Presenter Disclosures

Diabetes management: focusing on CV outcomes

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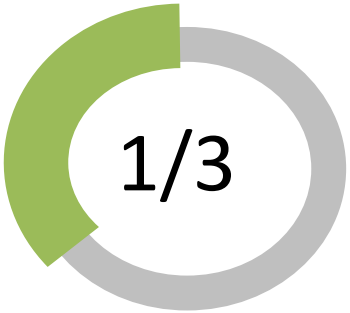
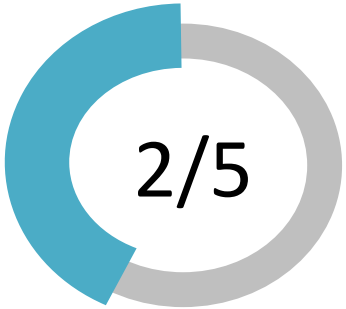
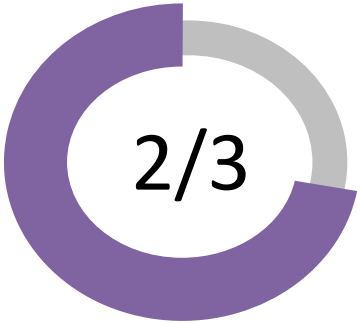
In Canada, People with Diabetes Account For…



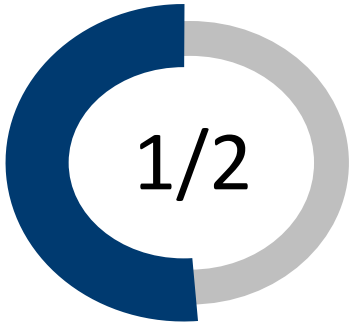
of all heart attacks & strokes



of all heart failure admissions



of all non-traumatic amputations



all patients starting dialysis

Booth, et al.; Hux, et al.; and Oliver, et al. Diabetes in Ontario: An ICES Practice Atlas. 2003. www.ices.on.ca.

SHOULD WE ADD AN ANTIHYPERGLYCEMIC AGENT TO REDUCE CARDIOVASCULAR OUTCOMES?

Cardiovascular Considerations for Add-On Antihyperglycemic Agents

CV considerations	Class	Agents	Relative A1C lowering	Risk of hypoglycemia	Heart failure	BP effect
CV superiority demonstrated as primary endpoint in RCT by ≥1 agent in class	GLP-1 receptor agonist	liraglutide, lixisenatide, dulaglutide, exenatide, semaglutide	↓↓/↓↓↓	Rare	Neutral	↓
	SGLT-2 inhibitor	empagliflozin, canagliflozin* dapagliflozin	↓↓/↓↓↓	Rare	↓	↓
CV safety demonstrated as primary endpoint in RCT by ≥1 agents in class	DPP-4 inhibitor	alogliptin, sitagliptin, saxagliptin, linagliptin	↓↓	Rare	Neutral ↑ saxa	Neutral
	Thiazolidinedione	pioglitazone, rosiglitazone	↓↓	Rare	↑	Neutral
	Insulin	glargine 100 u/mL, degludec, other basal/bolus/premixed	↓↓↓	Yes**	Neutral	Neutral
CV safety unknown or RCT results not yet available	Weight loss agent	orlistat	↓	None		
	α-glucosidase inhibitor	acarbose	↓	Rare		
	Meglitinide	nateglinide, repaglinide	↓↓	Yes		
	Sulfonylurea	gliclazide, glimepiride, glyburide	↓↓	Yes		

Agents in blue bold text showed CV superiority for MACE. Agents in black bold text showed CV safety.

*Increased lower extremity amputations. | **Lower hypoglycemia risk with newer generation basal insulins (*e.g.*, degludec, glargine 300 u/mL).

Adapted from: Mancini GB, et al. *Can J Cardiol* 2017;33(3):366-77.

