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REVIEW

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Recent developments in adjunct therapies for type 1 diabetes

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ABSTRACT

Introduction: There have been many recent advances in the treatment of type 1 diabetes (T1D) including in insulin formulations, continuous glucose monitoring (CGM) technology and automated insulin delivery. However, long-term optimal glycemic control is still only achieved in a minority.

Areas covered: Adjunct therapy – the use of therapeutic agents other than insulin – is one strategy aimed at improving outcomes. An ideal adjunct agent would improve glycemic control, reduce weight (or weight gain), reduce insulin requirement and prevent complications (e.g. cardiorenal) without increasing hypoglycemia. The amylin analogue pramlintide has been licensed in the USA, while the sodium glucose co-transporter-2 inhibitor (SGLT2i) dapagliflozin, was briefly (2019 – 2021) licensed for type 1 diabetes in Europe and the UK. However, other agents from the type 2 diabetes (T2D) arena including metformin, other SGLT2is, glucagon-like peptide-1 receptor agonists (GLP-1RA) and dipeptidyl peptidase-IV (DPP-4) inhibitors have been investigated.

Expert opinion: As evidence emerges for cardiorenal protection by SGLT2is and GLP-1RAs in T2D, it has become increasingly important to know whether people with T1D can also benefit. Here, we review recent trials of adjunct agents in T1D and discuss the efficacy and safety of these agents (alone and in combination) in an era in which continuous glucose monitoring is becoming standard of care.

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1. Introduction

One hundred years on from the first therapeutic use of insulin, type 1 diabetes (T1D) remains a lifelong condition associated with microvascular (retinopathy, neuropathy, nephropathy) and macrovascular (myocardial infarction, stroke, peripheral vascular disease) complications. These can be delayed or prevented by maintaining blood glucose parameters as near to normal as possible [1–4]. Internationally agreed targets for optimal glycemic control have been established [5,6], but on a population-wide basis are attained in only a minority of individuals, even within the healthcare systems of high-income countries [7]. In Scotland, UK, where there is near 100% case ascertainment, people with T1D have a life expectancy 11–13 years shorter than unaffected individuals. The commonest cause of premature mortality over 40 years old in T1D is cardiovascular death while in those under 40 years of age primary metabolic complications of diabetes including diabetic ketoacidosis and hypoglycemia are the commonest cause [8–10].

A complex interaction of physiological, psychological, and socio-economic barriers and challenges to achieving optimal glycemia are at play in everyday life, so improvements (or greater convenience) in devices for insulin delivery, insulin formulations (time:action profile) or glucose self-monitoring are obvious enabling strategies. Flash and continuous glucose monitoring technology have been demonstrated to be associated with improved glycemic control [11–13] and are rapidly becoming standard of care for people with T1D [6,14–17]. Hybrid closed-loop systems are also emerging into routine clinical practice. However, the evidence to date from nation-wide epidemiology in Scotland is that the impact of these innovations to date has been quite modest [18].

Another key barrier to achieving target glycemic control in a significant proportion of those with established T1D is 'double diabetes' in which there is 1) marked weight gain over time; 2) a high and increasing daily insulin requirement; 3) a positive family history of type 2 diabetes (T2D), particularly when two or more relatives are affected; and/or 4) a low eGDR (estimated glucose disposal rate). Affected individuals may have high normal BP (or hypertension) and relatively low HDL-C. Double diabetes has been estimated – depending on the definition – to be present in up to 50% of people with T1D [19–22]. Insulin-induced weight gain over time is an important driver of this process. Genetic factors are also likely to be implicated. A recent analysis examined 16,200 individuals in the T1D Exchange Clinic Registry. In people with familial T1D (at least one affected first degree relative) compared to sporadic T1D (no affected first-degree relatives) the incidence of hypertension, hyperlipidemia, atherosclerosis and retinopathy/maculopathy were significantly higher [23].

1.1. Background

Obvious candidates for adjunct therapy in T1D are agents used in T2D, particularly sodium glucose co-transporter-2

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Table 1. Properties of an ideal adjunct therapy in type 1 diabetes.

- HbA1c reduction*
- weight reduction*
- reduction in total daily insulin dose *
- no increase in hypoglycemia/ other unwanted effects
- improved cardiovascular/renal outcomes

Clinically-significant

inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs). Following large-scale cardiovascular outcome trials, these are now well established to provide weight reduction as well as cardiovascular and renal benefits. In the case of SGLT2is, robust improvements in renal and heart failure outcomes have even been observed in individuals without diabetes – so whether people with T1D could also benefit is an important unanswered question [24]. However, use of such therapies in T1D is associated with a specific set of risks, principally hypoglycemia and ketosis which must be counterbalanced with the anticipated benefits [25].

Here, we examine the current evidence base for several individual drug classes when used as adjunct therapies in T1D, alone and in combination. As many of the trials were conducted before the advent of widespread continuous glucose monitoring (and self-monitoring of blood ketones), we will also consider whether these changes in standard of care may provide a more favorable balance of efficacy and safety for some of these agents.

2. Individual agents

An 'ideal' adjunct therapy agent in T1D would fulfill certain criteria (Table 1). Below we consider the evidence to date for the various candidate agents with reference to these properties.

2.1. Pramlintide

This is the only adjunct agent currently licensed in T1D in the USA (from 2005 but not to date in Europe) and is marketed as Symlin [5,26]. It is a synthetic analogue of Amylin (otherwise known as islet amyloid polypeptide – IAPP), a 37 amino acid peptide co-secreted with insulin from pancreatic β-cells [27]. Amylin has at least four sets of actions that synergize with insulin to reduce postprandial glycemic excursions: 1) enhancing post-prandial satiety via central mechanisms thereby reducing caloric intake; 2) reducing dysfunctional glucagon secretion by pancreatic α-cells; 3) delaying gastric emptying (often dysfunctionally fast in diabetes); and 4) reducing hepatic glucose production [25,26]. In both T1D and T2D, endogenous physiological secretion of amylin is reduced [27].

Pramlintide is therefore administered as a subcutaneous injection three or four times daily prior to major meals. The usual starting dose in T1D is 15 micrograms per meal with up-titration to 30 or 60 micrograms (higher doses can be used in T2D) [26]. This clearly adds to the injection burden for individuals who are already taking multiple daily injections. Gastrointestinal (nausea, abdominal pain) as well as headache and fatigue are common adverse effects. Hypoglycemia – as with other adjunct therapies – is also an important consideration when pramlintide is administered with insulin and in clinical practice insulin down-titration is often required [26,28].

