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# **SGLT-2 INHIBITORS FOR TREATMENT OF HEART FAILURE AND CHRONIC KIDNEY DISEASE**

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# FACULTY DISCLOSURE/CONFLICT OF INTEREST

**I, Emily McCoy, have no actual or potential conflict of interest in relation to this program.**



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# OBJECTIVES

- ▶ Evaluate the current evidence for use of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in the treatment of heart failure and/or chronic kidney disease.
- ▶ Discuss pertinent guideline recommendations regarding the use of SGLT2i in patients with heart failure and/or chronic kidney disease.
- ▶ Identify patients with heart failure and/or chronic kidney disease who would be appropriate candidates for treatment with SGLT2i therapy.



# ABBREVIATIONS

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- ▶ ACC: American College of Cardiology
- ▶ ADR: adverse drug reaction
- ▶ AE: adverse effects
- ▶ AF: atrial fibrillation
- ▶ AHA: American Heart Association
- ▶ ASCVD: atherosclerotic cardiovascular disease
- ▶ CAD: coronary artery disease
- ▶ CHD: coronary heart disease
- ▶ CHQ-SAS: Chronic Heart Failure Questionnaire Self-Administered
- ▶ CKD: chronic kidney disease
- ▶ CVD: cardiovascular disease
- ▶ CVOT: cardiovascular outcomes trials
- ▶ DKD: diabetic kidney disease
- ▶ DLD: dyslipidemia
- ▶ DM: diabetes mellitus
- ▶ eGFR: estimated glomerular filtration rate
- ▶ ESRD: end stage renal disease



# ABBREVIATIONS

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- ▶ GDMT: guideline-directed medical therapy
- ▶ HFpEF: heart failure with preserved ejection fraction
- ▶ HFrEF: heart failure with reduced ejection fraction
- ▶ HHF: hospitalization for heart failure
- ▶ KCCQ: Kansas City Cardiomyopathy Questionnaire
- ▶ KDIGO: Kidney Disease Improving Global Outcomes
- ▶ LDL-C: low-density lipoprotein cholesterol
- ▶ MI: myocardial infarction
- ▶ MRA: mineralocorticoid receptor antagonist
- ▶ NSTEMI: non-ST-segment elevation myocardial infarction
- ▶ NT-proBNP: N terminal pro B-type natriuretic peptide
- ▶ NYHA: New York Heart Association
- ▶ SGLT2i: sodium-glucose cotransporter-2 inhibitors
- ▶ TIA: transient ischemic attack
- ▶ UA: unstable angina
- ▶ UACR: urinary albumin-to-creatinine ratio
- ▶ UTI: urinary tract infection

# INTRODUCTION

- ▶ T2DM is associated with both micro- and macrovascular complications
  - ▶ 2-5-fold greater risk of developing HF
  - ▶ 45% of people with HF have DM
  - ▶ Leading cause of CKD and ESRD globally
    - ▶ 40% of people with CKD have concomitant DM
- ▶ HF and CKD are associated with a diminished quality of life and limited life expectancy
  - ▶ HF prevalence: 5.7 million
  - ▶ CKD prevalence: 37 million



# INTRODUCTION

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- ▶ SGLT2i MOA: inhibit SGLT2 in the proximal convoluted tubule to prevent glucose reabsorption and increase glucosuria
- ▶ In large-scale trials in people with T2DM, SGLT2i shown to reduce the risk of ASCVD events, HHF, and risk of serious adverse renal events
  - ▶ Glucose-lowering efficacy declines at lower eGFR rates, but CV benefits preserved even in renal impairment
  - ▶ Cardiorenal benefits cannot be explained by glucose-lowering action alone
  - ▶ Cardioprotective mechanisms not fully understood



# ADA STANDARDS OF CARE: TREATING T2DM WITH CONCOMITANT HF OR CKD

First line therapy: metformin + lifestyle

HF  
Particularly  
HFrEF  
(LVEF <45%)

CKD (eGFR <60 mL/min/1.73m<sup>2</sup>)

DKD + albuminuria (particularly ≥300 mg/g)

