CARDIO-DIABETES CROSSFIRE
AT HF UPDATE

CHFS SCIC
Canadian Heart Failure Society
Société canadienne d'insuffisance cardiaque

Welcome and Introductions

Shelley Zieroth

MD, FRCPC, FCCS

@ShelleyZieroth

Faculty

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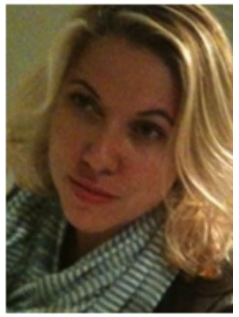

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Université de Montréal
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Conflict of Interest

Shelley Zieroth, MD, FRCPC, FCCS

- **Consulting Fees/Honoraria:** Amgen, AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, Servier, Akcea, Cardiol Therapeutics
- **Clinical Trials:** Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis

E**ileen O'Meara, MD**

- **Consulting Fees/Honoraria**: Amgen, AstraZeneca, Bayer, BMS/Pfizer Alliance, Novartis, Servier
- **Clinical Trials**: Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Merck

Lori Berard, RN, CDE

- **Consulting Fees/Honoraria:** AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Johnson & Johnson, Merck, Sanofi, Novo Nordisk
- **Clinical Trials:** N/A

Navdeep Tangri, MD, PhD, FRCPC

- **Consulting Fees/Honoraria**: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Triceda Inc.
- **Clinical Trials:** AstraZeneca, Johnson & Johnson

Disclosure of Commercial Support

Specific details of relationship:

- This program has received financial support from BI-Lilly Pharmaceuticals Canada in the form of an educational grant

Potential for conflict(s) of interest:

- Speakers have received honoraria from BI-Lilly Pharmaceuticals Canada
- BI-Lilly is the manufacturer and benefits from the sale of empagliflozin

Mitigating Potential Bias

Potential biases are acknowledged and are mitigated by presenting data supported by national and international guidelines, and as follows:

- Information presented is evidence-based
- Material has been developed and reviewed by a Planning Committee

Off-label uses of drugs will be discussed and identified as such by the speaker

Learning Objectives

After attending the symposium, participants will be able to:

- Identify individualized treatment options for CV and renal protection in patients with T2DM
- Explain the role of SGLT2 inhibitors in the prevention and treatment of heart failure
- Describe practical recommendations and tips when starting SGLT2 inhibitors

Accreditation

This event is an Accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada and approved by the Canadian Cardiovascular Society. You may claim a maximum of 1 hour.

Agenda

TIME	TOPIC	SPEAKER
12:35 p.m.	**Welcome and Introductions**	Shelley Zieroth, MD
12:45 p.m.	Diabetes Management: What Every Cardiologist Needs to Know	Lori Berard, RN
1:05 p.m.	Heart Failure Management	Eileen O'Meara, MD
1:25 p.m.	Chronic Kidney Disease Management	Navdeep Tangri, MD
1:45 p.m.	Closing Remarks	Shelley Zieroth, MD

#Cardiotwitter Question

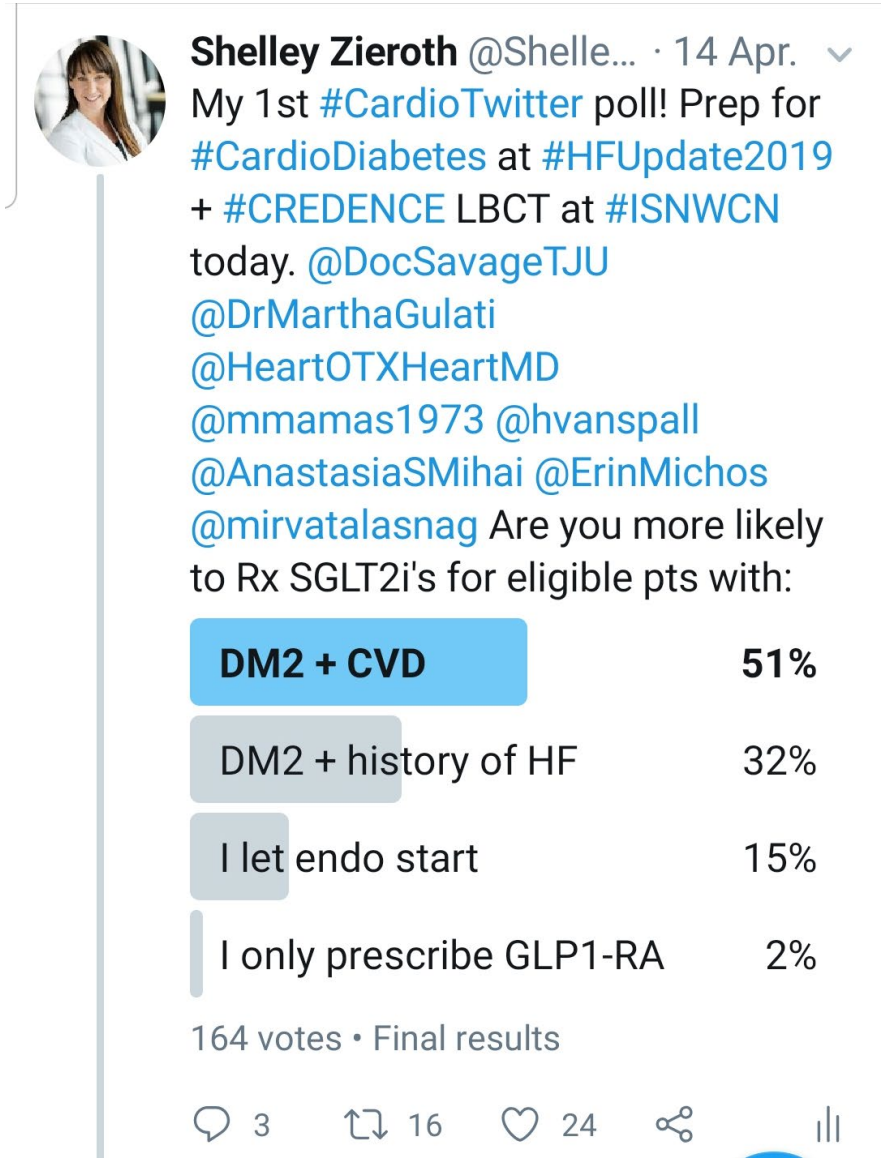
Shelley Zieroth @Shelle… · 14 Apr.

My 1st #CardioTwitter poll! Prep for #CardioDiabetes at #HFUpdate2019 + #CREDENCE LBCT at #ISNWCN today. @DocSavageTJU @DrMarthaGulati @HeartOTXHeartMD @mmamas1973 @hvanspall @AnastasiaSMihai @ErinMichos @mirvatalasnag Are you more likely to Rx SGLT2i's for eligible pts with:

ARS Question

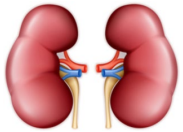
- Are you more likely to Rx SGLT2i's for eligible patients with :
  - T2DM + CVD = **62%**
  - T2DM + history of HF = **33%**
  - I let endocrinologist start = **5%**
  - I only prescribe GLP1-RA's = **0%**

#Cardiotwitter Answer



LEADER: Summary

Liraglutide in addition to standard of care reduced CV risk and improved overall survival in adults with T2D and age ≥50 yrs with established CVD or CKD or age ≥60 yrs with an additional risk factor

13%	22%	15%	14%	22%
				
↓ CV death, non-fatal MI, non-fatal stroke (NNT 3y = 66)	↓ CV death (NNT 3y = 104)	↓ All-cause mortality (NNT 3y = 98)	↓ Fatal and non-fatal MI (NNT 3y = 127)	↓ New or worsening nephropathy (NNT 3y = 85)

The overall safety profile of liraglutide was consistent with previous clinical trials and current label information

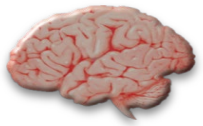
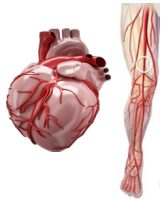
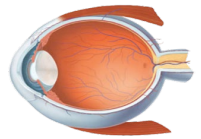
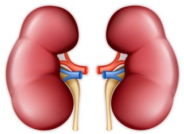
LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results – A Long Term Evaluation; CVD: cardiovascular disease; CKD: chronic kidney disease; T2D: type 2 diabetes; MI: myocardial infarction; NNT: number needed to treat

Liraglutide is not currently indicated for renal protection in Canada.

Marso S, et al. *N Engl J Med.* 2016;375:311-322. Slide courtesy of Dr. R. Goldenberg.

SUSTAIN-6: Summary

Semaglutide once weekly in addition to standard of care reduced CV risk in adults with T2D and age ≥50 yrs with established CVD or CKD or age ≥60 yrs with an additional risk factor

26%	39%	35%	76%	36%
				
↓ CV death, nonfatal MI, nonfatal stroke (NNT 2y =45)	↓ Nonfatal stroke (NNT 2y=91)	↓ Revascula-rization (NNT 2y=39)	↑ Retinopathy complications (NNH 2y=46)	↓ New or worsening nephropathy (NNT 2y=44)

The overall safety profile of semaglutide was consistent with previous clinical trials and the GLP-1RA class, except for the retinopathy results

SUSTAIN: Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; CVD: cardiovascular disease; CKD: chronic kidney disease; T2D: type 2 diabetes; MI: myocardial infarction; NNT: number needed to treat; NNH: number needed to harm

Semaglutide is not currently indicated for cardiovascular or renal protection in Canada and should not be used in patients with end stage renal impairment due to very limited clinical experience in this population.16.

Marso S et al. *N Engl J Med* 2016;375:1834-44. (courtesy of Dr. R. Goldenberg)

CANVAS Program: Summary

Canagliflozin in addition to standard of care reduced CV risk in adults with T2D and age ≥30 years with established CVD (66%) or age ≥50 yrs with ≥2 CV risk factors (34%)

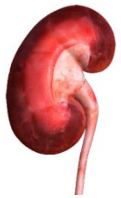
14%

↓ CV death, non-fatal MI, non-fatal stroke (P=0.02; NNT 5y = 44)

33%

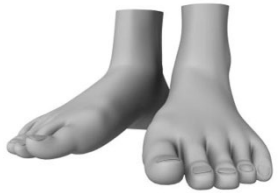
↓ HF hospitalization (NNT 5y = 63)

40%



↓ eGFR, dialysis, renal death (NNT 5y = 58)

97%



↑ Lower extremity amputations (P<0.001; NNH 5y = 69)

26%

No increased risk of amputations was observed in EMPA-REG OUTCOME or DECLARE

The primary prevention cohort accounted for fewer primary MACE events and while subgroup analysis did not show heterogeneity, no conclusion can be made regarding the CV benefit in this group (HR 0.98; 95% CI 0.74-1.30)

Canagliflozin is not indicated for slowing the progression of renal disease in patients with type 2 diabetes in Canada and contraindicated for use in patients with an eGFR of <45 mL/min/1.73m²

CVD: cardiovascular disease; HF: heart failure; MI: myocardial infarction; NNT: number needed to treat; NNH: number needed to harm;T2D: type 2 diabetes

Neal B, et al. *N Engl J Med.* 2017;377:644-57 ; ADA Annual Meeting 2017. Slide courtesy of Dr. R. Goldenberg.

