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SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS VERSUS GLICLAZIDE IN THE TREATMENT OF TYPE 2 DIABETES MELLITUS

HEALTH TECHNOLOGY ASSESSMENT SECTION
MEDICAL DEVELOPMENT DIVISION
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DISCLAIMER

Technology review is a brief report, prepared on an urgent basis, which draws on restricted reviews from analysis of pertinent literature, on expert opinion and / or regulatory status where appropriate. It has been subjected to an external review process. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of this review.

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DISCLOSURE

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EXECUTIVE SUMMARY

Background

In 2015, the number of people aged 20-79 years with diabetes worldwide has been estimated to be 415 million, with approximately 90% having type 2 diabetes (T2DM), incurring global health expenditure of US$673 billion. In Malaysia, the National Health Morbidity Survey (NHMS) 2015 reported prevalence of diabetes mellitus of 17.5% (3.5 million) among adults of 18 years and above which reflected a 15% increase compared to the diabetes prevalence of 15.2% (2.6 million) in NHMS 2011.

According to the Malaysian Statistics on Medicines 2011-2014 report, the most prescribed antidiabetic drug in 2014 was metformin (5.8 per 100 diagnoses) followed by gliclazide (2.7 per 100 diagnoses), incurring total estimated public and private expenditure of RM91 million and RM78 million respectively. Gliclazide has been used extensively in the treatment of T2DM as add-on therapy to metformin or monotherapy for those who cannot tolerate metformin. The newer antidiabetics, sodium-glucose co-transporter 2 (SGLT2) inhibitors, were only introduced to the Malaysian market in recent years.

The SGLT2 inhibitors have intermediate glucose-lowering efficacy and low risk of hypoglycaemia with added benefits of weight loss and reduction in blood pressure. These drugs are effective at all stages of disease progression with preserved glomerular function. However, SGLT2 inhibitors have several disadvantages such as high cost of treatment, increased risk of urogenital infections and decreased efficacy with declining estimated glomerular filtration rate. Recent cardiovascular outcome trials have demonstrated cardiovascular and renal protection benefits in patients taking SGLT2 inhibitors.

These glycaemic and non-glycaemic benefits have increased the favourability of SGLT2 inhibitors in the treatment of T2DM compared with conventional antidiabetics such as gliclazide. Gliclazide has well-established high glucose-lowering efficacy and low cost of treatment. However, gliclazide is associated with moderate risk of hypoglycaemia, weight gain, uncertain cardiovascular safety and high risk of secondary failure.

This technology review was requested by Senior Consultant Endocrinologist to review the evidence on SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) versus gliclazide in the treatment of T2DM with the intention of improving the management of T2DM in Malaysia.

Objective/aim

To assess the effectiveness, safety and cost-effectiveness of SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) versus gliclazide in T2DM.

Results and conclusions
A total of 222 records were identified through the Embase, Ovid and PubMed interfaces and 21 were identified from other sources (references of retrieved articles). One health technology assessment (HTA) report (systematic review and economic evaluation), five systematic reviews (five for effectiveness; four for safety), one randomised clinical trial and one retrospective cohort study were included in the review.

Effectiveness
As there was no head to head randomised controlled trial comparing SGLT2 inhibitors and gliclazide, relative effects on biomarkers had to be drawn from network meta-analysis. There was good level of retrievable evidence to suggest that in terms of glycaemic control (HbA1c reduction), canagliflozin 100mg, dapagliflozin 5mg and 10mg, and empagliflozin 10mg and 25mg were less effective than gliclazide. Only canagliflozin 300mg was found to be as effective as gliclazide. However, SGLT2 inhibitors had added benefits of significant reduction in body weight and some reduction in systolic blood pressure. Gliclazide was associated with weight gain. There was no retrievable evidence on blood pressure reduction for gliclazide.

As for cardiovascular and renal outcomes, effects of SGLT2 inhibitors had to be drawn from two systematic reviews of placebo-controlled trials, one randomised placebo-controlled trial, and one retrospective cohort study. For gliclazide, one systematic review reported that although nine studies comparing gliclazide with other oral glucose-lowering drugs as comparator group reported incidence of cardiovascular events (risk ratio 0.95 (95% CI 0.57, 1.61) and mortality (risk ratio 0.81 (95% CI 0.26, 2.47), none of the trials was designed to assess cardiovascular safety and/or efficacy. These studies reported limited number of cardiovascular events (11 cases in 1480 gliclazide users and 20 cases in 1508 comparator patients) and cardiovascular deaths (3 in 1602 gliclazide users and 7 in 1619 comparator patients). Some studies were conducted for a relatively short duration (13-16 months). There was no retrievable evidence on renal outcome for gliclazide.

One systematic review and meta-analysis based on placebo-controlled trials showed that SGLT2 inhibitors appeared to have moderate benefits on atherosclerotic major adverse cardiovascular events (MACE) and risk of cardiovascular death or hospitalisation for heart failure in patients with established atherosclerotic cardiovascular disease (ASCVD). In terms of risk of cardiovascular death or hospitalisation for heart failure, patients with history of heart failure would benefit from canagliflozin and dapagliflozin whereas patient without history of heart failure would benefit from dapagliflozin and empagliflozin. Patients without ASCVD but with multiple risk factors did not appear to benefit from SGLT2 inhibitors in terms of MACE and risk of cardiovascular death or hospitalisation for heart failure. Patients with eGFR <60ml/min/1.73m^2 would benefit from canagliflozin in terms of MACE and hospitalisation for heart failure.

In terms of risk of renal worsening, end-stage kidney disease or renal death, patients with ASCVD and those with eGFR ≥60ml/min/1.73m^2 would benefit from SGLT2 inhibitors. With regards to patients with eGFR <60ml/min/1.73m^2, there were inconclusive results from two systematic reviews and one randomised clinical trial. The magnitude of benefit for SGLT2 inhibitors appeared to be lesser in patients with more severe kidney disease at baseline.

In the retrospective cohort study, dapagliflozin showed better reduction in estimated 10-year cardiovascular risk for all four endpoints (fatal and non-fatal coronary heart disease; and fatal and non-fatal stroke) compared with gliclazide which reduced three endpoints except for fatal stroke.

More evidence is required in comparison with active comparators to establish the cardiovascular and renal protection of SGLT2 inhibitors which had only been demonstrated in placebo-controlled trials. In terms of overall efficacy outcomes among SGLT2 inhibitors, canagliflozin appeared to be most favourable, followed by empagliflozin and dapagliflozin.

Safety

There was good level of retrievable evidence to suggest that gliclazide was associated with significantly higher risk of hypoglycaemia compared with SGLT2 inhibitors. Although all three SGLT2 inhibitors were associated with low risk of hypoglycaemia, these drugs were associated with increased risk of genital infections. Fournier's gangrene was identified as a safety concern in patients receiving SGLT2 inhibitors. Rare occurrences of diabetic ketoacidosis and acute kidney injury had also been reported with the use of SGLT2 inhibitors. Patients taking canagliflozin had increased risk of bone fractures and were approximately twice as likely to undergo amputation. Among the SGLT2 inhibitors, empagliflozin and dapagliflozin appeared to have acceptable safety profile. However, the safety record of SGLT2 inhibitors remains to be established and continued monitoring for adverse events is required.

Cost-effectiveness

Based on a systematic review and cost-effectiveness model, all three SGLT2 inhibitors were not cost-effective compared with gliclazide from the perspective of the UK National Health Service and Personal Social Services, using 2014 prices, with costs and benefits discounted at 3.5% per year. Gliclazide was the least expensive, with total lifetime cost of £27,314. Canaglilfozin 300mg, dapagliflozin 10mg and empagliflozin 25mg were £5362, £5552 and £5,461 more expensive than gliclazide, respectively. If there were no direct quality of life impacts from weight changes, lifetime quality adjusted life years (QALYs) arising from diabetes, its complications and adverse events were highest for gliclazide at 10.392 QALYs. Gliclazide was estimated to be superior to canagliflozin, dapagliflozin and empagliflozin by 0.012 QALYs, 0.025 QALYs and 0.014 QALYs, respectively. Gliclazide dominated all SGLT2 inhibitors (less costly and more effective). Among the SGLT2 inhibitors, canagliflozin was the most favourable in terms of cost and QALYs, followed by empagliflozin and dapagliflozin. However, the cost-effectiveness modelling

did not include cost savings from improved cardiovascular and renal outcome of which data were not yet available at the time of assessment.

Organisational issues

World Health Organisation (WHO), American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD), Agency for Care and Effectiveness (ACE), Singapore and Ministry of Health, Malaysia have issued guidelines with regard to the use of SGLT2 inhibitors and gliclazide in the treatment of T2DM.

Methods

Literature search was done to search for published articles to assess the effectiveness, safety and cost-effectiveness of SGLT2 inhibitors versus gliclazide in T2DM. The following electronic databases were searched via interfaces of Embase, OVID: MEDLINE (1946 to present), EBM Reviews-Cochrane Database of Systematic Reviews (2005 to February 2019), EBM Reviews–Cochrane Central Register of Controlled Trials (January 2019), EBM Reviews–Database of Abstracts of Review of Effects (1st Quarter 2016), EBM Reviews–Health Technology Assessment (4th Quarter 2016), NHS economic evaluation database (1st Quarter 2016), PubMed and INAHTA database. The last search was run on 29th January 2019. An updated search was conducted between 30th April 2019 and 8th May 2019 based on feedback from one of the external reviewers.

Summary of efficacy outcomes for gliclazide and SGLT2 inhibitors (1).

Efficacy outcomes	Study	Unit of measurement	Specific population	Gliclazide 80-320mg	Canagliflozin 100mg	Canagliflozin 300mg	Dapagliflozin 5mg	Dapagliflozin 10mg	Empagliflozin 10mg	Empagliflozin 25mg
Glycaemic control (HbA1c, %)	Johnston (2017)	MD (95% CI)		-0.95 (-1.27, -0.64)*	-0.95 (-1.06, -0.84)*	-1.19 (-1.34, -1.04)*	N/A	-0.59 (-0.70, -0.48)*	-0.76 (-0.87, -0.65)*	-0.88 (-0.99, -0.77)*
	Mearns (2015)	WMD (95% CI)		-0.70 (-0.85, -0.56)*	-0.72 (-0.85, -0.59)*		N/A	-0.48 (-0.62, -0.33)*	-0.69 (-0.81, -0.57)*	
	Maloney (2019)	Change from baseline 8.0%		-1.04	-0.84	-1.01	-0.65	-0.73	-0.69	-0.77
	Jia (2019)	MD (95% CI)		-1.37 (-2.04, -0.71)*	N/A	N/A	-0.50 (-0.78, -0.21)*		N/A	N/A
	Toyama (2018)	Effect size (95% CI)		N/A	-0.43 (-0.65, -0.21)*		-0.25 (-0.36, 0.14)*		0.29 (-0.43, -0.15)*	
Weight changes (kg)	Johnston (2017)	MD (95% CI)		+1.97 (0.76, 3.20)*	-2.02 (-2.41, -1.65)*	-2.91 (-3.22, -2.59)*	N/A	-1.58 (-2.01, -1.14)*	-1.74 (-2.15, -1.33)*	-1.89 (-2.29, -1.49)*
	Mearns (2015)	WMD (95% CI)		+1.19 (0.39, 1.99)*	-2.15 (-2.63, -1.67)*		N/A	-2.17 (-2.78, -1.57)*	-2.08 (-2.52, -1.63)*	
	Maloney (2019)	Change from baseline 90kg		+2.40	-1.90	-2.30	-1.70	-1.90	-2.10	-2.40
	Toyama (2018)	Effect size (95% CI)		N/A	-1.31 (-1.52, -1.09)*		-1.50 (-2.02, -0.98)*		-1.38 (-1.72, -1.04)*	
SBP (mmHg)	Johnston (2017)	MD (95% CI)		N/A	-4.24 (-6.01, -2.44)*	-5.65 (-7.77, -3.53)*	N/A	–2.73 (-4.77, -0.74)*	-2.59 (-4.88, -0.33)*	-3.38 (-5.67, -1.11)*
	Mearns (2015)	WMD (95% CI)		N/A	-4.14 (-5.80, -2.48)*		N/A	-4.50 (-7.97, -1.03)*	-5.14 (-6.80, -3.48)*	
	Toyama (2018)	Effect size (95% CI)		N/A	-4.19 (-6.49, 1.89)*		-3.58 (-5.53, -1.62)*		-5.07 (-7.30, -2.85)*	
CV outcome	Zelniker (2019)	HR (95% CI) for:								
	- Placebo controlled trial	MACE	With ASCVD	N/A	0.82 (0.72, 0.95)*		N/A	0.90 (0.79, 1.02)	0.86 (0.74, 0.99)*	
		Hospitalisation for HF & CV death		N/A	0.77 (0.65, 0.92)*		N/A	0.83 (0.71, 0.98)*	0.66 (0.55, 0.79)*	
		MACE	With multiple risk factors	N/A	0.98 (0.74, 1.30)		N/A	1.01 (0.86, 1.20)	N/A	
		Hospitalisation for HF & CV death		N/A	0.83 (0.58, 1.19)		N/A	0.84 (0.67, 1.04)	N/A	
		Hospitalisation for HF & CV death	With HF	N/A	0.61 (0.46, 0.80)*		N/A	0.79 (0.63, 0.99)*	0.72 (0.50, 1.04)	
			Without HF	N/A	0.87 (0.72, 1.06)		N/A	0.84 (0.72, 0.99)*	0.63 (0.51, 0.78)*	
		MACE	With eGFR >90 ml/min/1.73m^2	N/A	0.84 (0.62, 1.13)		N/A	0.94 (0.80, 1.10)	1.10 (0.77, 1.57)	
		Hospitalisation for HF		N/A	0.76 (0.40, 1.47)		N/A	0.94 (0.69, 1.26)	0.67 (0.31, 1.44)	
		MACE	With eGFR 60 - <90 ml/min/1.73m^2	N/A	0.95 (0.80, 1.13)		N/A	0.95 (0.82, 1.09)	0.76 (0.61, 0.94)*	
		Hospitalisation for HF		N/A	0.76 (0.52, 1.12)		N/A	0.65 (0.51, 0.84)*	0.72 (0.48, 1.07)	
		MACE	With eGFR <60 ml/min/1.73m^2	N/A	0.69 (0.54, 0.89)*		N/A	0.92 (0.69, 1.23)	0.88 (0.69, 1.13)	
		Hospitalisation for HF		N/A	0.55 (0.37, 0.83)*		N/A	0.70 (0.44, 1.12)	0.59 (0.39, 0.88)*	

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CV, cardiovascular; ESKD, end-stage kidney disease; HbA1c, glycosylated haemoglobin; HR, hazard ratio; MACE, major adverse cardiovascular events; MD, mean difference; MI, myocardial infarction; N/A, not available; WMD, weighted mean difference; SBP, systolic blood pressure. Statistical significance * = p<0.05 or CI for MD/WMD/effect size not crossing the null value of 0 or CI for HR/RR not crossing the null value of 1.

Summary of efficacy outcomes for gliclazide and SGLT2 inhibitors (2).

Efficacy outcomes	Study		Unit of measurement	Gliclazide 80-320mg	Canagliflozin 100mg	Canagliflozin 300mg	Dapagliflozin 5mg	Dapagliflozin 10mg	Empagliflozin 10mg	Empagliflozin 25mg
CV outcome	Toyama (2018) - Placebo-controlled trial	RR (95% CI) for MACE	Patients with eGFR <60ml/min/1.73m^2	N/A	0.70 (0.55, 0.89)*		0.86 (0.60, 1.24)		0.87 (0.69. 1.11)	
		RR (95% CI) for HF		N/A	0.57 (0.38, 0.86)*		0.72 (0.46, 1.13)		0.49 (0.18, 1.37)	
	Perkovic (2019) - Placebo-controlled trial	HR (95% CI) for CV death, MI or stroke	Patients with eGFR 30 - <90ml/min/1.73m^2	N/A	0.80 (0.67, 0.95)*	N/A	N/A		N/A	
		HR (95% CI) for hospitalisation for HF		N/A	0.61 (0.47, 0.80)*	N/A	N/A		N/A	
Renal outcome	Zelniker (2019) - Placebo controlled trial	HR (95% CI) for composite outcome of worsening eGFR, ESKD, or renal death	Patients with ASCVD	N/A	0.59 (0.44, 0.79)*		0.55 (0.41, 0.75)*		0.54 (0.40, 0.75)*	
			Patients with multiple risk factors	N/A	0.63 (0.39, 1.02)		0.51 (0.37, 0.69)*		N/A	
			Patients with eGFR >90 ml/min/1.73m^2	N/A	0.44 (0.25, 0.78)*		0.50 (0.34, 0.73)*		0.21 (0.09, 0.53)*	
			Patients with eGFR 60 – 90 ml/min/1.73m^2	N/A	0.58 (0.41, 0.84)*		0.54 (0.40, 0.73)*		0.61 (0.37, 1.03)	
			Patients with eGFR <60 ml/min/1.73m^2	N/A	0.74 (0.48, 1.15)		0.60 (0.35, 1.02)		0.66 (0.41, 1.07)	
	Toyama (2018) - Placebo-controlled trial	HR (95% CI) for renal-specific composite outcome of doubling of serum creatinine level, ESKD, or renal death	Patients with eGFR <60 ml/min/1.73m^2	N/A	0.81 (0.37, 1.77)		0.70 (0.46, 1.07)		0.68 (0.43, 1.09)	
	Perkovic (2019) - Placebo-controlled trial		Patients with eGFR 60 - <90 ml/min/1.73m^2	N/A	0.81 (0.52, 1.26)	N/A	N/A		N/A	
			Patients with eGFR 45 - <60 ml/min/1.73m^2	N/A	0.47 (0.31, 0.72)*	N/A	N/A		N/A	
			Patients with eGFR 30 - <45 ml/min/1.73m^2	N/A	0.71 (0.53, 0.94)*	N/A	N/A		N/A	

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CV, cardiovascular; ESKD, end-stage kidney disease; HbA1c, glycosylated haemoglobin; HR, hazard ratio; MACE, major adverse cardiovascular events; MD, mean difference; MI, myocardial infarction; N/A, not available; WMD, weighted mean difference; SBP, systolic blood pressure. Statistical significance * = p<0.05 or CI for MD/WMD/effect size not crossing the null value of 0 or CI for HR/RR not crossing the null value of 1.

Summary of safety outcomes for gliclazide and SGLT2 inhibitors.

Safety outcomes	Source	Unit of measurement	Gliclazide 80-320mg	Canagliflozin 100mg	Canagliflozin 300mg	Dapagliflozin 5mg	Dapagliflozin 10mg	Empagliflozin 10mg	Empagliflozin 25mg
Hypoglycaemia risk	Mearns (2015)	RR (95% CI)	10.02 (2.07, 48.56)*	0.91 (0.33, 2.51)			0.97 (0.34, 2.76)		0.51 (0.17, 1.49)
	Maloney (2019)	RR	3.6	1.4	1.4	1.0	1.0	1.0	1.0
	Toyama (2018)	RR (95% CI)	N/A	1.51 (1.10, 2.07)*			1.01 (0.81, 1.26)		0.82 (0.72, 0.93)*
Urinary infections	Johnston (2017)	Incidence rate	N/A	1.1% - 8.2% vs placebo (1.1% - 6.3%)		N/A	2.3% - 8.6% vs placebo (2.3% - 4.0%)		5.4% - 9.4% vs placebo (5.2% - 11.0%)
	Mearns (2015)	RR (95% CI)	N/A	1.25 (0.78, 2.00)			1.28 (0.77, 2.14)		0.86 (0.57, 1.30)
	Toyama (2018)	RR (95% CI)	N/A	0.84 (0.57, 1.24)			0.94 (0.59, 1.50)		1.12 (0.94, 1.34)
Genital infections	Johnston (2017)	Incidence rate	N/A	1.1% - 9.2% vs placebo (1.1% - 2.6%)		2.3% - 15.7% vs placebo (0.8% - 1.3%)			3.1% - 6.3% vs placebo (0% - 1.8%)
	Mearns (2015)	RR (95% CI)	N/A	8.03 (2.44, 26.39)*			2.16 (0.97, 4.82)		6.84 (1.92, 24.37)*
	Toyama (2018)	RR (95% CI)	N/A	1.60 (0.44, 5.89)			3.94 (1.54, 10.09)*		3.93 (2.05, 7.53)*
Diabetic ketoacidosis	Johnston (2017)	Incidence rate	N/A	1 per 5000 patient-years in patients treated with SGLT2 inhibitors					
	Zelniker (2019)	HR (95% CI)	N/A	2.33 (0.76, 7.17)		N/A	2.18 (1.10, 4.30)*		1.99 (0.22, 17.80)
				<1 per 1000 patient-years in patients treated with SGLT2 inhibitors					
	Toyama (2018)	RR (95% CI)	N/A	3.43 (0.39, 29.88)			N/A		1.50 (0.22. 10.24)
	Perkovic (2019)	HR (95% CI)	N/A	10.80 (1.39, 83.65)*	N/A		N/A		N/A
				2.2 vs 0.2 per 1000 patient-years in placebo group					
	FDA (2015)	No. of events (Mac 2013 – Oct 2015)	N/A	48 cases			21 cases		4 cases
Bone fracture	Johnston (2017)	Incidence rate	N/A	18.1 per 1000 patient-years		N/A	9.4% (8/85) versus none on placebo		No increased risk after 3 years of treatment in the EMPA-REG trial.
	Zelniker (2019)	HR (95% CI)	N/A	1.26 (1.04, 1.52)*		N/A	1.04 (0.91, 1.18)		0.98 (0.76, 1.25)
	Toyama (2018)	RR (95% CI)	N/A	1.14 (0.78, 1.66)			1.72 (0.03, 105.92)		0.84 (0.57, 1.24)
	Perkovic (2019)	HR (95% CI)	N/A	0.98 (0.70, 1.37)	N/A		N/A		N/A
	FDA (2015)	Incidence rate	N/A	14 per 1000 patient-years	15 per 1000 patient-years		N/A		N/A
Amputation	Zelniker (2019)	HR (95% CI)	N/A	1.97 (1.41, 2.75)*		N/A	1.09 (0.84, 1.40)		1.01 (0.70, 1.44)
	Toyama (2018)	RR (95% CI)	N/A	2.17 (1.14, 4.10)*			N/A		0.89 (0.52, 1.53)
	Perkovic (2019)	HR (95% CI)	N/A	1.11 (0.79, 1.56)	N/A		N/A		N/A
	FDA (2017) – CANVAS trial	Incidence rate	N/A	5.9 vs 2.8 per 1000 patient-years in placebo group			N/A		N/A
		HR (95% CI)	N/A	2.24 (1.36, 3.69)*	N/A		N/A		
	FDA (2017) – CANVAS-R trial	Incidence rate	N/A	7.5 vs 4.2 per 1000 patient-years in placebo group			N/A		N/A
		HR (95% CI)	N/A	1.80 (1.10, 2.93)*			N/A		N/A
Acute kidney injury	Toyama (2018)	HR (95% CI)	N/A	0.80 (0.38, 1.71)			0.17 (0.01, 4.06)		0.67 (0.39, 1.14)
	Perkovic (2019)	HR (95% CI)	N/A	0.85 (0.64, 1.13)	N/A		N/A		N/A
	FDA (2016)	No. of events (Mac 2013 – Oct 2015)	N/A	73 cases			28 cases		N/A

CANVAS, Canagliflozin Cardiovascular Assessment Study; CANVAS-R, A Study of the Effects of Canagliflozin on Renal Endpoints;CI, confidence interval; EMPA-REG, Empagliflozin Cardiovascular Outcome Event Trial;FDA, US Food and Drug Administration; HR, hazard ratio; RR, relative risk; N/A, not available. Statistical significance * = CI for RR/HR not crossing the null value of 1.

SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS VERSUS GLICLAZIDE IN THE TREATMENT OF TYPE 2 DIABETES MELLITUS

1. INTRODUCTION

Diabetes is one of the non-communicable diseases with high disease prevalence and economic burden worldwide. In 2015, the number of people aged 20-79 years with diabetes has been estimated to be 415 million, with approximately 90% having type 2 diabetes mellitus (T2DM), incurring global health expenditure of US$673 billion.[1] The National Health Morbidity Survey (NHMS) 2015 reported prevalence of diabetes mellitus of 17.5% (3.5 million) among adults of 18 years and above in Malaysia, which reflected a 15% increase compared to the diabetes prevalence of 15.2% (2.6 million) in NHMS 2011.[2,3]

An estimated 5 million deaths were attributable to diabetes, equivalent to 12.8% of global all-cause mortality among people aged 20-79 years.[1] Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in people with T2DM.[4] Diabetes confers substantial independent ASCVD risk, and most people with T2DM have additional risk factors such as hypertension, dyslipidaemia, obesity, physical inactivity, chronic kidney disease (CKD) and smoking.[5,6]

The importance of glycaemic control has been demonstrated to reduce the risk of microvascular complications (kidney and eyes) and major cardiovascular events which in turn reduces mortality rates.[7,8] The most common diabetic complications among Malaysians were nephropathy (7.8%), retinopathy (6.7%), and ischaemic heart disease (5.3%) among 123,980 diabetic patients audited by the National Diabetes Registry in 2012.[9] The Malaysian acute coronary syndrome (ACS) registry reported that 46.3% were found to have diabetes among 17,771 patients with ACS between 2014 and 2015.[10]

Currently there are seven different classes of oral antidiabetic drugs available in Malaysia: biguanides, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 (DPP4) inhibitors and sodium-glucose co-transporter 2 (SGLT2) inhibitors.[11] According to the Malaysian Statistics on Medicines 2011-2014 report, the most prescribed antidiabetic drug in 2014 was metformin (5.8 per 100 diagnoses) followed by gliclazide (2.7 per 100 diagnoses), incurring total estimated public and private expenditure of RM91 million and RM78 million respectively.[12] Metformin is regarded as the first-line treatment for T2DM whereas sulfonylureas are the most common add-on therapy followed by DPP4 inhibitors. Gliclazide, a newer generation of sulfonylureas, is favoured over older generation sulfonylureas such as glibenclamide due to higher risk of hypoglycaemia particularly in the elderly.[11]

The SGLT2 inhibitors, were only introduced to the Malaysian market in recent years. In January 2014, Forxiga® containing dapagliflozin 5mg and 10mg tablets by AstraZeneca were the first to be registered for use in Malaysia; followed by Jardiance® containing empagliflozin 10mg and 25mg tablets by Boehringer Ingelheim in December 2015; and Invokana® containing canagliflozin 100mg and 300mg tablets by Janssen in April 2016.[13-15]

This technology review was requested by Senior Consultant Endocrinologist to review the evidence on SGLT2 inhibitors (empagliflozin, dapagliflozin and canagliflozin) versus gliclazide in the treatment of T2DM with the intention of improving the management of T2DM in Malaysia.

2. OBJECTIVE / AIM

To assess the effectiveness, safety and cost-effectiveness of SGLT2 inhibitors (empagliflozin, dapagliflozin and canagliflozin) versus gliclazide in T2DM.

3. TECHNICAL FEATURES

The SGLT2 inhibitors lower blood glucose by inhibiting SGLT2 receptors in the proximal segment of renal proximal tubule which prevents renal glucose resorption and increases glycosuria. The SGLT2 inhibitors are also associated with reduction of blood pressure, weight and serum uric acid levels. These pleiotropic effects are likely due to the glucose-induced osmotic diuresis caused by SGLT2 inhibition. While early weight loss may be contributed by osmotic diuresis and fluid loss, fat mass reduction induced by glycosuria-mediated steady caloric loss may explain the continued gradual weight loss by SGLT2 inhibitors. The risk of hypoglycaemia is theoretically absent with these drugs as the magnitude of glycosuria is dependent on the amount of filtered glucose load which is a linear function of plasma glucose concentration.[16]

The SGLT2 inhibitors have intermediate glucose-lowering efficacy (0.5-1.0% reduction of HbA1c). These drugs are effective at all stages of disease progression with preserved glomerular function as their mechanism of action does not depend on insulin secretion or action. However, SGLT2 inhibitors have several disadvantages such as high cost of treatment (daily cost >US$2), urogenital infections, polyuria, dehydration and decreased efficacy with declining estimated glomerular filtration rate (eGFR).[17] In 2016, the US Food and Drug Administration (FDA) approved a new indication for empagliflozin to reduce the risk of cardiovascular death in adult patients with T2DM and cardiovascular disease.[18] Recent cardiovascular outcome trials have demonstrated benefits in reducing hospitalisation for heart failure and progression of renal disease regardless of existing ASCVD or history of heart failure.[19]

These glycaemic and non-glycaemic benefits have increased the favourability of SGLT2 inhibitors in the treatment of T2DM compared with conventional antidiabetics such as gliclazide. Gliclazide has been used extensively in the treatment of T2DM as add-on therapy to metformin or monotherapy for those who cannot tolerate metformin. Gliclazide increases insulin secretion by closing K_{ATP} channels on pancreatic beta cell membranes. Gliclazide has established high glucose-lowering efficacy (1-2% reduction in HbA1c), reduced microvascular risk and low cost of treatment (daily cost <US$1). In cases of mild to moderate renal impairment, dose adjustment was not required for gliclazide.[11] However, gliclazide is associated with moderate risk of hypoglycaemia, weight gain, uncertain cardiovascular safety and high risk of secondary failure.[17]

Empagliflozin was the first SGLT2 inhibitor to be included in the Ministry of Health Medicines Formulary in September 2017 with specific indication for the treatment of T2DM to improve glycaemic control in adults as add-on therapy in combination with other glucose–lowering medicines including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control. Currently, empagliflozin is restricted to patients whose glycated haemoglobin (HbA1c) is ≤8.5% on dual combination antidiabetic therapy; whose body mass index (BMI) is ≥30kg/m^2; and with creatinine clearance of ≥45ml/min or eGFR ≥45ml/min/1.73m^2.[20] Both canagliflozin and dapagliflozin have not been included in the MOH Medicines Formulary. However, dapaglifozin has been approved for use via the Medicines Special Authorization Form in Ministry of Health institutions such as Hospital Kuala Lumpur.

Table 1 below shows the price per tablet and estimated annual drug cost per patient in Klang Valley based on the recommended dosage by Malaysian Clinical Practice Guidelines on Management of Type 2 Diabetes Mellitus[11] which shows that the cost of gliclazide is considerably low compared to that of canagliflozin, dapagliflozin and empagliflozin.

Table 1: Price per unit and estimated annual drug cost per patient.

Generic Name	**Brand Name**	**Price per Tablet (RM)** - Update year: 2019	**Recommended Dosage by CPG[11] (Min – Max)**	**Estimated Annual Drug Cost per Patient (RM)**
Canagliflozin 100mg film-coated tablet	[redacted] 100mg & 300mg film-coated tablet, [redacted]	[redacted]	100mg – 300mg OD	[redacted]
Canagliflozin 300mg film-coated tablet	[redacted]	[redacted]		
Dapagliflozin 10 mg film-coated tablet	[redacted] 10mg film-coated tablet, [redacted]	[redacted]	5mg – 10mg OD	[redacted]
Empagliflozin 10mg film-coated tablet	[redacted] 10mg & 25mg film-coated tablet, [redacted]	[redacted]	10mg – 25mg OD	[redacted]
Empagliflozin 25mg film-coated tablet	[redacted]	[redacted]		
Gliclazide 30mg modified release tablet	[redacted] 30mg modified release Tablet, [redacted]	[redacted]	30mg OM – 120mg OM	[redacted]
Gliclazide 60mg modified release tablet	[redacted] 60mg modified release tablet, [redacted]	[redacted]	30mg OM – 120mg OM	
Gliclazide 80mg tablet	Gliclazide 80mg tablet, [redacted]	[redacted]	40mg OM – 160mg BD	[redacted]

[a] Private retail pharmacy in Klang Valley; [b] Hospital Kuala Lumpur

4. METHODS

4.1 Searching

Electronic databases searched through the Ovid interface:

- MEDLINE (R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE (R) 1946 to present
- EBM Reviews – Cochrane Central Register of Controlled Trials – January 2019
- EBM Reviews – Database of Abstracts of Review of Effects – 1st Quarter 2016
- EBM Reviews – Cochrane Database of Systematic Reviews – 2005 to February 2019
- EBM Reviews – Health Technology Assessment – 4thQuarter 2016
- EBM Reviews – NHS Economic Evaluation Database – 1st Quarter 2016

Other databases:

- Embase
- Pubmed
- INAHTA

Other website:

- FDA

Additional articles were identified from reviewing the references of retrieved articles. General search engine was used to get additional web based information. The search was limited to English articles on humans. Appendix 1 showed the detailed search strategies. The last search was conducted on 29th January 2019. An updated search was conducted between 30th April 2019 and 8th May 2019 based on feedback from one of the external reviewers.

4.2 Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection. The inclusion and exclusion criteria were:

Inclusion criteria

Population	Adults aged 18 years and above with type 2 diabetes mellitus
Interventions	SGLT2 inhibitors given as mono or dual therapy a. Canagliflozin b. Dapagliflozin c. Empagliflozin
Comparators	Sulfonylurea given as mono or dual therapy a. Gliclazide Placebo

Outcomes	i. Glycaemic control (HbA1c) ii. Weight changes iii. Blood pressure control iv. Cardiovascular outcome v. Renal outcome vi. Mortality vii. Hypoglycaemia risk viii. Adverse effects of treatment, including urinary tract and genital infections, diabetic ketoacidosis, bone fracture and amputation ix. Cost, cost-effectiveness, cost utility, cost-analysis and economic evaluation x. Organisational - guidelines
Study design	Health technology assessment (HTA) reports, systematic review (SR) and meta-analyses, randomised controlled trials (RCT), cohort studies

Exclusion criteria

i. Animal / laboratory / case reports / case series / cross-sectional study
ii. Narrative review
iii. Non-English full text articles
iv. Evaluated sulfonylureas as a drug class instead of individual drugs

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) checklist and evidence were graded according to the US/Canadian Preventive Services Task Force (See Appendix 2).

5. RESULTS AND DISCUSSION

A total of 222 records were identified through the Embase, Ovid and PubMed interfaces, and 21 were identified from other sources (references of retrieved articles). After removal of 32 duplicates, 211 records were screened and 151 were excluded. Of these, 60 relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the 60 full text articles, eight full text articles were included and 52 full text articles were excluded. The articles were excluded due to the study being included in SR and meta-analysis (n=8), irrelevant study design (n=25), irrelevant population (n=3) and irrelevant comparator (n=16). The flow chart of included studies is shown in Figure 1.

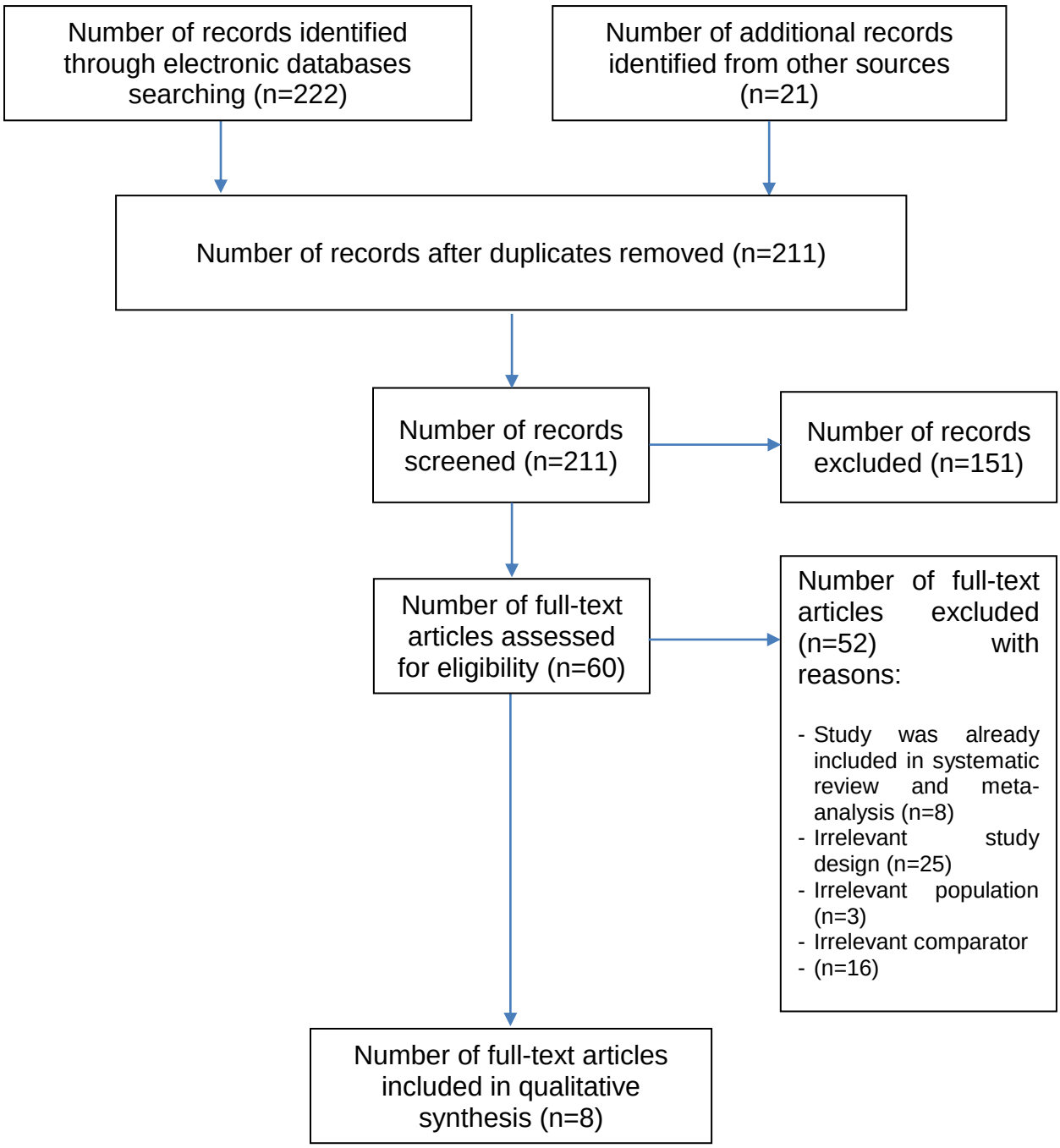

Figure 1. Flow chart of included studies

The eight full text articles finally selected for this review comprised of one HTA report (SR and economic evaluation), five SR (five for effectiveness, four for safety), one RCT and one retrospective cohort study.

Assessment of risk of bias in included studies

For systematic reviews included in the review, assessment of quality was conducted based on Critical Appraisal Skills Programme (CASP) checklist and the quality of evidence included in the SRs was summarised. Review author's judgements of risk of bias involved answering specific questions and assigning a judgement relating to the risk of bias as either:

+	Indicates YES (low risk of bias)
?	indicates UNKNOWN risk of bias
-	Indicates NO (high risk of bias)

The assessment of risk of bias revealed that most studies included were considered to have low risk of bias. However, the systematic review by Maloney et al. (2019) did not mention if assessment of quality was carried out.

The results of risk of bias of included studies are summarised as below.

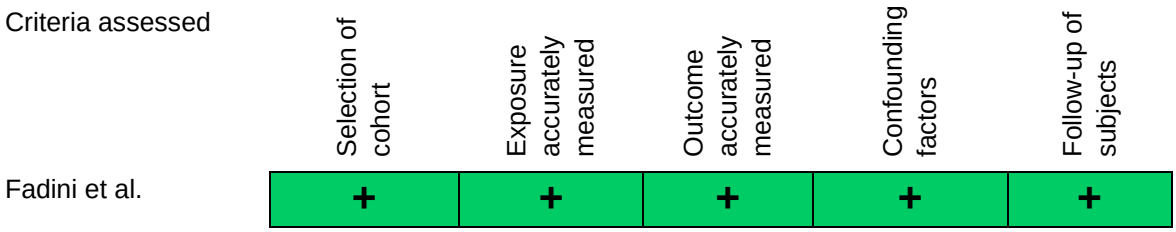

Figure 2a. Assessment of risk of bias of cohort.

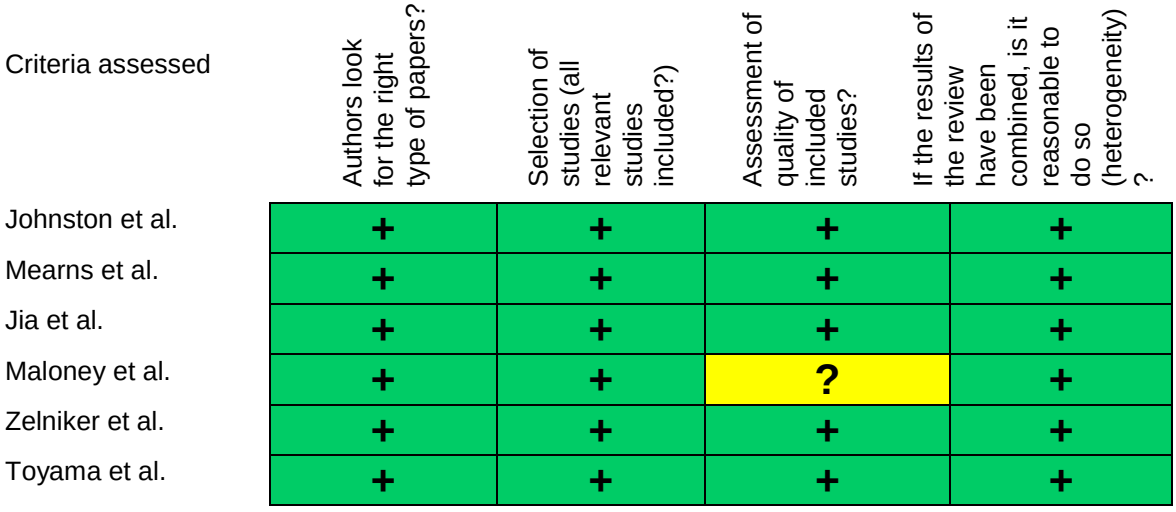

Figure 2b. Assessment of risk of bias of systematic review.

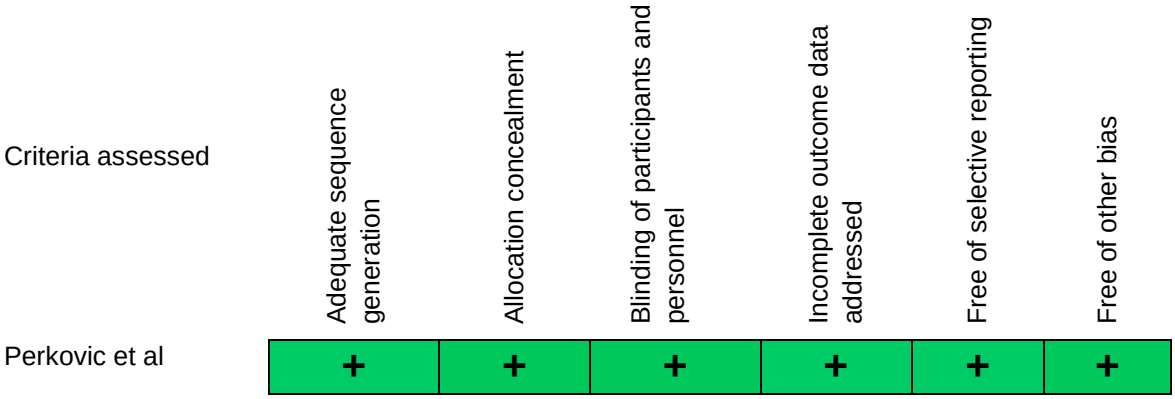

Figure 2c. Assessment of risk of bias of randomised controlled trial.

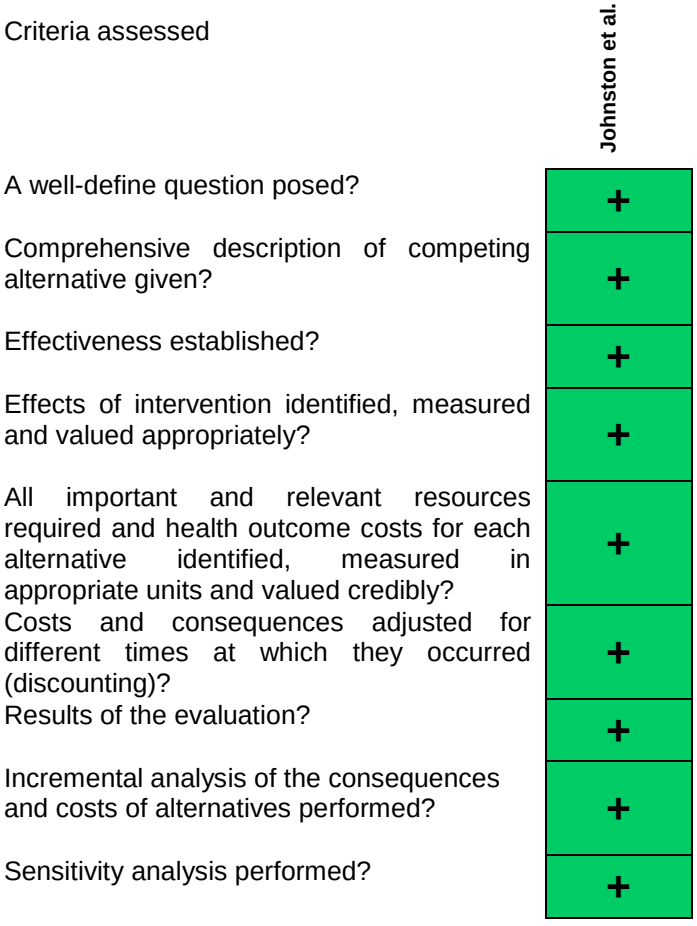

Figure 2d. Assessment of risk of bias of economic evaluation.

