Current evidence on the effect of DPP-4 inhibitor drugs on mortality in type 2 diabetic (T2D) patients: A meta-analysis



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Contents

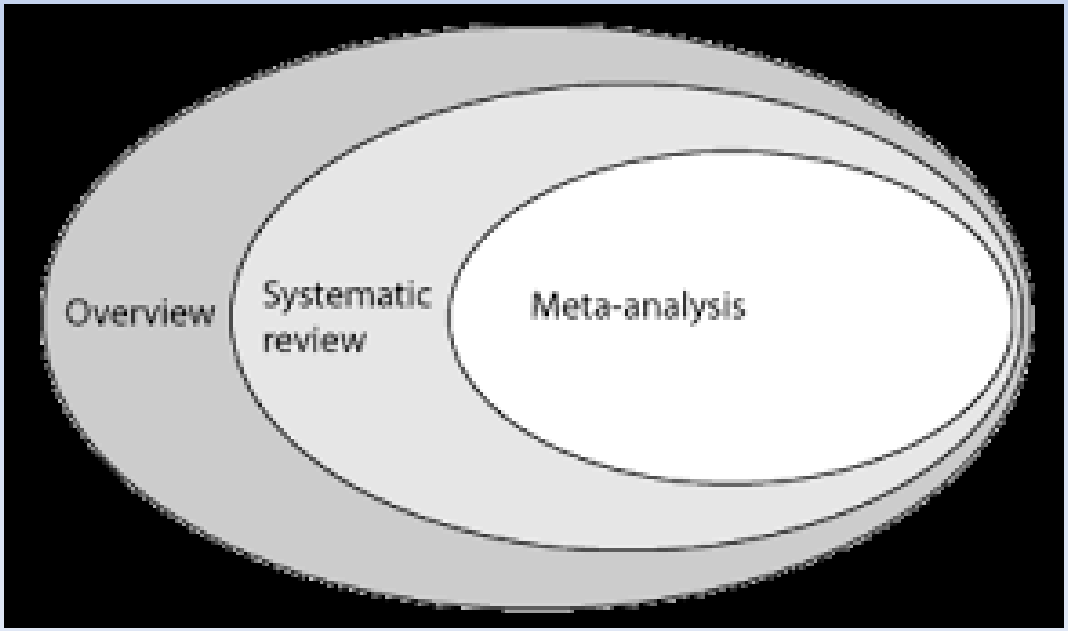
- Background
- Meta Analysis
- About Dipeptidyl peptidase-4 inhibitors (DPP-4)
- Material & Methods
- Study Findings
- Take Away Message
- Selected References



Background

- A meta analysis is a statistical procedure for the synthesis of the results several independent studies that are

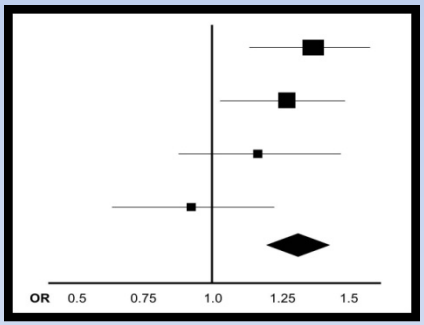
  " combinable"
- Meta-analysis is an observational study for evidence from various studies like randomised controlled trials (RCTs) etc.



Meta Analysis

Purpose

- Objective integration
- Provides a more precise estimate than treatment effect.
- Explains heterogeneity between the results of individual studies.



Essential Steps

- Study Objective ascertaining
- Hypothesis testing
- Subgroups of interest
- Proposed methods and criteria for identifying and selecting studies
- Extracting and analysing information using statistics.

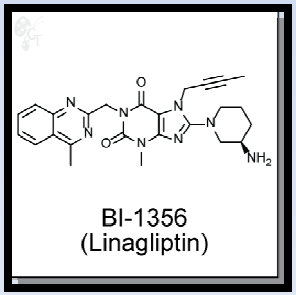
The effect of DPP-4 inhibitor drugs on mortality in type 2 diabetic (T2D) patients: A meta-analysis

- This meta-analysis throws light on the current understanding from concluded randomized controlled trials (RCTs) before 2014 on the extent of impact of dipeptidyl peptidase-4 inhibitor (DPP-4) drugs on overall mortality in patients of type 2 diabetes mellitus.

