious adverse event	633 (29.5)	729 (33.9)	0.002
Renal related adverse event	155 (7.2)	188 (8.7)	0.07
Volume depletion	127 (5.9)	90 (4.2)	0.01
Major hypoglycemia	14 (0.7)	28 (1.3)	0.04

- Median Follow Up: 2.4 years (IQR 2.0 to 2.7)
- Subgroup Analysis: dapagliflozin favored over placebo in patients with eGFR <45ml/min/1.73m^2 (HR0.63, 95% CI 0.51-0.78).

Author's Conclusion

"We found that participants with chronic kidney disease, with or without type 2 diabetes, who were randomly assigned to receive dapagliflozin had a lower risk of the primary composite outcome of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes than participants who were assigned to receive placebo."

Critique

Strengths

- Robust trial design increases internal validity
- Large patient population increases statistical power
- No specific eGFR cut off for discontinuation
- Consistent benefits for diabetic and nondiabetic patients

Limitations

- Trial stopped early due to recommendation from independent data monitoring committee
- Did not specify HF classification
- Unclear benefits if patient is not already receiving an ACEi/ARB or if no microalbuminuria

Take Home Points

Dapagliflozin significantly reduces the risk of cardiovascular and renal outcomes compared to placebo in patients with CKD with or without diabetes who are receiving an ACEi or ARB.

Post Hoc Analysis in HF[24]

- Background
  - Compared patients with HF (n=468) versus patients without HF (n=3,836)
- Results
  - Patients with HF were more likely to be older and have comorbidities (obesity, cardiovascular disease, atrial fibrillation, and diabetes). Additionally, patients with HF were more likely to use diuretics, beta-blockers, hydralazine, digoxin, and MRAs. Notably, no information on left ventricular ejection fraction was available.
  - Efficacy Endpoints: Although patients with HF were more likely to experience the primary outcome compared to patients without HF, the beneficial renal effects of dapagliflozin were similar between groups. There results were consistent in the cardiovascular outcomes as well.
  - Safety Endpoints: There was an initial "dip" in eGFR with dapagliflozin but the decline of eGFR was attenuated over time indicating long term renal protection. Adverse events were similar in both groups. Acute kidney injury was similar in both groups (3.4% vs 4.3%, HR 0.72, 95% CI 0.28-1.82).
- Conclusion: Dapagliflozin is equally effective in the prevention of renal and cardiovascular disease in patients with HF and CKD compared to patients without HF. No safety concerns noted.

