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Editorial:

Selection of Proper Antidiabetic Drugs for Diabetic Patients with Cardiovascular Diseases: Why So Important?

Md. Moklesur Rahman Sarker

Diabetes Obesity and Genome Research Group, Clinical Investigation Centre, Faculty of Medicine, University of Malaya, 50603, Kuala Lumpur, Malaysia.

The prevalence of type 2 diabetes mellitus is increasing all over the world. According to the World Health Organization (WHO) October 2013 report, 347 million people are affected by diabetes globally, and diabetic death will be projected to rise more than 50% in the next 10 years.[1] About 95% cases of diabetes are type 2 diabetes mellitus or non-insulin dependent diabetes or adult onset diabetes, which is a metabolic disorder in which hyperglycemia resulted because of insufficient production of insulin by the pancreas as well as resistance of the secreted insulin. Diabetes gradually leads to the damage, dysfunction and failure of several important organs, such as heart, kidneys, liver, nerves, and eyes[2] and to the ultimate death of the patients. Management of type 2 diabetes with antidiabetic drugs is a challenge because some drugs itself may worsen the diabetes-associated complications and morbidity of the patients. An expected antidiabetic drug should have sufficient capability to control hyperglycemia without adversely affecting the patients' condition on cardiovascular, kidney, liver and other diseases associated with diabetic patients. Biguanides (e.g., metformin), sulfonylureas (e.g., glimepiride, glipizide), thiazolidinediones (e.g., pioglitazone, rosiglitazone), α-glucosidase inhibitors (e.g., acarbose, voglibose), meglitinides (e.g., repaglinide, nateglinide), dipeptyl peptidase-4 (DPP-4) inhibitors (e.g., Sitagliptin, vildagliptin, linagliptin), glucagon like peptide (GLP)-1 analogues (e.g., exenatide, liraglutide), and insulin are treatment options for diabetes. The proper selection of an antidiabetic drug(s) varies from patient to patient which mainly depends on several factors including diabetes-related complications, such as heart diseases, high blood pressure, kidney diseases, etc. Type 2 diabetes mellitus leads to an increased risk of cardiovascular and microvascular diseases and mortality.[4,5] According to the WHO 2013 report, cardiovascular disease is responsible for 50-80% death of type 2 diabetes patients.[1] Many evidences suggest that antihyperglycemic drugs itself have potential role in the development and progression of cardiovascular diseases.[3,5] Therefore, the antidiabetic drugs should be chosen carefully in such a way that it does not aggravate the condition of cardiovascular disease in anyway rather the drug may contribute to the wellbeing of cardiovascular diseases. The role of metformin on cardiovascular diseases in patients with diabetes is still not clear.[6] The use of any drug from Sulfonylureas (e.g., glimepiride, glipizide. glibenclamide) highly elevates the incidence of cardiovascular events, stroke and increases the risk of mortality to diabetic patients.[7-9] The combination therapy of sulfonylurea and metformin also significantly associated with an increased risk of death or hospitalization for cardiovascular diseases.[10] The adverse effect of this combination therapy on cardiovascular diseases is believed to come from sulfonylureas, not from metformin. Sulfonylureas are widely used medications for type 2 diabetic patients, therefore, great precautions should be taken before prescribing any drug of this group or these drugs should be contraindicated for patients having any kind of cardiovascular or ischemic diseases in order to prevent drug-induced mortality in type 2 diabetes. Many studies reported that thiazolidinediones raise the risk of cardiovascular diseases, and heart failure [11-13], therefore, those drugs are contraindicated for diabetic patients with progressive heart diseases or heart failure. Preclinical and clinical studies suggested that newer classes of antidiabetic drugs, such as DPP-4 enzyme inhibitors, for example sitagliptin, vildagliptin, linagliptin and alogliptin, and incretin mimetics GLP-1 analogues, for example exenatide, liraglutide, have beneficial effects on blood vessels and heart. [14,15]

American Diabetic Association (ADA)[16] recommends metformin as initial pharmacological agent if not contra-indicated (mainly in case of severe renal impairment). As the adverse-effect of metformin on cardiovascular diseases has not been established, metformin can be recommended to prescribe for diabetic patients with cardiovascular diseases. ADA recommends the addition of a second oral agent or GLP-1 receptor agonist or insulin if the non-insulin monotherapy at maximal tolerated dose fails to achieve or maintain the HbA1c target over 3-6 months. It is noteworthy that in this second line therapy, any drug from sulfonylurea or thiazolidinedione groups is contraindicated for diabetic patients having any sort of cardiovascular problems. Other oral drugs may be considered; especially DPP-4 inhibitors may be a friendly alternative as second oral drug for the add-on therapy to metformin. As most of the diabetic patients die due to the progression and deterioration of cardiovascular diseases associated with diabetes or

*Diabetes Obesity and Genomics Research Group, Clinical Investigation Centre, Faculty of Medicine,University of Malaya, 50603, Kuala Lumpur, Malaysia. Tel: +60 3 7949 2886, Fax: +60 3 7954 1904, E-mail: dr.mokles@um.edu.my; moklesur2002@yahoo.com

drug-inducing effect, proper selection of antidiabetic drugs avoiding drugs from sulfonylureas and thiazolidinediones can save or prolong diabetic patients' life.

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