5.1 EFFICACY / EFFECTIVENESS

A total of one HTA report, five SRs, one RCT and one retrospective cohort study were included for the evaluation of efficacy/effectiveness. Outcome measures include glycaemic control (HbA1c), weight changes, blood pressure control, cardiovascular and renal outcome. There were no head-to-head comparisons between the SGLT2 inhibitors and gliclazide so relative effects on biomarkers had to be drawn from network meta-analysis (NMA). Traditional pair-wise meta-analysis were used to evaluate the efficacy and safety of two drugs based on evidence from RCTs that directly compare them. In the absence of such direct head-to-head comparisons, NMA would provide a statistical framework that incorporates evidence from both direct and indirect comparisons from a network of studies of different therapies and evaluates their relative treatment effects.[21]

Glycaemic control

The National Institute of Health Research (NIHR) published a HTA report in 2017 appraising canagliflozin, dapagliflozin and empagliflozin for monotherapy in the treatment of T2DM when metformin could not be used. The authors, Johnston et al., carried out SR and NMA to review the clinical effectiveness of three SGLT2 inhibitors in comparison with gliclazide modified release, pioglitazone, repaglinide and three DPP4 inhibitors (linagliptin, sitagliptin and vildagliptin). Primary measures of treatment effect were mean differences (MDs) in change from baseline for HbA1c, weight gain and systolic blood pressure (SBP). Cardiovascular outcome was not evaluated as there was only empagliflozin outcome trial available at the time of assessment.[22, level I]

The SR included studies published up to September 2015 sourced from Medline (1946 to February 2015) and Embase (1974 to February 2015). A total of 17 RCTs of monotherapy with trial duration of 24 – 26 weeks in people with T2DM unable to take metformin; baseline HbA1c of 7.5% or more; and dropout rates of no more than 20% were included in the NMA. Two trials were included for canagliflozin 100mg (n=285) and 300mg (n=197). Three trials were included for dapagliflozin 10mg (n=367). Two trials were included for empagliflozin 10mg (n=356) and 25mg (n=357). Three trials were included for gliclazide (n=588). The quality of the RCTs was assessed using the Cochrane risk of bias tool.[22, level I]

Bayesian NMA method with fixed effects model was used to analyse all data, preserving randomised treatment effects within trials and accounting for correlation between comparisons with three arms or four arms using WinBUGS 1.4.3 software. All results were reported as posterior medians of MDs with corresponding 95% credible intervals (CrIs). The statistical heterogeneity in treatment effect estimates was estimated using between-study variance with 95% CrI. The difference between indirect and direct estimates was calculated whenever indirect estimates could be constructed with a single common comparator to estimate inconsistency in the networks of evidence defined as disagreement between direct and indirect evidence with a 95% CrI excluding 0 for MD.[22, level I]

Based on pairwise comparison with placebo for HbA1c (%) in MD (95% CI), reduction was seen highest with canagliflozin 300mg [–1.19 (–1.34, –1.04)], followed by canagliflozin 100mg [–0.95 (–1.06, –0.84)], gliclazide [–0.95 (–1.27, –0.64)], empagliflozin 25mg [–0.88 (–0.99, –0.77)], empagliflozin 10mg [–0.76 (–0.87, –0.65)], lowest with dapagliflozin 10mg [–0.59 (–0.70, –0.48)]. None of the SGLT2 inhibitors were significantly more effective compared with gliclazide. The between-study variance was small, suggesting no heterogeneity, but the CrIs were wide, which reflected the small number of studies available for pairwise comparisons. Analyses based on direct versus indirect comparisons showed no evidence of inconsistency between direct and indirect evidence in the network for HbA1c. However, in some dapagliflozin trials, HbA1c improved in the placebo groups, reducing the placebo-adjusted improvement after dapagliflozin treatment whereas in the canagliflozin trials, HbA1c rose in placebo groups. The authors concluded that canagliflozin, dapagliflozin and empagliflozin were effective in improving glycaemic control. [22, level I]

A SR and NMA was conducted by Mearns et al. (2015) to assess the efficacy and safety of adjunctive antidiabetic agents in patients with inadequately controlled T2DM on metformin alone. Studies up to May 2014 were sourced from Medline, Cochrane Central, ClinicalTrials.gov and regulatory websites. Validity assessment was performed using Cochrane risk of bias tool. Traditional meta-analyses analysing changes in HbA1c, body weight and SBP as continuous variables were performed using StatsDirect version 2.7.8. Weighted mean differences (WMDs) and 95% confidence intervals (CIs) were calculated using DerSimonian and Laird random-effects model to account for between-study heterogeneity. When at least three studies making same direct comparison were available, likelihood of statistical heterogeneity (I^2) and publication bias (Egger's weighted regression) were assessed.[23, level I]

Random-effects NMA was performed using the package 'netmeta' (version 0.5–0) in R (version 3.0.2). Clinical superiority was regarded when one therapy improved HbA1c, body weight or SBP by at least 0.3%, 2.3 kg or 5 mmHg, respectively, versus a competitor. Sensitivity analyses calculating more conservative 99% CIs were performed to address the inherent limitations of multiple comparisons in the meta-analysis. Sixty-two RCTs (n=32,185) involving adult patients (≥18 years) with T2DM who showed inadequate response to stable, optimised metformin monotherapy at randomisation (≥1500 mg daily or maximally tolerated dose for ≥4 weeks) before randomisation, were included. Twenty-five agents including canagliflozin 100mg and 300mg (n=1,831), dapagliflozin 2.5mg – 10mg (n=495), empagliflozin 10mg and 25mg (n=1,617) and gliclazide 80mg – 320mg (n=1,259) were evaluated. Mean trial duration was 29 (12-52) weeks.[23, level I]

In terms of NMA estimate for change in HbA1c (%) versus placebo in WMD (95% CI), none of the SGLT2 inhibitors were significantly more effective or clinically superior to gliclazide. The reduction of HbA1c for gliclazide was -0.70 (-0.85, -0.56). Among the SGLT2 inhibitors, reduction of HbA1c was highest for canagliflozin [-0.72 (-0.85, -0.59)], followed by empagliflozin [-0.69 (-0.81, -0.57)], lowest for dapagliflozin [-0.48 (-0.62, -0.33)]. The I^2 for trials involving canagliflozin, dapagliflozin, empagliflozin and gliclazide showed no statistical heterogeneity (<50%). The authors concluded that the SGLT2 inhibitors were found to have similar HbA1c efficacy to

other non-insulin monotherapies. However, the authors disclosed that the study was funded by Boehringer Ingelheim.[23, level I]
A SR and model-based meta-analysis was conducted by Maloney et al. (2019) to compare glycaemic control, weight changes, and hypoglycaemia risk across 24 antihyperglycemic drugs used to treat type 2 diabetes. Data up to November 2017 were sourced from Medline (via PubMed), ClinicalTrials.gov, FDA summary basis of approval documents and drug labels, and sponsor websites. Excluded studies were studies run primarily in Asia, studies in special T2DM populations (hypertensive, obese, renally impaired, high cardiovascular risk, elderly and paediatric), studies with insulin background treatment, studies with sulfonylurea background treatment (for hypoglycemia analysis only), single arm studies, combination treatment arms, and phase I studies.[24, level I]

A total of 229 RCTs including 121,914 patients with T2DM were identified. Canagliflozin 100mg and 300mg (n=3,928), dapagliflozin 5mg and 10mg (n=4,019) empagliflozin 10mg and 25mg (n=4,932) and gliclazide 80mg–320mg were evaluated. Following a full Bayesian analysis, estimates for the change from placebo were determined for all regimens for drug naive population with a baseline HbA1c of 8.0%, baseline body weight of 90 kg and 26 weeks of treatment. Change in drug effect due to duration was taken into account, increasing (non-linearly) from 0% at week 0 to 100% (full effect) at week 26. Analyses were adjusted for duration of treatment (delay), drug dosages (dose response) and baseline HbA1c (scalar). All analyses were conducted with the use of SAS software, version 9.4 (SAS Institute).[24, level I]

In terms of HbA1c versus placebo, estimated treatment effect was seen highest with gliclazide (-1.04%), followed by canagliflozin 300mg (-1.01%), canagliflozin 100mg (-0.84%), empagliflozin 25mg (-0.77%), dapagliflozin 10mg (-0.73%), empagliflozin 10mg (-0.69%), lowest with dapagliflozin 5mg (-0.65%). The authors concluded that important differences between and within drug classes were identified. However, there may be conflict of interest as authors disclosed receiving consulting fees from pharmaceutical companies including Astra Zeneca, Boehringer Ingelheim and Janssen.[24, level I]

A SR and NMA was conducted by Jia et al. (2019) to compare the efficacy of hypoglycaemic drugs for T2DM by NMA of RCTs. Studies up to January 2018 were sourced from PubMed, Cochrane Library, ScienceDirect, EMBASE, FDA medical reviews and ClinicalTrials.gov website. A total of 75 RCTs (1991-2017) involving 33,830 adult patients with T2DM and a follow up of at least 28 days were included in NMA. Eleven oral hypoglycaemic drugs including dapagliflozin 2.5mg–10mg (n=1,646) and gliclazide 80-320mg (n=248) were evaluated as drug monotherapy for T2DM patients. Mean sample size was 451 patients with mean follow-up of 184 days. The RCT quality was assessed with Cochrane risk of bias tool. Evidence quality from meta-analysis was assessed with the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.[25, level I]

Primary outcome measures of antidiabetic efficacy were mean changes of HbA1c from baseline and their corresponding variation. Seventy-one RCTs reported HbA1c as primary outcomes. Pairwise meta-analyses (R software version 3.1.2) and NMA based on Bayesian hierarchical random-effects model (software package WINBUGS

version 1.4.3 and R) estimated overall effect sizes as MD and CI. Heterogeneity was assessed by I^2 and the Cochrane *Q* test. Subgroup and sensitivity analyses as well as meta-regression and publication bias were performed. Overall ranking was determined by overall effect sizes, probability of best treatment and surface of cumulative ranking curve area.[25, level I]

In terms of changes in HbA1c, dapagliflozin [MD -0.50 (-0.78, -0.21)] was less efficacious compared with gliclazide [MD -1.37 (-2.04, -0.71)], against placebo. Based on ranking analysis on HbA1c where rank 1 was the best and rank 12 was the worst, dapagliflozin ranked at 10 whereas gliclazide ranked at 2. Subgroup and sensitivity analyses found the results to be robust. Included RCTs were of high quality. Evidence strength from pairwise meta-analyses was moderate to high. Heterogeneities of pooled effect sizes were significantly high in pairwise meta-analyses (42/46 studies for efficacy estimates: I^2>75%). Meta-regression analysis indicated follow-up periods and risk of bias of included RCTs may be the source of heterogeneity. The authors conclude that repaglinide and metformin would be the best oral drugs for first-line monotherapy in T2DM.[25, level I]

A SR and MA was conducted by Toyama et al. (2019) to combine data from all the large-scale placebo-controlled cardiovascular outcome trials (CVOTs) of SGLT2 inhibitors to gain more reliable estimates of the efficacy and safety of specific outcomes overall and in relevant subgroups. Data from RCT of SGLT2 inhibitors that included reporting of effects on biomarkers, cardiovascular, renal or safety outcomes up to July-August 2018 were sourced from MEDLINE, EMBASE and the Cochrane Library and websites of the US, European and Japanese regulatory authorities. Risk of bias was assessed by two authors using Cochrane Risk of Bias tool. Twenty-seven studies with up to 7363 patients with T2DM and CKD defined as eGFR <60 mL/min/1.73m^2 were included in the evaluation of canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin and luseogliflozin versus placebo. Study duration ranged from seven days to a median of 4.2 years.[26, level I]

The biomarkers of interest were change from baseline in HbA1c, fasting glucose, systolic and diastolic blood pressure, body weight, albuminuria and serum potassium. Random effects models and inverse variance weighting were used to calculate relative risks (RR) with 95% CI. The percentage of variability across pooled estimates attributable to heterogeneity beyond chance was estimated using the I^2 statistic and also by calculating the *p* value for heterogeneity. Statistical analyses were performed using R version 3.4.4 with the package “meta” Version 4.9-1.[26, level I]

In terms of changes in HbA1c reported as effect size (95% CI), canagliflozin [-0.43 (-0.65, -0.21)] was more efficacious compared to dapaglflozin [-0.25 (-0.36, 0.14)] and empagliflozin [-0.29 (-0.43, -0.15)]. There was significant evidence of heterogeneity across SGLT2 inhibitors (I^2 = 65%; *p*-heterogeneity = 0.05) for the effect on HbA1c. The authors concluded that currently available data suggested that SGLT2 inhibitors reduced the risk of cardiovascular and renal outcomes in patients with T2DM and CKD, without clear evidence of additional safety concerns; however, the robustness of these findings requires confirmation in upcoming dedicated CKD outcome trials. There may be conflict of interest as authors disclosed receiving consulting fees from pharmaceutical companies including Astra Zeneca, Boehringer Ingelheim and Janssen.[26, level I]

A retrospective cohort nationwide multicentre study was conducted by Fadini et al. (2018) for the DApagliflozin Real World evIdeNce in Type 2 Diabetes (DARWIN-T2D) network. The study was designed to evaluate baseline clinical characteristics and change in glycaemic and extra-glycaemic effectiveness variables in patients initiated on dapagliflozin versus patients initiated on DPP4 inhibitors, gliclazide, or GLP-1RAs in 46 Italian diabetes specialist outpatient clinics. A total of 17,285 patients aged 18-80 years old with T2DM diagnosed for at least one year who were initiated on the evaluated drugs between 13th March 2015 to 31th December 2016 and not treated with SGLT2 inhibitors previously were included. Dapagliflozin 10mg (n=2,484) and gliclazide modified release 30mg or higher (n=5,960) were evaluated. Patients on dapagliflozin were initiated as add-on to metformin and/or insulin as this was the only combination reimbursed by the Italian National Health Service. Follow-up visit was three to 12 months after baseline.[27, level II-2]

An automated MyStar Connect software devised to manage people with diabetes was used to retrospectively extract relevant data from the same electronic chart system at all centres. Continuous variables were presented as mean ± SD, and categorical variables were presented as percentages. The two-tailed paired Student's t test was used to compare data collected at follow-up with those collected at baseline. Adjusting for multiple testing was performed using the Benjamini–Hochberg procedure.[27, level II-2]

Similar improvements in HbA1c were observed for dapagliflozin and gliclazide. A total of 830 patients initiated on dapagliflozin (33.4%) had a follow-up visit and showed significant improvements in HbA1c (−0.7% ± 1.2) after an average of 168 days (5.5 months). A total of 2,111 patients initiated on gliclazide (35.4%) had a follow-up visit and showed significant improvements in HbA1c (−0.6% ± 1.3) after an average of 185 days (6.1 months). The percentage of patients meeting the composite endpoint of simultaneous HbA1c and body weight reduction was 56.9% for dapagliflozin and 28.7% for gliclazide. There were significant differences among groups detected for most variables. Patients on dapagliflozin were younger; had longer diabetes duration; higher HbA1c level and blood pressure, and more obese than patients on gliclazide. Between-group comparisons of effectiveness were hampered by massive differences in baseline clinical characteristics that could not be overcome by propensity score matching which was intended to generate quasi-experimental comparisons that make retrospective studies closer to RCTs.[27, level II-2]

The authors concluded that this real-world study showed an initial channelling of dapagliflozin to difficult-to-treat patients and dapagliflozin provided significant benefits with regard to glucose control which were in line with findings from RCTs. However, metformin and insulin use were more common in the dapagliflozin group. More than half of patients receiving dapagliflozin (55.0%) were insulin-treated compared to 24.4% in the gliclazide group. There may also be conflict of interest as the study was sponsored and promoted by the Italian Diabetes Society through the partial (<50%) financial support from AstraZeneca.[27, level II-2]

Weight changes

The HTA report by Johnston et al. (2017) shows that based on pairwise comparison with placebo for weight changes (kg) in MD (95% CI), SGLT2 inhibitors were associated with significant weight reduction compared with gliclazide. Weight gain was observed in gliclazide group [+1.97 (0.76, 3.20)]. Weight reduction was seen highest with canagliflozin 300mg [–2.91 (–3.22, –2.59)], followed by canagliflozin 100mg [–2.02 (–2.41, –1.65)], empagliflozin 25mg [–1.89 (–2.29, –1.49)], empagliflozin 10mg [–1.74 (–2.15, –1.33)], lowest with dapagliflozin 10mg [–1.58 (–2.01, –1.14)]. The between-study variance was small, suggesting no heterogeneity, but the CrIs were wide, which reflected the small number of studies available for pairwise comparisons. Analyses based on direct versus indirect comparisons showed no evidence of inconsistency between direct and indirect evidence in the network for weight changes. The authors concluded that SGLT2 inhibitors have added benefits in some reduction of weight.[22, level I]

Mearns et al. (2015) reported that in terms of NMA estimate for change in body weight (kg) versus placebo in WMD (95% CI), SGLT2 inhibitors were significantly more effective and clinically superior to gliclazide. Weight gain was observed in patients taking gliclazide [+1.19 (0.39, 1.99)]. Similar weight reductions were observed for canagliflozin [-2.15 (-2.63, -1.67)], dapagliflozin [-2.17 (-2.78, -1.57)] and empagliflozin [-2.08 (-2.52, -1.63)]. The authors concluded that SGLT2 inhibitors have added benefits of weight loss.[23, level I]

In the study by Maloney et al. (2019), change in drug effect due to duration was taken into account for the weight analysis, increasing (non-linearly) from 0% at week 0 to 100% (full effect) at week 52 as the full effect on weight was assumed to be reached after 52 weeks of treatment. Similar weight reductions were observed for canagliflozin 100mg (-1.9kg), canagliflozin 300mg (-2.3kg), dapagliflozin 5mg (-1.7kg), dapagliflozin 10mg (-1.9kg), empagliflozin 10mg (-2.1kg) and empagliflozin 25mg (-2.4kg). Significant weight gain was observed for gliclazide 80mg – 320mg (+2.4kg). The authors concluded that important differences between and within drug classes were identified.[24, level I]

Toyama et al. (2019) reported that in terms of weight changes reported as effect size (95% CI), similar weight reductions were observed for canagliflozin [-1.31 (-1.52, -1.09)], dapagliflozin [-1.50 (-2.02, -0.98)] and empagliflozin [-1.38 (-1.72, -1.04)]. There was no evidence of heterogeneity across SGLT2 inhibitors for the effect on weight changes.[26, level I]

Fadini et al. (2018) reported that patients on dapagliflozin showed significant improvements in body weight (−2.7 kg ± 3.5; $p<0.001$) after an average of 168 days (5.5 months) compared to patients on gliclazide (−0.1kg ± 3.2; $p=0.393$) after an average of 185 days (6.1 months). The percentage of patients meeting the composite endpoint of simultaneous HbA1c and body weight reduction was 56.9% for dapagliflozin and 28.7% for gliclazide. The authors concluded that dapagliflozin provided significant benefits with regard to body weight that were in line with findings from RCTs.[27, level II-2]

Blood pressure control

The HTA report by Johnston et al. (2017) showed that based on pairwise comparison with placebo for SBP (mmHg) in MD (95% CI), reduction was seen highest with canagliflozin 300mg [–5.65 (–7.77, –3.53)], followed by canagliflozin 100mg [–4.24 (–6.01, –2.44)], empagliflozin 25mg [–3.38 (–5.67, –1.11)], empagliflozin 10mg [–2.59 (–4.88, –0.33)], lowest with dapagliflozin 10mg [–2.73 (–4.77, –0.74)]. No SBP data was available for gliclazide. The between-study variance was small, suggesting no heterogeneity, but the CrIs were wide, which reflected the small number of studies available for pairwise comparisons. Analyses based on direct versus indirect comparisons showed no evidence of inconsistency between direct and indirect evidence in the network for SBP. The authors concluded that SGLT2 inhibitors have added benefits in some reduction of SBP. [22, level I]

Mearns et al. (2015) reported that based on NMA estimate for change in SBP (mmHg) in WMD (95% CI), SGLT2 inhibitors were associated with SBP reduction but none were clinically superior to placebo. Similar reduction in SBP were observed for canagliflozin [-4.14 (-5.80, -2.48)], dapagliflozin [-4.50 (-7.97, -1.03)] and empagliflozin [-5.14 (-6.80, -3.48)]. No SBP data was available for gliclazide. The authors concluded that SGLT2 inhibitors have added benefits of SBP reduction.[23, level I]

Toyama et al. (2019) reported that in terms of SBP reported as effect size (95% CI), similar reductions were observed for canagliflozin [-4.19 (-6.49, -1.89)], dapagliflozin [-3.58 (-5.53, -1.62)] and empagliflozin [-5.07 (-7.30, -2.85)]. There was no evidence of heterogeneity across SGLT2 inhibitors for the effect on SBP.[26, level I]

Fadini et al. (2018) reported that patients on dapagliflozin showed significant improvements in SBP (−3.0 mmHg ±17.7; p<0.001) and diastolic blood pressure, DBP (−1.3 mmHg ± 9.9; p=0.004) after an average of 168 days (5.5 months) compared to patients on gliclazide [SBP (+0.1 mmHg ± 19.2; p=0.894); DBP (−0.3 mmHg ± 10.0; p=0.206) after an average of 185 days (6.1 months). Both dapagliflozin and gliclazide group received antihypertensive drugs such as angiotensin-converting enzyme (ACE) inhibitors, angiotension II receptor blockers, beta blockers and diuretics. The authors concluded that dapagliflozin provided significant benefits with regard to blood pressure that were in line with findings from RCTs. [27, level II-2]

Cardiovascular outcome

Fadini et al. (2018) estimated the risk of fatal and non-fatal coronary heart disease (CHD) and stroke for dapagliflozin and gliclazide using the United Kingdom Prospective Diabetes Study (UKPDS) risk engine. Only patients with complete set of data were included for this risk estimation.[27, level II-2] The UKPDS risk engine provides risk estimates and 95% CI, in individuals with T2DM not known to have heart disease for non-fatal and fatal CHD as well as non-fatal and fatal stroke. These can be calculated for any given duration of T2DM based on current age, sex, ethnicity, smoking status, presence or absence of atrial fibrillation and levels of HbA1c, SBP, total cholesterol and HDL cholesterol.[28]

Fadini et al. (2018) reported that patients on dapagliflozin (n=282) showed more significant reduction in estimated 10-year cardiovascular risk for all four endpoints: non-fatal CHD (-4.7 ± 9.9%), fatal CHD (-4.5 ± 9.4%), non-fatal stroke (-1.1 ± 5.3%), and fatal stroke (-0.6 ± 3.8%). Patients on gliclazide (n=602) showed significant reduction in estimated 10-year cardiovascular risk for three endpoints: non-fatal CHD (-4.5 ± 11.6%), fatal CHD (-4.2 ± 11.1%) and non-fatal stroke (-0.7 ± 6.1%).[27, level II-2]

In terms of lipid profile, patients on dapagliflozin (n=830) showed significant improvements in total cholesterol (−3.5 mg/dL ± 34.7); high-density lipoprotein, HDL cholesterol (+1.6 mg/dL ± 8.1) and triglycerides (−15.9 mg/dL ± 135.4) after an average of 168 days (5.5 months). Patients on gliclazide (n=2,111) showed significant improvements in total cholesterol (−8.0 mg/dL ± 31.3); triglyceride (−12.9 mg/dL ± 83.2) and low density lipoprotein, LDL cholesterol (−5.5 mg/dL ± 26.4) after an average of 185 days (6.1 months). However, statins were used in both dapagliflozin (63.3%) and gliclazide group (73.6%). The authors suggested that only dapagliflozin therapy was associated with a significant reduction in the projected risk of all four endpoints because of simultaneous improvements in glucose, body weight, blood pressure and lipids.[27, level II-2]

There was no retrievable evidence comparing canagliflozin and empagliflozin with gliclazide. However, a SR and meta-analysis by Zelniker et al. (2019) combined data from all the large-scale placebo-controlled CVOTs of SGLT2 inhibitors to gain more reliable estimates of the efficacy and safety of specific outcomes overall and in relevant subgroups. Studies up to September 2018 were sourced from PubMed & Embase. Risk of bias was assessed using Cochrane Risk of Bias tool. The study included 34,422 patients from three trials of randomised, placebo-controlled CVOTs: CANagliflozin cardioVascular Assessment Study (CANVAS) trial (n=10,142); Dapagliflozin Effect on CardiovascuLAR Events – Thrombolysis in Myocardial Infarction (DECLARE-TIMI 58) trial (n=17,160); and EMPAgliflozin cardiovascular outcome event trial in type 2 diabetes mellitus [EMPA-REG OUTCOME (n=7,020)]. Canagliflozin 100mg and 300mg, dapagliflozin 10mg and empagliflozin 10mg and 25mg were evaluated. Median follow-up time was 2.4 years for canagliflozin; 4.2 years for dapagliflozin and 3.1 years for empagliflozin. [19, level I] Insulin was used in both intervention and placebo arms; approximately 50% in CANVAS trial, 40% in DECLARE-TIMI trial and 48% in EMPA-REG trial.[29-31]

Efficacy outcomes included major adverse cardiovascular events [(MACE) myocardial infarction, stroke, or cardiovascular death], composite of cardiovascular death or hospitalisation for heart failure, and progression of renal disease [renal worsening, end-stage kidney disease (ESKD) or renal death]. Hazard ratios (HRs) with 95% CIs were pooled across trials, and efficacy outcomes were stratified by baseline presence of atherosclerotic cardiovascular disease (ASCVD), heart failure, and degree of renal function using fixed effects models. Heterogeneity was assessed using Cochrane Q statistic and I^2. Statistical analyses were done using R version 3.5.1 and the R package metaphor version 2.0-0.[19, level I]

In terms of MACE, canagliflozin and empagliflozin reduced MACE by 18% [HR 0.82 (0.72, 0.95)] and 14% [HR 0.86 (0.74, 0.99)] in patients with ASCVD. In patients without ASCVD but with multiple risk factors, SGLT2 inhibitors did not reduce MACE. In patients with eGFR <60ml/min per 1.73m^2, only canagliflozin reduced MACE by

31% [HR 0.69 (0.54, 0.89)]. Dapagliflozin did not reduce MACE in patients with or without ASCVD.[19, level I]

In terms of risk of cardiovascular death or hospitalisation for heart failure, canagliflozin, dapagliflozin and empagliflozin reduced the risk by 23% [HR 0.77 (0.65, 0.92)], 17% [HR 0.83 (0.71, 0.98)] and 34% [HR 0.66 (0.55, 0.79)] in patients with ASCVD, respectively. In patients without ASCVD but with multiple risk factors, SGLT2 inhibitors did not reduce the risk of cardiovascular death or hospitalisation for heart failure. In patients with history of heart failure, canagliflozin and dapagliflozin reduced the risk by 39% [HR 0.61 (0.46, 0.80)] and 21% [HR 0.79 (0.63, 0.99)]. In patients without history of heart failure, dapagliflozin and empagliflozin reduced the risk by 16% [HR 0.84 (0.72, 0.99)] and 37% [HR 0.63 (0.51, 0.78]]. In patients with eGFR <60ml/min per 1.73m^2, canagliflozin and empagliflozin reduced hospitalisation for heart failure by 45% [HR 0.55 (0.37, 0.83)] and 41% [HR 0.59 (0.39, 0.88)].[19, level I]

Patients without ASCVD but with multiple risk factors did not appear to benefit from SGLT2 inhibitors in terms of MACE and risk of cardiovascular death or hospitalisation for heart failure. In patients with ASCVD, canagliflozin and empagliflozin reduced both MACE and risk of cardiovascular death or hospitalisation for heart failure. In terms of risk of cardiovascular death or hospitalisation for heart failure, patients with history of heart failure would benefit most with canagliflozin whereas those without history of heart failure would benefit most with empagliflozin. Dapagliflozin appeared to reduce the risk of cardiovascular death or hospitalisation for heart failure moderately in patients with or without heart failure. Patients with more severe kidney at baseline would benefit from canagliflozin in terms of reduced MACE and hospitalisation for heart failure.[19, level I]

Multiple differences were found in the patient characteristics in each trial that might explain the observed variations with regard to cardiovascular death. There was slight variation in exact inclusion criteria and definitions of endpoints among the trials. The authors had concluded that SGLT2 inhibitors have moderate benefits on atherosclerotic MACE that seem confined to patients with established ASCVD. However, there may be conflict of interest as the authors declared receiving grants/fees from pharmaceutical companies including Astra Zeneca, Boehringer Ingelheim and Janssen.[19, level I]

In the SR and MA by Toyama et al., the main cardiovascular outcome was a composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. Random effects models and inverse variance weighting were used to calculate RR with 95% CI. In terms of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke, risk reductions were observed for canagliflozin [0.70 (0.55, 0.89)], dapagliflozin [0.86 (0.60, 1.24)] and empagliflozin [0.87 (0.69, 1.11)]. The authors concluded that currently available data suggest that SGLT2 inhibitors reduce the risk of cardiovascular outcomes in patients with T2DM and CKD, without clear evidence of additional safety concerns; however, the robustness of these findings requires confirmation in upcoming dedicated CKD outcome trials.[26, level I]

A randomised, double-blind placebo-controlled, multicentre clinical trial was conducted by Perkovic et al. (2019) for the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial to assess

the effects of canagliflozin 100mg on renal outcomes in 4,401 patients with T2DM and albuminuric CKD. All patients had an eGFR of 30 to <90 ml/minute/1.73m^2 and albuminuria (ratio of albumin [mg] to creatinine [g], >300 to 5000) and were treated with renin–angiotensin system blockade. Cardiovascular death, myocardial infarction, or stroke and hospitalization for heart failure were evaluated as secondary outcomes.
All cardiovascular outcomes that were part of the primary and secondary outcomes were adjudicated by independent adjudication committees whose members were unaware of trial-group assignments.[32, level I]

In the intention-to-treat population, a stratified Cox proportional-hazards model was used to analyse the primary and secondary outcomes, according to the category of eGFR at screening. Subgroup analyses were assessed by tests for the interaction between the trial group and the subgroup in stratified Cox proportional hazards models without adjustment for multiple testing. The numbers of patients who needed to be treated to prevent one event during 2.5 years (NNT) were calculated as the reciprocal of the between-group difference in cumulative incidence at 2.5 years on the basis of the Kaplan–Meier curve. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute).[32, level I]

In terms of cardiovascular death, myocardial infarction or stroke reported as HR (95% CI), canagliflozin reduced the risk in patients with eGFR 30 - <90ml/min/1.73m^2 by 20% [HR 0.80 (0.67, 0.95); NNT (95% CI): 40 (23, 165)]. In terms of hospitalisation for heart failure reported as HR (95% CI), canagliflozin reduced the risk in patients with eGFR 30 - <90ml/min/1.73m^2 by 39% [HR 0.61 (0.47, 0.80); NNT (95% CI): 46 (29, 124)]. The authors concluded that among patients with T2DM and CKD, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group at a median follow-up of 2.62 years. However, there may be conflict of interest as the trial was supported by Janssen Research and Development.[32, level I]

It is important to note that these evidences were derived from placebo-controlled trials.[19, level I; 26, level I; 32, level I] More evidence is needed to compare SGLT2 inhibitors with gliclazide through RCTs to confirm the superiority of SGLT2 inhibitors in terms of cardiovascular benefits.