Figure 10. Primary and Secondary Endpoints for Post Hoc Analysis in HF Patients

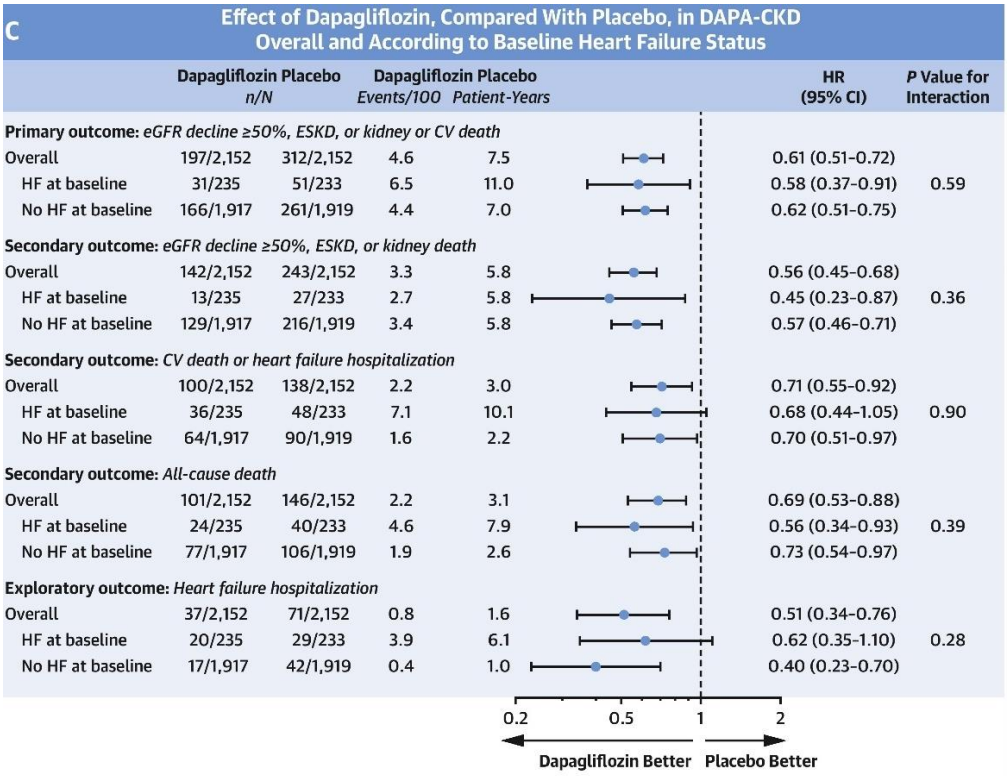


Table 3. Safety Endpoints for Post Hoc Analysis in HF

Safety Outcomes (HF only)	Dapagliflozin (n=235)	Placebo (n=233)	P value
Any serious AE	130 (55.3)	122 (52.4)	0.055
Renal AE	22 (9.4)	31 (13.3)	0.495
Volume depletion	21 (8.9)	12 (5.2)	0.503
Major hypoglycemia	2 (0.9)	6 (2.6)	0.556

Post Hoc Analysis in CKD Stage 4[25]

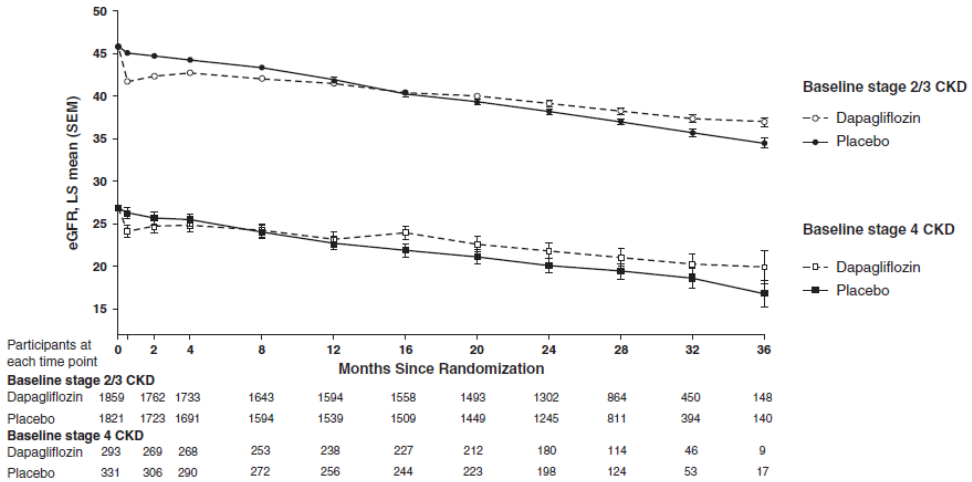
- Background
  - Compared patients with stage 4 CKD (n=624) versus stage 2/3 CKD (n=3,680)
- Results
  - At baseline, patients with stage 4 CKD were more likely to have high UACR and less likely to have type 2 diabetes compared to patients who had stage 2/3 CKD. Additionally, patients were less likely to receive RAAS inhibitors and more likely to receive diuretics.
  - Efficacy Endpoints: Found patients with stage 4 CKD experience similar reductions in the primary outcome compared with stage 2/3 CKD.
  - Safety Endpoints: Found patients with stage 4 CKD were more likely to experience an adverse event compared to patients with stage 2/3 CKD. Kidney related adverse reactions were also more common in patients with stage 4 CKD, however, this result was not statistically significant (15% vs 13%, HR 1.12, 95% CI 0.71-1.77)
- Conclusion:
  - Dapagliflozin has similar cardiovascular and renal benefits in patients with stage 4 CKD compared to patients with stage 2/3 CKD. Dapagliflozin can be safely used in patients with stage 4 CKD.

