Donald S. Nelinson*, PhD, Jose M. Sosa, MD and Robert J. Chilton, DO

SGLT2 inhibitors: a narrative review of efficacy and safety

Abstract: Type 2 diabetes mellitus (T2DM) is a cardio-renal-metabolic condition that is frequently associated with multiple comorbidities, including atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and chronic kidney disease (CKD). The sodium-glucose co-transporter-2 (SGLT2) inhibitors, which lower glycated hemoglobin, fasting and postprandial plasma glucose levels, body weight, and blood pressure, as well as reduce the risk of a range of cardiovascular and renal outcomes without increasing hypoglycaemic risk, have heralded a paradigm shift in the management of T2DM. These drugs are compatible with most other glucose-lowering agents and can be used in patients with a wide range of comorbid conditions, including ASCVD, HF, and CKD, and in those with estimated glomerular filtration rates as low as 30 mL/min/1.73 m^2. However, there are misunderstandings surrounding the clinical implications of SGLT2 inhibitors' mechanism of action and concerns about the key adverse events with which this class of drugs has been associated. This narrative review summarizes the data that support the efficacy of SGLT2 inhibitors in reducing the risks of cardiovascular and renal outcomes in patients with T2DM and comorbid conditions and clarifies information relating to SGLT2 inhibitor-related adverse events.

Keywords: cardiovascular risk reduction; chronic kidney disease; comorbidity; heart failure; primary care; type 2 diabetes mellitus; SGLT2.

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Type 2 diabetes mellitus (T2DM) is a cardio-renal-metabolic condition that is frequently associated with multiple comorbidities, including atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and chronic kidney disease (CKD).[1] Because managing multiple comorbidities in patients with T2DM may lead to polypharmacy[2] and, as a consequence, increased risk of adverse events,[3] drugs that manage multiple conditions are attractive options for clinicians. One such drug class is sodium-glucose co-transporter-2 (SGLT2) inhibitors.

Canagliflozin was the first of the four SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin) that are currently approved in the United States for use in conjunction with diet and exercise to lower blood glucose levels in adults with T2DM.[4–7] The original thesis behind these drugs' development was to capitalize on the body's renal handling of glucose, inhibiting SGLT2-mediated glucose uptake from the proximal renal tubule,[4–7] thereby promoting glycosuria and managing hyperglycemia. However, these insulin-independent, antihyperglycemic medications are now known to be pleiotropic agents with significant metabolic, cardiovascular, and renal benefits.[8] In addition to lowering glycated hemoglobin (HbA1c), fasting and postprandial plasma glucose levels, body weight, and blood pressure, SGLT2 inhibitors reduce the risk of a range of cardiovascular and renal outcomes[8,9] without increasing hypoglycemic risk.[8]

SGLT2 inhibitors are compatible with most other glucose-lowering agents[10] and can be used in patients with a wide range of comorbid conditions, including ASCVD, HF, and CKD,[11] as well as in those with estimated glomerular filtration rates (eGFR) as low as 30 mL/min/1.73 m^2.[6,11] Approved indications for drugs in this class currently include improvement of glycemic control in patients with T2DM and, within various patient sub-populations, reducing the risks of cardiovascular death, major adverse cardiovascular events, hospitalization for HF (hHF), end-stage kidney disease, and doubling of serum creatinine.[4–7] Multiple aspects of the cardio-renal-metabolic dysregulation that epitomizes T2DM can therefore be managed using one class of drugs.

However, there are misunderstandings surrounding the clinical implications of these agents' mechanism of action and concerns about the key adverse events with which this class of drugs has been associated. Moreover, in spite of SGLT2 inhibitors' advantages over some other drug classes in the management of T2DM, it is important to understand the role of this drug class within the armamentarium of recently introduced therapies such as the glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors).

This narrative review aims to address these issues, to summarize current data relating to the effects of SGLT2 inhibitors on outcomes in patients with T2DM and comorbid conditions, and to provide clinicians with an evidence base that will guide clinical decision-making.

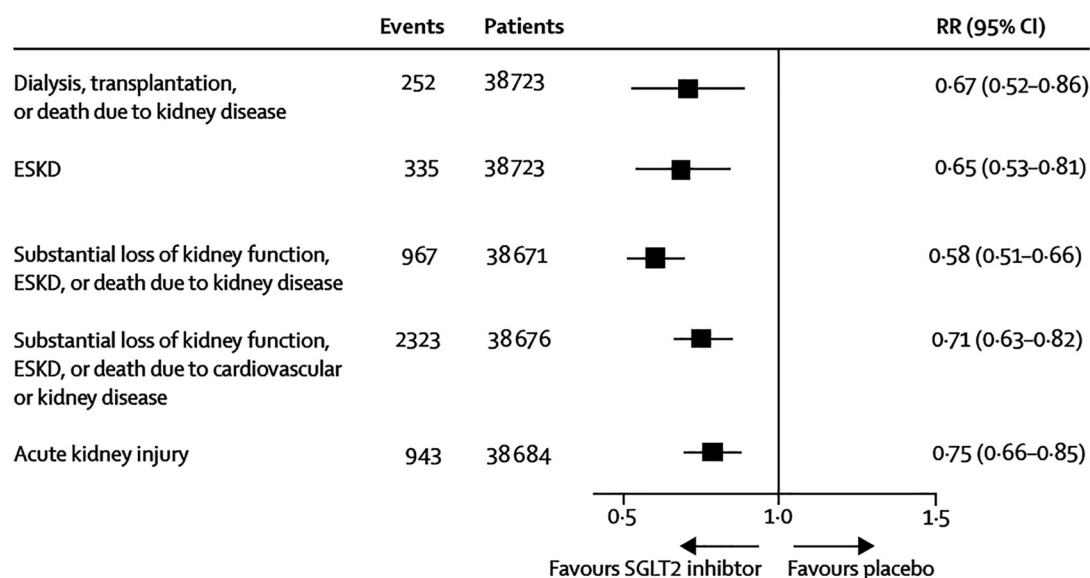# SGLT2 inhibitors: mechanism of action

The SGLT2 inhibitors ameliorate hyperglycemia by inhibiting SGLT2, a high-capacity, low-affinity transporter that is present in the early segment of the proximal convoluted renal tubule.[12] Under normal circumstances, SGLT2 is responsible for reabsorption of 90% of the glucose filtered at the glomerulus, with the remainder being transported back into the systemic circulation by SGLT1, which is located in the distal segment of the proximal convoluted tubule.[12] SGLT2 inhibition leads to glycosuria and lowering of blood glucose because SGLT1 – a low-capacity, high-affinity transporter[12] – cannot reabsorb all of the filtered glucose. However, because of physiological changes that occur in response to SGLT2 inhibitor administration, these agents only reduce renal glucose reabsorptive capacity by up to 50%.[12–14]