EMPA-REG OUTCOME: Summary

Empagliflozin in addition to standard of care reduced CV risk and improved overall survival in adults with T2D with established CVD

14%

↓ CV death, non-fatal MI, non-fatal stroke (NNT 3y = 63)

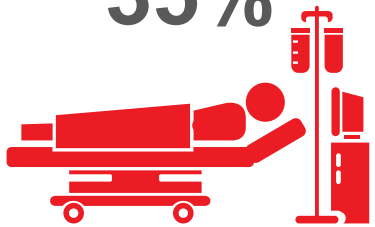
38%

↓ CV death (NNT 3y = 46)

32%

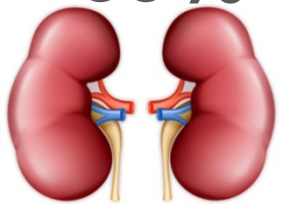
↓ All-cause mortality (NNT 3y = 39)

35%



↓ HF hospitalizations NNT 3y = 72

39%



↓ New or worsening nephropathy (NNT 3y = 17)

The overall safety profile of empagliflozin was consistent with previous clinical trials and current label information

Empagliflozin is not currently indicated for renal protection in Canada and is contraindicated in patients with eGFR less than 30 mL/min/1.73m2.

CVD: cardiovascular disease; MI: myocardial infarction; NNT: number needed to treat; T2D: type 2 diabetes; HF: heart failure

Zinman B, et al. *N Engl J Med.* 2015;373:2117-28. Wanner C, et al . *N Engl J Med*. 2016;375:323-334. Slide courtesy of Dr. R. Goldenberg.

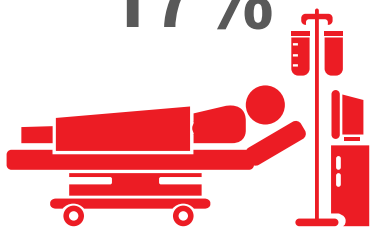
DECLARE–TIMI 58: Summary

Dapagliflozin in addition to standard of care in patients with type 2 diabetes aged ≥40 years with established ischemic cerebrovascular disease, Ischemic heart disease or PAD, or aged ≥55 years (men) ≥66 (women) with ≥1 cardiovascular risk factor.

7%

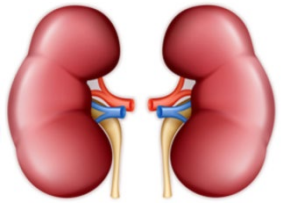
Non-significant reduction in CV death, non-fatal MI, non-fatal stroke

17%



↓ CV Death or HF hospitalizations (NNT 4yr = 108)

24%



↓ 40% decrease in eGFR to <60 ml/min/1.73m2, ESRD or renal or CV death (NNT 4 yr -100)

The overall safety profile of dapagliflozin was consistent with previous clinical trials and current label information

Dapagliflozin is not currently indicated for renal protection in Canada and is contraindicated in patients with eGFR less than 30 mL/min/1.73m2.

CVD: cardiovascular disease; MI: myocardial infarction; NNT: number needed to treat; T2D: type 2 diabetes; HF: heart failure

Note: Dapaglifozin is an SGLT2 inhibitor administered orally; it is not currently indicated for cardiovascular protection in Canada

Adapted from: Wiviott S et al. N Engl J Med 2018;DOI: 10.1056/NEJMoa1812389

Mrs. P

- 73 year old woman with NYHA 2, CCS 1 HFpEF
- Patients' Medical History:
  - Paroxysmal AF on DOAC
  - T2DM
  - Hypertension
  - Ex-smoker
  - MI 10 years ago
  - 1 hospitalization for HF in 2018
- MIBI 2017: LVEF 45%, fixed defect of inferior wall
- Medications:
  - Metformin 1000 mg po BID
  - Lasix 40 mg po OD
  - Ramipril 2.5 mg po OD
  - Metoprolol 25 mg po BID
  - Rivaroxaban 20 mg po OD
  - Atorvastatin 80 mg po OD
- Labs:
  - K 4.2, eGFR 72, hgb 130, hgbAIc 8.2, UACr neg
- Exam: BP 132/70, HR 80 irreg, JVP 3, S4, trace edema, chest clear

Diabetes Management: What Every Cardiologist Needs to Know

Lori Berard
RN
@ldb13

The Impact of Diabetes

Diabetes can **reduce lifespan** by up to15 years[1]

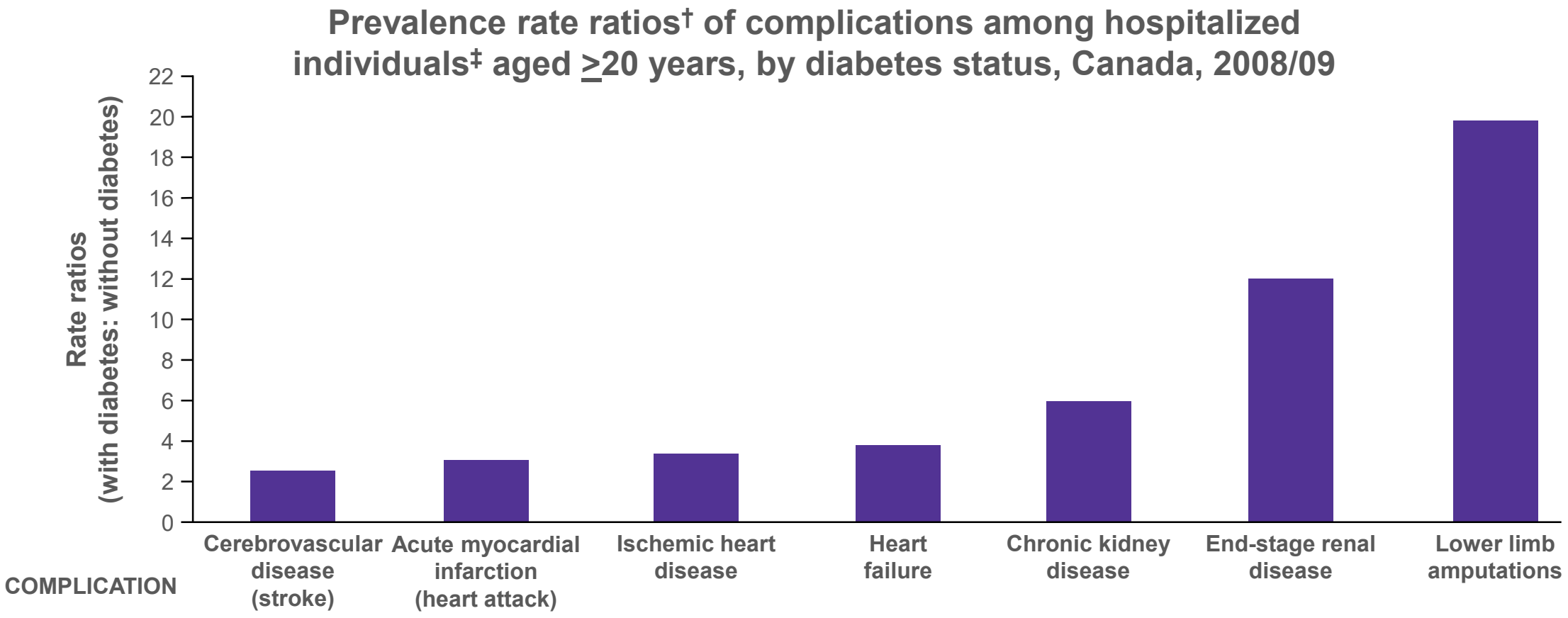
CV disease is the leading cause of **morbidity and mortality** in patients with T2DM [2]

80% of Canadians with diabetes will die of CVD[2]

By **2020**, diabetes is expected to cost the Canadian healthcare system **$16.9 billion** annually[3]

1. The Emerging Risk Factors Collaboration. Association of Cardiometabolic Multimorbidity With Mortality. JAMA. 2015;314(1):52-60. 2. Diabetes Canada. *Canada at the tipping point*. 2017. https://www.diabetes.ca/CDA/media/documents/publications-and-newsletters/advocacy-reports/canada-at-the-tipping-point-english.pdf (Accessed Dec 12, 2018). 3. *The cost of Diabetes in Canada. Diabetes Canada. (2017)*

Patients with Diabetes are More Likely to be Hospitalized for Many Conditions



† Rate ratios based on rates age-standardized to the 1991 Canadian population.
‡ A person with diabetes hospitalized with more than one complication was counted once in each category, except for cases of acute myocardial infarction, where regardless of multiple counts in the acute myocardial infarction category, the individual was counted only once under the broader ischemic heart disease category.
Source: Public Health Agency of Canada (August 2011); using 2008/09 data from the Canadian Chronic Disease Surveillance System (Public Health Agency of Canada).

