Update on CVOT in Diabetes

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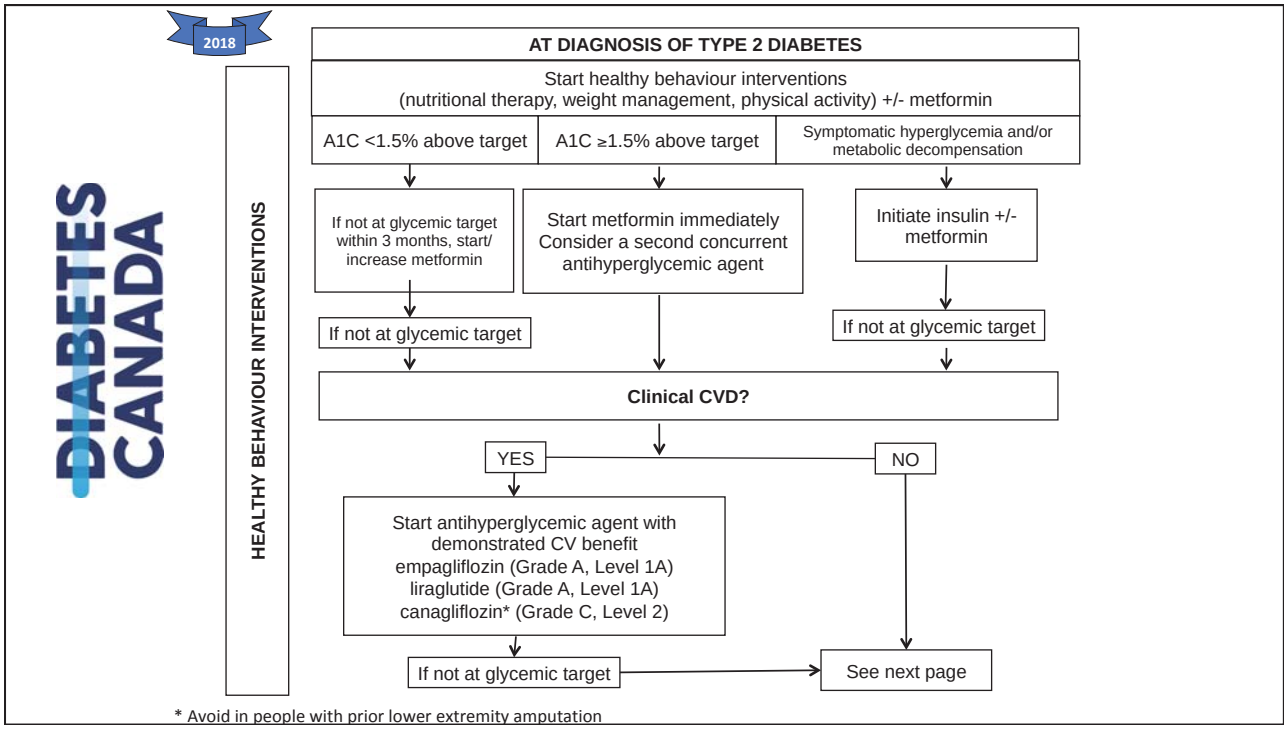
Objectives

- Review summary of CVOT data
- Identify different relevant patient populations for each outcome
- Review Diabetes Canada Guideline Recommendations



2018 Diabetes Canada CPG – Chapter 23. Cardiovascular Protection in People with Diabetes

2018

Recommendation 8[1]

In adults with type 2 diabetes with clinical CVD in whom glycemic targets are not achieved with existing antihyperglycemic medication(s) and with eGFR >30 mL/min/1.73m^2, an antihyperglycemic agent with demonstrated CV outcome benefit should be added to reduce the risk of major CV events [Grade A, Level 1A for empagliflozin; Grade A, Level 1A for liraglutide; Grade C, Level 2 for canagliflozin]

22% of all patients with T2DM have clinical CVD[2]

CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate.
1. Stone et al. Can J Diabetes 2018;42(Suppl 1):S162-9; 2. Iglay et al. Curr Med Res Opin. 2016;32:1243-52.

2018

Clinical CVD?

NO

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 Clinical CVD or CV risk factors Degree of hyperglycemia Other comorbidities (CHF, hepatic disease) Planning pregnancy Cost/coverage Patient preference	see Renal Impairment Appendix See Table Below

CHF: chronic heart failure; CVD: cardiovascular disease; DPP-4: dipeptidyl peptidase-4; eGFR: estimated glomerular filtration rate; GLP-1: glucagon like peptide-1; SGLT2: sodium/glucose cotransporter 2.