Effects of SGLT2 inhibitors on renal outcomes

Large, randomized, controlled trials have shown that SGLT2 inhibitors are associated with substantial benefits across a range of kidney-related outcomes[15] (Figure 1) and one drug in this class – canagliflozin – is approved by the Food and Drug Administration (FDA) to reduce the risk of end-stage renal disease (ESRD) and doubling of serum creatinine in adults with T2DM and diabetic nephropathy with albuminuria.[6] This approval is based on the results of the CREDENCE trial, in which canagliflozin reduced the risk of renal failure in patients with T2DM and albuminuric CKD.[16] Empagliflozin has also been shown to significantly reduce the rate of progression of renal disease and the risks of clinically relevant renal events in patients with T2DM, cardiovascular disease, and eGFR ≥30 mL/minute/1.73 m[2].[17]

These data are supported by the results of meta-analysis. Using data from >38,000 patients with T2DM who were receiving canagliflozin, dapagliflozin, or empagliflozin,

	Events	Patients		RR (95% CI)
Dialysis, transplantation, or death due to kidney disease	252	38 723		0·67 (0·52–0·86)
ESKD	335	38 723		0·65 (0·53–0·81)
Substantial loss of kidney function, ESKD, or death due to kidney disease	967	38 671		0·58 (0·51–0·66)
Substantial loss of kidney function, ESKD, or death due to cardiovascular or kidney disease	2323	38 676		0·71 (0·63–0·82)
Acute kidney injury	943	38 684		0·75 (0·66–0·85)

0·5 1·0 1·5

Favours SGLT2 inhibtor ← → Favours placebo

Figure 1: SGLT2 inhibition: effects on renal outcomes in patients with type 2 diabetes. Reprinted from The Lancet with permission from Elsevier. Neuen BL, Young T, Heerspink HJL, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2019;7(11):845-854. doi: 10.1016/S2213-8587(1930256-6).

Neuen et al.[15] found significant reductions vs placebo in the risks of a composite of renal dialysis, transplantation or death due to renal disease (33% reduction in risk), a composite of substantial loss of kidney function (sustained doubling of serum creatinine), ESRD or death due to renal disease (42%), acute kidney injury (25%), and ESRD (35%). The importance of this beneficial effect is emphasized by the fact that this reduction in ESRD risk is greater than that achieved with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs),[18] drug classes that are currently recommended for ESRD risk reduction in patients with T2DM, hypertension, and CKD.[11]

The renoprotective effects of SGLT2 inhibitors are also evident in data from real-world clinical practice, with one study[19] finding that patients with T2DM who initiated SGLT2 inhibitor therapy were significantly less likely to experience a renal adverse outcome (ESRD or 50% decline in eGFR) than those who initiated other glucose-lowering therapy (3.0 vs 6.3 events/10,000 patient-years). Taken together, that clinical trial and real-world data emphasize the magnitude of the reductions in renal risk that can be achieved using SGLT2 inhibitors in clinical practice.

The mechanism of SGLT2 inhibitors' renoprotective effects has not been established.[20] However, normalization of afferent arteriolar tone and glomerular filtration rate (GFR) may be involved. The SGLT2 transporter in the renal tubule reabsorbs not only glucose, but also sodium ions.[21] In healthy individuals, GFR is influenced by the sodium concentration within the distal tubule via the tubuloglomerular feedback mechanism: changes in sodium concentration, which are sensed by the cells of the macula densa within the juxta-glomerular apparatus, lead to changes in preglomerular arteriolar tone and consequent changes in GFR (Figure 2).[21]

Individuals with T2DM show increased tubular reabsorption of sodium,[21] which may derive in part from SGLT2 upregulation.[12,22] The resultant lowering of the sodium concentration at the macula densa leads to decreased afferent arteriolar tone, increased intraglomerular pressure, and increased GFR.[14,21] This glomerular hyperfiltration eventually leads to fibrosis within the glomerulus and tubulointerstitium.[23] By decreasing SGLT2-mediated reabsorption of sodium, SGLT2 inhibitors lead to increased sodium concentrations in the macula densa, with consequent normalization of afferent arteriolar tone, intraglomerular pressure, and GFR.[14,21] In addition to the changes in tubuloglomerular feedback effected by SGLT2 inhibitors, changes in oxidative stress, inflammation, and fibrosis may underlie the beneficial effects on progression of diabetic nephropathy to ESRD.[24]