Without albuminuria

SGLT2i with  
proven  
benefit in this  
population

Preferably  
SGLT2i with  
primary  
evidence of  
reducing  
CKD  
progression

OR SGLT2i  
with  
evidence of  
reducing  
CKD  
progression in  
CVOTs

OR GLP-1 RA  
with proven  
CVD benefit  
if SGLT2i not  
tolerated or  
CI

SGLT2i with  
proven CVD  
benefit

GLP-1 RA with  
proven CVD  
benefit





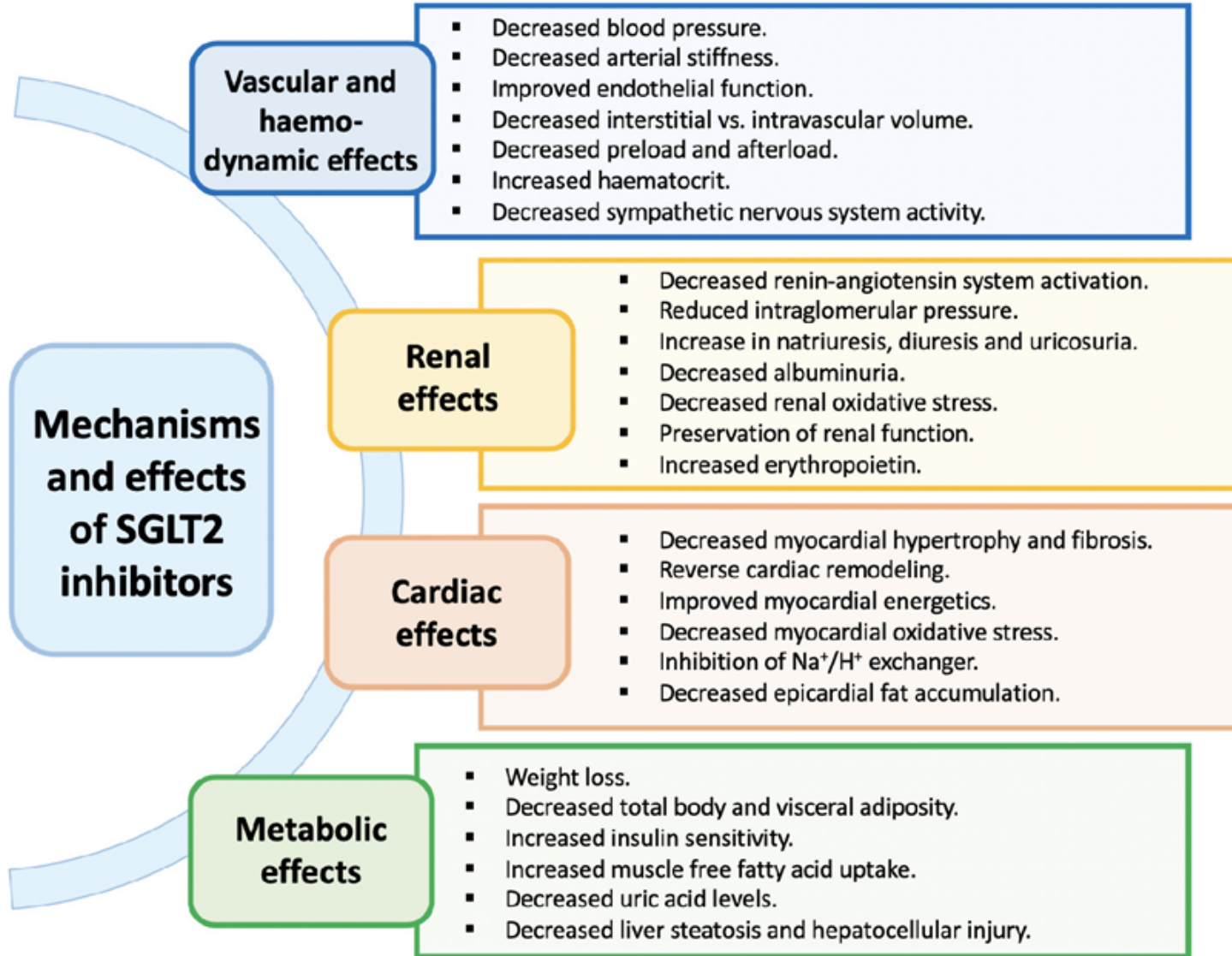
# HOW DID WE GET HERE?

## SGLT2i Trials Evaluating ASCVD Benefit

Medication	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin
Trial	EMPA-REG Outcome	CANVAS	DECLARE-TIMI 58	VERTIS CV
Patient population (All T2DM)	Established ASCVD	Established ASCVD or ≥50 years + >2 CV risk factors	Established ASCVD or multiple ASCVD risk factors	Established ASVD
Primary CV outcome (3 Point MACE)	<b>0.86</b> <b>(0.74-0.99)</b>	<b>0.86</b> <b>(0.75-0.97)</b>	0.93 (0.84-1.03)	0.97 (0.85-1.11)
CV death	<b>0.62</b> <b>(0.49-0.77)</b>	0.87 (0.72-1.06)	0.98 (0.82-1.17)	0.92 (0.77-1.11)
Myocardial infarction	0.87 (0.70-1.09)	0.89 (0.73-1.09)	0.89 (0.77-1.01)	1.04 (0.86-1.26)
Stroke	1.18 (0.89-1.56)	0.87 (0.74-1.01)	1.01 (0.84-1.21)	1.06 (0.82-1.37)
All-cause mortality	<b>0.68</b> <b>(0.57-0.82)</b>	0.87 (0.74-1.01)	0.93 (0.82-1.04)	0.93 (0.80-1.08)
HF hospitalizations	<b>0.65</b> <b>(0.50-0.85)</b>	<b>0.67</b> <b>(0.52-0.87)</b>	<b>0.73</b> <b>(0.61-0.88)</b>	<b>0.70</b> <b>(0.54-0.90)</b>
Renal outcome	<b>0.61</b> <b>(0.53-0.70)</b>	<b>0.73</b> <b>(0.67-0.79)</b>	<b>0.53</b> <b>(0.43-0.66)</b>	0.81 (0.63-1.04)

Outcomes reported as HR (95% CI)

N Engl J Med 2015;373:2117-128.  
 N Engl J Med 2017;377:644-57.  
 N Engl J Med 2019;380:347-57.  
 N Engl J Med 2020;383:1425-35.





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# SGLT2i Trials in HF

# CLASSIFICATION AND STAGES OF HEART FAILURE

- ▶ Heart failure with reduced ejection fraction (HFrEF): EF  $\leq$ 40%
- ▶ Heart failure with preserved ejection fraction (HFpEF): EF  $>$ 40%

ACC/AHA Stages of HF	NYHA Functional Classification
<b>A:</b> at high risk for HF, without structural heart disease or HF symptoms	<b>I:</b> no limitation of physical activity. Ordinary physical activity does not cause HF symptoms
<b>B:</b> structural heart disease, without s/s HF	<b>II:</b> slight limitation of physical activity. Comfortable at rest, but ordinary physical activity causes HF symptoms.
<b>C:</b> structural heart disease with prior/current HF symptoms	<b>III:</b> marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity causes HF symptoms.
<b>D:</b> refractory HF requiring specialized interventions	<b>IV:</b> unable to perform any activity without HF symptoms, or HF symptoms at rest.