The evidence supporting the use of pramlintide is primarily from three randomized controlled trials in T1D which have demonstrated modest glycemic benefits with HbA1c reduced by 0.3–0.4% (3–4 mmol/mol). There was also consistent evidence of weight loss of approximately 1 kg and a reduction in total daily insulin dosing of 6–12%. As such, pramlintide does appear to meet several of the desirable criteria for an adjunct agent [29–31]. However, disadvantages include an appreciable excess risk of hypoglycemia in the early months of use, adverse effects and an acquisition cost of approx. $2700 per month. Uptake has remained low over the last 17 years in the United States [29–32].

2.2. Metformin

Despite the emergence of newer agents, metformin remains a longstanding cornerstone of the management of T2D [33,34]. Although the full extent of its mechanisms of action remain incompletely understood [35], a key effect is reducing hepatic gluconeogenesis via activation of the cellular energy receptor AMPK with secondary inhibition of mitochondrial respiration, and an associated increase in whole body insulin sensitivity [35]. In several trials in T2D, including the UKPDS and HOME, it has been associated with reduced rates of major adverse cardiovascular outcomes, particularly myocardial infarction [36,37].

Use as an adjunct therapy in T1D was first investigated in the 1980s in various small and inconclusive studies measuring insulin sensitivity using the euglycaemic hyperinsulinaemic clamp technique. When the topic was taken up again in the 2000s, several small studies in adolescents and adults demonstrated reductions in weight and total daily insulin dose requirement but no consistent effect on HbA1c [38].

In the UK in 2015, on the basis of a meta-analysis of the available small trials, NICE (the National Institute of Health and Care Excellence) recommended consideration of metformin for adults with T1D who wished to improve their glycemic control while also limiting their total daily insulin dose. In particular, this was recommended for those with a BMI (Body Mass Index) >25 kg/m^2 (or >23 kg/m^2 in those from a South Asian background, i.e. a group likely to have features of 'double diabetes') [6].

Around the same time, the TID Exchange Trial examined metformin vs. placebo in 140 overweight adolescents with T1D. Modest reductions in insulin dose requirement and weight were observed with active treatment; however, the authors concluded that metformin could not be recommended for such individuals, highlighting significant rates of adverse gastrointestinal effects [39].

The REMOVAL trial was a placebo-controlled, double-blind, multi-site international trial of metformin vs placebo for 36 months in 428 adults with T1D (over the age of 40 years) with three or more pre-specified cardiovascular risk factors. Baseline mean HbA1c was 8.1% (65 mmol/mol) [SD 0.9] for metformin and 8.0% (64 mmol/mol) [0.8] for placebo. It

remains the largest and longest duration trial of metformin as adjunct therapy and the only one to incorporate a cardiovascular outcome of any type. The primary outcome was progression of mean far wall carotid intima media thickness (cIMT) as a surrogate for atherosclerosis progression, with maximal far wall cIMT (which does not exclude plaque) also pre-specified as a tertiary outcome. Of note, while the main results demonstrated no difference between active and placebo medication for the primary cIMT outcome, the tertiary maximal far wall cIMT outcome was reduced by metformin. This provides some proof of concept for a beneficial cardiovascular effect of metformin in T1D; interestingly the primary cIMT outcome was also reduced in nonsmokers as a subgroup [40]. Other benefits associated with metformin included weight loss of 1.17 kg ($p < 0.0001$), reduction in LDL cholesterol (−0.13 mmol/L $p = 0.012$) (secondary outcomes) and a reduction in insulin dose requirement by 2 units per day ($p = 0.045$; *post hoc* analysis) [41].

Guidelines published since the results of these two most recent trials have not advocated metformin in T1D [5,6]. It remains licensed for use in T1D only in France but is prescribed in a significant minority of people in other countries 'off label.' For example, in a cross-sectional interrogation of electronic health records in Scotland, 8% of people with T1D were currently prescribed metformin and 15% had been prescribed it previously [38].

Meanwhile, the focus in the adjunct therapy space has turned to other more recently introduced 'T2D' molecules for repurposing.

2.3. DPP-4 inhibitors

The incretins GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are released from the small intestine in response to a meal. Both promote glucose-dependent insulin secretion and GLP-1 is known to inhibit glucagon release in the absence of hypoglycemia [42]. GLP-1 and GIP are enzymatically inactivated by dipeptidyl peptidase-4 (DPP-4); over the last fifteen years oral inhibitors of this enzyme have become established in the management of T2D [43,44]. Large clinical trials have confirmed the safety profile of DPP-4 inhibitors, and their beneficial effect on HbA1c, although they do not confer weight loss or cardiovascular benefits [45–47].

Several small randomized control trials have been conducted to investigate the use of DPP-4 inhibitors in T1D and a meta-analysis of these has been undertaken by Guo et al. [48] Six eligible studies (four double-blind and two open-label) using different agents and targeting different study populations (sample size ranging from n = 14 to n = 125), over 4 to 52 weeks were included. No change in HbA1c was detected (weighted mean difference −0.00 [−0.16, 0.15] units/day, $p = 0.97$). However, across five studies that reported insulin dose, there was a small but significant reduction (weighted mean difference −2.41 units/day [−3.87;-0.94], $p = 0.001$). Overall, the quality of evidence to support efficacy of DPP-4 inhibitors for T1D was felt to be low due to inconsistency in study design and small sample size [48]. Ultimately, current evidence is insufficient to provide proof of concept for larger scale investigations.

2.4. SGLT2 inhibitors

SGLT2 inhibitors were first licensed for use in T2D in 2013. They act by inhibiting physiological reabsorption of glucose in renal proximal convoluted tubules by this specific transporter protein. Therapy with oral SGLT2is leads to glycosuria with an associated reduction in blood glucose and loss of approximately 200 kcal/day (as well as a modest osmotic diuresis). Several SGLT2 inhibitors are licensed for use in T2D in Europe and North America including dapagliflozin, empagliflozin, canagliflozin and ertugliflozin [49].

Overwhelming evidence from landmark cardiovascular outcome trials has accumulated, confirming reduced rates of major adverse cardiovascular outcomes with SGLT2 inhibitors in T2D, heart failure (both reduced and preserved ejection fraction) and chronic kidney disease (CKD) [22,50–53]. Beneficial effects on clinically relevant renal and heart failure outcomes (including mortality) have been clearly demonstrated, even in those without diabetes [49–56].

Eight double-blind clinical trials have examined the SGLT2 inhibitors dapagliflozin, sotagliflozin, empagliflozin, canagliflozin and ipragliflozin in T1D (Table 2). Sotagliflozin is considered a combined SGLT1 and SGLT2 inhibitor as it targets both renal SGLT2 and gastrointestinal SGLT1 albeit still with 20-fold affinity for SGLT2 vs SGLT1 (by contrast the respective fold affinities for SGLT2 vs SGLT1 for canagliflozin and empagliflozin are >250 and >2500) [57].

The Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes (DEPICT) programme investigated dapagliflozin as an adjunct agent in T1D. DEPICT-1 and DEPICT-2 were conducted in different geographic areas but had similar designs by which participants with sub-optimal glycemic control were randomized over 24 weeks (following an 8-week run in period) 1:1:1 to dapagliflozin 10 mg daily, dapagliflozin 5 mg daily or placebo in addition to their usual insulin therapy. This was followed by a 28-week extension period. Mean baseline HbA_{1c} was 8 · 53% (70 mmol/mol) in DEPICT-1 and 8.43% (68 mmol/mol) in DEPICT-2. In 833 and 815 participants respectively, DEPICT 1 and 2 demonstrated respective reductions in HbA1c of 0.33% (95% CI −0.49%, −0.17) and 0.20% (CI −0.34, −0.06) for 5 mg and 0.36% (CI −0.53, −0.20) and 0.25% (CI −0.38, −0.11) for 10 mg dapagliflozin. There was a reduction in body weight of 2.45 kg, 2.91 kg for the 5 mg and 10 mg doses, respectively, at 52 weeks. Hypoglycemia was not significantly increased [58–60].

The EASE programme (Empagliflozin as adjunctive to Insulin Therapy) comprised one Phase 2 clinical trial (EASE 1) and two Phase 3 trials examining the role of the SGLT2 inhibitor empagliflozin as an adjunct therapy. In addition to the doses of 10 and 25 mg daily as marketed in T2D, a lower 2.5 mg dose was also examined in EASE 3. Baseline mean HbA1c was 8.1–8.2% (65–66 mmol/mol). As with DEPICT, the EASE trials demonstrated modest (point estimate) reductions in HbA1c of 0.54% (week 26) and 0.45% (week 52) with empagliflozin 10 mg and 25 mg in EASE-2 and EASE-3 (0.52% (week 26)) but a more modest reduction of 0.28% with empagliflozin 2.5 mg in EASE-3. Body weight (point estimates) was reduced with the 2.5, 10 and 25 mg doses by

Table 2. Phase 3 SGLT2 inhibitor trials: summary of main results.

Trial Name	Drug	Participants & Trial duration	HbA1c change (%)	Total daily insulin dose change (%)	Weight change (kg)	Severe Hypo-glycemia* † (%)	DKA Rate † (%)
DEPICT-1	Dapagliflozin	833	−0.46	−5.5	−2.98	6.4	1.7
	10 mg	24 weeks	−0.48	−9.8	−2.29	7.6	1.4
	5 mg					7.3	1.2
	Placebo						
DEPICT-2	Dapagliflozin 10 mg	815	−0.42	−11.1	−3.74	8.4	2.6
	5 mg	24 weeks	−0.37	−10.8	−3.21	10.5	2.2
	Placebo					11.5	0
EASE 1	Empagliflozin25 mg	75	−0.49	−0.08**	−1.9	0.0	0
	10 mg	28 days	−0.36	−0.09**	−1.8	0.0	0
	2.5 mg		−0.35	−0.07**	−1.5	0.0	0
	Placebo					5.3	
EASE 2	Empagliflozin 25 mg	730	−0.45	−12.9	−3.6	Pooled Data	Pooled data
	10 mg	52 weeks	−0.37	−12	−3.2	2.7	3.3
	Placebo					4.1	4.3
EASE 3	Empagliflozin25 mg	975	−0.50	−12.6	−3.4	3.1	1.2
	10 mg	26 weeks	−0.44	−9.5	−3.0	1.2	0.8
	2.5 mg		−0.27	−6.4	−1.8		
	Placebo						
NCT 02139943	Canagliflozin 300 mg	351	−0.25	12.9	−4.2	6.8	6.0
	100 mg	18 weeks	−0.29	8.9	−2.6	2.6	4.3
	Placebo					1.7	0
inTANDEM-1	Sotagliflozin 400 mg	793	−0.31	−12.6	−4.43	6.5	4.2
	200 mg	52 weeks	−0.25	−8.0	−3.14	6.5	3.4
	Placebo					9.7	0.4
inTANDEM-2	Sotagliflozin 400 mg	782	−0.35	−8.2	−2.92	2.3	1.9 (all doses)
	200 mg	52 weeks	−0.37	−6.3	−2.18	5.0	0
	Placebo					5.0	
inTANDEM-3	Sotagliflozin 400 mg	1402	−0.46	−9.7	−2.98	3	3.0 (all doses)
	Placebo	24 weeks				2.4	0.6
NCT 02897219	Ipragliflozin	175	−0.36	−13.8	−2.92	0	0
	50 mg	24 weeks					0
	Placebo						

* Requiring external assistance.
** Reported as U/kg reduction in insulin dose.
† Percentage of participants experiencing at least one episode of severe hypoglycemia/ DKA in each dosing group.

Table 3. Candidate adjunct therapies vs the 'ideal' adjunct therapy.

	Ideal adjunct therapy	Pramlintide	Metformin	DPP-4 inhibitors	SGLT2 inhibitors	GLP1 receptor agonists
HbA1c reduction	✓	✓	✗	✗	✓	✓
Weight reduction	✓	✓	✓	✗	✓	✓
Reduced insulin dose requirement	✓	✓	✓	?	✓	✓
No increase in hypoglycemia*	✓	✓	✓	✓	✓	?
No increase in ketosis*	✓	✓	✓	✓	✗	✓
No increase in unwanted gastrointestinal effects	✓	✗	✗	✓	✓	✗
Improved cardiorenal outcome	✓	✗	? possible†	✗	? probable††	? probable†††

**with appropriate insulin dose adjustment.*
†surrogate outcomes and extrapolation from type 2 diabetes.
††extrapolation from type 2 diabetes and non-diabetic individuals.
†††extrapolation from type 2 diabetes.
N.B. Only pramlintide (USA), metformin (France) and ipragliflozin (Japan) are currently licensed for use as adjunct therapy in type 1 diabetes.

1.8, 3.0, and 3.4 kg, respectively ($p < 0.0001$) and total daily insulin dose was reduced in the range 6.4% to 13.1%, sustained over 52 weeks in EASE-2 and over 26 weeks in EASE-3. Hypoglycemia was not increased [61].

The inTANDEM programme examined sotagliflozin as an adjunct agent in T1D. In participants recruited from North American (inTANDEM 1) and European populations (inTANDEM 2) over 52 weeks, sotagliflozin at doses of 200 mg and 400 mg daily were investigated. inTANDEM 3 investigated sotagliflozin at 400 mg over 24 weeks. In all these trials, HbA1c, weight and total daily insulin dosing were reduced with no significant increase in hypoglycemia. Baseline HbA1c was 7.6% (60 mmol/mol), 7.8% (62 mmol/mol) and around 7.5% (reported for each treatment group individually: 58–60 mmol/mol) for inTANDEM 1, 2 and 3, respectively [62–64].

