



Muhammad Umar Wahab

University of Leicester, UK

Efficacy and cardiovascular effects of dipeptidyl peptidase-4 (DPP4) inhibitors: A systematic review

Background: The dipeptidyl peptidase-4 (DPP4) inhibitors (or “gliptins”) are an important new class of incretin-based therapy for treatment of type 2 diabetes mellitus (T2DM). These drugs prolong the action of incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), by inhibiting their breakdown. The incretin hormones increase insulin secretion and suppress glucagon levels. Evidence on the efficacy of these drugs in controlling glycemic levels in T2DM has been accumulating. Furthermore, given that the risk of cardiovascular (CV) disease is substantially greater in people with diabetes compared to those without diabetes, CV safety profiles of these agents have been considered important in their selection for T2DM treatment.

Aims: This paper reviews the efficacy and CV effects of DPP-4 inhibitors from published reports and randomized controlled trials (RCT), e.g. SAVOR-TIMI 53, EXAMINE, and TECOS, for evidence that these drugs are effective in controlling glycemia and have acceptable CV profiles in adult patients with T2DM.

Method: Relevant studies were searched on Medline, PubMed, Embase and Cochrane Central Register of RCT. We also searched relevant web sites, citations, references lists, and published abstracts presented at seminars and conferences. We reviewed RCT published in English from 2000-2015 on therapy efficacy and CV effects of DPP-4 Inhibitors. The

inclusion criteria for analysis included study duration of at least 12 weeks and enrolment of more than 30 participants. HbA1c reduction of at least 0.5%-1.0% was selected as efficacy outcome. CV effects were considered as major adverse cardiovascular events (MACE) in non-pregnant adults with T2DM. Type 1 diabetes mellitus patients were excluded from this review.

Results: A total of 59 studies met the selection criteria (Alogliptin 7, Linagliptin 7, Saxagliptin 8, Vildagliptin 15, Sitagliptin 22). The reviewed studies differed with regard to patient population and duration. However, DPP-4 inhibitors conclusively showed efficacy in lowering glycemic levels and achieving a meaningful reduction of HbA1c from the baseline when used as a monotherapy or as an add-on therapy, with a majority of T2DM patients achieving HbA1c levels of <7% (Table I). The Saxagliptin SAVOR-TIMI 53 trial showed that the drug is safe for cardiovascular patients with no significant increase in endpoint of MACE (HR1.02, CI 0.94-1.11, p=0.66), but slightly increases the risk of hospitalization with heart failures. EXAMINE trial using Alogliptin also showed the same results with no significant increase in MACE events as compared to placebo (HR 0.96, p<0.001). The TECOS trial using Sitagliptin did not show increased risk for major adverse CV events or hospitalization for heart failure. The differences in heart failure outcomes notwithstanding, the studies show similar findings

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for hospitalization for unstable angina, myocardial infarction, and CV death.

Discussion: DPP-4 Inhibitors have shown proven efficacy in controlling glycemia in T2DM. Results of the major CV outcome

trials with three DPP-4 inhibitors reassure that incretin-based therapies have neutral CV safety profiles in patients with T2DM. The heart failure findings in SAVOR-TIMI 53 require further study of the mechanism of action of saxagliptin on cardiac function in patients with T2DM.

Biography

Muhammad Umar Wahab got his MBBS degree from Khyber Medical College, Peshawar, in 2005. He did his House Job the following year in Medicine at Khyber Teaching Hospital, and in Surgery at prestigious Lady Reading Hospital, both in Peshawar. He then worked as a Medical Officer in a Surgical ward and clinic with Professor Dr. Abdus Samad Khan for a year and worked at the same time as a private General Practitioner. Later he served as an HIV Coordinator in a collaborative project of UNICEF and Center of Excellence for Rural Development (CERD) in Pakistan. Dr. Umar subsequently worked for two years as a General Practitioner in a general hospital of Ministry of Health, Saudi Arabia. He then moved to United Kingdom and completed his post-graduate diploma in Diabetes from Leicester University in April 2015. He was offered scholarship and completed his Master's Degree in Diabetes from prestigious South Wales University. He currently working as a Founding consultant Diabetologist in The Diabetes Centre, Islamabad and also state of the art Umar Diabetes and Foot Care Centre UDFC, Islamabad. He is a staunch advocate for diabetes awareness and education of general public, especially children, and has been instrumental in initiating Diabetes Awareness and Education program in Islamabad schools. While in clinical practice, Diabetes remained his area of keen interest and with this academic venture, he is well familiar with current trends, updated evidence based recommendations and guidelines to evaluate and manage all clinical conditions like Diabetes, Hypertension and Dyslipidaemia. He presented many state of the art presentations on many international forums like IDF, Diabetes UK.

dromarwahab@yahoo.com

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