ACTing on the EVIDENCE

ASSESS CHOOSE TRANSLATE

Cardiovascular Protection in Diabetes: Core Principles for Primary Care Practitioners

SGLT-2 inhibitors and safety

An educational programme for general practice developed by international experts.

What you will gain…

Participation in this fully accredited CPD programme gives you the opportunity to learn:

- An understanding of the benefits versus risks of SGLT-2 inhibitor therapy
- Perspective on the potential safety issues associated with the use of SGLT-2 inhibitors in type 2 diabetes
- Clinical insight into the risks of hypoglycaemia, genital and urinary tract infections, osmotic and volume-related adverse events, renal safety, fractures, amputations, diabetic ketoacidosis and malignancies.

'Acting on the Evidence' offers you the opportunity to obtain free CPD points

Expert panel

Dr Lawrence A Leiter
Division of Endocrinology and Metabolism
St Michael's Hospital

Professor of Medicine and Nutritional Sciences, University of Toronto, Toronto, ON, Canada

Dr Subodh Verma
Division of Cardiac Surgery
St Michael's Hospital

Professor of Surgery and Pharmacology & Toxicology University of Toronto, Toronto, ON, Canada

Canada Research Chair in Cardiovascular Surgery

Dr Ronald Goldenberg
Consultant Endocrinologist
North York General Hospital
Vaughan, ON, Canada

deNovo Medica

AstraZeneca
xxxx

This report was made possible by an unrestricted educational grant from AstraZeneca. The content of the report is independent of the sponsor. The expert participated voluntarily.

Module 6: SGLT-2 inhibitors and safety

Introduction

Click here to watch the video

Importantly, when any medication is prescribed, the potential benefits versus the potential risks must be balanced. The benefits versus risks of SGLT-2 inhibitors have been evaluated in numerous clinical trials, and potential cardiovascular, renal and metabolic benefits must be put into perspective relative to the risks. The only general risk associated with SGLT-2 inhibitor therapy is a small increase in genital mycotic infections.

Clinical trials evaluating benefits and safety of SGLT-2 inhibitor therapy

A recent meta-analysis of 45 different studies, including patients with a broad range of starting HbA_{1c}, looked at the metabolic efficacy of SGLT-2 inhibitors.[1] The HbA_{1c} reduction versus placebo is approximately 0.7%, although it is higher in patients starting with higher baseline HbA_{1c} levels. On average, there is a 1.7kg weight loss versus placebo, although there is a good deal of inter-individual variation in the amount of weight loss observed. The reduction in blood pressure averages 4mmHg systolic and 2mmHg diastolic.

Three large outcomes trials highlight the cardiovascular and renal benefits of SGLT-2 inhibitors. The first of these was the EMPA-REG OUTCOME study of empagliflozin,[2] with a significant 14% reduction in its primary three-point MACE endpoint of myocardial infarction, stroke and cardiovascular mortality, as well as a 35% reduced risk for hospitalisation for heart failure. The CANVAS Program[3] with canagliflozin showed an identical 14% reduction in its primary three-point MACE endpoint, and a 33% reduced risk for hospitalisation for heart failure. The most recent results are from the DECLARE-TIMI 58[4] trial of dapagliflozin, which included a much broader population of 17 000 patients, of whom 40% had established cardiovascular disease and 60% had multiple risk factors. Overall, the three-point MACE was reduced by 7%, demonstrating cardiovascular safety, but it was not significant for superiority. However, the second dual primary efficacy endpoint of cardiovascular death or hospitalisation for heart failure was reduced by a significant 17% (Figure 1). Importantly, while heart failure was a secondary endpoint in EMPA-REG OUTCOME and CANVAS Program, DECLARE-TIMI 58 was the only one of these studies to have cardiovascular death or hospitalisation for heart failure as a *primary* efficacy endpoint.

Other modules

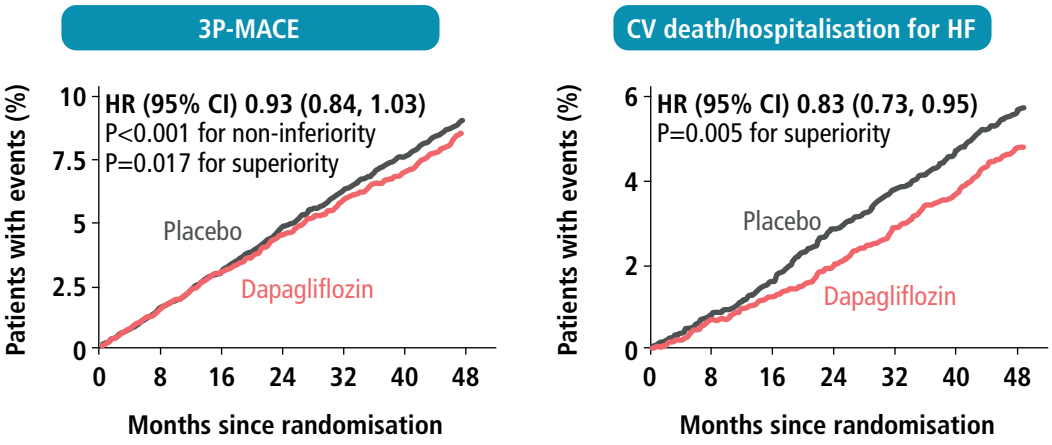
Module 1
Cardiovascular prevention and heart failure in diabetes

