A FLUID SHIFT: INTEGRATING SGLT-2 INHIBITORS INTO STANDARD HEART FAILURE CARE

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Disclosures

- Financial: None
- I intend to reference unlabeled/unapproved uses of drugs or products in my presentation.

Objectives

Pharmacist:

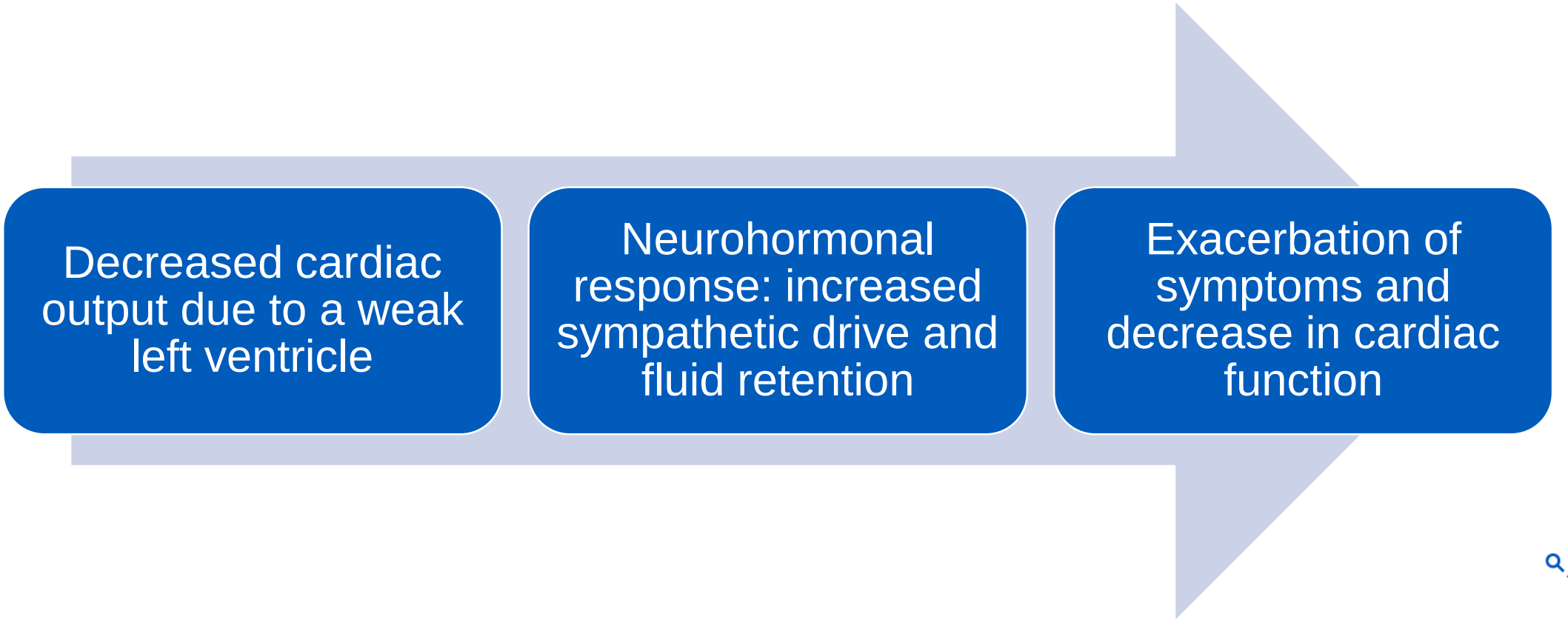
1. Describe the role of SGLT-2 inhibitors in the treatment of heart failure with reduced ejection fraction
2. Select appropriate patients for initiation of an SGLT-2 inhibitor
3. Navigate barriers to SGLT-2 initiation
4. Design an implementation and monitoring plan for SGLT-2 initiation in a patient with HFrEF

Technician:

1. Recognize SGLT-2 inhibitors that can be used for patients with heart failure
2. Identify key laboratory values that need to be assessed for SGLT-2 inhibitor initiation
3. Execute a plan to navigate cost barriers for SGLT-2 inhibitors

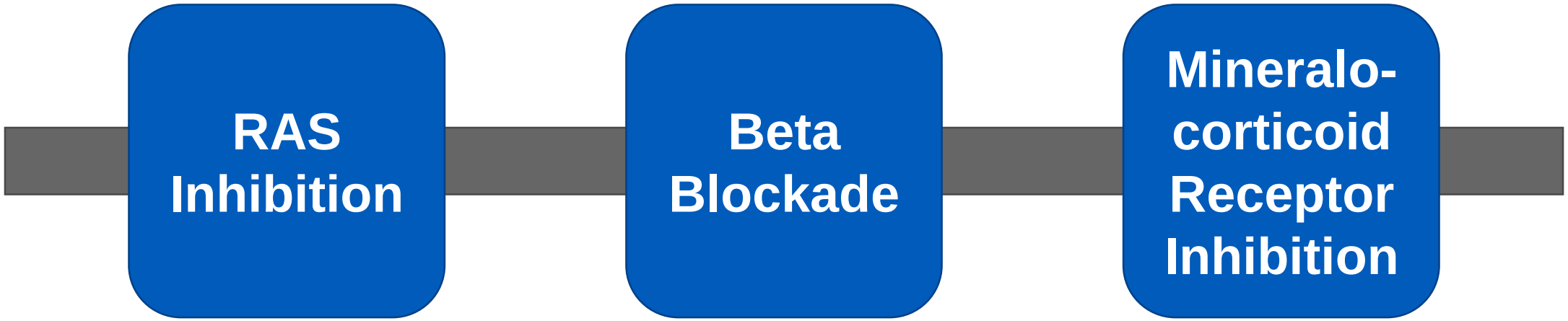
SGLT-2: Sodium-glucose co-transporter-2

Heart Failure with Reduced Ejection Fraction (HFrEF)



J Am Coll Cardiol. 70 (6) 776–803

Guideline directed medical therapy (GDMT)



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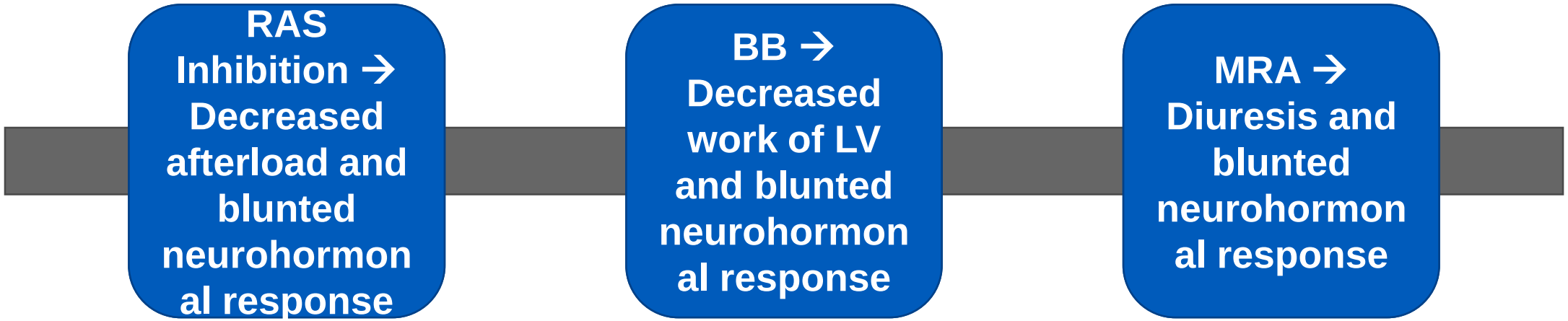
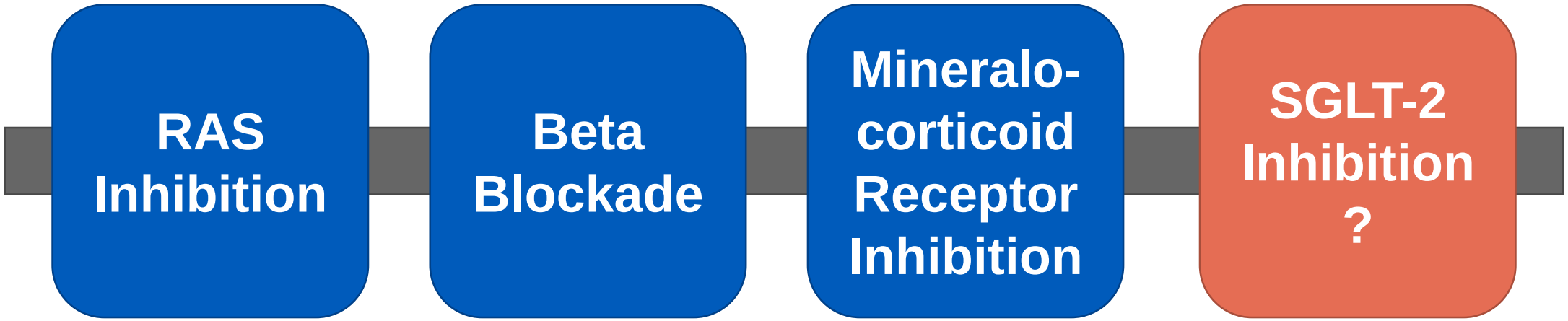
RAS: renin angiotensin system

Guideline directed medical therapy (GDMT)



J Am Coll Cardiol. 70 (6) 776–803
RAS: renin angiotensin system; BB: beta-blocker; MRA: mineralocorticoid receptor antagonist

New backbone of heart failure care?



