Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

in pregnancy have noted that some patients will still require insulin in the third trimester.[3]

For future consideration, metformin clearance is increased in pregnancy, but the effects on dose selection or efficacy are unknown. Metformin is excreted into the milk during lactation, and although caution is advised, no adverse effects have become evident. Initial studies indicated that infants who were exposed to metformin in utero subsequently gained weight normally and generally achieve slightly above average growth, but more data on child development would be welcome.[7]

Other potential adjuncts to insulin treatment in pregnancy include sulfonylureas such as glibenclamide. This drug has been shown to improve maternal glycaemic control but crosses the placenta and stimulates fetal insulin secretion, with consequent macrosomia and risk of hypoglycaemia to the fetus and neonate.[8] No adequate clinical data exist regarding the use of DPP-4 inhibitors, GLP-1 receptor agonists, or SGLT2 inhibitors in pregnancy, but these medications are not recommended on the basis of preclinical studies that suggest possible adverse effects during the late stages of fetal development.

In conclusion, MiTy[4] has provided prospective, controlled evidence to support the low-cost, potentially beneficial, metabolic effects of metformin with insulin in the management of pregnancy for type 2 diabetes and gestational diabetes, and substantiated a favourable safety profile for neonates.

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SGLT2 inhibitors and renal complications in type 1 diabetes

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Adding in non-insulin agents is one of several promising strategies under investigation to improve glycaemic control in type 1 diabetes. Unlike uptitration of insulin, the ideal so-called adjunct drug would not cause increased hypoglycaemia and weight gain.[1] It would also reduce rates of cardiovascular, renal, and other adverse outcomes by improving glycaemic control or other mechanisms. These complications still result in an average reduction in life expectancy of 11–13 years among people with type 1 diabetes.[2]

Of several drug classes repurposed from type 2 to type 1 diabetes, SGLT2 inhibitors have made the most progress. The concept behind these drugs is that inhibiting reabsorption of glucose (and sodium) in the proximal renal tubules reduces blood glucose only when it is above a reduced renal threshold, so hypoglycaemia is not increased, while weight is reduced due to urinary loss of glucose equivalent to approximately 200 kcal per day. Because adverse cardiovascular events are reduced in patients with type 2 diabetes with these drugs (as has been found in the EMPAREG, CANVAS, DECLARE-TIMI trials),[3] the hypothesis that this might also happen in type 1 diabetes is not unreasonable.

In this issue of *The Lancet Diabetes & Endocrinology*, Per-Henrik Groop and colleagues[4] report the effect of the SGLT2 inhibitor dapagliflozin on albuminuria in adults with type 1 diabetes in a post-hoc subgroup analysis of the DEPICT-1 and DEPICT-2 phase 3 trials.[5] They report that in the 251 (15%) of 1646 participants with albuminuria at baseline, dapagliflozin reduced urinary albumin excretion (the urinary albumin to creatinine ratio [UACR]) compared with placebo with a mean change from baseline at 52 weeks of −13·3% (95% CI −37·2 to 19·8) for dapagliflozin 5 mg and −31·1% (−49·9 to −5·2) for dapagliflozin 10 mg. This finding is biologically plausible given compelling recent evidence that dapagliflozin and

For a press release from **AstraZeneca about dapagliflozin in people with and without diabetes** see https://www.astrazeneca.com/media-centre/press-releases/2020/farxiga-phase-iii-dapa-ckd-trial-will-be-stopped-early-after-overwhelming-efficacy-in-patients-with-chronic-kidney-disease.html

other SGLT2 inhibitors reduce rates of end-stage kidney disease in patients with chronic kidney disease,[6] whether or not associated with type 2 diabetes. Mechanistically, SGLT2 inhibitors are thought to protect the glomerulus by reflex constriction of the afferent arteriole in response to renal tubular sodium loss rather than by relaxation of the efferent arteriole as with renin-angiotensin system blocking drugs.

Despite the many beneficial effects of SGLT2 inhibition in several conditions, including heart failure, their promotion of ketosis has been the major barrier to widespread uptake in type 1 diabetes, in which diabetic ketoacidosis still accounts for more than 20% of deaths.[7] This adverse effect is unlikely to be eliminated because many of the positive effects, particularly on heart failure outcomes, are thought to be mediated by increased availability of free fatty acids and ketone bodies for metabolism.