Module 2
Cardiovascular outcome trials in diabetes

Module 3
Renal protection in type 2 diabetes

Module 4
Review of renal therapies prior to SGLT-2 inhibitors

Module 5
Renal benefits of SGLT-2 inhibitors in diabetes



3P-MACE: 3-point major adverse cardiovascular events; HF: heart failure

Figure 1. Key efficacy results of DECLARE-TIMI 58[4]

Importantly, while heart failure was a secondary endpoint in EMPA-REG and CANVAS, DECLARE was the only one of these studies to have cardiovascular death or hospitalisation for heart failure as a primary efficacy endpoint

The overall safety in EMPA-REG OUTCOME was quite good although, as to be expected, there was a small increase in genital infections in both men and women. There were no significant increases in urinary tract infections (UTIs), events consistent with volume depletion, acute kidney injury (AKI), bone fractures or amputations (Table 1).[2]

Table 1. Adverse events of special interest in EMPA-REG OUTCOME[2]

	Placebo (n=2 333)		Empagliflozin 10mg (n=2 345)		Empagliflozin 25mg (n=2 342)	
	n%	Rate	n%	Rate	n%	Rate
Events consistent with UTI	423 (18.1)	8.2	426 (18.2)	8.0	416 (17.8)	7.8
Male	158 (9.4)	4.0	180 (10.9)	4.5	170 (10.1)	4.1
Female	265 (40.6)	22.8	246 (35.5)	18.8	246 (37.3)	20.4
Events consistent with genital infection	42 (1.8)	0.7	153 (6.5)	2.7	148 (6.3)	2.6
Male	25 (1.5)	0.6	89 (5.4)	2.2	77 (4.6)	1.8
Female	17 (2.6)	1.1	64 (9.2)	3.9	71 (10.8)	4.8
Events consistent with volume depletion	115 (4.9)	2.0	115 (4.9)	2.0	124 (5.3)	2.1
Diabetic ketoacidosis	1 (<0.1)	0.02	3 (0.1)	0.05	1 (<0.1)	0.02
Acute kidney injury	155 (6.6)	2.8	121 (5.2)	2.1	125 (5.3)	2.1
Bone fractures	91 (3.9)	1.6	92 (3.9)	1.6	82 (3.7)	1.5
Amputations[a]	43 (1.8)	–	42 (1.8)	–	46 (2.0)	–

[a] amputations were published post-hoc and were not systematically captured.
Rate = per 100 patient-years; Data are from individuals treated with >1 dose of the study drug.
UTI: urinary tract infection

Data from the CANVAS Program indicate an increased risk of general mycotic infections in both women and men. There was also an increase in symptoms of volume depletion and an approximate two-fold increased risk of amputation, as well as an increased risk for fractures (Figure 2).[3]

Outcome (number of participants with an event)	Event rate per 1 000 patient-years: Canagliflozin	Event rate per 1 000 patient-years: Placebo	Hazard Ratio (95% CI)
Female genital mycotic infection (n=196)[a]	69	18	4.37 (2.78–6.88)
Urinary tract infection (n=40)[a]	40	37	1.09 (0.89–1.34)
Hypoglycemia (n=551)[a]	50	46	1.13 (0.94–1.35)
Volume depletion (n=266)[a]	26	19	1.44 (1.09–1.90)
Male genital mycotic infection (n=503)	35	11	3.76 (2.91–4.86)
Adjudicated diabetic ketoacidosis (n=18)	0.6[b]	0.3	2.33 (0.76–7.17)
Serious renal-related (n=83)	2.5	3.3	0.76 (0.49–1.19)
Serious acute kidney injury (n=58)	1.6	2.5	0.68 (0.5–1.02)
Serious hyperkalaemia (n=15)	0.4	0.6	0.75 (0.27–2.11)
Neoplasms (n=71)	21	20	1.00 (0.86–1.16)
Venous thromboembolic events (n=50)	1.7	1.7	0.96 (0.54–1.71)
All amputations (n=187)	6.3	3.4	1.97 (1.41–2.75)
Adjudicated low-trauma fractures (n=379)	12	9.2	1.23 (0.99–1.52)
All adjudicated fractures (n=496)	15	12	1.26 (1.04–1.52)

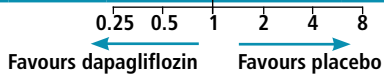
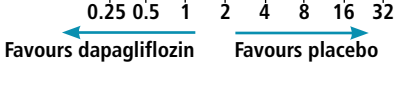


Figure 2. Main safety findings of the CANVAS Program[3]

In these large outcomes trials, the safety in general was quite good

In DECLARE-TIMI 58, overall serious adverse events were fewer in patients on dapagliflozin than on placebo. There was no increase in amputations or fracture, and no increase in symptoms of volume depletion (Figure 3).[4] As expected, there was a small increase in genital infections. In these large outcomes trials, the safety in general was quite good.