N Engl J Med 381;21. N Engl J Med 383;15. Lancet 2020; 396:819-29.

RAS: renin angiotensin system; SGLT-2: sodium-glucose co-transporter

Case JB

- JB is a 63 year old female with a history coronary artery disease (CAD), heart failure with reduced ejection fraction (HFrEF), and anxiety. She presents to her primary care physicians (PCP) office for her annual visit.

Home medications:

- Aspirin 81 mg daily
- Atorvastatin 80 mg daily
- Metoprolol succinate 50 mg daily
- Lisinopril 20 mg daily
- Spironolactone 25 mg daily
- Furosemide 40 mg daily
- Sertraline 50 mg daily

Vitals and pertinent labs:

- Blood pressure (BP): 112/72 mm Hg
- HR: 74 beats per minute (bpm)
- eGFR: 50 mL/min/1.73 m^2
- Serum creatinine: 1.4 mg/dL (baseline 1.5)
- Sodium: 136 mEq/L
- Potassium: 4.2 mEq/L

Case JB

- JB is a 63 year old female with a history coronary artery disease (CAD), heart failure with reduced ejection fraction (HFrEF), and anxiety. She presents to her primary care physicians (PCP) office for her annual visit.

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- Potassium: 4.2 mEq/L

Case JB

What medication regimen change could optimize JB's heart failure care?

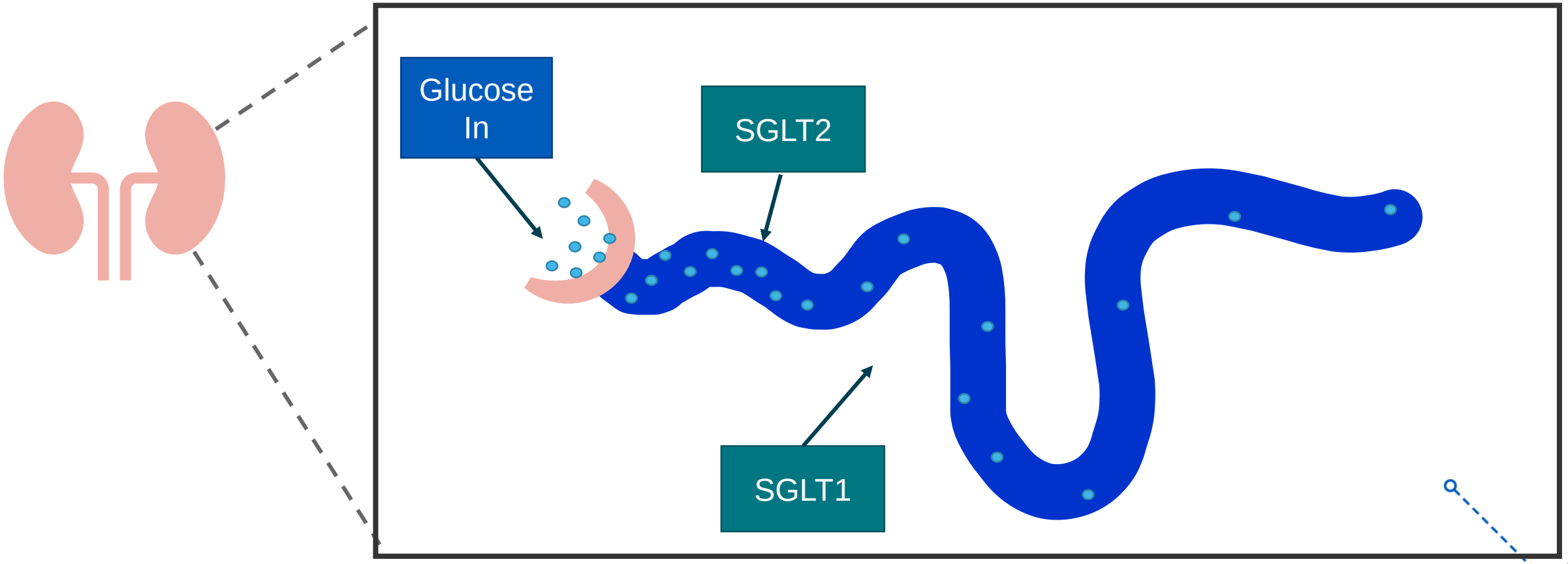
A. Addition of dapagliflozin 10 mg daily