Table 4. Efficacy and Safety Endpoints for Post Hoc Analysis in CKD Stage 4

Outcome	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	P-Value
Primary Endpoint: eGFR≥50%, ESKD, or Kidney or CV death • Overall • **Stage 4 CKD** • Stage 2/3 CKD	197/2152 **59/293** 138/1859	312/2152 **87/331** 225/1821	0.61 (0.51, 0.72) **0.73 (0.53, 1.02)** 0.58 (0.47, 0.71)	0.22
CV death or Hospitalization for HF • Overall • **Stage 4 CKD** • Stage 2/3 CKD	100/2152 **18/293** 82/1859	138/2152 **24/331** 114/1821	0.71 (0.55, 0.92) **0.83 (0.45, 1.53)** 0.69 (0.52, 0.92)	0.63

Safety Outcomes (CKD Stage 4 only)	Dapagliflozin (n=293)	Placebo (n=331)	P value
Any serious AE	101 (34.5)	138 (41.7)	0.49
Renal AE	43 (14.7)	44 (13.3)	0.13
Volume depletion	14 (4.8)	15 (4.5)	0.39
Major hypoglycemia	2 (0.7)	8 (2.4)	0.37

Figure 11. Mean Change in eGFR Compared between Stage 2/3 CKD and Stage 4 CKD



Packer M, Anker SD, Butler J; EMPEROR-Reduced Trial Investigators. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med.* 2020;383(15):1413-1424.[26]		
Objective	To determine if empagliflozin reduces CV mortality and heart failure hospitalizations in patients with heart failure with reduced ejection fraction (HFrEF) regardless of baseline renal function.	
Methods		
Study Design	Multicenter, double-blind, randomized, placebo-controlled trial • Conducted in 520 centers in 20 countries	
Population	**Inclusion Criteria** • Age ≥ 18 years old • Chronic HFrEF (LVEF < 40%, NYHA Class II-IV) • If EF ≤40% and hospitalization for HF within 12 months - required NT-proBNP ≥600pg/mL • If EF 36% to 40% - required NT-proBNP ≥2500pg/mL • If EF 31% to 35% - required NT-proBNP ≥1000pg/mL • If EF ≤30% - required NT-proBNP ≥600pg/mL • **NOTE:** Doubled NT-proBNP requirement in patients with atrial fibrillation (AF) • Body mass index <45kg/m^2	**Exclusion Criteria (Selected)** • MI, CABG, stroke or TIA within 90 days • Cardiomyopathy based on infiltrative disease (amyloidosis) or induced by chemotherapy within 12 months • Acute decompensated HF within 1 week of screening • AF with resting HR >110bpm • SBP > 180mmHg or SBP <100mmHg (with or without symptoms of hypotension) • AST/ALT/ALP >3x ULN • eGFR<20mL/min/1.73m^2 or requiring dialysis • History of ketoacidosis
Intervention	**Intervention (n=1863):** Empagliflozin 10mg PO once daily **Control (n=1867):** Placebo • Required to receive standard guideline directed medical therapy including an ACEi/ARB/ARNI and beta blocker unless not tolerated or contraindicated. • Presence or absence of CKD classified as eGFR< 60 or albumin-to-creatinine ratio > 300mg/g	
Outcomes	**Primary Outcome:** • Composite (HF Hospitalization and Cardiovascular Death) **Secondary Outcomes:** • HF Hospitalizations (first and recurrent) • Composite kidney endpoint: chronic dialysis or kidney transplant, or sustained reduction of ≥40% in eGFR or sustained eGFR <15 (for patients with baseline ≥ 30), or sustained eGFR <10 (for patients with baseline eGFR < 30). • All-cause hospitalization • Cardiovascular death • All-cause death	