Event	n (%): Dapagliflozin (N=8 574)	n (%): Placebo (N=8 569)	Hazard Ratio (95% CI)	P
Serious adverse event (AE)	2925 (34.1)	3100 (36.2)	0.91 (0.87–0.96)	<0.001
AE leading to discontinuation	693 (8.1)	592 (6.9)	1.15 (1.03–1.28)	0.01
Major hypoglycaemic event	58 (0.7)	83 (1.0)	0.68 (0.49–0.95)	0.02
Diabetic ketoacidosis	27 (0.3)	12 (0.1)	2.18 (1.10–4.30)	0.02
Amputation	123 (1.4)	113 (1.3)	1.09 (0.84–1.40)	0.53
Fracture	457 (5.3)	440 (5.1)	1.04 (0.91–1.18)	0.59
Symptoms of volume depletion	213 (2.5)	207 (2.4)	1.00 (0.83–1.21)	0.99
Acute kidney injury	125 (1.5)	175 (2.0)	0.69 (0.55–1.87)	0.002
Genital infection[a]	76 (0.9)	9 (0.1)	8.36 (4.19–16.68)	<0.001
Urinary tract infection	127 (1.5)	133 (1.6)	0.93 (0.73–1.18)	0.54
Cancer	481 (5.6)	486 (5.7)	0.99 (0.87–1.12)	0.83
Bladder cancer	26 (0.3)	45 (0.5)	0.57 (0.35–0.93)	0.02
Breast cancer	36 (0.4)	35 (0.4)	1.02 (0.64–1.63)	0.92
Hypersensitivity	32 (0.4)	36 (0.4)	0.87 (0.54–1.40)	0.57
Hepatic event	82 (1.0)	87 (1.0)	0.92 (0.68–1.25)	0.60



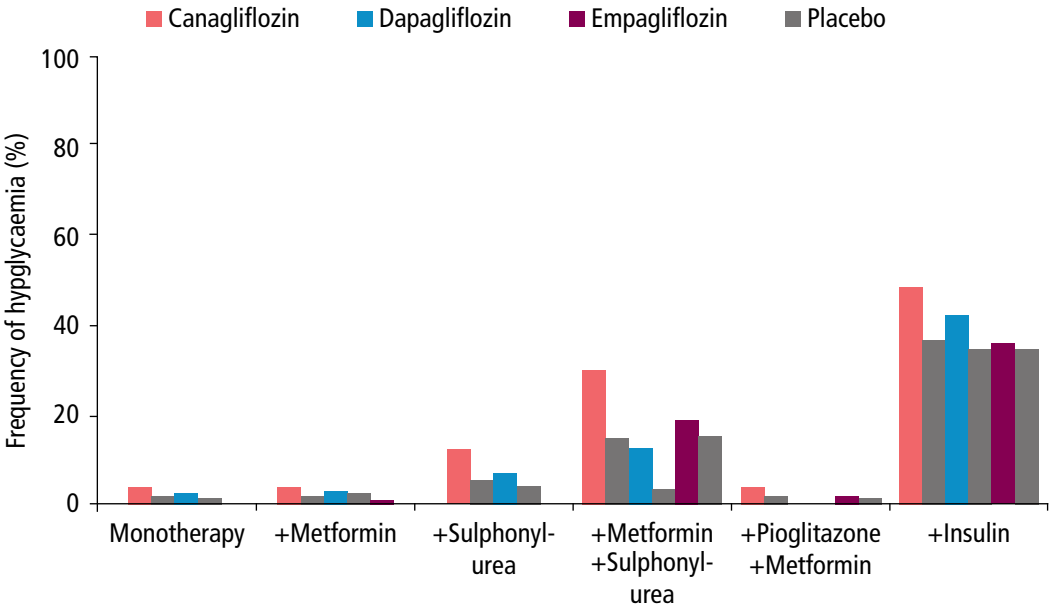
[a] serious AE or discontinued due to AE.

Figure 3. Key safety results of DECLARE-TIMI 58[4]

Potential safety issues in SGLT-2 therapy

Hypoglycaemia

There is no increased risk of hypoglycaemia with the use of SGLT-2 inhibitors unless they are combined with another agent that can cause hypoglycaemia, such as insulin or a sulphonylurea. SGLT-2 inhibitors will lower blood sugar down to a certain point but, by themselves, they will not lower glucose into the hypoglycaemic range. An important practice tip is that if hypoglycaemia becomes a concern, one should adjust the dose of the sulphonylurea or the insulin, but there is no need to stop or reduce the SGLT-2 inhibitor therapy (Figure 4).



Conclusions regarding the differences between the various SGLT-2 inhibitors cannot be made given the varying trial designs, duration of trials, participant populations, and study methodologies.

Figure 4. Frequency of hypoglycaemia with SGLT-2 inhibitors

Genital mycotic infections and UTIs

The results of a network meta-analysis of 52 different trials on the risk of genital mycotic infections is shown in Figure 5.[5] It is not possible to directly compare the studies across the various drugs, but overall there is a fairly similar odds ratio of 3.6 to 5, relative to placebo.[2,3,5] In the large outcomes trials, as expected, general mycotic infections increased with the use of SGLT-2 inhibitors. Pooled six-month data show that this increased risk occurs in both women and men, although the absolute risk is higher in women, uncircumcised men and in individuals with a history of general mycotic infections. Importantly, most people only have a single event that typically occurs early in SGLT-2 inhibitor therapy but usually responds well to standard treatment. A very important practical point is that there is no need to stop the SGLT-2 inhibitor if the patient has had a genital infection.