B. Addition of canagliflozin 100 mg daily

C. Increase furosemide to 80 mg daily

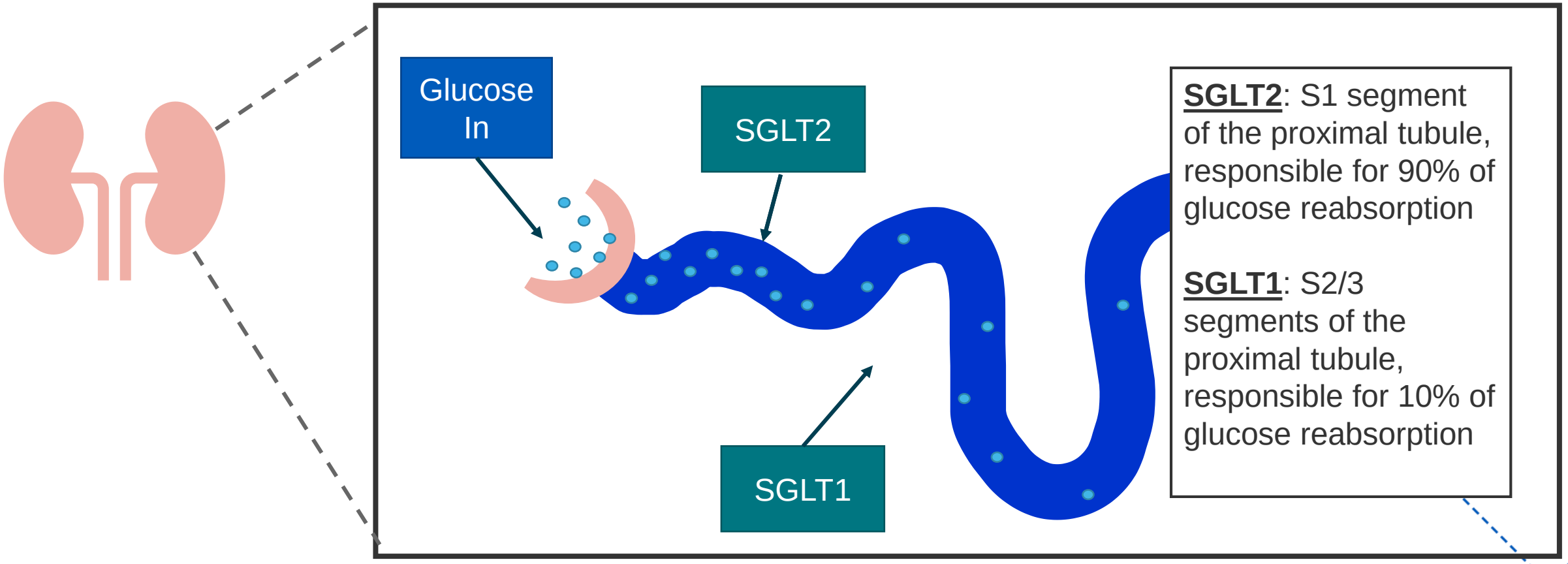
D. Add tolvaptan 15 mg daily

SGLT-2 Inhibitors: Mechanism of Action



Diabetologia. 61(10):2108-2117.
SGLT: Sodium-glucose co-transporter

SGLT-2 Inhibitors: Mechanism of Action



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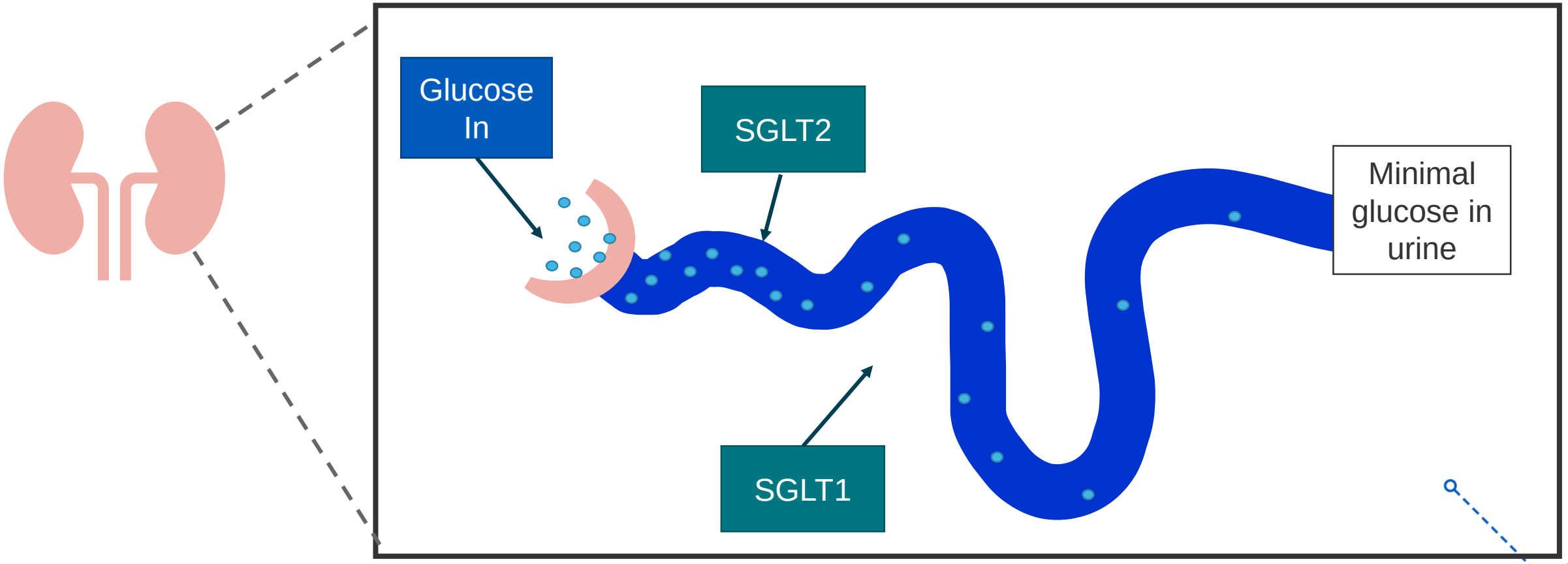

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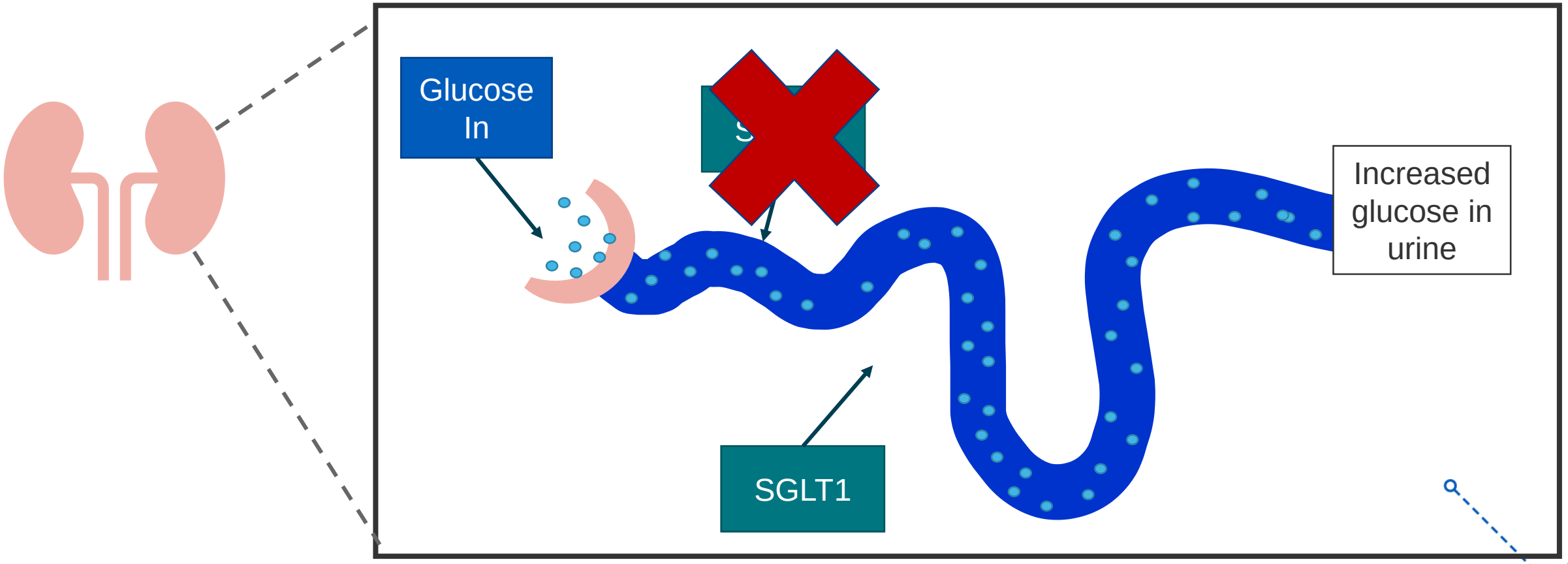

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SGLT: Sodium-glucose co-transporter

Cardiovascular Outcomes Studies

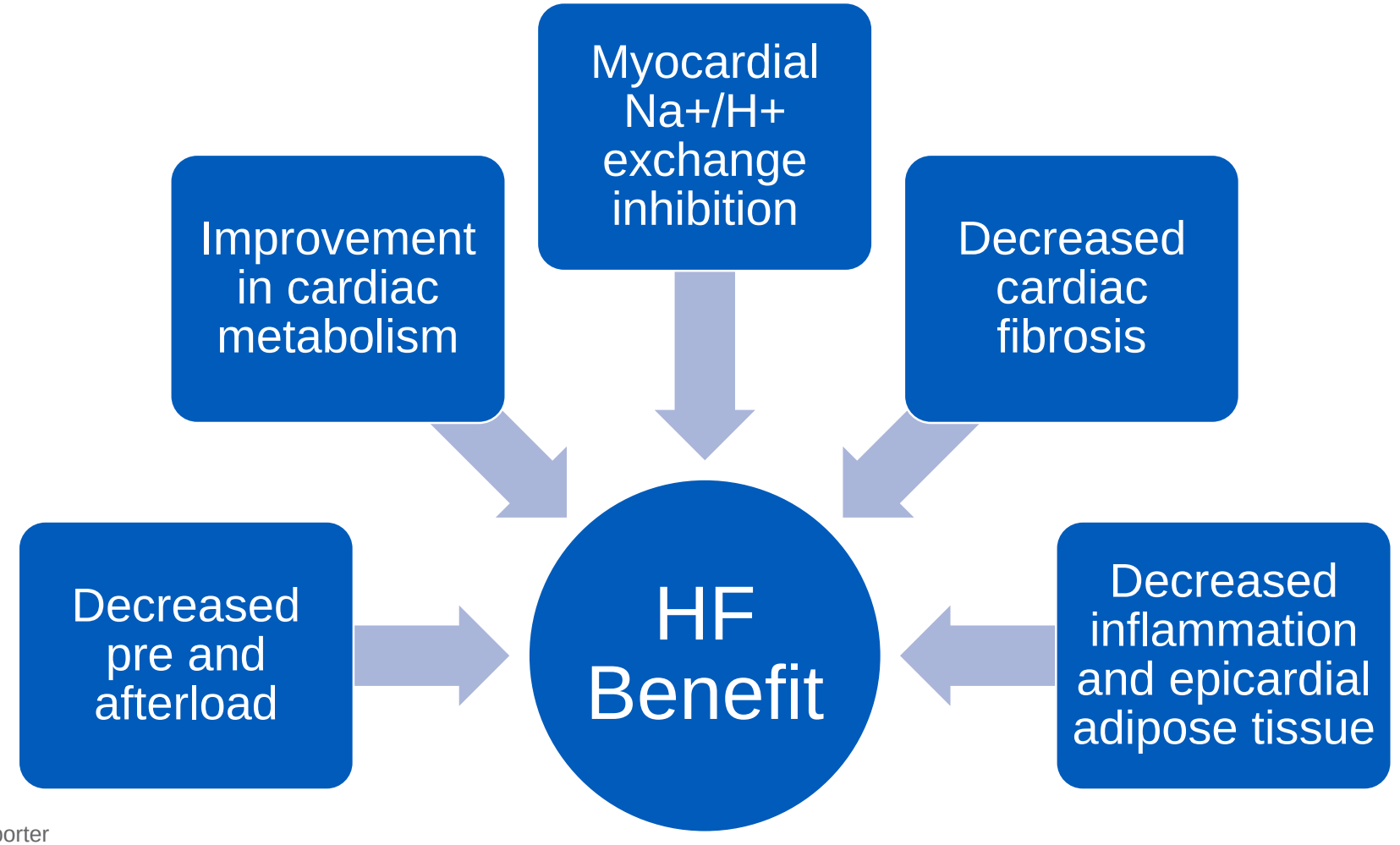
Study	n	Design	MACE Outcome	CV Death	HF Hospitalization
EMPA-REG OUTCOME 2015	7020	RDBPCT	Empagliflozin: 490 (10.5%) Placebo: 282 (12.1%) HR: **0.86** (95% CI 0.74-0.99); p<0.001 NI and 0.04 SP	Empagliflozin: 172 (3.7%) Placebo: 137 (5.9%) HR: **0.62** (95% CI 0.49-0.77); p<0.001	Empagliflozin: 126 (2.7%) Placebo: 95 (4.1%) HR: **0.65** (95% CI 0.50-0.85); p=0.002
CANVAS Program 2017	10142	RDBPCT	Canagliflozin: 29.6/1000 PY Placebo: 31.5/1000 PY HR: **0.86** (95% CI 0.75-0.97); p<0.001 NI and 0.02 SP	Canagliflozin: 11.6/1000 PY Placebo: 12.8/1000 PY HR: 0.87 (95% CI 0.72-1.06)^	Canagliflozin: 5.5/1000 PY Placebo: 8.7/1000 PY HR: **0.67** (95% CI 0.52-0.87)^
DECLARE-TIMI 58 2018	17160	RDBPCT	Dapagliflozin: 756 (8.8%) Placebo: 803 (9.4%) HR: 0.93 (95% CI 0.84-1.03); p<0.001 NI and p=0.17 SP	Dapagliflozin: 245 (2.9%) Placebo: 249 (2.9%) HR: 0.98 (95% CI 0.82-1.17)	Dapagliflozin: 212 (2.5%) Placebo: 286 (3.3%) HR: **0.73** (95% CI 0.61-0.88)
VERTIS CV 2020	8246	RDBPCT	Ertugliflozin: 653 (11.9%) Placebo: 327 (11.9%) HR: 0.97 (95% CI 0.85-1.11); p<0.001 NI	Ertugliflozin: 341 (6.2%) Placebo: 184 (6.7%) HR: 0.92 (95% CI 0.77-1.11)^	Ertugliflozin: 139 (2.5%) Placebo: 99 (3.6%) HR: **0.70** (95% CI 0.54-0.90)^

