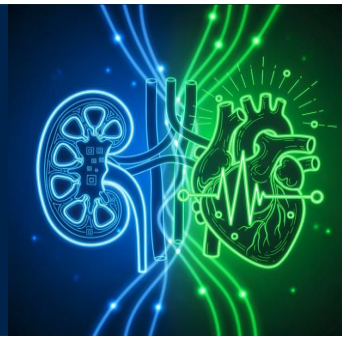
Targeting Aldosterone in HF and CKD



Sponsorship and Support

This presentation is sponsored by

PRIMARY CARE EDUCATION CONSORTIUM

and supported by an educational grant from Boehringer Ingelheim Pharmaceuticals, Inc.

In collaboration with

REGISTER NOW! FREE to JOIN!

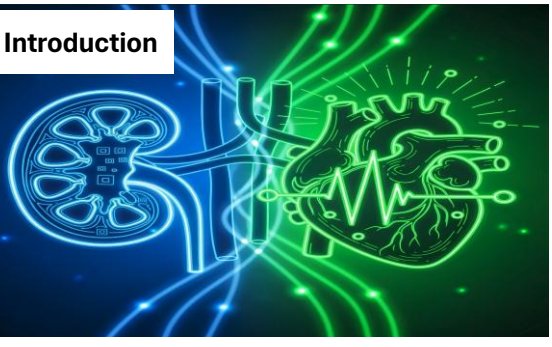
PCMG
Primary Care Metabolic Group

Join at **https://www.pcmg-us.org** for free CME, discounts on conferences and resources for clinicians interested in metabolic disorders.

Learning Objectives

Participants in this presentation should be able to…
Describe the role of aldosterone in HF and CKD, including its impact on cardiovascular and renal diseases, and clinical trials evaluating agents targeting aldosterone in these diseases.
Implement correct strategies for identification and diagnosis of HF and CKD.
Apply guideline recommendations and current evidence when designing guideline-directed medical therapy regimens for HF and CKD to reduce disease progression and improve patient outcomes.
Integrate multidisciplinary care into diagnosis and treatment of HF and CKD to promote coordinated management across care settings.

I. Introduction



Definitions of HF and CKD

- **CKD defined (KDIGO):**[1] "abnormalities of kidney structure or function, present for a minimum of at least 3 months, with implications for health"
  - Classified based on GFR and urine albumin-to-creatinine ratio (UACR)
- **HF defined (AHA/ACC/HFSA):**[2] "a complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of blood."
  - Classified by symptoms/stage and LVEF

ACC, American College of Cardiology; AHA, American Heart Association; CKD, chronic kidney disease; GFR, glomerular filtration rate; HF, heart failure; HFSA, Heart Failure Society of America; LVEF, left ventricular ejection fraction

1. KDIGO CKD Work Group. *Kidney Int.* 2024;105(4S):S117-S314. 2. Heidenreich et al. *Circulation.* 2022; 145(18):e895-e1032.

Definition and Staging of CKD

Risk of CKD progression, frequency of visits, and referral to nephrologist according to GFR and albuminuria shown.

Numbers in boxes are a guide to how many times per year the patient should be seen.

CKD is classified based on:
- GFR (G)
- Albuminuria (A)

GFR categories (mL/min/1.73 m²) Description and range				Albuminuria categories Description and range A1: Normal to mildly increased <30 mg/g <3 mg/mmol	A2: Moderately increased 30–299 mg/g 3–29 mg/mmol	A3: Severely increased ≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

Low risk (if no other markers of kidney disease, no CKD) · Moderately increased risk · High risk · Very high risk

de Boer IH, et al. *Diabetes Care*. 2022;45:3075-3090. Reprinted with permission of the American Diabetes Association, Inc. Copyright 2022.

CV Risk by KDIGO Stages

Observational study assessing CV and renal risk in 543,606 individuals using an electronic database in Japan

KDIGO	A1	A2	A3	Without urine protein test
(a) MACE1 (primary outcome)				
G2	1.00 (reference)	1.17 (1.12–1.21)	1.59 (1.52–1.67)	1.39 (1.36–1.42)
G3a	1.16 (1.12–1.20)	1.37 (1.29–1.46)	1.78 (1.68–1.89)	1.46 (1.42–1.50)
G3b	1.43 (1.34–1.51)	1.68 (1.53–1.84)	2.02 (1.88–2.17)	1.82 (1.74–1.90)
G4	1.86 (1.65–2.09)	2.25 (1.96–2.59)	2.44 (2.24–2.66)	2.64 (2.46–2.83)
G5	2.08 (1.46–2.96)	2.37 (1.69–3.33)	2.83 (2.54–3.15)	3.18 (2.90–3.47)
(b) MACE2 (*ad hoc* primary outcome)				
G2	1.00 (reference)	1.35 (1.28–1.43)	1.97 (1.85–2.09)	1.50 (1.45–1.55)
G3a	1.17 (1.11–1.23)	1.47 (1.35–1.59)	2.13 (1.97–2.30)	1.59 (1.52–1.66)
G3b	1.61 (1.49–1.73)	1.99 (1.78–2.22)	2.46 (2.25–2.69)	2.18 (2.07–2.31)
G4	2.35 (2.04–2.70)	2.62 (2.21–3.11)	3.12 (2.81–3.46)	3.60 (3.31–3.90)
G5	3.48 (2.31–5.25)	3.63 (2.42–5.44)	3.43 (3.00–3.93)	4.68 (4.20–5.21)

Data are HR (95% CI).