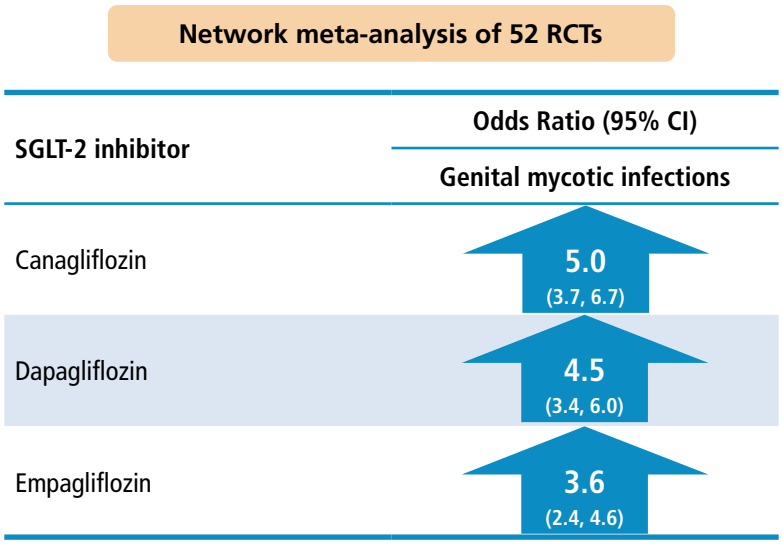


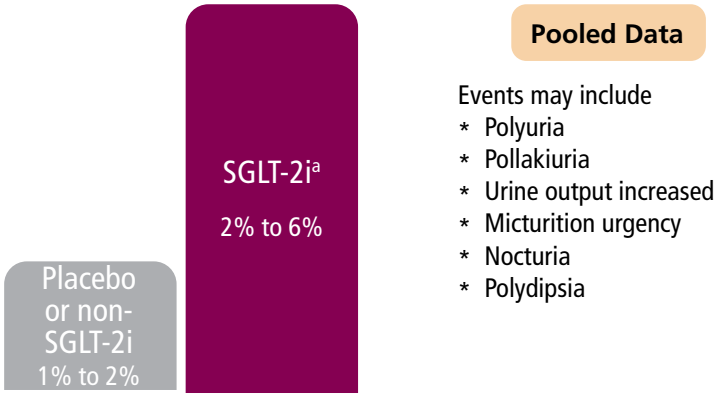
Figure 5. SGLT-2 inhibitors and genital mycotic infections[2,3,5]

However, even if there is this small increase in UTIs, it tends to take the form of lower tract (bladder) infections and there are very few, if any, cases of pyelonephritis or urosepsis

From the same network meta-analysis,[5] the odds ratio for UTIs ranged from 1 to 1.3, so there may be a small increased risk. Interestingly, in the three large outcomes trials practising careful data collection, UTIs were not increased with the use of SGLT-2 inhibitors. Pooled six-month data indicate a small increase in women that has not been observed in men in short-term trials. However, even if there is this small increase in UTIs, it tends to take the form of lower urinary tract (bladder) infections and there are very few, if any, cases of pyelonephritis or urosepsis.

Osmotic diuresis-related adverse events

Pooled data from the outcomes trials show a small increased risk of osmotic diuresis-related events, which may include polyuria, pollakiuria, urgency, nocturia or polydipsia (Figure 6). It is important to instruct patients to try to maintain adequate hydration.



[a] includes data for canagliflozin, dapagliflozin,empagliflozin and ertugliflozin.

Figure 6. Osmotic diuresis-related adverse events with SGLT-2 inhibitors

There is a small increased risk of volume-related adverse events such as hypotension, postural hypotension, dehydration, syncope and reduced urine output with SGLT-2 inhibitor treatment. This may be more common in the elderly, in those patients with estimated glomerular filtration rates (eGFRs) of 30-60ml/min/1.73m^2, in patients on loop diuretics, or patients on an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). Given the benefits of ACE inhibitors and ARBs and the small increased risk of volume-related adverse events with SGLT-2 inhibitors, it is important to emphasise that ACE inhibitor or ARB therapy should not be stopped inappropriately.

Using SGLT-2 inhibitors with diuretics

If a patient is already on a diuretic and you want to initiate an SGLT-2 inhibitor, do you need to adjust the dose of the diuretic? Useful guidance is contained in Figure 7,[6] which highlights that volume status is the starting point. If the patient is euvolaemic and if the blood pressure is normal, no dose adjustment is required if a patient is on a thiazide diuretic. If the patient is on a loop diuretic, you may consider reducing the dose thereof while monitoring blood pressure and weight: if blood pressure is stable, continue therapy; if increasing, re-institute the initial dose of the diuretic; and, if decreasing, stop the diuretic.

If the patient is hypervolaemic, the diuretic is continued and the blood pressure, electrolytes, creatinine and weight are monitored, assuming that the patient is not hypotensive. If the patient is hypertensive, continue diuretic therapy and monitor these various measures. If the patient is volume-contracted, stop the diuretic and monitor; initiate the SGLT-2 inhibitor only when the patient is euvolaemic. Finally, if the patient is hypotensive, do not start an SGLT-2 inhibitor at this point; rather hold or reduce the diuretic and re-institute if required. Once the patient's blood pressure is normal, you can then reconsider using the SGLT-2 inhibitor.

Although there is still concern about AKI, it is important to highlight that in these large trials where endpoints were carefully assessed, there was absolutely no increased risk.