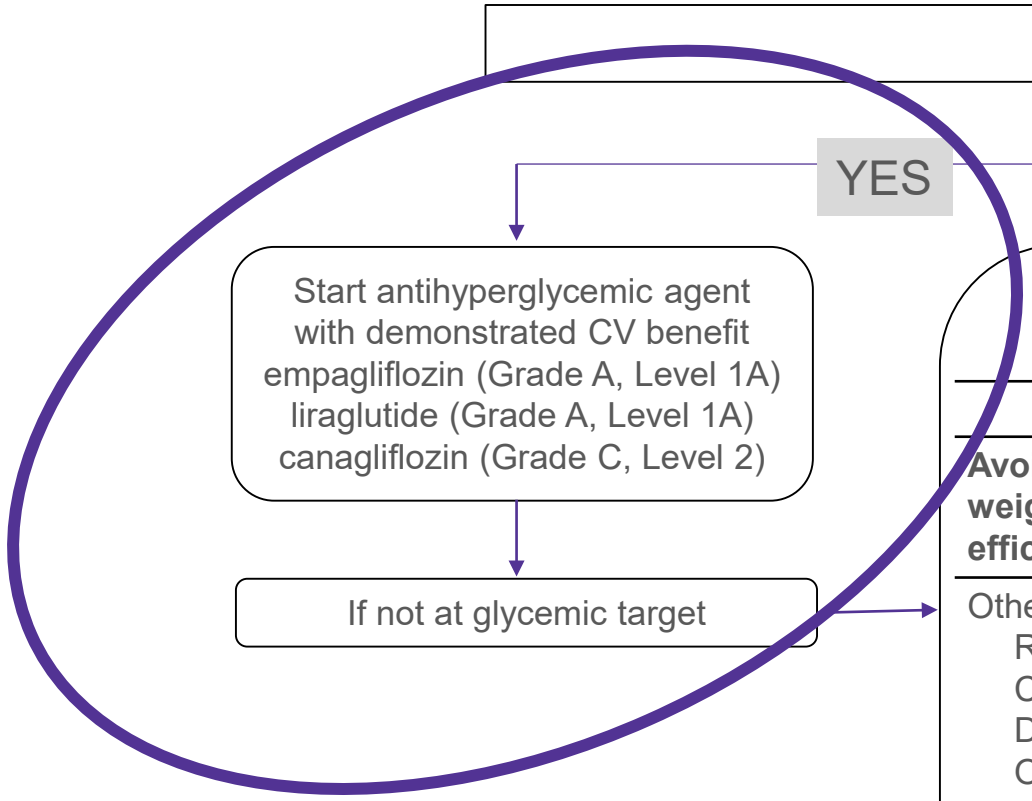
ABCDES³ of Diabetes Care

2018

- ✓A • A1C – optimal glycemic control (usually ≤7%)
- ✓B • BP – optimal blood pressure control (<130/80)
- ✓C • Cholesterol – LDL <2.0 mmol/L or >50% reduction
- ✓**D • Drugs to protect the heart**
  A – ACEi or ARB | S – Statin | A – ASA if indicated | **SGLT2i/GLP-1 RA with demonstrated CV benefit if T2DM with CVD and A1C not at target**
- ✓E • Exercise / Healthy eating
- ✓S • Screening for complications
- ✓S • Smoking cessation
- ✓S • Self-management, stress and other barriers

Beyond Metformin in the DC Algorithm

Add another agent best suited to the individual by prioritizing patient characteristics:



Add additional antihyperglycemic agent best suited to the individual based on the following:

Clinical Considerations	Choice of Agent
Avoidance of hypoglycemia and/or weight gain with adequate glycemic efficacy	**DPP-4 inhibitor, GLP-1 receptor agonist or SGLT2 inhibitor**
Other considerations:	
Reduced eGFR and/or albuminuria	See Appendix 7
Clinical CVD or CV risk factors	
Degree of hyperglycemia	See Table below.
Other comorbidities (CHF, hepatic disease)	
Planning pregnancy	
Cost/coverage	
Patient preference	

Adapted from Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes 2018; 42(Suppl1):S1-S325.

Choosing Between SGLT2i and GLP-1 RA
Drugs that Protect the Heart And Lower Glucose

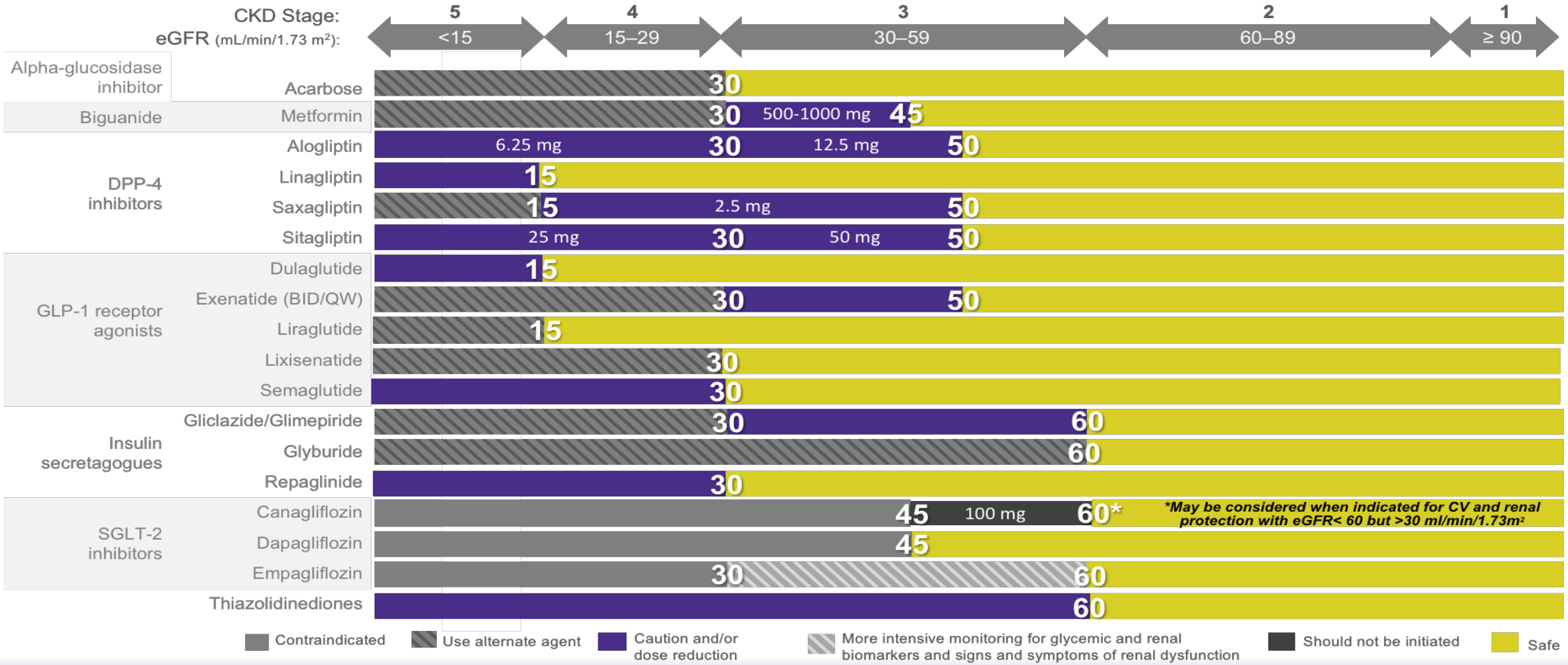
	SGLT2i	GLP-1RA
Relative A1C lowering	↓↓ to ↓↓↓	↓↓ to ↓↓↓
	Remember to adjust sulfonylurea as needed for hypoglycemia	
Weight loss	↓↓	↓↓
Hypoglycemia	Rare	Rare
Side effects	Genital infections, UTI, hypotension, dose-related changes in LDL-C, increased risk of fractures with canagliflozin; increased risk of lower extremity amputation with canagliflozin (avoid if prior amputation);caution with renal dysfunction, loop diuretics and the elderly; treatment should be withheld prior to major surgery or with serious illness or infection.	Gastrointestinal side effects, rare cases of acute gallstone disease; contraindicated with personal/family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2
Route of administration	Oral	Injectable
Dosing	Empagliflozin: Start at 10 mg OD; increase to 25 mg OD if needed for glycemic control Canagliflozin: Start at 100 mg OD; increase to 300 mg OD if needed for glycemic control	Liraglutide: Start at 0.6 mg OD and then titrate up to 1.8 mg OD ; increase to 0.5 mg QW; increase to 1.0 mg in 4 weeks if needed for glycemic control
Cost	$$$	$$$$

A1C: glycated hemoglobin; CrCl: creatinine clearance; eGFR: estimated glomerular filtration rate; GLP-1RA: glucagon like peptide-1 receptor agonist; UTI: urinary tract infection; LDL-C: low-density lipoprotein cholesterol; NNT: number needed to treat; OD: once daily; SGLT2i: sodium glucose co-transporter-2 inhibitor; OD: once daily; QW: Once-daily

*Superiority met ; **SUSTAIN-6 was not designed with pre-specified testing for superiority. However, the treatment effect of semaglutide and the accrual of more events than estimated resulted in a significantly lower risk of the primary outcome among patients in the semaglutide group.; #p<0.001; ##exploratory

Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes.* 2018;42(Suppl 1):S1-S325. . Zinman B *et al. N Engl J Med* 2015;373:2117; Neal B *et al. N Engl J Med* 2017;377:644; Marso et al., N Engl J Med. 2016 Jul 28;375(4):311-22; Marso et al., N Engl J Med. 2016 Nov 10;375(19):1834-1844;

Antihyperglycemic Agents and Renal Function



Adapted from Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes 2018; 42(Suppl1):S1-S325, Novo Nordisk Canada Inc. Ozempic Product Monograph. Date of Approval: January 4, 2018; and Boehringer Ingelheim (Canada) Ltd. Jardiance Product Monograph. Date of Revision: April 11, 2019; AstraZeneca Canada Inc. Forxiga Product Monograph. Date of Revision: April 3, 2019.

ARS

- What will be the most important self monitoring advice you can provide Mrs P when starting her on an SGLT2i to reduce her risk of CV events?
  - sick day protocol = **15%**
  - management of yeast infections = **12%**
  - monitor daily weights = **5%**
  - all of the above = **68%**

Sick Day Medication List (SADMANS)

If people with diabetes become ill and are unable to maintain adequate fluid intake, or have an acute decline in renal function (e.g., due to gastrointestinal upset or dehydration), they should be instructed to hold medications which will:

A) Increase risk for a decline in kidney function:

- Angiotensin-converting enzyme inhibitors
- Angiotensin receptor blockers
- Direct renin inhibitors
- Nonsteroidal anti-inflammatory drugs
- Diuretics
- SGLT2 inhibitors

B) Have reduced clearance and increase risk for adverse effects:

- Metformin
- Sulfonylureas (gliclazide, glimepiride, glyburide)

S sulfonylureas
A ACE inhibitors
D diuretics, direct renin inhibitors

M metformin
A angiotensin receptor blockers
N nonsteroidal anti-inflammatory
S SGLT2 inhibitors, sacubitril/valsartan

Modified from: Diabetes Canada. *Can J Diabetes* 2018; 42 (Suppl 1):S316.