MACE1: composite of myocardial infarction, stroke, heart failure hospitalization, and in-hospital death
MACE2: myocardial infarction hospitalization, stroke hospitalization, heart failure hospitalization, and in-hospital death

KDIGO, Kidney Disease: Improving Global Outcomes; MACE, major adverse cardiovascular events

Reproduced without modification from: Maruyama et al. *Clin Kidney J*. 2024;17(8):sfae228, under Creative Commons Attribution 4.0 International License (CC BY 4.0), https://creativecommons.org/licenses/by/4.0/legalcode

HF Staging and Classification by LVEF[1]

Stage	Description
Stage A	At-risk for HF
Stage B	Pre-HF
Stage C	Symptomatic HF
Stage D	Advanced HF

Type of HF	Criteria
HFrEF (HF with reduced EF)	LVEF ≤40%
HFimpEF (HF with improved EF)	Previous LVEF ≤40% and a follow-up measurement of LVEF >40%
HFmrEF (HF with mildly reduced EF)	LVEF 41%–49% Evidence of spontaneous or provokable increased LV filling pressures
HFpEF (HF with preserved EF)	LVEF ≥50% Evidence of spontaneous or provokable increased LV filling pressures

EF, ejection fraction

1. Heidenreich et al. *Circulation*. 2022; 145(18):e895–e1032.

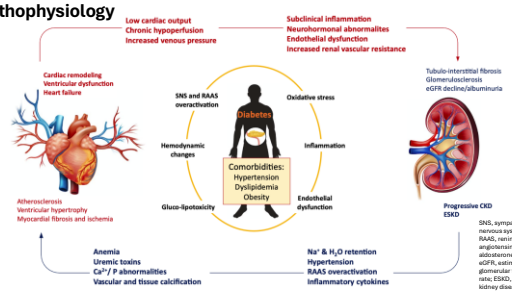
The Interconnected Relationship Between HF and CKD

- HF and CKD are independent, yet related, chronic diseases[1]
- Bidirectional relationship: patients with HF can experience CKD and vice versa[1]
- Shared risk factors and pathophysiology[1]

Shared Risk Factors[1]	Shared Pathophysiologic Mechanisms[1]
• Diabetes • Hypertension • Inflammation • Reduced physical activity • Obesity • Smoking	• Hemodynamic • Inflammatory/fibrotic • Metabolic

1. Lala A, et al. *Diabetes Obes Metab*. 2025;27(7):3568-3582.

Pathophysiology

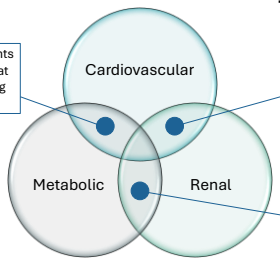


SNS, sympathetic nervous system; RAAS, renin-angiotensin aldosterone system; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease

Reproduced with minor spelling modifications from: Marassi M and Fadini GP. *Cardiovasc Diabetol*. 2023;22:195 under Creative Commons Attribution 4.0 International License (CC BY 4.0), https://creativecommons.org/licenses/by/4.0/legalcode

Coexistence of Cardio-Renal-Metabolic Systems

At least 50% of patients with T2D have or are at high risk of developing CV disease[1]



T2D and hypertension are the leading causes of >75% of ESKD cases in the US[3]

CKD affects up to 40% of patients with T2D[2]

ESKD, end-stage kidney disease; T2D, type 2 diabetes; US, United States

1. Wong K, et al. *J Diabetes Complications*. 2012;26:163-174. 2. Feng X, et al. *Kidney Med*. 2022;4(1):100385. 3. Burrows NR, et al. *MMWR Morb Mortal Wkly Rep*. 2022;71(1):412-415.

The Role of the Health Care Team in HF and CKD[1-4]

- Health care team management of cardio-renal-metabolic diseases is recommended
- CKD is underdiagnosed, and many clinicians are not routinely screening patients with diabetes or hypertension for elevated UACR
  - Early screening and diagnosis leads to optimized kidney and CV care
- HF remains unrecognized in certain populations, such as those with obesity and dyspnea

- Primary care clinicians (PCCs) are often the first source for care
  - More than 60% of patients with CKD seen in primary care, and HF is commonly co-managed in primary care
  - PCCs can coordinate care to ensure coordinated, multidisciplinary management of HF and CKD

1. Rangaswami J, et al. *Circulation*. 2019;142(17):e265-e268. 2. Kushner PR, et al. *Clin Diabetes*. 2022;40(4):401-412. 3. Arrigo D, et al. *Diabetes Care*. 2021;44:2025-2032; Shin J, et al. *Hypertension*. 2021;78:1042-1052. 4. Kosyakovsky LB, et al. *Circ Heart Fail*. 2024; 7(5):e011368.

