Original Article

Effect of Dipeptidyl Peptidase 4 Inhibitors on Cardiovascular Events in Type-2 Diabetes Patients with Renal Impairment: A Systematic Review and Meta-analysis

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Abstract

Background: Recent studies suggested that the increased risk of heart failure by DPP-4 inhibitors may have an interconnection with patients' baseline eGFR. We decided to investigate the effect of DPP-4 inhibitors and the degree of renal function on cardiovascular (CV) safety in type 2 diabetes (T2D) patients. **Materials and Methods:** Systemic search of literature that examined the DPP-4 inhibitors and reported cardiovascular outcomes in diabetes patients with renal impairment were performed. Studies were examined for inclusion criteria: Randomized controlled trials with reduced renal function taking DPP-4 inhibitors alone or in combination with other anti-diabetes agents reporting evaluable CV events for at least 24 weeks. **Result:** Analysis of four CV outcome studies (11,789 patients with eGFR ≤60 ml/min/1.73m^2) did not find any increase in primary composite endpoints with DPP-4 inhibitors in patients stratified by baseline renal function. Rate of hospitalization due to heart failure (hHF) is found to be non-inferior to placebo group in patients with renal insufficiency (RR 1.07; 95% CI, 0.96-1.20 $P = 0.26$). In moderate renal dysfunction, there is a significant increase in heart failure risk compared to placebo. (RR 1.27; 95% CI, 1.033 -1.5 8; $P = 0.024$). **Conclusion:** Treatment with DPP-4 inhibitors did not affect the risk of cardiovascular events regardless of baseline renal function, however, an increase in the risk of hHF in moderate renal function in T2D patients with high CV risk merits careful consideration. Further research would be necessitated to reach definitive conclusion to understand the effect of declining renal function on CV safety of DPP-4 inhibitors.

Keywords: Cardiovascular safety, DPP-4 inhibitors, renal impairment

Introduction

Type-2 Diabetes mellitus (T2D) has grown into pandemic proportion to impose a considerable healthcare burden across the globe. Incidence of microvascular and macrovascular complications is reported to be increased along with the increased prevalence of T2D with a consequent increase in kidney disease.[1] Approximately, 40% of patients with diabetes upon screening for decreased estimated glomerular filtration rate (eGFR) and albuminuria have evidence of chronic kidney disease (CKD).[2] In the adult Indian population, a community-based screening for CKD (SEEK-Screening and Early Evaluation of Kidney Disease) suggested a nearly 2-fold increased risk in the presence of diabetes.[3] In addition, cardiovascular (CV) events are reported to be increased by 19%–40% as the eGFR declines from ≥90 mL/min/1.73 m^2 to <45 mL/min/1.73 m^2.[4] Despite the common and dangerous coexistence of cardiometabolic conditions in T2D, the effect of optimal glycemic control on cardiovascular risk is not well defined in such patients. Furthermore, declining eGFR level limits treatment options of oral antidiabetic drug (OAD) available for achieving optimal glycemic control. In T2D patients with reduced renal function, various factors related to pharmacological treatment such as altered pharmacokinetics, increased hypoglycemic risk, concurrent drug interaction, and need of dosing adjustment introduce constraints in the routine use of conventional OADs.[5]

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Over the last decade, dipeptidyl peptidase inhibitor (DPP-4i), oral glucose-lowering agent has emerged as an important second-line option in type-2 diabetes management. This is one of the few effective treatment options available in renal compromised patients affording a better safety and tolerability profile like lower incidence of hypoglycemia and less weight gain. However, uncertainty around the risk of occurrence of heart failure (HF) with this class has attracted much attention due to its huge clinical implication, given the widespread use of this medication in current practice. Taking its good safety profile in renal impairment and ongoing controversy related to CV safety into consideration, we decided to evaluate the clinical impact of renal impairment on CV safety of DPP-4i in terms of cardiovascular outcome including heart failure in T2D patients.

Material and Methods

The objective is to understand how DPP-4i usage is linked to the risk of cardiovascular events in renal impaired patients with T2D. The conduct and results of the study are reported in accordance with the PRISMA statement.[6]

Randomized controlled trials with subjects with T2DM and declined renal function taking DPP-4i alone or in combination with other oral glucoselowering agents for the duration of at least 24 weeks reporting evaluable composite CV events and/or heart failure were included in this systemic review.