Heart Failure Management

Eileen O’Meara

MD

SGLT2 inhibitors and CV disease

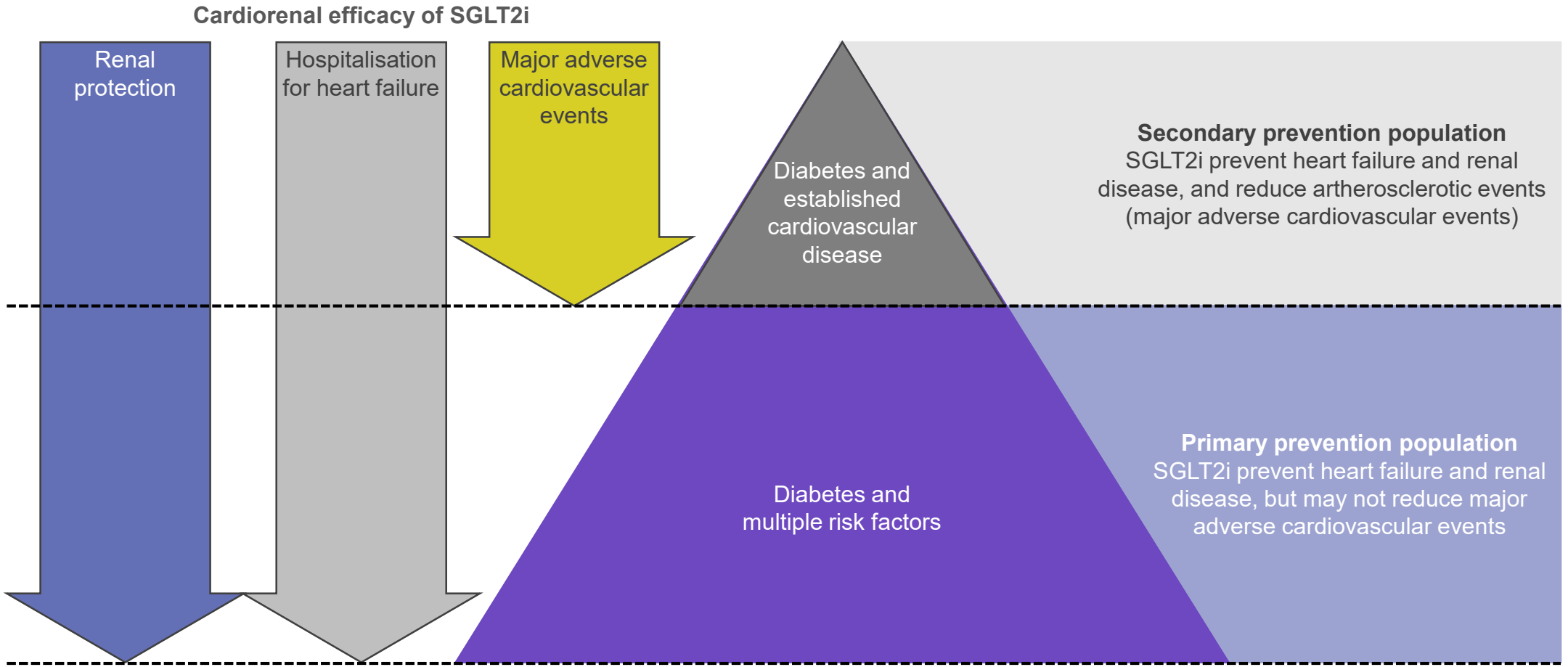


Figure: Cardiorenal benefits of SGLT2i in different patient populations
SGLT2i = sodium-glucose cotransporter-2 inhibitors

Lancet Volume 393, ISSUE 10166, P3-5, January 05, 2019
Pump, pipes, and filter: do SGLT2 inhibitors cover it all?, Verma, Juni, mazur

SGLT2 inhibition – Hypotheses for CV benefits

Potential Mechanisms of SGLT2 Inhibitors Associated with CV Benefits

Hemodynamic actions (via 'Natriuresis')

Cardiac/Vascular

- Plasma volume ↓
- Blood pressure ↓
- Pulse pressure ↓
- Double product ↓
- Arterial stiffness ↓
- Sympathetic tone ↓

→

- HF ↓
- CV death ↓
- Arrhythmia ↓(?)
- Mortality ↓

Renal

- TGF ↑
- Hyperfiltration ↓
- Intraglomerular pressure ↓

→

- eGFR →
- Proteinuria ↓
- Nephropathy ↓
- Renal event ↓

Metabolic actions (via 'Glycosuria')

Glycemic

- HbA1c ↓
- Insulin ↓
- Glucotoxicity ↓

Non-glycemic

- Body weight ↓
- TG ↓
- Fat mass ↓
- Uric acid ↓

→

- Insulin resistance ↓
- Inflammation ↓
- Oxidative stress ↓

→

- Endothelial function ↑(?)
- Atherosclerosis ↓(?)

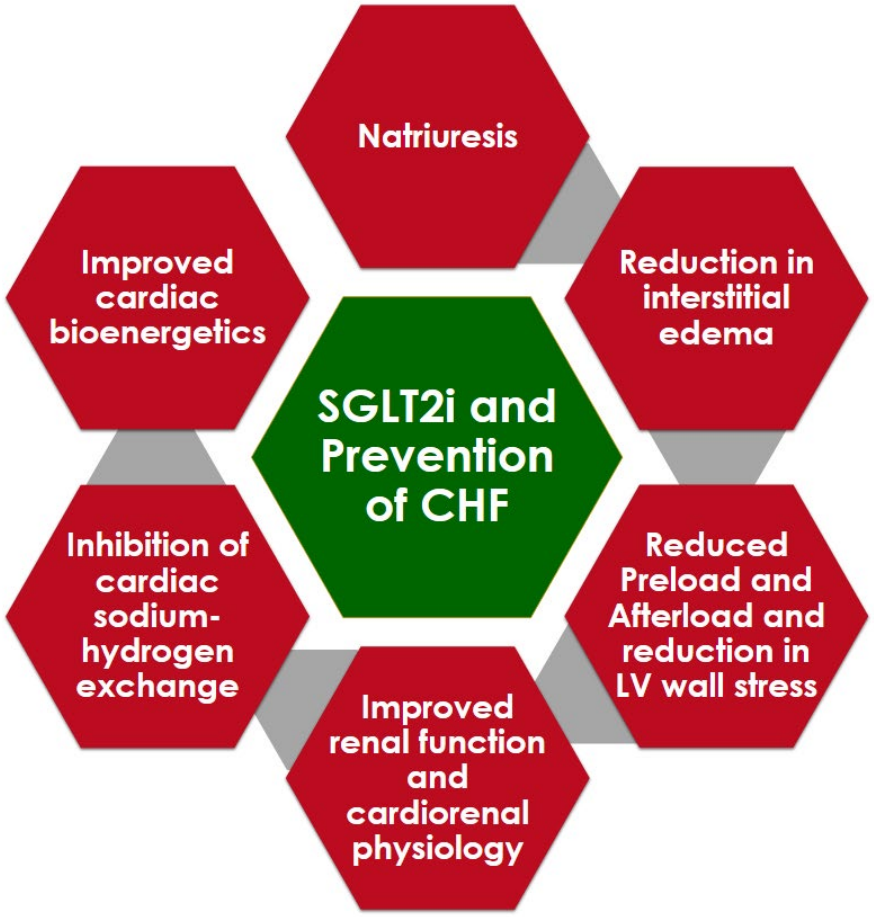
Energy

- Fuel-shift ↑
- Ketone bodies ↑

→

- Mitochondrial function ↑(?)
- Cardio/renal work efficiency ↑(?)

Tanaka A, Node K. J Cardiol. 2017 Mar;69(3):501-507.

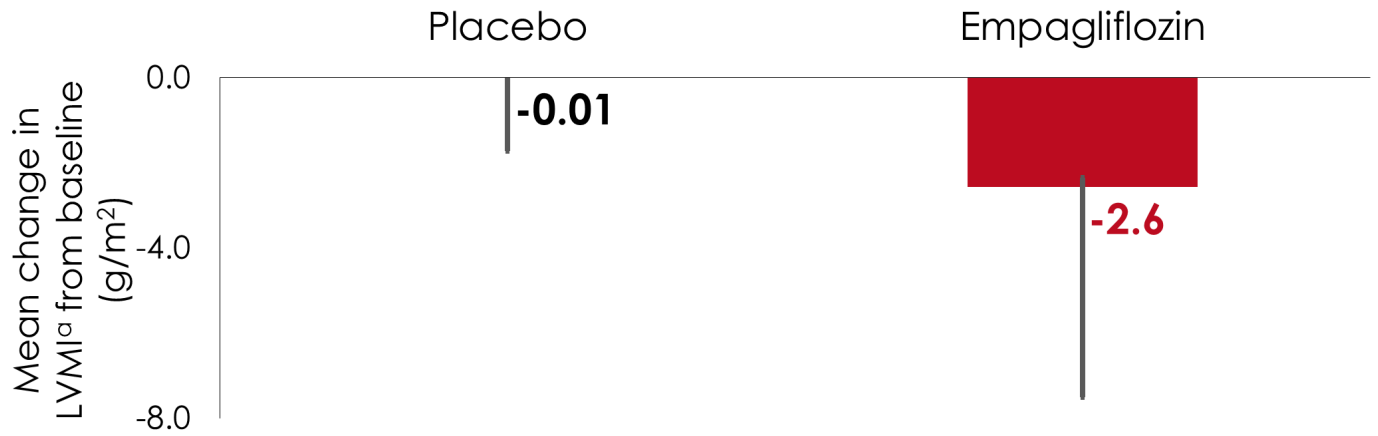


Farkouh ME, Verma S. *J Am Coll Cardiol.* 2018;71:2507-2510.

Empa-Heart: Mechanistic clues to SGLT2i's benefit

Primary Outcome
Empagliflozin Reduces LVMI[a]

	Placebo	Empagliflozin
Baseline LVMI[a] (g/m^2)	62.2	59.5

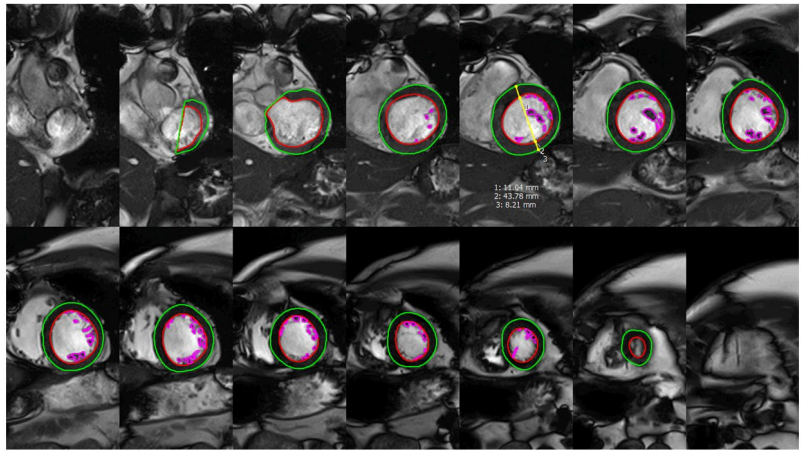


LVM regression (g)	**-0.39 (10.83)**	**-4.71 (15.43)**

EMPA-HEART

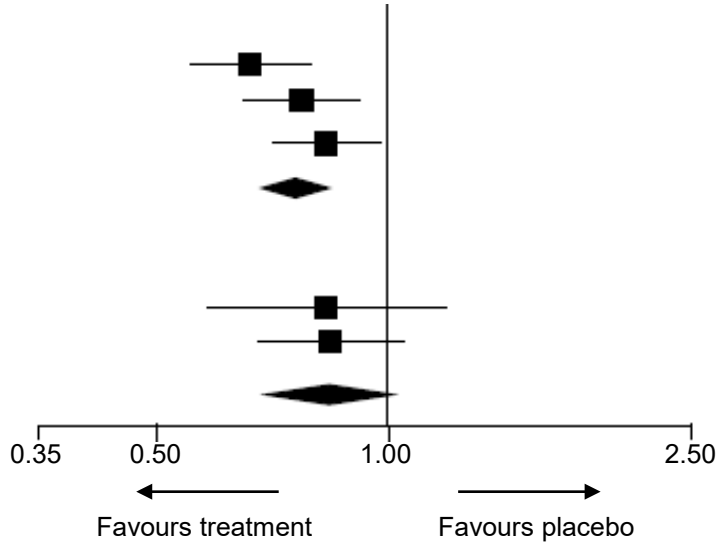
Data are presented as mean (95% CI) for the intention-to-treat population.
[a], LV mass with papillary muscle mass indexed to body surface area.