The increased intraglomerular pressure and hyperfiltration that characterizes diabetic nephropathy is accompanied by albuminuria.[25] Meta-analysis has shown that SGLT2 inhibitors are associated with a significant 24% reduction in albuminuria in people with T2DM and CKD (eGFR <60 mL/min/1.73 m^2).[8] Reductions in blood
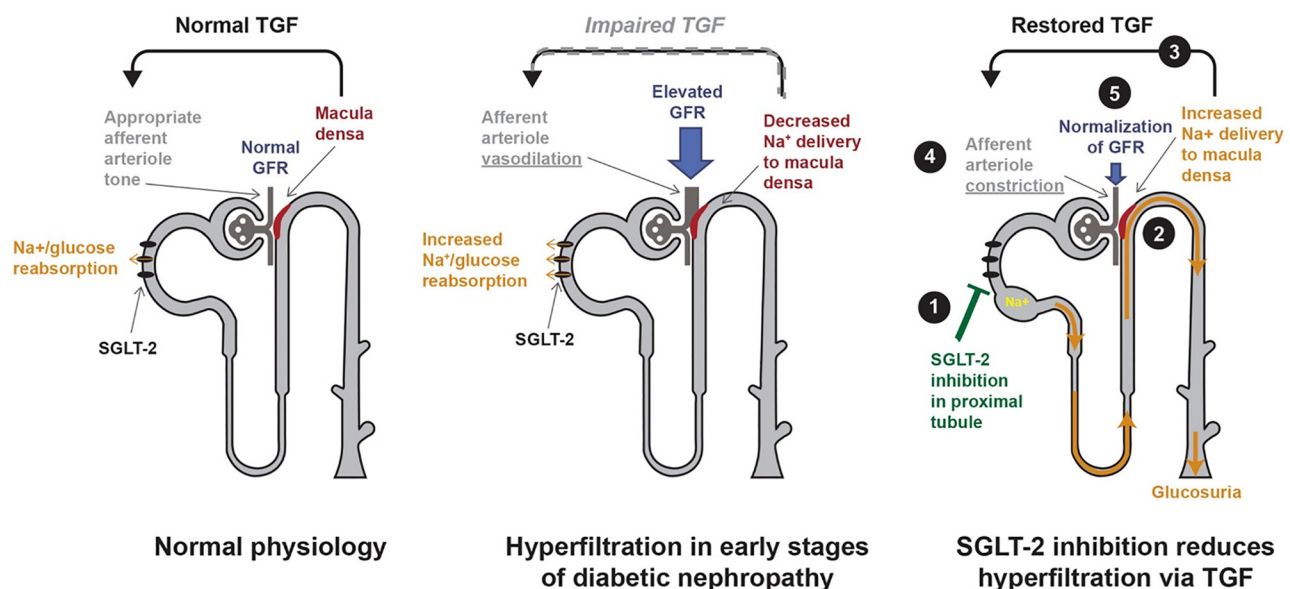
Figure 2: SGLT2 inhibitors: renal hemodynamic effects. TGF: Tubuloglomerular Feedback. Reproduced with permission from John Wiley and Sons. Chilton RJ. Effects of sodium-glucose cotransporter-2 inhibitors on the cardiovascular and renal complications of type 2 diabetes. Diabetes Obes Metab. 2020;22(1):16-29. doi: 10.1111/dom.13854.

pressure, intraglomerular pressure, and hyperfiltration appear to mediate this beneficial effect.[26]

The results of subgroup analysis have revealed some interesting and clinically relevant findings. For example, there is evidence that SGLT2 inhibitor-mediated improvements in renal function depend on albuminuric status at baseline, with increases in eGFR occurring over a two-year period in patients with normoalbuminuria or microalbuminuria at the time of SGLT2 inhibitor initiation and decreases in those with macroalbuminuria.[27] Moreover, meta-analysis has shown that although the renal benefits of SGLT2 inhibitors are significant in patients with eGFR levels of <45, 45–<60, 60–<90 and ≥ 90 mL/min/1.73 m^2, there is a trend for patients with higher eGFR to experience greater benefit and patients receiving renin-angiotensin system (RAS) blockers (ACEIs or ARBs) derive greater benefit from SGLT2 inhibition than those who are not receiving these therapies.[15] The fact that the renoprotective effects of RAS blockade and SGLT2 inhibition appear to be additive is clinically important, and it suggests that both approaches should be employed in at-risk patients in order to maximize risk reduction. Unlike ACEIs and ARBs, which are associated with increased risk of hyperkalemia,[2] SGLT2 inhibitors have no effect on serum potassium levels.[8]

Effects of SGLT2 inhibitors on cardiovascular outcomes

Atherosclerotic cardiovascular disease is the leading cause of morbidity and mortality in people with T2DM. As a consequence, this is a major focus of current guidelines for the management of this population[11] and the FDA now recommends that cardiovascular outcomes trials (CVOTs) should be conducted for all antihyperglycemic drugs that will be used in patients with T2DM.[28] Guideline recommendations relating to antihyperglycemic agents are frequently based on these drugs' cardioprotective properties.