1. Lipsombe et al. Can J Diabetes. 2018;42(Suppl 1):S88-103.

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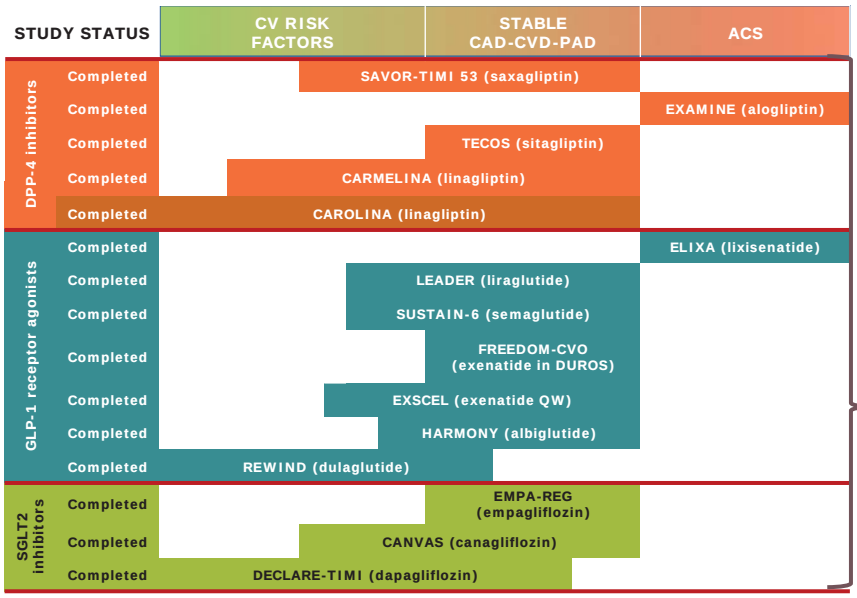
PATIENT CARDIOVASCULAR STATUS



>15 CVOTs have been initiated since the 2008 FDA guidance

Differences in baseline patient characteristics and trial design make it difficult to compare results across CVOTs

Adapted from clinicaltrials.gov; Schnell O, et al. Cardiovasc Diabetol. 2017;16(1):128.
ACS, acute coronary syndrome; CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral artery disease.

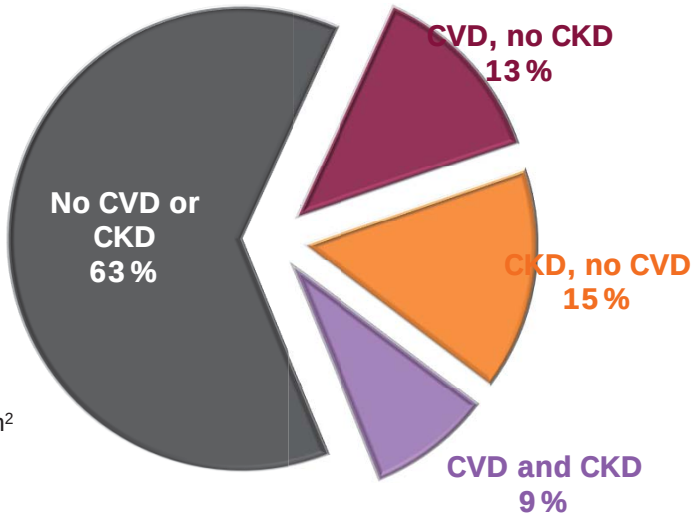
3 different types of patients, 2 different questions

1. With diabetes and established CVD
2. With diabetes and renal failure
3. With diabetes and multiple risk factors for CVD

Questions:

1. Is it safe? (non inferiority)
2. Does it reduce outcomes in the prespecified group (superiority)

Comorbidities in T2DM – who are our patients?



CKD = GFR < 60 mL/min/1.73 m^2 and/or albuminuria)

Iglay K et al. Curr Med Res Opin. 2016 Jul;32(7):1243-52.