There was no retrievable evidence on cardiovascular outcome for gliclazide. A SR and MA was conducted by Landman et al. (2014) on the safety and efficacy of gliclazide compared to other oral glucose-lowering drugs. Although nine studies reported incidence of cardiovascular events [risk ratio 0.95 (95% CI 0.57, 1.61)] and mortality [risk ratio 0.81 (95% CI 0.26, 2.47)] comparing gliclazide and comparator groups, none of the trials was designed to assess cardiovascular safety and/or efficacy. These studies reported limited number of cardiovascular events (11 cases in 1480 gliclazide users and 20 cases in 1508 comparator patients) and cardiovascular deaths (3 in 1602 gliclazide users and 7 in 1619 comparator patients). Some studies were conducted for a relatively short duration (13-16 months).[33]

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial reported that the strategy of

intensive glucose control involving gliclazide yielded 10% relative reduction in the combined outcome of macrovascular and microvascular events, compared with the standard glucose control group (without gliclazide). However, the risk reduction may not be attributable to the use of gliclazide alone as the intensive glucose control arm involved the use of glicazide and other drugs.[34]

Renal outcome

There was no retrievable evidence comparing SGLT2 inhibitors and gliclazide in terms of renal outcome. However, Zelniker et al. (2019) evaluated renal outcomes of SGLT2 inhibitors versus placebo in patients with T2DM using the CVOTs data. Renal outcome of interest included a standardised composite of worsening eGFR, ESKD or renal death.[19, level I]

Zelniker et al. (2019) reported that canagliflozin, dapagliflozin and empagliflozin reduced the risk of worsening eGFR, ESKD or renal death in patients with ASCVD by 41% [HR 0.59 (0.44, 0.79)], 45% [HR 0.55 (0.41, 0.75)] and 46% [HR 0.54 (0.40, 0.75)], respectively. In patients with multiple risk factors, only dapagliflozin reduced the risk by 49% [HR 0.51 (0.37, 0.69)]. In patients with eGFR >90ml/min per 1.73m^2, canagliflozin, dapagliflozin and empagliflozin reduced the risk by 56% [HR 0.44 (0.25, 0.78)], 50% [HR 0.50 (0.34, 0.73)], and 79% [HR 0.21 (0.09, 0.53)]. In patients with eGFR 60 to <90ml/min per 1.73m^2, canagliflozin and dapagliflozin reduced the risk by 42% [HR 0.58 (0.41, 0.84)] and 46% [HR 0.54 (0.40, 0.73)], respectively. In patients with eGFR <60ml/min per 1.73m^2, the SGLT2 inhibitors did not reduce the risk of worsening eGFR, ESKD or renal death.[19, level I]

For SGLT2 inhibitors, the magnitude of benefit was lesser in patients with more severe kidney disease at baseline. Patients with no renal impairment would benefit most from empagliflozin whereas patients with mild renal impairment would benefit from canagliflozin and dapagliflozin. Patients with moderate or severe renal impairment would not benefit from SGLT2 inhibitors in terms of risk of progression of renal disease.[19, level I]

In the SR and MA by Toyama et al., renal outcomes of interest were annual mean difference in kidney function between treatment and control (eGFR slope) and a composite of doubling of serum creatinine, ESKD or renal death. Random effects models and inverse variance weighting were used to calculate RR with 95% CI. In terms of eGFR slope reported as effect size (95% CI), canagliflozin [1.11 (0.74, 1.48)] had less annual decline compared with empagliflozin [1.71 (1.08, 2.34)]. In terms of doubling of serum creatinine, ESKD or renal death, empagliflozin had the greatest risk reduction of 32% [HR 0.68 (0.43, 1.09)] compared with canagliflozin [HR 0.81 (0.37, 1.77)] and dapagliflozin [HR 0.70 (0.46, 1.07)]. The authors concluded that currently available data suggest that SGLT2 inhibitors reduce the risk of renal outcomes in patients with T2DM and CKD, without clear evidence of additional safety concerns; however, the robustness of these findings requires confirmation in upcoming dedicated CKD outcome trials.[26, level I]

In the study by Perkovic et al., the primary outcome was ESKD defined as dialysis for at least 30 days, kidney transplantation, or an eGFR of <15 ml/minute/1.73m^2 sustained for at least 30 days), doubling of the serum creatinine level from baseline sustained for at least 30 days, or death from renal or cardiovascular disease. All renal outcomes that were part of the primary and secondary outcomes were adjudicated by independent adjudication committees whose members were unaware of trial-group assignments. Pre-specified stopping guidance that was provided to the data monitoring committee by the steering committee proposed possible recommendation of early cessation if clear evidence of benefit was observed for the primary outcome (p<0.01) and the composite of ESKD or death from renal or cardiovascular causes (p<0.025), with consideration of the overall balance of risks and benefits.[32, level I]

In the intention-to-treat population, a stratified Cox proportional-hazards model was used to analyse the primary and secondary outcomes, according to the category of eGFR at screening. Subgroup analyses were assessed by tests for the interaction between the trial group and the subgroup in stratified Cox proportional hazards models without adjustment for multiple testing. The numbers of patients who needed to be treated to prevent one event during 2.5 years (NNT) were calculated as the reciprocal of the between-group difference in cumulative incidence at 2.5 years on the basis of the Kaplan–Meier curve.[32, level I]

In terms of primary composite outcome (ESKD, doubling of serum creatinine, renal death or cardiovascular death) reported as HR (95% CI), canagliflozin reduced the risk in patients with eGFR 30 - <90ml/min/1.73m^2 by 30% [HR 0.70 (0.59, 0.82); NNT (95% CI): 22 (15, 38)]. In terms of renal-specific composite outcome of ESKD, doubling of serum creatinine or renal death, canagliflozin reduced the risk in patients with eGFR 30 - <90ml/min/1.73m^2 by 34% [HR 0.66 (0.53, 0.81); NNT (95% CI): 28 (19, 54)]. In patients with eGFR 60 - <90ml/min/1.73m^2, canagliflozin reduced the risk by 19% [HR 0.81 (0.52, 1.26)]. In patients with eGFR 45 - <60ml/min/1.73m^2, canagliflozin reduced the risk by 53% [HR 0.47 (0.31, 0.72)]. In patients with eGFR 30 - <45ml/min/1.73m^2, canagliflozin reduced the risk by 29% [HR 0.71 (0.53, 0.94)]. The authors concluded that among patients with type 2 diabetes and kidney disease, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group at a median follow-up of 2.62 years. However, there may be conflict of interest as the trial was supported by Janssen Research and Development.[32, level I]

Nevertheless, these evidences are derived from placebo-controlled trials.[19, level I; 26, level I; 32, level I] More evidence is needed to compare SGLT2 inhibitors with gliclazide to confirm the superiority of SGLT2 inhibitors in terms of renal benefits.

There was no retrievable evidence on renal outcome for gliclazide. Although the ADVANCE trial demonstrated that the intensive glucose lowering with gliclazide reduced the risk of new onset microalbuminuria by 9% (p=0.01), macroalbuminuria by 30% (p<0.001), new or worsening nephropathy by 21% (p=0.006), and ESKD by 65% (p=0.02), the improvement of kidney outcomes may be attributable to strict glycaemic control and/or other drugs including insulin.[35]

Summary

Table 2 shows the summary of efficacy outcomes for SGLT2 inhibitors and gliclazide based on the findings above.

Table 2: Summary of efficacy outcomes for gliclazide and SGLT2 inhibitors.

Efficacy outcomes	Study	Unit of measurement	Specific population	Gliclazide 80-320mg	Canagliflozin 100mg	Canagliflozin 300mg	Dapagliflozin 5mg	Dapagliflozin 10mg	Empagliflozin 10mg	Empagliflozin 25mg
Glycaemic control (HbA1c, %)	Johnston (2017)	MD (95% CI)		-0.95 (-1.27, -0.64)*	-0.95 (-1.06, -0.84)*	-1.19 (-1.34, -1.04)*	N/A	-0.59 (-0.70, -0.48)*	-0.76 (-0.87, -0.65)*	-0.88 (-0.99, -0.77)*
	Mearns (2015)	WMD (95% CI)		-0.70 (-0.85, -0.56)*	-0.72 (-0.85, -0.59)*		N/A	-0.48 (-0.62, -0.33)*	-0.69 (-0.81, -0.57)*	
	Maloney (2019)	Change from baseline 8.0%		-1.04	-0.84	-1.01	-0.65	-0.73	-0.69	-0.77
	Jia (2019)	MD (95% CI)		-1.37 (-2.04, -0.71)*	N/A	N/A	-0.50 (-0.78, -0.21)*		N/A	N/A
	Toyama (2018)	Effect size (95% CI)		N/A	-0.43 (-0.65, -0.21)*		-0.25 (-0.36, 0.14)*		0.29 (-0.43, -0.15)*	
Weight changes (kg)	Johnston (2017)	MD (95% CI)		+1.97 (0.76, 3.20)*	-2.02 (-2.41, -1.65)*	-2.91 (-3.22, -2.59)*	N/A	-1.58 (-2.01, -1.14)*	-1.74 (-2.15, -1.33)*	-1.89 (-2.29, -1.49)*
	Mearns (2015)	WMD (95% CI)		+1.19 (0.39, 1.99)*	-2.15 (-2.63, -1.67)*		N/A	-2.17 (-2.78, -1.57)*	-2.08 (-2.52, -1.63)*	
	Maloney (2019)	Change from baseline 90kg		+2.40	-1.90	-2.30	-1.70	-1.90	-2.10	-2.40
	Toyama (2018)	Effect size (95% CI)		N/A	-1.31 (-1.52, -1.09)*		-1.50 (-2.02, -0.98)*		-1.38 (-1.72, -1.04)*	
SBP (mmHg)	Johnston (2017)	MD (95% CI)		N/A	–4.24 (-6.01, -2.44)*	–5.65 (-7.77, -3.53)*	N/A	–2.73 (-4.77, -0.74)*	-2.59 (-4.88, -0.33)*	-3.38 (-5.67, -1.11)*
	Mearns (2015)	WMD (95% CI)		N/A	-4.14 (-5.80, -2.48)*		N/A	-4.50 (-7.97, -1.03)*	-5.14 (-6.80, -3.48)*	
	Toyama (2018)	Effect size (95% CI)		N/A	-4.19 (-6.49, 1.89)*		-3.58 (-5.53, -1.62)*		-5.07 (-7.30, -2.85)*	
CV outcome	Zelniker (2019) - Placebo controlled trial	HR (95% CI) for:								
		MACE	With ASCVD	N/A	0.82 (0.72, 0.95)*		N/A	0.90 (0.79, 1.02)	0.86 (0.74, 0.99)*	
		Hospitalisation for HF & CV death		N/A	0.77 (0.65, 0.92)*		N/A	0.83 (0.71, 0.98)*	0.66 (0.55, 0.79)*	
		MACE	With multiple risk factors	N/A	0.98 (0.74, 1.30)		N/A	1.01 (0.86, 1.20)	N/A	
		Hospitalisation for HF & CV death		N/A	0.83 (0.58, 1.19)		N/A	0.84 (0.67, 1.04)	N/A	
		Hospitalisation for HF & CV death	With HF	N/A	0.61 (0.46, 0.80)*		N/A	0.79 (0.63, 0.99)*	0.72 (0.50, 1.04)	
			Without HF	N/A	0.87 (0.72, 1.06)		N/A	0.84 (0.72, 0.99)*	0.63 (0.51, 0.78)*	
		MACE	With eGFR >90 ml/min/1.73m^2	N/A	0.84 (0.62, 1.13)		N/A	0.94 (0.80, 1.10)	1.10 (0.77, 1.57)	
		Hospitalisation for HF		N/A	0.76 (0.40, 1.47)		N/A	0.94 (0.69, 1.26)	0.67 (0.31, 1.44)	
		MACE	With eGFR 60 - <90 ml/min/1.73m^2	N/A	0.95 (0.80, 1.13)		N/A	0.95 (0.82, 1.09)	0.76 (0.61, 0.94)*	
		Hospitalisation for HF		N/A	0.76 (0.52, 1.12)		N/A	0.65 (0.51, 0.84)*	0.72 (0.48, 1.07)	
		MACE	With eGFR <60 ml/min/1.73m^2	N/A	0.69 (0.54, 0.89)*		N/A	0.92 (0.69, 1.23)	0.88 (0.69, 1.13)	
		Hospitalisation for HF		N/A	0.55 (0.37, 0.83)*		N/A	0.70 (0.44, 1.12)	0.59 (0.39, 0.88)*	

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CV, cardiovascular; ESKD, end-stage kidney disease; HbA1c, glycosylated haemoglobin; HR, hazard ratio; MACE, major adverse cardiovascular events; MD, mean difference; MI, myocardial infarction; N/A, not available; WMD, weighted mean difference; SBP, systolic blood pressure. Statistical significance * = p<0.05 or CI for MD/WMD/effect size not crossing the null value of 0 or CI for HR/RR not crossing the null value of 1.

Efficacy outcomes	Study		Unit of measurement	Gliclazide 80-320mg	Canagliflozin 100mg	Canagliflozin 300mg	Dapagliflozin 5mg	Dapagliflozin 10mg	Empagliflozin 10mg	Empagliflozin 25mg
CV outcome	Toyama (2018) - Placebo-controlled trial	RR (95% CI) for MACE	Patients with eGFR <60ml/min/1.73m^2	N/A	0.70 (0.55, 0.89)*		0.86 (0.60, 1.24)		0.87 (0.69. 1.11)	
		RR (95% CI) for HF		N/A	0.57 (0.38, 0.86)*		0.72 (0.46, 1.13)		0.49 (0.18, 1.37)	
	Perkovic (2019) - Placebo-controlled trial	HR (95% CI) for CV death, MI or stroke	Patients with eGFR 30 - <90ml/min/1.73m^2	N/A	0.80 (0.67, 0.95)*	N/A	N/A		N/A	
		HR (95% CI) for hospitalisation for HF		N/A	0.61 (0.47, 0.80)*	N/A	N/A		N/A	
Renal outcome	Zelniker (2019) - Placebo controlled trial	HR (95% CI) for composite outcome of worsening eGFR, ESKD, or renal death	Patients with ASCVD	N/A	0.59 (0.44, 0.79)*		0.55 (0.41, 0.75)*		0.54 (0.40, 0.75)*	
			Patients with multiple risk factors	N/A	0.63 (0.39, 1.02)		0.51 (0.37, 0.69)*		N/A	
			Patients with eGFR >90 ml/min/1.73m^2	N/A	0.44 (0.25, 0.78)*		0.50 (0.34, 0.73)*		0.21 (0.09, 0.53)*	
			Patients with eGFR 60 – 90 ml/min/1.73m^2	N/A	0.58 (0.41, 0.84)*		0.54 (0.40, 0.73)*		0.61 (0.37, 1.03)	
			Patients with eGFR <60 ml/min/1.73m^2	N/A	0.74 (0.48, 1.15)		0.60 (0.35, 1.02)		0.66 (0.41, 1.07)	
	Toyama (2018) - Placebo-controlled trial	HR (95% CI) for renal-specific composite outcome of doubling of serum creatinine level, ESKD, or renal death	Patients with eGFR <60 ml/min/1.73m^2	N/A	0.81 (0.37, 1.77)		0.70 (0.46, 1.07)		0.68 (0.43, 1.09)	
	Perkovic (2019) - Placebo-controlled trial		Patients with eGFR 60 - <90 ml/min/1.73m^2	N/A	0.81 (0.52, 1.26)	N/A	N/A		N/A	
			Patients with eGFR 45 - <60 ml/min/1.73m^2	N/A	0.47 (0.31, 0.72)*	N/A	N/A		N/A	
			Patients with eGFR 30 - <45 ml/min/1.73m^2	N/A	0.71 (0.53, 0.94)*	N/A	N/A		N/A	

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CV, cardiovascular; ESKD, end-stage kidney disease; HbA1c, glycosylated haemoglobin; HR, hazard ratio; MACE, major adverse cardiovascular events; MD, mean difference; MI, myocardial infarction; N/A, not available; WMD, weighted mean difference; SBP, systolic blood pressure. Statistical significance * = p<0.05 or CI for MD/WMD/effect size not crossing the null value of 0 or CI for HR/RR not crossing the null value of 1.

5.2 SAFETY

A total of one HTA, four SRs and one RCT were included for the assessment of safety in which endpoints of interest include hypoglycaemia risk, urinary tract infection (UTI), genital tract infection (GTI), diabetic ketoacidosis (DKA), bone fracture and amputation. The FDA safety reports on SGLT2 inhibitors included adverse events such as UTI, Fournier's gangrene, DKA, decreased bone mineral density (BMD), bone fractures, amputation and acute kidney injury (AKI).

Hypoglycaemia risk

The assessment group (AG) for the HTA report by Johnston et al. (2017) considers it reasonable to assume that SGLT2 inhibitors do not cause hypoglycaemia given the infrequency of reported hypoglycaemia, the similarities of the frequencies of hypoglycaemia in active and placebo arms, and the cut-off level used. The definition of hypoglycaemia for canagliflozin and empagliflozin trials used 4.0 mmol/l as the threshold. The three dapagliflozin trials used 3.5 mmol/l to define minor hypoglycaemic events. Rates of hypoglycaemia were not substantially different between canagliflozin (3.0% - 6.6%) and placebo groups (2.6% - 3.3%). Similar observation was reported for dapagliflozin and empagliflozin versus placebo groups as not more than two cases of hypoglycaemia occurred in any of the comparison groups over 24 weeks. No major hypoglycaemia cases were reported for all three SGLT2 inhibitors.[22, level I]

In the study by Mearns et al. (2015), the proportion of patients experiencing confirmed hypoglycemia, UTI and GTI on each drug therapy was meta-analysed using a random-effects model as dichotomous endpoints with weighted averages. In terms of NMA estimate for confirmed hypoglycaemia reported as RR and 95% CI, SGLT2 inhibitors were not associated with an increased risk of hypoglycaemia. Gliclazide [10.02 (2.07, 48.56)] was associated with significantly higher risk of hypoglycaemia compared with canagliflozin [0.91 (0.33, 2.51)], dapagliflozin [0.97 (0.34, 2.76)] and empagliflozin [0.51 (0.17, 1.49)]. The authors concluded that SGLT2 inhibitors had low risk of hypoglycaemia. [23, level I]

Maloney et al. (2019) reported that hypoglycemia risk versus placebo (in RR) for SGLT2 inhibitors [canagliflozin (1.4), dapagliflozin (1.0) and empagliflozin (1.0)] was generally very low compared with gliclazide (3.6).[24, level I]

Toyama et al. (2019) reported that in terms of hypoglycemia risk versus placebo (in RR), canagliflozin was associated with increased risk [1.51 (1.10, 2.07)] while empagliflozin was associated with less risk [0.82 (0.72, 0.93)]. There was no significant association of hypoglycaemia risk for dapagliflozin [1.01 (0.81, 1.26)].[26, level I]

Urogenital infections

The HTA report by Johnston et al. (2017) reported that main adverse events for SGLT2 inhibitors treatment of more than 24 weeks were UTIs and GTIs. The urogenital infections were more common in women, generally mild to moderate in severity and amenable to standard treatment. Canagliflozin was associated with a

slightly higher incidence of UTIs (1.1% - 8.2%) versus placebo (1.1% - 6.3%) and higher incidence of GTIs (1.1% - 9.2%) versus placebo (1.1% - 2.6%). GTIs were more frequent in females and older patients (55-80 years) – the risk was higher within first six months (1.1% - 6.6%). Dapagliflozin was associated with a higher incidence of UTIs (2.3% - 8.6%) versus placebo (2.3% - 4.0%) and GTIs (2.3% - 15.7%) versus placebo (0.8% - 1.3%). Empagliflozin was associated with a similar incidence of UTIs (5.4% - 9.4%) versus placebo (5.2% - 11.0%) and higher incidence of GTIs (3.1% - 6.3%) versus placebo (0% - 1.8%). The authors concluded that for SGLT2 inhibitors, common adverse effects were urinary and genital tract infections in a small proportion of users which were seldom serious. The safety record of SGLT2 inhibitors remains to be established. [22, level I]

Mearns et al (2015) reported that in terms of NMA estimate for UTI in RR (95% CI), SGLT2 inhibitors were not associated with an increased risk of UTI when compared to placebo: canagliflozin [1.25 (0.78, 2.00)], dapagliflozin [1.28 (0.77, 2.14)] and empagliflozin [0.86 (0.57, 1.30)]. In terms of NMA estimate for GTI in RR (95% CI), canagliflozin [8.03 (2.44, 26.39)] and empagliflozin [6.84 (1.92, 24.37)] were associated with an increased risk compared with placebo; with dapagliflozin trending towards an increased risk of GTI [2.16 (0.97, 4.82)]. There were no UTI and GTI data reported for gliclazide. The authors concluded that SGLT2 inhibitors have an increased risk of GTI. [23, level I]