To date, some of the most compelling data for SGLT2 inhibitor-based cardiovascular risk reduction relate to canagliflozin and empagliflozin. Data from the CANVAS and EMPA-REG trials[29,30] led to canagliflozin and empagliflozin being approved by the FDA for use in adults with T2DM and established cardiovascular disease to reduce the risk of major adverse cardiovascular events (MACE) and cardiovascular death, respectively.[5,6] The patient populations specified for these indications reflect the fact that, to date, the benefits of these agents on risk of
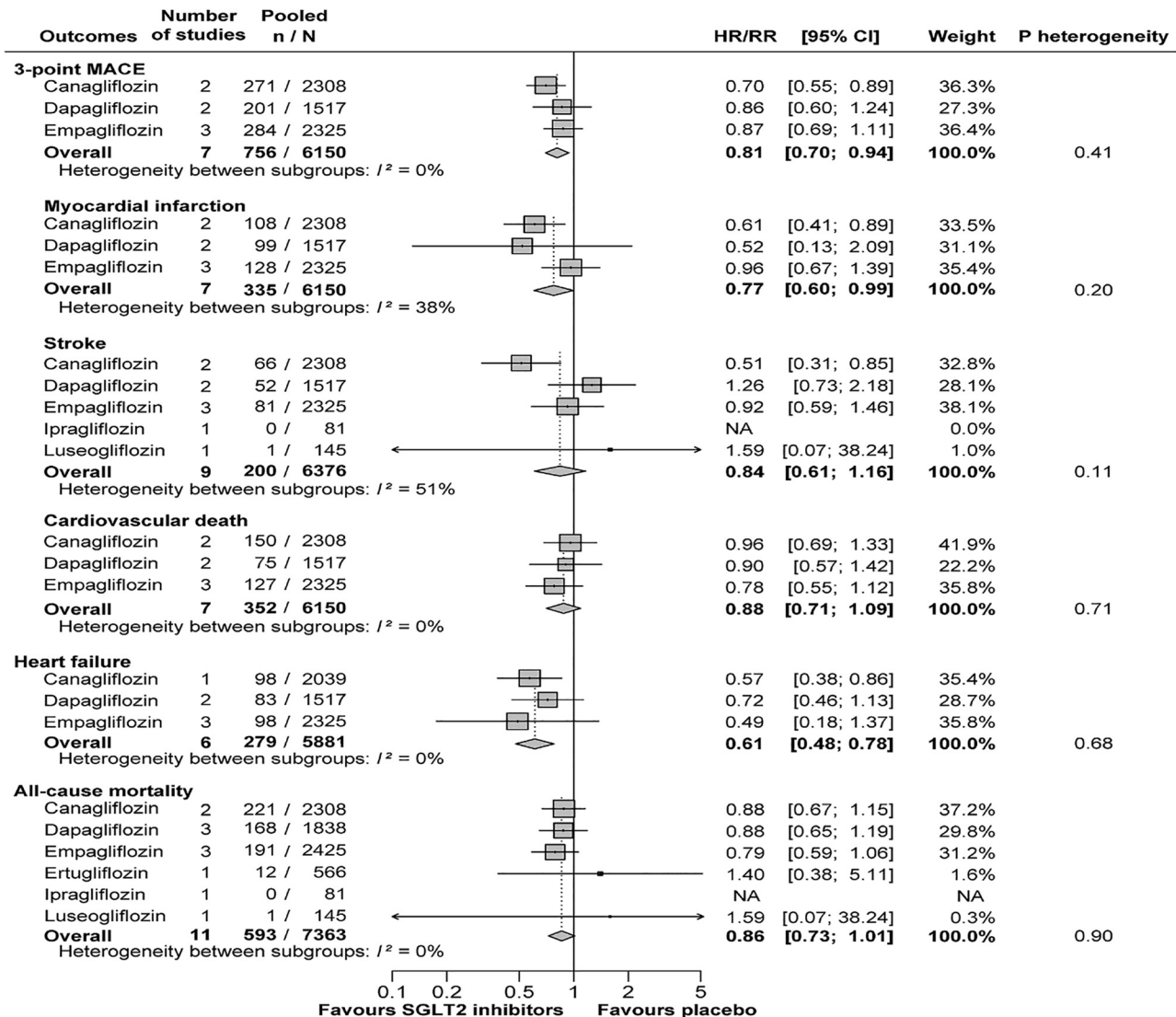
atherosclerotic MACE have been most apparent in patients with T2DM and established ASCVD.[31] However, the presence or absence of atherosclerotic cardiovascular disease does not appear to influence the effect of the SGLT2 inhibitors on hHF,[31] the cardiovascular condition for which the most compelling indication of a class benefit has emerged.[8] For example, in a meta-analysis of data from >34,000 patients with T2DM, Zelniker et al.[31] found that SGLT2 inhibitors significantly reduced the risk of MACE by 11%, but that this benefit was confined to patients with atherosclerotic cardiovascular disease at baseline. In contrast, the significant 23% reduction in risk of cardiovascular death or hHF was unaffected by prior atherosclerotic cardiovascular disease or HF.[31] In the recent VERTIS trial, ertugliflozin – the most recently approved SGLT2 inhibitor – also significantly reduced the risk of hHF in patients with T2DM and ASCVD (30% reduction in risk vs placebo).[32] However, in contrast to canagliflozin and empagliflozin, ertugliflozin had no effect on three-point MACE (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke).[32]

Meta-analysis has documented a particularly beneficial effect on hHF risk among patients with T2DM and CKD (eGFR <60 mL/min/1.73 m^2), in whom SGLT2 inhibitors are associated with significant reductions in both HF (risk ratio, 0.61) and 3-point MACE (0.81)[8] (Figure 3). It should be noted that – in contrast to the other SGLT2 inhibitors included in this meta-analysis – canagliflozin has shown significant benefit in prevention of myocardial infarction and stroke, as well as three-point MACE and HF[8] (Figure 3). The beneficial effects of dapagliflozin on risk of hHF in patients with T2DM who were at high cardiovascular risk, which was established in the DECLARE-TIM 58 trial,[33] has led to this drug gaining approval for reducing the risk of hHF in adults with T2DM and established cardiovascular disease or multiple cardiovascular risk factors.[4]

Adverse events

Early clinical trials involving the use of SGLT2 inhibitors raised concerns about associations with various adverse events. However, for some of these events – including urinary tract infections (UTIs) – early signals indicating a potential association have not been supported by further trial data (Figure 4). Diabetes itself is a strong and independent risk factor for UTIs.[34] This may stem from the increase in urinary glucose levels – and consequent predisposition to growth of commensal microorganisms – that is a consequence of hyperglycemia.[34] A logical consequence of this would be a

