Cardiovascular Safety of Saxagliptin in Patients With Type 2 Diabetes Mellitus: A Systematic Review And Meta-analysis

INTRODUCTION
- Cardiovascular (CV) disease is the leading cause of mortality and morbidity in patients with type 2 diabetes mellitus (T2DM).
- Each 1% increase in HbA1c increases the risk of heart failure (HF) hospitalization or HF death by 8%.
- The US FDA recommended in 2008 that CV safety should be assessed as a component of the clinical development program of any antihyperglycemic drugs.
- Saxagliptin is an orally active DPP-4 inhibitor approved for glycemic control in adults with T2DM.
- Cardiovascular safety of saxagliptin (and other DPP-4 inhibitors) is controversial with the recently reported SAVOR-TIMI 53 study suggesting that saxagliptin is associated with an increased risk of hospitalization due to heart failure.

OBJECTIVE
- To evaluate the association between saxagliptin and cardiovascular risk in patients with type 2 diabetes mellitus (T2DM).

MATERIALS AND METHODS
- Literature searches were performed in PubMed, CENTRAL, and ClinicalTrials.gov databases from inception.
- An initial search using the terms "diabetes mellitus," "saxagliptin," "safety," and "cardiovascular" was followed by a search of related citations.
- All randomised controlled trials (RCTs) that compared saxagliptin against placebo, or active antidiabetic drugs in adult patients (≥18 years) with T2DM, and reported cardiovascular outcomes were included.
- In addition, references of the included studies were screened for additional studies.
- Four authors independently screened titles, abstracts, and subsequently the full texts of all the potentially relevant studies. The same four authors extracted data and assessed risk of bias using the modified Jadad scale.

RESULTS
- A total of 19 trials involving 27,278 patients were included, with a mean HbA1c of 8.2±0.8%, mean age 60±11 years, and mean BMI 30±4.9 kg/m².
- A total of 16,469 received saxagliptin once daily and 10,819 received comparators.
- Overall, the risk of bias of included trials was low.

DISCUSSION
- Currently available drugs for the pharmacotherapy of T2DM, apart from insulin, include metformin, the insulin secretagogues (sulfonylureas and meglitinides), thiazolidinediones, o-glucoside inhibitors, the amylin analogue pramlintide, GLP-1 agonists, and the dipeptidyl peptidase 4 inhibitors (DPP-4Is).
- DPP-4 inhibitors inhibit the inactivation of the incretin hormones, glucagon-like peptide 1 (GLP-1) and glucagon-dependent insulinotropic peptide, resulting in increased glucose-dependent insulin secretion and suppression of glucagon secretion.
- Saxagliptin is a useful drug for the treatment of type 2 diabetes, both as monotherapy and in combination with other antihyperglycemic drugs.
- The recently reported SAVOR-TIMI 53 trial demonstrated that saxagliptin did not increase or decrease the rate of ischemic events.
- Subsequently, an analysis of pooled data from 20 clinical trials comprising over 9000 patients with T2DM evaluated saxagliptin was not associated with an increased risk for ischemic events.
- However, it was observed that the rate of hospitalization for heart failure was increased after treatment with saxagliptin.
- This increase in heart failure hospitalization risk was seen irrespective of age category, being highest among patients with elevated levels of natriuretic peptides, previous heart failure, or chronic kidney disease.

CONCLUSION
- Evidence suggests no increased risk of MI, cardiovascular mortality, CHF, or angina pectoris with saxagliptin 2.5 mg or 5 mg in T2DM patients.
- However, limited evidence suggests that saxagliptin 5 mg is associated with increased risk of heart failure among T2DM patients.
- Further studies are required to collaborate this finding.

REFERENCE