

CV safety of anti diabetic drugs: review of the literature and ongoing studies

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The benefit of glucose lowering in preventing cardiovascular disease (CVD) in type 2 diabetes (DM) is supported mainly by data from long-term studies of patients with DM of short-duration and without pre-existing CVD. There are no good evidence to support CVD events reduction by intensive glucose control in patients with long-standing DM with existing CVD.

The potential risks or benefits of different glucose-lowering agents on CVD are currently a topic of great interest with many un-answered questions. The limitations of many of the studies published until now include: 1. Lack of pre-specified CVD outcome; 2. Short duration of follow-up; 3. Usage of combined anti-diabetic therapies hampering the ability to analyze separately the effect of each drug on CVD events; 4. Heterogeneity of baseline patients' characteristics. These limitations led the FDA in 2008 to require that all manufactures of new anti-diabetic drugs report CVD outcome before approval.

Both observational and interventional studies provide data supporting the safety and beneficial effect of metformin in reducing CVD both as mono-therapy and in combination with insulin. Two recent large observational studies have shown an increased risk of CVD and all-cause mortality in patients who were treated with sulphonylureas compared with metformin although the UKPDS, ADVANCE and BARI-2D trials which used sulphonylureas as part of a multi-drug treatment did not support these findings. Nateglinide, another insulin secretagogues was not shown to reduce CVD outcome in the recently published randomized control trial NAVIGATOR conducted in patients with impaired glucose tolerance.

Another widely-used glucose-lowering drug which has raised concern is rosiglitazone since the publication of a large meta-analysis which found an association between its usage and IHD. Further data did not support these findings including the recently published RECORD trial but all data show consistently that both rosiglitazone and pioglitazone (both PPAR agonists) increase the risk of congestive heart failure by about two-fold. These conflicting data led the FDA to publish an alert about the possible association between rosiglitazone and increased CVD risk and preclude the usage of these drugs in patients with heart failure.

Acarbose an α -glucosidase inhibitor have been found to reduce the risk of myocardial infarction and CVD events both in subjects with impaired glucose tolerance (STOP-NIDDM) and in a meta-analysis of patients with type 2 DM. However these findings are based on small number of events and need further confirmation by larger trials with pre-specified CVD outcome. Another promising group of medications are the GLP-1 agonists. Several published studies have shown their beneficial effects on CVD risk factors. In addition animal studies and small human studies suggest that GLP-1 agonists may have a protective effect on the myocardium during ischemia. However there are currently no results of long-term studies with GLP-1 agonists with pre-specified CVD end-points.

Glucokinase – a novel therapeutic target for type 2 diabetes Mellitus

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Type 2 diabetes (T2DM) is characterized by inadequate pancreatic beta-cell function, usually in the face of increased insulin requirements due to peripheral insulin resistance. Agnostic genome-wide association studies have shown that the majority of the genetic variants associated with increased risk of diabetes affect the function of genes that are important modulators of beta-cell function or mass. Thus, beta-cell dysfunction is of primary importance in the pathogenesis of T2DM, and modulators of beta-cell function or mass are rational, novel therapeutic targets. The beta-cell regulates insulin secretion in response to changes in circulating glucose levels. After entering the beta-cell through specific transporters, glucose is metabolized, causing an increase in the intracellular ATP/ADP ratio. This, in turn, causes closure of the ATP sensitive K channel, which results in membrane depolarization, followed by opening of the voltage-gated calcium channels that cause calcium to enter the cells, stimulating a cascade of events that ultimately results in insulin secretion. Mutation analyses in a wide spectrum of monogenic diseases of glucose homeostasis have demonstrated that the primary regulator of glucose-mediated insulin secretion is glucokinase, the enzyme that catalyzes the first step in glucose metabolism. Heterozygosity for inactivating mutations in this gene cause one form of Maturity Onset Diabetes of the Young, while homozygosity for the same mutations cause severe neonatal diabetes. At the other end of the spectrum activating mutations in this gene cause hyperinsulinemic hypoglycemia of varying degrees of severity, depending on the activity of the mutation. More recently, common polymorphisms in the GCK gene have been associated with Type 2 Diabetes. In addition to the beta-cell, glucokinase is expressed in the liver, where its expression is regulated by insulin and its activity is controlled by a peptide called the Glucokinase Regulator Protein. In the liver, activation of this enzyme results in glucose phosphorylation and glycogen synthesis, which is translated into decreased hepatic glucose production. Recently, we identified a patient with a GK mutation that resulted in severe hypoglycemia that required partial pancreatectomy. Detailed examination of the pancreas revealed abnormally large pancreatic islets, some of which contained proliferating beta-cells. Based on this observation, we investigated the effect of glucokinase activation on beta-cell proliferation in a mouse model. Our findings show that glucokinase activation results in increased proliferation, and that this effect can be blocked by preventing beta-cell membrane depolarization, calcium entry, calcineurin signaling or insulin receptor-mediated signaling. Taken together, these studies demonstrate that increased intracellular glucose metabolism stimulates mouse beta-cell replication, which is regulated by a dual mechanism involving both calcineurin and the insulin receptor signaling, as both of these pathways are necessary for replication but neither is sufficient.