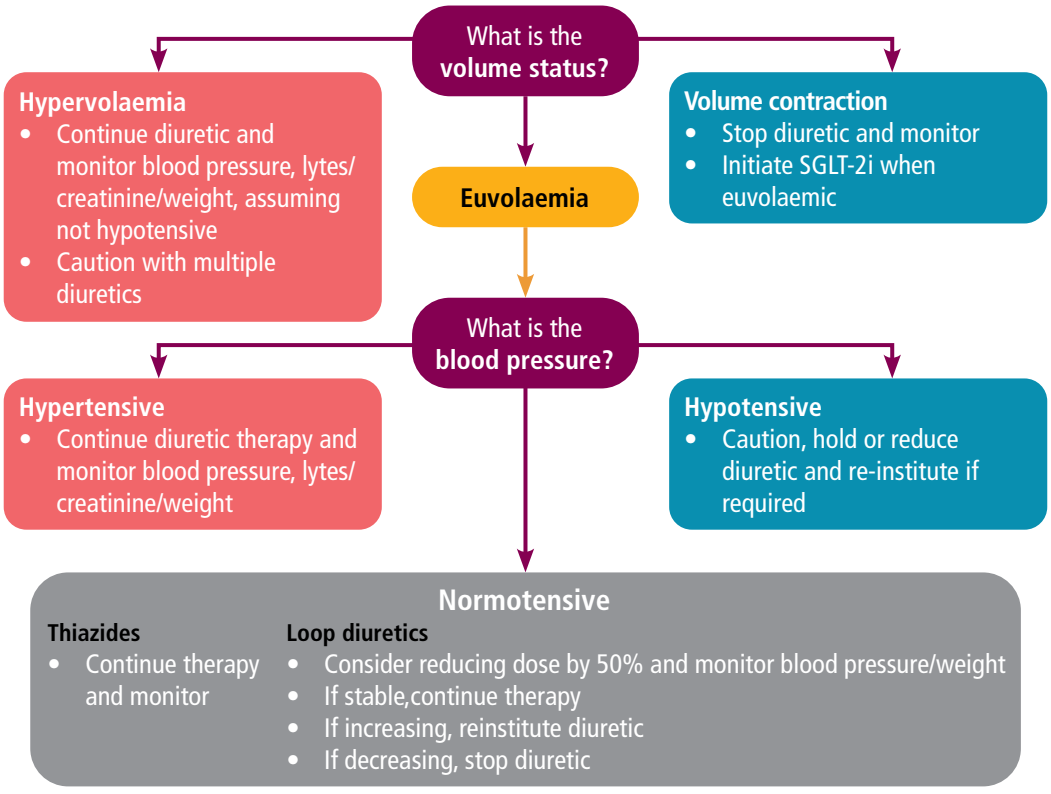


Figure 7. Diuretics and SGLT-2 inhibition[6]

Renal safety

With longer follow-up, eGFR is better in the patients on the SGLT-2 inhibitor versus placebo

An evaluation of the phase III studies for canagliflozin, dapagliflozin, empagliflozin and ertugliflozin shows that renal-related adverse events can include an increase in blood creatinine, decreased eGFR, renal impairment and renal failure. However, there was no consistent increase in risk of these renal events versus placebo.

Acute kidney injury

The risk of AKI may be increased or more likely in the elderly, those on renin-angiotensin system (RAS) blockade, those on diuretic therapy, and patients on non-steroidal anti-inflammatories or intravenous contrast. In EMPA-REG OUTCOME, the hazard ratio for AKI was only 0.76. In the CANVAS Program, there was a lower risk of serious renal-related events, serious AKI or serious hyperkalaemia. In DECLARE-TIMI 58, hazard ratios for the composite of 40% decrease in eGFR, end-stage renal disease, or death from renal causes, and also for AKI, were decreased in the patients receiving dapagliflozin (Figure 8).