The following comparisons were evaluated:

- Primary composite endpoint in DPP-4i group versus placebo group in renal impaired patients
- Hospitalization due to heart failure (hHF) in DPP-4i group versus placebo group in renal impaired patients.

To identify eligible studies, we searched MEDLINE, ClinicalTrials.gov (till January 2019), and Cochrane central library. Studies are eligible as mentioned in the above criteria.

Studies are excluded if they are not randomized control trial, observational studies, systemic review, no reported renal insufficiency in subjects, not human, study duration <24 weeks, and no information on composite CV endpoints.

Terms used to search the studies were "gliptin and diabetes mellitus and composite primary outcome or cardiovascular outcomes," "DPP 4i and heart failure and renal function," "primary CV outcomes and gliptins and status of renal function," "MACE and gliptins and renal impairment or dysfunction or function or chronic kidney disease or failure".

For each outcome, data was pulled from the number of participants randomized and the number analyzed in each treatment group. We verified dichotomous outcomes by recording the number of participants reporting the event and the event number assessed in each treatment group. We calculated the results using risk ratios (RRs) for dichotomous data as a measure of treatment effect.

Cochrane Collaboration's tool is used to assess the risk of bias of included randomized controlled trials.[7] The items are included such as random sequence generation, allocation concealment, blinding of participants, and assessors of outcomes (i.e., heart failure or hospital admission for heart failure), and adjudication of the outcomes.

The statistical heterogeneity was assessed by looking at the forest plots for overlapping confidence interval (CI), applying the χ^2 test ($P < 0.10$ considered statistically significant), and the I2 to identify moderate levels of heterogeneity. We analyzed the data using Comprehensive Meta-analysis Version 2, Biostat, (Englewood, NJ, USA). This is a systematic review and meta-analysis of previously published original studies and, therefore, ethical approval was not needed.

Results

Four randomized controlled trials involving a total of 43587 patients met our inclusion criteria and were included in the final meta-analysis: Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS),[8] Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 trial (SAVOR TIMI 53),[9] Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE),[10] and Cardiovascular and Renal Microvascular Outcome Study with Linagliptin (CARMELINA).[11] The trial flow is summarized in Figure 1. A total of 11,789 patients reported the CV events in renal compromise patients with baseline eGFR ≤60 mL/min/1.73 m^2 [Table 1]. All four trials are large, prospective trials with blindly adjudicated endpoint and have long follow-up time (>52 weeks). Baseline demographics between treatment and placebo arm have good comparability.

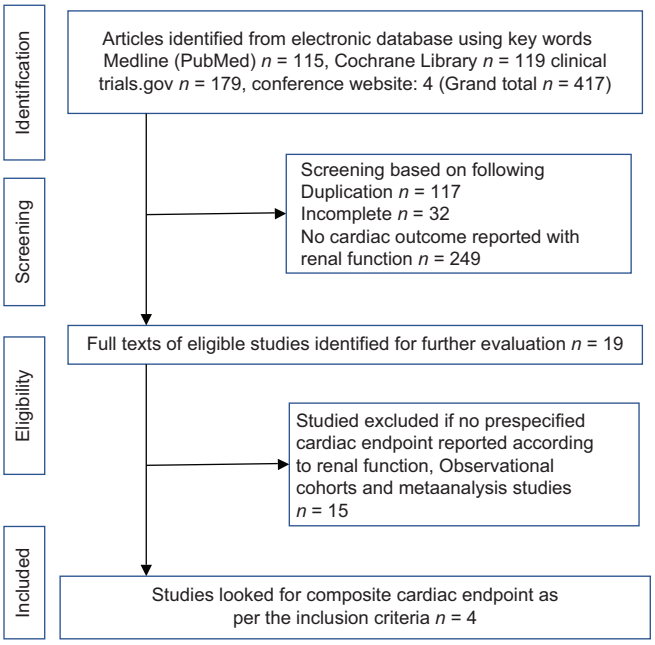

Figure 1: Search strategy flow chart

Table 1: Primary CV composite events and hHF across renal function observed with DPP-4 inhibitor in dedicated CV outcome studies