Outcomes	Number of studies	Pooled n / N		HR/RR	[95% CI]	Weight	P heterogeneity
3-point MACE							
Canagliflozin	2	271 / 2308		0.70	[0.55; 0.89]	36.3%	
Dapagliflozin	2	201 / 1517		0.86	[0.60; 1.24]	27.3%	
Empagliflozin	3	284 / 2325		0.87	[0.69; 1.11]	36.4%	
Overall	**7**	**756 / 6150**		**0.81**	**[0.70; 0.94]**	**100.0%**	0.41
Heterogeneity between subgroups: $I^2 = 0\%$							
Myocardial infarction							
Canagliflozin	2	108 / 2308		0.61	[0.41; 0.89]	33.5%	
Dapagliflozin	2	99 / 1517		0.52	[0.13; 2.09]	31.1%	
Empagliflozin	3	128 / 2325		0.96	[0.67; 1.39]	35.4%	
Overall	**7**	**335 / 6150**		**0.77**	**[0.60; 0.99]**	**100.0%**	0.20
Heterogeneity between subgroups: $I^2 = 38\%$							
Stroke							
Canagliflozin	2	66 / 2308		0.51	[0.31; 0.85]	32.8%	
Dapagliflozin	2	52 / 1517		1.26	[0.73; 2.18]	28.1%	
Empagliflozin	3	81 / 2325		0.92	[0.59; 1.46]	38.1%	
Ipragliflozin	1	0 / 81		NA		0.0%	
Luseogliflozin	1	1 / 145		1.59	[0.07; 38.24]	1.0%	
Overall	**9**	**200 / 6376**		**0.84**	**[0.61; 1.16]**	**100.0%**	0.11
Heterogeneity between subgroups: $I^2 = 51\%$							
Cardiovascular death							
Canagliflozin	2	150 / 2308		0.96	[0.69; 1.33]	41.9%	
Dapagliflozin	2	75 / 1517		0.90	[0.57; 1.42]	22.2%	
Empagliflozin	3	127 / 2325		0.78	[0.55; 1.12]	35.8%	
Overall	**7**	**352 / 6150**		**0.88**	**[0.71; 1.09]**	**100.0%**	0.71
Heterogeneity between subgroups: $I^2 = 0\%$							
Heart failure							
Canagliflozin	1	98 / 2039		0.57	[0.38; 0.86]	35.4%	
Dapagliflozin	2	83 / 1517		0.72	[0.46; 1.13]	28.7%	
Empagliflozin	3	98 / 2325		0.49	[0.18; 1.37]	35.8%	
Overall	**6**	**279 / 5881**		**0.61**	**[0.48; 0.78]**	**100.0%**	0.68
Heterogeneity between subgroups: $I^2 = 0\%$							
All-cause mortality							
Canagliflozin	2	221 / 2308		0.88	[0.67; 1.15]	37.2%	
Dapagliflozin	3	168 / 1838		0.88	[0.65; 1.19]	29.8%	
Empagliflozin	3	191 / 2425		0.79	[0.59; 1.06]	31.2%	
Ertugliflozin	1	12 / 566		1.40	[0.38; 5.11]	1.6%	
Ipragliflozin	1	0 / 81		NA		NA	
Luseogliflozin	1	1 / 145		1.59	[0.07; 38.24]	0.3%	
Overall	**11**	**593 / 7363**		**0.86**	**[0.73; 1.01]**	**100.0%**	0.90
Heterogeneity between subgroups: $I^2 = 0\%$							

0.1   0.2   0.5   1   2   5
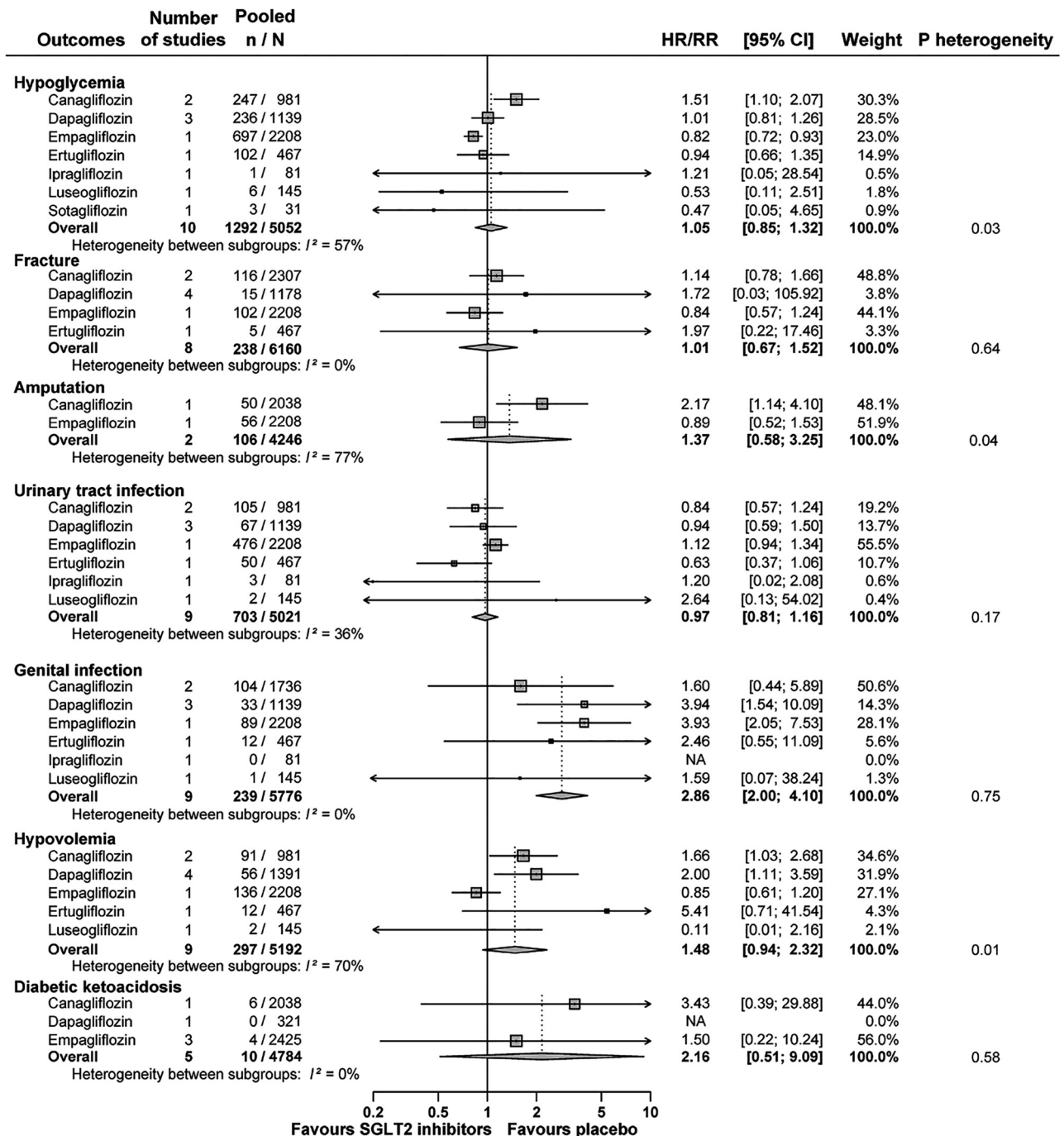**Favours SGLT2 inhibitors   Favours placebo**