Statistical Analysis	Determined 841 primary outcome events needed to provide 90% to detect a 20% reduction in the primary outcome Calculated 2850 patients needed to generate at least 841 primary outcome events but was increased to 3600 patients to ensure power was met. Used intention to treat analysis Used Cox proportional-hazards models in post hoc analysis
Results	
Baseline Characteristics	

Characteristic	No CKD		CKD	
	Empagliflozin (n=879)	**Placebo (n=867)**	**Empagliflozin (n=981)**	**Placebo (n=997)**
Age, mean, yr	63.7±11.2	62.3±11.3	70.4±9.5	70.1±9.8
Male, n (%)	204 (23.2)	183 (21.1)	232 (23.6)	273 (27.4)
Body mass index, median (IQR), kg/m^2	27.86±5.47	27.64±5.49	28.08±5.44	27.91±5.19
eGFR, mL/min/1.73 m^2, mean	79.0±13.8	79.1±14.0	46.5±15.0	47.4±15.1
eGFR < 60 mL/min/1.73 m^2	0	0	893 (91.0)	906 (90.9)
UACR, mg/g, median (IQR)	15 (6,44)	16 (6, 43)	36 (11, 194)	36 (11, 160)
Ejection Fraction, %	27.4±6.0	26.8±6.0	28.0±5.9	27.5±6.2
NYHA Class				
II	683 (77.7)	671 (77.4)	713 (72.7)	728 (73.0)
III	193 (22.0)	192 (22.1)	262 (26.7)	262 (26.3)
IV	3 (0.3)	4 (0.5)	6 (0.6)	7 (0.7)
Medical History, n (%)				
T2DM	402 (45.7)	384 (44.3)	523 (53.3)	542 (54.4)
Atrial Fibrillation	244 (29.8)	261 (30.1)	420 (42.8)	444 (44.5)
Ischemic Cause of HF	433 (49.3)	416 (48.0)	548 (55.9)	528 (53.0)
Medications				
ACEi	447 (50.9)	440 (50.7)	420 (42.8)	395 (39.6)
ARB	207 (23.5)	194 (22.4)	244 (24.9)	261 (26.2)
ARNI	166 (18.9)	161 (18.6)	172 (17.5)	225 (22.6)
Diuretics	722 (82.1)	732 (84.4)	887 (90.4)	903 (90.6)
MRA	648 (73.7)	665 (76.7)	656 (66.9)	687 (68.9)
Beta Blocker	834 (94.9)	820 (94.6)	929 (94.7)	946 (94.9)

Outcomes

Outcome	CKD		No CKD		P value
	Empagliflozin (n=981)	Placebo (n=997)	Empagliflozin (n=879)	Placebo (n=867)	
Cardiovascular death or HF hospitalization	219 (22.3)	273 (27.4)	142 (16.2)	187 (21.6)	0.63
	HR 0.78 (0.65, 0.93)		HR 0.72 (0.58, 0.90)		
Cardiovascular Death	106 (10.8)	121 (12.1)	81 (9.2)	79 (9.1)	0.53
	HR 0.88 (0.68, 1.14)		HR 1.00 (0.74, 1.37)		
First and Recurrent HF Hospitalization	245	349	143	203	0.78
	HR 0.73 (0.57, 0.94)		HR 0.69 (0.51, 0.93)		
Renal Composite	20 (2.0)	38 (3.8)	10 (1.1)	20 (2.3)	0.78
	HR 0.53 (0.31, 0.91)		HR 0.46 (0.22, 0.99)		

- **Analysis Based on eGFR Subgroups:** The primary outcome was not significantly different between eGFR subgroups (p=0.12). No significant difference based on eGFR group for the composite renal outcome. No significant difference found in change of slope between empagliflozin and placebo (p=0.68).