# DEFINE-HF

## Methodology

- ▶ Patients:
  - ▶ EF  $\leq$ 40%
  - ▶ NYHA Class II-III
  - ▶ eGFR  $\geq$ 30 mL/min/1.73m<sup>2</sup>
  - ▶ Elevated NT-proBNP or BNP
  - ▶  $\pm$  T2DM
- ▶ Intervention: dapagliflozin 10 mg/d vs. placebo
- ▶ Duration: 12 weeks

## Results

- ▶ Baseline characteristics
  - ▶ 62 years; 72.5% male; 59.7% White; 37.9% Black; EF ~25%; ~62% T2DM
- ▶ NT-proBNP:
  - ▶ 1133 pg/dL vs. 1191 pg/dL
  - ▶ 0.95 (0.84-1.08)
- ▶ NT-proBNP reduction  $\geq$ 20% or KCCQ improvement  $\geq$ 5 points:
  - ▶ 61.5% vs. 50.4%
  - ▶ 1.8 (1.0-3.1), p=0.039

# SGLT2 TRIALS IN HFREF- METHODOLOGY

Trial	DAPA-HF	EMPEROR-Reduced
<b>Inclusion Criteria</b>	NYHA II-IV + EF ≤40% + elevated NT-proBNP ± DM	NYHA II-IV + EF ≤40% + elevated NT-proBNP ± DM
<b>Intervention</b>	Dapagliflozin 10 mg/d (n=2373)	Empagliflozin 10 mg/d (n=1863)
<b>Comparator</b>	Placebo (n=2371)	Placebo (n=1867)
<b>Median Follow-up</b>	18.2 months	16 months
<b>Primary Outcome</b>	CV death or worsening HF (HHF or urgent visit requiring IV therapy)	CV death or HHF
<b>Secondary and other Pre-specified Outcomes</b>	CV death or HHF Total hospitalizations for HF and CV deaths Quality of life All-cause mortality Worsening renal function	HHF Total hospitalizations Rate of eGFR decline Quality of life All-cause mortality Composite renal outcome



# SGLT2i TRIALS IN HFREF- BASELINE CHARACTERISTICS

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Trial	DAPA-HF	EMPEROR-Reduced
Age (yr)	66.2	67.2
Female sex (%)	23.8	23.5
Race (%)		
White	70.0	71.1
Black	5.1	6.6
Asian	23.3	18.1
Other	1.6	4.2
NYHA Functional Class (%)		
II	67.7	75.1
III	31.5	24.4
IV	0.8	0.5
LVEF (%)	31.2	27.7
Medical History (%)		
HHF	47.4	31.0
AF	38.6	35.6
DM	41.8	49.8
eGFR (mL/min/1.73m <sup>2</sup> )	66.0	61.8
HF Therapy (%)		
Beta-blocker	96.0	94.7
Renin-angiotensin inhibitor	84.5	70.5
Sacubitril-valsartan	10.5	18.3
MRA	71.5	70.1



# SGLT2i TRIALS IN HFREF- RESULTS

Trial	DAPA-HF	EMPEROR-Reduced
<b>Primary Outcome</b>	<b>0.74 (0.65-0.85)</b> NNT=21	<b>0.75 (0.65-0.86)</b> NNT=19
<b>Select Secondary Outcomes</b>		
<b>CV death or HHF</b>	<b>0.75 (0.65-0.85)</b>	NA
<b>HHF</b>	0.70 (0.59-0.83)*	<b>0.70 (0.58-0.81)</b>
<b>CV Death</b>	0.82 (0.69-0.98)*	0.92 (0.75-1.12)*
<b>Mean slope of change in eGFR</b>	NA	<b>1.73 (1.10-2.37)</b>
<b>All-cause mortality</b>	0.83 (0.71-0.97)*	0.92 (0.77-1.10)*
<b>Renal outcome</b>	Worsening renal function 0.71 (0.44-1.16)*	Composite renal outcome 0.50 (0.32-0.77)*
<b>Total hospitalizations</b>	For HF and CV death <b>0.75 (0.65-0.88)</b>	For any cause 0.85 (0.75-0.95)*
<b>Change in KCCQ</b>	<b>1.18 (1.11-1.26)</b>	1.7 (0.5-3.0)*

Results reported as hazard ratio

\*Not included in testing hierarchy



# SGLT2i IN HF: EMPERIAL SERIES

- ▶ Evaluated effects of empagliflozin on exercise ability and patient-reported outcomes in patients with both HFrEF and HFpEF, ± T2DM
- ▶ Included:
  - ▶ HFrEF (EF ≤40%, n=312)
  - ▶ HFpEF (EF>40%, n=315)
- ▶ Intervention: empagliflozin 10 mg/d vs. placebo
- ▶ Median follow-up: 12 weeks
- ▶ Primary endpoint: 6-minute walk test distance (6MWTd) change to week 12
- ▶ Select secondary endpoints:
  - ▶ KCCQ total symptom score
  - ▶ Chronic HF Questionnaire Self-Administered Standardized format (CHQ-SAS)

Baseline Characteristic	EMPERIAL-Reduced		EMPERIAL-Preserved	
	PBO (n=156)	Empagliflozin (n=156)	PBO (n=158)	Empagliflozin (n=157)
Age (yr)	70.0	69.0	75.0	74.0
Female sex (%)	28.8	22.4	41.8	44.6
Race (%)				
White	85.3	83.3	85.4	87.3
Black/AA	11.5	15.4	12.0	10.2
Asian	1.3	0.6	1.3	1.6
Other	1.3	0.6	1.3	0.6
Median 6MWTD (min)	309.0	306.0	299.5	297.0
Median KCCQ	68.8	68.8	68.2	64.6
NYHA Class (%)				
II	64.7	64.7	79.7	74.5
III	35.3	35.3	20.3	24.8
DM (%)	64.1	55.8	47.5	54.8
HF Medications (%)				
Beta-blockers	94.2	94.9	89.2	89.2
ACEi/ARB	59.0	51.9	75.9	73.2
ARNI	34.0	39.1	3.8	3.2
MRA	55.8	60.9	31.6	35.0
Loop diuretics	89.1	86.5	66.5	77.1
Thiazide diuretics	15.4	5.8	22.8	18.5

