Recent innovations in the pharmacotherapy of type 2 diabetes are important, in view of the epidemic of type 2 diabetes and the individual and global economic costs of the disease. Although overall control of the disease has improved, more than 40% of patients on current therapies do not reach glycated haemoglobin (HbA1c) targets as suggested by clinical practice guidelines.1

The pathway for new drug development in diabetes traditionally involved 6–12-month studies that focussed on reduction of HbA1c. Historically, phase 3 clinical trials for a new antidiabetic agent involved 1000–3000 patients in total, a sample size that would be able to detect adverse events at the time of approval with frequency rates greater than 0·2%. However, emerging concerns about the long-term cardiovascular safety of diabetes drugs, caused in part by meta-analysis of clinical trials,2 sparked a major shift in the diabetes drug-development model. After much deliberation, the US Food and Drug Administration (FDA) issued new guidance for assessment of cardiovascular risk of drugs before and after approval.3 The implementation of these guidelines will certainly enhance understanding of the safety of new antidiabetic agents. However, adherence to the guidelines will also add substantially to the cost and time needed to complete the approval process.

New diabetes drugs should offer clear advantages over available agents, and lower glucose via mechanisms associated with either neutral or beneficial effects on cardiovascular health. The most recently approved drug classes, agonists at the glucagon-like peptide 1 receptor (GLP-1R) (exenatide, liraglutide) and inhibitors of dipeptidyl peptidase 4 (DPP-4) (sitagliptin, vildagliptin, saxagliptin, alogliptin) seem to fulfi l both criteria, although defi nitive cardiovascular outcome studies have not been completed. GLP-1R agonists improve glycaemia by stimulation of insulin secretion and inhibition of glucagon secretion and gastric emptying. Although thiazolidinediones, insulin secretagogues, and insulin often lead to weight gain, GLP-1R agonists induce satiety, leading to weight loss in most patients. Unlike sulphonylureas, glinides, or insulin, GLP-1R agonists and DPP-4 inhibitors lower glycaemia in a glucose-dependent manner, thereby reducing the risk of hypoglycaemia. Importantly, the GLP-1R is expressed in cardiomyocytes, endothelial cells, macrophages, and in regions of the central and peripheral nervous system that regulate cardiovascular function. Hence GLP-1R activation produces direct and indirect actions on the blood vessels and heart in patients with diabetes.4

GLP-1R activation is directly cardioprotective in normal and diabetic animals. Interestingly, GLP-1(9–36), a metabolite of endogenous GLP-1, is also cardioprotective, which complicates the prediction of cardiovascular actions attributable to DPP-4 inhibitors and structurally distinct GLP-1R agonists.4 Additionally, GLP-1R activation reduces postprandial intestinal lipoprotein secretion in rodents and human beings, and attenuates the development of atherosclerosis in mouse models of dyslipidaemia. GLP-1R is expressed on monocytes and macrophages, and agonists here reduce inflammation in normal, injured, and atherosclerotic blood vessels, and in hearts from animal models of diabetic cardiomyopathy. DPP-4 inhibition might also be cardioprotective; cardiovascular events were not increased in an analysis of phase 2 and 3 trials in patients treated with saxagliptin.4,5 Nevertheless, because rosiglitazone showed protective and anti-inflammatory actions in preclinical and proof-of-concept studies in human beings, healthy scepticism is needed about the available data on the cardiovascular actions of GLP-1R agonists and DPP-4 inhibitors.

What have we learned about the cardiovascular actions of GLP-1R agonists from clinical studies? Both
exenatide and liraglutide reduce blood pressure and bodyweight in most patients. A retrospective analysis of cardiovascular events in patients with diabetes treated with all available anti-diabetic agents from 2005 to March, 2009, showed that being given twice-daily exenatide was associated with a statistically significant lowered risk of cardiovascular events and cardiovascular-related hospital admissions. Although small increases in heart rate have been seen in some patients treated with exenatide or liraglutide, the clinical importance of this finding remains uncertain.

Patients’ satisfaction and compliance with multiple daily injections are problematic; thus strategies designed to prolong the action of GLP-1R agonists and reduce the frequency of injection have appeal. The first once-weekly formulation of exenatide seems to be more effective than twice-daily exenatide, and a New Drug Application for exenatide once weekly was submitted to the FDA in May, 2009, with a revised new drug application resubmitted in April, 2010. The manufacturers received a second complete response letter from the FDA in October, 2010, with a new request for a thorough QT (tQT) cardiac study in patients exposed to high levels of exenatide. This request for new electrocardiographic data came as a surprise to most diabetologists. First, inter-individual variability in the pharmacokinetics of circulating exenatide after the once-weekly injection, with the potential for some individuals with renal impairment to have higher blood concentrations, has been known for over 3 years. Results of the original tQT study, with single-dose exenatide, have been available since June, 2009, and do not seem to show a consistent dose-dependent QT abnormality. Moreover, a tQT study for liraglutide did not reveal a link between GLP-1R activation and QT prolongation.

Lessons learned from rosiglitazone have led to earlier initiation of cardiovascular outcome studies for diabetes drugs, including TECOS (sitagliptin, NCT00790205), SAVOR-TIMI (saxagliptin, NCT01107886), LEADER (liraglutide, NCT00393718) and EXCEL (exenatide once weekly, NCT01144338). These ongoing trials are adequately powered for safety and to show superiority rather than non-inferiority.

Assessment of the benefit-risk ratio for new drugs is challenging and the clinical community has high expectations for the efficacy and safety of new agents. Indeed, the recent report on cardiovascular outcomes with sibutramine exemplifies the risks inherent when establishing drug safety in populations at high risk for cardiovascular events. Striking the balance between maximisation of efforts to ensure drug safety before approval in a transparent manner, without discouraging innovation and new drug development, seems more important than ever. All stakeholders will need to become increasingly thoughtful about risk tolerance and regulatory requirements for new agents if we are to foster an environment that encourages development of improved drugs to combat the diabetes epidemic of the 21st century. The challenges and uncertainties involved in development of drugs for metabolic disorders are further highlighted by the FDA’s recent request for cardiovascular outcome studies as a condition for approval of the obesity agent naltrexone plus bupropion.  

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DJD has received research funding from Merck,Novo Nordisk, Roche,Arena, and Metabolex for prediabetes trials, and travel and accommodation expenses from the Endocrine Society. ABG has received consultancy fees from Merck, CV Therapeutics,Novo Nordisk, and Daichi Sanyo: ABG works on investigator-initiated clinical trials sponsored by the American Diabetes Association and National Institutes of Health, for which: Caraco Pharmaceuticals provides drug and placebo,LifeScan provides blood-glucose monitoring supplies,Merdodia provides assay supplies, Nestlé provides a nutritional supplement, and Medtronic provides glucose-monitoring supplies. ABG was a site investigator for a trial sponsored by Eli Lilly, and one by Daichi Sanyo: ABG has received travel or accommodation payments from the Endocrine Society, the American Diabetes Association, the American Association of Clinical Endocrinologists, the National Institutes of Health, the US Food and Drug Administration, and the Drug Information Association.

Comment