Source of data

The present meta-analysis was aimed at of all randomized controlled trials involving DPP-4 inhibitors that were published before February 2014 was carried out. Published articles in bibliographic and abstracting electronic databases such as Pubmed central, Cochrane reviews and other medical journals served as the data sources for the present study.

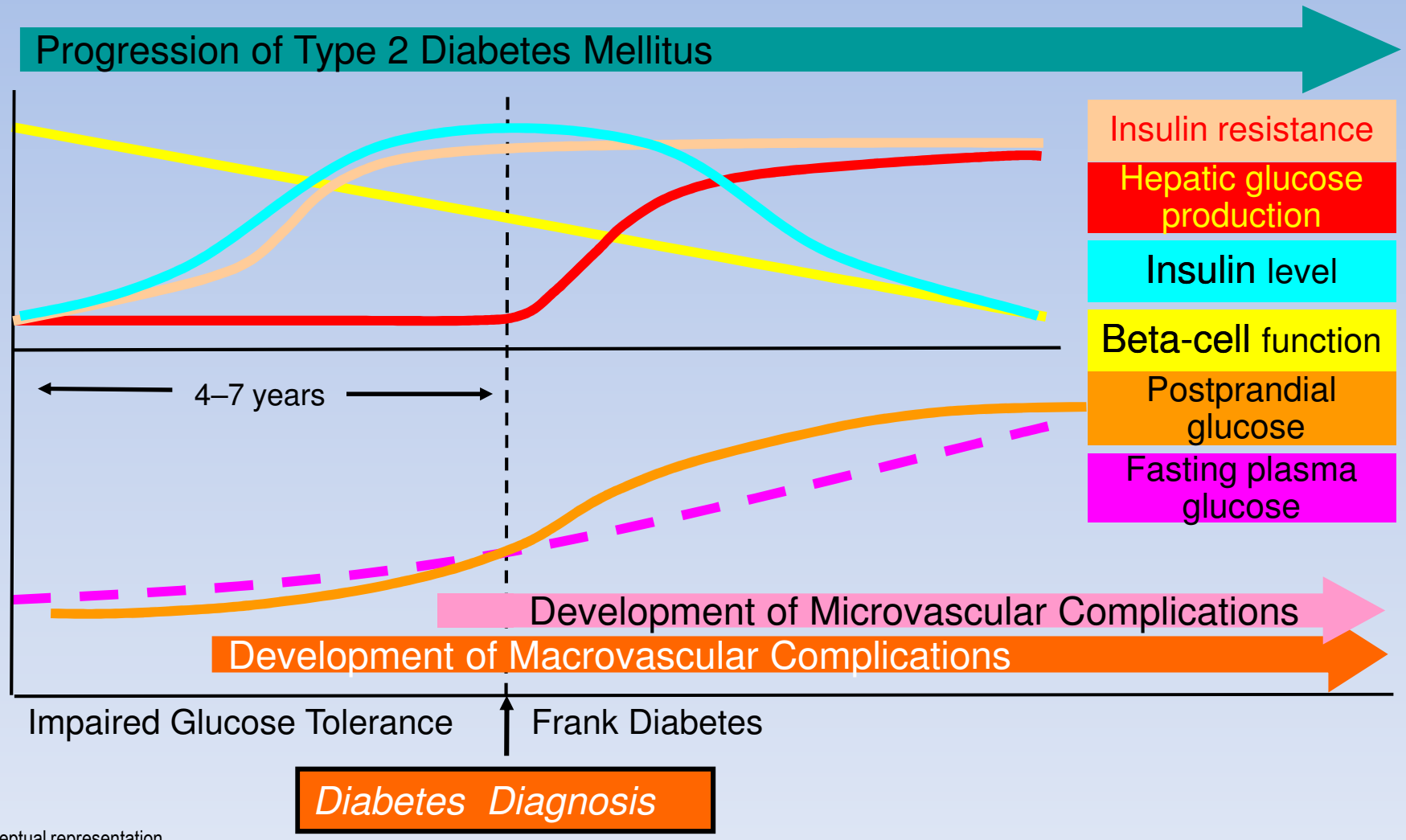
Clinical endpoints



Risk ratio, Coronary artery disease on mortality,

Cardiovascular mortality or All cause mortality.