Figure 3: SGLT2 inhibitors: effects on cardiovascular outcomes and all-cause mortality in patients with type 2 diabetes and chronic kidney disease. (Estimated glomerular filtration rate <60 mL/min/1.73 m^2). Reproduced with permission from John Wiley and Sons. Toyama T, Neuen BL, Jun M, et al. Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: A systematic review and meta-analysis. Diabetes Obes Metab. 2019;21(5):1237-1250. doi: 10.1111/dom.13648.

further increase in risk in association with SGLT2 inhibitor administration[35] and a series of cases in which people with diabetes experienced progression of a UTI to urosepsis or pyelonephritis led the FDA to issue a warning about the risk of serious UTIs in SGLT2 inhibitor-treated patients.[36] The potential association between this drug class and UTIs has not, however, been borne out by follow-up studies, with recent meta-analyses[8,37] reporting risk ratios close to 1.00 for UTI in association with SGLT2 inhibitor use (Figure 4).

Although UTI risk is not increased by SGLT2 inhibitor use, the risk of genital infections does seem to be exacerbated by this class of drugs. For example, in the EMPA-REG trial,[30] empagliflozin-treated patients showed a significantly higher

incidence of this adverse event than those receiving placebo (6.4% vs 1.8% of patients), with a substantially higher incidence in women (empagliflozin vs placebo, 10.1% vs 2.6%) than men (5.0% vs 1.5%; $P<0.001$ for all). These data are reinforced by the results of the meta-analyses cited above, which demonstrated risk ratios of 3.3 (95% confidence interval [CI], 2.74–3.99)[27] and 2.86 (95% CI, 2.00–4.10)[8] for genital infection in association with SGLT2 inhibitor use in people with T2DM (Figure 4).

A particularly serious type of genital infection is Fournier's gangrene. This extremely rare but potentially fatal condition, which is characterized by necrotizing fasciitis of the perineal soft tissues, primarily affects

Outcomes	Number of studies	Pooled n / N	HR/RR	[95% CI]	Weight	P heterogeneity
Hypoglycemia						
Canagliflozin	2	247 / 981	1.51	[1.10; 2.07]	30.3%	
Dapagliflozin	3	236 / 1139	1.01	[0.81; 1.26]	28.5%	
Empagliflozin	1	697 / 2208	0.82	[0.72; 0.93]	23.0%	
Ertugliflozin	1	102 / 467	0.94	[0.66; 1.35]	14.9%	
Ipragliflozin	1	1 / 81	1.21	[0.05; 28.54]	0.5%	
Luseogliflozin	1	6 / 145	0.53	[0.11; 2.51]	1.8%	
Sotagliflozin	1	3 / 31	0.47	[0.05; 4.65]	0.9%	
Overall	10	1292 / 5052	1.05	[0.85; 1.32]	100.0%	0.03
Heterogeneity between subgroups: I^2 = 57%						
Fracture						
Canagliflozin	2	116 / 2307	1.14	[0.78; 1.66]	48.8%	
Dapagliflozin	4	15 / 1178	1.72	[0.03; 105.92]	3.8%	
Empagliflozin	1	102 / 2208	0.84	[0.57; 1.24]	44.1%	
Ertugliflozin	1	5 / 467	1.97	[0.22; 17.46]	3.3%	
Overall	8	238 / 6160	1.01	[0.67; 1.52]	100.0%	0.64
Heterogeneity between subgroups: I^2 = 0%						
Amputation						
Canagliflozin	1	50 / 2038	2.17	[1.14; 4.10]	48.1%	
Empagliflozin	1	56 / 2208	0.89	[0.52; 1.53]	51.9%	
Overall	2	106 / 4246	1.37	[0.58; 3.25]	100.0%	0.04
Heterogeneity between subgroups: I^2 = 77%						
Urinary tract infection						
Canagliflozin	2	105 / 981	0.84	[0.57; 1.24]	19.2%	
Dapagliflozin	3	67 / 1139	0.94	[0.59; 1.50]	13.7%	
Empagliflozin	1	476 / 2208	1.12	[0.94; 1.34]	55.5%	
Ertugliflozin	1	50 / 467	0.63	[0.37; 1.06]	10.7%	
Ipragliflozin	1	3 / 81	1.20	[0.02; 2.08]	0.6%	
Luseogliflozin	1	2 / 145	2.64	[0.13; 54.02]	0.4%	
Overall	9	703 / 5021	0.97	[0.81; 1.16]	100.0%	0.17
Heterogeneity between subgroups: I^2 = 36%						
Genital infection						
Canagliflozin	2	104 / 1736	1.60	[0.44; 5.89]	50.6%	
Dapagliflozin	3	33 / 1139	3.94	[1.54; 10.09]	14.3%	
Empagliflozin	1	89 / 2208	3.93	[2.05; 7.53]	28.1%	
Ertugliflozin	1	12 / 467	2.46	[0.55; 11.09]	5.6%	
Ipragliflozin	1	0 / 81	NA		0.0%	
Luseogliflozin	1	1 / 145	1.59	[0.07; 38.24]	1.3%	
Overall	9	239 / 5776	2.86	[2.00; 4.10]	100.0%	0.75
Heterogeneity between subgroups: I^2 = 0%						
Hypovolemia						
Canagliflozin	2	91 / 981	1.66	[1.03; 2.68]	34.6%	
Dapagliflozin	4	56 / 1391	2.00	[1.11; 3.59]	31.9%	
Empagliflozin	1	136 / 2208	0.85	[0.61; 1.20]	27.1%	
Ertugliflozin	1	12 / 467	5.41	[0.71; 41.54]	4.3%	
Luseogliflozin	1	2 / 145	0.11	[0.01; 2.16]	2.1%	
Overall	9	297 / 5192	1.48	[0.94; 2.32]	100.0%	0.01
Heterogeneity between subgroups: I^2 = 70%						
Diabetic ketoacidosis						
Canagliflozin	1	6 / 2038	3.43	[0.39; 29.88]	44.0%	
Dapagliflozin	1	0 / 321	NA		0.0%	
Empagliflozin	3	4 / 2425	1.50	[0.22; 10.24]	56.0%	
Overall	5	10 / 4784	2.16	[0.51; 9.09]	100.0%	0.58
Heterogeneity between subgroups: I^2 = 0%						

