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REVIEW

New Treatments for Type 2 Diabetes: Cardiovascular Protection Beyond Glucose Lowering?

Dilshani Jayawardene, MBBS [a], Glenn M. Ward, BSC, MBBS, FRACP, DPhil (Oxon), FRCPath [a], David N. O'Neal, MBBS, MD, FRACP [a], Geetha Theverkalam, MBBS, DRANZCOG [a], Andrew I. MacIsaac, MBBS, FRACP, MD [b], Richard J. MacIsaac, MBBS, FRACP, PhD [a*]

[a]Departments of Endocrinology & Diabetes and Medicine, St Vincent's Hospital Melbourne & University of Melbourne, Australia
[b]Department of Cardiology, St Vincent's Hospital Melbourne & University of Melbourne, Australia

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The health burden of type 2 diabetes mellitus (T2DM) is increasing worldwide, with a substantial portion of this burden being due to the development of cardiovascular (CV) disease. Multiple individual randomised clinical trials of intensive versus conventional glucose control, based on the use of traditional oral hypoglycaemic agents, have failed to convincingly show that intensive glucose control significantly reduces CV disease outcomes. In recent times, two new approaches to lowering glucose levels have become available. One targets the ''incretin effect'' which involves the modulation of peptide hormones that normally regulate glucose levels when nutrients are given orally. The other approach is based on inhibiting the sodium-glucose co-transporter 2 (SGLT-2) in the tubules of the kidney to promote glycosuria. Incretin-based therapies, especially glucagon-like peptide-1 receptor analogues, reduce glucose levels, with a low risk of hypoglycaemia, by increasing insulin secretion, inhibiting glucagon release and increasing satiety. Clinical and experimental studies have also shown favourable effects on CV disease risk factors such as dyslipidaemia, blood pressure, and improvements in endothelial function and cardiac contractility. Similarly, SGLT-2 inhibitors reduce glucose levels with a low risk for hypoglycaemia and have positive effects on multiple CV disease risk factors. Whether the beneficial effects of these new glucose lowering approaches on surrogate markers of CV disease risk translates to an improvement in CV events remains unknown. Several CV outcome trials are currently being performed to show that at a minimum, these novel glucose lowering agents are safe, but also have positive CV benefits.

Keywords Type 2 diabetes • Cardiovascular • Glucose • GLP-1 • DPP-4 • SGLT-2

Introduction

Type 2 diabetes mellitus (T2DM) is an independent cardiovascular (CV) disease risk factor and people with diabetes have a two- to four-fold increased risk for developing CV disease compared to those without diabetes. This increased risk persists even after accounting for traditional risk factors such as smoking, hypertension, obesity, and dyslipidaemia [1]. The increasing incidence and prevalence of T2DM, affecting almost 382 million people worldwide, the progressive natural history of the disease and the potential for multi-system complications to develop, emphasise

*Corresponding author. 4th Floor, Daly Wing, 35 Victoria Parade PO Box 2900, Fitzroy, Victoria 3065, Australia. Tel.: +61 3 9231 3569; fax: +61 3 9231 3590, Emails: r.macisaac@unimelb.edu.au, Richard.MacIsaac@svha.org.au

the urgent need for effective treatment and preventative strategies [2].

Many studies have demonstrated a relationship between chronic hyperglycaemia and the development of CV disease. However, strategies that reduce chronic hyperglycaemia, based on the use of traditional glucose lowering agents such as insulin, sulfonylureas and metformin, have not clearly reduced CV events in individual interventional studies such as the United Kingdom Prospective Diabetes Study (UKPDS), the Veterans Affairs Diabetes Trial (VADT), the Action to Control Cardiovascular Risks in Diabetes (ADVANCE) study and the Action to Control Cardiovascular Risks in Diabetes (ACCORD) study [3–6]. Similarly, the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) study showed that normalising fasting sugar levels with the early initiation of insulin therapy, even in the setting of impaired glucose tolerance, had no additional benefit on the incidence of CV mortality and morbidity compared with conventional glucose control strategies [7]. The demonstration of the benefits of glucose lowering on CV events in T2DM are confined to meta-analysis of data from individual trials and the results of one long-term follow-up observational study (UKPDS-80) of patients with newly diagnosed diabetes that were originally randomised to intensive glucose control in an interventional study [8–10]. Results from this follow-up study suggest that early strict glucose control generates a ''legacy-effect'' that takes many years before eventually being translated into protection from CV events [9,10].