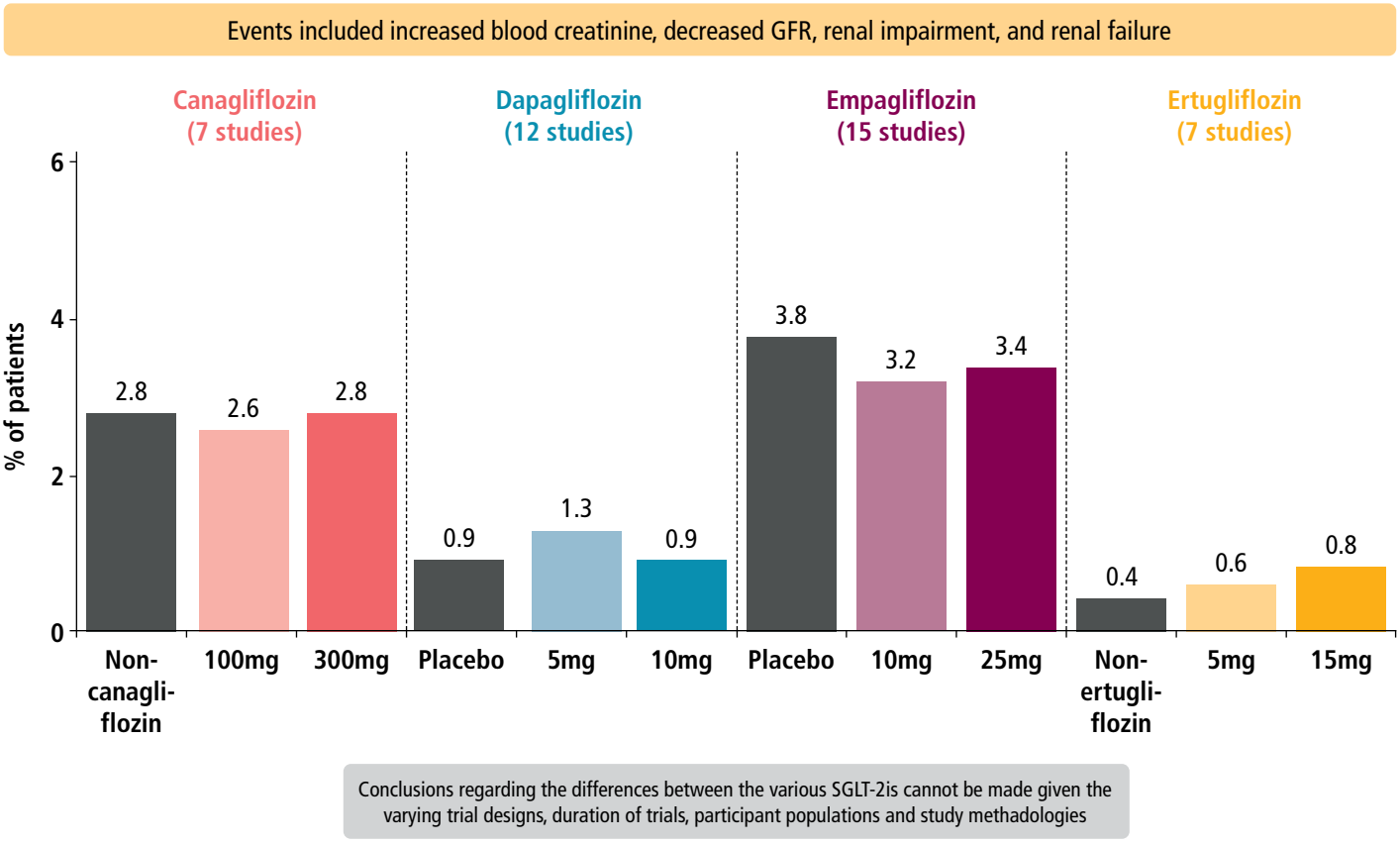
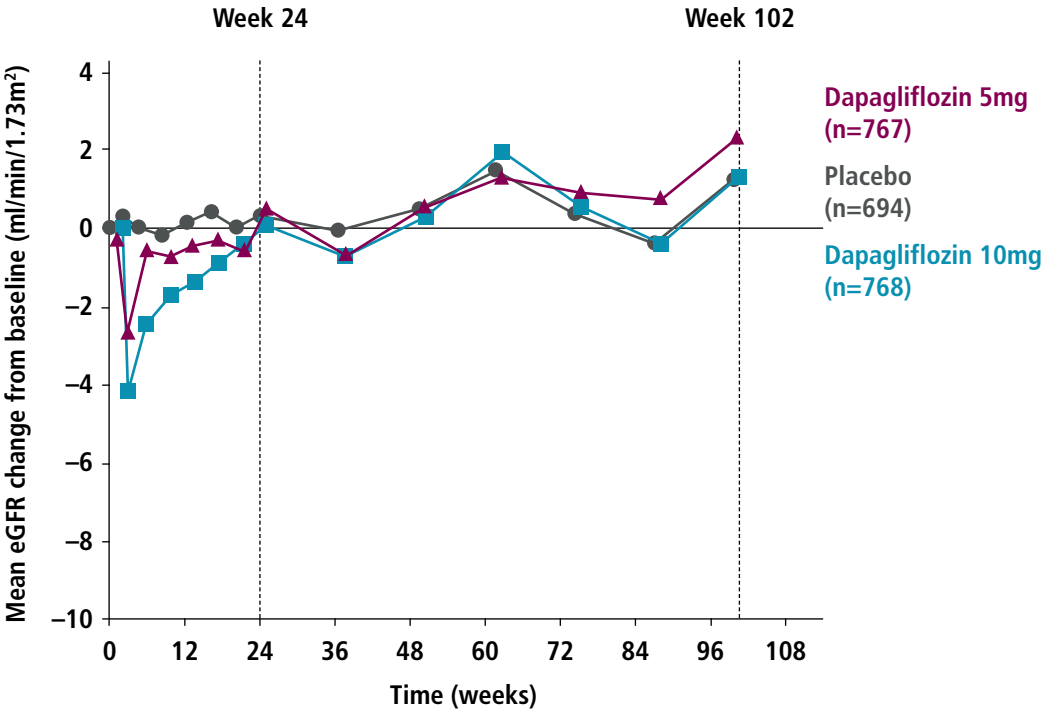


Figure 8. Renal-related adverse events with SGLT-2 inhibitors in phase III studies

Impact of SGLT-2 inhibition on eGFR

Data from the CANVAS Program and EMPA-REG OUTCOME show a very consistent pattern of an early drop in eGFR shortly after starting the SGLT-2 inhibitor. This is similar to what occurs with ACE inhibitors or ARBs, but eGFR remains relatively stable after this initial drop, whereas in the placebo group there is a gradual decrease in eGFR over time. With longer follow-up, eGFR is better in the patients on the SGLT-2 inhibitor versus placebo. Dapagliflozin data also show the identical phenomenon of an early drop in eGFR, which then stabilises again (Figure 9). Further analysis of the DECLARE trial will be forthcoming.