A small phase 2 trial lasting 18 weeks examined canagliflozin added to insulin at doses of 100 mg and 300 mg daily [65]. This provided comparable results to the other trials in the class with reductions in HbA1c, weight and total daily insulin dose with no increase in low blood sugars. A further agent from the class, ipragliflozin has been investigated in people with T1D in Japan showing reductions in HbA1c and weight [66].

The above information alone would indicate that SGLT2 inhibitors meet many of the criteria required of an ideal adjunct therapy. However, significant rates of ketosis and diabetic ketoacidosis (DKA) as adverse events have prevented wide-spread uptake of these agents as adjunct therapy in T1D. This is thought to occur because increased glucagon is secreted by pancreatic α-cells as an adaptive/compensatory response to renal loss of glucose resulting in lipid oxidation from adipose tissue and hepatic ketogenesis at the expense of carbohydrate utilization, particularly if regular insulin doses are down titrated to prevent hypoglycemia [67]. In addition, SGLT2 inhibitors may directly stimulate α-cells to produce glucagon [68]. All trials to date in T1D have reported increased rates of DKA with all doses of SGLT2 inhibitors. Difference in absolute rates between trial programmes may at least in part be due to differences in event triggering processes and adjudication procedures; however, the relative risk of DKA compared with placebo appeared lower for dapagliflozin in the DEPICT programme than for other agents and without a clear dose dependence, albeit with the incidence approximately three times higher than placebo. The proportion experiencing definite DKA over 52 weeks was 3.5% with 10 mg dapagliflozin daily, 4.0% with dapagliflozin 5 mg and 1.1% with placebo. In all cases, severity was graded mild or moderate [69].

Based on the above data, two SGLT2 inhibitors have been licensed for use in T1D. Ipragliflozin and dapagliflozin are both licensed in Japan; and in 2019 the European Medicines Agency (EMA) approved dapagliflozin for use in overweight (BMI > 27 kg/m^2) people with T1D when glycemic control is not achieved despite optimal insulin therapy. This was soon followed in the UK by National Institute for Health and Care Excellence (NICE) approval of the cost-effectiveness of dapagliflozin 5 mg for use in the NHS for this indication, expecting that 90,000 people with T1D in the UK would be eligible. However, during the COVID-19 pandemic, due to concerns of increased rates of ketosis during viral infection, a precautionary principle in relation to SGLT2 inhibitors was advocated by professional bodies, including the Association of British Clinical Diabetologists, and many prescriptions were interrupted or discontinued [70]. On 2 November 2021, the manufacturer AstraZeneca voluntarily withdrew the adjunct therapy indication in the UK and Europe. The company advised that this was not due to any safety concerns. In the USA, no SGLTi has been approved to date by the FDA for the adjunct therapy indication in type 1 diabetes [70,71].

At the time of writing, Japan remains the principal market for SGLT2is as adjunct therapy in T1D and real-world data is emerging: in a recent retrospective observational cohort study of 11,475 people with T1D – of whom 1,898 were prescribed SGLT2 inhibitors – the hazard ratio for DKA was 1.66 (95% confidence interval 1.33–2.06; $p < 0.001$) with the mean time to DKA, if it occurred, approximately 30 days [72].

As a result of the above circumstances, future opportunities even for real-world assessment of SGLT2 inhibitors in T1D seem limited at present and there is little prospect of a large-scale cardiovascular outcome trial to assess whether there could be long-term benefits on cardiovascular and/or renal outcomes. The TID charity JDRF (Juvenile Diabetes Research Foundation) has called for the manufacturing company to reinstate the adjunct indication and (anecdotally including from our own experience) many people with diabetes who

experienced benefits remain keen to continue on these agents 'off label' (with appropriate mitigation strategies including home blood ketone monitoring) [69,73].

2.5. GLP-1 receptor agonists

The first GLP-1RA was licensed for use in T2D in 2007. The class, which includes liraglutide, semaglutide, dulaglutide and extended-release exenatide, now has an established role in the management of T2D. As mentioned above, in the context of DPP-4 inhibition, native GLP-1 is an important incretin and exerts insulinotropic effects by binding to GLP-1 receptors on pancreatic β-cells. "Although insulinotropic effects may not be relevant in most people with T1D, GLP-1 RAs have other effects which may be of benefit (particularly in 'double diabetes')" including suppression of prandial glucagon release by α-cells [42], reducing appetite/promoting satiety (via central effects), weight reduction, delayed gastric emptying and reducing postprandial glucose excursions [74]. In addition, like SGLT2 inhibitors, all of these agents with the exception of exenatide have been demonstrated in large-scale cardiovascular outcome trials in T2D to reduce rates of major adverse cardiovascular events [75–81]. There has been significant interest in exploring GLP-1RAs for use as an adjunct to insulin in T1D, particularly given the association of intensive insulin therapy with weight gain and subsequent escalation in insulin dose requirements (and potentially cardiovascular risk) in a significant subgroup of individuals.

Initial small clinical trials of GLP-1RAs as adjunct therapy in T1D with considerable heterogeneity in study design reported no significant reduction in HbA1c compared to placebo [82–85], while others reported changes in HbA1c that waned toward the end of the study period [86–89]. As with metformin, more consistent findings were significant reductions in daily insulin dose requirement and weight [82,86–90]. Adverse events reported were predominantly gastrointestinal upset, and there were no significantly increased rates of hypoglycemia.

The largest randomized control trials to date investigating GLP-1RAs in T1D are the ADJUNCT ONE [91] and ADJUNCT TWO [92] trials. ADJUNCT ONE was a 52-week randomized, placebo-controlled, double-blind trial, which randomized 1,398 adults with T1D to liraglutide (0.6 mg, 1.2 mg or 1.8 mg subcutaneous once daily) or placebo. To recruit a cohort reflective of the T1D population, inclusion criteria were broad and participants were not excluded based on residual β-cell function, severe hypoglycemia/ hypoglycemic unawareness, or history of ketoacidosis. The trial used a 'treat-to-target' design, with insulin dose increased as needed to achieve optimal HbA1c throughout the study period following initial dose reductions on commencing trial drug. The primary outcomes of interest were HbA1c, total daily insulin dose and weight loss. Baseline HbA1c was 8.2% (66 mmol/mol) and 8.1% (65.0 mmol/mol) in the ADJUNCT 1 and ADJUNCT 2 trials, respectively.

