Benefit/Risk Tool

The Benefit/Risk Tool is a quick reference guide to support clinicians with treatment decisions concerning SGLT2i therapies. The Tool aims to provide clarity regarding common areas of confusion in clinical practice associated with risk of LLAs and bone fractures, late and early use of SGLT2i treatments within the T2DM pathway, and risk of DKA.

The traffic light system highlights the types of people or situations you may encounter in terms of risk:

- Low risk (green): Evidence supports SGLT2i prescribing in these situations
- Moderate risk (amber): Prescribe with caution
- High risk (red): Do not prescribe

An evidence level has been assigned to each risk category, based on RCT and observational data, as well as NICE/SIGN guidelines and the licensed indication for each therapy within the SGLT2i class of medicines. The level of evidence has been scored according to the ADA Evidence-Grading System (summarised below).[22]

ADA evidence-grading system for "Standards of Medical Care in Diabetes"[22]

Grade level	Description
A	Clear evidence from well-conducted, generalisable RCTs that are adequately powered, including: • Evidence from a well-conducted multicentre trial or meta-analysis that incorporated quality ratings in the analysis • Compelling non-experimental evidence
B	Supportive evidence from well-conducted cohort studies Supportive evidence from a well-conducted case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

NB. Where data are conflicting or lacking, advice has been provided that is based upon expert opinion and experience in T2DM management

Abbreviations
T2DM, Type 2 diabetes mellitus; SGLT2i, sodium-glucose co-transporter-2 inhibitor; ADA, American Diabetes Association; RCT, randomised controlled trial; BMI, body mass index; LLAs, lower leg amputations; PAD, peripheral arterial disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; UTIs, urinary tract infections; DKA, diabetic ketoacidosis; CKD, chronic kidney disease.

Risk category	Clinical situation	Potential implications[2-7]	Evidence level[22]
Low risk Evidence supports SGLT2i prescribing	First-line (metformin intolerant)		A + B + E
	Second-line to metformin		A + B + E
	Third-line (add-on to second-line therapies)		A + B + E
	Combination with basal insulin or multiple daily injections of insulin[¶]		A + B + E
	Established CVD		A + B + E
	No history of LLA		A
	No history of PAD		A
	Microalbuminuria		A
	eGFR ≥60 mL/min/1.73m^{2*‡}		A + B + E
	Overweight or obese		A + B + E
	Vulnerable to the effects of hypoglycaemia		A
Moderate risk Prescribe SGLT2i with caution	History of PAD	LLA risk	A + C
	Osteoporosis	LLA/bone fracture risk	A + B + E
	Frail/elderly	LLA/bone fracture/falls risk	A + B
	History of foot ulceration	LLA risk	A
	History of fractures	Bone fracture risk	A + C
	GLP-1 receptor agonist combination		A + additional evidence required to support decision
	Ketogenic diet	DKA risk	E
	High HbA1c levels (86 mmol/mol or 10%)[♦]	DKA risk	A + B + E
	Steroid therapy	DKA risk/outside of licensed indication	E
	Cognitive impairment		E
	BMI <25	DKA risk	E
High risk Do not prescribe SGLT2i	Previous LLA	LLA risk	A + C
	Existing diabetic foot ulcers	LLA risk	A
	DKA (or previous episode of DKA)	DKA risk	E + conflicting evidence
	Eating disorders	DKA risk	E
	Rapid progression to insulin (within 1 year)	DKA risk	E
	Latent autoimmune diabetes	DKA risk	A + E
	Excessive alcohol intake	DKA risk/outside of licensed indication	A + E
	Diabetes due to pancreatic disease	DKA risk/outside of licensed indication	A + E
	Stage 3 CKD/eGFR <60 mL/min/1.73m^{2*‡}	Outside of licensed indication	
	Receiving loop diuretics**	Not recommended for use with SGLT2is	
	Type 1 diabetes (diagnosed or suspected)	Outside of licensed indication	
	Genetic diabetes	Outside of licensed indication	
	Acute illness[†]	Outside of licensed indication	
	Pregnancy (or suspected pregnancy), planning pregnancy or breastfeeding	Outside of licensed indication	
	Recent major surgery	Outside of licensed indication	

[¶]SGLT2i therapies should be prescribed with caution in people requiring a rapid reduction in insulin dose, due to insulinopenia, which may increase DKA risk.[2-4]

*Decisions should be based upon recent eGFR measurement, rather than historical tests. [‡]SGLT2i therapies may be initiated in people with eGFR ≥60 mL/min/1.73m^2. Individuals already treated with canagliflozin or empagliflozin who demonstrate renal decline may continue treatment until eGFR reaches <45 mL/min/1.73m^2. Dapagliflozin should be discontinued for those who demonstrate eGFR <60 mL/min/1.73m^2.[2-4] Urinary symptoms, due to glucosuria, can be an issue for people prescribed SGLT2i medicines.[2-4] However, UTIs are relatively rare and these medicines may be prescribed for people with a history of UTIs.

♦Monitor HbA1c levels regularly and cease SGLT2is if elevated levels continue, following treatment initiation.**SGLT2i treatments are not currently recommended for use alongside loop diuretics. However, this may be subject to change as the evidence-base evolves. EMPA-REG and CANVAS CV outcome trials included subgroups of people with T2DM who were receiving loop diuretics and ongoing trials aim to evaluate co- prescribing of these agents.[12,16,27] [†]SGLT2i treatment should be suspended in individuals with acute illness until fully recovered.[2-4,41,42]