Small molecule glucokinase activators are currently under development by several pharmaceutical companies for the treatment of T2DM. While many challenges still remain, including potential issues with hypoglycemia, the possibility that these drugs could enhance beta-cell replication opens new prospects for the long-term effect of this class of drugs on the preservation of beta-cell mass in patients with T2DM.

SGLT Inhibitors in the treatment of diabetes: An overview

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Agents approved to treat T2DM act by increasing insulin levels, improving insulin sensitivity or altering intestinal glucose absorption. While efficacious, these agents can be associated with hypoglycemia, weight gain, fluid retention, congestive heart failure, osteoporosis and gastrointestinal adverse events. Sodium-glucose co-transporters (SGLT) are responsible for glucose uptake from the intestine (SGLT1) and from the lumen of the renal tubule (SGLT1 and SGLT2). Potent and selective inhibitors of SGLT 1 and SGLT2 are in clinical development for the treatment of diabetes. In preclinical models of insulin resistance and T2DM, SGLT2 inhibitors increase urinary glucose excretion, improve glycemic control while reducing insulin secretion, increase beta cell mass, reduce weight gain, improve insulin sensitivity and lipid profiles and reduce urinary albumin excretion. While SGLT1 inhibitors have advanced only to phase 1 clinical development, several oral SGLT2 inhibitors are being studied in phase 3 clinical trials. In subjects with T2DM, SGLT2 inhibitors increase urinary glucose excretion, lower fasting and postprandial glucose levels and HbA1c without increasing hypoglycemia, are associated with weight loss, and reduce systolic blood pressure. Despite increases in glucosuria, urinary output is only mildly increased and symptoms due to increased urinary output or dehydration have not generally been apparent. Except for mild increases in BUN and decreases in creatinine clearance, possibly due to an osmotic diuresis, no abnormalities in renal function have been noted. While increases in genital infections (balanitis and vulvovaginal mycotic infections) have been seen in subjects treated with SGLT2 inhibitors, increases in urinary tract infections have not been noted. In summary, although no agents are approved, in clinical trials, SGLT2 inhibitors have been shown to improve glycemic control without causing hypoglycemia and associated with weight loss. Given the novel insulin-independent mechanism, SGLT2 inhibitors are predicted to be efficacious when used in combination with other antihyperglycemic agent classes and to be efficacious across the spectrum of beta cell dysfunction from IFG/IGT to beta cell exhaustion. By virtue of weight loss and reductions in blood pressure, SGLT2 inhibitors may favorably affect cardiovascular risk. Reduced insulin demands associated with SGLT2 inhibitors could decrease beta cell stress and possibly slow the progression of T2DM. While long-term clinical data are needed to adequately profile safety and tolerability, SGLT2 inhibitors could represent a unique and valuable addition to the antihyperglycemic therapeutic armamentarium.