Role of the PCC[1,2]

- Facilitate early screening, diagnosis, and intervention
- Implement interventions early when indicated to prevent CV and renal morbidity/mortality and slow HF/CKD progression
  - Lifestyle interventions
  - Optimized risk factor management
  - Guideline-directed medical therapy (GDMT)
  - Initiation of agents with evidence of cardiovascular and kidney benefit
- Refer to specialists as appropriate
- Coordinate multidisciplinary care

1. Shubrook JH, et al. *Postgrad Med*. 2022;134(4):376-387. 2. Kushner PR, et al. *Clin Diabetes*. 2022; 40(4):401-412.

II. The Role of Aldosterone in HF and CKD

and Emerging Agents Targeting Aldosterone

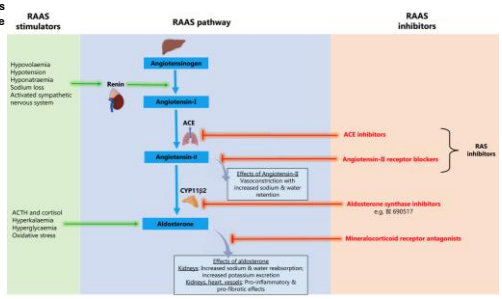
Aldosterone's Effects on the Vascular System[1]

- Effects of aldosterone on the vascular system contribute to the development of various CV and metabolic diseases, including HF and CKD
- Alterations in physiology due to aldosterone results in worse clinical outcomes

Physiologic Consequences of Excess Aldosterone
Inflammation
Oxidative stress
Endothelial dysfunction
Fibrosis
Hypertrophic remodeling

1. Otsuka H, et al. *Int J Mol Sci*. 2023;24(6):5370.

Aldosterone's Effects on the Vascular System



Agents Targeting Aldosterone to Treat HF and CKD

MRAs[1,2]
Oxidative stress occurs due to the binding of aldosterone to the mineralocorticoid receptor, providing mechanistic rationale for MRAs in HF and CKD
Steroidal MRAs: • Spironolactone • Eplerenone
Nonsteroidal MRAs: • Finerenone (indications for CKD associated with T2D and for HF)

1. Otsuka H, et al. *Int J Mol Sci*. 2023;24(6):5370. 2. Attiranno M, et al. *JACC Adv*. 2025; 4(6 Pt 1):101762.

Finerenone: Phase 3 Trials in T2D and CKD

	FIDELIO-DKD[1]	FIGARO-DKD[2]
Design	Randomized, double-blind, placebo-controlled, multicenter, phase 3, event-driven	
Subjects	Adults (N = 5734) with: • T2D • Treated with ACE-I or ARB • UACR 30-300 eGFR 25-60 and diabetic retinopathy or UACR ≥300 and eGFR 25-75	Adults (N = 7437) with: • T2D • Treated with ACE-I or ARB • UACR 30-300 and eGFR 25-90 or UACR ≥300 and eGFR ≥60
Randomized treatment	Finerenone 10 or 20 mg/d or placebo Titration based on potassium level and change in eGFR	
Primary endpoint	Composite of time to first occurrence of kidney failure, sustained decrease of eGFR ≥40% over ≥4 wks, or kidney-related death	Composite of time to first occurrence of CV death, nonfatal myocardial infarction, nonfatal stroke, or HF hospitalization
Median follow up	2.6 years	3.4 years
Results published	October 2020	August 2021

UACR in mg/g and eGFR in mL/min/1.73 m²

1. Bakris GL, et al. *N Engl J Med*. 2020;383(23):2219-2229. 2. Pitt B, et al. *N Engl J Med*. 2021;385(24):2252-2263.

Finerenone: FINEARTS-HF Phase 3 Trial

- International, double-blind, placebo-controlled trial
- Patients with HF and LVEF ≥40% assigned 1:1 to finerenone or placebo once daily, in addition to usual therapy
- Median follow up of 32 months

Outcome	Finerenone Events (N or %)	Placebo Events (N or %)	Ratio (95% CI), P value
Composite of total worsening HF events and death from CV causes	1083 (624 of 3003 patients)	1283 (719 of 2998 patients)	**Rate Ratio: 0.84 (0.74–0.95), P=.007**
Worsening HF events	824	1024	**Rate Ratio: 0.82 (0.71–0.94), P=.006**
Death from CV causes	8.1%	8.7%	HR: 0.93 (0.78–1.11)

Finerenone was associated with an increased risk of hyperkalemia and a reduced risk of hypokalemia

1. Solomon SD, et al. *N Engl J Med*. 2024;391(16):1475-1485.

Agents Targeting Aldosterone to Treat HF and CKD

Aldosterone Synthase Inhibitor (ASi) Therapies[1]

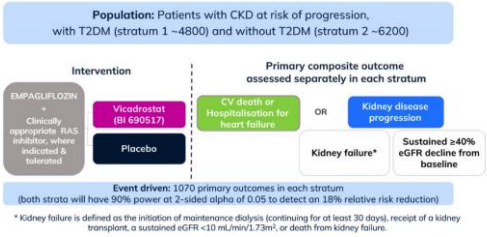
Suppress synthesis of aldosterone; can limit aldosterone-related adverse events by blocking synthesis rather than blocking the mineralocorticoid receptor

Vicadrostat
- EASi-HF (phase 3)
- EASi-KIDNEY (phase 3)