Toyama et al. (2019) reported that in terms of UTI (in RR), SGLT2 inhibitors were not associated with an increased risk of UTI [canagliflozin: 0.84 (0.57, 1.24); dapagliflozin: 0.94 (0.59, 1.50); empagliflozin: 1.12 (0.94, 1.34)]. However, an increased risk of GTI was observed for dapagliflozin [3.94 (1.54, 10.09)] and empagliflozin [3.93 (2.05, 7.53)]. Canagliflozin was not associated with an increased risk of GTI [1.60 (0.44, 5.89)].[26, level I]

In 2015, FDA revised labels of SGLT2 inhibitors for diabetes to include warnings about serious UTI which may result in hospitalisation. A total of 19 cases of life-threatening blood infections (urosepsis) and kidney infections (pyelonephritis) that started as UTIs infections with the use of SGLT2 inhibitors were reported to FDA Adverse Event Reporting System (FAERS) from March 2013 through October 2014. All 19 patients were hospitalised, and a few required admissions to an intensive care unit or dialysis in order to treat kidney failure.[36]

In August 2018, FDA issued a warning about rare occurrences of necrotizing fasciitis of the perineum, also known as Fournier's gangrene, with the use of SGLT2 inhibitors in T2DM. In the period of five years from March 2013 to May 2018, 12 cases of Fournier's gangrene were identified in patients taking a SGLT2 inhibitor based on the reports submitted to FAERS and findings from medical literature. Although having diabetes is a risk factor for developing Fournier's gangrene; this condition is still rare among diabetic patients. These cases have occurred in both females (n=5) and males (n=7) in almost equal frequency.[37]

Fournier's gangrene developed within several months of treatment initiation and the drug was stopped in most cases. The adverse event affecting the genital area is a life-threatening infection requiring urgent antibiotics and surgical intervention which may lead to hospitalisation, multiple surgeries, and death in severe cases. All 12

patients were hospitalised and required surgery. Some patients required multiple disfiguring surgeries, some developed complications, and one patient died. In comparison, only six cases of Fournier's gangrene (all in men) were identified in review of other antidiabetic drug classes over a period of more than 30 years. The FDA have required a new warning about this risk to be added to the prescribing information of all SGLT2 inhibitors and to the patient medication guide under the FDA drug approvals and database.[37]

An increase in occurrence of Fournier's gangrene was reported by a recent review of post-marketing cases using data from FAERS and published case reports. The study identified 55 unique cases of Fournier's gangrene in adult patients receiving SGLT2 inhibitors between 1 March 2013 and 31 January 2019. The patients ranged in age from 33 to 87 years; 39 were men, and 16 were women. Time to onset after initiation of SGLT2 inhibitor therapy ranged from five days to 49 months. All patients had surgical debridement and were severely ill. Reported complications included diabetic ketoacidosis (n = 8), sepsis or septic shock (n = 9), and AKI (n = 4). Eight patients had faecal diversion surgery, two patients developed necrotizing fasciitis of a lower extremity that required amputation, and one patient required a lower-extremity bypass procedure due to gangrenous toes. Three patients died. For comparison, the FDA identified 19 FG cases associated with other anti-glycaemic agents between 1984 and 31 January 2019: metformin (n = 8), insulin glargine (n = 6), short-acting insulin (n = 2), sitagliptin plus metformin (n = 2), and dulaglutide (n = 1). These patients ranged in age from 42 to 79 years; 12 were men, and 7 were women. Two patients died. The authors concluded that Fournier's gangrene was a newly identified safety concern in patients receiving SGLT2 inhibitors and physicians prescribing these agents should be aware of this possible complication and have a high index of suspicion to recognize it in its early stages.[38]

Diabetic ketoacidosis

Johnston et al. (2017) reported that DKA appeared rare – about one per 5000 patient-years in patients treated with SGLT2 inhibitors based on an estimated 500,000 patient-years of use. The authors suggested that the safety record of SGLT2 inhibitors remains to be established and continued monitoring for DKA is required.[22, level I]

Zelniker et al. (2019) reported that dapagliflozin showed an increased risk of DKA [HR 2.18 (95% CI 1.10, 4.30). However, the event rates for all SGLT2 inhibitors were low (<one per 1000 patient-years). The authors concluded that SGLT2 inhibitors are overall well tolerated and generally safe drugs. Although SGLT2 inhibitors appeared to increase the risk of DKA, the rates were very low and risk can be reduced with proper patient education and vigilance.[19, level I]

Toyama et al. reported that canagliflozin [RR 3.43 (95% CI 0.39. 29.88) and empagliflozin [RR 1.50 (95% CI 0.22, 10.24)] were not associated with increased risk of DKA.[26, level I]

Perkovic et al. reported that canagliflozin group showed an increased risk of DKA [HR 10.80 (95% CI 1.39, 83.65); 2.2 versus 0.2 per 1000 patient-years in placebo group].[32, level I]

In 2015, FDA revised labels of SGLT2 inhibitors to include warnings about too much acid in the blood. Seventy-three cases of ketoacidosis in patients with type 1 or type 2 diabetes treated with SGLT2 inhibitors (canagliflozin [n=48], dapagliflozin [n=21], and empagliflozin [n = 4]) were reported to FAERS between March 2013 and May 2015. Forty-four of the 73 cases occurred in patients with T2DM. Fifteen cases were reported in patients with type 1 diabetes which was not an approved indication for this drug class. All patients required hospitalisation or treatment in an emergency department. In many cases, DKA was not immediately recognised because the blood glucose levels were below those typically expected for DKA which delayed treatment in some cases. Fifty-three out of 73 cases (73%) reported a concurrent event associated with DKA, the most common of which were dehydration, infection, and changes in insulin dose. SGLT2 inhibitor was discontinued in 78% of the cases (57/73). There was no trend demonstrating a relationship between the dose of SGLT2 inhibitor and the risk of DKA. Potential risk factors for developing DKA with an SGLT2 inhibitor identified in these cases included: infection, low carbohydrate diet or an overall reduction of caloric intake, reduction in dose of exogenous insulin or discontinuation of exogenous insulin, discontinuation of an oral insulin secretagogue, and alcohol use.[36]

In 2015, the Malaysian National Pharmaceutical Control Bureau (NPCB) approved a Direct Healthcare Professional Communication (DHPC) for Forxiga® (dapagliflozin) regarding the risk of DKA in view of more than 350 reports suspected to be related to SGLT2 inhibitor received by the World Health Organisation (WHO) International Adverse Drug Reaction database (VigiBase®) between 2014 and 2015. Serious and sometimes life-threatening cases of DKA in patients treated with SGLT2 inhibitors were reported, the majority requiring hospitalisation. A few of the reports involved off-label use in patients with type 1 diabetes mellitus. From 2014 till August 2015, the Malaysian NPCB received 21 ADR reports with 29 adverse events, suspected to be related to dapagliflozin. None of these reports involved DKA related to dapagliflozin. The most commonly reported adverse events were urinary system disorders, such as polyuria, pollakiuria, UTI, and urinary frequency. Other adverse events included skin infection, pruritus of the genital, blisters over the foreskin, and low back pain. All reports were given a causality of C3 (possibly-related to the drug) as there were concomitant drugs or underlying disease that may have contributed to the adverse events. The Malaysian NPCB advises that SGLT2 inhibitors should be discontinued if metabolic acidosis is confirmed, and take appropriate measures to correct the acidosis and monitor blood glucose levels.[39]

Bone fracture and amputation

Johnston et al. (2017) reported that the risk of fracture was small but increased by around 30% in people taking canagliflozin. The incidence per 1000 patient-years was 18.1 for canagliflozin and 14.2 for other regimens. Eight of 85 (9.4%) people on dapagliflozin 10 mg suffered fractures, compared with none on placebo. Fractures were not increased after three years of empagliflozin treatment in the EMPA-REG trial. The authors suggested that that the safety record of SGLT2 inhibitors remains to be established and continued monitoring for fractures is required.[22, level I]

Zelniker et al. (2019) reported that canagliflozin showed an increased risk of lower limb amputation (HR 1.97 (95% CI 1.41, 2.75) and fractures (HR 1.26 (95% CI 1.04, 1.52). Patients taking canagliflozin were almost twice as likely to undergo lower limb amputation. The authors commented that an increased risk of amputation and fracture was seen only in the CANVAS trial.[19, level I]

Toyama et al. reported that in terms of bone fracture reported in RR (95% CI), the SGLT2 inhibitors were not associated with an increased risk [canagliflozin: 1.14 (0.78, 1.66); dapagliflozin: 1.72 (0.03, 105.92); empagliflozin: 0.84 (0.57, 1.24)]. In terms of amputation reported in RR (95% CI), canagliflozin was associated with an increased risk [2.17 (1.14, 4.10)] whereas empagliflozin was not associated with an increased risk [0.89 (0.52, 1.53)].[26, level I]

Perkovic et al. reported no significant difference in the risk of lower limb amputation between canagliflozin group and the placebo group [HR 1.11 (95% CI 0.79, 1.56); 12.3 versus 11.2 per 1000 patient-years in the placebo group]. Similar rates of fracture were also reported for both groups [HR 0.98 (95% CI 0.70, 1.37)]. However, during the trial, an increased risk of lower limb amputation was identified in another trial of canagliflozin (CANVAS). A protocol amendment for the CREDENCE trial in May 2016 asked investigators to examine patients' feet at each trial visit and temporarily interrupt the assigned treatment in patients with any active condition that might lead to amputation.[32, level I]

In October 2015, FDA issued a warning on decreases in BMD and an increased risk of bone fractures in people taking canagliflozin. A clinical trial evaluated changes to BMD over two years in 714 elderly individuals showed that canagliflozin caused greater loss of BMD at the hip and lower spine than a placebo. At two years, patients randomised to canagliflozin 100 mg and canagliflozin 300 mg had placebo-corrected declines in BMD at the total hip of 0.9% and 1.2%, respectively, and at the lumbar spine of 0.3% and 0.7%, respectively. The occurrence of bone fractures was evaluated in nine pooled clinical trials with a mean duration of exposure to canagliflozin of 85 weeks. The incidence rates of adjudicated bone fractures were 1.1, 1.4, and 1.5 per 100 patient-years of exposure in the comparator (includes placebo and active comparators), canagliflozin 100 mg, and canagliflozin 300 mg groups, respectively. Fractures occurred as early as 12 weeks after treatment initiation and were more likely to be low trauma (e.g., arising after falls from no more than standing height) and affect the upper extremities. Information about the risk of decreased BMD was included in the *Adverse Reactions* section and information about bone fractures was added as a new *Warning and Precaution* of the drug label.[40]

In Malaysia, the product registration holder of Invokana® had issued a DHPC letter on the risk of lower limb amputation during treatment with canagliflozin in agreement with the National Pharmaceutical Regulatory Agency (NPRA) in 2016. The local product information of Invokana® was updated with information on the risk of lower limb amputation during treatment with canagliflozin-containing products. Up until December 2016, the NPRA did not receive any ADR reports related to these products. The NPRA advises that canagliflozin may be stopped if a patient develops

a significant complication, such as a lower-extremity skin ulcer, osteomyelitis or gangrene, at least until the complication has resolved.[41]

In May 2017, FDA issued a statement confirming the risk of leg and foot amputations with the use of canagliflozin based on new data from two large clinical trials which showed that leg and foot amputations occurred about twice as often in patients treated with canagliflozin compared to placebo group. The CANVAS trial showed that over a year's time, the risks of amputation were 5.9 out of every 1,000 patients on canagliflozin and 2.8 out of every 1,000 patients on placebo. The CANVAS-R (A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants with Type 2 Diabetes Mellitus) trial showed that the risks of amputation were 7.5 per 1,000 patient-years on canagliflozin and 4.2 per 1,000 patient-years on placebo. The most common amputations were of the toe and middle of the foot. However, amputations involving the leg, below and above the knee, also occurred. Some patients had more than one amputation, some involving both limbs. New warnings (including *Boxed Warning*) regarding this risk were required to be added to the drug label.[42]

Acute kidney injury

Toyama et al. reported that the SGLT2 inhibitors were not associated with an increased risk of AKI [canagliflozin: HR 0.86 (95% CI 0.17, 4.31); dapagliflozin: HR 0.65 (95% CI 0.43, 0.96); empagliflozin: HR 0.60 (95% CI 0.41, 0.88)].[26, level I] Perkovic et al. reported canagliflozin group was not associated with increased risk of acute kidney injury [HR 0.85 (95% CI 0.64, 1.13)].[32, level I]

In 2016, FDA issued statement to strengthen AKI warnings for canagliflozin and dapagliflozin. Between March 2013 to October 2015, 101 cases of AKI with sufficient detail to confirm the diagnosis and demonstrate a temporal relationship with canagliflozin (n=73) and dapaglifozin (n=28) were identified from FAERS database. The adverse event occurred within one month of treatment initiation in approximately half of the cases (n=58) and most patients improved after stopping it. Some cases occurred in patients who were younger than 65 years [median age 57 years (range 28-79)]. Some patients were dehydrated, had low blood pressure, or were taking other medicines that can affect the kidneys. Hospitalisation for evaluation and management of AKI was necessary in 96 of the 101 cases, and 22 cases involved admission to an intensive care unit. Four deaths occurred during hospitalisation. Fifteen patients received dialysis, and of these, three patients had a history of CKD or previous AKI, and six reported concomitant use of both an ACE inhibitor and a diuretic. Of the 101 cases, 51 reported concomitant ACE inhibitor use, 26 reported concomitant diuretic use, and six reported concomitant NSAID use. A prior history of CKD was reported in ten of the 101 cases. Forty-five of the 101 cases reported a change in renal function (median elevation of serum creatinine from baseline in 32 patients was 1.6 mg/dl; median decrease in eGFR from baseline in 13 patients was 46 mL/min/1.73m^2). Out of 78 cases reporting drug discontinuation, 56 cases reported improvement, demonstrating reversibility of this adverse event in majority of cases. Eleven patients did not recover, which included the four deaths mentioned previously. Three patients recovered with sequelae upon discontinuation, suggesting that AKI may not be fully reversible in some situations.[43]

Summary

Table 3 shows the summary of safety outcomes for gliclazide and SGLT2 inhibitors based on the above findings.

Table 3: Summary of safety outcomes for gliclazide and SGLT2 inhibitors.

Safety outcomes	Source	Unit of measurement	Gliclazide 80-320mg	Canagliflozin 100mg	Canagliflozin 300mg	Dapagliflozin 5mg	Dapagliflozin 10mg	Empagliflozin 10mg	Empagliflozin 25mg
Hypoglycaemia risk	Mearns (2015)	RR (95% CI)	10.02 (2.07, 48.56)*	0.91 (0.33, 2.51)			0.97 (0.34, 2.76)		0.51 (0.17, 1.49)
	Maloney (2019)	RR	3.6	1.4	1.4	1.0	1.0	1.0	1.0
	Toyama (2018)	RR (95% CI)	N/A	1.51 (1.10, 2.07)*			1.01 (0.81, 1.26)		0.82 (0.72, 0.93)*
Urinary infections	Johnston (2017)	Incidence rate	N/A	1.1% - 8.2% vs placebo (1.1% - 6.3%)		N/A	2.3% - 8.6% vs placebo (2.3% - 4.0%)		5.4% - 9.4% vs placebo (5.2% - 11.0%)
	Mearns (2015)	RR (95% CI)	N/A	1.25 (0.78, 2.00)			1.28 (0.77, 2.14)		0.86 (0.57, 1.30)
	Toyama (2018)	RR (95% CI)	N/A	0.84 (0.57, 1.24)			0.94 (0.59, 1.50)		1.12 (0.94, 1.34)
Genital infections	Johnston (2017)	Incidence rate	N/A	1.1% - 9.2% vs placebo (1.1% - 2.6%)		2.3% - 15.7% vs placebo (0.8% - 1.3%)			3.1% - 6.3% vs placebo (0% - 1.8%)
	Mearns (2015)	RR (95% CI)	N/A	8.03 (2.44, 26.39)*			2.16 (0.97, 4.82)		6.84 (1.92, 24.37)*
	Toyama (2018)	RR (95% CI)	N/A	1.60 (0.44, 5.89)			3.94 (1.54, 10.09)*		3.93 (2.05, 7.53)*
Diabetic ketoacidosis	Johnston (2017)	Incidence rate	N/A	1 per 5000 patient-years in patients treated with SGLT2 inhibitors					
	Zelniker (2019)	HR (95% CI)	N/A	2.33 (0.76, 7.17)		N/A	2.18 (1.10, 4.30)*		1.99 (0.22, 17.80)
				<1 per 1000 patient-years in patients treated with SGLT2 inhibitors					
	Toyama (2018)	RR (95% CI)	N/A	3.43 (0.39, 29.88)			N/A		1.50 (0.22. 10.24)
	Perkovic (2019)	HR (95% CI)	N/A	10.80 (1.39, 83.65)* 2.2 vs 0.2 per 1000 patient-years in placebo group	N/A		N/A		N/A
	FDA (2015)	No. of events (Mac 2013 – Oct 2015)	N/A	48 cases			21 cases		4 cases
Bone fracture	Johnston (2017)	Incidence rate	N/A	18.1 per 1000 patient-years		N/A	9.4% (8/85) versus none on placebo		No increased risk after 3 years of treatment in the EMPA-REG trial.
	Zelniker (2019)	HR (95% CI)	N/A	1.26 (1.04, 1.52)*		N/A	1.04 (0.91, 1.18)		0.98 (0.76, 1.25)
	Toyama (2018)	RR (95% CI)	N/A	1.14 (0.78, 1.66)			1.72 (0.03, 105.92)		0.84 (0.57, 1.24)
	Perkovic (2019)	HR (95% CI)	N/A	0.98 (0.70, 1.37)	N/A		N/A		N/A
	FDA (2015)	Incidence rate	N/A	14 per 1000 patient-years	15 per 1000 patient-years		N/A		N/A
Amputation	Zelniker (2019)	HR (95% CI)	N/A	1.97 (1.41, 2.75)*		N/A	1.09 (0.84, 1.40)		1.01 (0.70, 1.44)
	Toyama (2018)	RR (95% CI)	N/A	2.17 (1.14, 4.10)*			N/A		0.89 (0.52, 1.53)
	Perkovic (2019)	HR (95% CI)	N/A	1.11 (0.79, 1.56)	N/A		N/A		N/A
	FDA (2017) – CANVAS trial	Incidence rate	N/A	5.9 vs 2.8 per 1000 patient-years in placebo group			N/A		N/A
		HR (95% CI)	N/A	2.24 (1.36, 3.69)*	N/A		N/A		
	FDA (2017) – CANVAS-R trial	Incidence rate	N/A	7.5 vs 4.2 per 1000 patient-years in placebo group			N/A		N/A
		HR (95% CI)	N/A	1.80 (1.10, 2.93)*			N/A		N/A
Acute kidney injury	Toyama (2018)	HR (95% CI)	N/A	0.80 (0.38, 1.71)			0.17 (0.01, 4.06)		0.67 (0.39, 1.14)
	Perkovic (2019)	HR (95% CI)	N/A	0.85 (0.64, 1.13)	N/A		N/A		N/A
	FDA (2016)	No. of events (Mac 2013 – Oct 2015)	N/A	73 cases			28 cases		N/A

CANVAS, Canagliflozin Cardiovascular Assessment Study; CANVAS-R, A Study of the Effects of Canagliflozin on Renal Endpoints;CI, confidence interval; EMPA-REG, Empagliflozin Cardiovascular Outcome Event Trial;FDA, US Food and Drug Administration; HR, hazard ratio; RR, relative risk; N/A, not available. Statistical significance * = CI for RR/HR not crossing the null value of 1.

5.3 COST-EFFECTIVENESS

A cost-effectiveness modelling was conducted by Johnston et al. (2017) for the NIHR HTA report using the UKPDS outcome model version 1 (OM1) to review the cost-effectiveness of canagliflozin, dapagliflozin and empagliflozin in people with T2DM who are unable to take metformin as monotherapy. A SR and NMA were conducted and Bayesian statistical methods with fixed effects model was used to synthesise effectiveness evidence from RCTs.[22, level I]

The Assessment Group (AG) model considered patient's progression from monotherapy through various treatment intensifications over a 40-year time horizon in annual cycles, taking into consideration the patient's evolutions of HbA1c, SBP, total cholesterol, HDL, body mass index (BMI), hypoglycaemia event rates, adverse events (including UTI and GTI) and treatment costs. Despite possibility of increasing mortality with an event rate of one per 5000 patient-years, DKA was not included as there was no simple means of incorporating this mortality into the OM1 modelling. Risk of fracture was also not included in the modelling.[22, level I]

Baseline risk factors such as 59.8 years old, 57% male, duration of diabetes for two years, HbA1c 8.40% and BMI 31.9kg/m^2; and baseline complication rate such as myocardial infarction, ischaemic heart disease, stroke, congestive heart failure, amputation and renal failure from the National Institute for Health and Care Excellence (NICE) clinical guideline were applied in the model. The authors noted that the OM1 would tend to over-predict event rates [roughly double the number of myocardial infarctions over ten years and higher rates of IHD and 10-year mortality than those of outcome model version 2 (OM2)], and so overstate the benefits and cost savings arising from any avoidance of the complications of diabetes that are associated with the more effective treatment. Although the OM2 being more recent and more reflective of current practice was more preferable than OM1, OM2 was not made available to the AG at the time of assessment.[22, level I]

Outcomes were expressed in terms of quality adjusted life years (QALYs). Costs were considered from the perspective of UK National Health Service and Personal Social Services (PSS), using 2014 prices from the PSS Research Unit Costs of Health and Social Care index, with costs and benefits discounted at 3.5% per year. Probabilistic results were based upon 1000 probabilistic sensitivity analyses iterations, each with a patient cohort of 50,000 with 100 inner loops. All scenario analyses were run deterministically with a cohort of 50,000 patients and 1000 inner loops to reduce Monte Carlo error.[22, level I]

The AG modelling suggested that gliclazide was the least expensive, with total cost of £27,314. Canaglilfozin 300mg, dapagliflozin 10mg and empagliflozin 25mg were £5362, £5552 and £5,461 more expensive than gliclazide, respectively. The lifetime total costs among SGLT2 inhibitors were relatively similar – canagliflozin 300 mg (£32,676), dapagliflozin 10mg (£32,866) and empagliflozin 25mg (£32,775).[22, level I]

If there were no direct quality of life (QoL) impacts from weight changes, lifetime QALYs arising from diabetes, its complications and adverse events were highest for gliclazide at 10.392 QALYs. Gliclazide was estimated to be superior to canagliflozin, dapagliflozin and empagliflozin by 0.012 QALYs, 0.025 QALYs and 0.014 QALYs,

respectively. Among SGLT2 inhibitors, canagliflozin 300mg yielded the highest QALYs (10.380), followed by empagliflozin 25mg (10.378 QALYs) and dapagliflozin 10mg yielding the lowest QALYs (10.367). Gliclazide was found to dominate all SGLT2 treatments (less costly and more effective). [22, level I]

If direct QoL impacts from weight changes were included, assuming that monotherapy weight changes were retained over the patient lifetime, canagliflozin, dapagliflozin and empagliflozin would yield an additional 0.147 QALYs, 0.101 QALYs, 0.114 QALYs compared with gliclazide, respectively.[22 Level I] This translates to incremental cost-effectiveness ratios (ICERs) of £[redacted] per QALY gained, £[redacted] per QALY gained and £[redacted] per QALY gained for canagliflozin, dapagliflozin and empagliflozin, respectively, which are above the NICE cost-effectiveness threshold of £20,000 - £30,000.[44]

If weight losses rebound after one year, the net gains would fall to 0.058 QALYs, 0.038 QALYs and 0.050 QALYs. If weight losses rebound at treatment change, the net gains would fall to 0.074 QALYs, 0.048 QALYs and 0.061 QALYs. Both scenarios would yield higher ICERs compared to the scenario where weight losses assumed to persist indefinitely. The AG results showed some sensitivity to whether patients add insulin to their existing treatments or switch to it, the application of a common 7.5% HbA1c baseline and applying a reduced –0.47% HbA1c effect for gliclazide. Under these scenarios, SGLT2 inhibitors still remain dominated by gliclazide.[22, level I]

The AG concluded that dapagliflozin, canagliflozin and empagliflozin were not cost-effective compared with gliclazide.[22, level I] However, the cost-effectiveness modelling did not include cost savings from improved cardiovascular and renal outcome of which data were not yet available at the time of assessment.