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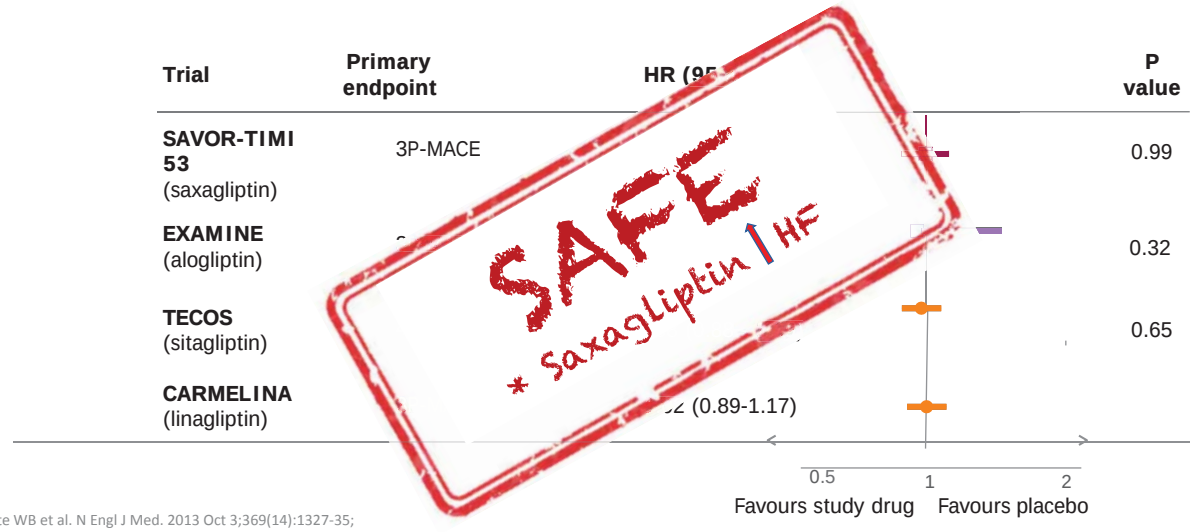
DIABETES CANADA

Add additional antihyperglycemic agent best suited to the individual by prioritizing patient characteristics (*agents listed in alphabetical order by CV outcome data*):

Class	Effect on CVD Outcomes	Hypo-glycemia	Weight	Relative A1C Lowering when added to metformin	Other therapeutic considerations	Cost
GLP-1R agonists	lira: Superiority in T2DM with clinical CVD exenatide LAR & lixi: Neutral	Rare	↓↓	↓↓ to ↓↓↓	GI side-effects, Gallstone disease Contraindicated with personal / family history of medullary thyroid cancer or MEN 2 Requires subcutaneous injection	$$$$
SGLT2 inhibitors	Cana & empa: Superiority in T2DM patients with clinical CVD	Rare	↓↓	↓↓ to ↓↓↓	Genital infections, UTI, hypotension, dose-related changes in LDL-C. Caution with renal dysfunction, loop diuretics, in the elderly. Dapagliflozin not to be used if bladder cancer. Rare diabetic ketoacidosis (may occur with no hyperglycemia). Increased risk of fractures and amputations with canagliflozin. Reduced progression of nephropathy & CHF hospitalizations with empagliflozin and canagliflozin in those with clinical CVD	$$$
DPP-4 Inhibitors	alo, saxa, sita: Neutral	Rare	Neutral	↓↓	Caution with saxagliptin in heart failure Rare joint pain	$$$
Insulin	glar: Neutral degludec: noninferior to glar	Yes	↑↑	↓↓↓↓	No dose ceiling, flexible regimens Requires subcutaneous injection	$-$$$$
Thiazolidinediones	Neutral	Rare	↑↑	↓↓	CHF, edema, fractures, rare bladder cancer (pioglitazone), cardiovascular controversy (rosiglitazone), 6-12 weeks for maximal effect	$$
α-glucosidase inhibitor (acarbose)		Rare	Neutral	↓	GI side-effects common Requires 3 times daily dosing	$$
Insulin secretagogue: Meglitinide		Yes	↑	↓↓	More rapid BG-lowering response Reduced postprandial glycemia with meglitinides but usually requires 3 to 4 times daily dosing.	$$
Sulfonylurea		Yes	↑	↓↓	Gliclazide and glimepiride associated with less hypoglycemia than glyburide. Poor durability	$
Weight loss agent (orlistat)		None	↓	↓	GI side effects Requires 3 times daily dosing	$$$

DPP-4inhibitors: Pts with DM2 + CVD



White WB et al. N Engl J Med. 2013 Oct 3;369(14):1327-35;
Scirica BM et al. N Engl J Med. 2013 Oct 3;369(14):1317-26;
Green JB et al. N Engl J Med. 2015 Jul 16;373(3):232-42.
JAMA. 2019 Jan 1;321(1):69-79. doi: 10.1001/jama.2018.18269.