End Diastolic LV Contours



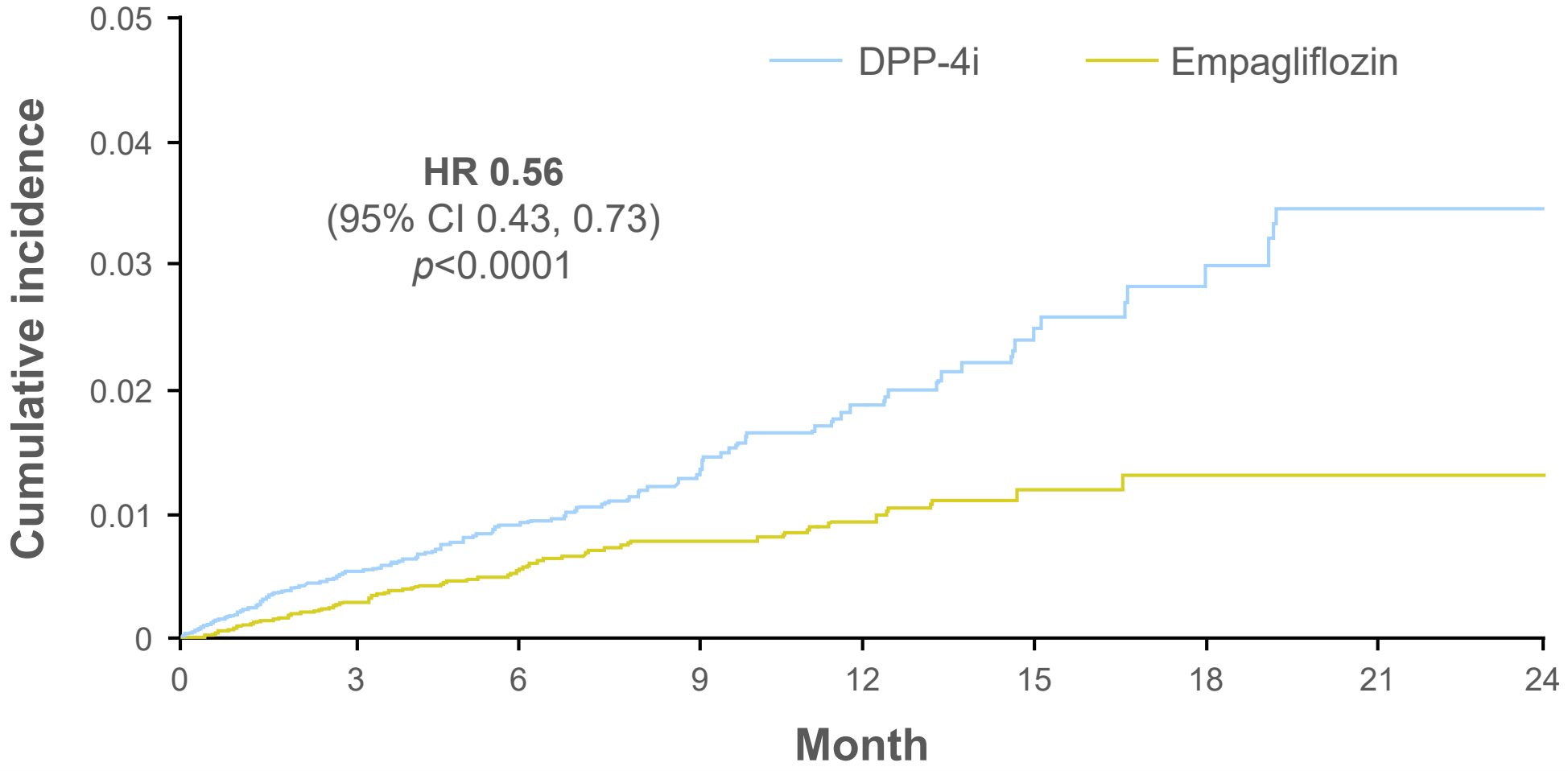
SGLT2i's reduce HF Hospitalizations

	Patients		Events	Events per 1000 Patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (nN)	Placebo (nN)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687/7020	2333/7020	463	19.7	30.1	30.9		0.66 (0.55-0.79)
CANVAS Program	3756/6656	2900/6656	524	21.0	27.4	32.8		0.77 (0.65-0.92)
DECLARE-TIMI 58	3474/6974	3500/6974	597	19.9	23.9	36.4		0.83 (0.71-0.98)
Fixed effects model for atherosclerotic cardiovascular disease (p<0.0001)								**0.76 (0.69-0.84)**
Patients with multiple risk factors								
CANVAS Program	2039/3486	1447/3486	128	8.9	9.8	30.2		0.83 (0.58-1.19)
DECLARE-TIMI 58	5108/10186	5078/10186	316	7.0	8.4	69.8		0.84 (0.67-1.04)
Fixed effects model for multiple risk factors (p=0.0634)								**0.84 (0.69-1.01)**



Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by the presence of established atherosclerotic cardiovascular disease
Atherosclerotic cardiovascular disease: Q statistic=3.49, p=0.17, I^2=42.7%; multiple risk factors: Q statistic=0.0, p=0.96, I^2=0%. The p value for subgroup differences was 0.41. Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

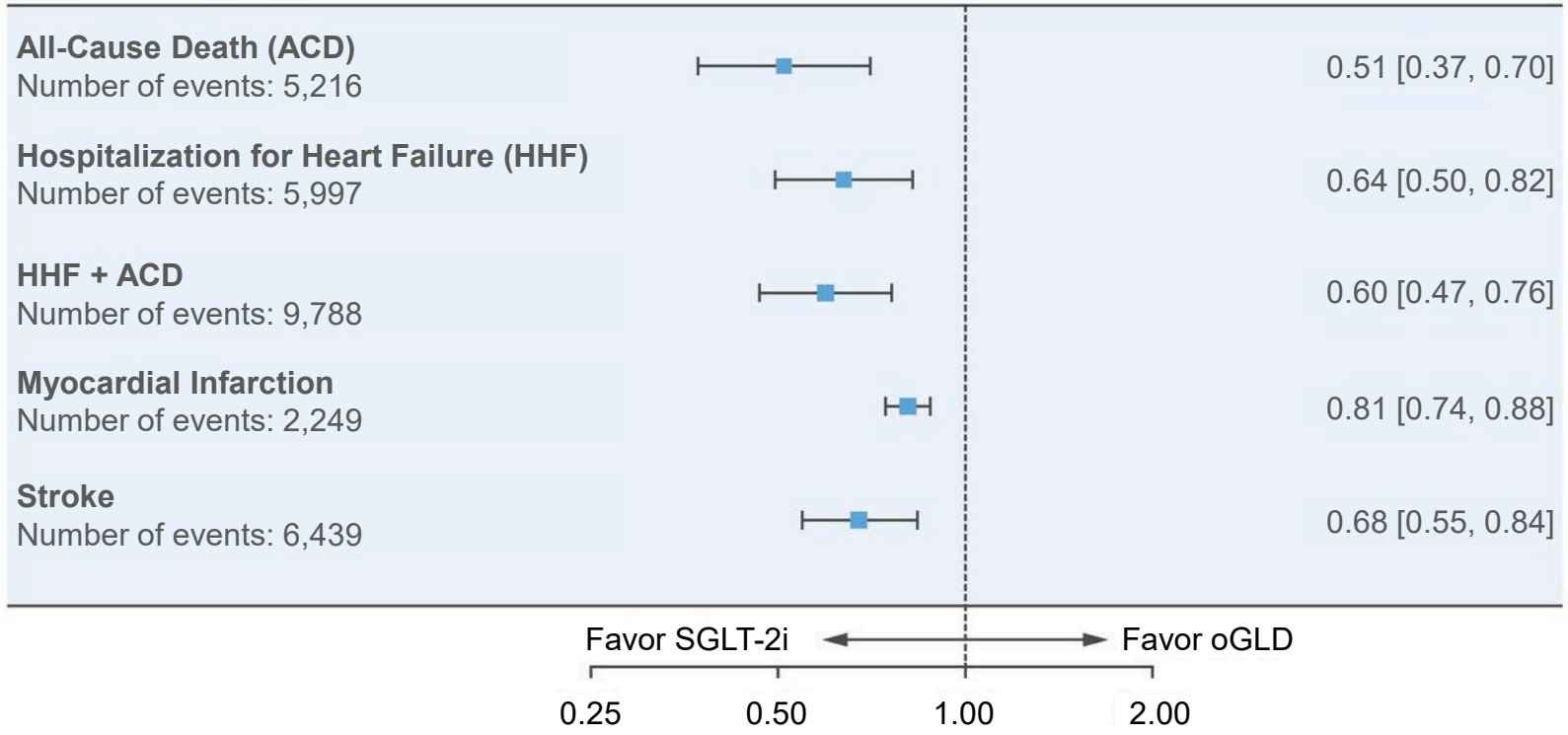
EMPRISE Real World Data: Empagliflozin was associated with a reduced risk of HHF† in routine clinical practice compared with DPP-4i



†Broad definition HHF data shown
1:1 propensity score-matched cohorts; DPP-4i, dipeptidyl peptidase-4 inhibitor; HHF, hospitalisation for heart failure
Patorno E *et al. AHA* 2018; poster 1112

CVD REAL

CENTRAL ILLUSTRATION: Lower Cardiovascular Risk Associated With SGLT-2 Inhibitors