0.2　0.5　1　2　5　10
Favours SGLT2 inhibitors　Favours placebo

Figure 4: SGLT2 inhibitors: effects on safety outcomes in patients with type 2 diabetes and chronic kidney disease. (Estimated glomerular filtration rate <60 mL/min/1.73m^2). Reproduced with permission from John Wiley and Sons. Toyama T, Neuen BL, Jun M, et al. Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: A systematic review and meta-analysis. Diabetes Obes Metab. 2019;21(5):1237-1250. doi: 10.1111/dom.13648.

middle-aged and elderly men.[38] Historically (data from 2001 and 2004), this condition affected men and women in a ratio of approximately 40:1, and was responsible for approximately 0.003% of hospitalizations in men aged 50–79 years in the United States annually.[38] More recently, a potential association between SGLT2 inhibitor administration and Fournier's gangrene was reported, with 55 cases identified over the six-year period to January 2019.[39] The ratio of men to women (2.4:1) differed from historical data and the incidence was markedly higher

than that previously recorded among patients receiving other antidiabetic drug classes (19 cases recorded over a 35-year period).[39] As a result of these reports, the FDA required inclusion of a warning about the risk of Fournier's gangrene in the prescribing information and patient medication guides of all SGLT2 inhibitors.[40]

The question of whether SGTL2 inhibitor administration increases the risk of amputation of the toes, feet, or legs has been debated and clinical trials have yielded varying results (Figure 4). In the CANVAS clinical trial program,[29] which enrolled patients with T2DM at high cardiovascular risk, canagliflozin-treated patients were at significantly higher risk of amputation than those who received placebo (hazard ratio [HR], 1.97; 95% CI, 1.41–2.75). These findings were, however, refuted by the results of the CREDENCE trial,[16] which reported a similar incidence of amputation in canagliflozin- and placebo-treated patients with T2DM and albuminuric CKD (HR, 1.11; 95% CI, 0.79–1.56), with absolute event rates of 12.3 and 11.2 events/1,000 patient-years, respectively. The CREDENCE results are supported by data from four administrative claims databases from the United States involving new users of canagliflozin (n=142,800) or non-SGLT2 inhibitor antidiabetic agents (n=460,885),[41] which showed HRs for below-knee lower extremity amputation for canagliflozin vs non-SGLT2 inhibitors of 0.75 (95% CI, 0.40 to 1.41; on-treatment analysis) and 1.01 (95% CI, 0.93 to 1.10; intent-to-treat analysis). In spite of these data, a boxed warning relating to the risk of lower limb amputation, which was added by the FDA to the prescribing information for canagliflozin-containing products in 2017, remains in place.[6] There is no evidence of an amputation-related signal from large clinical trials involving the SGLT2 inhibitors, dapagliflozin[42] or empagliflozin,[43] although there is a suggestion that the incidence of nontraumatic lower limb amputation may be increased in ertugliflozin-treated patients, with potential evidence of a dose-related effect.[7] This is reflected by a warning in the ertugliflozin prescribing information.[7]

Given the ongoing uncertainty about the role of SGLT2 inhibitors in the pathogenesis of amputation, it has been recommended that the use of these agents – and of canagliflozin in particular – should be avoided in patients with a history of amputation or ongoing foot ulceration.[44] Current American Diabetes Association (ADA) guidelines recommend that the feet of all people with diabetes should be evaluated at least annually to identify risk factors for ulcers and amputations, and that patients with evidence of claudication or who have reduced or absent pedal pulses should be referred for assessment of ankle-brachial index.[11]

A link between canagliflozin administration and increased risk of bone fracture has also been observed. This association, which was first noted in one of the two clinical trials that comprised the CANVAS program,[45] led the FDA to add a warning about fracture risk to the prescribing information of all canagliflozin-containing medications.[46] However, no such safety signal was evident in other studies in which canagliflozin was used, including the CREDENCE trial,[16,47] and the increased fracture risk observed in CANVAS may have been a chance finding.[45] Given the increased fracture risk that is inherent in patients with T2DM,[48] the absence of an obvious pathogenetic mechanism linking SGLT2 inhibition and fracture,[49] and the results of a recent meta-analysis involving data for canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin that reported a HR for risk of fracture of 1.01 (95% CI, 0.67–1.52) for SGLT2 inhibitors vs placebo[8] (Figure 4), the existence of a class effect is deemed unlikely.

Concerns about the potential for SGLT2 inhibitors to induce hypotension have led to inclusion of a warning on the prescribing information of all drugs in this class relating to assessment of volume status prior to initiation of, and during, therapy.[4–7] This is supported by meta-analysis of data from >5,000 individuals showing significantly lower systolic and diastolic blood pressures in association with SGLT2 inhibitor administration, as well as a trend for hypovolemia (risk ratio, 1.48; 95% CI, 0.94–2.32[8]; Figure 4). Lower blood pressure may, however, be beneficial in many people with T2DM.[50]

Diabetic ketoacidosis (DKA) is described as a rare but potentially fatal consequence of SGLT2 inhibitor administration,[8] and meta-analysis has shown a trend for increased risk in SGLT2 inhibitor-treated patients[8] (Figure 4). Although DKA is typically associated with hyperglycemia, affected SGLT2 inhibitor-treated patients are frequently euglycemic.[51] Plausible mechanisms by which these agents may increase the risk of DKA include reduced insulin secretion, with consequent increased synthesis of free fatty acids which are converted to ketone bodies, and stimulation of glucagon secretion which leads to ketone body synthesis.[52] Risk factors for DKA in SGLT2 inhibitor-treated patients include insufficient hydration or carbohydrate intake and a recent decrease in insulin dose.[51] The prescribing information of all SGLT2 inhibitors includes a warning relating to ketoacidosis risk.[4–7]