SGLT2 inh

Pts with DM2 and CVD

Canagliflozin – CANVAS program

- CANVAS: 65.6%

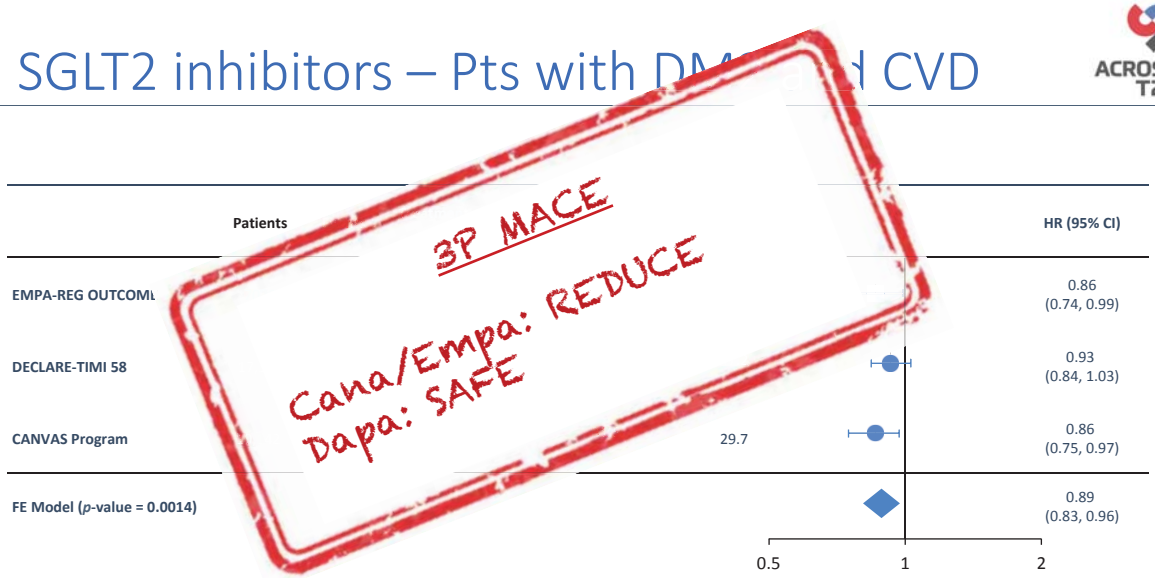
Empagliflozin – EMPA REG

- EMPA-REG: 99.5%

Dapagliflozin – DECLARE TIMI-58

- DECLARE-TIMI: 41%

SGLT2 inhibitors – Pts with DM and CVD



Q statistic = 1.20; p=0.55; I^2=0%

Comparisons of trials should be interpreted with caution due to differences in study design, populations and methodology

CVOT, cardiovascular outcomes trial; MACE, major adverse cardiovascular events; PY, patient-years; SGLT2,

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Diabetes and Heart Failure

Heart failure is

one of **most common** CV complications of diabetes

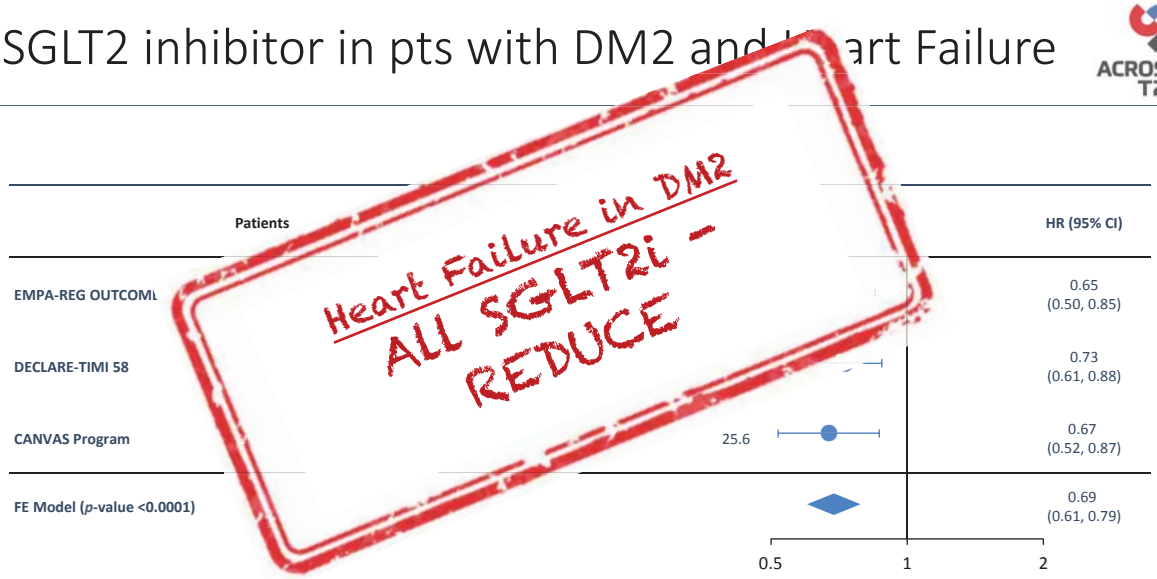
the **most disabling and deadly** complication of diabetes

