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EC CLINICAL AND EXPERIMENTAL ANATOMY

Editorial

# Glucose Lowering Medications in Type 2 Diabetes and Cardiovascular Diseases

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**Received:** February 17, 2020; **Published:** February 18, 2020

Prevalence of type 2 diabetes mellitus (T2DM) is on the increase worldwide, more so, in sub Saharan Africans due to ageing of the population, improving survival of people living with diabetes, obesity, increased urbanization and westernization, dietary changes and physical inactivity. Type 2 DM is a major cardiovascular disease (CVD) risk factor; an independent predictor of cardiovascular disease. It is associated with vascular complications. Macrovascular complications of DM (myocardial infarction, stroke and heart failure) constitute the major cause of death in 75 - 80% of people living with T2DM. No wonder, cardiologists have been quoted to define T2DM as a cardiovascular disease characterized by hyperglycaemia.

Other cardiovascular disease risk factors which are commonly found in persons with T2DM include hypertension, dyslipidaemia (decreased HDL-c, increased triglycerides and increased small density LDL-c), visceral obesity, physical inactivity, low grade inflammation and endothelial dysfunction. With diagnosis of T2DM [1], risk of CVD is doubled and the relative risk of myocardial infarction (MI) and stroke is increased by 80% and 50% respectively, in those with versus those without DM. Death from CVD in those living with T2DM is 2 - 4 fold higher than in the non-diabetic population.

Improved glycaemic control as evidenced by decreased HbA1c to < 7% has been shown to decrease risks of microvascular complications (nephropathy, retinopathy and neuropathy) in persons living with DM [2,3]. Good glycaemic control, however, has failed to reduce the risks of macrovascular complications and mortality from T2DM. All anti-diabetic medications lower blood glucose and HbA1c to a varying degree but with different cardiovascular effects. Some glucose lowering medications worsen, improve or have no effects on cardiovascular outcomes.

Following the observation that Rosiglitazone increased cardiovascular risk by doubling the risk of heart failure and increasing the risk of MI, the U.S Food and Drug Administration (FDA) in 2008 gave a mandate that all new anti-diabetic drugs be subjected to cardiovascular outcome trials (CVOTs) to assess their CV safety and improvement in cardiovascular outcomes. This was logical, being that the macrovascular complications of T2DM were the major cause of deaths in persons living with type 2 diabetes. Emphasis then shifted from blood glucose lowering to a more holistic approach to diabetes care. This write up, therefore, is aimed to familiarize the primary care physicians, cardiologists, nephrologists and the medical community with the CV benefits and harms of the most commonly used anti-diabetic medications. The sodium glucose co-transporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists have demonstrated cardiovascular benefits especially in those at highest risk for CVD through mechanisms that may have nothing to do with their glucose lowering effects.

Glucose lowering medications that have favorable CV outcomes and are indicated in eligible patients with cardiovascular disease include the SGLT-2 inhibitors (Empagliflozin and Canagliflozin) and the GLP-1 receptor agonists (Liraglutide and Semaglutide). They had

a favorable CVOT data associated with their use. Similarly, metformin, in a substudy of the UKPDS involving overweight and obese T2DM patients [4], was shown to decrease MI risk by 39%, Dm related deaths by 32% and all-cause mortality by 36%. Metformin is currently recommended by ADA [5] and AACE [6] as the first line anti-diabetic medication as it is associated with a modest HbA1c reduction of 1 - 1.5%, weight loss, cost effectiveness, absence of hypoglycaemia and cardiovascular benefits.

The sulphonylureas and insulin confer no CV benefits onT2DM patients but are used as second or third line drugs in patients without established CVD. The DPP-4 inhibitors have neutral effects on CV outcomes except for Saxagliptin. Rosiglitazone and Saxagliptin of the Thiazolidinedione and DPP-4 inhibitor classes of glucose lowering drugs respectively have unfavorable CV benefits. Rosiglitazone increased risks of HF and MI while Saxagliptin caused increased risk of heart failure hospitalization in the relevant CVOTs.

The take home from all these is the need to assess for CVD in all patients living with T2DM and to take into considerations presence of established CVD or CV risk factors in the choice of second line glucose lowering agents. In other words, glucose lowering agents should be tailored to the individual patient's comorbidities. Macrovascular complications of DM must be mitigated as much as possible to reduce morbidity and mortality from T2DM. In summary, metformin, Empagliflozin, Canagliflozin, Liraglutide and Semaglutide are the glucose lowering drugs that have been shown to have CV benefits.

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**Volume 3 Issue 3 March 2020**