SGLT-2 INHIBITORS – FROM DIABETES TO HEART FAILURE AND RENAL INJURY

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Disclosures

- I sit on the Diabetes Canada clinical practice guidelines committee
- I will present information from this source and from other sources
- My research is focused on diabetes prevention, reversal, and management using nonpharmacological strategies. My research is funded by the CIHR, Heart & Stroke Foundation, Lawson Foundation, and JR McConnell Foundations

Learning objectives

1) Recognize clinical situations in which SGLT-2 inhibitors may be beneficial, irrespective of diabetes status
2) Be aware of agents for which there is specific evidence of benefit
3) Appreciate contraindications and potential for adverse effects

Key points in type 2 diabetes

- 3 SGLT-2 inhibitors available presently: canagliflozin (Invokana) 100 mg daily, dapagliflozin (Forxiga) 10 mg daily, empagliflozin (Jardiance) 10 mg daily

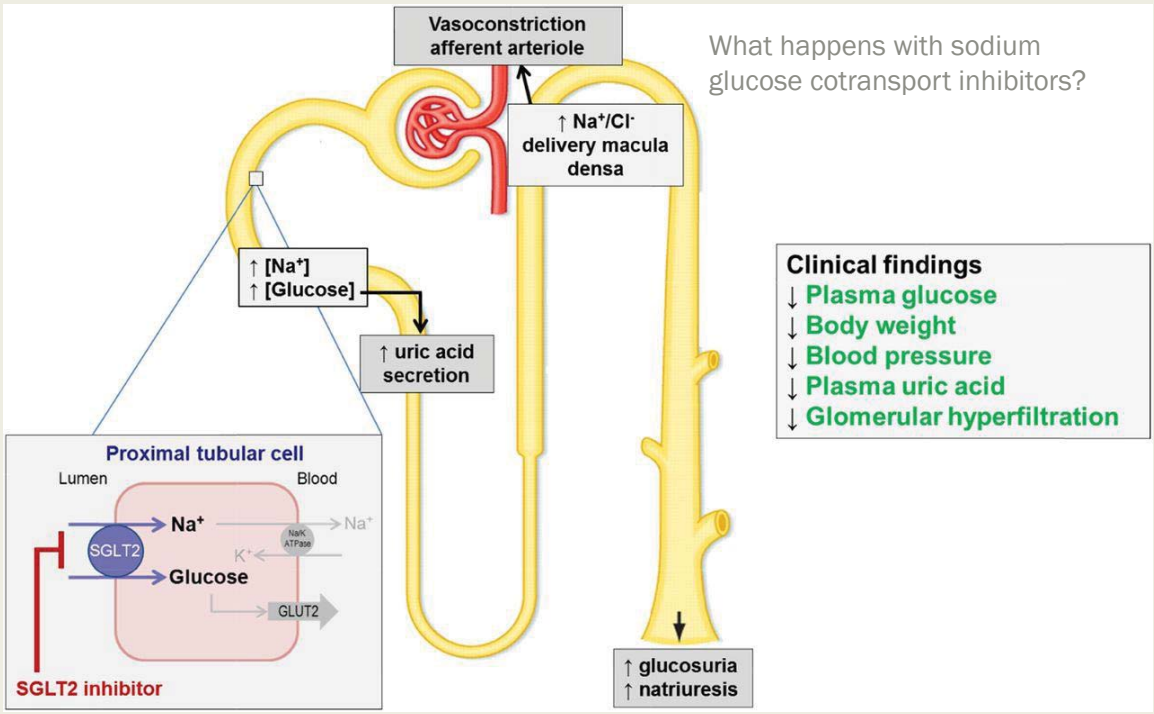
- In type 2 diabetes:
  - Lower glucose levels if eGFR > 30
  - Reduce chronic kidney disease progression in CVD and for canagliflozin with CKD and proteinuria
  - Reduce heart failure hospitalization in persons with CVD
  - empagliflozin shown to lower CVD and all-cause mortality in persons with CVD
  - canagliflozin and dapagliflozin studies examined mixed populations of CVD and its risk factors

eGFR is estimated glomerular filtration rate. Estimates how well kidneys are filtering through glomeruli. We usually estimate filtration of creatinine. Common equations use sex, age, body weight, serum creatinine level.