Other investigational ASi therapies such as lorundrostat and baxdrostat are primarily being studied in resistant hypertension

1. Kobayashi M, et al. *Eur Heart J*. 2025;46(27):2618-2642.

Vicadrostat: EASi-KIDNEY Study Design



Vicadrostat: EASi-HF Trials

- **EASi-HF Preserved** (NCT06424288)
  - Patients with HFpEF
    - LVEF ≥40%, symptomatic heart failure
  - Evaluating vicadrostat in combination with empagliflozin, in addition to standard of care
- **EASi-HF Reduced** (NCT06935370)
  - Patients with HFrEF
    - LVEF <40%, symptomatic chronic heart failure
  - Evaluating vicadrostat in combination with empagliflozin, in addition to standard of care

III. Early Identification and Diagnosis of HF and CKD

Importance of Early Identification and Diagnosis

- Early recognition and diagnosis of HF and CKD can help:[1,2]
  - Reduce diagnostic delays
  - Implement earlier treatment to modify the disease course
  - Improve quality of life
  - Mitigate CV and renal adverse outcomes
  - Reduce morbidity and mortality

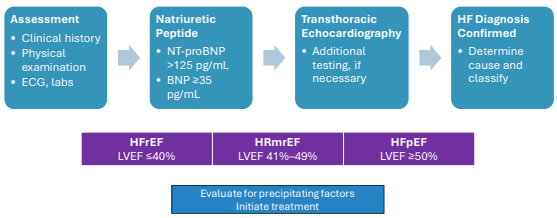
1. KDIGO CKD Work Group. *Kidney Int*. 2024;105(4S):S117-S314. 2. Heidenreich et al. *Circulation*. 2022;145(18):e895-e1032.

Screening and Diagnosis: HF[1]

- **Standardized screening for HF remains challenging** due to the heterogeneity of risk factors across different patient populations
  - Based on symptoms, clinical history
- **LVEF is key in classifying patients** with HF
  - Differing prognosis and response to treatments
  - Most clinical trials select patients based on EF

1. Heidenreich et al. *Circulation*. 2022;145(18):e895-e1032.

HF Diagnostic Algorithm[1]



1. Heidenreich et al. *Circulation*. 2022;145(18):e895-e1032.

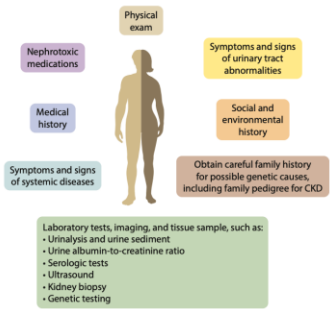
Screening and Diagnosis: CKD[1]

- Despite the increasing recognition of the true burden of CKD, there remains controversy and lack of consensus as to the utility of population screening for CKD
- Patients with risk factors should be screened for CKD

Risk Factors for CKD
Hypertension
Diabetes
CV disease (including HF)
Prior acute kidney injury/acute kidney disease

1. KDIGO CKD Work Group. *Kidney Int*. 2024;105(4S):S117-S314.

CKD: Clinical Evaluation of Cause



CKD Diagnosis: Laboratory Evaluation

What defines CKD diagnosis?

Persistent urine ACR ≥30 mg/g

and/or

Persistent eGFR <60 mL/min/1.73 m²

and/or

Other evidence of kidney damage

What to do with a positive result?

Repeat and confirm:
- Evaluate possible temporary or spurious causes
- Consider using cystatin C and creatinine to more precisely estimate GFR
- Only persistent abnormalities define CKD

Initiate evidence-based treatments

de Boer IH, et al. *Diabetes Care*. 2022;45:3075-3090. Reprinted with permission of the American Diabetes Association, Inc. Copyright 2022.

Case Scenario #1

- A patient with newly diagnosed T2D and hypertension presents to the clinic with multiple risk factors for CV, renal, and metabolic diseases.
- **When and how should the patient be tested for HF and CKD?**

IV. Guideline-Directed Management of HF and CKD

Guideline Recommendations

Early screening, diagnosis, and comprehensive, coordinated care optimize outcomes in HF and CKD

2024 KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD[1]

2022 KDIGO Guidelines for Diabetes and CKD Management[2]

Circulation

AHA/ACC/HFSA CLINICAL PRACTICE GUIDELINE

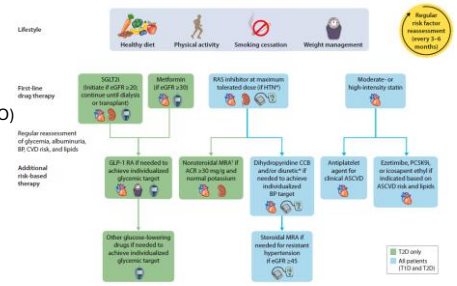
2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

2022 AHA/ACC/HFSA Guideline for the Management of HF[3]

1. KDIGO CKD Work Group. *Kidney Int*. 2024;105(4S):S117-S314. 2. de Boer IH, et al. *Diabetes Care*. 2022;45:3075-3090. 3. Heidenreich et al. *Circulation*. 2022; 145(18):e895-e1032.