CV = cardiovascular; HF = heart failure; HR = hazard ratio; MACE = Major adverse cardiovascular event; NI = non-inferiority; PY = patient years; RDBPCT = Randomized, double-blind, placebo-controlled trial; SP = superiority

^ Exploratory

N Engl J Med 373;22. N Engl J Med 377;7. N Engl J Med 380;4. N Engl J Med 383;15.

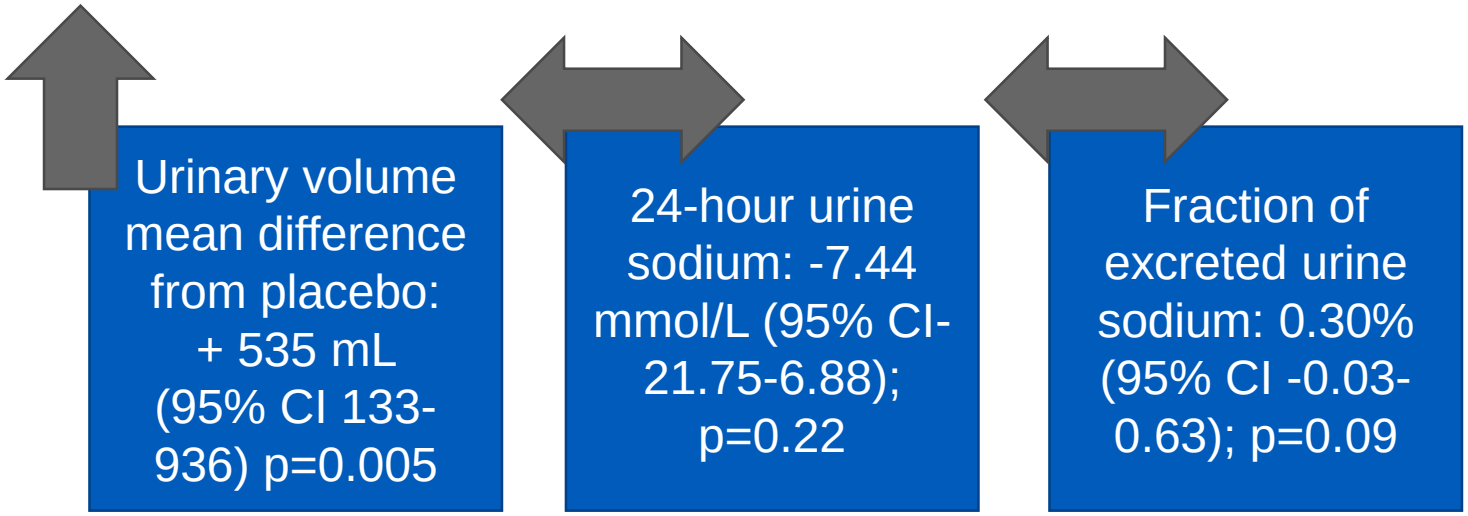
SGLT-2 Inhibitors: *Proposed* Mechanism(s) of Action for HF Benefit



Diabetologia. 61(10):2108-2117.
SGLT: Sodium-glucose co-transporter

RECEDE-CHF Trial: Day 3

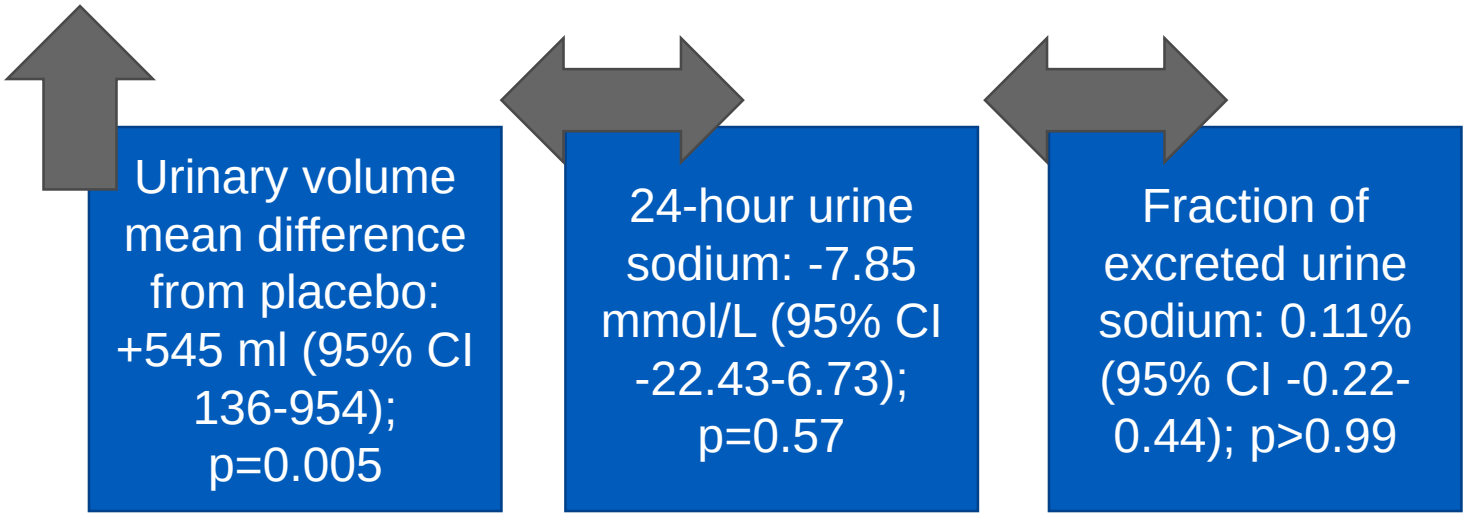
- Randomized, double-blind, placebo controlled, crossover trial
  - Empagliflozin 25 mg daily or placebo
- Patients: Type II diabetes mellitus + HFrEF taking a loop diuretic



Increase in urine output without an increase in amount or fraction of sodium excreted at 3 days

Circulation 142: 1713.

RECEDE-CHF Trial: Week 6



Similar outcomes on day 3 and week 6:

- Diuretic effect WITHOUT high risk for hyponatremia
- May provide selective reduction in interstitial rather than intravascular fluid

Circulation 142: 1713.

DAPA-HF Trial

Title/Citation	McMurray, John JV, et al. "Dapagliflozin in patients with heart failure and reduced ejection fraction." New England Journal of Medicine 381.21 (2019): 1995-2008.
Funding	AstraZeneca
Trial Design	Randomized, double blind, placebo controlled trial
Null Hypothesis	There is no difference between dapagliflozin and placebo on rate worsening heart failure or death from cardiovascular (CV) causes