CCS 2017 HF Guidelines: HF *Prevention* in Type 2 DM

Recommendations

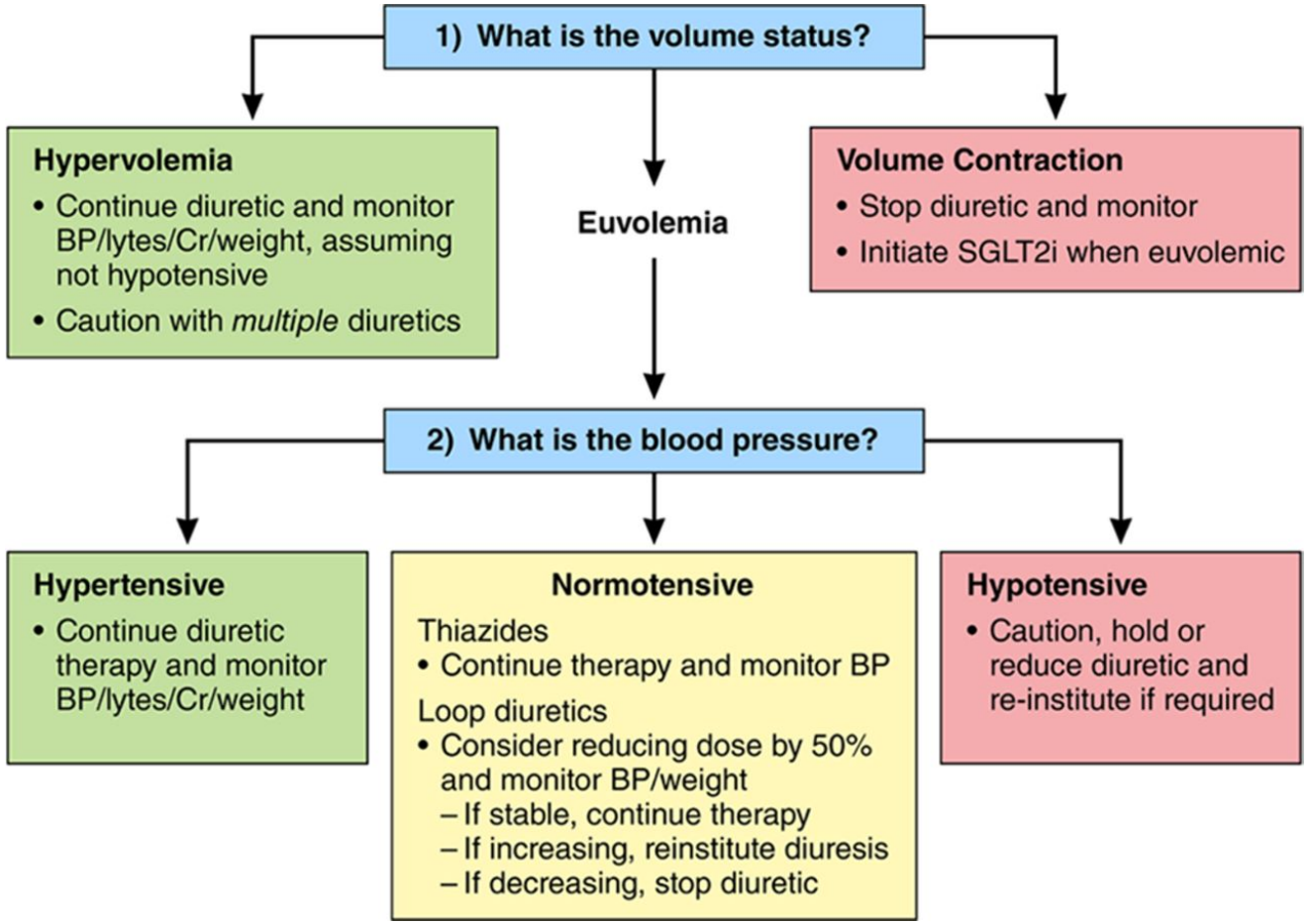
- We recommend that diabetes should be treated according to the Canadian Diabetes Association's national guidelines to achieve optimal control of blood glucose levels
  (Strong Recommendation, Moderate Quality Evidence)

- We suggest that the use of empagliflozin, a SGLT-2 inhibitor, be considered for patients with type 2 diabetes and established cardiovascular disease for the prevention of HF-related outcomes
  (Weak Recommendation, Low Quality Evidence)

Diabetes in Heart Failure Checklist

- ✓Treat heart failure in people with diabetes the SAME as you would a person without diabetes
- ✓METFORMIN recommended if eGFR >30 mL/min/1.73 m^2
- ✓If eGFR <60 mL/min, use Renin Angiotensin Aldosterone system or sacubitril/valsartan blockade carefully
- ✓Do NOT use thiazolidinediones
- ✓Avoid saxagliptin in patients with heart failure and diabetes

Proposed Management of Concomitant Diuretics When Initiating SGLT2 Inhibitors in Patients T2DM



David Z.I. Cherney, and Jacob A. Udell Circulation. 2016

Mrs. P

- 6 months ago following a routine Echo it was noted her LVEF had declined to 35%. You initiated her on triple therapy and she stable has NYHA 2 symptoms. She has not been hospitalized.
- Her Cr is 90 with an eGFR of 55
- She is asking if SGLT2i is a good option for her (“she read in her favourite magazine about a new drug that can lower her sugars and help her lose weight”)

ARS

- Would you prescribe a SGLT2i for patients:
  - Prevention of HF in T2DM patients with CVD = **12%**
  - T2DM with HFpEF = **2%**
  - T2DM with HFrEF = **2%**
  - All of the above = **82%**
  - I don’t know = **2%**

What's coming up with SGLT2s and heart failure?

DAPA-HF: Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients with Chronic HF

Population:
- ≥18 years of age
- Established documented diagnosis of symptomatic HFrEF (NYHA functional class II-IV) for ≥ 2 months
- LVEF ≤40%
- NTproBNP ≥ 600 pg/ml
- eGFR ≥30 ml/min/ 1.73m^2
- Stable SoC HFrEF treatment

N = ~4500

Randomization 1:1

- Placebo + SoC
- Dapagliflozin 10 mg + SoC

Primary endpoint:

Time to first occurrence of any of the components of the composite:
- CV death or hospitalization for HF or an urgent HF visit

Secondary endpoints:
- Time to first occurrence of CV death or hHF
- Total number of (first and recurrent) hHF and CV death
- Change from baseline in KCCQ at 8 months
- Time to first occurrence of renal composite (≥50% sustained decline in eGFR, ESRD or renal death)

Study Start: Feb 2017

Estimated Study Completion: BEFORE Fall 2019! ➔ AHA 2019?

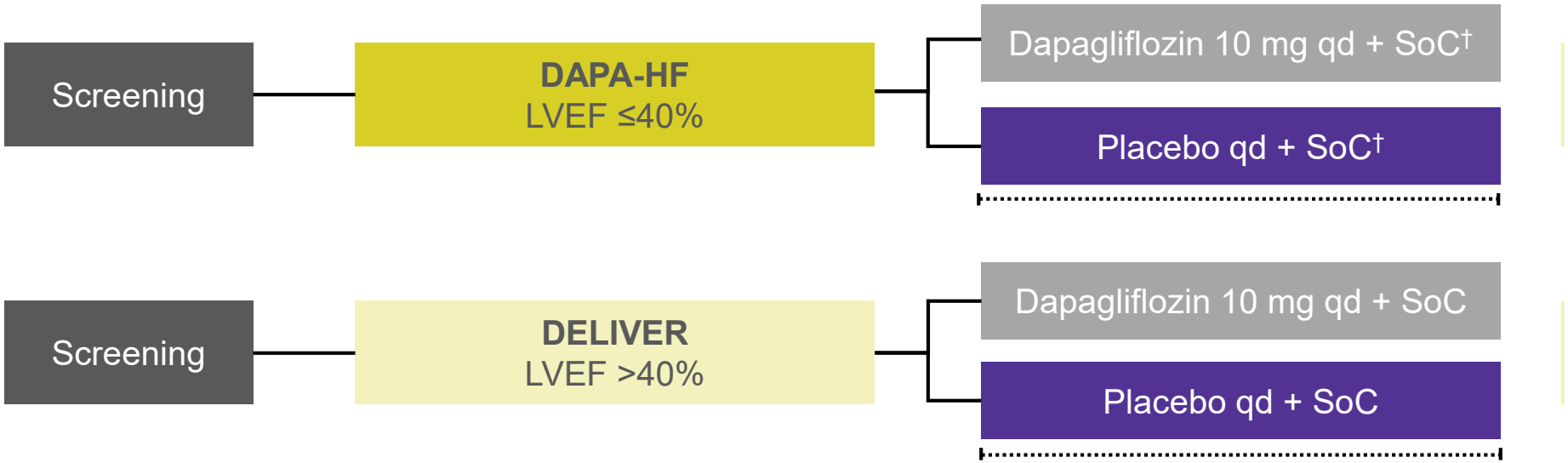
CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; N, number of patients; NTproBNP, N-terminal pro b-type natriuretic peptide; SCV, study closure visit; SED, study end date; SoC, standard of care

https://clinicaltrials.gov/show/NCT03036124

What's coming up with SGLT2s and heart failure?
DAPA-HF and DELIVER

Aim: To investigate the safety and efficacy of dapagliflozin versus placebo on top of guideline-directed medical therapy in patients with heart failure with **reduced** or **preserved ejection fraction**

Population: T2D and non-T2D, age ≥18 years, chronic HF (NYHA II–IV)



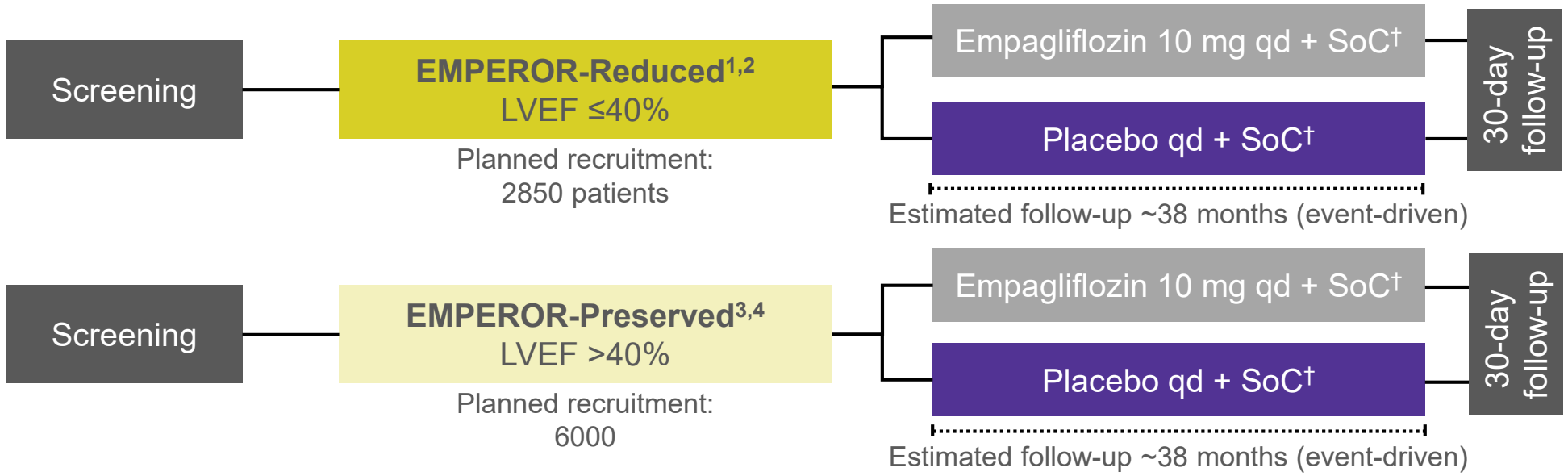
What's coming up with SGLT2s and heart failure?