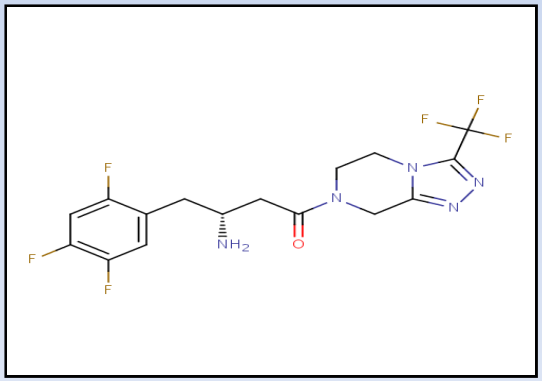
Development and Progression of Type 2 Diabetes



[a]Conceptual representation.
From :Ramlo-Halsted et al. *Primary Care.* 1999; 26(4):771–789.

About DPP-4 Inhibitors

- **Mode of action:** Dipeptidyl peptidase-4 inhibitor drugs block the enzyme DPP-4 thereby breakdown of GLP-1,GIP in the bloodstream.
- **HbA1c reduction in monotherapy : 0.5-0.8 %**
- **Reduction in FBG: 15-30 mg/dl**
- **Reduction in PPG: 35-50 mg/dl**
- **Side effects:** Possible hypoglycemia when it is used alongwith insulin or insulin secretagogues. Nasopharyngitis (the common cold), headache, nausea, hypersensitivity and skin reactions, have been observed in clinical studies.