Key points irrespective of diabetes status

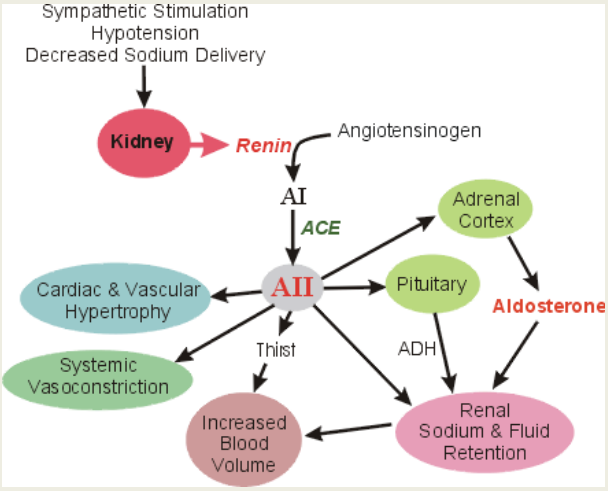
- In **reduced ejection fraction** heart failure:
  - dapagliflozin and empagliflozin reduce heart failure hospitalization, cardiovascular death, and all-cause mortality
- In **preserved ejection fraction** heart failure:
  - empagliflozin reduces heart failure hospitalization
- In **low GFR** with moderate to severe increased ACR (urine albumin to creatinine ratio):
  - dapagliflozin reduces rates of kidney transplantation, dialysis, renal disease progression

HFrEF: left ventricular ejection fraction ≤ 40%



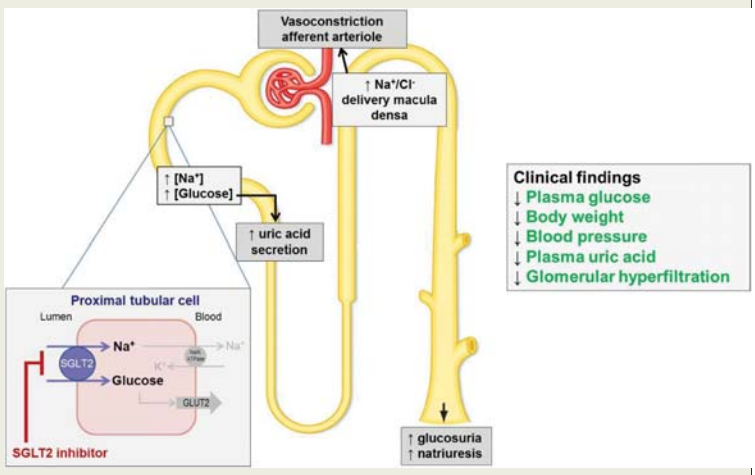
Impacts on RAAS?

Heart failure stimulates the RAAS system



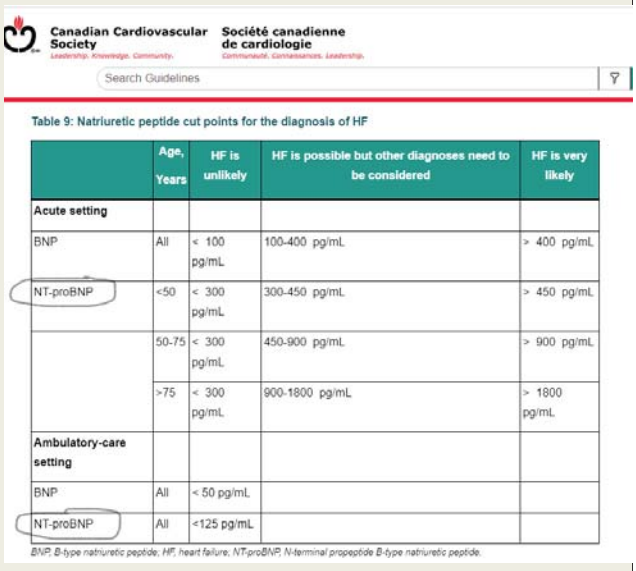
A I, angiotensin I; A II, angiotensin II;
ACE, angiotensin converting enzyme