5.4 ORGANISATIONAL ISSUES

5.4.1 Guidelines / Recommendations

World Health Organisation (WHO)

The World Health Organisation (WHO) published a guideline on second- and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus in 2018. For the second-line treatment in T2DM, WHO recommends to give a sulfonylurea to patients who do not achieve glycaemic control with metformin alone or who have contraindications to metformin (strong recommendation, moderate quality evidence). For the third-line treatment in T2DM, WHO recommends to introduce human insulin treatment to patients who do not achieve glycaemic control with metformin and/or sulfonylurea (strong recommendation, very low-quality evidence). If insulin is unsuitable, a DPP4 inhibitor, SGLT2 inhibitor or a thiazolidinedione may be added (weak recommendation, very low-quality evidence). These newer oral hypoglycaemic agents were formerly reviewed as first-line treatment options by the WHO Expert Committee on the Selection and Use of Essential Medicines and were not found to be superior to metformin and sulfonylurea.[45]

The Guideline Group acknowledged that SGLT2 inhibitors look particularly promising, particularly for survival, but acknowledged that the evidence was derived from placebo-controlled studies. SGLT2 inhibitors led to the greatest weight loss of all classes of medicines included in the NMA. One study showed that empagliflozin, when compared to placebo, had a protective effect on a composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke in people at high cardiovascular risk. More evidence is needed to determine whether this is a class effect and whether there is a cardio-protective effect in the general population of people with T2DM. Because SGLT2 inhibitors are a relatively new class of drugs, more safety data is likely to emerge from ongoing trials and from their use outside trial populations. The Guideline Group also noted the lack of RCTs on how each new drug class compares with all the others (particularly new agents versus old ones) and concluded that the evidence reviewed did not convincingly show the superiority or inferiority of any one class.[45]

While sulfonylureas showed a similar effect in lowering HbA1c compared to newer medicines, they also showed higher odds of severe hypoglycaemia compared to SGLT2 inhibitors. The Guideline Group noted the absence of estimates of absolute risk for severe hypoglycaemia in these trial reports but recognised that observational studies have shown that the risk of hypoglycaemia of varying severity in patients without renal impairment treated with sulfonylureas to be in the range from 0.2 to 1.8 events per 100 person-years which the Guideline Group considered not to be very high. The Guideline Group also recognised that there was large heterogeneity between the studies in how severe hypoglycaemia was defined. The Guideline Group concluded that the newer oral hypoglycaemic agents are currently substantially more expensive compared to sulfonylureas, and that the modest clinical benefit (fewer events of severe hypoglycaemia and weight loss with SGLT2 inhibitors) does not sufficiently outweigh the current price difference in the context of a public health approach.[45]

American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD)

In 2018, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) published an update to prior position statements, published in 2012 and 2015, on the management of T2DM in adults. Metformin remains the first-line therapy for the treatment of T2DM. An SGLT2 inhibitor with proven cardiovascular benefit is recommended for patients with clinical cardiovascular disease. It is noted that empagliflozin has superior cardiovascular benefit compared to canagliflozin. For patients with CKD or clinical heart failure, an SGLT2 inhibitor with proven benefit is recommended. It is noted that canagliflozin and empagliflozin have shown reduction in heart failure and progression of CKD in CVOTs. If there is a compelling need to minimise hypoglycaemia, minimise weight gain or promote weight loss in those without established ASCVD or CKD, an SGLT2 inhibitor is recommended for those with inadequate response to metformin. If cost is a major issue, a sulfonylurea with lower risk of hypoglycaemia such as gliclazide is recommended for patients without established ASCVD or CKD and unable to achieve desired HbA1c target with metformin alone.[17]

Agency for Care Effectiveness (ACE), Singapore

The Agency for Care Effectiveness (ACE), the national HTA agency in Singapore, has published technology guidance on SGLT2 inhibitors for treating T2DM in October 2018. The Ministry of Health's Drug Advisory Committee has recommended that dapagliflozin 5mg and 10mg, and empagliflozin 10mg and 25mg for the management of T2DM, in the following circumstances:[46]

- as a dual therapy in combination with metformin for patients with HbA1c measurement greater than 7% despite treatment with metformin monotherapy and when sulfonylureas are contraindicated or not tolerated or the person is at significant risk of hypoglycaemia or its consequences; or
- as a dual therapy in combination with a sulfonylurea for patients with HbA1c measurement greater than 7% despite treatment with sulfonylurea monotherapy and when metformin is contraindicated or not tolerated; or
- as a triple therapy in combination with metformin and a sulfonylurea for patients with HbA1c measurement greater than 7% despite treatment with optimal doses of dual therapy.

The Committee agreed that all SGLT2 inhibitors could be considered as a class given their same mechanism of action and considered that they were clinically comparable in effectiveness and safety. The Committee noted that SGLT2 inhibitors were not considered clinically superior to sulfonylureas in terms of HbA1c reduction using a minimal clinically important difference of 0.5%. However, the Committee also noted that when compared with sulfonylureas in dual therapy, SGLT2 inhibitors were superior in weight loss (-4.75kg), SBP reduction (-4.96mmHg), and were associated with lower risk of hypoglycaemia but higher risk of genital and urinary infections. The cost-effectiveness model comparing SGLT2 inhibitors to sulfonylureas in dual therapy with metformin over a lifetime period found that the ICER would fall in the range of less than SG$15,000 per QALY gained. The Committee considered that the ICERs were within an acceptable range of cost-effectiveness in sensitivity analyses.[46]

Ministry of Health Malaysia

The Clinical Practice Guidelines on Management of Type 2 Diabetes Mellitus was published by Ministry of Health Malaysia in 2015. Metformin is still the preferred choice as first line therapy. Other oral antidiabetic drugs are acceptable alternatives. If glycaemic targets are not achieved, intensification of treatment should be made every three months.[11]

According to the suggested treatment approach for specific patient profiles, the SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) are recommended as fourth line for patients with normal weight; third line for overweight patients; second line for obese patients and third line for those with increased risk of hypoglycaemia. The SGLT2 inhibitors are not recommended for patients with CKD stage 3-5 (eGFR <60ml/min/1.73m^2) as efficacy of SGLT2 inhibitors depends on renal function. These drugs are also not recommended for those on concomitant treatment with loop diuretic.[11]

As for second generation sulfonylurea (including gliclazide), this class is recommended as second line for patients with normal weight; third line for overweight patients; fourth line for obese patients; third line for those with CKD stage 3. Second generation sulfonylureas are not recommended for those with increased risk of hypoglycaemia and CKD stage 4-5. As these drugs are highly protein bound, administration of drugs that can displace them (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), anti-thyroid drugs, sulpha drugs, anticoagulants and beta-blockers) can increase the risk of hypoglycaemia.[11]

5.7 LIMITATIONS

This technology review has several limitations. The selection of studies was done by one reviewer. Language restriction was applied during the search where only English full text articles were included in this report. As there was no head to head RCT comparing SGLT2 inhibitors and gliclazide, relative effects on biomarkers had to be drawn from NMA. As for cardiovascular and renal outcomes, effects of SGLT2 inhibitors had to be drawn from two systematic reviews and meta-analyses, one randomised placebo-controlled trial and one retrospective cohort study. The duration of study ranged from 12 to 52 weeks which may not be sufficiently long to establish cardiovascular and renal protection benefits as well as safety record of SGLT2 inhibitors. Continued monitoring for adverse events with the use of SGLT2 inhibitors is advocated. Relative comparison between gliclazide and SGLT2 inhibitors was not possible due to lack of evidence evaluating the cardiovascular and renal outcomes of gliclazide. Papers evaluating sulfonylureas as comparator by drug class were not included in this technology review. Due to within-class differences among sulfonylureas,[24] effects of sulfonylureas by drug class should not be extrapolated to gliclazide. Results should be interpreted with caution as there may be conflict of interest in some of the studies included in this technology review.

6. CONCLUSION

6.1 Effectiveness

As there was no head to head randomised controlled trial comparing SGLT2 inhibitors and gliclazide, relative effects on biomarkers had to be drawn from network meta-analysis. There was good level of retrievable evidence to suggest that in terms of glycaemic control (HbA1c reduction), canagliflozin 100mg, dapagliflozin 5 and 10mg, and empagliflozin 10mg and 25mg were less effective than gliclazide. Only canagliflozin 300mg was found to be as effective as gliclazide. However, SGLT2 inhibitors had added benefits of significant reduction in body weight and some reduction in systolic blood pressure. Gliclazide was associated with weight gain. There was no retrievable evidence on blood pressure reduction for gliclazide.

As for cardiovascular and renal outcomes, effects of SGLT2 inhibitors had to be drawn from two systematic reviews of placebo-controlled trials, one randomised placebo-controlled trial, and one retrospective cohort study. For gliclazide, one systematic review reported that although nine studies comparing gliclazide with other oral glucose-lowering drugs as comparator group reported incidence of cardiovascular events (risk ratio 0.95 (95% CI 0.57, 1.61) and mortality (risk ratio 0.81 (95% CI 0.26, 2.47), none of the trials was designed to assess cardiovascular

safety and/or efficacy. These studies reported limited number of cardiovascular events (11 cases in 1480 gliclazide users and 20 cases in 1508 comparator patients) and cardiovascular deaths (3 in 1602 gliclazide users and 7 in 1619 comparator patients). Some studies were conducted for a relatively short duration (13-16 months). There was no retrievable evidence on renal outcome for gliclazide.

One systematic review and meta-analysis based on placebo-controlled trials showed that SGLT2 inhibitors appeared to have moderate benefits on atherosclerotic major adverse cardiovascular events (MACE) and risk of cardiovascular death or hospitalisation for heart failure for patients with established atherosclerotic cardiovascular disease (ASCVD). In terms of risk of cardiovascular death or hospitalisation for heart failure, patients with history of heart failure would benefit from canagliflozin and dapagliflozin whereas patient without history of heart failure would benefit from dapagliflozin and empagliflozin. Patients without ASCVD but with multiple risk factors did not appear to benefit from SGLT2 inhibitors in terms of MACE and risk of cardiovascular death or hospitalisation for heart failure. Patients with eGFR <60ml/min/1.73m^2 would benefit from canagliflozin in terms of MACE and hospitalisation for heart failure.

In terms of risk of renal worsening, end-stage kidney disease or renal death, patients with ASCVD and those with eGFR ≥60ml/min/1.73m^2 would benefit from SGLT2 inhibitors. With regards to patients with eGFR <60ml/min/1.73m^2, there were inconclusive results from two systematic reviews and one randomised clinical trial. The magnitude of benefit for SGLT2 inhibitors was lesser in patients with more severe kidney disease at baseline.

In the retrospective cohort study, dapagliflozin showed better reduction in estimated 10-year cardiovascular risk for all four endpoints (fatal and non-fatal coronary heart disease; and fatal and non-fatal stroke) compared with gliclazide which reduced three endpoints except for fatal stroke.

More evidence is required in comparison with active comparators to establish the cardiovascular and renal protection of SGLT2 inhibitors which had only been demonstrated in placebo-controlled trials. In terms of overall efficacy outcomes among SGLT2 inhibitors, canagliflozin appeared to be most favourable, followed by empagliflozin and dapagliflozin.

6.2 Safety

There was good level of retrievable evidence to suggest that gliclazide was associated with significantly higher risk of hypoglycaemia compared with SGLT2 inhibitors. Although all three SGLT2 inhibitors were associated with low risk of hypoglycaemia, these drugs were associated with increased risk of genital infections. Fournier's gangrene was identified as a safety concern in patients receiving SGLT2 inhibitors. Rare occurrences of diabetic ketoacidosis and acute kidney injury had also been reported with the use of SGLT2 inhibitors. Patients taking canagliflozin had increased risk of bone fractures and were approximately twice as likely to undergo amputation. Among the SGLT2 inhibitors, empagliflozin and dapagliflozin appeared to have acceptable safety profile. However, the safety record of SGLT2

inhibitors remains to be established and continued monitoring for adverse events is advocated.

6.3 Cost-effectiveness

Based on a systematic review and cost-effectiveness model, all three SGLT2 inhibitors were not cost-effective compared with gliclazide from the perspective of the UK National Health Service and Personal Social Services, using 2014 prices, with costs and benefits discounted at 3.5% per year. Gliclazide was the least expensive, with total lifetime costs of £27,314. Canaglilfozin 300mg, dapagliflozin 10mg and empagliflozin 25mg were £5362, £5552 and £5,461 more expensive than gliclazide, respectively. If there were no direct quality of life impacts from weight changes, lifetime quality adjusted life years (QALYs) arising from diabetes, its complications and adverse events were highest for gliclazide at 10.392 QALYs. Gliclazide was estimated to be superior to canagliflozin, dapagliflozin and empagliflozin by 0.012 QALYs, 0.025 QALYs and 0.014 QALYs, respectively. Gliclazide dominated all SGLT2 inhibitors (less costly and more effective). Among the SGLT2 inhibitors, canagliflozin was the most favourable in terms of cost and QALYs, followed by empagliflozin and dapagliflozin. However, the cost-effectiveness modelling did not include cost savings from improved cardiovascular and renal outcome of which data were not yet available at the time of assessment.

6.4 Organisational issues

World Health Organisation (WHO), American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD), Agency for Care and Effectiveness (ACE), Singapore and Ministry of Health, Malaysia have issued guidelines with regard to the use of SGLT2 inhibitors and gliclazide in the treatment of T2DM.

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OTHER DATABASES

8. APPENDIX

8.1 Appendix 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE® In-process & other Non-Indexed citations and OvidMEDLINE® 1946 to present

Database: Ovid MEDLINE(R) and In-Process & Other Non-Indexed Citations <1946 to January 28, 2019>
Search Strategy:

1 Diabetes Mellitus, Type 2/ (119427)
2 (Type 2 adj1 Diabetes).Tw. (107680)
3 (Non Insulin Dependent adj1 Diabetes Mellitus).Tw. (6802)
4 Sodium-Glucose Transporter 2/ (612)
5 Sodium Glucose Co Transporter 2 Inhibitor*.Tw. (372)
6 Sodium Glucose Cotransporter 2 Inhibitor*.Tw. (559)
7 Sodium-Glucose Transporter 2 Inhibitor*.Tw. (34)
8 Sglt2 Inhibit*.Tw. (1383)
9 Sglt-2 Inhibit*.Tw. (366)
10 Canagliflozin.Tw. (673)
11 Empagliflozin.Tw. (742)
12 Dapagliflozin.Tw. (704)
13 Gliflozin*.Tw. (68)
14 Gliclazide/ (854)
15 Gliclazide.Tw. (1134)
16 1 Or 2 Or 3 (160179)
17 4 Or 5 Or 6 Or 7 Or 8 Or 9 Or 10 Or 11 Or 12 Or 13 (3203)
18 14 Or 15 (1278)
19 16 And 17 And 18 (12)
20 Limit 19 To (English language and humans) (11)

Embase	('non insulin dependent diabetes mellitus'/exp OR 'diabetes mellitus type 2' OR 'diabetes mellitus type ii' OR 'diabetes mellitus, non insulin dependent' OR 'diabetes mellitus, non-insulin-dependent' OR 'diabetes mellitus, type 2' OR 'diabetes mellitus, type ii' OR 'diabetes type 2' OR 'diabetes type ii' OR 'dm 2' OR 'niddm' OR 'non insulin dependent diabetes' OR 'non insulin dependent diabetes mellitus' OR 'noninsulin dependent diabetes' OR 'noninsulin dependent diabetes mellitus' OR 'type 2 diabetes' OR 'type 2 diabetes mellitus' OR 'type ii diabetes') AND ('sodium glucose cotransporter 2 inhibitor'/exp OR 'sglt2 inhibitor' OR 'sglt2 inhibitors' OR 'gliflozin' OR 'gliflozins' OR 'sodium dependent glucose cotransporter 2 inhibitor' OR 'sodium glucose co-transporter 2 inhibitor' OR 'sodium glucose cotransporter 2 inhibitor' OR 'sodium-glucose transporter 2 inhibitors' OR 'empagliflozin'/exp OR 'empagliflozin' OR 'jardiance' OR 'dapagliflozin'/exp OR 'dapagliflozin' OR 'farxiga' OR 'forxiga' OR 'canagliflozin'/exp OR 'canagliflozin' OR 'invokana') AND ('gliclazide'/exp OR 'diamicron' OR 'gliclazide' OR 'glimicron') AND 'human'/de AND [english]/lim
EBM Reviews - Cochrane Central Register of Controlled Trials	Same MeSH, keywords, limits used as per MEDLINE search
EBM Reviews - Database of Abstracts of Review of Effects	
EBM Reviews - Cochrane database of systematic reviews	
EBM Reviews - Health Technology Assessment	
EBM Reviews- NHS economic evaluation database	
PubMed	((((((type 2 diabetes[MeSH Terms]) OR type 2 diabetes) OR Non insulin dependent diabetes mellitus)) AND ((((((((((sodium glucose co transporter 2 inhibitor*) OR sodium glucose cotransporter 2 inhibitor*) OR sodium-glucose transporter 2 inhibitor*) OR sglt2 inhibit*) OR sglt-2 inhibit*) OR Canagliflozin) OR Empagliflozin) OR Dapagliflozin)) OR Sodium-Glucose Transporter 2[MeSH Terms]))) AND ((Gliclazide[MeSH Terms]) OR gliclazide))
INAHTA	SGLT2 inhibitors, canagliflozin, dapagliflozin, empagliflozin, gliclazide

8.2 Appendix 2: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomised controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomisation.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

8.3. Appendix 3: EVIDENCE TABLE

Evidence Table : Effectiveness
Question : What is the clinical effectiveness of SGLT2 inhibitors compared with gliclazide in the treatment of type 2 diabetes mellitus (T2DM)?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
1. Johnston R, Uthman O, Cummins E et al. Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation. Health Technol Assess. 2017;21(2):1-218.	**Systematic review and network meta-analysis (NMA)** To review the clinical effectiveness and cost-effectiveness of dapagliflozin, canagliflozin and empagliflozin in monotherapy in people who cannot take metformin. Primary measures of treatment effect were mean difference (MDs) in change from baseline for HbA1c, weight gain and systolic blood pressure (SBP). Data source: MEDLINE (1946 to February 2015), EMBASE (1974 to February 2015) and Web of Science. Studies up to September 2015 were included. Quality of RCTs was assessed using Cochrane risk of bias tool. Bayesian NMA method with fixed effects model was used to analyse all the data, preserving randomised treatment effects within trials and accounting for correlation between comparisons with three arms or four arms using the WinBUGS 1.4.3 software. All results were reported as posterior medians of MDs with corresponding 95% credible intervals (CrIs).	**I**	Seventeen RCTs of monotherapy with minimum duration of 24 weeks or more in people with type 2 diabetes unable to take metformin; baseline HbA1c of 7.5% or more; and dropout rates of no more than 20%. Canagliflozin: two trials • 100mg (n=285) • 300mg (n=197) Dapagliflozin: three trials • 10mg (n=367) Empagliflozin: two trials • 10mg (n=356) • 25mg (n=357) Gliclazide: three trials (n=588)	Canagliflozin 100mg & 300mg, Dapagliflozin 10mg, Empagliflozin 10mg & 25mg	Gliclazide	Trial duration: 24-26 weeks	Based on pairwise comparison with placebo for HbA1c (%) in MD (95% CI), reduction was seen highest with canagliflozin 300mg, lowest with dapagliflozin 10mg. No SGLT2 inhibitors were significantly more effective compared with gliclazide. • Canagliflozin 100mg: –0.95 (–1.06, –0.84) • Canagliflozin 300mg: –1.19 (–1.34, –1.04) • Dapagliflozin 10mg: –0.59 (–0.70, –0.48) • Empagliflozin 10mg: –0.76 (–0.87, –0.65) • Empagliflozin 25mg: –0.88 (–0.99, –0.77) • Gliclazide: –0.95 (–1.27, –0.64) Based on pairwise comparison with placebo for weight changes (kg) in MD (95% CI), SGLT2 inhibitors were associated with significant weight reduction compared with gliclazide. • Canagliflozin 100mg: –2.02 (–2.41, –1.65) • Canagliflozin 300mg: –2.91 (–3.22, –2.59) • Dapagliflozin 10mg: –1.58 (–2.01, –1.14) • Empagliflozin 10mg: –1.74 (–2.15, –1.33) • Empagliflozin 25mg: –1.89 (–2.29, –1.49) • Gliclazide: +1.97 (0.76, 3.20) Based on pairwise comparison with placebo for SBP (mmHg) in MD (95% CI), reduction was seen highest with canagliflozin 300mg, lowest with dapagliflozin 10mg. No SBP data was available for gliclazide. • Canagliflozin 100mg: –4.24 (–6.01, –2.44) • Canagliflozin 300mg: –5.65 (–7.77, –3.53) • Dapagliflozin 10mg: –2.73 (–4.77, –0.74) • Empagliflozin 10mg: –2.59 (–4.88, –0.33) • Empagliflozin 25mg: –3.38 (–5.67, –1.11) Authors' conclusion: Dapagliflozin, canagliflozin and empagliflozin were effective in improving glycaemic control, with added benefits of some reductions in blood pressure and weight.	The between-study variance was small, suggesting no heterogeneity, but the CrIs were wide, reflecting the small number of studies available for pairwise comparisons. Analyses based on direct versus indirect comparisons showed no evidence of inconsistency between direct and indirect evidence in the network for HbA1c, weight gain, and SBP. In some dapagliflozin trials HbA1c improved in the placebo groups, reducing the placebo-adjusted improvement after dapagliflozin treatment. Patients in one dapagliflozin trial had a low baseline HbA1c, and hence less chance of a large reduction. In the canagliflozin trials, HbA1c rose in placebo groups.

Evidence Table : Effectiveness
Question : What is the clinical effectiveness of SGLT2 inhibitors compared with gliclazide in the treatment of type 2 diabetes mellitus (T2DM)?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
2. Mearns ES, Sobieraj DM, White CM et al. Comparative efficacy and safety of antidiabetic drug regimens added to metformin monotherapy in patients with type 2 diabetes: a network meta-analysis. PloS One. 2015;10(4):1-28	**Systematic review and network meta-analysis (NMA)** To assess the efficacy and safety of adjunctive antidiabetic agents in patients with inadequately controlled T2DM on metformin alone. Data source: MEDLINE Cochrane CENTRAL, ClinicalTrials.gov, regulatory websites. Validity assessment was performed using Cochrane Risk of Bias Tool. Trials up to May 2014 were included. Traditional meta-analyses analyzing changes in HbA1c, body weight and SBP as continuous variables were performed using StatsDirect version 2.7.8. Weighted (absolute) mean differences (WMDs) and associated 95% confidence intervals (CIs) were calculated using a DerSimonian and Laird random-effects model to account for between-study heterogeneity. When at least three studies making same direct comparison were available, the likelihood of statistical heterogeneity (I^2) and publication bias (Egger's weighted regression) were assessed. Random-effects NMA was performed using the package 'netmeta' (version 0.5–0) in R (version 3.0.2). Clinical superiority was regarded when one therapy improved HbA1c, body weight or SBP by at least 0.3%, 2.3 kg or 5 mmHg, respectively, versus a competitor. Sensitivity analyses calculating more conservative 99% CIs were performed to address the inherent limitations of multiple comparisons in the meta-analysis.	**I**	Sixty-two RCTs (n=32,185) evaluating 25 agents were included. Adult patients (≥18 years) with T2DM who showed inadequate response to stable, optimized metformin monotherapy at randomisation (≥1500 mg daily or maximally tolerated dose for ≥4 weeks) before randomisation. Canagliflozin: n=1,831 Dapagliflozin: n=495 Empagliflozin: n=1,617 Gliclazide: n=1,259	Canagliflozin 100mg & 300mg Dapagliflozin 2.5-10mg Empagliflozin 10mg & 25mg	Gliclazide 80-320mg	Mean trial duration: 29 (12-52) weeks	In terms of NMA estimate for change in HbA1c (%) versus placebo in WMD (95% CI), no SGLT2 inhibitors were significantly more effective or clinically superior to gliclazide. • Canagliflozin: -0.72 (-0.85, -0.59) • Dapagliflozin: -0.48 (-0.62, -0.33) • Empagliflozin: -0.69 (-0.81, -0.57) • Gliclazide: -0.70 (-0.85, -0.56) In terms of NMA estimate for change in body weight (kg) versus placebo in WMD (95% CI), SGLT2 inhibitors were significantly more effective and clinically superior to gliclazide. • Canagliflozin: -2.15 (-2.63, -1.67) • Dapagliflozin: -2.17 (-2.78, -1.57) • Empagliflozin: -2.08 (-2.52, -1.63) • Gliclazide: +1.19 (0.39, 1.99) In terms of NMA estimate for change in SBP (mmHg) versus placebo in WMD (95% CI), SGLT2 inhibitors were associated with SBP reduction but none were clinically superior to placebo. No SBP data was available for gliclazide. • Canagliflozin: -4.14 (-5.80, -2.48) • Dapagliflozin: -4.50 (-7.97, -1.03) • Empagliflozin: -5.14 (-6.80, -3.48) Authors' conclusion: The SGLT2 inhibitors were found to provide similar HbA1c efficacy to other non-insulin monotherapies with the added benefits of weight loss, reduced SBP and a low risk of hypoglycemia; but at a cost of an increased risk of GTI.	I^2 for trials involving canagliflozin, dapagliflozin, empagliflozin and gliclazide <50%. I^2>50% represents important statistical heterogeneity. This work was supported by Boehringer Ingelheim.