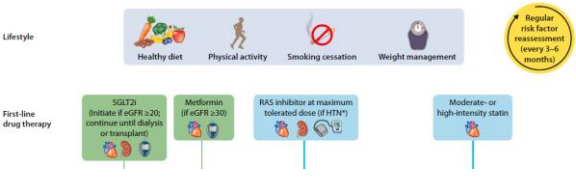
Approach for Improving Outcomes in Diabetes and CKD

(ADA and KDIGO)

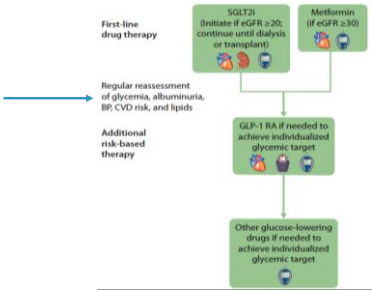


de Boer IH, et al. *Diabetes Care*. 2022;45:3075-3090. Reprinted with permission of the American Diabetes Association, Inc. Copyright 2022.

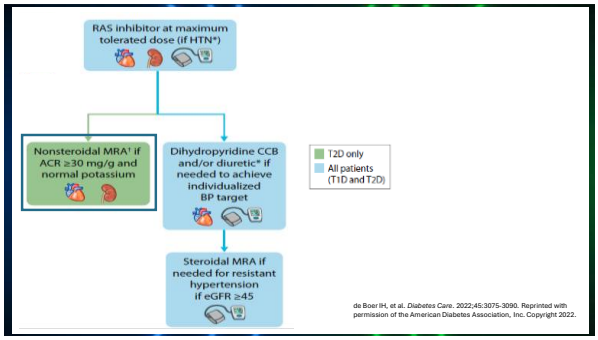
Approach for Improving Outcomes in Diabetes and CKD



de Boer IH, et al. *Diabetes Care*. 2022;45:3075-3090. Reprinted with permission of the American Diabetes Association, Inc. Copyright 2022.



de Boer IH, et al. *Diabetes Care*. 2022;45:3075-3090. Reprinted with permission of the American Diabetes Association, Inc. Copyright 2022.



de Boer IH, et al. *Diabetes Care*. 2022;45:3075-3090. Reprinted with permission of the American Diabetes Association, Inc. Copyright 2022.

SGLT2 Inhibitors: Kidney Outcome Trial Results

Agent	Canagliflozin	Dapagliflozin	Empagliflozin
Study	CREDENCE (n = 4,401)	DAPA-CKD (n = 4,304; **2,906 w/diabetes**)	EMPA-KIDNEY (n = 6,609; **3,040 w/diabetes**)
Median follow-up (years)	2.6	2.4	2.0
Key kidney-related enrollment criteria	eGFR 30 to < 90 UACR: > 300 to 5000 mg/g	eGFR 25 to 75 UACR: 200 to 5000 mg/g	eGFR 20 to 45 (any UACR) eGFR 45 to 90 (UACR ≥200 mg/g)
Mean baseline eGFR	56 mL/min/1.73 m^2	43 mL/min/1.73 m^2	37 mL/min/1.73 m^2
Median Baseline UACR	927 mg/g	949 mg/g	329 mg/g
Kidney outcome(s)	**Primary Outcome** • ESKD (dialysis, transplantation, or sustained eGFR < 15 mL/min/1.73m^2), doubling of SCr, or death from renal causes **HR: 0.70 (0.59-0.82)**	**Primary Outcome** • ≥ 50% decrease in eGFR, ESKD, or death from renal or cardiovascular causes **HR: 0.61 (0.51-0.72)**	**Primary Outcome** • ≥ 40% decrease in eGFR, decrease in eGFR to <10 mL/min/1.73 m^2, ESKD, or death from renal causes **HR: 0.72 (0.64-0.82)**

Perkovic V, et al. *N Engl J Med*. 2019;380:2295-2306; Heerspink HJL, et al. *N Engl J Med*. 2020;383:1436-1446; The EMPA-KIDNEY Collaborative Group. *N Engl J Med*. 2023;388:117-127.

SGLT2 Inhibitors and AKI Hospitalization

- SGLT-2 inhibitors often withheld during AKI among patients hospitalized with acute HF
- Retrospective study of 3305 patients
  - 356 patients received SGLT-2 inhibitor following AKI diagnosis
  - **Rate of renal recovery not significantly different** between those exposed and unexposed to SGLT-2 inhibitors following AKI (HR 0.94, 95% CI 0.79-1.11, *P*=0.46)
  - SGLT-2 inhibitor exposure associated with **lower risk of 30-day mortality** (HR 0.45, 95% CI 0.23-0.87, *P*=0.02)

Conclusion: in adults with hospitalized with AKI and acute HF, exposure to SGLT-2 inhibitors leads to decreased mortality and no delay in recovery of kidney function

Aklilu AM, et al. *Kidney360*. 2023. doi: 10.34067/KID.0000000000000250 AKI, acute kidney injury