# SGLT2i IN HF: EMPERIAL SERIES RESULTS

## EMPERIAL-Reduced

- ▶ Primary endpoint (6MWTD)
  - ▶ Difference: -4.0 m
  - ▶ P-value: 0.42
- ▶ Secondary endpoints
  - ▶ KCCQ-TSS
    - ▶ Difference: 3.13
  - ▶ CHQ-SAS
    - ▶ Difference: 0.10

## EMPERIAL-Preserved

- ▶ Primary endpoint (6MWTD)
  - ▶ Difference: 4.0 m
  - ▶ P-value: 0.37
- ▶ Secondary endpoints
  - ▶ KCCQ-TSS
    - ▶ Difference: 2.08
  - ▶ CHQ-SAS
    - ▶ Difference: -0.07

# SGLT2i IN ACUTE HEART FAILURE: SOLOIST-WHF

- ▶ Included: T2DM recently hospitalized for HF
- ▶ Intervention: sotagliflozin 200-400 mg/d (n=608) vs. placebo (n=614)
- ▶ Median follow-up: 9 months
- ▶ Primary endpoint: death from CV causes and hospitalizations/urgent visits for HF
- ▶ Select secondary endpoints:
  - ▶ Total number hospitalizations/urgent visits for HF
  - ▶ Death from CV causes
  - ▶ Death from any cause
  - ▶ Hospitalization for HF, nonfatal MI, and nonfatal stroke
  - ▶ Quality of life
  - ▶ Change in eGFR

# SGLT2i IN ACUTE HEART FAILURE: SOLOIST-WHF BASELINE CHARACTERISTICS

- ▶ Age: 69 years
- ▶ Female sex: 32.6%
- ▶ Race or ethnic group
  - ▶ White: 93.3%
  - ▶ Black: 4.1%
  - ▶ Asian: 1.3%
  - ▶ Other/Unknown: 1.3%
- ▶ LVEF: 35%
- ▶ HF Therapy
  - ▶ Beta-blocker: 92.8%
  - ▶ ACEi: 41.8%
  - ▶ ARB: 40.8%
  - ▶ ARNI: 15.3%
  - ▶ MRA: 92.8%
  - ▶ Loop diuretic: 95.4%
  - ▶ Other diuretic: 10.9%

# SGLT2I IN ACUTE HEART FAILURE: SOLOIST-WHF RESULTS

Endpoint	Sotagliflozin (n=608)	PBO (n=614)	HR or Difference	P Value
<b>Primary Endpoint</b>	51.0%	76.3%	<b>0.67 (0.52-0.85)</b>	<0.001
<b>Secondary Endpoints in order of hierarchical testing</b>				
Total HHF/urgent HF visits	40.4%	63.9%	<b>0.64 (0.49-0.83)</b>	<0.001
Death from CV causes	10.6%	12.5%	0.84 (0.58-1.22)	0.36
Death from CV cause, HHF, nonfatal MI, nonfatal stroke	51.4%	71.0%	0.72 (0.56-0.92)	NR
Death from CV causes, HHF and urgent HF visits, HF events during hospitalization	54.7%	80.6%	0.68 (0.57-0.86)	
Death from any cause	13.5%	16.3%	0.82 (0.59-1.14)	
Mean change in KCCQ score	17.7	13.6	4.1 (1.3-7.0)	
Mean change eGFR (mL/min/1.73m <sup>2</sup> )	-0.34	-0.18	-0.16 (-1.30-0.98)	



# ONGOING TRIALS OF SGLT2i IN HF

Study (Year)	Number of Patients	Study Population	Agent and dose	Comparator	Primary Endpoint
SCF DETERMINE-Reduced (2021)	313	HFrEF	Dapagliflozin 10 mg/d	Placebo	6-minute walk test and KCCQ
DETERMINE-Preserved (2021)	504	HFpEF	Dapagliflozin 10 mg/d	Placebo	6-minute walk and KCCQ
EMPEROR-Preserved (2021)	5988	HFpEF	Empagliflozin 10 mg/d	Placebo	CV death or HF hospitalization
DELIVER (2022)	6100	HFpEF	Dapagliflozin 10 mg/d	Placebo	HF event and CV death
EMPULSE (2021)	530	Acute HF	Empagliflozin 10 mg/d	Placebo	All-cause death, HF event, and KCCQ
DAPA-RESIST (2022)	120	Acute HF in patients with HFrEF, renal impairment, and diuretic resistance	Dapagliflozin 10 mg/d	Metolazone 5-10 mg/d	Diuretic effect based on weight
DAPA-ACT TIMI (2023)	2400	Acute HF in patients with HFrEF	Dapagliflozin 10 mg/d	Placebo	CV death or worsening HF



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# SGLT2i Trials in CKD



# DIAGNOSIS AND STAGING OF CKD

## 1.1: DEFINITION OF CKD

1.1.1: CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health. (Not Graded)

### Criteria for CKD (either of the following present for >3 months)

Markers of kidney damage (one or more)	Albuminuria (AER $\geq 30$ mg/24 hours; ACR $\geq 30$ mg/g [ $\geq 3$ mg/mmol]) Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR $< 60$ ml/min/1.73 m <sup>2</sup> (GFR categories G3a-G5)

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

## Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories		
				Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min per 1.73 m <sup>2</sup> ) Description and range	G1	Normal or high	$\geq 90$			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk.