		PRIMARY OUTCOME	SECONDARY OUTCOMES				
	Medication		CV Death	All cause mortality	Nonfatal MI	Nonfatal Stroke	Hospitalization for Heart Failure
EMPA-REG OUTCOME[1] HR (95% CI)	Empagliflozin	MACE 0.86 (0.74, 0.99)	0.62 (0.49, 0.77)	0.68 (0.57-0.82)	NS	NS	0.65 (0.50, 0.85)
CANVAS[2] HR (95% CI)	Canagliflozin	MACE 0.86 (0.75, 0.97)	NS	NS	NS	NS	0.67 (0.52, 0.87)
DECLARE[6] HR (95% CI)	Dapagliflozin	hHF/ CV Mortality 0.83 (0.73-0.95)	NS	NS	NS	NS	0.73 (0.61-0.88)
LEADER[3] HR (95% CI)	Liraglutide	MACE 0.87 (0.78, 0.97)	0.78 (0.66, 0.93)	0.85 (0.74,0.97)	NS	NS	NS
SUSTAIN-6[4] HR (95% CI)	Semaglutide	MACE 0.74 (0.58, 0.95)	NS	NS	NS	0.61 (0.38, 0.99)	NS
PIONEER-6[4] HR (95% CI)	Semaglutide oral	MACE 0.79 (0.57,1.11)	0.49 (0.27,0.92)	0.51 (0.31,0.84)	NS	NS	NS
REWIND[5] HR (95% CI)	Dulaglutide	MACE 0.88 (0.79-0.99)	NS	NS	NS	0.76 (0.61-0.95)	NS

CV, cardiovascular; CVOT, cardiovascular outcome trial, HR, hazard ratio; NS, not significant; MI, myocardial infarction; hHF hospitalization for heart failure

1 Zinman B, et al. *N Engl J Med* 2015;373(22):2117-28. 2 Neal B, et al, *N Engl J Med* 2017;377:644-57. 3 Marso S, et al. *N Engl J Med* 2016;375(4):311-22. 4 Marso S, et al. *N Engl J Med* 2016;375:1834-44. 5 Gerstein H, et al. Lancet June 2019.
6. Wiviott S, et al. *N Engl J Med 2018.*

DAPA HF: International, multicentre, event-driven, randomized, double-blind, parallel group, placebo-controlled study

Inclusion criteria

- Adults ≥18 yrs
- NYHA Class II-IV HF
- LVEF ≤40%
- Nt-proBNP ≥600 pg/ml*
- eGFR ≥30 ml/min/1.73 m^2
- Stable SoC HF treatment

1:1 Double-blind

Placebo once daily
Added to current background therapy

Dapagliflozin 10 mg once daily
Added to current background therapy

No. of randomized patients: 4,744

- **Duration is event-driven: 844 events**
- **Powered for superiority (power 90%)**
  - HR of 0.80 for dapagliflozin vs. placebo, and using a one-sided alpha of 2.5%

Estimated Study duration ~33 month

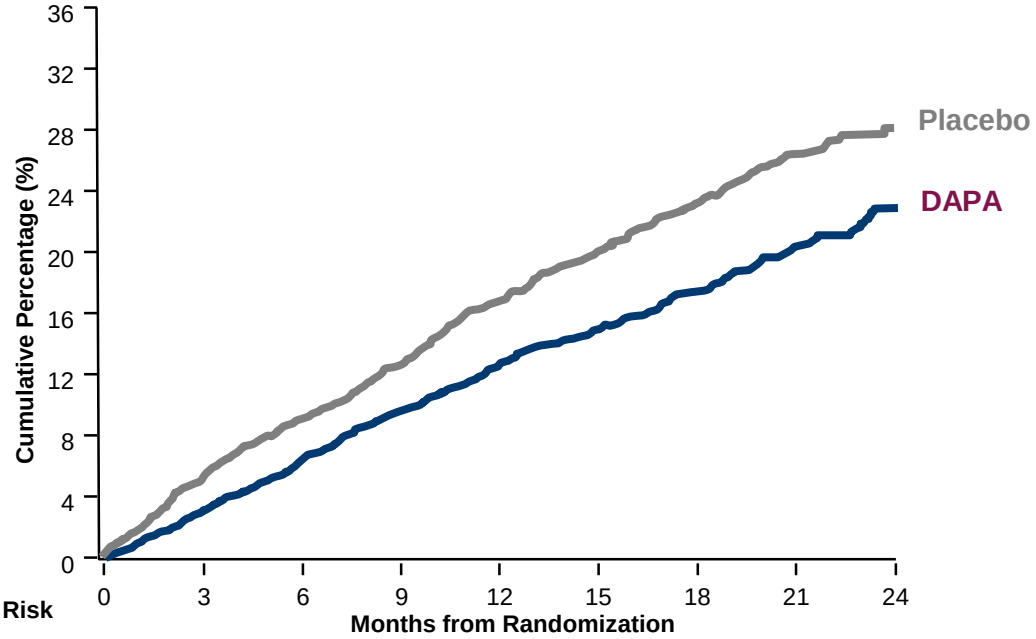
Estimated Average follow-up ~24 months

Primary endpoint: Composite of CV death or HF event

* ≥400 pg/mL if hospitalised for heart failure within the previous 12months; ≥900 pg/mL with atrial fibrillation or atrial flutter
HF event: hospitalisation for heart failure or urgent treatment visit for HF