HbA1c was reduced in all treatment groups in a dose-dependent manner falling by 0.54%, 0.49%, 0.43% and 0.34% over the study period in those randomized to the 1.8 mg, 1.2 mg, 0.6 mg and placebo groups, respectively. The effect tended to wane by 52 weeks but remained significant with comparison to placebo for liraglutide 1.8 mg daily (estimated treatment difference (ETD) −0.2% [95%CI −0.32; −0.07] p = 0.0019) and 1.2 mg (ETD −0.15% [CI −0.27; −0.03], p = 0.0164) groups. The greatest reduction in these groups was seen for individuals with detectable C-peptide at screening. Insulin dose requirement reduced significantly compared to placebo in those allocated to the 1.8 mg (−5%, estimated treatment ratio (ETR) 0.92 [CI 0.88;0.96], p < 0.0001) and 1.2 mg doses (−2%, ETR 0.95 [CI 0.91;0.99] p = 0.0148), but rose in the 0.6 mg liraglutide (+4%) and placebo (+4%) groups. Significant, dose-dependent, reductions in body weight were also seen in the liraglutide treatment groups with mean loss of 4.0 kg with 1.8 mg (ETD −4.9 [CI −5.65; −4.16] p < 0.0001), 2.7 kg (ETD −3.55 [CI −4.29; −2.81] p < 0.0001) with 1.2 mg, and 1.3 kg (ETD – 2.19 [CI −2.91; −1.47] p < 0.0001) with 0.6 mg liraglutide daily. Rates of adverse events were dose-dependent with the most frequent being gastrointestinal side effects. There was no significant difference between groups in rates of severe hypoglycemia but 82% of participants experienced symptomatic hypoglycemia, with higher rates in the 1.8 mg and 1.2 mg treatment groups compared to placebo (estimated rate ratio (ERR) of 1.31 [CI 1.07; 1.59], p = 0.0081, and 1.27 [CI 1.03; 1.55], p = 0.0219, respectively). Participants with detectable fasting C-peptide at baseline (>30 pmol/L) experienced lower rates of symptomatic hypoglycemia. Rates of 'hyperglycaemia with ketosis' were also higher in the 1.8 mg liraglutide treated group compared with placebo (p = 0.0205), but cases of confirmed DKA were low with only eight episodes in all participants over the trial period. The authors speculated that increased rates of hyperglycemia accompanied by ketosis were due to a combination of increased reporting in the context of gastrointestinal side effects and lipolysis driven by reduction in insulin dosing.

ADJUNCT TWO [92] was a 26-week placebo-controlled, double-blind trial comparing liraglutide (1.8, 1.2 and 0.6 mg) vs placebo in a similar population to ADJUNCT ONE [91]. However, rather than a 'treat to target' approach, insulin doses were 'capped' for each participant individually prior to randomization.

Using this study design, HbA1c did not fall in the placebo group, but significant placebo-corrected reductions were seen for all active treatment groups: ETD – 0.35% [95%CI –0.50; –0.20] p < 0.0001); −0.23% [CI – 0.38; – 0.08], p = 0.0021; –0.24% ([CI – 0.39; – 0.10], p = 0.0011) for 1.8, 1.2 and 0.6 mg groups, respectively. As with ADJUNCT ONE, the most marked decrease in HbA1c occurred in the first 3 months of the study with a gradual increase toward the end of the study period. Moreover, significant reductions in total daily insulin requirement were seen with all liraglutide doses at 26 weeks compared with placebo (estimated treatment ratio (ETR) 0.9 [CI 0.86; 0.93], p < 0.0001; 0.93 [CI 0.90; 0.96], p < 0.0001; 0.95 [CI 0.92; 0.99], p = 0.0075 – for 1.8, 1.2 and 0.6 mg groups respectively). Additionally, there was a dose-dependent reduction in mean body weight from baseline to week 26 with liraglutide (p < 0.0001 for all liraglutide doses compared to placebo). Participants receiving liraglutide were more likely to

achieve a composite target of HbA1c <7.0% (53 mmol/mol) with no severe hypoglycemia (odds ratio 2.02 [CI 1.05–3.87] p = 0.0343).

There was an excess of adverse events (the majority gastrointestinal) in those treated with liraglutide but no clear increase in those classified as severe. However, perhaps as a result of a study design that 'capped' insulin dosing to avoid hypoglycemia there was a significantly higher rate of hyperglycemia with ketosis with liraglutide 1.8 mg compared with placebo (estimated rate ratio 3.96 [CI 1.49;1.55], p = 0.0059). There was no significant excess of severe hypoglycemia in any group, although rates of symptomatic hypoglycemia were higher than with placebo in the 1.2 mg liraglutide group (but not with the 1.8 mg or 0.6 mg doses). As with ADJUNCT ONE, the greatest HbA1c reductions were seen for individuals with detectable C-peptide at screening but in this case across all doses.

Post hoc analysis of the ADJUNCT trials confirmed significantly greater HbA1c reductions with liraglutide in individuals with detectable C-peptide, but no differences in efficacy or safety according to baseline HbA1c, BMI or insulin regimen (basal-bolus vs continuous subcutaneous insulin) [93].

There is therefore convincing evidence that GLP-1RAs can promote improved glycemic control, weight loss and reduction in insulin burden in T1D. It is also a testable hypothesis that the cardiovascular benefits demonstrated in T2D might also be realized in T1D. However, prior to embarking on a trial of that nature, the safety profile of these agents in T1D, particularly in relation to hypoglycemia and hyperglycemia with ketosis, should be further evaluated with exploration of methods for mitigation. One approach may be for all participants to use continuous glucose monitoring (with built-in hypoglycemia alarms) while avoiding capping insulin: this is increasingly becoming 'standard of care' in T1D at least in high-income countries (but was not in routine use at the time of the ADJUNCT trials).

2.6. Combination adjunct therapy – a direction for the future?

The prospect has arisen more recently of trialing combinations of adjunct therapies in T1D. This concept is particularly appealing given the cardiorenal outcome benefits of SGLT2is and GLP-1RAs. Moreover, if (as argued above), ketosis with SGLT2 inhibitors is driven by hyperglucagonaemia, co-administration of a GLP-1RAs (which reduces glucagon secretion) is a potential mitigation strategy. There is some evidence for this hypothesis from studies in human islets [68].

In one small trial examining combination adjunct therapy, when dapagliflozin or placebo was added over a 12-week study period in 26 people with T1D already on liraglutide a 0.66% reduction in HbA1c was observed with additional weight loss of 1.9 kg and no increase in hypoglycemia. There were, however, two cases of DKA necessitating discontinuation of dapagliflozin [94]. A 52-week JDRF funded two-center trial with semaglutide and dapagliflozin (NCT03899402) is currently in progress.