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# SGLT2I TRIALS IN CKD- METHODOLOGY

Trial	CREDESCENCE	DAPA-CKD
<b>Inclusion Criteria</b>	T2DM, A1C 6.5%-12.0%, eGFR 30 to <90 mL/min/1.73m <sup>2</sup> , UACR >300-5000 mg/g	Adults ±T2DM with eGFR 25-75 mL/min/1.73m <sup>2</sup> + UACR 200-5000 mg/g
<b>Intervention</b>	Canagliflozin 100 mg/d (n=2202)	Dapagliflozin 10 mg/d (n=2152)
<b>Comparator</b>	Placebo (n=2199)	Placebo (n=2152)
<b>Median Follow-up</b>	2.62 years	2.4 years
<b>Primary Outcome</b>	ESRD, doubling of SCr from baseline, death from renal or CV causes	Decline of ≥50% eGFR, onset of ESRD, death from renal or CV causes
<b>Secondary Outcomes</b>	<ul style="list-style-type: none"> <li>• HHF or death from CV causes</li> <li>• CV death, MI, stroke</li> <li>• HHF</li> <li>• ESRD, doubling SCr, renal death</li> <li>• CV death</li> <li>• Death from any cause</li> <li>• CV death, MI, stroke, hospitalization for HF or UA</li> </ul>	<ul style="list-style-type: none"> <li>• Decline of ≥50% eGFR, onset of ESRD, death from renal causes</li> <li>• HHF or death from CV causes</li> <li>• Death from any cause</li> </ul>

N Engl J Med 2020;383:1436-46.

N Engl J Med 2019;380:2295-306.



# SGLT2i TRIALS IN CKD- BASELINE CHARACTERISTICS

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Trial	CREDENCE	DAPA-CKD
Age (yr)	62.9	61.8
Female sex (%)	34.6	32.9
Race (%)		
White	67.5	52.2
Black	5.1	4.8
Asian	19.3	34.8
Other	8.1	8.1
BP (mm Hg)		
SBP	139.8	136.7
DBP	78.2	77.5
eGFR (mL/min/1.73m <sup>2</sup> )	56.3	43.2
UACR (mg/g)	923	965
T2DM (%)	100	67.6
CVD (%)	50.5	37.8
HF (%)	14.9	10.9
CKD Medications (%)		
RAAS Inhibitor	>99.9	98.4
Diuretic	46.6	43.1



# SGLT2i TRIALS IN CKD- RESULTS

Trial	CREDESCENCE	DAPA-CKD
Primary Outcome	<b>0.70 (0.59-0.82)</b> NNT=23	<b>0.61 (0.51-0.72)</b> NNT=19
<b>Secondary Outcomes</b>		
Decline of $\geq 50\%$ eGFR, onset of ESRD, death from renal causes	NA	<b>0.56 (0.45-0.68)</b>
HHF or death from CV causes	<b>0.69 (0.57-0.83)</b>	<b>0.71 (0.55-0.92)</b>
CV death, MI, stroke	<b>0.80 (0.67-0.95)</b>	NA
HHF	<b>0.61 (0.47-0.80)</b>	NA
ESRD, doubling SCr, renal death	<b>0.66 (0.53-0.81)</b>	NA
Death from any cause	0.83 (0.68-1.02)	<b>0.69 (0.53-0.88)</b>
CV death, MI, stroke, hospitalization for HF or UA	0.74 (0.63-0.86)	NA

# ONGOING TRIALS OF SGLT2i IN CKD

Study (Year)	Number of Patients	Study Population	Agent and dose	Comparator	Primary Endpoint
EMPA-Kidney (2022)	6609	CKD (without T2DM or ASCVD)	Empagliflozin 10 mg/d	Placebo	Kidney disease progression or CV death
ZENITH-CKD (2022)	660	CKD ±DM	Dapagliflozin 10 mg/d	Zibotentan Placebo	Change in UACR
DECODED (2026)	2500	ESRD + ASCVD	Dapagliflozin 10 mg/d		CV death, MI, or ischemic stroke

# META-ANALYSIS OF CV AND RENAL OUTCOMES

Population	All-cause mortality	CV mortality	HHF	MI	Composite kidney outcome
Overall	<b>0.84</b> (0.78-0.91)	<b>0.84</b> (0.76-0.93)	<b>0.69</b> (0.64-0.74)	<b>0.91</b> (0.84-0.99)	<b>0.62</b> (0.56-0.70)
T2DM + HF	<b>0.79</b> (0.69-0.91)	<b>0.82</b> (0.70-0.96)	<b>0.71</b> (0.61-0.83)	0.92 (0.69-1.21)	<b>0.63</b> (0.45-0.89)
T2DM w/o HF	0.84 (0.68-1.03)	0.83 (0.61-1.11)	<b>0.71</b> (0.60-0.83)	0.88 (0.78-1.00)	<b>0.52</b> (0.43-0.63)
HF ± T2DM	<b>0.85</b> (0.77-0.94)	<b>0.86</b> (0.77-0.97)	<b>0.69</b> (0.62-0.76)	0.92 (0.69-1.21)	<b>0.58</b> (0.44-0.76)
T2DM + CKD	0.82 (0.67-1.00)	0.84 (0.68-1.03)	<b>0.61</b> (0.48-0.77)	<b>0.72</b> (0.54-0.97)	<b>0.68</b> (0.77-0.94)

Results reported as HR (95% confidence interval)



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# Guideline Recommendations for SGLT2i Use in HF and CKD