Investigating the relationship between intensive glycaemic control and CV outcomes has been hampered by the inability to safely intensify glucose lowering strategies with a low risk of hypoglycaemia and the avoidance of other side-effects such as weight gain. Recently, two new classes of glucose lowering medications have been released onto the Australian market that may help to further delineate the relationship between glucose lowering and CV disease and possibly even offer CV benefits over and beyond glucose lowering. One class of medication targets the so called ''incretin effect'', whilst the other inhibits a sodium-glucose transporter in the renal tubules to induce glycosuria. Both classes of medication lower glucose levels with a low risk of hypoglycaemia and have beneficial effects on blood pressure (BP), body weight and possibly other deleterious risk factors and metabolic pathways implicated in the development of CV disease. Here we briefly review the evidence as to whether more contemporary pharmacological agents for lowering glucose levels offer CV disease protection beyond their glucose lowering effects.

Newer Glucose Lowering Therapies

Two new approaches to lowering glucose levels are now available. One targets the ''incretin effect'' which involves the modulation of peptide hormones that normally regulate glucose levels when nutrients are given orally. The other approach is based on inhibiting the sodium-glucose co-transporter 2 (SGLT-2) in the tubules of the kidney to promote glycosuria. Medications that target the ''incretin effect'' are usually classified into the Glucagon Like Peptide-1 (GLP-1) receptor analogues and Dipeptidyl Peptidase-4 (DDP-4) inhibitors. The incretins are a family of gut hormones that lower blood glucose levels via the so-called ''incretin effect''. This phenomenon accounts for the two- to three-fold increase in plasma insulin concentrations observed after the oral ingestion compared to the intravenous administration of an equivalent glucose load. The two principal incretin peptide hormones, GLP-1 secreted by intestinal L cells, and glucose-dependent insulinotropic polypeptide (GIP) secreted by intestinal K cells, are released after nutrients enter the small intestine. A key function of the incretins is to enhance the glucose sensing and insulin secretory capacity of the pancreas during postprandial hyperglycaemia.

Additionally, activating the GLP-1 receptor has other beneficial effects such as inhibition of glucagon release from the pancreas, a slowing of gastric emptying, and increased satiety [11]. Normally GLP-1 has a very short half-life and is quickly degraded by the dipetidyl peptidase 4 (DPP-4) enzyme. Two pharmacological approaches have been taken to target the ''incretin-system'' to develop new glucose lowering medications. One approach has been to develop GLP-1 receptor analogues that are resistant to degradation by the DPP-4 enzyme, hence enhancing their half-life. The other approach has been to develop inhibitors of the DPP-4 enzyme, with the aim of increasing plasma levels of native GLP-1 by inhibiting its degradation. Of note, the modification of native GIP, to date, has not been shown to have any therapeutic potential for the treatment of T2DM [12,13].

Incretin Based Therapy: Glucagon Like Peptide-1 (GLP-1) Receptor Analogues

The currently GLP-1 receptor analogues that have been developed for clinical use are shown in Table 1. However, only two of these GLP-1 receptor analogues are available on the Australian market, Exenatide and Liraglutide. GLP-1 receptors, apart from being found on pancreatic beta-calls, are also widely distributed in various cell types including: cardiac myocytes, endothelial cells, vascular smooth muscle cells and in regions of the CNS. This wide range of receptor expression may have potential beneficial implications for incretin based therapy over and above that related to glucose lowering.

Exenatide is the synthetic version of a naturally occurring 39-amino acid peptide found in the saliva of the Gila monster lizard (Exendin-4). A meta-analysis of studies reported a greater decline of the HbA1c in the exenatide group compared with placebo (weighted mean difference in change in HbA1c -1.01%, 95% CI -1.18 to -0.84), as well as a higher proportion of these patients being more likely to achieve glycaemic goals of HbA1c $\leq$ 7% compared with placebo [14,15]. In clinical practice, most patients are given a trial of exenatide, 5 mcg bid for a month with a dose escalation to 10 mcg bid if nausea and vomiting are not major side-effects.