3. Expert opinion

Over the next decade, continuous glucose monitoring technology will increasingly become standard of care worldwide. Newer systems may integrate ketone measurement and 'high ketone' alarms in addition to 'low glucose' to allow early detection of ketosis. CSII (continuous subcutaneous insulin infusion) or insulin pumps will likely also become standard of care for the majority of people living with T1D at least in higher income countries, with hybrid-closed loop systems increasingly being adopted. Obesity rates will continue to rise and with this the proportion of people with 'double diabetes.'

No adjunct therapy candidate that has been evaluated to date in people with T1D meets the criteria for an ideal agent and few have been licensed for clinical use (Table 3). There remains a clear unmet need for evidence-based strategies for improving glycemic control and preventing complications in T1D. Therefore, adjunct therapy remains a critical area of ongoing research, not least with respect to the potential cardioprotective and renoprotective roles of these agents. Widespread access to enhanced glucose and ketone monitoring – including alarm functions – is likely to shift the risk: benefit ratio in favor of adjunct therapies over the coming decade. Whether combination strategies can improve safety of adjunct agents in people with T1D must be clarified as proof of concept potentially for larger scale cardiovascular outcome trials such as those now routinely conducted in T2D.

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Declaration of interest

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JR Petrie is the co-Chief Investigator for JDRF-funded trial (NCT03899402) of combination adjunct therapy mentioned in the text. This trial has non-financial support from Astra Zeneca (donation of investigational medicinal product to US site only) and supplementary financial support from Novo Nordisk due to a 10% COVID-19 related budget cut from the main funder. He also reports personal fees from Merck KGaA (Lectures), research support from Merck KGaA (Grant), personal fees from Novo Nordisk (Lectures/Advisory), personal fees from AGMedNet (Adjudication Committees), personal fees from IQVIA (Adjudication Committees), personal fees from Biocon (Consultancy), all outside the submitted work.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. McHardy K, Petrie J. First among equals: macleod, banting, and the discovery of insulin in Toronto. In: Jörgens V, Porta M, editors. Unveiling diabetes - historical milestones in diabetology. Frontiers in diabetes. Basel (Karger); 2020: Vol. 29:73–83.
2. Nathan DM, Genuth S, Lachin K, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977–986.
3. Epidemiology of Diabetes Interventions and Complications (EDIC). Research Group. Design, implementation, and preliminary results of a long-term follow-up of the diabetes control and complications trial cohort. Diabetes Care. 1999;22(1):99–111.
4. The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular outcomes in type 1 diabetes: the DCCT/EDIC study 30-year follow-up. Diabetes Care. 2016;39(5):686–693.
5. American Diabetes Association. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2021. Diabetes Care. 2021;44(Suppl 1):S111–S124.
6. National Institute for Health and Care Excellence. Type 1 diabetes in adults: diagnosis and management NICE guideline [NG17], National Institute for Health and Care Excellence, London, UK. 2015. Last updated March 2022
7. McKnight J, Wild S, Lamb M, et al. Glycaemic control of Type 1 diabetes in clinical practice early in the 21st century: an international comparison. Diabetic Med. 2015;32(8):1036–1050.
8. Livingstone SJ, Levin D, Looker HC, et al. Estimated life expectancy in a Scottish cohort with type 1 diabetes, 2008-2010. J Am Med Assoc. 2015;313(1):37–44.
9. Ruiz PL, Chen L, Morton JI, et al. Mortality trends in type 1 diabetes: a multicountry analysis of six population-based cohorts. Diabetologia. 2022;65(6):964–972.
10. Livingstone SJ, Looker HC, Hothersall EJ, et al. Risk of cardiovascular disease and total mortality in adults with type 1 diabetes: Scottish registry linkage study. PLoS Med. 2012;9(10):e1001321.
11. Beck RW, Bergenstal RM, Laffel LM, et al. Advances in technology for management of type 1 diabetes. Lancet. 2019;394 (10205):1265–1273.
12. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care. 2019;42(8):1593–1603.
13. Kushner PR, Kruger DF. The changing landscape of glycemic targets: focus on continuous glucose monitoring. Clin Diabetes. 2020;38(4):348–356.
14. Professional Practice Commitee. Standards of medical care in diabetes—2020. Diabetes Care. 2020;43(Suppl 1):S3.
15. Petrie JR, Peters AL, Bergenstal RM, et al. Improving the clinical value and utility of CGM systems: issues and recommendations: a joint statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group. Diabetologia. 2017;60(12):2319–2328.
16. Rodbard D. Continuous glucose monitoring: a review of recent studies demonstrating improved glycemic outcomes. Diabetes Technol Ther. 2017;19(S3):S25–S37.
17. Beck RW, Riddlesworth T, Ruedy K, et al. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections. J Am Med Assoc. 2017;317 (4):371–378.
18. Jeyam A, Gibb F, McKnight J, et al. Marked improvements in glycaemic outcomes following insulin pump therapy initiation in people with type 1 diabetes: a nationwide observational study in Scotland. Diabetologia. 2021;64(6):1320–1331.
19. Kietsiriroje N, Pearson S, Campbell M, et al. Double diabetes: a distinct high-risk group? Diabetes Obes Metab. 2019;21 (12):2609–2618.
20. Merger SR, Kerner W, Stadler M, et al. Prevalence and comorbidities of double diabetes. Diabetes Res Clin Pract. 2016; 119: 48–56.
21. Ferreira-Hermosillo A, Ibarra-Salce R, Rodríguez-Malacara R, et al. Comparison of indirect markers of insulin resistance in adult patients with double diabetes. BMC Endocr Disord. 2020;20(1):87.
22. Cleland SJ, Fisher BM, Colhoun HM, et al. Insulin resistance in type 1 diabetes: what is 'double diabetes' and what are the risks? Diabetologia. 2013;56(7):1462–1470.
23. Tallon EM, Redondo MJ, Shyu C, et al. Contrast pattern mining with the T1D exchange clinic registry reveals complex phenotypic factors and comorbidity patterns associated with familial versus sporadic type 1 diabetes. Diabetes Care. 2022;45(3):e56–e59.
24. Kluger AY, Tecson KM, Barbin CM, et al. Cardiorenal outcomes in the CANVAS, DECLARE-TIMI 58, and EMPA-REG OUTCOME trials: a systematic review. Rev Cardiovasc Med. 2018;19(2):41–49.
25. Taylor SI, Blau JE, Toher KI, et al. SGLT2 inhibitors as adjunctive therapy for type 1 diabetes: balancing benefits and risks. Lancet Diabetes Endocrinol. 2019;7(12):949–958.
26. U.S. Food & Drug Administration. Symlin (Pramlintide Acetate) injection. 2005 [cited 2022 Apr 6]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/21-332_Symlin.cfm#:~:text=Approval%20Date%3A%203%2F16%2F2005
27. Hieronymus L, Griffin S. Role of amylin in type 1 and type 2 diabetes. Diabet Educat. 2015;41(1 Suppl):47S–56S.
28. Edelman S, Maier H, Wilhelm K. Pramlintide in the treatment of diabetes mellitus. BioDrugs. 2008;22(6):375–386.
29. Edelman S, Garg S, Frias J, et al. A double-blind, placebo-controlled trial assessing pramlintide treatment in the setting of intensive insulin therapy in type 1 diabetes. Diabetes Care. 2006;29 (10):2189–2195.
30. Ratner RE, Dickey R, Fineman M, et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in Type 1 diabetes mellitus: a 1-year, randomized controlled trial. Diabetic Med. 2005;21(11):1204–1212.
31. Whitehouse F, Kruger DF, Fineman M, et al. A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. Diabetes Care. 2002;25(4):724–730.
32. Alrefai HA, Latif KA, Hieronymus LB, et al. Pramlintide: clinical strategies for success. Diabetes Spectr. 2010;23(2):124–130.
33. Bailey CJ. Metformin: historical overview. Diabetologia. 2017;60 (9):1566–1576.
34. Bailey CJ. Metformin: its botanical background. Pract Diabetes Int. 2004;21(3):115–117.
35. Rena G, Hardie D, Pearson E, et al. The mechanisms of action of metformin. Diabetologia. 2017;60(9):1577–1585.
36. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352 (9131):854–865.
37. Petrie J, Rossing P, Campbell I. Metformin and cardiorenal outcomes in diabetes: a reappraisal. Diabetes Obes Metab. 2020;22(6):904–915.
38. Livingstone R, Boyle JG, Petrie JR. A new perspective on metformin therapy in type 1 diabetes. Diabetologia. 2017;60(9):1594–1600.
39. Libman IM, Miller KM, DiMeglio LA, et al. Effect of metformin added to insulin on glycemic control among overweight/obese