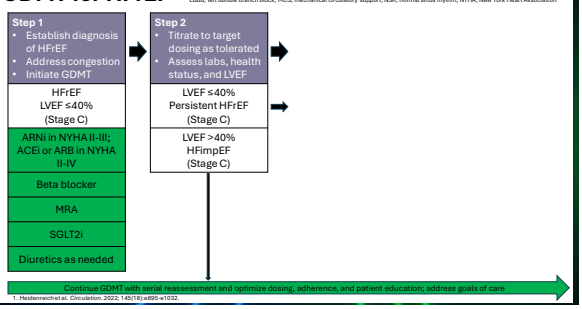
GDMT for HFrEF[1]

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; hydral-nitrates, hydralazine and isosorbide dinitrate; LBBB, left bundle branch block; MCS, mechanical circulatory support; NSR, normal sinus rhythm; NYHA, New York Heart Association

1. Heidenreich et al. *Circulation*. 2022; 145(18):e895-e1032.

GDMT for HFrEF[1]

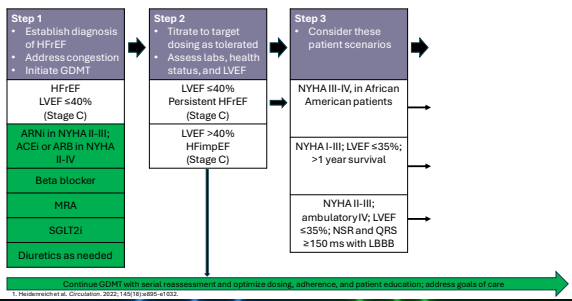
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; hydral-nitrates, hydralazine and isosorbide dinitrate; LBBB, left bundle branch block; MCS, mechanical circulatory support; NSR, normal sinus rhythm; NYHA, New York Heart Association



1. Heidenreich et al. *Circulation*. 2022; 145(18):e895-e1032.

GDMT for HFrEF[1]

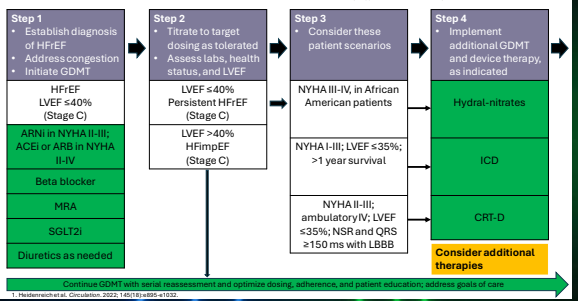
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; hydral-nitrates, hydralazine and isosorbide dinitrate; LBBB, left bundle branch block; MCS, mechanical circulatory support; NSR, normal sinus rhythm; NYHA, New York Heart Association



1. Heidenreich et al. *Circulation*. 2022; 145(18):e895-e1032.

GDMT for HFrEF[1]

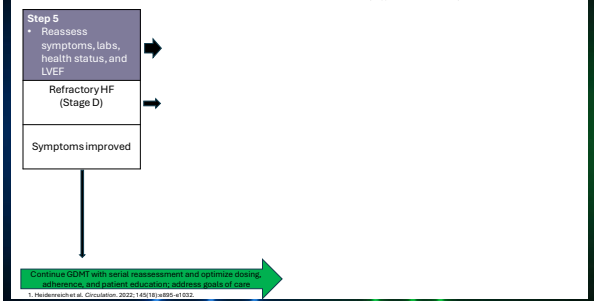
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; hydral-nitrates, hydralazine and isosorbide dinitrate; LBBB, left bundle branch block; MCS, mechanical circulatory support; NSR, normal sinus rhythm; NYHA, New York Heart Association



1. Heidenreich et al. *Circulation*. 2022; 145(18):e895-e1032.

GDMT for HFrEF[1]

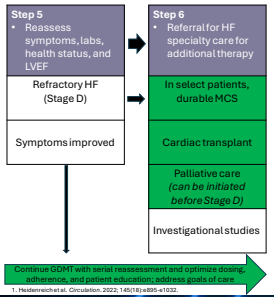
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; hydral-nitrates, hydralazine and isosorbide dinitrate; LBBB, left bundle branch block; MCS, mechanical circulatory support; NSR, normal sinus rhythm; NYHA, New York Heart Association



1. Heidenreich et al. *Circulation*. 2022; 145(18):e895-e1032.

GDMT for HFrEF[1]

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; hydral-nitrates, hydralazine and isosorbide dinitrate; LBBB, left bundle branch block; MCS, mechanical circulatory support; NSR, normal sinus rhythm; NYHA, New York Heart Association



1. Heidenreich et al. *Circulation*. 2022; 145(18):e895-e1032.

SGLT2 Inhibitors: HF Trial Results

Agent	Dapagliflozin	Dapagliflozin	Empagliflozin	Empagliflozin	Sotagliflozin
Study	DAPA-HF (n = 4,744)	DELIVER (n = 6,263)	EMPEROR-Reduced (n = 3,730)	EMPEROR-Preserved (n = 5,988)	SOLOIST-WHF (n = 1,222)
Median follow-up (years)	1.5	2.3	1.33	2.2	0.75*
Patients	NYHA class II, III, or IV HF and EF ≤40%	HF and EF >40%	NYHA class II, III, or IV HF and EF ≤40%	NYHA class II, III, or IV HF and EF >40%	T2D, recently hospitalized for worsening HF
HF outcomes	Composite of worsening heart failure or CV death **HR: 0.74 (0.65-0.85)**	Composite of worsening heart failure or CV death **HR: 0.82 (0.73-0.92)**	Composite of hospitalization for heart failure or CV death **HR: 0.75 (0.65-0.86)**	Composite of hospitalization for heart failure or CV death **HR: 0.79 (0.69-0.90)**	Composite of urgent visits or hospitalizations for HF and CV death **HR: 0.67 (0.52-0.85)**