SGLT-2 inhibitors increase sodium delivery which downregulates RAAS



Heart failure abnormal heart function resulting in symptoms/signs of reduced cardiac output and/or pulmonary or systemic congestion

- Classification Canadian Cardiovascular Society:
  - *HF with preserved ejection fraction (HFpEF): LVEF ≥ 50%*
  - *HF with a mid-range ejection fraction (HFmEF): LVEF 41-49%*
  - *HF with a reduced ejection fraction (HFrEF): LVEF ≤ 40%*


Canadian Cardiovascular Society / Société canadienne de cardiologie

Search Guidelines

Table 9: Natriuretic peptide cut points for the diagnosis of HF

	Age, Years	HF is unlikely	HF is possible but other diagnoses need to be considered	HF is very likely
Acute setting				
BNP	All	< 100 pg/mL	100-400 pg/mL	> 400 pg/mL
NT-proBNP	<50	< 300 pg/mL	300-450 pg/mL	> 450 pg/mL
	50-75	< 300 pg/mL	450-900 pg/mL	> 900 pg/mL
	>75	< 300 pg/mL	900-1800 pg/mL	> 1800 pg/mL
Ambulatory-care setting				
BNP	All	< 50 pg/mL		
NT-proBNP	All	<125 pg/mL		

BNP, B-type natriuretic peptide; HF, heart failure; NT-proBNP, N-terminal propeptide B-type natriuretic peptide.

HEART FAILURE WITH REDUCED EF

HFreF

HFrEF therapies follow HF pathophysiology and are evidence-based

- RAAS pathways themselves
  - *ACE inhibitors, Angiotensin receptor blockers, Aldosterone receptor agonists*
- Enhancement of the natriuretic peptide stimulated by heart failure induced atrial and ventricular stretch
  - *ARNI*
- Reducing activation of RAAS
  - *Reduce sympathetic stimulation*
    - Beta-blockers
  - *Increase distal sodium delivery in nephron*
    - SGLT2 inhibitors

Characteristics in the two studies looking at SGLT-2 inhibitors with or without type 2 diabetes in HF with reduced ejection fraction

Dapagliflozin, *NEJM*, 2019

- 40% T2D, 40% GFR < 60
- Appropriate rEF therapy
- Mean EF around 30%; entry required 40% or less
- Minimum NT proBNP 900 with atrial fib or flutter, 400 with HF hosp past year, 600 otherwise (pg/ml)

Empagliflozin, *NEJM*, 2020

- 50% T2D, 50% GFR < 60
- Appropriate rEF therapy
- Mean EF around 30%; entry required 40% or less
- HF hosp prior year OR Minimum PT proBNP
  - *2500 with EF 36 to 40%*
  - *1000 with EF 31 to 35*
  - *600 with 30% or less*
  - *Double above with atrial fib*

Hazard ratio and confidence intervals

- Similar interpretation as odds ratio and relative risk
- The 'hazard' is an instantaneous risk
- A hazard ratio is the instantaneous risk in one group divided by the instantaneous risk in the other
- A ratio of 1 implies no difference
- Less than 1 means that the group on the top had lower hazards relative to group on bottom (reference group)
- More than 1 means that group on the top had lower hazards relative to group on bottom
- Compute 95% interval around the HR
  - *Conclusive if does not include 1*
  - *Gives an idea of the uncertainty of the estimate (wider interval if more uncertain)*

