## *EDITORIAL*

# MANAGEMENT OF HYPERGLYCEMIA IN TYPE2 DIABETES: OLDER AND NEWER DRUGS

Type 2 diabetes is a chronic, progressive, and incompletely understood metabolic disease defined by the presence of chronic hyperglycemia. Although resistance to some actions of insulin and inadequate secretion of insulin for the given metabolic state are the critical abnormalities in type 2 diabetes, several other factors contribute to the hyperglycemic state.

Both the prevalence and incidence of type 2 diabetes are increasing worldwide, particularly in developing countries, in conjunction with increased obesity rates and westernization of lifestyle.Type 2 diabetes remains a leading cause of cardiovascular disorders, blindness, end-stage renal failure, amputations, and hospitalizations.

Prospective randomized trials[ UK Prospective Diabetes Study (UKPDS)] have documented reduced rates of microvascular complications in type 2 diabetic patients treated to lower glycemic targets.

In 2008, three short-term studies [(ACCORD), (ADVANCE), (VADT) ] reported that every HbA1c reduction of 1% may be associated with a 15% relative risk reduction in nonfatal myocardial infarction without benefits on stroke and overall mortality

Successful research and development efforts have yielded new agents and new classes of drugs that are now available for the treatment of diabetes mellitus. For type 2 diabetes, sulphonylureas and metformin are now joined by thiazolidinediones, DPP4 inhibitors and GLP1 analogues in the therapeutic armamentarium. Many more drugs in these latter classes are currently in development, as well as SGLT2 inhibitors, next generation PPAR modulators, glucokinase inhibitors, HSD11B1 inhibitors and many others. The persistent urgent medical need for newer and better treatments for diabetes is testament to the rapidly increasing prevalence of the disease on a global scale, from 171 million cases in 2000 to a projected 366 million cases by the year 2030.

Metformin is the cornerstone of type 2 diabetes treatment.. It does not cause weight gain and may result in a slight weight loss, and it rarely causes hypoglycemia; gastrointestinal side effects may occur, especially if therapy is initiated at higher dose.01

Use of Sulfonylurea (e.g., glipizide) is associated with modest weight gain and hypoglycemia. In addition, studies have demonstrated a secondary failure rate that may exceed other drugs, ascribed to an exacerbation of islet dysfunction .Meglitinides (e.g., repaglinide) have actions similar to those of sulfonylureas but have a short duration of action (hours) and are most effective preprandially

Thiazolidinediones (TZDs) are peroxisome proliferator–activated receptor They do not increase the risk of hypoglycemia and may be more durable in their effectiveness than sulfonylureas and metformin Pioglitazone appeared to have a modest benefit on cardiovascular events as a secondary outcome in one large trial involving patients with overt macro vascular disease rosiglitazone, is no longer widely available owing to concerns of increased myocardial infarction risk . Pioglitazone has recently been associated with a possible increased risk of edema and/or heart failure and bladder cancer

Drugs focused on the incretin system have been introduced more recently. Their main advantage is weight loss, which is modest in most patients but can be significant in some. A limiting side effect is nausea and vomiting, particularly early in the course of treatment. The oral dipeptidyl peptidase 4 (DPP-4)

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inhibitors are weight neutral. Typically, neither of the incretin based classes cause hypoglycemia by themselves. The long-term safety of these agents (including their potential for causing pancreatitis), as well as their effects on the risk of cardiovascular disease, are unknown.

Other FDA-approved agents are used less frequently because of the smaller reductions in glycated hemoglobin levels (typically, approximately 0.6%) and, in some cases, side effects Alpha-glucosidase inhibitors (e.g., acarbose) is associated high frequency of gastrointestinal side effects . The bile acid sequestrant colesevelam reduces hepatic glucose production and increases incretin levels by unknown mechanisms; it also reduces LDL cholesterol levels. The dopamine agonist bromocriptine activates D2 dopamine receptors and increases insulin sensitivity by unknown mechanisms; a rapid-release form was approved by the FDA for this indication. Pramlintide, an amylin mimetic, is an injectable agent that stimulates receptors for amylin. It suppresses glucagon secretion delays gastric emptying, and decreases appetite.

The glucose-lowering effectiveness of noninsulin pharmacological agents is said to be high for metformin, sulfonylureas, TZDs, and GLP-1 agonists (expected HbA1c reduction; 1.0–1.5%) and generally lower for meglitinides, DPP-4 inhibitors, AGIs, colesevelam, and bromocriptine (;0.5–1.0%).

Due to the progressive b-cell dysfunction that characterizes type 2 diabetes, insulin replacement therapy is frequently required

In 2002 inzucchi and colleagues from Yale University found that most diabetic medications in combination confer additional benefit and long term micro and marovascular riswk reduction was demonstrated only with sulphonylureas and metformin.

Generally clinician must choose between older less expensive medications (eg. Metformin or Sulfoynuria) and the newer more expensive medications e.g TZDs meglinides. In addition clinician must consider the concerns about(1) glucose lowering efficacy of each drugs,(2)Effect on long term clinical outcome e.g. cardiovascular mortality (3)Safety of drug.

As supported by a number of professional guidelines, the presence of diabetes warrants consideration of aggressive primary and secondary cardiovascular risk modification therapies that include but extend well beyond strategies to improve glycemic control.

Compared with newer, more expensive agents (thiazolidinediones, alpha-glucosidase inhibitors, and meglitinides), older agents (second-generation sulfonylureas and metformin) have similar or superior effects on glycemic control, lipids, and other intermediate end points. Large, long-term comparative studies are needed to determine the comparative effects of oral diabetes agents on hard clinical end points.

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*J Dhaka Med Coll. 2012; 21(1) : 1-2.*

**References**

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