NYHA, New York Heart Association; EF, ejection fraction

*Trial ended early due to lack of funding

McMurray JJV, et al. *N Engl J Med*. 2019;381:1995-2008; Solomon SD, et al. *N Engl J Med*. 2022;387:1089-1098; Packer M, et al. *N Engl J Med*. 2020;383:1413-1424; Anker SD, et al. *N Engl J Med*. 2021; 385:1451-1461; Bhatt DL, et al. *N Engl J Med*. 2021;384:117-128.

SGLT2 Inhibitors: Expanded Indications

Medication	Expanded Indications
Canagliflozin	...to reduce to reduce the risk of MACE* in adults with T2D and established CVD ...to reduce the risk of ESKD, doubling of serum creatinine, CV death, and hospitalization for HF in adults with T2D and diabetic nephropathy with albuminuria
Dapagliflozin	...to reduce the risk of hospitalization for HF in adults with T2D and established CVD or multiple CV risk factors ...to reduce the risk of CV death and hospitalization for HF, and urgent HF visit in adults with heart failure ...to reduce the risk of sustained eGFR decline, ESKD, CV death, and hospitalization for HF in adults with CKD at risk of progression
Empagliflozin	...to reduce the risk of CV death and hospitalization for HF in adults with HF ...to reduce the risk of CV death in adults with T2D and established CVD
Sotagliflozin	...to reduce the risk of CV death, hospitalization for HF, and urgent HF visit in adults with HF or T2D with CKD and other CV risk factors

*Composite of CV death, nonfatal MI, nonfatal stroke

Invokana [Package Insert]. Updated December 2024. Accessed March 17, 2025. Farxiga [Package Insert]. Updated October 2024. Accessed March 17, 2025. Jardiance [Package Insert]. Updated September 2023. Accessed March 17, 2025. Inpefa [Package Insert]. Updated January 2024. Accessed March 17m, 2025.

FLOW Trial: T2D/CKD Outcomes with Semaglutide

- Patients: 3533 adults with T2D and CKD randomized 1:1 to semaglutide 1.0 mg once weekly or placebo
- Trial stopped early at median follow-up of 3.4 years
- Results (all statistically significant in favor of semaglutide):

Outcome	Semaglutide vs Placebo
Primary outcome: major kidney disease events, a composite of the onset of kidney failure, at least a 50% reduction in the eGFR from baseline, or death from kidney or cardiovascular causes	**HR 0.76**; 95% CI, 0.66 to 0.88; *P* = .0003
Kidney-specific components of the primary outcome	**HR 0.79**; 95% CI, 0.66 to 0.94
Death from cardiovascular causes	**HR 0.71**; 95% CI, 0.56 to 0.89
Risk of major adverse cardiovascular events	**HR 0.82**; 95% CI, 0.68 to 0.98; *P* = .029
Risk of death from any cause	**HR 0.80**; 95% CI, 0.67 to 0.95; *P* = 0.01

Conclusion: semaglutide reduced the risk of clinically important kidney outcomes and death from CV causes in patients with T2D and CKD

Perkovic V, et al. *N Engl J Med*. 2024; May 24 online ahead of print. doi:10.1056/NEJMoa2403347

GLP-1 RAs and Kidney Benefits in Patients Without T2D

SELECT trial analysis

- Long-term kidney outcomes in patients with obesity/overweight and cardiovascular disease who did not have diabetes
- Kidney composite endpoint:
  - Death from kidney disease, initiation of chronic kidney replacement therapy, onset of persistent eGFR < 15 mL/min/1.73 m^2, persistent ≥50% reduction in eGFR or onset of persistent macroalbuminuria
- Semaglutide 2.4 mg compared to placebo
  - 22% reduction in the kidney composite endpoint
  - 1.8% with semaglutide, 2.2% with placebo, *P* = 0.02

Colhoun HM, et al. *Nat Med*. May 25, 2024. online ahead of print. doi:10.1038/s41591-024-03015-5

Combined SGLT-2 Inhibitor and MRA Benefit

Joint analysis of randomized trials (CREDENCE, FIDELIO-DKD, and DAPA-CKD)

Outcome	Combination Treatment Events/Patients	Conventional Treatment Events/Patients	Hazard Ratio (95% CI)
Doubling of SCr, ESKD, or death due to kidney failure	405/5035	550/5040	**0.50 (0.44–0.57)**
ESKD	324/5035	400/5040	**0.59 (0.51–0.69)**
All-cause mortality	387/5035	445/5040	**0.75 (0.65–0.86)**

- Patients had T2D and CKD
- Conventional Treatment: ACE inhibitor or ARB
- Combination treatment: SGLT-2 inhibitor and nonsteroidal MRA

Estimated event-free survival from composite kidney outcome incremental gain was 6.7 years with combination treatment