# PATIENT CASE 1

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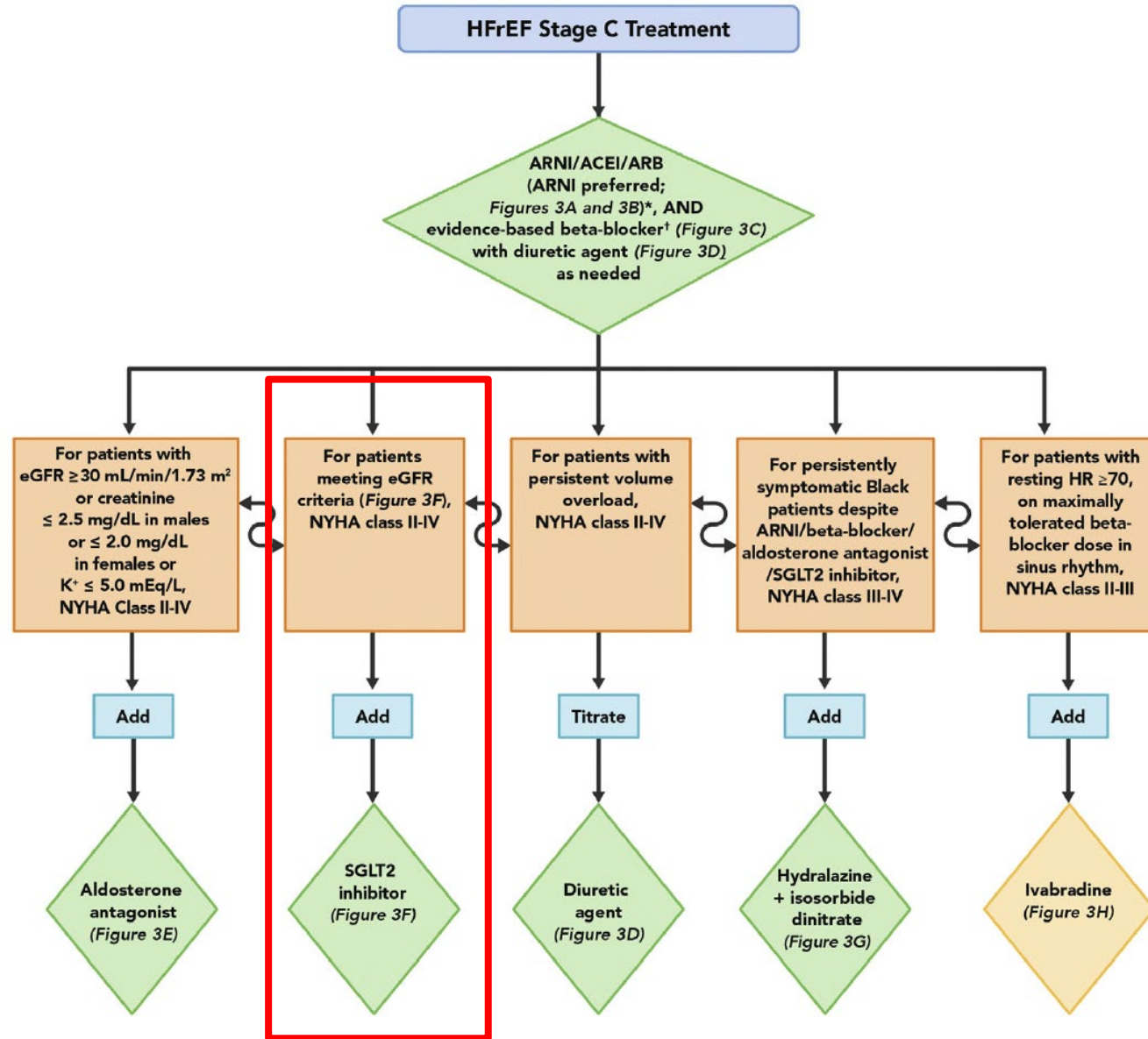
B.H. is a 65-year-old female with a past medical history significant for HTN, MI, and HFrEF (EF = 30%). She is currently taking sacubitril/valsartan 97/103 mg PO twice daily, metoprolol succinate 100 mg PO daily, furosemide 40 mg daily, atorvastatin 40 mg PO daily, and aspirin 81 mg PO daily. She has no s/s volume overload at today's visit, and her labs are within normal limits (eGFR 65 mL/min/1.73m<sup>2</sup>).

Vitals: BP 128/70 mm Hg, HR 60 bpm, weight 80 kg, BMI 29 kg/m<sup>2</sup>

1. Is this patient a candidate for SGLT2i therapy at this time?
2. If so, which SGLT2i would be reasonable to initiate?
3. What if the patient had HFpEF?



# 2021 ACC EXPERT CONSENSUS DECISION PATHWAY





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# 2021 ACC EXPERT CONSENSUS DECISION PATHWAY

- ▶ Indication
  - ▶ HFrEF (EF  $\leq$ 40%) with or without DM
  - ▶ NYHA Class II-IV
  - ▶ Administered in conjunction with background GDMT for HF
- ▶ Select dapagliflozin or empagliflozin
  - ▶ 10 mg/d
  - ▶ Starting and target dose
- ▶ Ensure eGFR  $\geq$ 30 mL/min/1.73m<sup>2</sup> for dapagliflozin
- ▶ Ensure eGFR  $\geq$  20 mL/min/1.73m<sup>2</sup> for empagliflozin

# 2021 ACC EXPERT CONSENSUS DECISION PATHWAY: CONTRAINDICATIONS AND CAUTIONS FOR SGLT2i USE

## C) SGLT2 Inhibitors

### Contraindications

- Not approved for use in patients with type I diabetes due to increased risk of diabetic ketoacidosis
- Known hypersensitivity to drug
- Lactation (no data)
- On dialysis

### Cautions

- For HF care, dapagliflozin, eGFR <30 mL/min/1.73 m<sup>2</sup>
- For HF care, empagliflozin, eGFR <20 mL/min/1.73 m<sup>2</sup>
- Pregnancy
- Increased risk of mycotic genital infections
- May contribute to volume depletion. Consider altering diuretic dose if applicable
- Ketoacidosis in patients with diabetes:
  - Temporary discontinuation before scheduled surgery is recommended to avoid potential risk for ketoacidosis
  - Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level
- Acute kidney injury and impairment in renal function: consider temporarily discontinuing in settings of reduced oral intake or fluid losses
- Urosepsis and pyelonephritis: evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated
- Necrotizing fasciitis of the perineum (Fournier's gangrene): rare, serious, life-threatening cases have occurred in both female and male patients; assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise



# PATIENT CASE 2

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K.A. is a 60-year-old male with CKD, HTN, and T2DM. He is currently taking lisinopril 40 mg PO daily, amlodipine 10 mg PO daily, chlorthalidone 25 mg PO daily, and metformin 1000 mg twice daily.