N Engl J Med 381;21

DAPA-HF: Methods

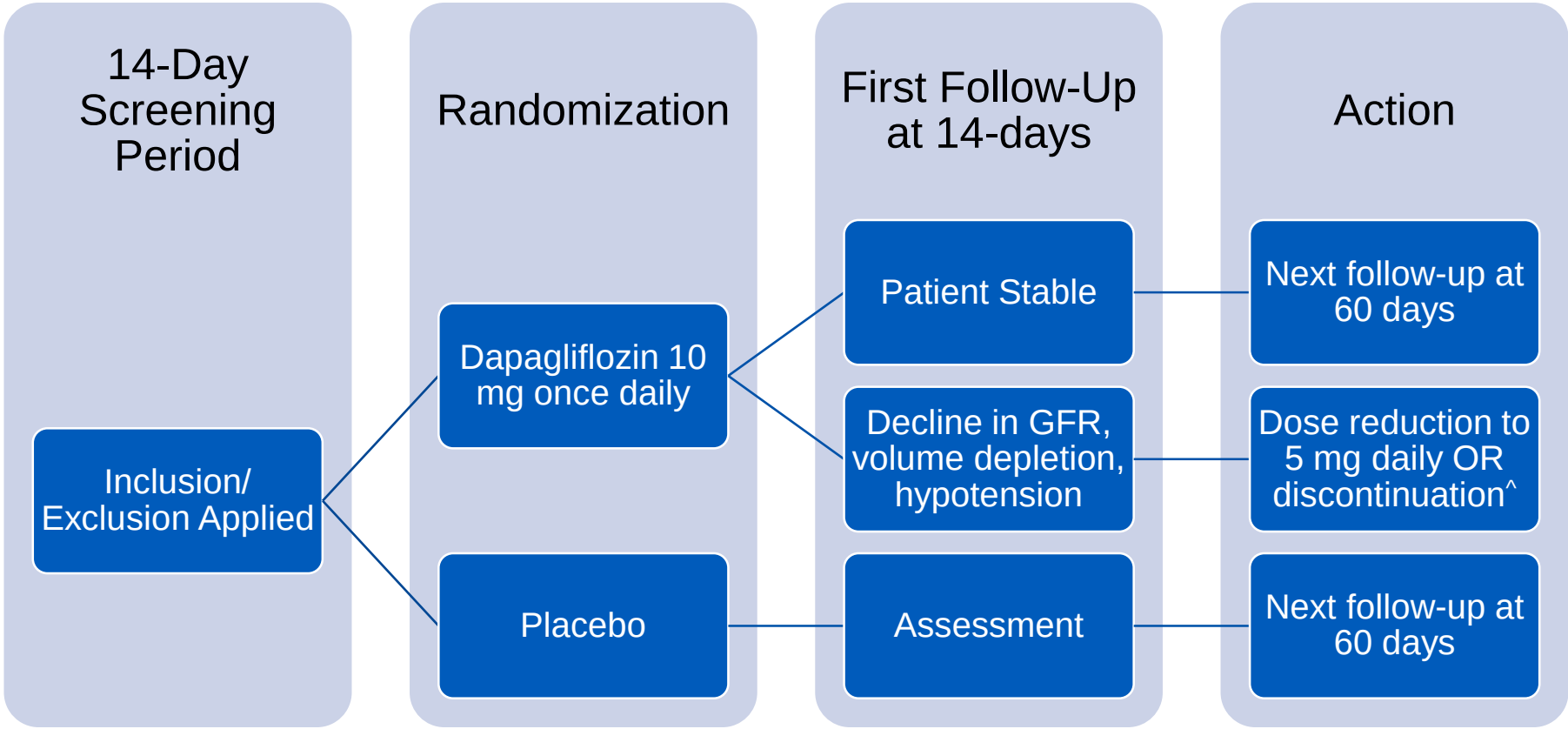
- Enrollment:

Inclusion Criteria	Exclusion Criteria
• 18 years old • EF ≤ 40% • NYHA II-IV • NT-proBNP 600 pg/mL • Receiving GDMT	• Recent treatment with SGLT2 inhibitor • Type 1 diabetes • Symptomatic hypotension or SBP < 95 mm Hg • GFR < 30 mL/min/1.73 m2 of BSA

GFR: glomerular filtration rate; EF: ejection fraction; GDMT = guideline directed medical therapy; NT-proBNP: N-terminal-pro B-type natriuretic peptide; NYHA: New York Heart Association SBP: systolic blood pressure; SGLT-2: sodium-glucose co-transporter-2

N Engl J Med 381;21

DAPA-HF: Intervention and Monitoring



^ Subsequent increase in dose or reinitiation of treatment if possible

GFR: glomerular filtration rate

N Engl J Med 381;21

DAPA-HF: Endpoints

Primary Outcome

- Composite: worsening HF or CV death
  - Worsening HF = unplanned hospitalization or an urgent visit resulting in IV therapy for heart failure

Secondary Outcomes

- Composite: HF hospitalization or CV death
  - Each component alone
- KCCQ: change from baseline to 8 months
- Composite: worsening renal function, end stage renal disease, or renal death

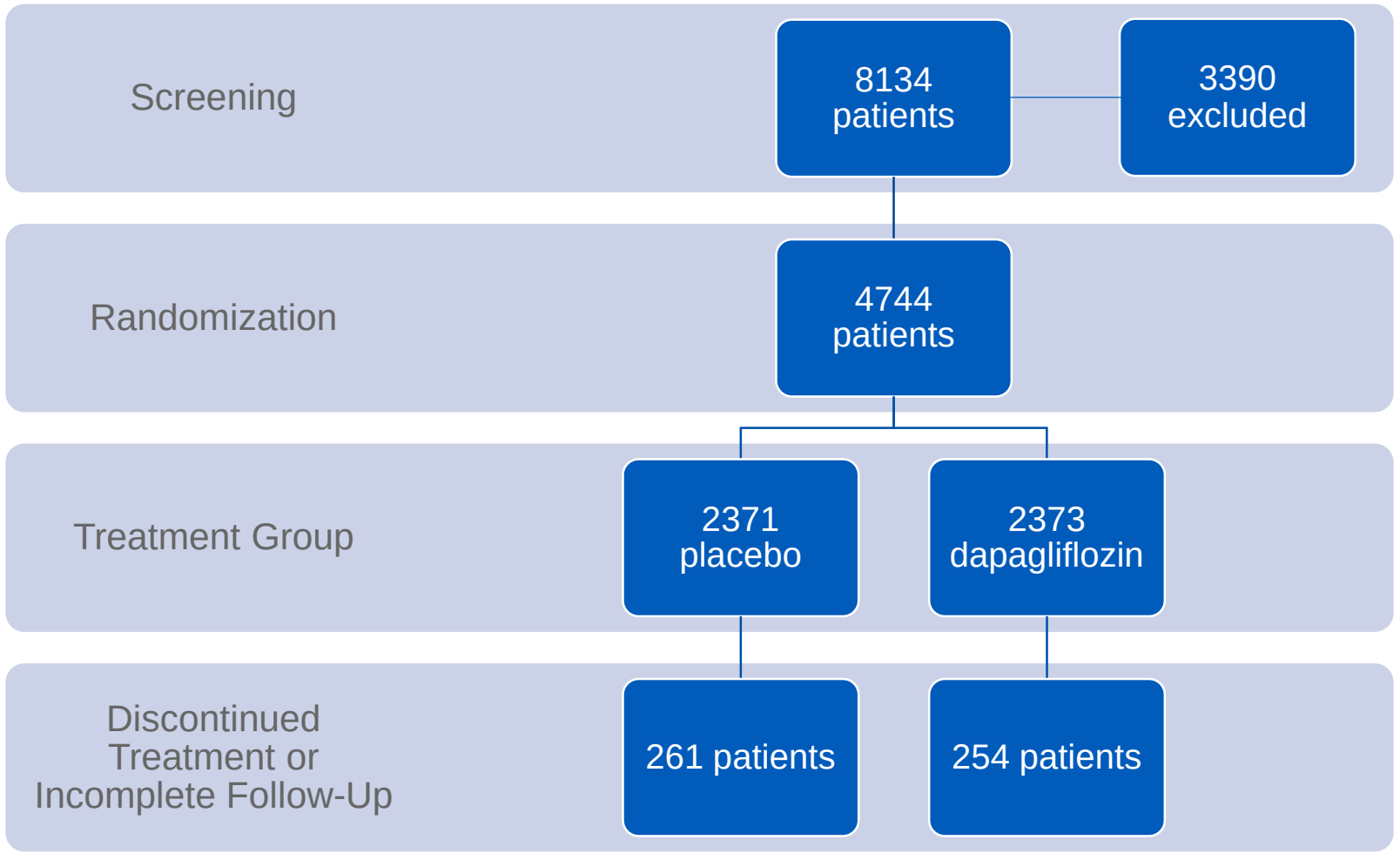
Safety Outcomes

- Serious adverse events

CV: cardiovascular; HF: heart failure; IV: Intravenous; KCCQ: Kansas city cardiomyopathy questionnaire

N Engl J Med 381;21

DAPA-HF: Results



Reasons for Exclusion:

12 died

15 adverse event

84 declined

3279 did not meet eligibility criteria

N Engl J Med 381;21

DAPA-HF: Baseline Characteristics

Characteristic	Dapagliflozin (n=2373)	Placebo (n=2371)
Age (years), mean ± SD	66.2 ± 11.0	66.5 ± 10.8
Female sex, n (%)	564 (23.8)	545 (23.0)
NYHA Class, n (%) II III IV	 1606 (67.7) 747 (31.5) 20 (0.8)	 1597 (67.4) 751 (31.7) 23 (1.0)
Ejection Fraction (%), mean ± SD	31.2 ±6.7	30.9 ± 6.9
NT-proBNP (pg/mL), median (IQR)	1428 (857-2655)	1446 (857-2641)
Medical History, n (%) HF Hospitalization Atrial Fibrillation Type II Diabetes mellitus	 1124 (47.4) 916 (38.6) 993 (41.8)	 1127 (47.5) 902 (38.0) 990 (41.8)

HF = heart failure; IQR = interquartile range; NYHA = New York Heart Association; SD = standard deviation

