NEW DEVELOPMENTS IN DIABETES CARE

CARDIOVASCULAR RISK AND PSYCHOSIS IN DIABETES

New agents and cardiovascular risk

**KEY MESSAGES**

- Cardiovascular outcomes trials for diabetes drugs are now mandatory and many have been completed or are nearing completion.
- Trials have shown the DPP-4 inhibitors to be non-inferior to placebo in respect of cardiovascular outcomes and have reassured us of their pancreatic safety.
- The novel SGLT-2 inhibitors have achieved modest reductions in HbA1c, with a very low incidence of hypoglycaemia, a reduction in blood pressure and some weight loss.
- A number of new insulins, as well as such novel agents as the once-weekly GLP-1 analogues and the glucokinase activators, also show great promise.

In his presentation at the annual conference of the Faculty of Consulting Physicians of South Africa, which was held in Cape Town recently, Dr Aslam Amod first turned the spotlight on cardiovascular outcomes trials of the DPP-4 inhibitors. “There are many such trials ongoing,” he said, noting that they have their roots in a 2005 study by Nissen et al in which numerous patients on a drug called muraglitazar died of cardiac causes, despite the drug’s seeming effectiveness. Further to this, highlighting the needs for such trials, the FDA set out criteria for them.

The EXAMINE study enrolled diabetic patients who had experienced an acute coronary syndrome. The DPP-4 inhibitor, alogliptin, was found to be non-inferior to placebo in respect of the primary endpoint of cardiovascular death. Likewise, the SAVOR trial showed that saxagliptin was non-inferior to placebo plus standard care. While it did not increase cardiovascular risk, there was, however, an unexplained increase in hospitalisation for heart failure. Pancreatic events with the DPP-4s are a special area of interest, but there was no sign of any pancreatic issues (pancreatic cancer or pancreatitis) in SAVOR.

Overall, when added to standard care, saxagliptin neither increased nor reduced the risk of the study’s primary composite endpoint of cardiovascular death, myocardial infarction or ischaemic stroke. It improved glycaemic control with a slight increase in hypoglycaemia. “The heart failure endpoint merits further investigation, especially in patients with an elevated baseline risk for heart failure,” said Dr Amod.

The TECOS study has shown non-inferiority of sitagliptin, but the final results have yet to be published.

Moving on to the new SGLT-2 inhibitors, Dr Amod underscored that the kidneys play a significant role in glucose balance. The renal threshold for glucose is increased in diabetes, a process facilitated by the sodium glucose co-transporters (SGLTs) 1 and 2, which transfer glucose and sodium from the lumen into the cytoplasm of tubular cells via a secondary active transport mechanism. SGLT-1 works in both the liver and intestine as
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well as the kidneys, while SGLT-2 works only in the kidneys. The latter is therefore the predominant focus of intervention in diabetes, as blocking the former may cause diarrhoea.

Three agents are currently approved by the FDA and EMA – canagliflozin, dapagliflozin and empagliflozin – and several others are in research. “How good are they?” asked Dr Amod. “They lower HbA1c modestly, but achieve this without a glucosuric effect. They are in-sulin-independent and have no effect on counter-regulatory responses. They lower both fasting and post-prandial glucose. They induce weight loss, and although the effect plateaus at 2-3 months, it is sustained at one year. They also reduce systolic/diastolic blood pressure by 3-5/2-3mmHg.”

When it comes to adverse effects, they predispose to mycotic genital infections, but not urinary tract infections. The incidence of hypoglycaemia is low when the SGLT-2s are used as monotherapy, but increases when they are added to sulphonylurea or insulin therapy. There are some safety concerns, with initial volume depletion causing dehydration, unstable blood pressure and syncope, especially in elderly patients. Long-term studies are needed to assess their safety in patients with renal dysfunction and there has been an FDA warning that they may be implicated in diabetic ketoacidosis. Where cardiovascular safety is concerned, they have been associated with slight increases in both LDL and HDL cholesterol. There has been one reported case of hepatic toxicity. They may increase the risk of osteoporosis in certain patients. “We are awaiting various long-term outcome studies, the first of which is expected at the end of 2016,” Dr Amod said.

There are quite a few new basal insulins in the picture. These include insulin degludec, an ultra-long-acting analogue with a half-life of 40 hours that allows for skipped or delayed doses and is associated with less nocturnal hypoglycaemia than glargine. It has also shown positive results in combination with liraglutide, reducing HbA1c by 2.5% with associated weight loss. U300 glargine has a flatter profile than the original insulin glargine, with less nocturnal hypoglycaemia. Inhaled insulins are also making a comeback further to the development of new delivery systems.