There is a very high rate preserved ejection fraction heart failure in diabetes (HfpEF)

The effects of glucose-lowering therapies on heart failure vary

McMurray JJ et al. Lancet Diabetes Endocrinol. 2014 Oct;2(10):843-51; Gilbert R, Krum H. Lancet. 2015 May 23;385(9982):2107-17.

SGLT2 inhibitor in pts with DM2 and Heart Failure



Q statistic = 0.60; p=0.74; I^2=0%

Comparisons of trials should be interpreted with caution due to differences in study design, populations and methodology

CVOT, cardiovascular outcomes trial; HHF, hospitalisation for heart failure; PY, patient-years; SGLT2, sodium-glucose co-transporter-2

Zelniker A *et al. Lancet* 2019;393:31

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SGLT2 inh

Pts with Heart Failure with AND Without DM2

Dapagliflozin

DAPA HF

- Patients with DM2: (42%)

Empagliflozin

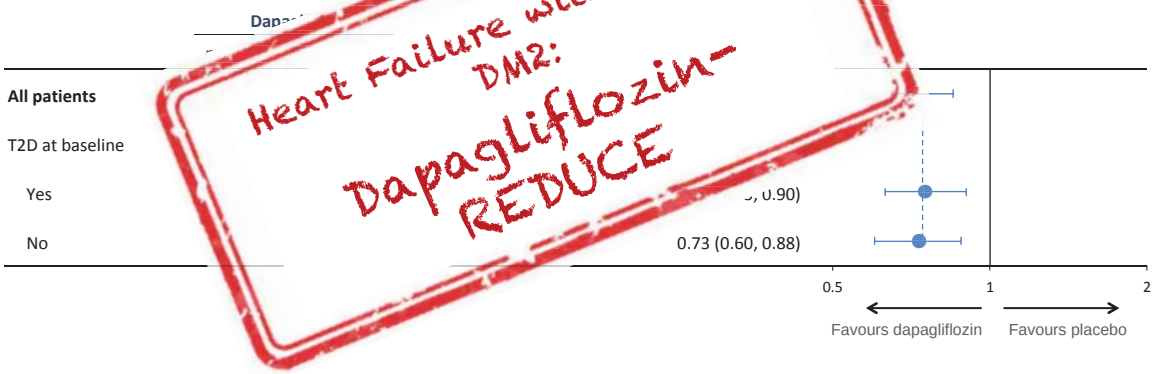
EMPEROR- reduced

EMPEROR – preserved (Stay Tuned!)

DAPA-HF: SGLT2i – Pts with Heart Failure with OR without DM2

ACROSS T2D

The effect of dapagliflozin on the primary composite … patients with or without T2D at baseline



Heart Failure with or w/o DM2: Dapagliflozin- REDUCE

*Worsening HF (unplanned hospitalisation for HF or urgent visit resulting in intravenous therapy for HF) or cardiovascular death
HF, heart failure; T2D, type 2 diabetes
McMurray J *et al. N Engl J Med* 2019; doi: 10.1056/NEJMoa1911303