Vitals: BP 136/82 mm Hg, HR 70 bpm, weight 95 kg, BMI 33 kg/m<sup>2</sup>

Pertinent labs: A1C 8%, UACR 300 mg/g (confirmed on repeat testing), and GFR 35 mL/min/1.73m<sup>2</sup>; all other labs are within normal limits.

1. Should SGLT2i therapy be initiated in this patient?
2. If so, which SGLT2i would be reasonable to initiate?
3. What if the patient did NOT have albuminuria?

# 2020 KDIGO GUIDELINE FOR DM MANAGEMENT IN CKD

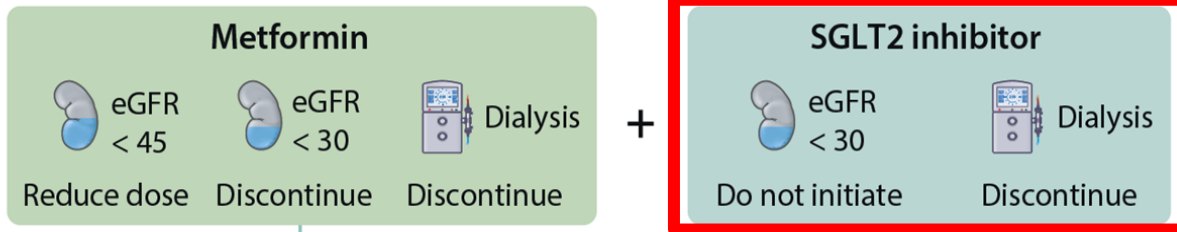


Lifestyle therapy

Physical activity  
Nutrition  
Weight loss



First-line therapy



**SGLT2i Options per KDIGO:**  
 Canagliflozin 100-300 mg/d  
 Dapagliflozin 5-10 mg/d  
 Empagliflozin 10-25 mg/d

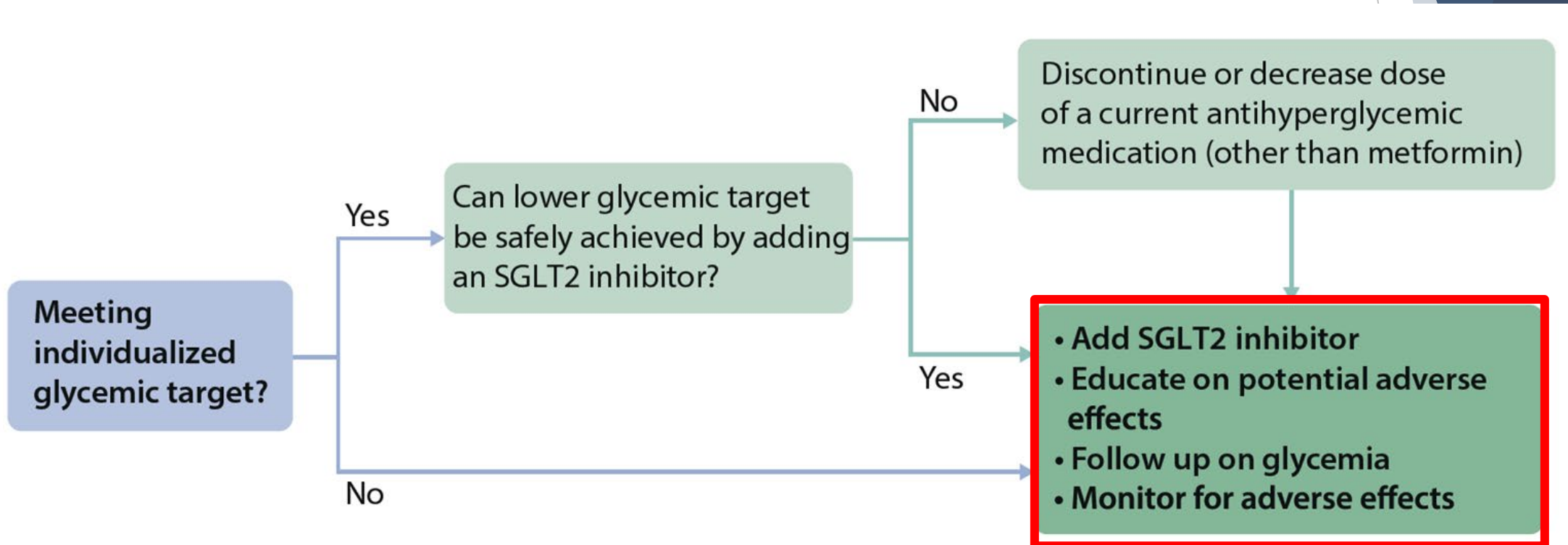


Additional drug therapy as needed for glycemic control

- GLP-1 receptor agonist (preferred)
- DPP-4 inhibitor
- Sulfonylurea
- Alpha-glucosidase inhibitor
- Insulin
- TZD

- Guided by patient preferences, comorbidities, eGFR, and cost
- Includes patients with eGFR < 30 ml/min per 1.73 m<sup>2</sup> or treated with dialysis
- See Figure 20

# 2020 KDIGO GUIDELINE FOR DM MANAGEMENT IN CKD IF ALREADY ON ANTIHYPERGLYCEMIC AGENTS





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# 2020 KDIGO GUIDELINE FOR DM MANAGEMENT IN CKD ADDITIONAL RECOMMENDATIONS

- ▶ The choice of an SGLT2i should prioritize agents with documented kidney or CV benefits and take eGFR into account.
- ▶ It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when patients may be at greater risk for ketosis).
- ▶ If a patient is at risk for hypovolemia, consider decreasing thiazide or loop diuretic dosages before commencement of SGLT2i treatment, advise patients about symptoms of volume depletion and low blood pressure, and follow up on volume status after drug initiation.