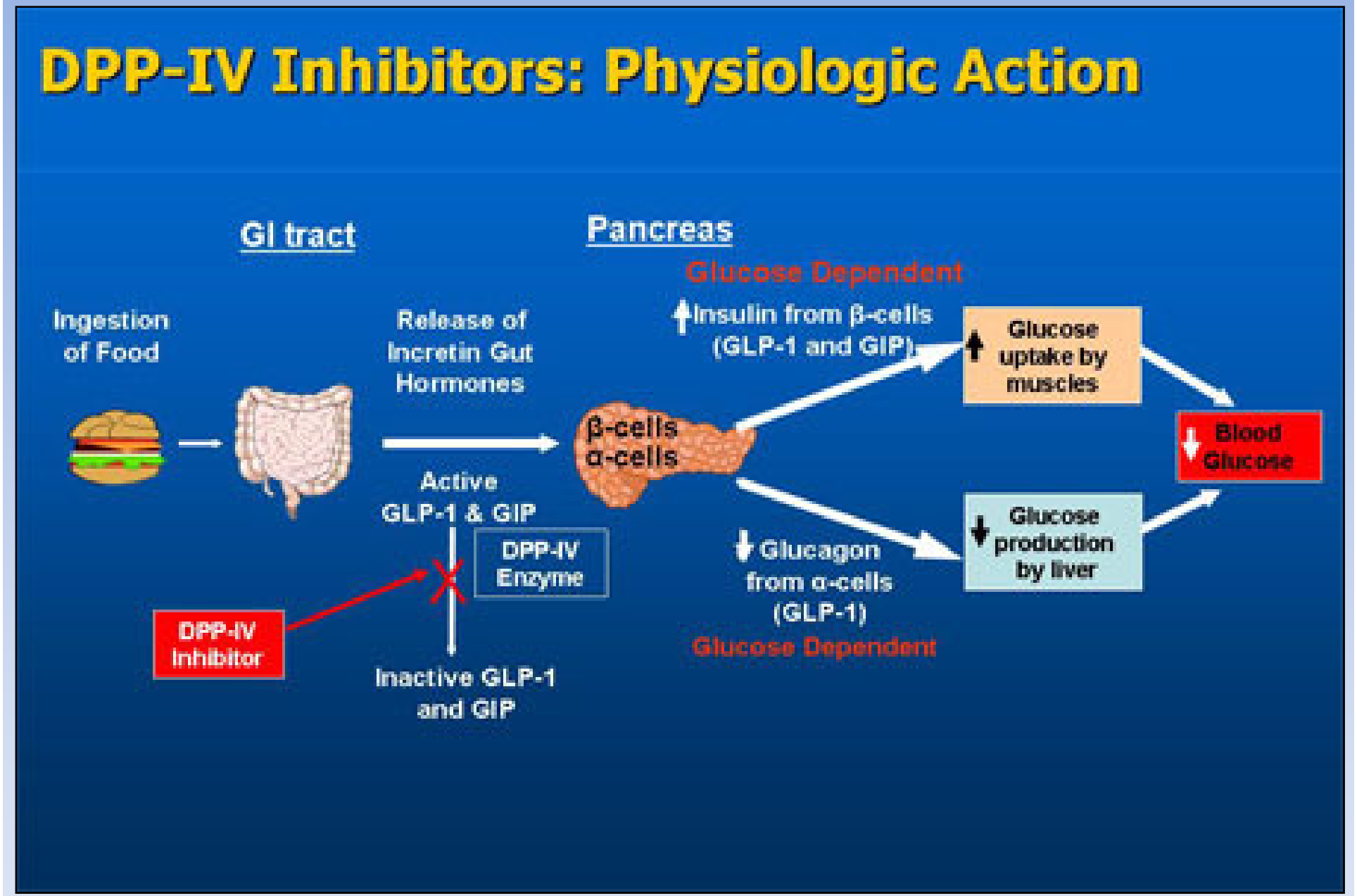
Structure of sitagliptin

Typical HbA1C Reduction

Approved Antidiabetic Medications in the United States			
Medication	**Route of Administration**	**Year of Introduction or FDA Approval**	**Efficacy as Monotherapy (% Reduction in A1C)**
Insulin	Subcutaneously	**1921**	**2.5**
Sulfonylureas	Oral	1946	1.5
Metformin*	Oral	1995	1.5
Alpha-glycosidase Inhibitors	Oral	1995	0.5-0.8
Thiazolidinediones	Oral	1997	0.8-1.0
Glinides	Oral	1997	1.0-1.5
GLP-1 Analogs	Subcutaneously	2005	0.6
Amylin Analogs	Subcutaneously	2005	0.6- 2.1
DPP-IV Inhibitors	Oral	2006	0.5-0.9

*Adapted from Nathan DM. *N Engl J Med.* 2007;356(5):437-440.

DPP-IV Inhibitors: Physiologic Action



Adapted from Kieffer TJ, Habener JF. *Endocr Rev*. 1999;20:876–913; Ahrén B. *Curr Diab Rep*. 2003;2:365–372; Drucker DJ. *Diabetes Care*. 2003;26:2929–2940; Holst JJ. *Diabetes Metab Res Rev*. 2002;18:430–441.

TABLE 1

SUMMARY OF KEY BENEFITS AND RISKS OF MEDICATIONS

Benefits are classified according to major effects on fasting glucose, postprandial glucose, and nonalcoholic fatty liver disease (NAFLD). Eight broad categories of risks are summarized. The intensity of the background shading of the cells reflects relative importance of the benefit or risk.*