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GLP1 agonists

Pts with DM2 and CVD

Liraglutide – LEADER
- LEADER: 81.3%

Semaglutide – SUSTAIN-6
- SUSTAIN 6: 83.0%

Dulaglutide – REWIND
- REWIND: 31%

GLP1 agonists – Pts with DM2 and CVD

* Not commercially available in Canada
3P, 3-point MACE; 4P, 4-point MACE
Adapted from: Holman RR, Bethel MA, Mentz RJ, et al. N Engl J Med. 2017 [epub ahead of print]; Marso SP, et al. N Engl J Med. 2016;375(4):311-322; Marso SP, et al. N Engl J Med. 2016;375(19):1834-1844; Pfeffer M
al. N Engl J Med. 2015;373(23):2247-2257; Hernandez AF, et al. The Lancet. 2018 [epub ahead of print]. Eli Lilly and Company "Trulicity® (dulaglutide) demonstrates superiority in reduction of cardiovascular events fo
range of people with type 2 diabetes " available at: Press https://investor.lilly.com/news-releases/news-release-details/trulicityr-dulaglutide-demonstrates-superiority-reduction.

3 different types of patients, 2 different questions

1. With diabetes and established CVD
2. With diabetes and renal failure
3. With diabetes and multiple risk factors for CVD

Questions:

1. Does it improve renal outcomes?
2. Does it reduce heart disease in renal patients?

SGLT2i
Pts with DM2 and Renal Failure

Does it reduce renal outcomes?

EXPLORATORY
Canagliflozin – CANVAS program
Empagliflozin – EMPA REG
Dapagliflozin – DECLARE TIMI-58
PRIMARY ANALYSIS
Canagliflozin – CREDENCE
Dapagliflozin – DAPA CKD (due to be completed 2020)

SGLT2i – Pts with DM2 and Renal Failure

ACROSS T2D

Trial	SGLT2i n event/ N analysed (%)	SGLT2i Rate/ 1000 PY	Placebo			p-value
Dedicated cardiovascular outcomes trials: ex						
EMPA-REG OUTCOME[1] Doubling of serum creatinine,* RRT death from kidney causes						<0.001†
DECLARE-TIMI 58[2] ≥40% decrease in eG min/1.73 m², new ESR. kidney causes						NR
CANVAS Program[3] Doubling of serum creatini death from kidney causes						NR
Dedicated kidney outcon						
CREDENCE[4] Doubling of serum creatinine, ES death from kidney causes		2199	40.4	0.66 (0.53, 0.81)		<0.001

0.25 0.5 1 2

Favours SGLT2i Favours placebo

Renal Failure
Canagliflozin
Empa/dapa (likely)
REDUCE

Comparisons of trials should be interpreted with caution due to differences in study design, populations and methodology

*Accompanied by eGFR ≤45 ml/min/1.73 m²; †Nominal *p*-value. eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; ESRD, end-stage renal disease; NR, not reported; PY, patient-years; RRT, renal replacement therapy; SGLT2i, sodium-glucose co-transporter-2 inhibitor

1. Wanner C *et al. N Engl J Med* 2016;375:323; 2. Wiviott SD *et al. N Engl J Med* 2019;380:347; 3. Perkovic V *et al. Lancet Diabetes Endocrinol* 2018;6:691; 4. Perkovic V *et al. N Engl J Med* 2019; doi: 10.1056/NEJMoa1811744