EMPEROR-Reduced and EMPEROR-Preserved

Phase III randomised double-blind placebo-controlled studies

Aim: To investigate the safety and efficacy of empagliflozin versus placebo on top of guideline-directed medical therapy in patients with heart failure with **reduced** or **preserved ejection fraction**

Population: T2D and non-T2D, age ≥18 years, chronic HF (NYHA II–IV)



*Based on blinded assessment of event rate; †Guideline-directed medical therapy

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SoC, standard of care

1. ClinicalTrials.gov. NCT03057977; 2. Zannad F *et al. ESC-HF* 2018; poster P1755; 3. ClinicalTrials.gov. NCT03057951; 4. Butler J *et al. ESC-HF* 2018; poster P972

Update on Mrs. P

Started on SGLT2 inhibitor

- Creatinine went from 120 to 144 mml/L:
  - Creatinine back to 130 mmol/L 2 weeks later
  - Last seen 08/4/2019, stable NYHA 2, NT-proBNP 2293
  - Creatinine 130 mmol/L - eGFR 35 ml/min, Urine ACR 70 mg/mmol
  - Kidney Failure Risk – 12 % over 5 years

Current meds: EF 35%, no ICD, NYHA 2

- Metformin 500 mg po BID
- Empa 10 mg po OD
- Lasix 80 mg po OD
- Sac/valsartan 50 mg po BID
- Metoprolol 25 mg po BID
- Atorvastatin 80 mg po OD
- Rivaroxaban dose 15 mg po OD

Chronic Kidney Disease Management

Navdeep Tangri

MD, PhD, FRCPC

@NavTangri

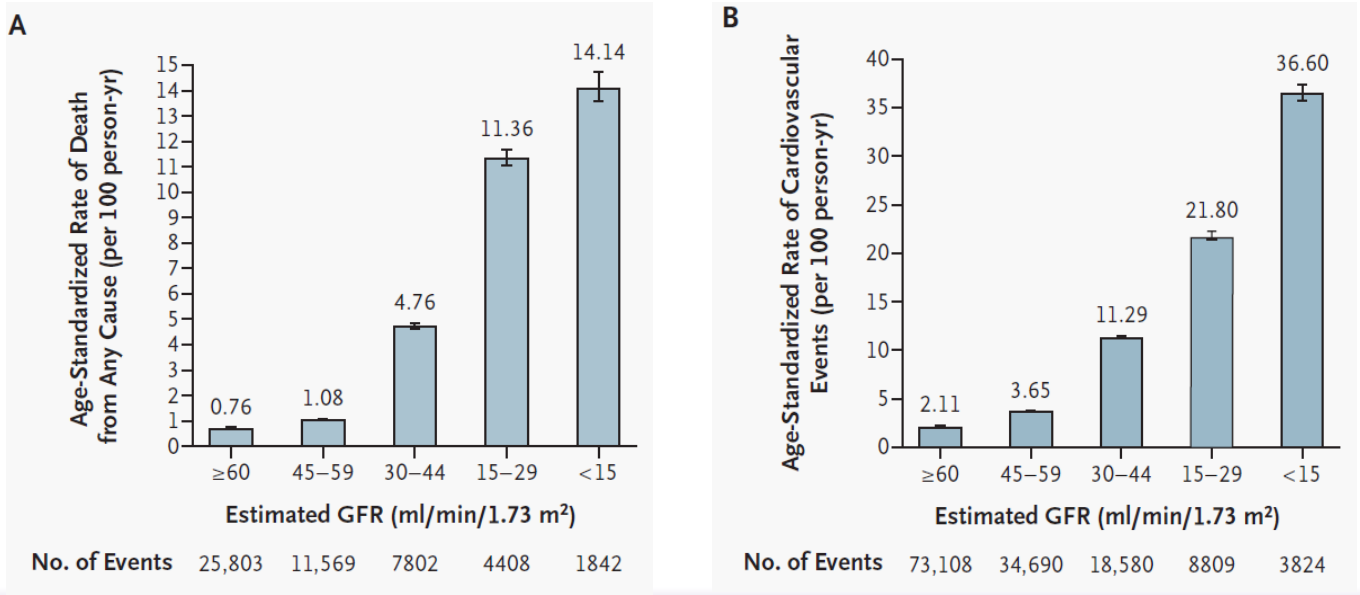
CKD is associated with adverse outcomes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

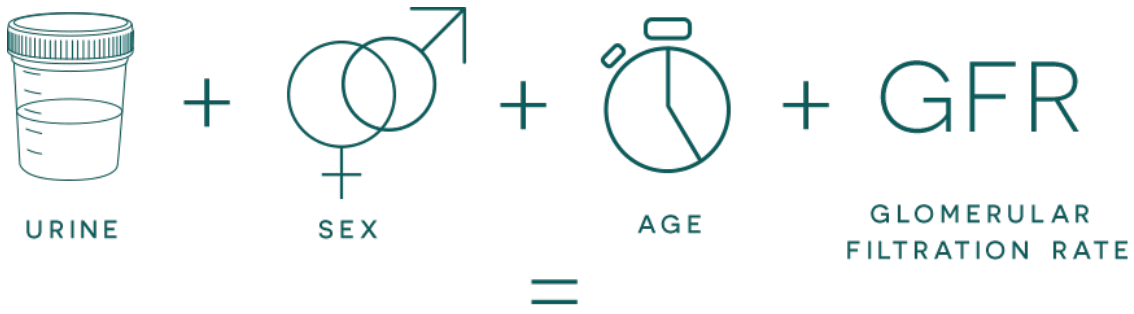
Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization

Alan S. Go, M.D., Glenn M. Chertow, M.D., M.P.H., Dongjie Fan, M.S.P.H., Charles E. McCulloch, Ph.D., and Chi-yuan Hsu, M.D.



Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004 Sep 23;351(13):1296-305. Erratum in: N Engl J Med. 2008;18(4):4.

Importance of Albuminuria - Risk



KDIGO Heatmap

Composite Ranking for Relative Risks by GFR and Albuminuria: KDIGO 2009

GFR Stages, Description and Range (mL/min/1.73m^2)				Albuminuria Stages, Description and Range (mg/g)				
				A1		A2	A3	
				optimal and high-normal		high	very high and nephrotic	
				<10	10-29	30-299	300-1999	≥2000
	G1	high and optimal	>105					
			90-104					
	G2	mild	75-89					
			60-74					
	G3a	mild-moderate	45-59					
	G3b	moderate-severe	30-44					
	G4	severe	15-29					
	G5	kidney failure	<15					

Levin, Adeera, et al. "Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease." *Kidney International Supplements* 3.1 (2013): 1-150.

Tangri, Navdeep, et al. "A predictive model for progression of chronic kidney disease to kidney failure." *Jama* 305.15 (2011): 1553-1559.

Published CVOTs demonstrating superiority
Secondary Renal Outcomes

	TRIAL	SECONDARY OUTCOMES				
		New or worsening nephropathy	Doubling of SrCr	Progression to MAU / of albuminuria	Initiation of RRT	Composite : 40% ↓eGFR, RRT, renal death
CV TRIALS	**EMPA-REG** HR (95% CI)	0.61 (0.53, 0.70)	0.56 (0.39, 0.79)	0.62* (0.54, 0.72)	0.45 (0.40, 0.75)	0.54 (0.40, 0.75)
	CANVAS HR (95% CI)	NR	NR	0.73** (0.67, 0.79)	NR	0.53 (0.33,0.84)
	DECLARE HR (95% CI)	NR	NR	NR	NR	0.53

NR, not reported; NS, not significant; * Progression to microalbuminuria; ** Progression of albuminuria. This was defined as more than a 30% increase in albuminuria and a change from either normoalbuminuria to microalbuminuria or macroalbuminuria, or from microalbuminuria to macroalbuminuria; §End-stage kidney disease, defined as dialysis, transplantation, or a sustained estimated GFR of <15 ml / min / 1.73 m^2; ‡End-stage kidney disease, doubling of serum creatinine level, or renal death.

1. Zinman B, et al.. *N Engl J Med* 2015;373:2117-28. 2 Neal B. et al, *N Engl J Med* 2017;377:644-57. 3. Wiviott SD et al. *N Engl J Med* 2018;DOI:10.1056/NEJMoa1812389. 4. Marso S et al. *N Engl J Med* 2016;375:311-22. 5. Marso S et al. *N Engl J Med* 2016;375:1834-44. 6. Perkovic V, et al. *N Engl J Med* 2019; DOI: 10.1056/NEJMe1904740.