Evidence Table : Effectiveness
Question : What is the clinical effectiveness of SGLT2 inhibitors compared with gliclazide in the treatment of type 2 diabetes mellitus (T2DM)?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
3. Maloney A, Rosenstock J, Fonseca V. A Model-Based Meta-Analysis of 24 Antihyperglycemic Drugs for Type 2 Diabetes: Comparison of Treatment Effects at Therapeutic Doses. Clin Pharmacol Ther. 2019:1-19. doi:10.1002/cpt.1307.	**Systematic review and model-based meta-analysis** To compare glycemic control, weight changes, and hypoglycemia risk across 24 antihyperglycemic drugs used to treat type 2 diabetes. Data source: Medline (via PubMed), ClinicalTrials.gov, FDA summary basis of approval documents and drug labels, and sponsor websites. Analyses were adjusted for duration of treatment (delay), drug dosages (dose response) and baseline glycated haemoglobin (scalar). Change from Baseline in HbA1c = Placebo + Delay · Dose Response · Scalar Following a full Bayesian analysis, estimates for the change from placebo were determined for all regimens for drug naïve population with a baseline HbA1c of 8.0%, baseline body weight of 90 kg, and 26 weeks of treatment. All analyses were conducted using SAS software, version 9.4 (SAS Institute). The models were developed using data up to November 15, 2017.	**I**	A total of 229 RCTs including 121,914 patients with T2DM were identified. Exclusion criteria: studies run primarily in Asia, studies in special T2DM populations (hypertensive, obese, renally impaired, high cardiovascular risk, elderly and paediatric), studies with insulin background treatment, studies with sulfonylurea background treatment (for hypoglycemia analysis only), single arm studies, combination treatment arms, and phase I studies. Canagliflozin [n=3,928 (3.2%)] Dapagliflozin [n=4,019 (3.3%)] Empagliflozin [n=4,932 (4.0%)] Gliclazide [n=3,172 (2.6%)]	Canagliflozin 100mg & 300mg, Dapagliflozin 5mg & 10mg, Empagliflozin 10mg & 25mg	Gliclazide 80-320mg	26 weeks Change in drug effect due to duration was taken into account, increasing (nonlinearly) from 0% at week 0 to 100% (full effect) at week 26. For the weight analysis, the value 26 was replaced with 52 (i.e. the full effect on weight would only be reached after 52 weeks of treatment).	In terms of HbA1c versus placebo, highest estimated treatment effect was seen with gliclazide, lowest was seen with dapagliflozin 5mg. • Canagliflozin 100mg: -0.84% • Canagliflozin 300mg: -1.01% • Dapagliflozin 5mg: -0.65% • Dapagliflozin 10mg: -0.73% • Empagliflozin 10mg: -0.69% • Empagliflozin 25mg: -0.77% • Glicazide 80-320mg: -1.04% Weight loss was similar across SGLT2 inhibitors. Large weight increase was observed for gliclazide. • Canagliflozin 100mg: -1.90kg • Canagliflozin 300mg: -2.30kg • Dapagliflozin 5mg: -1.70kg • Dapagliflozin 10mg: -1.90kg • Empagliflozin 10mg: -2.10kg • Empagliflozin 25mg: -2.40kg • Glicazide 80-320mg: +2.40kg Authors' conclusion: Important differences between and within drug classes were identified.	Authors disclosed receiving consulting fees from pharmaceutical companies including Astra Zeneca, Boehringer Ingelheim and Janssen.

Evidence Table : Effectiveness
Question : What is the clinical effectiveness of SGLT2 inhibitors compared with gliclazide in the treatment of type 2 diabetes mellitus (T2DM)?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
4. Jia Y, Lao Y, Zhu H et al. Is metformin still the most efficacious first-line oral hypoglycaemic drug in treating type 2 diabetes? A network meta-analysis of randomised controlled trials. Obes Rev. 2019;20(1):1-12.	**Systematic review and network meta-analysis (NMA)** To compare the efficacy of hypoglycaemic drugs for T2D by NMA of RCTs. Data source: PubMed, Cochrane Library, ScienceDirect, EMBASE, FDA medical reviews and ClinicalTrials.gov. Trials up to January 2018 were included. Eleven oral hypoglycaemic drugs evaluated by 75 RCTs (1991-2017) as drug monotherapy for T2DM patients. RCT quality was assessed with Cochrane risk of bias tool. Evidence quality from meta-analysis (MA) was assessed with GRADE approach. Pairwise MA (R software version 3.1.2) and NMA based on Bayesian hierarchical random-effects model [software package WINBUGS (version 1.4.3) and R] estimated overall effect sizes as MDs and 95% CIs. Heterogeneity was assessed by I^2 and the Cochrane *Q* test. Subgroup and sensitivity analyses as well as meta-regression and publication bias were performed. Overall ranking was determined by overall effect sizes, probability of best treatment and surface of cumulative ranking curve area.	**I**	A total of 33,830 adult patients with T2DM and a follow up of at least 28 days were included in NMA. Mean sample sizes was 451 patients. 1. Dapagliflozin [n=1,646 (4.87%)] 2. Gliclazide [n=248 (0.73%)] 3. Glimepiride [n=775 (2.29%)] 4. Glipizide [n=270 (0.80%)] 5. Glyburide [n=458 (1.36%) 6. Metformin [n=2,967 (8.77%)] 7. Nateglinide [n=730 (2.16%)] 8. Repaglinide [n=1,273 (3.76%)] 9. Saxagliptin [n=739 (2.18%)] 10. Sitagliptin [n=10,215 (30.20%)] 11. Vildagliptin [n=1,488 (4.40%) 12. Placebo [n=13,021 (38.50%)]	Dapagliflozin 2.5, 5 or 10mg	Gliclazide 80-320mg	Mean follow-up: 184 days	Outcome measures were mean changes of HbA1c (primary outcome) and fasting plasma glucose, FPG (secondary outcome) from baseline and their corresponding variation in MDs and 95% CIs. Seventy-one and 58 RCTs reported HbA1c and FPG as primary outcomes, respectively. In terms of HbA1c, dapagliflozin [-0.50 (-0.78, -0.21)] was less efficacious compared with gliclazide [-1.37 (-2.04, -0.71)], against placebo. In terms of FPG, there was no difference between dapagliflozin [-1.10 (-1.69, -0.50)] and gliclazide [-1.09 (-2.18, 0.11)], against placebo. Based on ranking analysis on HbA1c where rank 1 was the best and rank 12 was the worst, dapagliflozin ranked at 10 whereas gliclazide ranked at 2. Subgroup and sensitivity analyses found the results to be robust. Included RCTs were of high quality. Evidence strength from pairwise MA was moderate to high. Heterogeneities of pooled effect sizes were significantly high in pairwise MA (42/46 studies for efficacy estimates: I^2>75%). Meta-regression analysis indicated follow-up periods and risk of bias of included RCTs may be the source of heterogeneity. Authors' conclusion: This meta-analysis showed that repaglinide and metformin would be the best oral drugs for first-line monotherapy of type 2 diabetes.	Studies involving dapagliflozin and gliclazide had ≥84 days follow up (full treatment effect of HbA1c would reach by 84 days).

Evidence Table : Effectiveness
Question : What is the clinical effectiveness of SGLT2 inhibitors compared with gliclazide in the treatment of type 2 diabetes mellitus (T2DM)?

<table>
<tr><th>Bibliographic citation</th><th>Study Type/Methods</th><th>LE</th><th>Number of Patients & Patient Characteristic</th><th>Intervention</th><th>Comparison</th><th>Length of Follow Up (If Applicable)</th><th>Outcome Measures/Effect Size</th><th>General Comments</th></tr>
<tr>
<td>5. Fadini GP, Zatti G, Baldi I et al. Use and effectiveness of dapagliflozin in routine clinical practice: An Italian multicentre retrospective study. Diabetes Obes Metab. 2018;20(7):1781-6.

DARWIN-T2D: DApagliflozin Real World evIdeNce in Type 2 Diabetes</td>
<td>Retrospective cohort nationwide multicentre study

To evaluate baseline clinical characteristics and change in glycaemic and extra-glycaemic effectiveness variables in patients initiated on dapagliflozin vs patients initiated on DPP-4 inhibitors, gliclazide, or GLP-1RAs in 46 Italian diabetes specialist outpatient clinics.

Automated MyStar Connect software was used to retrospectively extract relevant data from the same electronic chart system at all centres.

Continuous variables were presented as mean ± SD, and categorical variables as percentages. Comparison between the two groups was performed using the two-tailed unpaired Student's t test or χ^2 test. Adjusting for multiple testing was performed using the Benjamini–Hochberg procedure. The two-tailed paired Student's t test was used to compare data collected at follow-up with those collected at baseline.

The risk of fatal and non-fatal coronary heart disease (CHD) and stroke were estimated using UKPDS risk engine (only patients with complete set of data included).</td>
<td>II-2</td>
<td>17,285 patients aged 18-80 with T2DM diagnosed for at least one year, who were initiated on the following drugs between 13th March 2015 to 31th December 2016 and not treated with SGLT2 inhibitors previously were included.

Patients on dapagliflozin were initiated as add-on to metformin and/or insulin as this was the only combination reimbursed by the Italian National Health Service.

1. Dapagliflozin [n=2,484 (14.4%)]
2. Sitagliptin (n=3,772 (21.8%)
3. Alogliptin [n=1299 (7.5%)]
4. Vildagliptin [n=1,292 (7.5%)]
5. Saxagliptin [n=231 (1.3%)]
6. Gliclazide [n=5,960 (34.5%)]
7. Liraglutide [n=1,647 (9.5%)]
8. Exenatide extended release [n=600 (3.5%)]</td>
<td>Dapagliflozin 10mg</td>
<td>Gliclazide modified release 30mg or higher</td>
<td>Follow-up visit: 3 to 12 months after baseline

Dapagliflozin: n=830 (33.4%), average of 168 days (5.5 months)

Gliclazide: n=2111 (35.4%), average of 185 days (6.1 months)</td>
<td>Patients on dapagliflozin showed significant improvements in
• FPG (−28.2 mg/dL ± 54.5)
• HbA1c (−0.7% ± 1.2)
• Body weight (−2.7 kg ± 3.5)
• Systolic blood pressure (−3.0 mmHg ± 17.7)
• Diastolic blood pressure (−1.3 mmHg ± 9.9)
• Total cholesterol (−3.5 mg/dL ± 34.7)
• HDL cholesterol (+1.6 mg/dL ± 8.1)
• Triglycerides (−15.9 mg/dL ± 135.4)

Patients on gliclazide showed significant improvements in
• FPG (−14.8 mg/dl ± 49.6)
• HbA1c (−0.6% ± 1.3)
• Total cholesterol (−8.0 mg/dL ± 31.3)
• Triglyceride (−12.9 mg/dL ± 83.2)
• LDL cholesterol (−5.5 mg/dL ± 26.4).

Patients on dapagliflozin showed more significant reduction in estimated 10-year cardiovascular risk.
<table>
<tr><th></th><th>Dapagliflozin (n=282)</th><th>Gliclazide (n=602)</th></tr>
<tr><td>CHD</td><td>-4.7 ± 9.9%*</td><td>-4.5 ± 11.6%*</td></tr>
<tr><td>Fatal CHD</td><td>-4.5 ± 9.4%*</td><td>-4.2 ± 11.1%*</td></tr>
<tr><td>Stroke</td><td>-1.1 ± 5.3%*</td><td>-0.7 ± 6.1%*</td></tr>
<tr><td>Fatal Stroke</td><td>-0.6 ± 3.8%*</td><td>-0.2 ± 5.3%</td></tr>
</table>
*p<0.05

Authors' conclusion:
This real-world study showed an initial channelling of dapagliflozin to difficult-to-treat patients. Nonetheless, dapagliflozin provided significant benefits with regard to glucose control, body weight and blood pressure that were in line with findings from RCTs.</td>
<td>Patients on dapagliflozin were younger; had longer diabetes duration; higher FPG level, HbA1c level and blood pressure; and more obese than patients on gliclazide.

Between-group comparisons of effectiveness were hampered by massive differences in baseline clinical characteristics that could not be overcome by propensity score matching.

The study was sponsored and promoted by the Italian Diabetes Society, through partial (<50%) financial support from AstraZeneca.</td>
</tr>
</table>

Evidence Table : Effectiveness
Question : What is the clinical effectiveness of SGLT2 inhibitors compared with gliclazide in the treatment of type 2 diabetes mellitus (T2DM)?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
6. Zelniker TA, Wiviott SD, Raz I et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019;393(10166):31-39.	**Systematic review and meta-analysis (MA)** To combine data from all the large-scale placebo-controlled cardiovascular outcome trials of SGLT2 inhibitors to gain more reliable estimates of the efficacy and safety of specific outcomes overall and in relevant subgroups. Data source: PubMed & Embase for trials published up to September 2018. Risk was bias was assessed using Cochrane Risk of Bias tool. Efficacy outcomes included major adverse cardiovascular events [(MACE) myocardial infarction, stroke, or cardiovascular death], composite of cardiovascular death or hospitalisation for heart failure, and progression of renal disease (renal worsening, end-stage renal disease or renal death). Hazard ratios (HRs) with 95% CIs were pooled across trials, and efficacy outcomes were stratified by baseline presence of atherosclerotic cardiovascular disease (ASVD), heart failure, and degree of renal function using fixed effects models. Heterogeneity was assessed using Cochrane Q statistic and I^2. Statistical analyses were done using R version 3.5.1 and the R package metaphor version 2.0-0.	**I**	34,422 patients from 3 trials of randomised, placebo-controlled cardiovascular outcome trials were included. Canagliflozin: one trial (CANVAS) n = 10,142 Dapagliflozin: one trial (DECLARE-TIMI) n = 17,160 Empagliflozin: one trial (EMPA-REG) n = 7,020	Canagliflozin 100mg & 300mg, Dapagliflozin 10mg, Empagliflozin 10mg & 25mg	Placebo	Median follow-up time: Canagliflozin: 2.4 years Dapagliflozin: 4.2 years Empagliflozin: 3.1 years	**MACE**: HR (95% CI) In patients with ASCVD, canagliflozin and empagliflozin reduced MACE by 18% [HR 0.82 (0.72, 0.95)] and 14% [HR 0.86 (0.74, 0.99)]. In patients with multiple risk factors (without ASCVD), SGLT2 inhibitors did not reduce MACE. In patients with eGFR <60ml/min per 1.73m^2, canagliflozin reduced MACE by 31% [HR 0.69 (0.54, 0.89)]. **Risk of cardiovascular death or hospitalisation for heart failure**: HR (95% CI) In patients with ASCVD, canagliflozin, dapagliflozin and empagliflozin reduced the risk by 23% [HR 0.77 (0.65, 0.92)], 17% [HR 0.83 (0.71, 0.98)] and 34% [HR 0.66 (0.55, 0.79)]. In patients with multiple risk factors (without ASCVD), SGLT2 inhibitors did not the risk of cardiovascular death or hospitalisation for heart failure. In patients with history of heart failure, canagliflozin and dapagliflozin reduced the risk by 39% [HR 0.61 (0.46, 0.80)] and 21% [HR 0.79 (0.63, 0.99)]. In patients without history of heart failure, dapagliflozin and empagliflozin reduced the risk by 16% [HR 0.84 (0.72, 0.99)] and 37% [HR 0.63 (0.51, 0.78]]. In patients with eGFR <60ml/min per 1.73m^2, canagliflozin and empagliflozin reduced hospitalisation for heart failure by 45% [HR 0.55 (0.37, 0.83)] and 41% [HR 0.59 (0.39, 0.88)].	Authors declared receiving grants/ fees from pharmaceutical companies including Astra Zeneca, Boehringer Ingelheim and Janssen. Multiple differences were found in the patient characteristics in each trial that might explain the observed variations with regard to cardiovascular death. There was slight variation in exact inclusion criteria and definitions of endpoints among the trials.

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
							Risk of progression of renal disease: HR (95% CI) In patients with ASCVD, canagliflozin, dapagliflozin and empagliflozin reduced the risk by 41% [HR 0.59 (0.44, 0.79)], 45% [HR 0.55 (0.41, 0.75)] and 46% [HR 0.54 (0.40, 0.75)]. In patients with multiple risk factors (without ASCVD), dapagliflozin reduced the risk by 49% [HR 0.51 (0.37, 0.69)]. In patients with eGFR >90ml/min per 1.73m^2, canagliflozin, dapagliflozin and empagliflozin reduced the risk by 56% [HR 0.44 (0.25, 0.78)], 50% [HR 0.50 (0.34, 0.73)], and 79% [HR 0.21 (0.09, 0.53)]. In patients with eGFR 60 to <90ml/min per 1.73m^2, canagliflozin and dapagliflozin reduced the risk by 42% [HR 0.58 (0.41, 0.84)] and 46% [HR 0.54 (0.40, 0.73)]. In patients with eGFR <60ml/min per 1.73m^2, the SGLT2 inhibitors did not reduce the risk of progression of renal disease. Authors' conclusion: SGLT2 inhibitors had moderate benefits on atherosclerotic MACE that seem confined to patients with established ASCVD. However, they had robust benefits on reducing hospitalisation for heart failure and progression of renal disease regardless of existing atherosclerotic cardiovascular disease or a history of heart failure.	

Evidence Table : Effectiveness
Question : What is the clinical effectiveness of SGLT2 inhibitors compared with gliclazide in the treatment of type 2 diabetes mellitus (T2DM)?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
7. 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 and Metab. 2019.	**Systematic review and meta-analysis (MA)** To combine data from all the large-scale placebo-controlled cardiovascular outcome trials of SGLT2 inhibitors to gain more reliable estimates of the efficacy and safety of specific outcomes overall and in relevant subgroups. Data source: MEDLINE, EMBASE and the Cochrane Library until 7 August 2018 and websites of the US, European and Japanese regulatory authorities until 27 July 2018 for data from RCT of SGLT2 inhibitors that included reporting of effects on biomarkers, cardiovascular, renal or safety outcomes. Risk of bias was assessed by two authors using Cochrane Risk of Bias tool. The biomarkers of interest were: change from baseline in HbA1c, fasting glucose, systolic and diastolic blood pressure, body weight, albuminuria and serum potassium. The main cardiovascular outcome was a composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. Other cardiovascular outcomes were cardiovascular death, fatal or non-fatal myocardial infarction, fatal or nonfatal stroke, hospitalised or fatal heart failure and all-cause mortality. Renal outcomes of interest were: annual mean difference in kidney function between treatment and control (eGFR slope) and a composite of doubling of serum creatinine, ESKD or renal death.	**I**	Twenty-seven studies with up to 7363 patients with T2DM and CKD defined as eGFR <60 mL/min/1.73m^2 Individual trial data were supplemented or substituted, outcome by outcome, with information from pooled analyses when the pooled Analyses provided more data and were clearly identified as not overlapping with another report.	Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin, Ipragliflozin, Luseogliflozin	Placebo	Study duration ranged from 7 days to a median of 4.2 years	**HbA1c (%):** Effect size (95% CI) Canagliflozin: -0.43 (-0.65, -0.21) Dapagliflozin: -0.25 (-0.36, 0.14) Empagliflozin: -0.29 (-0.43, -0.15) **Weight changes (kg):** Effect size (95% CI) Canagliflozin: -1.31 (-1.52, -1.09) Dapagliflozin: -1.50 (-2.02, -0.98) Empagliflozin: -1.38 (-1.72, -1.04) **Systolic blood pressure (mmHg):** Effect size (95% CI) Canagliflozin: -4.19 (-6.49, -1.89) Dapagliflozin: -3.58 (-5.53, -1.62) Empagliflozin: -5.07 (-7.30, -2.85) **Cardiovascular death, non-fatal myocardial infarction or non-fatal stroke:** RR (95% CI) Canagliflozin: 0.70 (0.55, 0.89) Dapagliflozin: 0.86 (0.60, 1.24) Empagliflozin: 0.87 (0.69, 1.11) **EGFR slope:** Effect size (95% CI) Canagliflozin: 1.11 (0.74, 1.48) Empagliflozin: 1.71 (1.08, 2.34) **ESKD, doubling of serum creatinine or renal death:** HR (95% CI) Canagliflozin: 0.81 (0.37, 1.77) Dapagliflozin: 0.70 (0.46, 1.07) Empagliflozin: 0.68 (0.43, 1.09) Authors' conclusion: Currently available data suggest that SGLT2 inhibitors reduce the risk of cardiovascular and renal outcomes in patients with T2DM and CKD, without clear evidence of additional safety concerns; however, the robustness of these findings requires confirmation in upcoming dedicated CKD outcome trials.	Significant heterogeneity (I^2 26-75%) for hypoglycaemia and amputation. This work was not specifically funded but it was supported in part by programme grant funding provided by the National Health and Medical Research Council of Australia, which had no role in study design, data collection, data analysis, data interpretation or writing of the report. Authors declared receiving support/fees from pharmaceutical companies including Astra Zeneca, Boehringer Ingelheim and Janssen.

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
	Differences in treatment effect and standard error for effects in biomarkers were calculated as the mean difference (MD) and standard error (SE) from baseline across the entire follow-up period, or to end of follow-up, pooled by the generic inverse variance method with a random-effects model. In studies with more than two intervention arms (eg, different SGLT2 inhibitor doses), the effects on the continuous outcome for the different doses were combined by weighting with sample size, to obtain a mean overall difference for SGLT2 inhibitor vs placebo. For cardiovascular and renal outcomes, hazard ratios (HR) and 95% CI, or the incidence rate ratio and 95% CI (based upon events/participant years), or the risk ratio (based upon events/participant numbers) were used, in order of preference. When calculating risk ratios in studies comparing different doses, the number of events and participants were combined across active treatment arms and compared to control to obtain an estimate for SGLT2 inhibitor vs placebo. The same was done when data were provided for eGFR subgroups but not for individuals with CKD overall. Risk ratios expressed as relative risks (RR), obtained using a random effects model, were used as the summary measure of association across studies. The percentage of variability across pooled estimates attributable to heterogeneity beyond chance was estimated using the I^2 statistic and also by calculating the P value for heterogeneity. Statistical analyses were performed using R Version 3.4.4 with the package “meta” Version 4.9-1.							