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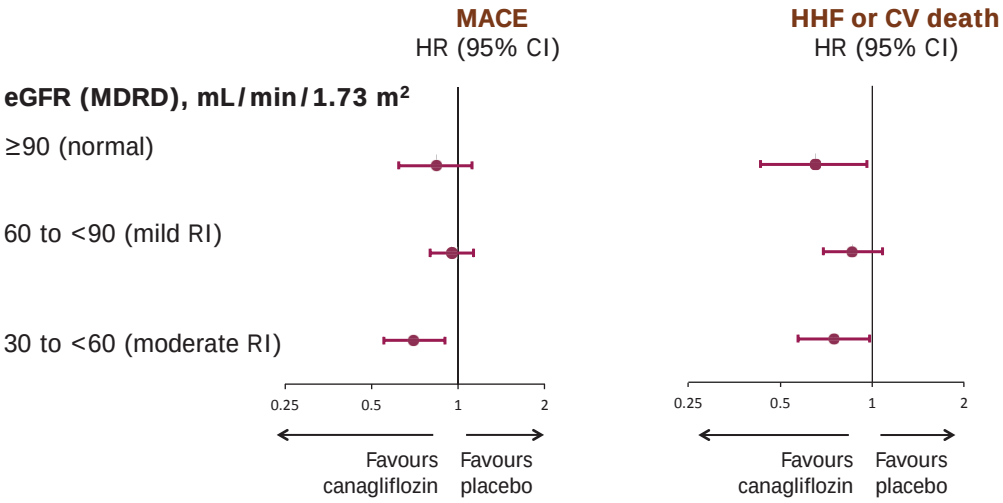
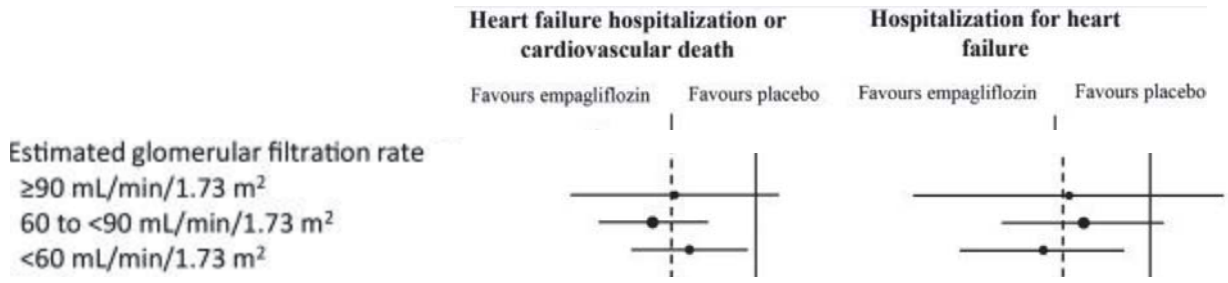
CANVAS – CV benefits across GFR range



Adapted from Neal B et al. N Engl J Med. 2017 Aug 17;377(7):644-657 and Radholm K et al. Circulation.2018;137:DOI: 10.1161/CIRCULATIONAHA.118.034222.

EMPA REG – CV outcomes at different GFR ranges



Zinman B et al. N Engl J Med. 2015 Nov 26;373(22):2117-28 and Fitchett D et al. Eur Heart J. 2016 May 14;37(19): 1526-34.

New Renal Impairment Considerations (based on clinical data and not product monographs)

DIABETES CANADA 2018

Medication	CKD 3A (eGFR 45–59mL/min)	CKD 3B (eGFR 30–44 mL/min)	CKD 4 (eGFR 15–29 mL/min)	CKD 5 (eGFR <15 mL/min or dialysis)
Metformin‡	Dose adjustment not required	Reduce dose (500–1,000 mg/day) Do not initiate, can maintain	Use alternative agent due to risk of accumulation	
GLP-1 receptor agonists				
Dulaglutide	Dose adjustment not required			Caution as safety not established
Exenatide/ Exenatide ER	Dose adjustment not required (>50 mL/min)	Caution (30–50 mL/min)	Use alternative agent due to risk of accumulation	
Lixisenatide	Dose adjustment not required		Use alternative agent as safety not established	
Liraglutide	Dose adjustment not required			Use alternative agent as safety not established
SGLT2 inhibitors				
Canagliflozin‡	Can maintain at 100 mg daily, do not initiate for glycemic control. May be initiated when indicated for CV and renal protection*	Use alternative agent because of limited glycemic efficacy. May be considered when indicated for CV and renal protection*	Use alternative agent due to lack of glycemic efficacy	
Dapagliflozin‡	Use alternative agent due to lack of glycemic efficacy			
Empagliflozin‡	Can maintain, do not initiate for glycemic control. May be initiated when indicated for CV and renal protection*	Use alternative agent because of limited glycemic efficacy. May be considered when indicated for CV and renal protection*	Use alternative agent due to lack of glycemic efficacy	

Adapted from Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes. 2018 Apr;42 (Suppl 1):S315.

3 different types of patients, 2 different questions

- With diabetes and established CVD
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- Questions:
  - Is it safe? (non inferiority)
  - Does it reduce outcomes in the prespecified group (superiority)

What were the risk factors?