Clinical Trial	DPP-4i evaluated	Study population	Background therapy %	Duration of study (years)	Proportion of patients with baseline eGFR <60 mL/min/1.73 m²	Status of renal function eGFR (MDRD) mL/min/1.73 m²	% patients in respective baseline eGFR level	Primary Composite endpoint according to baseline eGFR value		Hospitalization of Heart failure according to baseline eGFR value	
								DPP-4i Users Events/total	Comparator/ placebo Events/total	DPP-4i Users events/total	Comparator/ placebo Events/total
TECOS[8,19]	Sitagliptin	14,735	Metformin 81%	3.0	3321 (22.5%)[#]	60-89	54.2	414/3943	385/3936	109/3943	105/3936
			statin 80%			45-59	17.5	184/1252	209/1286	56/1252	51/1286
			Insulin 23%			30-44	5.4	75/414	70/369	35/414	33/369
			TZD 2.7%								
			RAAS blockers 78.3%								
SAVOR TIMI 53 1[9,18]	Saxagliptin	16,492	Metformin 69.9%	2.1	2576 (15.61%)	>50	84.4	459/6986	452/6930	172/6986	139/6930
			Statin 78%			30-≤50	13.6	128/1122	125/1118	96/1122	66/1118
			Insulin 41%			<30	2.1	26/172	32/164	21/171	23/164
			TZD 6.0%								
			RAAS blockers 81.8%								
EXAMINE[10]	Alogliptin	5380	Metformin 66.2%	1.5	1544 (29%)	>60	70	160/1929	185/1886	NA	NA
			Statin 90%			≤60	29	145/772	132/793	NA	NA
			Beta blocker 80%								
			Insulin 30%								
			RAAS blockers 81.5%								
CARMELINA[11,20]	Linagliptin	6980	Metformin 54.8%,	2.2	4348 (62.3)	≥60	37	NA	NA	36/1294	41/1337
			SU 34.9%,			≥45<60	19.7	184/1984	179/1995	38/690	32/658
			Insulin 57.9%			≥30≤45	27.7	250/1510	241/1490	76/994	85/944
			Beta-blockers 4.1%			<30	15.21	NA	NA	59/516	68/546
			RAAS blockers 81%								
Total		43587			11789			2025/20084	2010/19967	698/17382	643/17288

NA: Not available, MDRD: Modification of Diet in Renal Disease study equation; [#]Per inclusion criteria, the study included 9.3% of patients with eGFR <50 mL/min/1.73 m². TECOS, trial evaluating cardiovascular outcomes with sitagliptin; SAVOR-TIMI 53, saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus-thrombolysis in myocardial infarction trial; EXAMINE, examination of cardiovascular outcomes with alogliptin versus standard of care trial; CARMELINA, cardiovascular safety and renal microvascular outcome study with linagliptin

Cardiac outcomes of interest and other endpoints are adequately described across the renal function. Meta-analysis is performed in patients with mild, moderate, and severe renal impairment described in CV outcome studies. The primary analysis is carried out by using the random effect model and reported as relative risk (RR) with 95% confidence intervals (CIs).

To our knowledge, this is the first study to investigate the comparative effect of DPP-4i on cardiovascular outcomes including hospitalization of heart failure (hHF) in patients stratified based on various stages of baseline renal function.

The analysis suggested no increase in the primary composite CV risk with DPP-4i in renal impaired patients (RR 1.002, 95% CI 0.95–1.06; *P* = 0.96) [Figure 2]. When stratified by baseline eGFR values, we are not able to find any increase in CV risk in patients with renal dysfunction when compared to the control arm. Rate of hospitalization due to heart failure risk was non-inferior to the placebo group (RR 1.07, 95% CI 0.96–1.20 *P* = 0.26) [Figure 3]. On closer analysis, the hospitalization rate of heart failure is slightly higher in DPP-4i users with moderate renal dysfunction, especially in stage 3a [Figure 4] relative to placebo (RR 1.27, 95% CI 1.033–1.58 *P* = 0.024). Other DPP-4is like sitagliptin and linagliptin in the similar range of baseline eGFR have not reported any significant rise in rate of hHF compared to placebo arm.