McMurray et al European Journal of Heart Failure 2019 doi:10.1002/ejhf.1432

Primary Endpoint: CV Death or hHF or an Urgent HF Visit[1]



No. at Risk									
DAPA	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

26% RRR

HR 0.74 (0.65, 0.85)
p=0.00001

NNT = 21

DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; NNT = number needed to treat.

1. McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

2019 ADA/EASD Update: Overall Approach to Glucose-Lowering Medication in Type 2 Diabetes

TOP TIPS!

FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD OR HF[‡]

Consider independent of individualized HbA_{1C} target

Added high-risk patients

ASCVD PREDOMINATES
- **Established ASCVD**
- **Indicators of high ASCVD risk (age ≥55 years + LVH or coronary, carotid, lower extremity artery stenosis >50%)**

PREFERABLY
GLP-1 RA with proven CVD benefit[1]
OR
SGLT2i with proven CVD benefit[1] if eGFR adequate[2]

HF OR CKD PREDOMINATES
- **Particularly HFrEF (LVEF < 45%)**
- **CKD: Specifically eGFR 30-60 ml min/1.73m^2 or UACR >30 mg/g, particularly UACR >300 mg/g**

PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]
OR
If SGLT2i not tolerated or contraindicated or if eGFR less than adequate,[2] add GLP-1 RA with proven CVD benefit[1]

1. Proven CVD benefit means it has a label indication of reducing CVD events. 2. Be aware that SGLT2i labeling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use. 3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozin has primary HF outcome data in DAPA-HF. [‡]Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications. ADA = American Diabetes Association; EASD = European Association for the Study of Diabetes; ASCVD = atherosclerotic cardiovascular disease; GLP-1RA = glucagon-like peptide-1 receptor agonists; SGLT2i = sodium glucose co-transporter 2 inhibitors; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; CVD = cardiovascular disease; UACR = urinary albumin-to-creatinine ratio; LVEF = left ventricular ejection fraction; eGFR = estimated glomerular filtration rate; CVOTs = cardiovascular outcome trials; LVH = left ventricular hypertrophy; CKD = chronic kidney disease. Adapted from: Buse JB, et al. *Diabetes Care* 2020;43:487-93. Updates to the 2018 consensus report are indicated in **magenta** font.

Practical Considerations

Characteristic	Empagliflozin	Canagliflozin	Dapagliflozin	Liraglutide	Semaglutide	Dulaglutide
Class	SGLT2 inhibitor	SGLT2 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	GLP-1 receptor agonist	GLP-1 receptor agonist
Route of administration	Oral once daily	Oral once daily	Oral once daily	SC injection daily	SC injection once weekly Oral sema not yet available	SC injection once weekly
Dosage	10 mg or 25 mg	100 mg or 300 mg	10mg	0.6 mg x 1 wk then 1.2 mg x 1 wk then 1.8mg SC	0.25 mg x 4 wk then 0.5 mg May increase to 1 mg SC per week	Up to 1.5mg week
Cost	~$90/month	~$90/month	~$90/month	~$225/month	~$225/month	~$225/month
eGFR	eGFR > 30	eGFR > 30	eGFR > 45	eGFR >15	eGFR >15 (caution 15-29)	eGFR >15
Wt loss	↓↓	↓↓	↓↓	↓↓	↓↓↓↓	↓↓
BP	↓↓↓	↓↓↓	↓↓↓	↓	↓	↓

eGFR, estimated glomular filtration rate; GLP-1, glucagon-like peptide 1; SC, subcutaneous; SGLT2, sodium glucose cotransporter 2

If Starting SGLT2i

- Explain mechanism of action
- Drink water – stay hydrated
- Proper genital hygiene
- Inform other HCPs
- Stop in acute illness / preoperative
- Do not use in type 1 diabetes
- SADMANS

If Starting a GLP1RA

- Refer to someone else to teach injection or you can teach in your office
- Counsel about nausea that will resolve
- Avoid in persons with Hx of MEN2, medullary thyroid cancer, gastroparesis or pancreatitis

