concentrations rise because there is insufficient insulin to maintain normal glucose homoeostasis and to overcome any underlying resistance to its metabolic actions. Such a defect might be associated with, cause, and/or be magnified by other abnormalities, including those related to fatty acid and lipoprotein metabolism, visceral fat deposition, hepatic function, autonomic function, and glucagon, incretin, steroid, renin–angiotensin, and catecholamine physiology. Any or all of these factors (and others) might promote cardiovascular disease through various known and unknown mechanisms. Large long-term clinical trials of insulin-replacement therapy,[11] incretins, and other approaches targeting one of more of these abnormalities that are either underway or about to start[12] are certain to shed more light on the link between dysglycaemia and serious outcomes.

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I have given advice to Sanofi-Aventis, GlaxoSmithKline, Eli Lilly, Novo Nordisk, AstraZeneca, Bristol-Myers Squibb, Roche, Medtronic, Merck, Bayer, Bioavail, and Jansen Ortho. I have been an investigator in clinical trials with Sanofi-Aventis, GlaxoSmithKline, Novo Nordisk, Merck, and Roche. I have been on research committees or given presentations for or made a video for Sanofi-Aventis, GlaxoSmithKline, Servier, Bayer, Eli Lilly, and Novo Nordisk. I have received travel or accommodation expenses and honoraria when consulting.

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Dapagliflozin, an SGLT2 inhibitor, for diabetes

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In the 2nd century, Aretaeus of Cappadocia considered polyuria as a compensatory mechanism in patients with diabetes (*diabaino* in Ionian Greek, meaning "go through") and concluded that the disease was caused by a fault in the kidneys. However, the organ's role in normal glucose homoeostasis has received little attention in the treatment of type 2 diabetes in modern times.

The kidneys contribute to glucose homoeostasis in three ways: gluconeogenesis of 15–55 g per day, utilisation of 25–35 g glucose, and reabsorption of glucose. In healthy people, around 180 g of glucose is filtered by the kidneys in 24 h but nearly all of this is reabsorbed by sodium-glucose transporter 2 (SGLT2) expressed in the proximal tubules.[1]

Glucose reabsorption in the kidney should be the primary target for the regulation of glucose homoeostasis in people with hyperglycaemia. This mechanism is independent from β-cell capacity and insulin resistance, the two major pathogenetic determinants for progression of glucose intolerance. Clinical investigations in patients with familial renal glycosuria, caused by a mutation of the *SLC5A2* gene that encodes SGLT2, have shown that despite glycosuria of 50 g to more than 100 g per day, these patients are asymptomatic without relevant loss of electrolytes and with no increased risk of urogenital infections.[2] On the basis of this clinical experience, a new class of SGTL2 inhibitors was developed at the beginning of this century, and some of them are in phase 3 clinical trials.[3] A non-specific SGLT1/2 inhibitor—phlorizin—has already shown beneficial effects on diabetes in animal experiments, but because of serious gastrointestinal side-effects resulting from additional inhibition of SGLT1, the drug could not be considered for clinical use.[4]

In *The Lancet* today, Clifford Bailey and colleagues[5] present results from the first large-scale clinical study

investigating the efficacy of the SGLT2 inhibitor dapagliflozin. The trial included 534 patients with type 2 diabetes who had insufficient glycaemic control with preceding metformin treatment. There was a dose-dependent reduction in HbA_{1c} in patients treated with dapagliflozin, with a reduction of 0·84% in patients assigned to a maximum dose of 10 mg per day compared with a reduction of 0·3% in the placebo group. Beyond glucose control, treatment with dapagliflozin reduced bodyweight and decreased systolic and diastolic blood pressure. The clinical significance of these effects, attributed to mild osmotic diuresis and renal elimination of glucose, remains to be clarified.

By contrast with previous phase 1 and 2 studies, in which no increased risk for urinary tract infections was reported,[6] in today's study a slightly higher incidence of genital infections was seen in patients assigned to dapagliflozin than in those assigned to placebo. The increase in blood urea-nitrogen and packed-cell volume seen during treatment with dapagliflozin might reflect haemoconcentration caused by osmotic diuresis and needs to be measured carefully in continuing trials of SGLT2 inhibitors. Whether SGLT2 inhibitors promote sustained weight loss is unclear, but 1 g of glucose excreted in the urine equates to energy depletion of about 4 kcal.

By contrast with patients who have benign familial glycosuria, patients with diabetes might also show anomalies in immune response and impaired cellular defence against infection of the urinary tract and against genital fungal infection.[7] Many patients with diabetes have asymptomatic bacteriuria and pyelonephritis in combination with dysfunction of the efferent urinary tract by comparison with the non-diabetic population.[8] Such latent infections might be activated by increased glycosuria. Even though, so far, no clinically significant increase in the risk of urinary tract infections has been seen with SGLT2 inhibitors, a final appraisal requires long-term observational studies that directly measure colonisation with pathogens.

One of the major goals in the treatment of type 2 diabetes is to decrease the cardiovascular risk caused by the coincidence of obesity, hyperglycaemia, dyslipidaemia, hypertension, and endothelial dysfunction in an individual patient. Therefore the assessment of new therapeutic approaches should not be judged solely by their glucose-lowering efficacy, but rather by considering the effect on the overall cardiovascular risk profile in patients with type 2 diabetes. Selective SGLT2 inhibitors represent an innovative new class of oral antidiabetic agents at a time when disappointing results of large trials with established antidiabetic drugs, such as ACCORD[9] or RECORD,[10] require a critical re-evaluation of antidiabetic treatment. Beyond reducing glucotoxicity, dapagliflozin might improve cardiovascular outcome by reducing overweight and blood pressure.