Primary composite outcomes and their components in the two studies looking at SGLT-2 inhibitors with or without type 2 diabetes in HF with reduced ejection fraction

Dapagliflozin, *NEJM*, 2019

Variable	Dapagliflozin (N=2373)		Placebo (N=2371)		Hazard or Rate Ratio or Difference (95% CI)
	values	*events/100 patient-yr*	*values*	*events/100 patient-yr*	
Efficacy outcomes					
Primary composite outcome — no. (%)†	386 (16.3)	11.6	502 (21.2)	15.6	0.74 (0.65 to 0.85)
Hospitalization or an urgent visit for heart failure	237 (10.0)	7.1	326 (13.7)	10.1	0.70 (0.59 to 0.83)
Hospitalization for heart failure	231 (9.7)	6.9	318 (13.4)	9.8	0.70 (0.59 to 0.83)
Urgent heart-failure visit	10 (0.4)	0.3	23 (1.0)	0.7	0.43 (0.20 to 0.90)
Cardiovascular death	227 (9.6)	6.5	273 (11.5)	7.9	0.82 (0.69 to 0.98)

Empagliflozin, *NEJM*, 2020

Variable	Empagliflozin (N=1863)		Placebo (N=1867)		Hazard Ratio or Absolute Difference (95% CI)†
		events/100 patient-yr		*events/100 patient-yr*	
Primary composite outcome — no. (%)	361 (19.4)	15.8	462 (24.7)	21.0	0.75 (0.65 to 0.86)
Hospitalization for heart failure	246 (13.2)	10.7	342 (18.3)	15.5	0.69 (0.59 to 0.81)
Cardiovascular death	187 (10.0)	7.6	202 (10.8)	8.1	0.92 (0.75 to 1.12)

Characteristics in the two studies looking at SGLT-2 inhibitors with or without type 2 diabetes in HF with reduced ejection fraction

Death from any cause

Dapagliflozin, *NEJM*, 2019

Death from any cause — no. (%)	276 (11.6)	7.9	329 (13.9)	9.5	0.83 (0.71 to 0.97)

Empagliflozin, *NEJM*, 2020

Death from any cause — no. (%)	249 (13.4)	10.1	266 (14.2)	10.7	0.92 (0.77 to 1.10)

Subgroups with or without type 2 diabetes

Dapagliflozin, *NEJM*, 2019

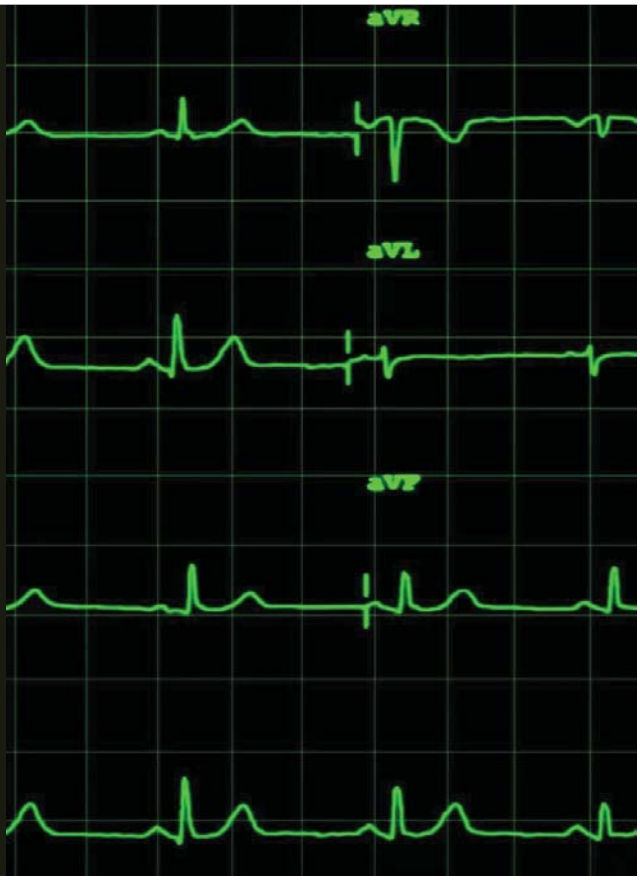
Type 2 diabetes at baseline				
Yes	215/1075	271/1064		0.75 (0.63–0.90)
No	171/1298	231/1307		0.73 (0.60–0.88)