Funnel plot symmetry indicated no publication bias [Supplementary Figure]. The potential for bias in the studies

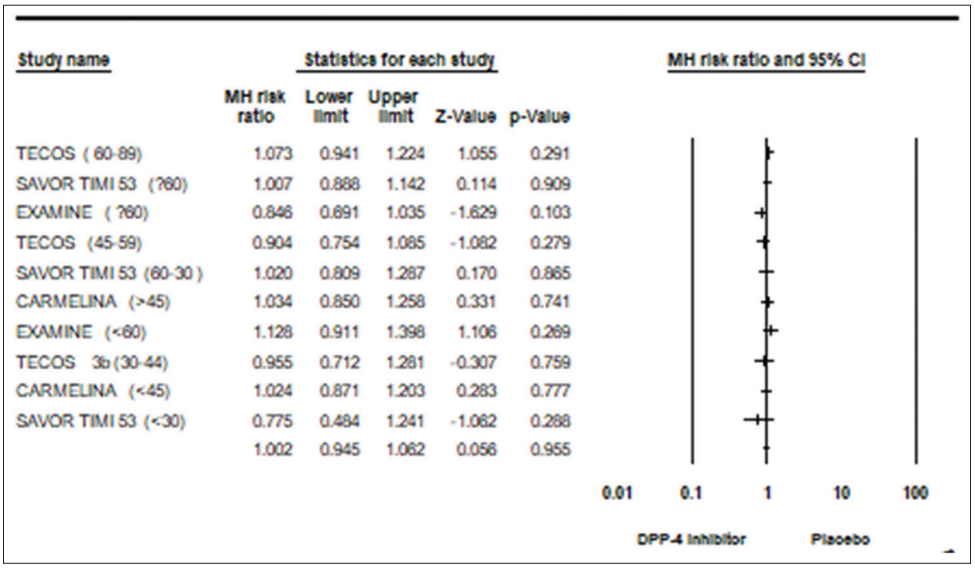

Figure 2: The relative risk of primary composite endpoints with DPP-4 inhibitors vs placebo in T2D with renal impairment in dedicated cardiovascular outcome studies. Heterogeneity: Chi 2 = 7.618 df = 9 (*P* = 0.573) I2 0.000 Tau squared 0.000. Test for overall effect: Z =0.057 (*P* = 0.95)

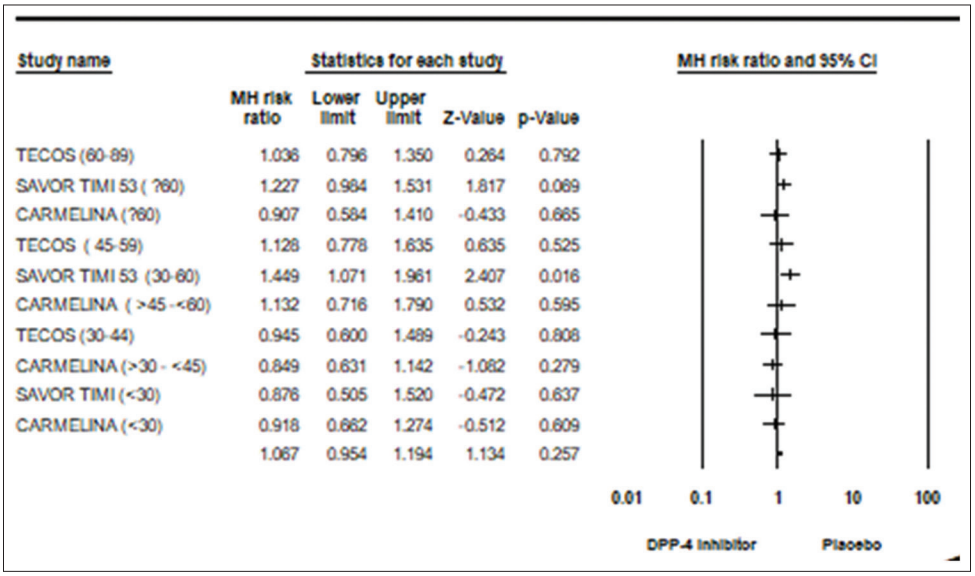

Figure 3: The relative risk of hHF with DPP-4 inhibitors vs placebo in T2D patients with RI in dedicated cardiovascular outcome studies. Heterogeneity: Chi 2 = 10.061 df = 9 (*P* = 0.35) I2 10.54 tau squared 0.003. Test for overall effect: Z (1.19 *P* = 0.26)