Safety Outcomes (CKD only)	Empagliflozin (n=981)	Placebo (n=995)
Serious adverse event	462 (47.1)	513 (51.6)
Acute renal failure	123 (12.5)	130 (13.1)
Volume depletion	116 (11.8)	110 (11.1)
Confirmed hypoglycemia	16 (1.6)	19 (1.9)

Author's Conclusion

"The current study demonstrates the favorable effects of empagliflozin on the primary efficacy outcome of time-to-first–cardiovascular death or HF hospitalization and the key secondary end points of total HF hospitalizations and eGFR slope, as well as a reduction in serious kidney outcomes in patients with and without CKD and across the spectrum of kidney function, irrespective of degree of kidney injury measured by eGFR or albuminuria."

Critique

Strengths

- Based off large patient population from randomized controlled trial (larger, more severe CKD population than DAPA-HF)
- Measured albumin-to-creatinine ratio

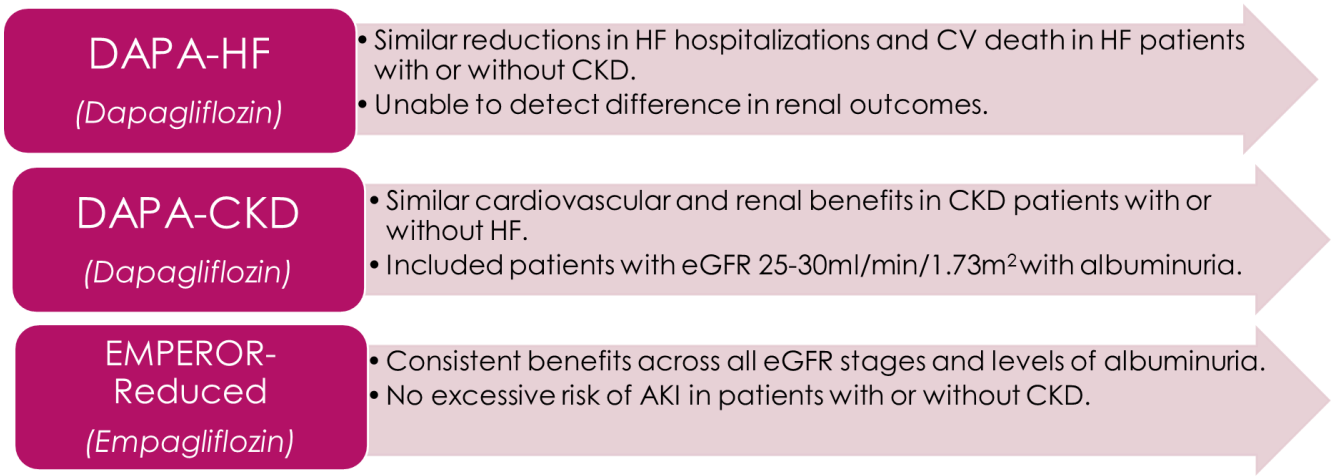
Limitations

- Post hoc analysis
- Low event rate in renal outcomes
- Not powered to assess outcomes across all categories of eGFR and albuminuria

Take Home Points

Empagliflozin significantly reduced HF hospitalizations and CVD regardless of eGFR or presence of albuminuria. Renal outcomes were also significantly improved with empagliflozin versus placebo including clinical outcome along with slope of eGFR

Figure 12. Summary of Current Evidence[22-26]