adolescents with type 1 diabetes: a randomized clinical trial. J Am Med Assoc. 2015;314(21):2241–2250.
40. Timmons J, Greenlaw N, Boyle J, et al. Metformin and carotid intima-media thickness in never-smokers with type 1 diabetes: the REMOVAL trial. Diabetes Obes Metab. 2021;23(6):1371–1378.
41. Petrie JR, Chaturvedi N, Ford I, et al. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2017;5(8):597–609.
- **REMOVAL Trial is the largest trial to date examing metformin as an adjunct agent in T1D**
42. Seino Y, Fukushima M, Yabe D. GIP and GLP-1, the two incretin hormones: similarities and differences. J Diabetes Investig. 2010;1 (1–2):8–23.
43. Holst J, Deacon C. Inhibition of the activity of dipeptidyl-peptidase IV as a treatment for type 2 diabetes. Diabetes. 1998 Nov;47 (11):1663–1670.
44. Drucker D, Nauck M. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 receptor inhibitors in type 2 diabetes. Lancet. 2006 Nov;368(9548):1696–1705.
45. Rosenstock J, Perkovic V, Johansen O, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal Risk. The CARMELINA randomized clinical trial. J Am Med Assoc. 2019 January;321 (1):69–79.
46. White W, Cannon C, Heller S, et al. Aloglitpin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013 October;369(14):1327–1335.
47. Scirica B, Bhatt D, Braunwalk E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013 October;369(14):1317–1326.
48. Guo H, Hang C, Huang Y, et al. The efficacy and safety of DPP4 inhibitors in patients with type 1 diabetes: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2016 November;121:184–191.
49. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385 (16):1451–1461.
50. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383 (15):1413–1424.
51. McMurray J, Solomon S, Inzucchi S, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995–2008.
52. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373 (22):2117–2128.
53. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):343–357.
54. European Society of Cardiology. DAPA-CKD trial meets primary endpoint in patients with chronic kidney disease. 2020 [cited 2022 Apr 6]. Available from: https://www.escardio.org/The-ESC/Press-Office/Press-releases/DAPA .
55. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377 (7):644–657.
56. Lilly Investors. Jardiance® phase III EMPA-KIDNEY trial will stop early due to clear positive efficacy in people with chronic kidney disease. 2022 [cited 2022 Apr 6]. Available from: https://investor.lilly.com/news-releases/news-release-details/jardiancer-phase-iii-empa-kidney-trial-will-stop-early-due-clear .
57. Deeks ED. Sotagliflozin: a review in type 1 diabetes. Drugs. 2019;79 (18):1977–1987.
58. Dandona P, Mathieu CM, Phillip M, et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes: the DEPICT-1 52-week study. Diabetes Care. 2018;41 (12):2552–2559.
- **The DEPICT Trials examined dapagliflozin as an adjunct agent in T1D – demonstrating glycaemic and weight benefits but increased risk of ketosis**
59. Mathieu CM, Dandona P, Gillard P, et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (the DEPICT-2 study): 24-week results from a randomized controlled trial. Diabetes Care. 2018;41(9):1938–1946.
- **The DEPICT Trials examined dapagliflozin as an adjunct agent in T1D – demonstrating glycaemic and weight benefits but increased risk of ketosis**
60. Mathieu CM, Dandona P, Birkenfeld AL, et al. Benefit/risk profile of dapagliflozin 5 mg in the DEPICT-1 and −2 trials in individuals with type 1 diabetes and body mass index =27 kg/m2. Diabetes Obes Metab. 2020;22(11):2151–2160.
61. Rosenstock J, Marquard J, Laffel LM, et al. Empagliflozin as adjunctive to insulin therapy in type 1 diabetes: the EASE trials. Diabetes Care. 2018;41(12):2560–2569.
- **The EASE trials examined empagliflozin as an adjunct agent in T1D - like DEPICT, this demonstrated glycaemic and weight benefits but at the cost of increased ketosis**
62. Garg SK, Henry RR, Banks P, et al. Effects of sotagliflozin added to insulin in patients with type 1 diabetes. N Engl J Med. 2017;377 (24):2337–2348.
63. Buse JB, Garg SK, Rosenstock J, et al. Sotagliflozin in combination with optimized insulin therapy in adults with type 1 diabetes: the North American inTandem1 study. Diabetes Care. 2018;41 (9):1970–1980.
- **The inTandem Studies examined the SGLT-1/SGLT-2 inhibitor sotagliflozin with similar results to the EASE and DEPICT Studies**
64. Danne T, Cariou B, Banks P, et al. HbA 1c and hypoglycemia reductions at 24 and 52 weeks with sotagliflozin in combination with insulin in adults with type 1 diabetes: the European inTandem2 study. Diabetes Care. 2018;41(9):1981–1990.
- **The inTandem Studies examined the SGLT-1/SGL-2 inhibitor sotagliflozin with similar results to the EASE and DEPICT Studies**
65. Henry RR, Thakkar P, Tong C, et al. Efficacy and safety of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to insulin in patients with type 1 diabetes. Diabetes Care. 2015;38 (12):2258–2265.
66. Kaku K, Isaka H, Sakatani T, et al. Efficacy and safety of ipragliflozin add-on therapy to insulin in Japanese patients with type 1 diabetes mellitus: a randomized, double-blind, phase 3 trial. Diabetes Obesity Metab. 2019;21(10):2284–2293.
67. Ferrannini E, Baldi S, Frascerra S, et al. Shift to fatty substrate utilization in response to sodium-glucose cotransporter 2 inhibition in subjects without diabetes and patients with type 2 diabetes. Diabetes. 2016;65(5):1190–1195.
68. Bonner C, Kerr-Conte J, Gmyr V, et al. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. Nat Med. 2015;21(5):512–517.
69. Juvenile Diabetes Research Foundation. Our response to the withdrawal of dapagliflozin (Forxiga) for type 1 diabetes. [cited 2022 Apr 6]. Available from: https://jdrf.org.uk/information-support/treatments-technologies/our-response-to-the-withdrawal-of-dapagliflozin-for-type-1-diabetes/ .
70. Phillip M, Mathieu C, Lind M, et al. Long-term efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes: pooled 52-week outcomes from the DEPICT-1 and −2 studies. Diabetes Obes Metab. 2021;23(2):549–560.
71. Limited AUK. Forxiga (dapagliflozin) 5mg should no longer be used for the treatment of Type 1 Diabetes Mellitus. 2021. [cited 2022 Apr 6]. Available from: https://assets.publishing.service.gov.uk/media/619374948fa8f5037ffaa083/20211102-uk-dhpc-forxiga-T1D-withdrawal.pdf .
72. Mukai J, Kanno S, Kubota R. A literature review and meta-analysis of safety profiles of SGLT2 inhibitors in Japanese patients with diabetes mellitus. Sci Rep. 2021;11(1):13472.
73. Garg S, Peters A, Buse J, et al. Strategy for mitigating DKA risk in patients with type 1 diabetes on adjunctive treatment with SGLT inhibitors: a STICH protocol. Diabetes Technol Ther. 2018;20 (9):571–575.