GLP-1 RAs and Nausea: Making it Better

- Set appropriate treatment expectations
  - While common, GI side effects are manageable and transient (typically resolves after 4–8 weeks)
- Use a slow dose escalation
  - Starting at a lower dose and titrating upward can also reduce the incidence of nausea
- Respect satiety
  - Recommend eating small meals throughout the day
  - Avoid consuming high fat foods
  - Patients might find that nausea is more tolerable if they have an empty stomach at the time of dosing (e.g., before bed)

Tella SH, et al. *Ther Adv Endocrinol Metab* 2015;6(3):109-34. Meier JJ. *Nat Rev Endocrinol* 2012;12:728-42. Ross SA. *Am J Med* 2013;126(9 Suppl 1):S38-48.

Risk Factors for Hypoglycemia in Patients on Insulin Secretagogues and/or Insulin

- Use of insulin secretagogues and insulin therapy
- Missed or irregular meals
- Advanced age
- Duration of diabetes
- Impaired awareness of hypoglycemia
- renal dysfunction

Amiel SA, et al. *Diabet Med* 2008;25(3):245-54.

If Patient is on Secretagogue or Insulin, When do you Add-on Other Meds?

1. Counsel about the risk of hypoglycemia
2. If A1C <8%, reduce or stop sulfonylurea
3. Do NOT stop the insulin
4. Communicate / coordinate changes with primary care physician/diabetes specialist / diabetes care team

Antihyperglycemic Consideration in Heart Failure

- Metformin remains initial drug (if eGFR >30)
- Consider SGLT2i (empa, cana or dapa) to prevent hospitalization for heart failure and dapa to reduce/treat patients with HFrEF to reduce hHF and CV
- Avoid or use caution with saxagliptin
- Avoid TZD class

empa, empagliflozin; cana, canagliflozin; eGFR estimated glomular filtration rate, SGLT2i, sodium glucose cotransporter 2; TZD, thiazolidinedione

Mancini GBJ, et al. *Can J Cardiol* 2018;34:1350-61. Esekowitz JA, et al. *Can J Cardiol* 2017;33:1342-433. Connelly KA, et al. *Can J Diabetes* 2018;42(S1):S196-200.

Guidelines are Evolving to Recommend SGLT2 Inhibitors to Help Reduce the Risk of Hospitalization Due to Heart Failure

Canadian Cardiovascular Society (CCS) Guidelines provide a strong recommendation that:

- SGLT2 inhibitors, such as dapagliflozin, should be used in patients with T2D aged >50 years with additional **risk factors for** atherosclerotic cardiovascular disease to reduce the risk of hospitalization for heart failure

- SGLT2 inhibitors, such as dapagliflozin, canagliflozin and empagliflozin, should be used for treatment of patients **with T2D and atherosclerotic cardiovascular disease** to reduce the risk of heart failure hospitalization and death.

McDonald M, et al. Can J Cardiol 2020;36 :159-169

Clinical Lessons for SGLT2 Inhibitors

- Do not use in T1DM
- Be cautious with insulin dose reductions and do not hold insulin in acute illness (must continue to do SMBG regularly)
- Hold SGLT2 inhibitors during acute illness (SADMANS), prolonged fasting, perioperative
- If unwell (*e.g.* nausea / vomiting, malaise), check electrolytes, bicarb and calculate anion gap
- AVOID IN ICU patients

DKA, diabetic ketoacidosis; SMBG, self-monitoring blood glucose; SGLT2, sodium glucose cotransporter 2; T1DM, Type 1 Diabetes Mellitus

Rosenstock J , et al. *Diabetes Care* 2015;38:1638-42.

Final Messages

- Two classes of antihyperglycemic agents include agents that reduce CV events
  - SGLT2i: Empagliflozin, Canagliflozin, Dapagliflozin
  - GLP1-RA: Liraglutide, Semaglutide, Dulaglutide
- 2 agents have proven reduction in mortality in T2DM and CVD
  - empagliflozin and liraglutide (semaglutide)
- Reduce or stop the secretagogue if A1c <8% and adding either SGLT2 inhibitor or GLP1 receptor agonist
- Look at the eGFR
- Remember sick day management with acute illness (SADMANS)
- Do not routinely stop the patient's insulin when admitted to hospital
- May consider using BOTH classes of drugs together!!!!