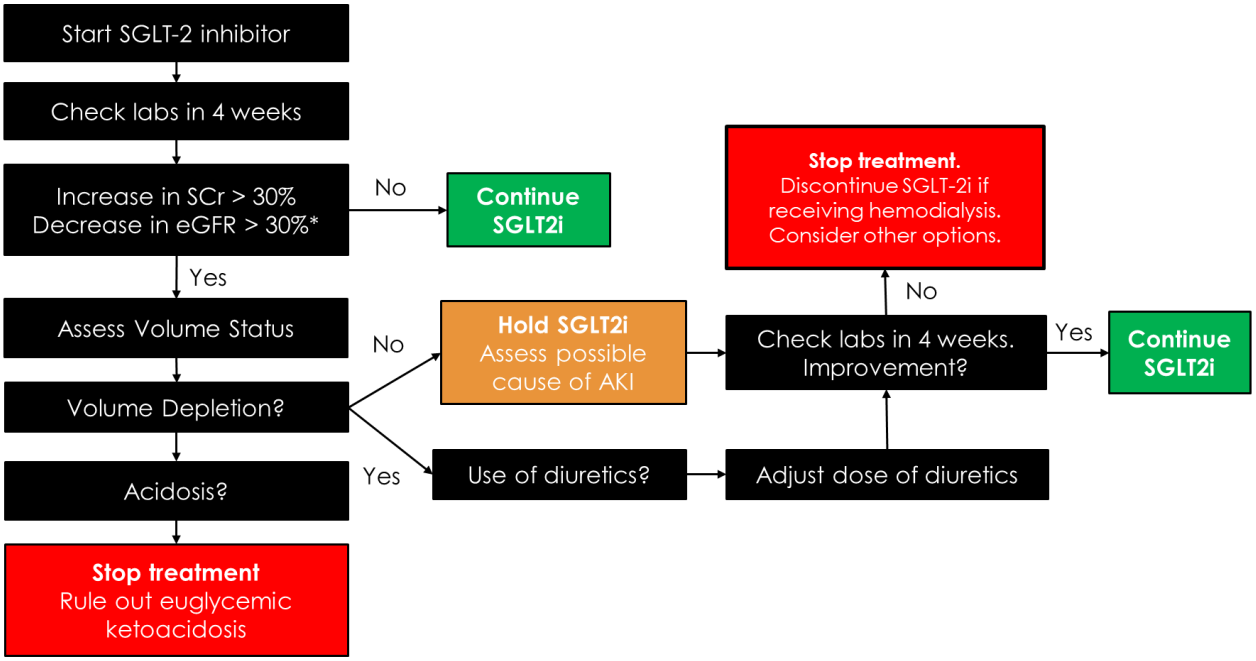
Conclusion

- Based on consistent benefits and lack of significant adverse events across the spectrum of eGFR, initiation of dapagliflozin and empagliflozin are likely safe and effective below the recommended eGFR cut offs.
    - Expected initial drop in eGFR is most likely due to changing intrarenal hemodynamics, not kidney injury.
- Monitoring[16]
    - Before Initiating a SGLT2i
        - Consider temporarily decreasing diuretic dose.
        - Consider decreasing the dose of antihypertensive medications.
    - After Initiating a SGLT2i
        - Assess renal function periodically throughout treatment.
        - Consider withholding treatment if
            - Reduced oral intake (acute illness, fasting)
            - Fluid losses (GI illness or excessive heat exposure)

Table 5. Final Recommendations by eGFR

eGFR	45-59	30-44	25-29	20-24	15-19	<15 or Dialysis
Dapagliflozin						
Cardiovascular Benefits	DAPA-HF	DAPA-HF	DAPA-CKD	**OK**	**Unknown**	**Unknown**
Renal Benefits	DAPA-CKD	DAPA-CKD	DAPA-CKD	**OK**	**Unknown**	**Unknown**
Empagliflozin						
Cardiovascular Benefits	Emperor Reduced	Emperor Reduced	Emperor Reduced	Emperor Reduced	**OK**	**Unknown**
Renal Benefits	Emperor Reduced	Emperor Reduced	Emperor Reduced	Emperor Reduced	**OK**	**Unknown**

Figure 13. Assessing Renal Function After Starting a SGLT-2 Inhibitor[27,28]



* Based on increased risk of overall AEs and renal related AEs with canagliflozin in T2DM

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