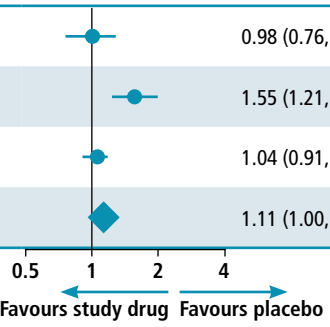
eGFR, estimated glomenular filtration rate.
Includes data after rescue in the placebo-controlled pool of treated patients.
FDA Briefing Document. NDA 202293.2011. www.fida.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugs, AdvisoryCommitte/UCM262994.pdf. Accessed 31 March 2014.

Figure 9. Impact of dapagliflozin on eGFR

Fractures

In the CANVAS Program there was an increased risk of fractures (adjudicated low-trauma fractures or all adjudicated fractures) observed in the CANVAS trial but not in the CANVAS-R trial, the data for both of which were combined in the CANVAS Program. With regard to fractures in the CANVAS trial as compared to the other completed outcomes trials, the results were different with canagliflozin and there is currently no clear explanation as to why. No increase in fractures was observed in EMPA-REG OUTCOME and DECLARE-TIMI 58 (Figure 10).[7] There are fewer data to date with ertugliflozin, but seven pooled phase III trials have not shown an increase in fractures.

Trial	Patients	Events	Events per 1 000 patient-years		Weights (%)	HR (95% CI)
			SGLT-2i	Placebo		
EMPA-REG OUTCOME	7 020	270	NA	NA	17.7	0.98 (0.76, 1.25)
CANVAS Program	10 142	NA	15.4	11.9	18.2	1.55 (1.21, 1.97)
DECLARE-TIMI 58	17 143	897	13.6	13.2	64.1	1.04 (0.91, 1.18)
Fixed effects model (P=0.0564)						1.11 (1.00, 1.23)



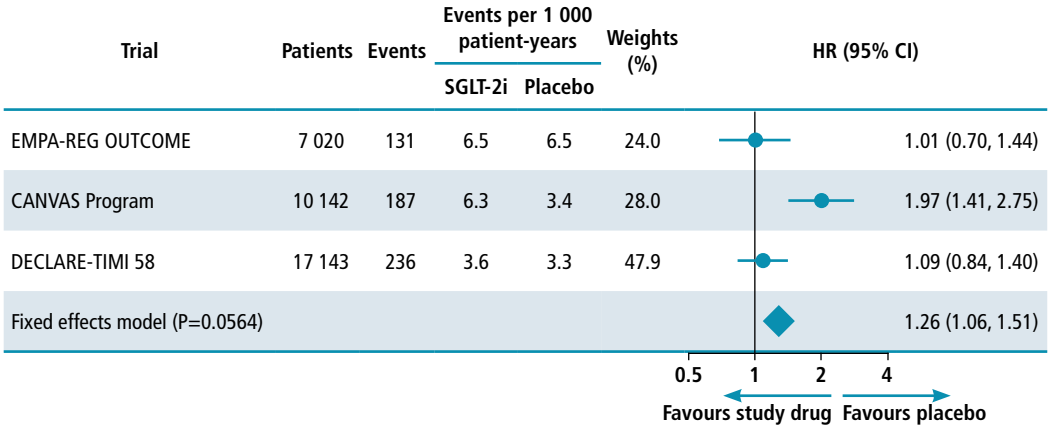
Data are not from head-to-head trials and should not be compared direcctly

Figure 10. Risk of fractures across the SGLT-2 inhibitor outcomes trials[7]

Amputations

Overall, there was a doubling of risk of amputations in the CANVAS Program. Of these, 71% were classified 'minor', i.e. of the toe or metatarsals, with the remainder being major amputations either above or below the knee. The hazard ratio was similar for the minor and major amputations. The strongest predictor of amputation was prior amputation, with a hazard ratio of almost 21; other predictors included a history of peripheral vascular disease with a hazard ratio of 3.1, male sex, neuropathy, HbA_{1c} >8%, and the presence of cardiovascular disease. Amputation risk factors were similar in both groups.

Independent of the risk factors, canagliflozin treatment increased the amputation risk. The absolute risk increase for the overall study was small at 0.29%. The greatest absolute risk increase was in those with prior amputation (3.7%), compared to those without a prior amputation (0.23%). When evaluating the three SGLT-2 inhibitor outcomes trials, the CANVAS Program appears to be the outlier with an almost doubling in risk for amputation, whereas there is no signal of increased risk in EMPA-REG OUTCOME or DECLARE-TIMI 58 (Figure 11).[7] *Post-hoc* analysis of EMPA-REG OUTCOME showed an increase in amputation risk with empagliflozin. With ertugliflozin, data are limited; pooled phase III trials show an imbalance in amputations but given the very small numbers, these data are indefinite.



Data are not from head-to-head trials and should not be compared direcctly

Figure 11. Risk of amputations across the SGLT-2 inhibitor outcomes trials[7]

Diabetic ketoacidosis[8,9]

Diabetic ketoacidosis (DKA) is very infrequent and occurs in less than 0.1% of SGLT-2 inhibitor-treated patients with type 2 diabetes. Most cases occur in patients who are relatively insulin-deficient, and it is typically associated with a precipitant, whether that be an intercurrent infection, surgery or a different cause. It is important to note that DKA may occur with blood sugars that are less elevated than one would typically see with DKA, called 'euglycaemic DKA'. It is very rare for the blood sugar to be normal, but you may see DKA with blood sugars of 10-15mmol/l versus the more typical 20-25mmol/l.