For advice from the **Association of British Clinical Diabetologists** see https://abcd.care/sites/abcd.care/files/site_uploads/COvID_Front_Door_v2.0.pdf

Nevertheless, of the SGLT2 inhibitors that have entered phase 3 trials in type 1 diabetes, dapagliflozin (DEPICT programme) and sotagliflozin (inTandem programme) have relatively favourable therapeutic profiles.[7,8] In pooled analyses of dapagliflozin, a dose of 5 mg per day on average reduced HbA_{1c} by 0·34% versus placebo at 52 weeks in the context of a three times increase in adjudicated diabetic ketoacidosis risk versus placebo (4·62 events per 100 patient years in the dapagliflozin group *vs* 1·27 events per 100 patient years in the placebo group), decreasing substantially in those with a BMI of 27 kg/m² or higher (1·86 *vs* 1·17 per 100 patient years).[5] Based on such therapeutic profiles, both dapagliflozin and sotagliflozin were granted a European (but not US) license for adjunct therapy in type 1 diabetes in the first half of 2019 for those with a BMI of 27 kg/m² or higher. The UK National Institute for Healthcare Excellence (NICE) subsequently recommended both drugs (dapagliflozin in August, 2019, and sotagliflozin in February, 2020) to be cost-effective for use within the UK National Health Service for individuals who additionally had a relatively high insulin requirement (≥0·5 units/kg per day) and had completed an evidence-based quality-assured structured education programme. Notably, as of August, 2020, dapagliflozin is widely available but sotagliflozin has yet to be launched in many countries.

For more on **European license of dapagliflozin** see https://www.astrazeneca.com/media-centre/press-releases/2019/forxiga-approved-in-europe-for-type-1-diabetes22032019.html

For **NICE recommendation for use of dapagliflozin s**ee https://www.nice.org.uk/guidance/ta597

For **NICE recommendation for use of sotagliflozi**n see https://www.nice.org.uk/guidance/ta622

NICE estimated that around 90 000 of the estimated 370 000 adults with type 1 diabetes in the UK might be eligible for SGLT2 inhibition.[9] However, more than 1 year on from approval, uptake has been much lower (Petrie JR, unpublished). Although many diabetologists have cared for people with type 1 diabetes who have derived great benefit from dapagliflozin (usually in the context of regular blood ketone monitoring; Petrie JR, unpublished), their enthusiasm has been tempered by small numbers of patients who have been admitted to hospital for severe treatment-resistant diabetic ketoacidosis attributed to SGLT2 inhibitor therapy, in some cases presenting late due to relative euglycaemia.[10] The strength of this perception was reinforced during the early months of the COVID-19 pandemic by guidance from the Association of British Clinical Diabetologists that SGLT2 inhibitors should be stopped in all people with diabetes (even those with type 2) who had been admitted to hospital.

Some UK centres and clinics went even further and proactively contacted stable patients with type 1 diabetes to advise discontinuation of the drug, even those who were able to skip doses on sick days as recommended. As SGLT2 inhibitors are restarted now that the UK is coming out of the COVID-19 lockdown, can re-introduction now be informed by the knowledge that renoprotection is an additional and previously unrecognised benefit of dapagliflozin?

The analysis by Groop and colleagues[4] has some limitations. Because it was based on a non-prespecified surrogate measure in small numbers of individuals during relatively short-term follow-up, they could not report on clinical renal outcomes. The 26·8% (SE 9·0) reduction in mean percentage change UACR from baseline to week 52 observed in those allocated to the placebo group indicated considerable regression to the mean. Additionally, despite evidence suggesting dose-dependence of dapagliflozin, reduction in UACR with the recommended dose of dapagliflozin (5 mg per day) was not significant. This finding is in contrast with significant reduction in UACR with sotagliflozin (200 mg per day), but no significant reduction with the higher dose (400 mg per day).[8]

Despite these considerations, when taken in the context of evidence with SGLT2 inhibition in other conditions and data for sotagliflozin, the dapagliflozin analysis by Groop and colleagues contributes to proof of concept for renoprotection for this class of drug in type 1 diabetes and helps support the benefit rather than the

risk of treatment. However, adequately powered trials based on clinical outcomes are clearly still required for the use of these and other adjunct therapies in type 1 diabetes.

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