Heerspink HJL, et al. *Diabetes Obes Metab*. 2023. doi:10.1111/dom.15232

Combined SGLT2 Inhibitor and MRA Benefit

The CONFIDENCE trial

- Patients had T2D and CKD (eGFR 30 to 90 mL/min/1.73 m^2 and UACR of 100 to ≤5000 mg/g)
  - Protocol required that patients were taking an ACE inhibitor or ARB
- Randomized 1:1:1 to finerenone + placebo, placebo + empagliflozin, or finerenone + empagliflozin
- Stratified by eGFR and UACR

Safety Outcome	Empagliflozin and Finerenone	Empagliflozin Alone	Finerenone Alone
Hyperkalemia	9.3%	11.4%	3.8%
>30% drop in eGFR at day 30	6.3%	3.8%	1.1%

Agarwal R, et al. *N Engl J Med*. 2025;393(6):533-543.

Combined SGLT2 Inhibitor and MRA Benefit

The CONFIDENCE trial – primary outcome

Outcome	Empagliflozin and Finerenone	Empagliflozin Alone	Finerenone Alone
Reduction in UACR from baseline to 180 days	52%	32%	29%
Least-squares mean ratio of the difference in change from baseline (vs combination)	—	0.71; 95% CI, 0.61 to 0.82; **P<.001**	0.68; 95% CI, 0.59 to 0.79; **P<.001**

Combination therapy reduced UACR by 29% more than finerenone alone and by 32% more than empagliflozin alone over 180 days of treatment

Agarwal R, et al. *N Engl J Med*. 2025;393(6):533-543.

Overcoming Barriers to Use of Evidence-Based Therapies

Barriers in Primary Care	Potential Solutions
Lack of clinician awareness and knowledge of cardiometabolic conditions	• Concise and consistent practice guidelines • Actionable and patient-centered recommendations • Automated decision support tools integrated into electronic health records • Improved team-based care
Complex patient characteristics	
Lack of clinician time and resources	
Inadequate collaboration with and access to specialists	
Lack of clear parameters for specialist referral and difficult referral processes	

Nee R, et al. *Nephrol Dial Transplant*. 2023;38(3):532-541.

Case Scenario #1 (continued)

- A patient with newly diagnosed T2D and hypertension presents to the clinic with multiple risk factors for CV, renal, and metabolic diseases, and shows evidence of HF and CKD.

- **After diagnoses of HF and CKD are established, what treatments might be initiated to reduce cardiorenal risk?**

V. Multidisciplinary Care for HF and CKD

Team-Based Care for Patients with HF and/or CKD

- Collaboration with specialists and primary care
  - Endocrinologists
  - Cardiologists
  - Nephrologists
  - Other specialists
  - PCCs including NPs and PAs

NPs, nurse practitioners; PAs, physician associates; PCCs, primary care clinicians

Team-Based Care for Patients with HF and/or CKD

- Collaboration with care team members
  - Pharmacists
  - Dietitians
  - Physical therapists
  - Social workers
  - Community health workers
  - Others

Need for Multidisciplinary Care

- Multidisciplinary approach for cardio-renal-metabolic diseases is recommended[1]
- Patients often have access to specialized care only at a late stage in the disease trajectory[2]
- PCCs are uniquely positioned to facilitate multidisciplinary management of HF and CKD[2]

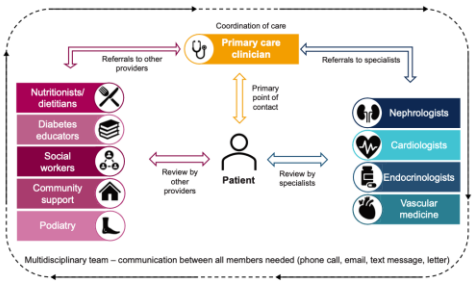
1. Rangaswami J, et al. *Circulation*. 2020;142(17):e265-e268. 2. Kushner PR, et al. *Clin Diabetes*. 2022;40(4):401-412.

PCC Coordination of Multidisciplinary Care

- Ensure T2D, CVD/HF, and CKD are not treated as separate problems
- Expertise of each specialty should be maximized
- Refer patients in a timely manner when appropriate
- Team includes:
  - Nephrologists
  - Cardiologists
  - Endocrinologists
  - Diabetes educators
  - Social workers
  - Community support
- Establish a clear chain of communication between PCCs and specialists
- Changes to monitoring or treatment plan should be made clear to the multidisciplinary team

Kushner PR, et al. *Clin Diabetes*. 2022;40(4):401-412.

Multidisciplinary care for patients with cardio-renal-metabolic disease



Kushner PR, et al. *Clin Diabetes*. 2022;40(4):401-412. Reprinted with permission of the American Diabetes Association, Inc. Copyright 2022.

Case Scenario #2

- A patient with a longstanding history of T2D, HF, CKD, and hypertension, a recent HF exacerbation, and declining kidney function presents to the clinic.
- **How do you proceed with involving other members of the health care team to ensure the patient receives holistic care?**

Special Resource Toolkit

Visit the website via the QR code or the URL below for more information on this topic and to review the presentation.

URL: https://www.pcmg-us.org/toolkit/hfckd