DAPA-HF: Clinical Outcomes

Outcome	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)	p-value
Primary Composite Outcome, n (%)	386 (16.3)	502 (21.2)	0.74 (0.65-0.85)	<0.001
Worsening HF	237 (10.0)	326 (13.7)	0.70 (0.59-0.83)	
HF Hospitalization	231 (9.7)	318 (13.4)	0.70 (0.59-0.83)	
Urgent HF Visit	10 (0.4)	23 (1.0)	0.43 (0.20-0.90)	
CV Death	227 (9.6)	273 (11.5)	0.82 (0.69-0.98)	
Change in KCCQ Score, mean ± SD	6.1 ± 18.6	3.3 ± 19.2	1.18 (1.11-1.26)	<0.001
Worsening Renal Function, n (%)	28 (1.2)	39 (1.6)	0.71 (0.44-1.16)	NA

CV = cardiovascular; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionairre; SD = standard deviation

N Engl J Med 381;21

DAPA-HF: Safety Outcomes

Outcome	Dapagliflozin (n=2368)	Placebo (n=2368)	p-value
Discontinuation for adverse event, n (%)	111 (4.7)	116 (4.9)	0.79
Volume depletion, n (%)	178 (7.5)	162 (6.8)	0.40
Renal adverse event, n (%)	153 (6.5)	170 (7.2)	0.36
Fracture, n (%)	49 (2.1)	50 (2.1)	1.00
Amputation, n (%)	13 (0.5)	12 (0.5)	1.00
Major hypoglycemia, n (%)	4 (0.2)	4 (0.2)	NA
Diabetic ketoacidosis, n (%)	3 (0.1)	0	NA
Urinary tract infection, n (%)	11 (0.5)	17 (0.7)	NA
Fournier’s gangrene, n (%)	0	1 (< 0.1)	NA

N Engl J Med 381:21

DAPA-HF: Subgroup Analyses

Type II Diabetes at Baseline	• No difference
Age	• No difference in those less than or equal compared to greater than 65
NYHA Class	• Performed better in patients with NYHA class II compared to III and IV • Class II: HR 0.63 (95% CI 0.52-0.75) • Class III and IV: HR 0.90 (95% CI 0.74-1.09)
Baseline eGFR	• No difference in those less than or equal compared to greater than 60 mL/min/1.73m^2

eGFR: estimated glomerular filtration rate; HF: Hazard ratio; NYHA: New York Heart Association

N Engl J Med 381;21

DAPA-HF: Author's Conclusion

- Worsening heart failure and death from CV causes occurred less frequently in patients with dapagliflozin treatment compared to placebo
- Dapagliflozin resulted in fewer HF symptoms than placebo as assessed by KCCQ
- Benefits occurred in patients with and without type II diabetes

CV: Cardiovascular; HF: Heart failure; KCCQ: Kansas city cardiomyopathy questionnaire
N Engl J Med 381;21

EMPEROR-Reduced Trial

Title/Citation	Packer, Milton, et al. "Cardiovascular and renal outcomes with empagliflozin in heart failure." New England Journal of Medicine 383.15 (2020): 1413-1424.
Funding	Boehringer Ingelheim and Eli Lilly
Trial Design	Randomized, double blind, placebo controlled trial
Null Hypothesis	There is no difference between empagliflozin and placebo on rate heart failure hospitalization or cardiovascular death

N Engl J Med 383:15

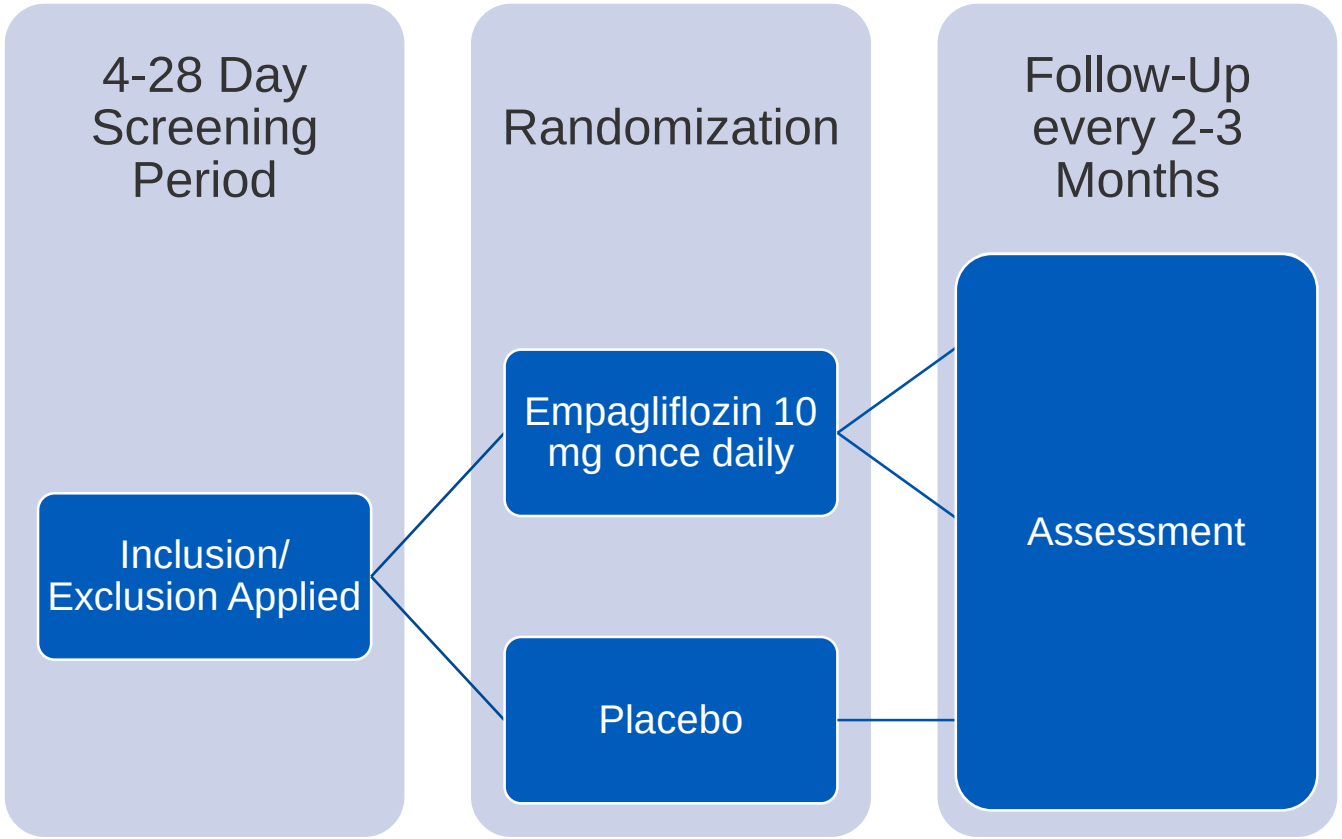
EMPEROR-Reduced: Methods

- Enrollment:

Inclusion Criteria	Exclusion Criteria
• 18 years old • EF ≤ 40% • NYHA II-IV • Receiving GDMT • HF hospitalization within 1 year or particularly high NT-proBNP levels	• Recent treatment with SGLT2 inhibitor • Symptomatic hypotension or SBP < 100 mm Hg • eGFR < 20 mL/min/1.73m^2

EF: ejection fraction; eGFR: estimated glomerular filtration rate; GDMT: guideline directed medical therapy; HF: heart failure; NYHA: New York Heart Association;
N Engl J Med 383;15

EMPEROR-Reduced: Intervention and Monitoring



N Engl J Med 383:15

EMPEROR-Reduced: Endpoints

Primary Outcome	• Composite: hospitalization for heart failure or CV death
Secondary Outcomes	• Composite: HF hospitalization or CV death • Each component alone • Rate of decline in the estimated GFR
Safety Outcomes	• Serious adverse events

CV: cardiovascular; HF: heart failure

N Engl J Med 383;15

EMPEROR-Reduced: Baseline Characteristics

Characteristic	Empagliflozin (n=1863)	Placebo (n=1867)
Age (years), mean ± SD	67.2 ± 10.8	66.5 ± 11.2
Female sex, n (%)	437 (23.5)	456 (24.4)
NYHA Class, n (%) II III IV	 1399 (75.1) 455 (24.4) 9 (0.5)	 1401 (75.0) 455 (24.4) 11 (0.6)
Ejection Fraction, mean ± SD	27.7 ± 6.0	27.2 ± 6.1
NT-proBNP (pg/mL), median (IQR)	1887 (1077-3429)	1926 (1153-3525)
Medical History, n (%) HF Hospitalization Atrial Fibrillation Type II Diabetes mellitus	 577 (31.0) 664 (35.6) 927 (49.8)	 574 (30.7) 705 (37.8) 929 (49.8)
GFR (mL/min/1.73 m^2), mean ± SD	61.8 ± 21.7	62.2 ± 21.5

GFR = glomerular filtration rate; HF = heart failure; NYHA = New York Heart Association; SD = standard deviation

