

Title of the review	Dipeptidyl peptidase-4 inhibitors associated heart failure events in adult patients with type-2 diabetes mellitus treated with dipeptidyl peptidase-4 inhibitors: A systematic review and meta-analysis
First reviewer	Shishir Nepal
Team of reviewers	Shiva Prasad Nepal

1. Background to review

Diabetes mellitus is a clinical syndrome showing hyperglycemia caused by insulin deficiency which maybe relative or absolute deficiency. Broadly diabetes mellitus has been divided into four categories; Type 1, Type 2, Gestational and Other specific types [1,2]. Type 1 diabetes is caused by autoimmunity mediated destruction of beta cells in islets of pancreas. Type 2 diabetes is more complex condition than type 1 and is often characterized by combination of insulin resistance in liver and muscle cells and improper pancreatic beta cell functions [3]. Non-pharmacological approaches in managing diabetes mellitus revolves around adequate glycemic control which can be achieved by diet, weight management and lifestyle changes. Pharmacological interventions aim at reducing HbA1c glycated hemoglobin, blood glucose level, insulin replacement, decreasing insulin resistance. Ultimately these aim at reducing micro and macro vascular complications, neuropathy, retinopathy, ketoacidosis and other complications [4]. Oral antidiabetic medications are effective in type 2 diabetes patients in reducing hyperglycemia. They include sulfonylureas, meglitinides, thiazolidinediones, alpha glucosidase inhibitors, (dipeptidyl peptidase-4) DPP-4 inhibitors, and (Sodium Glucose Transporter-2) SGLT-2 inhibitors. DPP-4 Inhibitors work by blocking action of dipeptidyl peptidase enzyme which is responsible for rapid degradation of (Glucagon like peptide-1) GLP-1. GLP-1 is one of the groups of “incretins” which are responsible for release of insulin in glucose dependent manner as insulin secretion is enhanced when blood glucose level is elevated. Additionally, GLP-1 slows gastric emptying, suppresses appetite, and promotes weight loss, ideal for type-2 diabetes management. DPP-4 inhibitors increase endogenous GLP-1 to achieve its anti-diabetic effect, as GLP-1 promotes insulin release in glucose dependent manner it is less likely to cause hypoglycemia unlike sulfonylureas [5,6]. DPP-4 Inhibitor class drugs include saxagliptin, linagliptin, sitagliptin, alogliptin and others. Common side effects of these class drugs include upper respiratory tract infections, nasopharyngitis, arthralgia, headache and urinary tract infections [7]. US Food and Drug Administration’s review committee had issued warnings regarding severe joint pains likely attributed to DPP-4 inhibitors class drugs and increased heart failure risks for saxagliptin and alogliptin and their combination with metformin [8,9]. The proposed mechanism is increased sympathetic activation of cardiac myocytes and potentiation of Stromal cell derived growth factor-1, neuropeptide-y, substance-P resulting in cardiac myocytes death and ultimately heart failure [10]. Some studies has been done regarding use of DPP-4 inhibitors and increased risk of heart failure among type-2 diabetic patients but results have been inconclusive [11]. Some studies have shown increased risk of heart failure while others show opposite with increased ejection fraction [12], therefore this study aims at drawing inferences regarding the use of DPP-4 Inhibitors among type-2 diabetic patients and risk of heart failure associated with DPP-4 Inhibitors intake.

2. Specific objectives

1. To identify any association or risks relating to heart failure events with intake of dipeptidyl peptidase-4 inhibitor drugs among patients with type-2 diabetes treated with dipeptidyl peptidase-4 inhibitors. There has not been a conclusive study done regarding this research question.
2. To synthesize Risk-ratio of heart failure events associated with dipeptidyl peptidase-4 inhibitor intake in type-2 diabetes patients treated with dipeptidyl peptidase-4 inhibitors

3. a) Criteria for including studies in the review	
i. Population, or participants and conditions of interest	Adult patients with type-2 diabetes mellitus aged 18 years and above, any gender, with or without history of heart failure, journal articles from any part of the world in English language
ii. Interventions or exposures	Dipeptidyl peptidase-4 Inhibitor drugs ‘gliptins’
iii. Comparisons or control groups	Patients with type-2 diabetes mellitus who were given placebo
iv. Outcomes of interest	Risk-Ratio (RR) of heart failure events
v. Setting	Hospital admissions, Clinics
vi. Study designs	Randomized controlled trials (RCTs)

3. b) Criteria for excluding studies not covered in inclusion criteria
Pediatric patients, studies not reporting quantitative data for heart failure events, studies other than randomized controlled trials, studies in languages other than English, non-open access and non-full text available studies.

4. Search methods	
Electronic databases	pubmed/medline mdpi doaj clinicaltrials.gov google scholar
Other methods used for identifying relevant research	Reference checking
Journals hand searched	N/A

5. Methods of review	
Details of methods	Two main reviewers and any disagreements will be resolved through discussion.
Quality assessment	The methodological quality and risk of bias of included studies will be independently assessed by two reviewers. Randomized controlled trials will be assessed using Cochrane Risk of Bias tool (RoB 2).

Data extraction	Data extraction will be done in MS-Excel as .csv file by two reviewers independently and later tallied and discussed to be used in the synthesis. Data Zotero ver.7 will be used for keeping track of references Both reviewers will review independently then data will be tallied and final extraction will be done through discussion. MS-Excel file will be made for recording final data from extraction.
Narrative synthesis	Narrative synthesis will be done alongside any meta-analysis and will be carried out using a framework which consists of four elements; 1. Developing a theory of how the intervention works, why and for whom 2. Developing a preliminary synthesis of findings of included studies 3. Exploring relationships within and between studies 4. Assessing the robustness of the synthesis
Meta-analysis	Meta-Analysis will be done if data suffices. Based on the data gathered meta-analysis will be done using Random effect model for Risk-Ratios. Heterogeneity will be tested using I^2 , Tau, Tau squared, df, Q, and p statistics.
Grading evidence	N/A

6. Presentation of results	
Additional material	PRISMA 2020 Flow Diagram of the selection process. Protocol Data extraction table Forest plots of studies included in the final review Funnel plot

Outputs from review	Open access journals
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7. Timeline for review – when do you aim to complete each stage of the review	
Protocol	1 week
Literature searching	1 week
Quality appraisal	3 days
Data extraction	3 days
Synthesis	3 days
Writing up	1 week

References

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