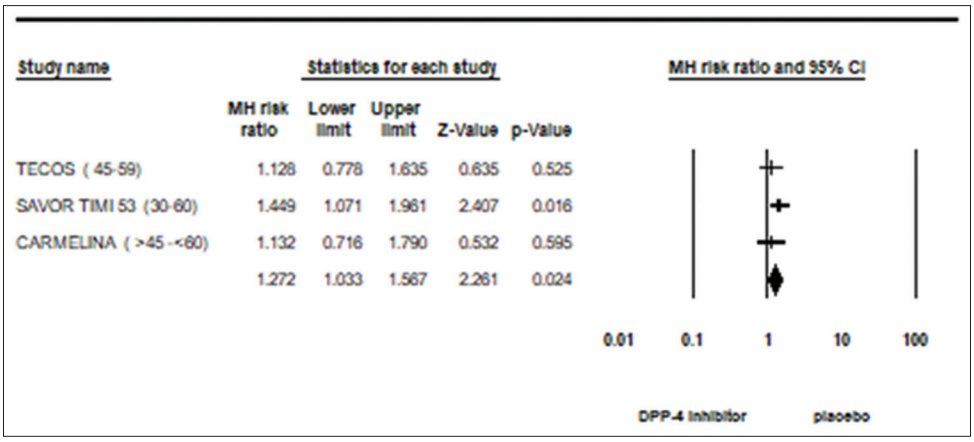

Figure 4: The relative risk of hHF with DPP-4i in moderate (3a) renal impairment in dedicated cardiovascular outcome studies. Heterogeneity: Chi 2 = 1.367 df = 2 (*P* = 0.505) I2 0.000. Test for overall effect: Z (2.261 *P* = 0.024)

was evaluated using the Cochrane collaboration tool for assessing the risk of bias in randomized trials. All included trials were at low risk of bias.

Discussion

The present study demonstrated no increase in major cardiovascular risk with DPP-4i in T2D patients with renal impairment compared to placebo group. [Figure 2] Moreover, this analysis also failed to detect any signal of increase in the risk of hospitalization due to heart failure with DPP-4i in renal impaired patients. [Figure 3] Patients with moderate renal dysfunction (stage 3a) were apparently associated with increase in the risk of heart failure hospitalization in DPP-4 inhibitor group relative to placebo. [Figure 4] Skewed data due to the inclusion of a large cohort of SAVOR TIMI 53 trial may be a plausible interpretation for the observation.

The previous meta-analysis reported consistent results of demonstrating neutrality with CV outcomes between DPP-4i and placebo groups in T2DM patients.[12-14] Other meta-analysis exclusively looking into dedicated CV outcome trials did not find any significant increase in the risk of hHF with DPP-4i similar to findings in the present analysis.[15-17]

In the last decade, rosiglitazone debate raised concerns over CV safety of different glucose-lowering agents and since then, CV safety of antihyperglycemic drugs and optimum glucose control remain a matter of controversy. This was followed by the emergence of a strong signal for hHF in patients receiving saxagliptin in the large prospective CV outcome trial in SAVOR-TIMI 53 in 2013 (HR 1.27, 95% CI 1.07–1.51 *P* = 0.007).[9] Later post-hoc analysis highlighted a moderate association with baseline eGFR level 30–50 mL/min/1.73 m^2 (HR 1.46, 95% CI 1.07–2.00 *P* = 0.02 vs placebo as one of related factors).[18] Similarly, the result from another CV outcome trial EXAMINE (2013) showed a nominal increase in CV events with alogliptin in a patient subgroup with baseline eGFR <60 mL/min per 1.73 m^2 (HR 1.15, 95% CI 0.91–1.46 *P* = 0.046) compared with those with eGFR ≥60 mL/min per 1.73 m^2 (HR 0.84, 95% CI 0.68–1.04; *P* interaction = 0.046).[10] In TECOS trial, no heterogeneity for the effect of sitagliptin on hHF was observed irrespective of baseline eGFR value, though patients with eGFR <30 mL/min were excluded from the trial.[8,19] Subsequently, cardiorenal outcome of linagliptin was evaluated in CARMELINA study.[11] Though the participants had a higher proportion of patients with stage 3 to stage 5 (62.3%) and as low as eGFR of 15 mL/min, endpoints of hHF like incidence of hHF (HR 0.90, 95%CI 0.74–1.08 *P* = 0.26) were not affected with linagliptin by categories of estimated glomerular filtration rate at baseline.[20] The possible mechanism of differential effect of each DPP-4 inhibitor on the risk of HF in renal compromise patients is elusive because of the lack of robust evidence in such complex patient profile in the literature.