EMPEROR-Reduced: Clinical Outcomes

Outcome	Empagliflozin (n=1863)	Placebo (n=1867)	HR (95% CI)	p-value
Primary Composite Outcome, n (%) Hospitalization for HF CV Death	361 (19.4) 246 (13.2) 187 (10.0)	462 (24.7) 342 (18.3) 202 (10.8)	0.75 (0.65-0.86) 0.69 (0.59-0.81) 0.92 (0.75-1.12)	<0.001
Mean Slope of Change in eGFR (mL/min/1.73 m^2/year), mean ± SD	-0.55 ± 0.23	-2.28 ± 0.23	1.73 (1.10-2.37)	<0.001
Change in KCCQ Score, mean ± SD	5.8 ± 0.4	4.1 ± 0.4	1.7 (0.5-3.0)	NA

CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; SD = standard deviation

N Engl J Med 383:15

EMPEROR-Reduced: Safety Outcomes

Outcome	Empagliflozin (n=1863)	Placebo (n=1867)
Discontinuation, n (%)	303 (16.3)	335 (18.0)
Volume depletion, n (%)	197 (10.6)	184 (9.9)
Fracture, n (%)	45 (2.4)	42 (2.3)
Amputation, n (%)	13 (0.7)	10 (0.5)
Major hypoglycemia, n (%)	27 (1.4)	28 (1.5)
Diabetic ketoacidosis, n (%)	0 (0)	0 (0)
Urinary Tract Infections, n (%)	91 (4.9)	83 (4.5)
Complicated	19 (1.0)	15 (0.8)
Genital Infections, n (%)	31 (1.7)	12 (0.6)
Complicated	6 (0.3)	5 (0.3)

N Engl J Med 383:15

EMPEROR-Reduced: Subgroup Analyses

Type II Diabetes at Baseline	• No difference
Age	• No difference in those less than or equal compared to greater than 65

NYHA Class	• Performed better in patients with NYHA class II compared to III and IV
	  • Class II: HR 0.71 (95% CI 0.59-0.84)
	  • Class III and IV: HR 0.83 (95% CI 0.66-1.04)

Baseline eGFR	• No difference in those less than or equal compared to greater than 60 mL/min/1.73m^2

CI: confidence interval; HR: Hazard ratio; NYHA: New York Heart Association
N Engl J Med 383;15

EMPEROR-Reduced: Author's Conclusion

- Heart failure hospitalizations and CV death occurred less frequently in patients with empagliflozin treatment compared to placebo, mainly driven by a reduction in HF hospitalizations
- Use of empagliflozin did not result in fewer HF symptoms than placebo as assessed by KCCQ
- Benefits occurred in patients with and without type II diabetes

CV: Cardiovascular; HF: Heart failure; KCCQ: Kansas city cardiomyopathy questionnaire
N Engl J Med 383;15

Bottom Line: SGLT2-Inhibitors in HFrEF

- 13% **REDUCTION** in all-cause death
- 14% **REDUCTION** in CV death
- 26% **REDUCTION** in HF hospitalizations

Lancet 2020; 396:819-29.

Patient Selection

- Utilize criteria from randomized controlled trials:
  - Ejection fraction ≤ 40%
  - NYHA class II-IV
    - Probably sooner/lower stages = better outcomes!
  - Hemodynamically stable
  - Regardless of other GDMT?
    - New ACC guidance suggests other GDMT should be initiated first

Presence or absence of TIIDM should NOT be a factor in this decision!

GDMT: guideline directed medical therapy; NYHA: New York Heart Association; TIIDM: type II diabetes mellitus

Patient Selection

- Contraindications
  - Not approved in type I diabetes
  - Lactation (no data)
  - Dialysis

Dosing

- Study dosing: 10 mg once daily for both dapagliflozin and empagliflozin
- Renal cut-offs:
  - Dapagliflozin: eGFR ≥ 30 mL/min/1.73 m^2
  - Empagliflozin: eGFR ≥ 20 mL/min/1.73 m^2
- Important notes:
  - DAPA-CKD trial: Dapagliflozin 10 mg daily was utilized in patients with an eGFR down to 25 mL/min/1.73 m^2 which resulted in superior renal outcomes than placebo

eGFR: estimated glomerular filtration rate

N Engl J Med 381;21; N Engl J Med 383;15; N Engl J Med 2020; 383:1436-1446

Patient Selection: NYHA Class

NYHA Class II

Study	HR (95% CI)
DAPA-HF	0.63 (0.52-0.75)
EMPEROR-Reduced	0.71 (0.59-0.84)
Meta Analysis	0.67 (0.59-0.76)

NYHA Class III-IV

Study	HR (95% CI)
DAPA-HF	0.90 (0.74-1.09)
EMPEROR-Reduced	0.83 (0.66-1.04)
Meta Analysis	0.87 (0.75-1.01)

SGLT-2 inhibitors appear to have more reduction in the composite of first hospitalization for HF or CV death in patients with NYHA Class II HF compared to higher classes

CI: confidence interval; CV: cardiovascular; HF: heart failure; HR: hazard ratio; NYHA: New York Heart Association; SGLT-2: sodium-glucose co-transporter-2

N Engl J Med 381;21. N Engl J Med 383;15. Lancet 2020; 396:819-29.

Patient Selection: Order of Initiation

DAPA-HF

GDMT	n (%)
ACEI/ARB/ARNI	2257 (95.1)
Beta-Blocker	2278 (96.0)
MRA	1696 (71.5)

EMPEROR-Reduced

GDMT	n (%)
ACEI/ARB/ARNI	1654 (88.8)
Beta-Blocker	1765 (94.7)
MRA	1306 (70.1)

Almost all patients initiated on an SGLT-2 inhibitor were on GDMT at baseline

ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, ARNI: angiotensin receptor blocker/neprilysin inhibitor, GDMT: guideline-directed medical therapy; MRA: mineralocorticoid receptor antagonist; SGLT-2: sodium-glucose co-transporter-2

N Engl J Med 381;21. N Engl J Med 383;15.

Patient Selection: Order of Initiation

DAPA-HF: MRA Use

GDMT	^HR (95% CI)
With MRA	0.74 (0.63-0.87)
Without MRA	0.74 (0.57-0.95)

EMPEROR-Reduced: MRA Use

GDMT	^HR (95% CI)
With MRA	0.76 (0.59-0.97)
Without MRA	0.75 (0.63-0.88)

However, there appears to be no difference in efficacy in patients who are or are not on an MRA, suggesting initiation before an MRA could be beneficial as well

^HR for primary outcome of study;
CI: confidence interval; HR: hazard ratio; MRA: mineralocorticoid receptor antagonist
N Engl J Med 381;21. N Engl J Med 383;15.

Patient Selection: Order of Initiation

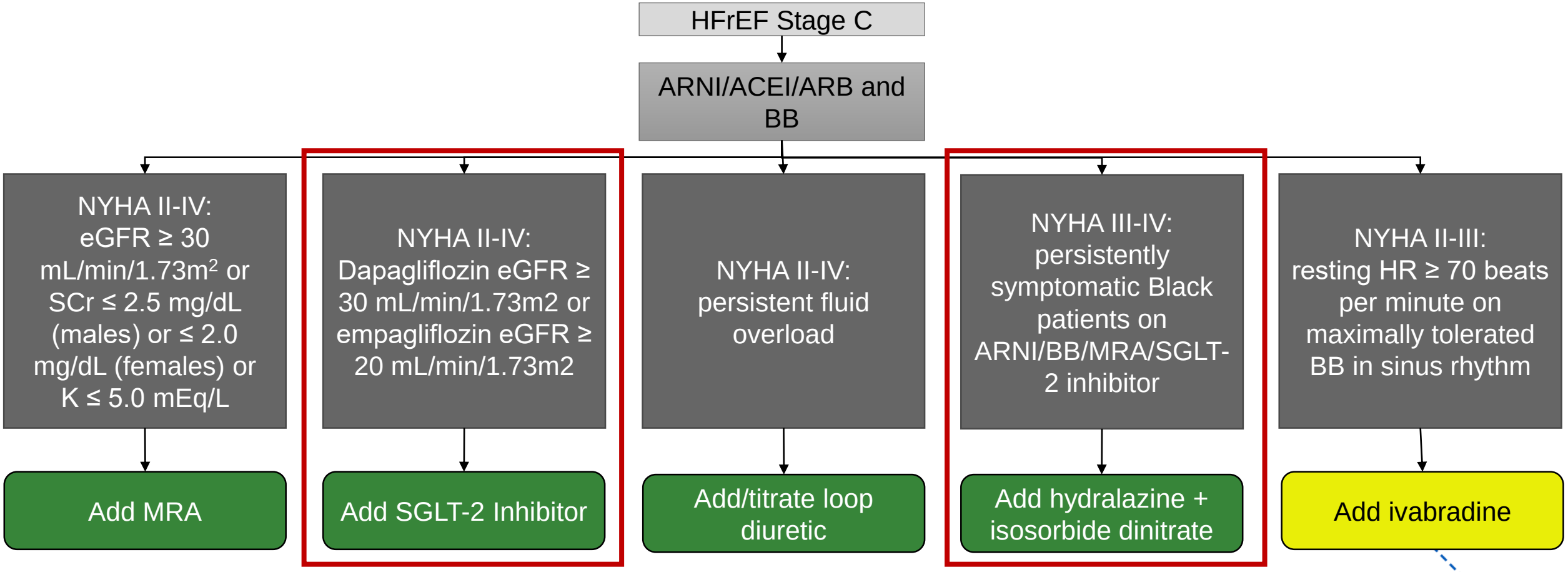
- Post-hoc analysis of DAPA-HF
  - Assessing primary composite outcome: worsening HF or CV death

GDMT Backbone	• RAS blocker/BB/MRA: HR 0.72 (95% CI 0.61–0.86) • No RAS blocker/BB/MRA: HR 0.77 (95% CI 0.63–0.94) • P-value for interaction: 0.64
GDMT Dosing	• ≥ 50% TD RAS blocker/BB + MRA: HR 0.70 (95% CI 0.48-1.01) • < 50% TD RAS blocker/BB + MRA: HR 0.75 (95% CI 0.65-0.87) • P-value for interaction: 0.65

Background GDMT or dosing may not impact dapagliflozin's ability to decrease CV death and heart failure hospitalizations

CI: confidence interval; CV: cardiovascular; GDMT: guideline directed medical therapy; HR: hazard ratio;
Eur Heart J 41;2379.