Looking to what’s still on the horizon, Dr Amod observed that there are over 200 chemical entities for diabetes currently under investigation. Some have novel modes of action, others are ‘me too’ agents. He concluded by making particular mention of the once-weekly GLP-1 analogues and the glucokinase activators. “The glucokinase enzyme has an exceptionally high impact on glucose homeostasis, so these agents have great promise.”
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Double, double, toil and trouble – psychosis and diabetes

KEY MESSAGES

- There is an established link between mental illness and cardiometabolic disease
- It is a myth that, in those with mental illness, cardiovascular disease or diabetes is exclusively a consequence of antipsychotic medication; it is therefore counterproductive to blame only the drugs
- Screening needs to be directed, with treatment being introduced further thereto
- A multidisciplinary team and defined referral pathways are essential
- Where there is pre-existing diabetes, mental illness itself as well as medication may worsen glycaemic control
- It would be preferable to use weight-neutral medications when using medications to manage the diabetes
- There is a need to move away from the artificial separation of ‘mental health’ and ‘physical health’ towards ‘health’ as a single entity.

There is an established link between mental illness/psychosis and cardiovascular disease and diabetes, Professor Roger Chen told delegates. Psychosis is characterised by delusions and hallucinations that hinder an individual’s ability to function.

Psychosis can take the form of schizophrenia, delusional disorder, schizoaffective disorder and schizophreniform disorder, among others. Schizophrenia is regarded as the most serious, with a worldwide lifetime prevalence of 1%. Sufferers may experience frequent acute, incapacitating exacerbations throughout life. Psychosis can take the form of schizophrenia, delusional disorder, schizoaffective disorder and schizophreniform disorder, among others. Schizophrenia is regarded as the most serious, with a worldwide lifetime prevalence of 1%. Sufferers may experience frequent acute, incapacitating exacerbations throughout life. Schizophrenia patients die earlier, losing up to 30 years of life, and while suicide is a more common cause than in the general population, cardiovascular disease is the most common cause of death.

“We need to improve the care of these patients and this requires us to talk to each other. Psychiatrists and endocrinologists generally operate in separate domains. Working together will ensure that we improve these patients’ health,” he said.

Diabetes is more common in schizophrenia patients than in the general population. The increase in diabetes is often attributed to the drugs used to treat the schizophrenia, but this is not the whole truth. “Traditional risk factors such as obesity and poor diet and little physical activity confer a substantial risk. The medications alone are not responsible for inducing type 2 diabetes.”

Schizophrenia patients have a higher prevalence of cardiovascular risk factors, including obesity, smoking, hypertension, dyslipidaemia and diabetes itself. The CATIE Schizophrenia Trial found higher rates of smoking, diabetes, hypertension and low LDL cholesterol levels in these patients. “The overall rate of diabetes in patients with schizophrenia was 36%, two-thirds of them had atherogenic dyslipidaemia, two-thirds were active smokers and three-quarters were sedentary and engaged in minimal exercise.”

A variety of antipsychotic drugs are used to treat schizophrenia, including clozapine, olanzapine, risperidone, amisulpride, quetiapine, aripiprazole and ziprasidon. As mentioned earlier, there is a widely held belief that antipsychotics are the sole cause of diabetes in schizophrenics, but this is not true, even though they may play a substantial contributory role. Professor Chen elaborated on this. “The atypical antipsychotics, including olanzapine and risperidone, have multiple mechanisms associated with weight gain and an impact on satiety. A significant proportion of the metabolic disease is caused by weight gain, which is also predicted by histamine H1 receptor affinity, notably with clozapine and olanzapine.”

In addition to weight gain, sleep disturbances too have a profound effect on health and are a common comorbidity in schizophrenia. These may play a role in

Professor Roger Chen
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cardiovascular and metabolic complications. “Many schizophrenia patients have significant circadian rhythm fragmentation. This sleep deprivation and loss may play a role in their higher incidence of diabetes, as these circadian rhythms disorders can raise insulin resistance and impair glucose tolerance.”

There is no ‘magic bullet’ when it comes to pharmacotherapy for weight gain. “We need a one-stop, cross- and multidisciplinary approach as the best strategy for treating obesity and diabetes in schizophrenics.” Lifestyle intervention also has an important role to play, as exercise has been shown to have benefit and ‘cause happiness’.9

Concluding, he underscored again that when treating cardiometabolic disease in the presence of mental illness, it is counterproductive to blame the former on antipsychotic medication only. A multidisciplinary team is essential. “We need to move away from seeing mental health and physical health as two totally separate domains. There is only ‘health’ and to optimise that we need to work together.”

References