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# 2020 KDIGO GUIDELINE FOR DM MANAGEMENT IN CKD ADDITIONAL RECOMMENDATIONS

- ▶ A reversible decrease in the eGFR with commencement of SGLT2i treatment may occur and is generally not an indication to discontinue therapy.
- ▶ Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 30 ml/min per 1.73 m<sup>2</sup>, unless it is not tolerated or kidney replacement therapy is initiated.
- ▶ SGLT2i have not been adequately studied in kidney transplant recipients, who may benefit from SGLT2i treatment, but are immunosuppressed and potentially at increased risk for infections; therefore, the recommendation to use SGLT2i does not apply to kidney transplant recipients.



SGLT2i Dose range	eGFR 30 to <60 mL/min/1.73m <sup>2</sup>	eGFR <30 mL/min/1.73m <sup>2</sup>
Canagliflozin 100-300 mg/d	100 mg/d	<p>UACR &gt;300: if previously on 100 mg/d, may continue.</p> <p>UACR ≤300: manufacturer labeling does not recommend use, but some experts use 100 mg/d off label.</p>
Dapagliflozin 5-10 mg/d	<p>No adjustment if eGFR ≥45.</p> <p>30 to &lt;45: DM: do not recommend use</p> <p>HF: no adjustment needed</p> <p>DKD/CKD: no adjustment needed</p>	<p>DM: use is CI</p> <p>HF: U.S. manufacturer states insufficient evidence to support dosage recommendation.</p> <p>DKD/CKD: no adjustment if GFR ≥25; not studied in patients with eGFR &lt;25.</p>
Empagliflozin 10-25 mg/d	<p>U.S. manufacturer recommends to not initiate if eGFR&lt;45.</p> <p>Should not be used for glucose benefit if eGFR&lt;45.</p>	<p>Manufacturer states CI.</p> <p>In patients previously on empagliflozin, some experts use off label at 10 mg/d for DKD.</p> <p>Renal and cardiac benefits shown to eGFR ≥20.</p>
Ertugliflozin 5-15 mg/d	Not recommended for initiation or continued use	CI

# SAFETY OF SGLT2i

- ▶ Mycotic genital infections
  - ▶ Associated with increased risk (OR 3.95, 95% CI 3.01-5.18)
  - ▶ Most mild and responded to standard therapy
  - ▶ Rarely led to treatment d/c
  - ▶ Evaluate patients who c/o groin redness, swelling, and pain
- ▶ Euglycemic ketoacidosis
  - ▶ Associated with increased risk (OR 2.86, 95% CI 1.39-5.86)
  - ▶ Measuring beta-hydroxybutyrate recommended if DKA diagnosis is in doubt
  - ▶ Stop if DKA diagnosed and 24 hours before elective surgery
  - ▶ Avoid alcohol, prolonged fasting, very low carb or ketogenic diets while on therapy



# SAFETY OF SGLT2i

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- ▶ Hypoglycemia
  - ▶ Not associated with greater risk (OR 0.92; 95% CI 0.84-1.01)
- ▶ Amputation
  - ▶ Not associated with greater risk overall (OR 1.25, 95% CI 0.97-1.62)
  - ▶ Canagliflozin is associated with higher risk
    - ▶ D/C if infection (including osteomyelitis), new pain/tenderness, or sores/ulcers involving lower limbs
  - ▶ Consider risk factors, counsel patients on preventative foot care
- ▶ Bone fracture
  - ▶ Not associated with greater risk overall (HR 1.04, 95% CI 0.91-1.18)
- ▶ Hypotension
  - ▶ Assess volume status prior to initiation
  - ▶ Continue to monitor BP while on therapy

Curr Cardiol Rep 2021;23:59.  
Am Heart J 2021;232:10-22.  
Diabetes Ther 2021;12:55-70.



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# SUMMARY COMPARISON OF SGLT2i USE

Medication	ASCVD	HF	CKD
Canagliflozin (Invokana)	X (FDA Indication)	X (Off label, data from CVOTs)	X (FDA Indication)
Dapagliflozin (Farxiga)		X (FDA Indication)	X (FDA Indication)
Empagliflozin (Jardiance)	X (FDA Indication)	X (Off label, but primary HF data)	X (Off label, data from DM CVOTs)
Ertugliflozin (Steglatro)		X (Off label, data from CVOTs)	

# SUMMARY AND TAKE HOME POINTS

- ▶ SGLT2i therapy has been proven to reduce HHF and progression of CKD
- ▶ People with HF or CKD should be evaluated for initiation of SGLT2i therapy
  - ▶ HF: with or without concomitant T2DM
  - ▶ CKD: with concomitant T2DM
- ▶ Therapy should include GDMT prior to initiation of SGLT2i
- ▶ Medication selection and dosing depends on medication, indication, and eGFR



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# QUESTIONS?

Thank you for attending this AUHSOP continuing education program. The Attendance Code for this program is \_\_\_\_\_. Participants must enter the attendance code to advance to the program evaluation page within the course.

Please direct any questions to: [hsopce@auburn.edu](mailto:hsopce@auburn.edu)



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