There are a number of precipitants for SGLT-2 inhibitor-associated DKA and measures can be taken to avoid this. If patients are on insulin, you should not reduce the dose excessively. If the patient has an acute illness, hold the SGLT-2 inhibitor while the patient is ill. Patients scheduled to have bariatric surgery are often told to follow a low-carbohydrate

diet pre-operatively; hold the SGLT-2 inhibitor at this point. If patients have major elective surgical procedures, hold the SGLT-2 inhibitor therapy for three days prior as these drugs have a relatively long half-life. If patients are at risk of dehydration, the SGLT-2 inhibitor may be held until they are able to maintain hydration. Patients should not be on a low-carbohydrate diet; if they are, one should hold the SGLT-2 inhibitor until normal diet resumes. If the patient has an alcohol binge, one should stop the SGLT-2 inhibitor and reassess whether it is appropriate for that patient to continue with this therapy later.

Malignancies

There was an early imbalance in risk for bladder cancer with dapagliflozin, probably related to an ascertainment bias. This was assessed very carefully in DECLARE-TIMI 58 and, if anything, bladder cancer occurred less frequently in patients on dapagliflozin. There was no increase in breast cancer. There does not appear to be any signal with regard to increased risk of cancer with the use of SGLT-2 inhibitors.

In which individuals should SGLT-2 inhibitors *not* be considered or be prescribed with caution?

There does not appear to be any signal with regard to increased risk of cancer with the use of SGLT-2 inhibitors

SGLT-2 inhibitors should not be initiated in patients with renal impairment. The cut-off for eGFR varies from drug to drug and from country to country, so this should be based on local product monographs. Canagliflozin, in its label, is not recommended for patients on loop diuretics. Hold the SGLT-2 inhibitor during acute illnesses causing volume depletion. One should use SGLT-2 inhibitors with caution in patients prone to hypotension or volume depletion, if there is history of recurrent mycotic infections or UTIs, hypoglycaemia, and if patients are being treated with sulphonylureas or insulin. SGLT-2 inhibitors are not approved for use during pregnancy and are not currently approved for type 1 diabetes.

Key messages

- There is a low frequency of adverse events in SGLT-2 inhibitor outcomes trials (Table 2)[10]
- In the EMPA-REG OUTCOME trial, the only adverse event that was increased significantly was genital infections
- The CANVAS Program showed an increased risk of amputations, fractures and symptoms of volume depletion, in addition to the risk of general mycotic infections
- In the DECLARE-TIMI 58 trial, there was a non-significant increased risk of genital infections
- The use of SGLT-2 inhibitors has been associated with a lower risk of MACE, reduced cardiovascular mortality and heart failure, and better renal outcomes over and above the benefits of improved glycaemic control without hypoglycaemia, weight loss and blood pressure reduction
- In certain susceptible patients there may be an increase in osmotic-related adverse events and volume depletion-related adverse events. DKA is rare but can occur with a euglycaemic state. Bone fractures and amputations were seen with canagliflozin, but not with the other agents.

Table 2. SGLT-2 inhibitors benefits versus risks

Benefits	Risks
• Lower risk of MACE • Reduced cardiovascular mortality and heart failure • Better renal outcomes • Glucose control (without hypoglycaemia) • Weight loss • Blood pressure reduction	• Genital mycotic infections • Osmotic-related adverse events • Volume depletion-related adverse events • Rare DKA, that can be euglycemic • Bone fractures (canagliflozin) • Amputations (canagliflozin)

References

Click on reference to access the scientific article

1. Vasilakou D, Karagiannis T, Athanasiadou E, *et al*. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: A systematic review and meta-analysis. *Ann Intern Med* 2013; **159**(4): 262-274.
2. Zinman B, Wanner C, Lachin JM, *et al*. Empagliflozin, cardiovascular outcomes and mortality in type 2 diabetes. *N Engl J Med* 2015; **373**(22): 2117-2128.
3. Neal B, Perkovic V, Mahaffey KW, *et al*. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; **377**: 644-657.
4. Wiviott SD, Raz I, Bonaca MP, *et al*. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019; **380**(4): 347-357.
5. Li D, Wang T, Shen S, *et al*. Urinary tract and genital infections in patients with type 2 diabetes treated with SGLT-2 inhibitors: A meta-analysis of randomised controlled trials. *Diab Obes Metab* 2017; **19**(3): 348-355.
6. Cherney DZI, Udell JA. Use of sodium glucose cotransporter 2 inhibitors in the hands of cardiologists. *Circulation* 2016; **134**(24): 1915-1917.
7. Zelniker TA, Wiviott SD, Raz I, *et al*. SGLT-2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcomes trials. *Lancet* 2016; **393**(1016): 31-39.
8. Goldenberg RM, Berard LD, Cheng AYY, *et al.* SGLT2 inhibitor-associated diabetic ketoacidosis: Clinical review and recommendations for prevention and diagnosis. *Clin Ther* 2016; **38**(12): 2654-2664.
9. Handelsman Y, Henry RR, Bloomgarden ZT, *et al.* American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the association of SGLT-2 inhibitors and diabetic ketoacidosis. *Endocr Pract* 2016; **22**(6): 753-762.
10. Scheen AJ. SGLT-2 inhibitors: benefit/risk balance. *Curr Diab Rep* 2016; **16**(10): 92-96.

Published by

© 2020 deNovo Medica

Reg: 2012/216456/07

70 Arlington Street, Everglen, Cape Town, 7550

Tel: (021) 976 0485 | info@denovomedica.com