Empagliflozin, *NEJM*, 2020

Diabetes	200/927	265/929		0.72 (0.60–0.87)
No diabetes	161/936	197/938		0.78 (0.64–0.97)

HEART FAILURE WITH PRESERVED EJECTION FRACTION

HFpEF



What about therapies for HFpEF?

	Candesartan (n=1514)	Placebo (n=1509)	Unadjusted hazard ratio (95% CI)	p	Adjusted hazard ratio (95% CI)*	p
Cardiovascular death or hospital admission for CHF	333 (22·0%)	366 (24·3%)	0·89 (0·77–1·03)	0·118	0·86 (0·74–1·00)	0·051
Cardiovascular death	170 (11·2%)	170 (11·3%)	0·99 (0·80–1·22)	0·918	0·95 (0·76–1·18)	0·635
Hospital admission for CHF	241 (15·9%)	276 (18·3%)	0·85 (0·72–1·01)	0·072	0·84 (0·70–1·00)	0·047
Cardiovascular death, hospital admission for CHF, MI	365 (24·1%)	399 (26·4%)	0·90 (0·78–1·03)	0·126	0·87 (0·75–1·00)	0·051
Cardiovascular death, hospital admission for CHF, MI, stroke	388 (25·6%)	429 (28·4%)	0·88 (0·77–1·01)	0·078	0·86 (0·75–0·99)	0·037
Cardiovascular death, hospital admission for CHF, MI, stroke, coronary revascularisation procedure	460 (30·4%)	497 (32·9%)	0·91 (0·80–1·03)	0·123	0·91 (0·80–1·03)	0·130

MI=Myocardial infarction. *Covariate-adjusted model for variables shown in table 1.

CHARM-Preserved, Yusuf and colleagues, *Lancet* , 2003
Ejection fraction of 40% or more

Table 2. Incidence Rates of the Primary Composite Outcome, Its Components, and Additional Secondary Outcomes.*

Outcome	Spironolactone (N=1722)		Placebo (N=1723)		Hazard Ratio with Spironolactone (95% CI)†	P Value
	Participants with Event	Incidence Rate	Participants with Event	Incidence Rate		
	no. (%)	*no./100 person-yr*	*no. (%)*	*no./100 person-yr*		
Primary outcome	320 (18.6)	5.9	351 (20.4)	6.6	0.89 (0.77–1.04)	0.14
Components of the primary outcome						
Death from cardiovascular causes	160 (9.3)	2.8	176 (10.2)	3.1	0.90 (0.73–1.12)	0.35
Aborted cardiac arrest	3 (0.2)	0.05	5 (0.3)	0.09	0.60 (0.14–2.50)	0.48
Hospitalization for heart failure	206 (12.0)	3.8	245 (14.2)	4.6	0.83 (0.69–0.99)	0.04
Additional secondary outcomes						
Death from any cause	252 (14.6)	4.2	274 (15.9)	4.6	0.91 (0.77–1.08)	0.29
Hospitalization for any reason	766 (44.5)	18.8	792 (46.0)	20.0	0.94 (0.85–1.04)	0.25
Myocardial infarction	65 (3.8)	1.2	64 (3.7)	1.1	1.00 (0.71–1.42)	0.98
Stroke	57 (3.3)	1.0	60 (3.5)	1.1	0.94 (0.65–1.35)	0.73

* Some participants had more than one component of the primary outcome and are included once for the primary outcome and once for each component they had.
† Shown are unadjusted hazard ratios calculated with the use of Cox proportional-hazards models.