Most of the DPP-4is like sitagliptin (87%), saxagliptin (75%), and alogliptin (60%–71%) except linagliptin (5%) are excreted renally affecting their safety profile in altered renal status resulting in increased plasma accumulation of drug and/or metabolites (2.3-, 2.9-, and 2.1-, and 1.7-fold in subjects with moderate renal impairment, respectively).[21] The theoretical problem with exposure to a high level of the agents due to poor renal clearance may carry risks yet unknown due to the ubiquitous presence of DPP-4 enzyme in the human body.[22]

In vitro results demonstrated the off-target deleterious effects of saxagliptin on cardiomyocytes indicating a possible link between DPP-4 inhibition and its potential relationship with heart failure risk, though unconfirmed.[23]

Interaction with ACE inhibitors cannot be ruled out due to unclear mechanism but may relate to blockade of the peptides like substance *P* and/or neuropeptide Y with DPP-4 inhibitors.[24]

The consequence of declined renal clearance might act synergistically with therapeutic plasma concentration of concurrent medications to promote toxicity such as heart

failure with thiazolidinedione therapy. Higher proportion of patients on thiazolidinedione (6%) and insulin (41%) is noted in SAVOR study hinting toward their synergistic action and complex interplay leading to high propensity of potential heart failure risk. Possibly because the sodium-retentive action of thiazolidinedione within the renal tubules is insulin-dependent.[25]

The present meta-analysis provides a distinct perspective to the CV safety of DPP-4i considering the incongruous evidence with new therapies in difficult-to-treat patients. This favorable impact of DPP-4i use in renal compromise patients is a welcome finding but still need a cautious approach while interpreting the results in complex patient setting.

Furthermore, mechanistic trials are necessitated to understand discordant observation reported in the SAVOR-TIMI trial to represent either a potential side effect of saxagliptin *per se* or a class effect. Even this disparate results in patients with an advanced stage of CKD, which may have an influence on the patient's health outcome, especially with high cardiovascular risk, need careful consideration. Additional studies will be required in patients with CKD to stratify the risk-benefit effect of DPP-4i. However, because various studies have excluded patients with ESRD on dialysis, the safety of DPP4 inhibitors was not well characterized in this subset of populations.

There are number of important caveats to be acknowledged with regard to the present meta-analysis such as heterogeneity in baseline variables of study cohorts makes it difficult to compare the CV endpoints in different CV outcome studies. Second, even though the incorporated studies are well-designed randomized clinical trials with enough sample size, the studies were less in number having primary focus on high CV risk making its applicability doubtful in population with less CV risk. Individual CV endpoint of composite outcome like nonfatal MI, nonfatal stroke, and all-cause mortality was not assessed separately ensuing a considerable limitation on a definite conclusion on the safety of DPP-4i in patients**.**

Future trials should be emphasized on exploring the differential impact of DPP-4i on the risk of HF hospitalization and its clinical implication, with the additional inclusion of patients with low eGFR.

Conclusion

The study concludes that there is no increase in major cardiovascular risk with DPP-4i in patients with type-2 diabetes with renal impairment. However, moderate renal dysfunction may be associated with a significant increase in the risk of heart failure in patients with the usage of DPP-4i but needs elaborate attention to understand the absolute correlation. As such, the class effect question remains a pertinent one, and any further light regarding the usage of DPP-4i in renal impairment and subsequent CV outcomes will be of great interest.

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Nil.

Conflict of interest

Dr. Maneesha Khalse is salaried employee of Lupin Limited Pharmaceutical Company, Mumbai, Maharashtra, India.

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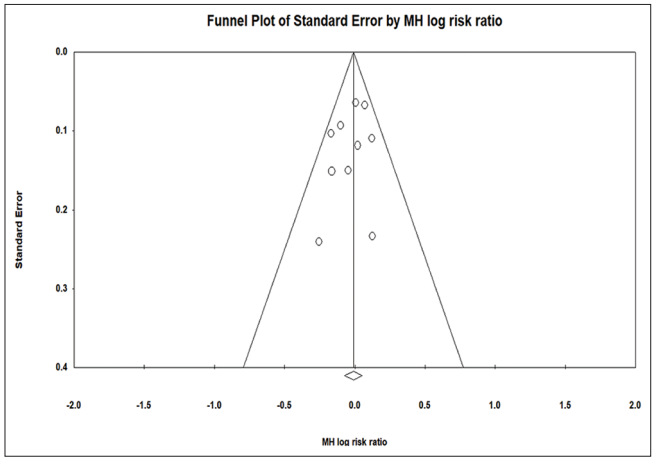

Supplement Figure: Funnel plot showing publication bias for the effect of DPP-4 inhibitors on primary composite cardiac events in T2D patients with renal impairment