Glucose reabsorption in the proximal tubules of the kidneys as a target for controlling hyperglycaemia by specific SGLT2 inhibitors brings us back to the roots of diabetes. Dapagliflozin was only moderately effective as an add-on drug in reducing glycaemic load in patients with type 2 diabetes who were insufficiently controlled with metformin according to an internationally accepted treatment algorithm. The only relevant adverse effect was a minor increase in genital infections. But the net balance of this novel group of oral antidiabetic drugs looks promising. Long-term trials should be designed with careful monitoring of urogenital infections on the basis of comparative investigations with established oral antidiabetic drugs. In the absence of randomised trials, SGLT2 inhibitors are candidates for add-on therapy to metformin as shown in today's study. Because of the role of glucotoxicity in the pathophysiology of type 2 diabetes,[11] and in view of weight loss and low risk of hypoglycaemia, SGLT2 inhibitors in the future also might be considered for the treatment of early-stage and late-stage type 2 diabetes.

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MH is a member of the steering committees for the RECORD (GlaxoSmithKline) and ORIGIN trials (Sanofi-Aventis), is a national leader for the TECOS (Oxford University) and TIDE (McMaster University) trials, and has received honoraria for lectures from Bayer, Novo-Nordisk, GlaxoSmithKline, Sanofi-Aventis, MSD, and Roche. TF has received honoraria for lectures from Takeda, Eli Lilly, Novartis, GlaxoSmithKline, Sanofi-Aventis, and Novo-Nordisk, and is on advisory boards for Eli Lilly, Boehringer Ingelheim, Biodel, and Sanofi-Aventis.

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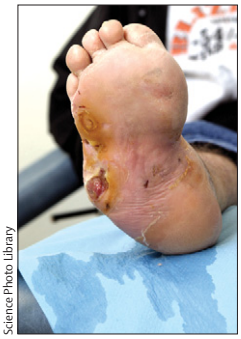
Longacting exenatide in diabetes: DURATION-3



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Incretins have been the focus of antihyperglycaemic drug development for nearly a decade. Two broad classes of agents, glucagon-like peptide-1 (GLP-1) analogues and dipeptidyl peptidase-4 (DPP-4) inhibitors, have been in clinical use. The Diabetes Management for Improving Glucose Outcomes (AMIGO trials),[1–3] with the GLP-1 receptor agonist exenatide, showed that exenatide reduced blood glucose (overall reduction in glycosylated haemoglobin [HbA_{1c}]: 0·8% from baseline and 0·9% *vs* placebo) with low risk of hypoglycaemia.

Exenatide has to be given subcutaneously twice daily, so researchers have focused on developing more convenient longer-acting compounds: exenatide as a poly-lactide-glycolide microsphere suspension with 3% peptide content, given once weekly; and liraglutide, a GLP-1 analogue, with substitution of Lys34 with Arg34 and an attachment of C-16 free fatty acids via a glutamoyl spacer to Lys26, given once daily. In a 30-week, randomised open-label trial in almost 300 patients with type 2 diabetes, treatment with longacting exenatide led to better improvements in fasting blood glucose, glucagon, and HbA_{1c} than did exenatide given twice daily.[4] In a subsequent extended 52-week study, longacting exenatide maintained reduction of HbA_{1c} by an average of 2%, and patients who switched to the longacting form showed further improvement in glycaemic control.[5] Limited data also showed similar benefits with longacting compared with twice-daily exenatide on bodyweight (about 4 kg), blood pressure, triglycerides,[4,6,7] and hepatic aminotransferases.[8]

In *The Lancet* today, Michaela Diamant and colleagues[9] show superior efficacy of longacting exenatide compared with insulin glargine in reduction of HbA_{1c}, postprandial glycaemic excursions, and weight over 26 weeks, in an open-label randomised trial (DURATION-3) in about 450 patients with type 2 diabetes. Fasting blood glucose, however, was better controlled with glargine. Additionally, more patients discontinued exenatide than glargine due to nausea and injection-site reactions. Drug-induced nausea, although less common with longacting than with twice-daily exenatide,[4] could be troublesome in patients who are taking multiple drugs including metformin and who have diabetic gastroparesis.

Is longacting exenatide an important advance for the treatment of type 2 diabetes? More probably,[10] enthusiasm about this drug is similar to that seen in the initial phase of development and use curve of any new drug. Historical data that show novel and prohibitive adverse reactions with approved drugs have taught us to be cautiously optimistic. In particular, it will take time and specifically designed trials for accrual of valid cardiovascular safety data. In this context, a preliminary study found that 72-h GLP-1 infusion improved severe myocardial dysfunction in patients with myocardial infarction after they had undergone primary angioplasty.[11] However, the long-term effects of sustained use of a GLP-1 receptor agonist on pancreatic β cells in human beings are not known. On the positive side, regeneration and controlled growth of β cells might occur, as has been shown in animals, and indirectly by restoration of first-phase insulin secretion in human studies.[12] On the downside, unfavourable pancreatic effects (eg, anecdotal reports of pancreatitis with exenatide, and one case of oedematous pancreatitis in Diamant and colleagues' study) should be strictly monitored. Further, we do not know yet whether use of DPP-4 inhibitors and GLP-1 analogues will lead to unfavourable dysregulation of growth of pancreatic ductal cells[13] or thyroid C cells[14] in human beings as seen in animal studies, another concern that needs careful investigation.