- **This paper describes mitigation techniques against DKA when using SGLT-2 inhibitors in T1D. Point of care blood ketone testing is now widespread. This may allow effective mitigation to allow safe use of SGLT-2 inhibitors in contemporary T1D management**

74. Holst J. The physiology of glucagon-like peptide 1. Physiol Rev. 2007 October;87(4):1409–1439.
75. Gerstain H, Colhoun H, Dagenais G, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019;394 (10193):121–130.
76. Holman R, Bethel M, Mentz R, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017;377(13):1228–1239.
77. Hernandez A, Green J, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet. 2018;392 (10157):1519–1529.
78. Marso S, Bain S, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375 (19):1834–1844.
79. Husain M, Birkenfeld A, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019;381(9):841–851.
80. Marso S, Daniels G, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375 (4):311–322.
81. Pfeffer M, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med. 2015;373 (23):2247–2257.
82. Johansen N, Dejgaard T, Lund A, et al. Efficacy and safety of meal-time administration of short-acting exenatide for glycaemic control in type 1 diabetes (MAG1C): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2020;8 (4):313–324.
83. Frandsen C, Dejgaard T, Holst J, et al. Twelve-week treatment with liraglutide as add-on to insulin in normal-weight patients with poorly controlled type 1 diabetes: a randomized, placebo-controlled, double-blind parallel study. Diabetes Care. 2015;38(12):2250–2257.
84. Dubé M, D'Amours M, Weisnagel S. Beyond glycaemic control: a cross-over, double-blinded, 24-week intervention with liraglutide in type 1 diabetes. Diabetes Obes Metab. 2018 January;20(1):178–184.
85. Kielgast U, Krarup T, Holst J, et al. Four weeks of treatment with liraglutide reduces insulin dose without loss of glycemic control in type 1 diabetic patients with and without residual beta-cell function. Diabetes Care. 2011 July;34(7):1463–1468.
86. Kuhadiya N, Ghanim H, Mehta A, et al. Addition of liraglutide to insulin in patients with type 1 diabetes: a randomized placebo-controlled clinical trial of 12 weeks. Diabetes Care. 2016;39(6):1027–1035.
87. Dejgaard T, Schmidt S, Frandsen C, et al. Liraglutide reduces hyperglycaemia and body weight in overweight, dysregulated insulin-pump-treated patients with type 1 diabetes: the Lira Pump trial-a randomized, double-blinded, placebo-controlled trial. Diabetes Obes Metab. 2020;22(4):492–500.
88. Herold K, Reynolds J, Dziura J, et al. Exenatide extended release in patients with type 1 diabetes with and without residual insulin production. Diabetes Obes Metab. 2020;22 (11):2045–2054.
89. Kuhadiya N, Prohaska B, Ghanim H, et al. Addition of glucagon-like peptide-1 receptor agonist therapy to insulin in C-peptide-positive patients with type 1 diabetes. Diabetes Obes Metab. 2018;21 (4):1054–1057.
90. Jiang LL, Wang SQ, Ding B, et al. The effects of add-on exenatide to insulin on glycemic variability and hypoglycemia in patients with type 1 diabetes mellitus. J Endocrinol Invest. 2017;41 (5):539–547.
91. Mathieu C, Zinman B, Hemmingsson J, et al. Efficacy and safety of liraglutide added to insulin treatment in type 1 diabetes: the ADJUNCT ONE treat-to-target randomized trial. Diabetes Care. 2016;39(10):1702–1710.

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92. Ahrén B, Hirsch I, Pieber T, et al. Efficacy and safety of liraglutide added to capped insulin treatment in subjects with type 1 diabetes: the ADJUNCT TWO randomized trial. Diabetes Care. 2016;39 (10):1693–1701.

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93. Dejgaard T, von Scholten B, Christiansen E, et al. Efficacy and safety of liraglutide in type 1 diabetes by baseline characteristics in the ADJUNCT ONE and ADJUNCT TWO randomized controlled trials. Diabetes Obes Metab. 2021;23(12):2752–2762.
94. Kuhadiya N, Ghanim H, Mehta A, et al. Dapagliflozin as additional treatment to liraglutide and insulin in patients with type 1 diabetes. J Clin Endocrinol Metab. 2016;101(9):3506–3515.