Evidence Table : Effectiveness
Question : What is the clinical effectiveness of SGLT2 inhibitors compared with gliclazide in the treatment of type 2 diabetes mellitus (T2DM)?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
8. Perkovic V, Jardine MJ, Neal B et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019. CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial	**Randomised, double-blind placebo-controlled, multicentre clinical trial** To assess the effects of the SGLT2 inhibitor canagliflozin on renal outcomes in patients with type 2 diabetes and albuminuric chronic kidney disease. Primary outcome • End-stage kidney disease (ESKD): (dialysis for at least 30 days, kidney transplantation, or an eGFR of <15 ml/minute/1.73m^2 sustained for at least 30 days according to central laboratory assessment), doubling of the serum creatinine level from baseline sustained for at least 30 days according to central laboratory assessment, or death from renal or cardiovascular disease. Secondary outcomes: • Cardiovascular death or hospitalization for heart failure; • Cardiovascular death, myocardial infarction, or stroke; • Hospitalization for heart failure; • ESKD, doubling of the serum creatinine level, or renal death • Death from any cause; • Cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure or for unstable angina; • ESKD, renal death, or cardiovascular death • Dialysis, kidney transplantation or renal death All renal and cardiovascular outcomes that were part of the primary and secondary outcomes were adjudicated by independent adjudication committees whose members were unaware of trial-group assignments.	**I**	4401 patients with type 2 diabetes and albuminuric chronic kidney disease All patients had an eGFR of 30 to <90 ml/minute/1.73 m^2 and albuminuria (ratio of albumin [mg] to creatinine [g], >300 to 5000) and were treated with renin–angiotensin system blockade.	Canagliflozin 100mg	Placebo	Median follow-up of 2.62 years	**Primary composite outcome (ESKD, doubling of serum creatinine, renal death or cardiovascular death:** HR (95% CI) In patients with eGFR 30 - <90ml/min/1.73m^2, canagliflozin reduced the risk by 30% [HR 0.70 (0.59, 0.82)]. NNT (95% CI): 22 (15, 38) **Cardiovascular death, myocardial infarction or stroke:** HR (95% CI) In patients with eGFR 30 - <90ml/min/1.73m^2, canagliflozin reduced the risk by 20% [HR 0.80 (0.67, 0.95)]. NNT (95% CI): 40 (23, 165) **Hospitalisation for heart failure:** HR (95% CI) In patients with eGFR 30 - <90ml/min/1.73m^2, canagliflozin reduced the risk by 39% [HR 0.61 (0.47, 0.80)]. NNT (95% CI): 46 (29, 124) **Renal-specific composite outcome of ESKD, doubling of serum creatinine or renal death**: HR (95% CI) In patients with eGFR 30 - <90ml/min/1.73m^2, canagliflozin reduced the risk by 34% [HR 0.66 (0.53, 0.81)]. NNT (95% CI): 28 (19, 54) In patients with eGFR 60 - <90ml/min/1.73m^2, canagliflozin	The trial was supported by Janssen Research and Development. During trial, an increased risk of lower limb amputation was identified in another trial of canagliflozin (CANVAS). A protocol amendment for the present trial in May 2016 asked investigators to examine patients' feet at each trial visit and temporarily interrupt the assigned treatment in patients with any active condition that might lead to amputation. The trial was stopped early after a planned interim analysis on the recommendation of the data and safety

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
	Pre-specified stopping guidance that was provided to the data monitoring committee by the steering committee proposed possible recommendation of early cessation if clear evidence of benefit was observed for the primary outcome (p<0.01) and the composite of ESKD or death from renal or cardiovascular causes (p <0.025), with consideration of the overall balance of risks and benefits. In the intention-to-treat population, a stratified Cox proportional-hazards model was used to analyse the primary and secondary outcomes, according to the category of eGFR at screening. Subgroup analyses were assessed by tests for the interaction between the trial group and the subgroup in stratified Cox proportional hazards models without adjustment for multiple testing. All available measurements were used with no distinction made for missing outcomes for patients who were alive and outcomes that were not observed because of death. The numbers of patients who needed to be treated to prevent one event during 2.5 years (NNT) were calculated as the reciprocal of the between-group difference in cumulative incidence at 2.5 years on the basis of the Kaplan–Meier curve. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute).						reduced the risk by 19% [HR 0.81 (0.52, 1.26)]. In patients with eGFR 45 - <60ml/min/1.73m^2, canagliflozin reduced the risk by 53% [HR 0.47 (0.31, 0.72)]. In patients with eGFR 30 - <45ml/min/1.73m^2, canagliflozin reduced the risk by 29% [HR 0.71 (0.53, 0.94)]. Authors' conclusion: In patients with type 2 diabetes and kidney disease, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group at a median follow-up of 2.62 years.	monitoring committee.

Evidence Table : Safety
Question : Is SGLT2 inhibitors safe compared with glicazide in the treatment of T2DM?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
1. Johnston R, Uthman O, Cummins E et al. Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation. Health Technol Assess. 2017;21(2):1-218.	**Systematic review and network meta-analysis (NMA)** To review the clinical effectiveness and cost-effectiveness of dapagliflozin, canagliflozin and empagliflozin in monotherapy in people who cannot take metformin. Data source: MEDLINE (1946 to February 2015) and EMBASE (1974 to February 2015) Ovid MEDLINE, EMBASE and Web of Science. Studies up to September 2015 were included. Wider range of studies were used for adverse events (AEs). Data for adverse events were obtained from trials and other studies in combination therapy as well as monotherapy. Quality of the RCTs was assessed using the Cochrane risk of bias tool.	**I**	RCTs of monotherapy with minimum duration of 24 weeks or more in people with type 2 diabetes unable to take metformin; baseline HbA1c of 7.5% or more; and dropout rates of no more than 20%. Canagliflozin: 2 trials • 100mg (n=285) • 300mg (n=197) Dapagliflozin: 3 trials • 10mg (n=367) Empagliflozin: 2 trials • 10mg (n=356) • 25mg (n=357)	Canagliflozin 100mg & 300mg, Dapagliflozin 10mg, Empagliflozin 10mg & 25mg	Placebo	24 – 102 weeks	Given the infrequency of reported hypoglycaemia, the similarities of the frequencies of hypoglycaemia inactive and placebo arms, and the cut-off level used, the assessment group (AG) considered it reasonable to assume that SGLT2 inhibitors do not cause hypoglycaemia. Main AEs were urinary tract infections (UTIs) and genital area infections (GTIs). The urogenital infections were more common in women, generally mild to moderate in severity and amenable to standard treatment. Canagliflozin was associated with a slightly higher incidence of UTIs (1.1% - 8.2%) versus placebo (1.1% - 6.3%) and higher incidence of GTIs (1.1% - 9.2%) versus placebo (1.1% - 2.6%). Dapagliflozin was associated with a higher incidence of UTIs (2.3% - 8.6%) versus placebo (2.3% - 4.0%) and GTIs (2.3% - 15.7%) versus placebo (0.8% - 1.3%). Empagliflozin was associated with a similar incidence of UTIs (5.4% - 9.4%) versus placebo (5.2% - 11.0%) and higher incidence of GTIs (3.1% - 6.3%) versus placebo (0% - 1.8%). There were concerns following reports of diabetic ketoacidosis (DKA) and bone loss. DKA appeared rare – about 1 per 5000 patient-years in patients treated with SGLT2 inhibitors. The risk of fracture was small but increased by around 30% in people taking canagliflozin. The incidence per 1000 patient-years was 18.1 for canagliflozin versus 14.2 for other regimens. Eight of 85 (9.4%) people on dapagliflozin 10 mg suffered fractures, compared with none on placebo. Fractures were not increased after three years of empagliflozin treatment in the empagliflozin outcomes trial. Authors' conclusion: The safety record of SGLT2 inhibitors remained to be established. Common adverse effects were urinary and genital tract infections in a small proportion of users which were seldom serious. Continued monitoring for DKA and fractures was required.	

Evidence Table : Safety
Question : Is SGLT2 inhibitors safe compared with glicazide in the treatment of T2DM?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
2. Mearns ES, Sobieraj DM, White CM et al. Comparative efficacy and safety of antidiabetic drug regimens added to metformin monotherapy in patients with type 2 diabetes: a network meta-analysis. PloS One. 2015;10(4):1-28	**Systematic review and network meta-analysis (NMA)** To assess the efficacy and safety of adjunctive antidiabetic agents in patients with inadequately controlled T2DM on metformin alone. Data source: MEDLINE and Cochrane CENTRAL, ClinicalTrials.gov, regulatory websites. Validity assessment was performed using Cochrane Risk of Bias Tool. The proportion of patients experiencing confirmed hypoglycemia, UTI and GTI on each drug therapy was meta-analysed using a random-effects model as dichotomous endpoints with weighted averages reported as relative risks (RRs) and associated 95% CIs. When at least 3 studies making same direct comparison were available, the likelihood of statistical heterogeneity (I^2) and publication bias (Egger's weighted regression) were assessed. Random-effects NMA was performed using the package 'netmeta' (version 0.5–0) in R (version 3.0.2). Clinical superiority was regarded when one therapy improved HbA1c, BW or SBP by at least 0.3%, 2.3 kg or 5 mmHg, respectively, versus a competitor. Sensitivity analyses calculating more conservative 99%Cis were performed to address the inherent limitations of multiple comparisons in the meta-analysis.	**I**	Sixty-two RCTs (n=32,185) evaluating 25 agents were included. Adult patients (≥18 years) with T2DM who showed inadequate response to stable, optimized metformin monotherapy at randomisation (≥1500 mg daily or maximally tolerated dose for ≥4 weeks) before randomisation. Canagliflozin: n=1,831 Dapagliflozin: n=495 Empagliflozin: n=1,617 Gliclazide: n=1,259	Canagliflozin 100mg & 300mg Dapagliflozin 2.5-10mg Empagliflozin 10mg & 25mg	Gliclazide 80-320mg	Mean trial duration: 29 (12-52) weeks	In terms of NMA estimate for confirmed hypoglycaemia in RR (95% CI), SGLT2 inhibitors were not associated with an increased risk. Gliclazide was associated with significantly higher risk compared with SGLT2 inhibitors. • Canagliflozin: 0.91 (0.33, 2.51) • Dapagliflozin: 0.97 (0.34, 2.76) • Empagliflozin: 0.51 (0.17, 1.49) • Gliclazide: 10.02 (2.07, 48.56) In terms of NMA estimate for UTI in RR (95% CI), no treatment was associated with an increased risk of UTI. No UTI data was reported for gliclazide. • Canagliflozin: 1.25 (0.78, 2.00) • Dapagliflozin: 1.28 (0.77, 2.14) • Empagliflozin: 0.86 (0.57, 1.30) In terms of NMA estimate for GTI in RR (95% CI), canagliflozin and empagliflozin were associated with an increased risk. No GTI data was reported for gliclazide. • Canagliflozin: 8.03 (2.44, 26.39) • Dapagliflozin: 2.16 (0.97, 4.82) • Empagliflozin: 6.84 (1.92, 24.37) Authors' conclusion: The SGLT2 inhibitors was found to provide similar HbA1c efficacy to other non-insulin monotherapies with the added benefits of weight loss, reduced SBP and a low risk of hypoglycemia; but at a cost of an increased risk of GTI.	I^2 for trials involving canagliflozin, dapagliflozin, empagliflozin and gliclazide <50%. I^2>50% represents important statistical heterogeneity

Evidence Table : Safety
Question : Is SGLT2 inhibitors safe compared with glicazide in the treatment of T2DM?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
3. Maloney A, Rosenstock J, Fonseca V. A Model-Based Meta-Analysis of 24 Antihyperglycemic Drugs for Type 2 Diabetes: Comparison of Treatment Effects at Therapeutic Doses. Clin Pharmacol Ther. 2019:1-19.	**Systematic review and model-based meta-analysis** To compare glycemic control, weight changes, and hypoglycemia risk across 24 antihyperglycemic drugs used to treat type 2 diabetes. Data source: Medline (via Pubmed), ClinicalTrials.gov, FDA summary basis of approval documents and drug labels, and sponsor websites. For hypoglycemia analysis, relative risk (RR) versus placebo was calculated using the hypoglycaemia category "documented" as the reference category. All drug regimens are displayed with the total daily dose, implicitly assuming standard treatment regimens. All analyses were conducted with the use of SAS software, version 9.4 (SAS Institute). The models were developed using data up to November 15, 2017.	**I**	A total of 229 RCTs including 121,914 patients with T2D were identified. Exclusion criteria: studies run primarily in Asia, studies in special type 2 diabetes populations (hypertensive, obese, renally impaired, high cardiovascular risk, elderly and paediatric), studies with insulin background treatment, studies with sulphonylurea background treatment (for hypoglycemia analysis only), single arm studies, combination treatment arms, and phase I studies. Canagliflozin: [n=3,928 (3.2%)] Dapagliflozin: [n=4,019 (3.3%)] Empagliflozin: [n=4,932 (4.0%)] Gliclazide: [n=3,172 (2.6%)]	Canagliflozin 100mg & 300mg, Dapagliflozin 5mg & 10mg, Empagliflozin 10mg & 25mg	Gliclazide 80-320mg	26 weeks Change in drug effect due to duration was taken into account, increasing (nonlinearly) from 0% at week 0 to 100% (full effect) at week 26.	Hypoglycemia risk versus placebo (RR) for SGLT2 inhibitors was generally very low compared to gliclazide. • Canagliflozin 100mg: 1.4 • Canagliflozin 300mg: 1.4 • Dapagliflozin 5mg: 1.0 • Dapagliflozin 10mg: 1.0 • Empagliflozin 10mg: 1.0 • Empagliflozin 25mg: 1.0 • Glicazide 80-320mg: 3.6 Authors' conclusion: Important differences between and within drug classes were identified.	Authors disclosed receiving consulting fees from pharmaceutical companies including Astra Zeneca, Boehringer Ingelheim and Janssen.

Evidence Table : Safety
Question : Is SGLT2 inhibitors safe compared with glicazide in the treatment of T2DM?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
4. Zelniker TA, Wiviott SD, Raz I et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019;393(10166):31-39.	**Systematic review and meta-analysis (MA)** To combine data from all the large-scale placebo-controlled cardiovascular outcome trials of SGLT2 inhibitors to gain more reliable estimates of the efficacy and safety of specific outcomes overall and in relevant subgroups. Data source: PubMed & Embase for trials published up to September 2018. Risk was bias was assessed using Cochrane Risk of Bias tool. Safety endpoints include lower limb amputation, fractures and DKA. Hazard ratios (HRs) with 95% CIs were pooled across trials using fixed effects models. Heterogeneity was assessed using Cochrane Q statistic and I^2. Statistical analyses were done using R version 3.5.1 and the R package metaphor version 2.0-0.	**I**	34,422 patients from 3 trials of randomised, placebo-controlled cardiovascular outcome trials were included. Canagliflozin: one trial (CANVAS) n = 10,142 Dapagliflozin: one trial (DECLARE-TIMI) n = 17,160 Empagliflozin: one trial (EMPA-REG) n = 7,020	Canagliflozin 100mg & 300mg, Dapagliflozin 10mg, Empagliflozin 10mg & 25mg	Placebo	Median follow-up time: Canagliflozin: 2.4 years Dapagliflozin: 4.2 years Empagliflozin: 3.1 years	**DKA** Dapagliflozin showed an increased risk of DKA [HR 2.18 (95% CI 1.10, 4.30). However, the event rates for all SGLT2 inhibitors were low (<one per 1000 patient-years). **Lower limb amputation & fractures** Canagliflozin showed an increased risk of lower limb amputation (HR 1.97 (95% CI 1.41, 2.75) and fractures (HR 1.26 (95% CI 1.04, 1.52). Authors' conclusion: Overall, SGLT2 inhibitors were well tolerated and generally safe drugs. SGLT2 inhibitors appeared to increase the risk of DKA, but the rates were very low and risk could be reduced with proper patient education and vigilance. An increased risk of amputation and fracture was seen only in one trial.	Authors declared receiving grants/fees from pharmaceutical companies including Astra Zeneca, Boehringer Ingelheim and Janssen.

Evidence Table : Safety
Question : Is SGLT2 inhibitors safe compared with glicazide in the treatment of T2DM?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
5. 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 and Metab. 2019.	**Systematic review and meta-analysis (MA)** To combine data from all the large-scale placebo-controlled cardiovascular outcome trials of SGLT2 inhibitors to gain more reliable estimates of the efficacy and safety of specific outcomes overall and in relevant subgroups. Data source: MEDLINE, EMBASE and the Cochrane Library until 7 August 2018 and websites of the US, European and Japanese regulatory authorities until 27 July 2018 for data from RCT of SGLT2 inhibitors that included reporting of effects on biomarkers, cardiovascular, renal or safety outcomes. Risk of bias was assessed by two authors using Cochrane Risk of Bias tool. Safety outcomes of interest were: UTI, GTI, hypovolaemia, hypoglycaemia, amputation, bone fracture, ketoacidosis, renal-related adverse events, acute kidney injury and hyperkalaemia. The definition of many of these safety outcomes, particularly hypovolaemia and renal-related adverse events, was dependent on the reports and, therefore, was difficult to establish; thus, direct comparability of definitions for most safety outcomes could not be assured. Hazard ratio (HR) and 95% CI, or the incidence rate ratio and 95% CI (based upon events/participant years), or the risk ratio (based upon events/participant numbers) were used, in order of	**I**	Twenty-seven studies with up to 7363 patients with T2DM and CKD defined as eGFR <60 mL/min/1.73m^2 Individual trial data were supplemented or substituted, outcome by outcome, with information from pooled analyses when the pooled Analyses provided more data and were clearly identified as not overlapping with another report.	Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin, Ipragliflozin, Luseogliflozin	Placebo	Study duration ranged from 7 days to a median of 4.2 years	**Hypoglycaemia:** RR (95% CI) Canagliflozin: 1.51 (1.10, 2.07) Dapagliflozin: 1.01 (0.81, 1.26) Empagliflozin: 0.82 (0.72, 0.93) **UTI:** RR (95% CI) Canagliflozin: 0.84 (0.57, 1.24) Dapagliflozin: 0.94 (0.59, 1.50) Empagliflozin: 1.12 (0.94, 1.34) **GTI**: RR (95% CI) Canagliflozin: 1.60 (0.44, 5.89) Dapagliflozin: 3.94 (1.54, 10.09) Empagliflozin: 3.93 (2.05, 7.53) **DKA:** RR (95% CI) Canagliflozin: 3.43 (0.39. 29.88) Empagliflozin: 1.50 (0.22, 10.24) **Fracture:** RR (95% CI) Canagliflozin: 1.14 (0.78, 1.66) Dapagliflozin: 1.72 (0.03, 105.92) Empagliflozin: 0.84 (0.57, 1.24) **Amputation**: RR (95% CI) Canagliflozin: 2.17 (1.14, 4.10) Empagliflozin: 0.89 (0.52, 1.53) **Acute kidney injury:** RR (95% CI) Canagliflozin: 0.86 (0.17, 4.31) Dapagliflozin: 0.65 (0.43, 0.96) Empagliflozin: 0.60 (0.41, 0.88) Authors' conclusion: Currently available data suggest that SGLT2 inhibitors reduce the risk of cardiovascular and renal outcomes in patients with T2DM and CKD, without clear evidence of additional safety concerns; however, the robustness of	Significant heterogeneity (I^2 26-75%) for hypoglycaemia and amputation. This work was not specifically funded but it was supported in part by programme grant funding provided by the National Health and Medical Research Council of Australia, which had no role in study design, data collection, data analysis, data interpretation or writing of the report. Authors declared receiving support/fees from pharmaceutical companies including Astra Zeneca, Boehringer Ingelheim and

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	preference. When calculating risk ratios in studies comparing different SGLT2 inhibitor doses, the number of events and participants were combined across active treatment arms and compared to control to obtain an estimate for SGLT2 inhibitor vs placebo or active control. The same was done when data were provided for eGFR subgroups but not for individuals with CKD overall. Wherever possible, trial level data were used. Risk ratios expressed as relative risks (RR), which were obtained using a random effects model, were used as the summary measure of association across studies. The percentage of variability across pooled estimates attributable to heterogeneity beyond chance was estimated using the I^2 statistic and also by calculating the P value for heterogeneity. Statistical analyses were performed using R Version 3.4.4 with the package "meta" Version 4.9-1.						these findings requires confirmation in upcoming dedicated CKD outcome trials.	Janssen.

Evidence Table : Safety
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6. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJ, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019. CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial	**Randomised, double-blind placebo-controlled, multicentre clinical trial** To assess the effects of the SGLT2 inhibitor canagliflozin on renal outcomes in patients with type 2 diabetes and albuminuric chronic kidney disease. Safety evaluations included laboratory testing and assessments of adverse events. All renal and cardiovascular outcomes that were part of the primary and secondary outcomes, as well as key safety outcomes (fractures, pancreatitis, ketoacidosis, and renal-cell carcinoma), were adjudicated by independent adjudication committees whose members were unaware of trial-group assignments. Pre-specified stopping guidance that was provided to the data monitoring committee by the steering committee proposed possible recommendation of early cessation if clear evidence of benefit was observed for the primary outcome (p<0.01) and the composite of ESKD or death from renal or cardiovascular causes (p <0.025), with consideration of the overall balance of risks and benefits. All available measurements were used with no distinction made for missing outcomes for patients who were alive and outcomes that were not observed because of death. The data set for all treated patients through 30 days after the last dose was used for the safety analyses (on-treatment analysis) and the on-study analysis that included all treated patients through the end of the trial was used to evaluate selected	**I**	4401 patients with type 2 diabetes and albuminuric chronic kidney disease All patients had an eGFR of 30 to <90 ml/minute/1.73 m^2 and albuminuria (ratio of albumin [mg] to creatinine [g], >300 to 5000) and were treated with renin–angiotensin system blockade.	Canagliflozin 100mg	Placebo	Median follow-up of 2.62 years	**DKA** Canagliflozin group showed an increased risk of DKA [HR 10.80 (1.39, 83.65)]. **Amputation** Canagliflozin group was not associated with increased risk of amputation [HR 1.11 (0.79, 1.56). **Fracture** Canagliflozin group was not associated with increased risk of fracture [HR0.98 (0.70, 1.37)]. **Acute kidney injury** Canagliflozin group was not associated with increased risk of acute kidney injury [HR 0.85 (0.64, 1.13)]. Authors' conclusion: In patients with type 2 diabetes and kidney disease, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group at a median follow-up of 2.62 years.	The trial was supported by Janssen Research and Development. During the trial, an increased risk of lower limb amputation was identified in another trial of canagliflozin (CANVAS). A protocol amendment for the present trial in May 2016 asked investigators to examine patients' feet at each trial visit and temporarily interrupt the assigned treatment in patients with any active condition that might lead to amputation. The trial was stopped early after a planned interim analysis on the recommendation of the data and

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	adverse events, including cancer, amputation, and fracture. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute).							safety monitoring committee.

Evidence Table : Cost-effectiveness
Question : Is SGLT2 inhibitors cost-effective compared with gliclazide in the treatment of T2DM?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments

1. Johnston R, Uthman O, Cummins E et al. Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation. Health Technol Assess. 2017;21(2):1-218.	**Cost-effectiveness analysis** To review the cost-effectiveness of canagliflozin, dapagliflozin and empagliflozin in people with type 2 diabetes. Cost-effectiveness modelling was done using United Kingdom Prospective Diabetes Study outcome model version 1 (UKPDS OM1). Systematic review and NMA were conducted. Bayesian statistical methods with fixed effects model was used to synthesise effectiveness evidence from RCTs. The model considered patient's progression from monotherapy through various treatment intensifications over a 40-year time horizon in annual cycles, taking into consideration the patient's evolutions of HbA1c, SBP, TC/HDL, body mass index (BMI), hypoglycaemia event rates, adverse events (including UTI and GTI) and treatment costs. Complications of diabetes (MI, IHD, stroke, CHF, amputation, blindness and renal failure) were considered. Outcomes were expressed in terms of quality adjusted life years (QALYs). Costs were considered from the perspective of the UK NHS and Personal Social Services, using 2014 prices, with costs and benefits discounted at 3.5% per year. Probabilistic results were based upon 1000 probabilistic sensitivity analyses (PSA) iterations, each with a patient cohort of 50,000 with 100 inner loops. All scenario analyses were run deterministically with a cohort of 50,000 patients and 1000 inner loops to reduce Monte Carlo error.	**I**	Adult patients with type 2 diabetes, unable to take metformin starting monotherapy. NICE clinical guideline baseline risk factors (59.8 years old, 57% male, duration of diabetes for 2 years, HbA1c 8.40%, BMI 31.9kg/m^2) and baseline complication rates were applied.	Canagliflozin 100 mg, dapagliflozin 10 mg, empagliflozin 10 mg, empagliflozin 25 mg,	Gliclazide MR		**Base-case estimates:** Gliclazide was the least expensive, with total costs of £27,314. Canaglilfozin 300mg, dapagliflozin 10mg and empagliflozin 25mg were £5362, £5552 and £5,461 more expensive than gliclazide, respectively. If there were no direct quality of life (QoL) impacts from weight changes, lifetime QALYs arising from diabetes, its complications and adverse events were highest for gliclazide at 10.392 QALYs. Gliclazide was estimated to be superior to canagliflozin, dapagliflozin and empagliflozin by 0.012, 0.025 and 0.014 QALYs, respectively. Therefore, gliclazide dominated all treatments. Including direct QoL impacts from weight changes and assuming that monotherapy weight changes were retained over the patient lifetime, canagliflozin, dapagliflozin and empagliflozin would yield an additional 0.147, 0.101, 0.114 QALYs compared with gliclazide. If weight losses rebound after one year, then canagliflozin, dapagliflozin and empagliflozin would yield an additional 0.058, 0.038, 0.050 QALYs compared with gliclazide. The AG results showed some sensitivity to whether patients add insulin to their existing treatments or switch to it, the application of a common 7.5% HbA1c baseline and applying a reduced –0.47% HbA1c effect for gliclazide. Authors' conclusion: The AG modelling results suggested that dapagliflozin, canagliflozin and empagliflozin were not cost-effective compared with gliclazide.	The OM1 predicts roughly double the number of MIs over 10 years, and higher rates of IHD and 10-year mortality than those of the OM2. OM1 will tend to over-predict event rates and so overstate the benefits and cost savings arising from any avoidance of the complications of diabetes that are associated with the more effective treatment. DKA, fractures, cost savings from reduced ASCVD, hospitalisation for heart failure and progression of renal disease were not incorporated into the model.