Concerns about increased risk of hypoglycemia are misplaced. There is no indication from meta-analysis of data from >5,000 patients that this is a risk of SGLT2 inhibitor administration per se (risk ratio, 1.05; 95% CI, 0.85–1.32[8]; Figure 4), and this aligns with the mechanism of action of these drugs, which do not stimulate the release of insulin or affect endogenous glucose synthesis in response to hypoglycaemia.[53] However, hypoglycemic risk may be increased if doses of concomitantly administered insulin/insulin secretagogue are not decreased when SGLT2 inhibitor

therapy is initiated, and the prescribing information for all four SGLT2 inhibitors currently approved for use in the United States carries a warning to this effect.[4–7]

Finally, we draw readers' attention to a recent case report[54] that cited a case of rosuvastatin myotoxicity secondary to concomitant rosuvastatin-canagliflozin use. The patient, who had tolerated rosuvastatin well for >five years, experienced severe muscle pain and hepatotoxicity within 15 days of initiating treatment with canagliflozin, with plasma rosuvastatin levels 15-fold higher than expected at the time of hospital admission. The authors speculated that, as a result of its effects on drug transporters, canagliflozin administration led to increased intestinal absorption and decreased hepatocellular uptake and excretion of rosuvastatin. The potential for interaction between these two drugs should be considered in patients who would benefit from both statins and SGLT2 inhibitors.

SGLT2 inhibitor use in perspective

There are clear advantages of an osteopathic medical approach to the management of T2DM, a condition in which an initial metabolic problem frequently progresses to cardiovascular and renal pathology.[1] Andrew Taylor Still, who founded osteopathic medicine, regarded the body as an integrated organism in which no part functions independently.[55] Osteopathic medical practitioners' holistic approach to patient care is well served by SGLT2 inhibitors, a drug class that effectively manages many aspects of the cardio-renal-metabolic spectrum of abnormalities from which patients with T2DM suffer. These proven benefits of SGLT2 inhibitors on patient outcomes led a group of endocrinologists and cardiologists to issue a consensus statement which recommends that patients with T2DM who are at high cardiovascular and/or renal risk should receive a SGLT2 inhibitor with proven cardiovascular and/or renal benefit (or a GLP-1 RA) as second- or third-line therapy after metformin.[56] Furthermore, the fact that canagliflozin reduces the risk of both cardiovascular and renal events in diabetic patients with CKD and well controlled glycemia has led to suggestions that SGLT2 inhibitors should be considered as add-on or even first-line therapy in all patients with diabetes based on cardiovascular and/or renal risk, without regard for level of glycemic control.[57]

These recommendations are echoed by current ADA guidelines[11] which recommend that SGLT2 inhibitors should be used in patients with T2DM who have established ASCVD and who have or are at high risk of HF. Drugs of this class, or a GLP-1 RA, are also recommended for patients with T2DM who have ASCVD but who are not at risk of HF, and those with CKD.[11] SGLT2 inhibitors with proven cardiovascular and/or renal benefit should be used, as appropriate.[11]

Prescription of SGLT2 inhibitors in the United States is thwarted, however, by lack of insurance coverage. Many insurers, including Medicare and Medicaid, do not cover this class of antihyperglycemic agents[58] and many private insurance companies mandate that the patient must fail to achieve glycemic control with multiple other agents before SGLT2 inhibitors can be prescribed.[59] These factors, combined with lack of familiarity and concerns about adverse events, may deter physicians from prescribing these drugs.[60]

Although SGLT2 inhibitors have many advantages in the management of T2DM, it is important that physicians have these agents in perspective within the armamentarium of recently introduced therapies for T2DM (SGLT2 inhibitors, GLP-1 RAs and DPP-4 inhibitors) and that treatment decisions are based on each patient's spectrum of comorbid conditions. For example, GLP-1 RAs are generally most suitable for patients with ASCVD, whereas SGLT2 inhibitors are indicated for patients with HF.[1] For patients with CKD, optimal therapy may be dictated by the severity of disease, GLP-1 RAs being indicated for patients with more advanced disease, and SGLT2 inhibitors for those in the earlier stages.[1] Risk of hypoglycaemia and bodyweight are additional considerations, with GLP-1 RAs, SGLT2 inhibitors and DPP-4 inhibitors being well-suited for patients who need to minimize hypoglycaemic risk, and GLP-1RAs and SGLT2 inhibitors being preferable for bodyweight reduction.[1] There are also potential benefits of using GLP-1 RAs and SGLT2 inhibitors in combination.[61]

Within the class of SGLT2 inhibitors, different drugs are best suited to different patients, and the patient's eGFR, comorbidities and perceived risk of various adverse outcomes will dictate which SGLT2 inhibitor should be used. For example, SGLT2 inhibitors have eGFR lower limits at initiation of 30 mL/min/1.73 m^2 (canagliflozin), 45 mL/min/1.73 m^2 (dapagliflozin, empagliflozin) and 60 mL/min/1.73 m^2 (ertugliflozin), and are approved for reductions in the risks of MACE (canagliflozin), cardiovascular death (dapagliflozin, empagliflozin), hHF(dapagliflozin) and adverse renal outcomes (canagliflozin) in various subsets of the population of patients with T2DM.[4–7]

Conclusion

The SGLT2 inhibitors have generated new possibilities in the management of T2DM. Initially introduced as drugs that provide effective management of glycemia, the ability of these drugs to provide cardiovascular and renal

protection has been recognized because of mandatory safety outcomes trials. The SGLT2 inhibitors thus herald a paradigm shift in the management of T2DM, in which one class of drugs can aid in management of hyperglycemia, without increasing hypoglycemic risk, while simultaneously reducing the risk of secondary cardiovascular events and ameliorating the advance of renal disease. With the anticipated inclusion of the SGLT2 inhibitor, dapagliflozin, in the pharmacological armamentarium available for management of patients with HF who do not have diabetes, the indications for these drugs may soon expand. Clinicians should ensure they are ready to take full advantage of the benefits that these drugs can offer their patients, and should consider SGLT2 inhibitors as a preferred class of antihyperglycemic drug for patients with T2DM.

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