Pitt and colleagues, *NEJM*, 2014
Ejection fraction of 45% or more

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Empagliflozin in Heart Failure with a Preserved Ejection Fraction

Eligibility and some characteristics

- Adult , NYHA functional class 2 to 4
- Half had type 2 diabetes and half atrial fib
- Ejection fraction more than 40%
  - *Averaged 54%; one third 40 to 50%*
- NT-proBNP
  - more than 300 pg/ml in general
  - more than 900 pg/ml in context of atrial fibrillation
  - Median was 950 to 1000 range

Primary outcome

- Adjudicated cardiovascular death or hospitalization for heart failure
  - *Primary hospitalization diagnosis or ED visit lasting more than 12 hours (or over 24 hours if treatment only oral diuretics)*
  - *One or more of dyspnea, reduced exercise tolerance, fatigue, dizziness, confusion, pedal edema, weight gain due to volume overload*
  - *At least two exam findings or one finding plus lab criteria*
  - *HF specific treatment or intensification*

EMPEROR-preserved outcomes

Variable	Empagliflozin (N=2997)		Placebo (N=2991)		Hazard Ratio or Difference (95% CI)
		events per 100 patient-yr		*events per 100 patient-yr*	
Primary composite outcome — no. (%)	415 (13.8)	6.9	511 (17.1)	8.7	0.79 (0.69–0.90)
Hospitalization for heart failure	259 (8.6)	4.3	352 (11.8)	6.0	0.71 (0.60–0.83)
Cardiovascular death	219 (7.3)	3.4	244 (8.2)	3.8	0.91 (0.76–1.09)

Diabetes at baseline			
Yes	239/1466	291/1472	0.79 (0.67–0.94)
No	176/1531	220/1519	0.78 (0.64–0.95)
LVEF at baseline			
<50%	145/995	193/988	0.71 (0.57–0.88)
≥50% to <60%	138/1028	173/1030	0.80 (0.64–0.99)
≥60%	132/974	145/973	0.87 (0.69–1.10)

CHRONIC KIDNEY DISEASE

Kidney disease

- SGLT inhibition also causes sodium excretion (natriuresis)
- This causes a tubuloglomerular feedback that reduces intraglomerular pressure
- This can slow down renal injury, even in the absence of type 2 diabetes

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health. CKD is classified based on Cause, GFR category (G1–G5), and Albuminuria category (A1-A3), abbreviated as CGA.

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min/1.73 m²) Description and range				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
	G1	Normal or high	≥ 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.
GFR, glomerular filtration rate.

DAPA-CKD, 2020 in persons with or without type 2 diabetes

GFR (mild to severely decreased)
25 to 75

Urinary ACR (moderately to severely increased)
200 to 5000 mg/g
22.5 to 565 mg/mmol in SI units

Stable dose of ACE inhibitor or ARB for at least 4 weeks prior, if tolerated

Excluded: lupus, polycystic kidney disease, ANCA vasculitis

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ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

Primary outcome
Sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Dapagliflozin (N=2152)	Placebo (N=2152)
≥60 ml/min/1.73 m^2	234 (10.9)	220 (10.2)
45 to <60 ml/min/1.73 m^2	646 (30.0)	682 (31.7)
30 to <45 ml/min/1.73 m^2	979 (45.5)	919 (42.7)
<30 ml/min/1.73 m^2	293 (13.6)	331 (15.4)
Hemoglobin — g/liter	128.6±18.1	127.9±18.0
Serum potassium — mEq/liter	4.6±0.5	4.6±0.6
Urinary albumin-to-creatinine ratio§		
Median (interquartile range)	965 (472–1903)	934 (482–1868)
>1000 — no. (%)	1048 (48.7)	1031 (47.9)
Type 2 diabetes — no. (%)	1455 (67.6)	1451 (67.4)
Cardiovascular disease — no. (%)¶	813 (37.8)	797 (37.0)
Heart failure — no. (%)	235 (10.9)	233 (10.8)
Previous medication — no. (%)		
ACE inhibitor	673 (31.3)	681 (31.6)
ARB	1444 (67.1)	1426 (66.3)
Diuretic	928 (43.1)	954 (44.3)