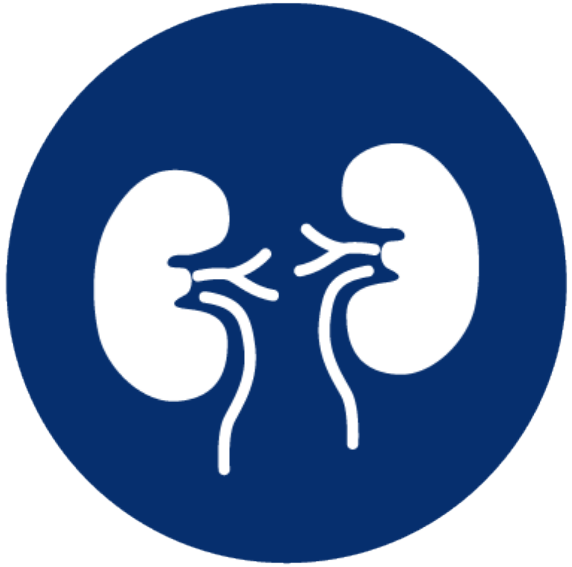
Many Renal Effects of SGLT2 Inhibition Have Been Proposed

↓ Intraglomerular pressure

↓ Glucose

↓ BP/arterial stiffness

↓ Volume



↓ Albuminuria

↓ Oxidant stress

↓ Intrarenal angiotensinogen upregulation

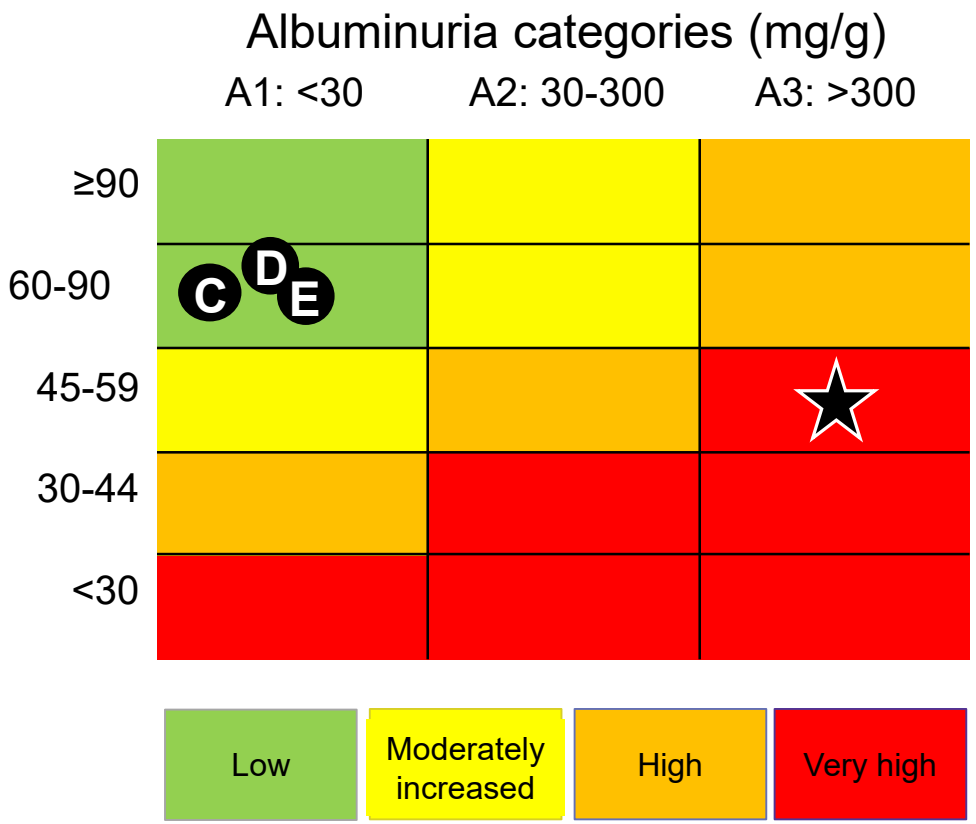
↓ Inflammation/fibrosis

And many others…

ARS

- At what eGFR should we not prescribe SGLT2 inhibitors?
  - < 60 = **0%**
  - < 45 = **4%**
  - < 30 = **82%**
  - It’s a moving target after Credence = **14%**

CREDENCE



	Mean eGFR (mL/min/1.73 m²)	Median UACR (mg/g)
D DECLARE	85	13
C CANVAS Program	76	12
E EMPA-REG OUTCOME	74	18
★ CREDENCE	56	927

Sustained RRT Events

DECLARE	Not reported
CANVAS Program	18
EMPA-REG OUTCOME	11
CREDENCE	**176**

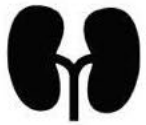
CREDENCE: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy

The George Institute for Global Health

Study design and participants

4401 patients with T2DM & UACR >300 mg/g

62 years

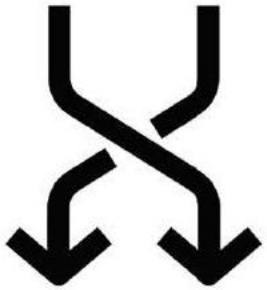


eGFR 57

UACR 927 mg/g

Intervention

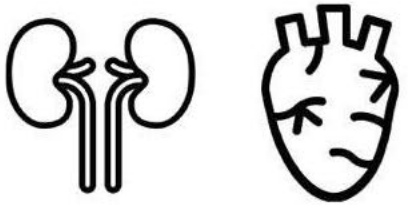
Stable on maximum dose tolerated ACEi or ARB for 4 weeks



Canagliflozin **Placebo**

Outcomes

Primary outcome
(Doubling of serum creatinine, ESKD, death due to cardiovascular or kidney disease)



HR 0.70
(95% CI 0.59-0.82)

NNT 21

End-stage kidney disease

HR 0.68
(95% CI 0.54-0.86)

NNT 42

No increased risk of:

Amputations

HR 1.10
(95% CI 0.79-1.56)

Fractures

HR 0.98
(95% CI 0.70-1.37)

Conclusion

In patients with type 2 diabetes and kidney disease, canagliflozin reduces the risk of kidney failure and cardiovascular events

Credence Summary

	Hazard ratio (95% CI)	*P* value	
Primary			
1. ESKD, doubling of serum creatinine, or renal or CV death	0.70 (0.59–0.82)	0.00001	✔
Secondary			
2. CV death or hospitalization for heart failure	0.69 (0.57–0.83)	<0.001	✔
3. CV death, MI, or stroke	0.80 (0.67–0.95)	0.01	✔
4. Hospitalization for heart failure	0.61 (0.47–0.80)	<0.001	✔
5. ESKD, doubling of serum creatinine, or renal death	0.66 (0.53–0.81)	<0.001	✔
6. CV death	0.78 (0.61–1.00)	0.0502	Not significant
7. All-cause mortality	0.83 (0.68–1.02)	–	Not formally tested
8. CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina	0.74 (0.63–0.86)	–	Not formally tested

Published CVOTs demonstrating superiority Secondary Renal Outcomes

	TRIAL	SECONDARY OUTCOMES				
		New or worsening nephropathy	Doubling of SrCr	Progression to MAU / of albuminuria	Initiation of RRT	Composite : 40% ↓eGFR, RRT, renal death
CV TRIALS	**LEADER** HR (95% CI)	0.78 (0.67, 0.92)	NR	NR	NR	NR
	SUSTAIN-6 HR (95% CI)	0.64 (0.46, 0.88)	NR	NR	NR	NR

NR, not reported; NS, not significant; * Progression to microalbuminuria; ** Progression of albuminuria. This was defined as more than a 30% increase in albuminuria and a change from either normoalbuminuria to microalbuminuria or macroalbuminuria, or from microalbuminuria to macroalbuminuria; §End-stage kidney disease, defined as dialysis, transplantation, or a sustained estimated GFR of <15 ml / min / 1.73 m^2; ‡End-stage kidney disease, doubling of serum creatinine level, or renal death.

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What's Coming Up with SGLT2i's and CKD?

Study	Setting	Trial ID	Primary completion
Credence	T2DM and CKD	NCT02065791	Reported
Dapa-CKD	Chronic kidney disease	NCT03036150	Nov 2020
Scored	T2DM and CKD	NCT03315143	Mar 2022
Empa-Kidney	Chronic kidney disease	NCT03594110	Jun 2022

#Cardiotwitter Question

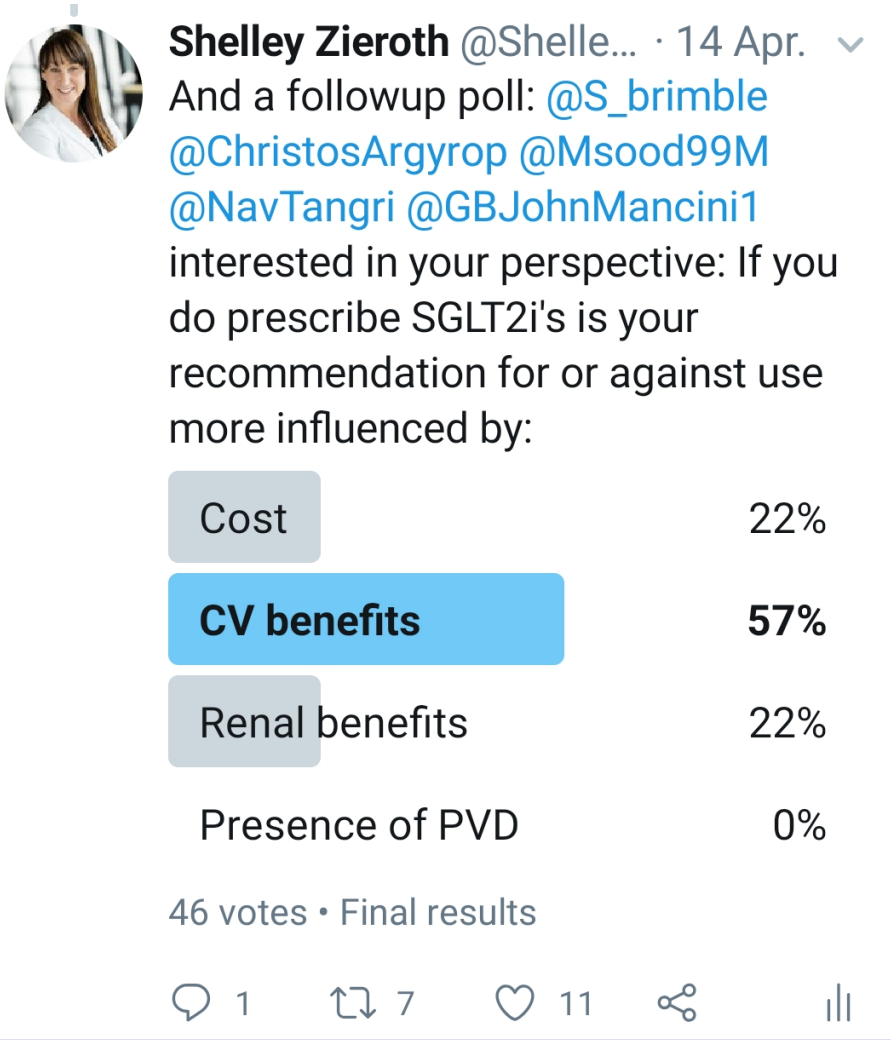
Shelley Zieroth @Shelle... · 14 Apr.

And a followup poll: @S_brimble @ChristosArgyrop @Msood99M @NavTangri @GBJohnMancini1 interested in your perspective: If you do prescribe SGLT2i's is your recommendation for or against use more influenced by:

ARS Question

- If you do prescribe SGLT2i's is your recommendation for or against use influenced by:
  - Cost = **29%**
  - CV benefits = **63%**
  - Renal benefits = **6%**
  - Presence of PVD = **2%**

#Cardiotwitter Answer



Closing Remarks

Shelley Zieroth
MD, FRCPC, FCCS
@ShelleyZieroth