New Guidance for GDMT in HFrEF?



ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, ARNI: angiotensin receptor blocker/neprilysin inhibitor, eGFR: estimated glomerular filtration rate; GDMT: guideline-directed medical therapy; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; SCr: serum creatinine; SGLT-2: sodium-glucose co-transporter-2

Adapted from: J Am Coll Cardiol. Jan 11, 2021. Epublished DOI: 10.1016/j.jacc.2020.11.022

Monitoring: Adverse Events

Event	DAPA-HF		EMPEROR-Reduced	
	Dapagliflozin (n=2373)	Placebo (n=2371)	Empagliflozin (n=1863)	Placebo (n=2371)
Severe hypoglycemic event, n (%)	4 (0.2)	4 (0.2)	6 (0.3)	7 (0.4)
Ketoacidosis, n (%)	3 (0.1)	0 (0)	0 (0)	0 (0)
Volume depletion, n (%)	170 (7.2)	153 (6.5)	197 (10.6)	184 (9.9)
Bone fractures, n (%)	48 (2.0)	47 (2.0)	45 (2.4)	42 (2.3)
Lower limb amputation, n (%)	13 (0.5)	12 (0.5)	13 (0.7)	10 (0.5)
Fournier's Gangrene, n (%)	0	1 (0.1)	1 (0.1)	0

N Engl J Med 381;21. N Engl J Med 383;15. Lancet 2020; 396:819-29.

Volume/diuretic changes: REFORM Trial

- Small, randomized placebo controlled trial (n=56)
  - Randomization: dapagliflozin 10 mg or placebo
  - Follow-up: 1 year

Dapagliflozin group:

Change in loop diuretic dose^	• Dapagliflozin: -16.0 mg ± 18.1 mg • Placebo: 12.3 mg ± 28.3 mg • p=0.001
Stop or reduce loop diuretic dose	• Dapagliflozin: 30 (53.6%) • Placebo: 6 (10.7%) • p=0.001

^ Furosemide equivalents

Diabetes Care 2020;43:1356–1359

Volume/diuretic changes

- Post hoc analysis of DAPA-HF
  - Benefit of dapagliflozin was consistent irrespective of baseline diuretic use

Volume depletion adverse events with a loop diuretic

- Dapagliflozin with diuretic: 162 (8.1%)
- Dapagliflozin without diuretic: 16 (4.3%)
- Interaction p-value: 0.004

Volume depletion adverse events with ≥ 50% dose MRA

- Dapagliflozin with high dose MRA: 117/1479 (7.9)
- Dapagliflozin with low dose MRA: 12 (5.6)
- Interaction p-value: 0.01

These findings suggest a potential need to decrease or discontinue concomitant diuretic treatment in patients newly initiated on an SGLT-2 Inhibitor

MRA: mineralocorticoid receptor antagonist; SGLT-2: sodium-glucose co-transporter-2
Eur Heart J 41:2379.

Volume/Diuretic Changes

- Patients on an SGLT-2 inhibitor that experience AKI due to hypovolemia/fluid loss
  - Consider temporary discontinuation

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Monitoring: Impact on Systolic Blood Pressure

CV Trials in Patients with TIIDM

Study	mm Hg SBP mean (95% CI)
CANVAS Program	-3.93 (-4.30 to -3.56)
DECLARE-TIMI 58^	-2.7 (-3.0 to -2.4)

HF Trials with & without TIIDM

Study	mm Hg SBP mean ± SD
DAPA-HF	-1.92 ± 14.92
EMPEROR-Reduced	-2.4 ± 0.4

Appears to be a small change in systolic blood pressure with the addition of an SGLT-2 inhibitor, regardless of TIIDM or HF diagnoses

^Least squares mean

CI: confidence interval; HF: heart failure; SBP: systolic blood pressure; SD: standard deviation; SGLT-2: sodium-glucose co-transporter-2; TIIDM: type II diabetes mellitus

N Engl J Med 381;21. N Engl J Med 383;15. Lancet 2020; 396:819-29.

Monitoring: Impact on Diastolic Blood Pressure

CV Trials in Patients with TIIDM

Study	mm Hg DBP mean (95% CI)
CANVAS Program	-1.39 (-1.61 to -1.17)
DECLARE-TIMI 58^	-0.7 (-0.9 to -0.6)

HF Trials with & without TIIDM

Study	DBP mean ± SD
DAPA-HF	0.90 (0.74-1.09)
EMPEROR-Reduced	0.83 (0.66-1.04)

Appears to be a small change in diastolic blood pressure with the addition of an SGLT-2 inhibitor, regardless of TIIDM or HF diagnoses

^Least squares mean

CI: confidence interval; DBP: diastolic blood pressure HF: heart failure; SD: standard deviation; SGLT-2: sodium-glucose co-transporter-2; TIIDM: type II diabetes mellitus

N Engl J Med 381;21. N Engl J Med 383;15. Lancet 2020; 396:819-29.

Cost

- Manufacturers offer coupons for commercial insurance
  - Dapagliflozin
  - Empagliflozin
- Patient Assistance
  - Dapagliflozin
  - Empagliflozin

Price for 30-day Supply	Dapagliflozin	Empagliflozin
AWP Price^	$620.87	$626.90
Average Commercial Insurance Price	$20.15	$0-163
Average Medicare Price	$36.11	$0-135
Average Medicaid Price	$2.90-3.06	$0-10

AWP: average wholesale price
^Redbook price accessed 12/1/2020

Other Considerations

- Ketoacidosis in patients with diabetes:
  - Temporary discontinuation prior to surgery
    - Unclear if this is necessary in patients without diabetes (?)
  - Assess patients with metabolic acidosis for ketoacidosis regardless of glucose level

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Case JB

- JB is a 63 year old female with a history coronary artery disease (CAD), heart failure with reduced ejection fraction (HFrEF), and anxiety. She presents to her primary care physicians (PCP) office for her annual visit.

Home medications:

- Aspirin 81 mg daily
- Atorvastatin 80 mg daily
- Metoprolol succinate 50 mg daily
- Lisinopril 20 mg daily
- Spironolactone 25 mg daily
- Furosemide 40 mg daily
- Sertraline 50 mg daily

Vitals and pertinent labs:

- Blood pressure (BP): 112/72 mm Hg
- HR: 74 beats per minute (bpm)
- eGFR: 50 mL/min/1.73 m^2
- Serum creatinine: 1.4 mg/dL (baseline 1.5)
- Sodium: 136 mEq/L
- Potassium: 4.2 mEq/L

Case JB

What medication regimen change could optimize JB's heart failure care?

A. Addition of dapagliflozin 10 mg daily

B. Addition of canagliflozin 100 mg daily

C. Increase furosemide to 80 mg daily

D. Add tolvaptan 15 mg daily

Case JB

What medication regimen change could optimize JB's heart failure care?

A. **Addition of dapagliflozin 10 mg daily**

B. Addition of canagliflozin 100 mg daily

C. Increase furosemide to 80 mg daily

D. Add tolvaptan 15 mg daily

Case JB

What type of monitoring is required for JB after the medication change?

A. Potassium in one month

B. Sodium in one month

C. Blood pressure in one month

D. Volume status in one month

Case JB

What type of monitoring is required for JB after the medication change?

A. Potassium in one month

B. Sodium in one month

C. Blood pressure in one month

D. Volume status in one month

Heart Failure with Preserved Ejection Fraction

- **DELIVER trial:**
  - Dapagliflozin 10 mg versus placebo

- **EMPEROR-Preserved:**
  - Empagliflozin 10 mg versus placebo
  - Primary composite outcome: CV death or heart failure hospitalization
  - News release that this hit its primary outcome!

What are my next steps…?

- Consider SGLT-2 inhibitors in EVERY patient with HFrEF, regardless of your practice site!
  - Inpatient: May need to add an agent to formulary
  - All settings: May need to check insurance coverage/pricing for each patient
- Educate your providers on the benefits, dosing, and monitoring associated with the medication
- Watch for FDA approval of empagliflozin for HFrEF (any maybe HFpEF!)
- Monitor patients after initiation for potential changes in volume/diuretic need

THANK YOU!
QUESTIONS?

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