Table 2. Primary and Secondary Outcomes and Adverse Events of Special Interest.*

Outcome	Dapagliflozin		Placebo		Hazard Ratio (95% CI)
	no./total no. (%)	*events/100 patient-yr*	*no./total no. (%)*	*events/100 patient-yr*	
Primary outcome					
Primary composite outcome	197/2152 (9.2)	4.6	312/2152 (14.5)	7.5	0.61 (0.51–0.72)
Decline in estimated GFR of ≥50%	112/2152 (5.2)	2.6	201/2152 (9.3)	4.8	0.53 (0.42–0.67)
End-stage kidney disease	109/2152 (5.1)	2.5	161/2152 (7.5)	3.8	0.64 (0.50–0.82)
Estimated GFR of <15 ml/min/1.73 m^2	84/2152 (3.9)	1.9	120/2152 (5.6)	2.8	0.67 (0.51–0.88)
Long-term dialysis†	68/2152 (3.2)	1.5	99/2152 (4.6)	2.2	0.66 (0.48–0.90)
Kidney transplantation†	3/2152 (0.1)	0.1	8/2152 (0.4)	0.2	—
Death from renal causes	2/2152 (<0.1)	0.0	6/2152 (0.3)	0.1	—
Death from cardiovascular causes	65/2152 (3.0)	1.4	80/2152 (3.7)	1.7	0.81 (0.58–1.12)

Genital infections

- Vaginitis and balanitis related to the glucose in the urine
- Mostly women and uncircumcised men
- Topical antifungals, oral fluconazole responsive
- Do not need to discontinue

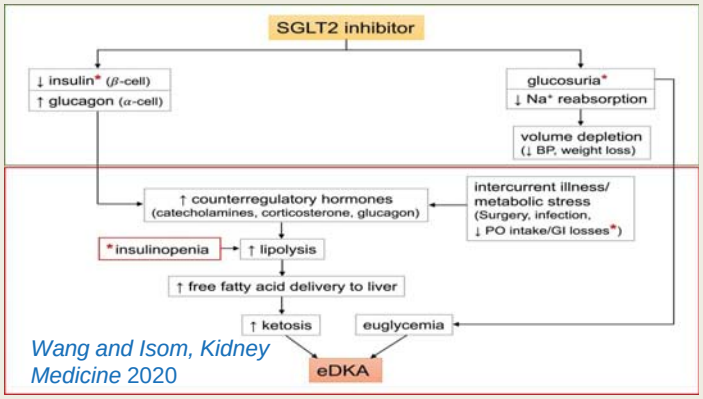
Example- Empagliflozin in HFrEF

Selected adverse events of interest

Hypotension	176 (9.4)	163 (8.7)
Symptomatic hypotension	106 (5.7)	103 (5.5)
Volume depletion	197 (10.6)	184 (9.9)
Ketoacidosis	0 (0.0)	0 (0.0)
Hypoglycemic events*	27 (1.4)	28 (1.5)
In patients with type 2 diabetes	20 (2.2)	22 (2.4)
In patients without type 2 diabetes	7 (0.7)	6 (0.6)
Urinary tract infections	91 (4.9)	83 (4.5)
Complicated urinary tract infections	19 (1.0)	15 (0.8)
Genital infections	31 (1.7)	12 (0.6)
Complicated genital infections	6 (0.3)	5 (0.3)
Bone fractures	45 (2.4)	42 (2.3)
Events leading to lower limb amputation	13 (0.7)	10 (0.5)

Euglycemic diabetic ketoacidosis

	Active treatment	Placebo
Dapagliflozin HFrEF	2 out of 2368	1 out of 2368
Empagliflozin HFrEF	0 out of 1863	0 out of 1863
Empagliflozin HFpEF	4 out of 2996	5 out of 2989
Dapagliflozin CKD	0 out of 2152	2 out of 2152