	MEDICATIONS*									
	Metformin (MET)	DPP4 inhibitor	GLP-1 Agonist (Incretin Mimetic)	Sulfonylurea (SU)	Glinide**	Thiazolidinedione (TZD)	Colesevelam	Alpha-glucosidase inhibitor (AGI)	Insulin	Pramlintide
BENEFITS										
Postprandial Glucose (PPG) - lowering	Mild	Moderate	Moderate to Marked	Moderate	Moderate	Mild	Mild	Moderate	Moderate to Marked	Moderate to Marked
Fasting glucose (FPG) - lowering	Moderate	Mild	Mild	Moderate	Mild	Moderate	Mild	Neutral	Moderate to Marked	Mild
Nonalcoholic fatty liver disease (NAFLD)	Mild	Neutral	Mild	Neutral	Neutra	Moderate	Neutral	Neutral	Neutral	Neutral
RISKS										
Hypoglycemia	Neutral	Neutral	Neutral	Moderate	Mild	Neutral	Neutral	Neutral	Moderate to Severe	Neutral
Gastrointestinal Symptoms	Moderate	Neutral	Moderate	Neutral	Neutral	Neutral	Moderate	Moderate	Neutral	Moderate
Risk of use with renal insufficiency	Severe	Reduce Dosage	Moderate	Moderate	Neutral	Mild	Neutral	Neutral	Moderate	Unknown
Contraindicated in Liver Failure or Predisposition to Lactic Acidosis	Severe	Neutral	Neutral	Moderate	Moderate	Moderate	Neutral	Neutral	Neutral	Neutral
Heart failure / Edema	Contra-indicated in CHF	Neutral	Neutral	Neutral	Neutral	Mild / Moderate Contraindicated in class 3,4 CHF	Neutral	Neutral	Neutral unless with TZD	Neutral
Weight Gain	Benefit	Neutral	Benefit	Mild	Mild	Moderate	Neutral	Neutral	Mild to Moderate	Benefit
Fractures	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral
Drug-Drug interactions	Neutral	Neutral	Neutral	Moderate	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral

* *The abbreviations used here correspond to those used on the algorithm (Fig. 1).*

** *The term 'glinide' includes both repaglinide and nateglinide.*

Available at www.aace.com/pub

Materials & Methods

- The article selection criteria for the meta analysis included all randomized placebo-controlled trials of at least one year duration and those which measured at least one of the following clinical endpoints: risk ratio, coronary artery disease mortality, cardio-vascular mortality or all-cause mortality. Information on sample size, follow up period, drug used, and clinical outcomes was abstracted independently by the authors.

- The present meta-analysis compiled pooled data from 18 randomised controlled trials (RCTs) fulfilling the inclusion criteria of the study (18 trials, 5903 patients) showed a significant relative risk reduction of coronary artery disease mortality, cardiovascular disease mortality and on all-cause mortality without any significant heterogeneity and inconsistency between the trials.

Study Findings

Meta analysis study findings (18 trials, 5903 patients)

- DPP-4 inhibitors were associated with a smaller decline in HbA1C levels.
- DPP-4 inhibitors were inferior to GLP-1 agonists in reducing HbA1C.
- No differences were observed with DPP-4 inhibitors versus other antihyperglycemic therapies with regard to all-cause mortality.
- An increased risk for hypoglycemia was seen with sulfonylurea + metformin combination therapy vs DPP-4 inhibitor + metformin combination therapy

Take Home Message



- From the pooled meta-analysed findings it was inferred about that the dipeptidyl peptidase-4 inhibitors that no significant differences were observed with DPP-4 inhibitors versus other anti hyperglycemic therapies with regard to all-cause mortality. DPP-4 inhibitor monotherapy do not have any major risk or benefit over other alternatives as far as cardiovascular system risk is concerned.
  - A combination of DPP-4 inhibitors+ metformin therapy is favoured statistically against DPP-4 monotherapy.

Selected References

- Karagiannis T, Paschos P, Paletas K, Matthews DR, Tsapas A. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis.
  BMJ. 2012 Mar 12;344:e1369. doi: 10.1136/bmj.e1369.
- Diabetes Obes Metab. 2014 Oct;16(10):977-83. doi: 10.1111/dom.12306. Epub 2014 May 22.
- Cochrane Database Syst Rev. 2008 Apr 16;(2):CD006739. doi: 10.1002/14651858.CD006739.pub2.
- Cardiovasc Ther. 2014 Aug;32(4):147-58. doi: 10.1111/1755-5922.12075.


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