- Dyslipidemia
- Hypertension
- CKD (GFR<60)
- Smoking
- Obesity
- Increase hsCRP

Primary Prevention

SGLT2 inhibitors

Canagliflozin – CANVAS Program (34%)

Dapagliflozin – DECLARE TIMI 58 (59%)

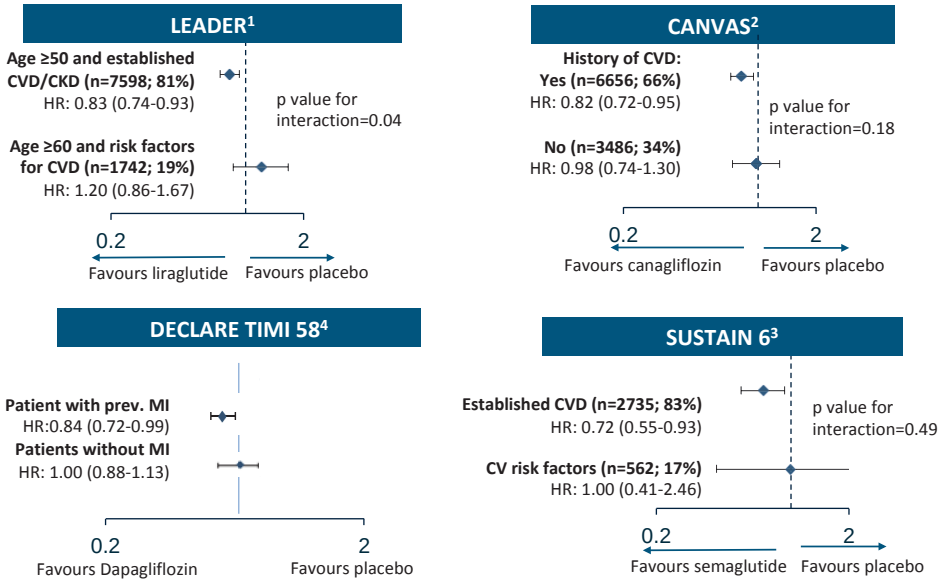
GLP1 Agonists

Liraglutide – LEADER (19%)

Semaglutide – SUSTAIN 6 (17%)

Dulaglutide – REWIND (69%)

Patients with DM2, WITHOUT CV disease



REWIND: with and without CV di

ACROSS T2D

MACE – 1° prevention
GLP1a, canagliflozin, dapagliflozin
SAFE

Gerstein HC *et al. La* 019;394:121

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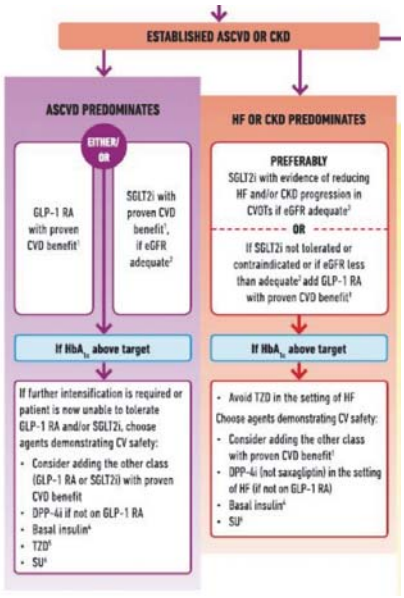
Med Management for Type 2 ADA EASD Algorithm, 2019

- Metformin is first line, if not well controlled WITH CVD
- If ASCVD predominates
  - Use GLP1 or SGLT2i
- If HF or CKD predominates
  - Use SGLT2i first
  - Consider GLP1 if cannot use SGLT2i



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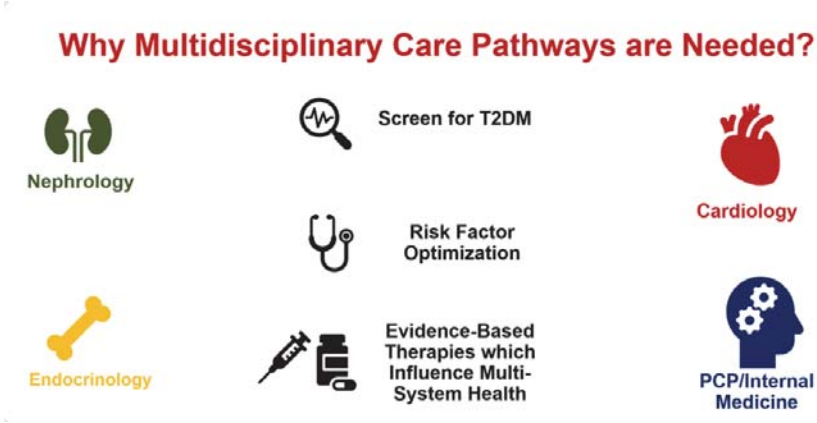
Let's All Work Together



The official American College of Cardiology (ACC) account.