Wang and Isom, Kidney Medicine 2020

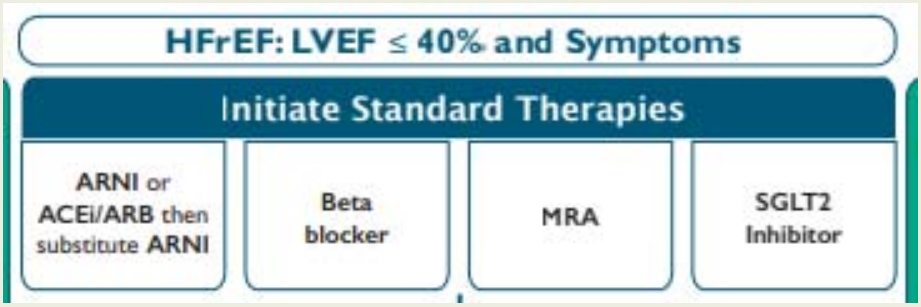
None in those without diabetes.

Sick day management

- Hold when not eating or drinking to prevent DKA, hypovolemia, hypotension
  - *in preparation for a surgery or other procedure*
  - *Intercurrent illness*
  - *Other reasons for fasting*

GUIDELINES AND MEDICATION REIMBURSEMENT PLANS

Canadian Cardiovascular Society Guidelines



- ARNI: Angiotensin receptor neprilysin inhibitor
  - *sacubitril with valsartan*
- ACEi: Angiotensin converting enzyme inhibitor like ramipril, perindopril, enalpril, lisinopril
- ARB: Angiotensin receptor blocker like candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
- Beta blocker like carvedilol, metoprolol, bisoprolol
- Mineralocorticoid receptor antagonist/aldosterone antagonist like spironolactone or eplerenone

For what indications can we prescribe these medications under the public health plan in Quebec?

- **For glycemic control in type 2 diabetes:** canagliflozin, dapagliflozin, empagliflozin
  - ***EN148****: in combo with metformin if a sulfonuylurea is not tolerated, contraindicated, or not effective (A1C high);*
  - ***EN149****: in combo with sulfonylurea if metformin is not tolerated, contraindicated, or not effective;*
  - ***EN167****: if neither sulfonylurea nor metformin are tolerated or if they are both contraindicated (cana and dapa)*
- **For cardiovascular disease in context of type 2 diabetes:** empagliflozin
  - ***EN 179****: Cardiovascular disease indication with the requirements that the A1C is above 7% and other antihyperglycemic agents are prescribed*
- **For heart failure with reduced ejection fraction irrespective of diabetes status:** dapagliflozin
  - ***CV399****: with the following:*
  - *New York Heart Association (NYHA)* ***class II or III*** *heart failure;*
  - *left ventricular systolic dysfunction (with an ejection fraction* ***≤ 40%****);*
  - *on angiotensin converting enzyme inhibitor* ***(ACEI)*** *or angiotensin II receptor antagonist* ***(ARB) for at least 4 weeks****, in combination with a* ***beta-blocker****,* ***unless contraindicated or intolerance***

Key points irrespective of diabetes status

- In **reduced ejection fraction** heart failure:
  - dapagliflozin and empagliflozin reduce heart failure hospitalization, cardiovascular death, and all-cause mortality
  - This is supported by CCS guidelines and dapagliflozin is covered by the RAMQ plan for this indication
- In **preserved ejection fraction** heart failure:
  - empagliflozin reduces heart failure hospitalization
  - No specific guidelines yet and not covered for this indication under RAMQ plan
- In **low GFR** with moderate to severe increased ACR (urine albumin to creatinine ratio):
  - dapagliflozin reduces rates of kidney transplantation, dialysis, renal disease progression
  - No specific guidelines yet and not covered for this indication under RAMQ plan