Dipeptidyl peptidase-4 inhibitors and risk of heart failure in type 2 diabetes: systematic review and meta-analysis of randomised and observational studies

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ABSTRACT

OBJECTIVES

To examine the association between dipeptidyl peptidase-4 (DPP-4) inhibitors and the risk of heart failure or hospital admission for heart failure in patients with type 2 diabetes.

DESIGN

Systematic review and meta-analysis of randomised and observational studies.

DATA SOURCES

Medline, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov searched up to 25 June 2015, and communication with experts.

ELIGIBILITY CRITERIA

Randomised controlled trials, non-randomised controlled trials, cohort studies, and case-control studies that compared DPP-4 inhibitors against placebo, lifestyle modification, or active antidiabetic drugs in adults with type 2 diabetes, and explicitly reported the outcome of heart failure or hospital admission for heart failure.

DATA COLLECTION AND ANALYSIS

Teams of paired reviewers independently screened for eligible studies, assessed risk of bias, and extracted data using standardised, pilot tested forms. Data from trials and observational studies were pooled separately; quality of evidence was assessed by the GRADE approach.

RESULTS

Eligible studies included 43 trials (n=68 775) and 12 observational studies (nine cohort studies, three nested case-control studies; n=1 777 358). Pooling of 38 trials reporting heart failure provided low quality evidence for a possible similar risk of heart failure between DPP-4 inhibitor use versus control (42/15 701 *v* 33/12 591; odds ratio 0.97 (95% confidence interval 0.61 to 1.56); risk difference 2 fewer (19 fewer to 28 more) events per 1000 patients with type 2 diabetes over five years). The observational studies provided effect estimates generally consistent with trial findings, but with very low quality evidence. Pooling of the five trials reporting admission for heart failure provided moderate quality evidence for an increased risk in patients treated with DPP-4 inhibitors versus control (622/18 554 *v* 552/18 474; 1.13 (1.00 to 1.26); 8 more (0 more to 16 more)). The pooling of adjusted estimates from observational studies similarly suggested (with very low quality evidence) a possible increased risk of admission for heart failure (adjusted odds ratio 1.41, 95% confidence interval 0.95 to 2.09) in patients treated with DPP-4 inhibitors (exclusively sitagliptin) versus no use.

CONCLUSIONS

The relative effect of DPP-4 inhibitors on the risk of heart failure in patients with type 2 diabetes is uncertain, given the relatively short follow-up and low quality of evidence. Both randomised controlled trials and observational studies, however, suggest that these drugs may increase the risk of hospital admission for heart failure in those patients with existing cardiovascular diseases or multiple risk factors for vascular diseases, compared with no use.

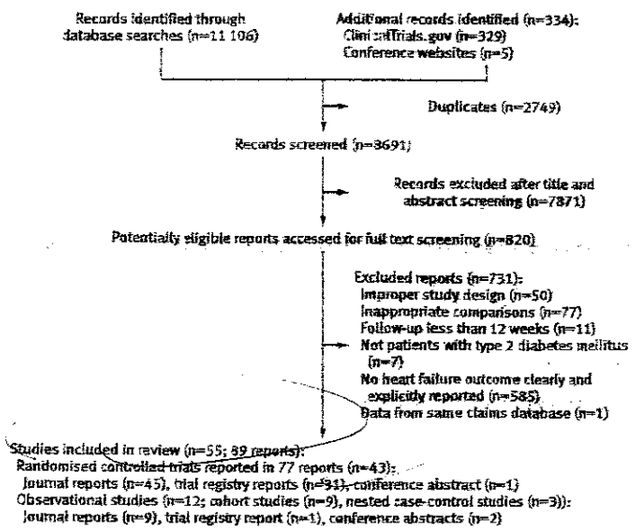

Table 3 | GRADE evidence profile of DPP-4 inhibitors and risk of heart failure in type 2 diabetes

Quality assessment						Summary of findings					
						Study event rates			Anticipated absolute effects (5- year time frame)§		
No of participants (studies), follow-up period	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	With control	With DPP-4 inhibitors	Relative risk (95% CI)	Risk with control	Risk difference with DPP-4 inhibitors (95% CI)	Quality of evidence
Heart failure											
28 292 (38), 12-206 weeks	Serious limitation, due to risk of bias*	No serious limitations	No serious limitations	Serious limitation, confidence interval includes important benefit and harm	Undetected	33/12 591 (0.26%)	42/15 701 (0.27%)	Odds ratio 0.97 (0.61 to 1.56)	50 per 1000†	2 fewer (19 fewer to 28 more)	⊕⊕◯◯ **Low** due to risk of bias and imprecision
Hospital admission for heart failure											
37 028 (5), 1-3 years	No serious limitations	No serious limitations	No serious limitations	Serious limitation, confidence interval includes no harm and important harm	Undetected	552/18 474 (3%)	622/18 554 (3.4%)	Odds ratio 1.13 (1.00 to 1.26)	60 per 1000‡	8 more (0 more to 16 more)	⊕⊕⊕◯ **Moderate** due to imprecision

*Most trials had unclear risk of bias on random sequence generation and allocation concealment (web appendix 7), and the follow-up (median of 52 weeks) was not long enough for heart failure to occur in patients at low risk of cardiovascular disease.
†Baseline risk estimate for heart failure in a five year time frame comes from the control arm of the cohort study we identified to best represent our target population (Kannan 2015[19]), with 528 events of heart failure in 13 185 participants (4.0%) at four year follow-up across the control and intervention arms.
‡Baseline risk estimate for hospital admission for heart failure in a five year time frame comes from control arms of the five trials we identified to best represent our target population (fig 3) with 552 events in 18 474 participants (30 per 1000) over a 2.5 year follow-up period, in the absence of observational studies providing more credible baseline risk estimates.
§Units are no of events per 1000 patients with type 2 diabetes mellitus over a five year time frame.

Table 6 | Risk of heart failure or hospital admission for heart failure among patients with type 2 diabetes receiving DPP-4 inhibitor treatment

Comparison	No of studies (events or cases, patients)	DPP-4 inhibitors (events/patients)	Control (events/ patients)	Effect estimate (95% CI)	Cardiovascular morbidities at baseline
Heart failure					
Randomised controlled trials					
DPP-4 inhibitors *v* control	38 (75, 28 292)	42/15 701	33/12 591	Pooled OR 0.97 (0.61 to 1.56)	Typically without CVD
Observational studies					
DPP-4 inhibitors *v* SU	1 (11, 616)	8/436	3/153	Unadjusted OR 0.88 (0.22 to 3.48)	With or without CVD
DPP-4 inhibitors *v* SU	1 (528, 13 185)	NR	NR	Adjusted HR 1.10 (1.04 to 1.17)	No history of CVD or congestive heart failure
Sitagliptin *v* SU	1 (2, 2607)	1/1874	1/733	Unadjusted OR 0.39 (0.02 to 6.26)	NR
Sitagliptin use *v* no use	1 (457, 5027)	—	—	Adjusted OR 0.75 (0.38 to 1.46)	Admission to hospital for an acute coronary syndrome event
Hospital admission for heart failure					
Randomised controlled trials					
DPP-4 inhibitors *v* control	5 (1174, 37 028)	622/18 554	522/18 474	Pooled OR 1.13 (1.00 to 1.26)	CVD or multiple risk factors for vascular disease
Observational studies					
DPP-4 inhibitors *v* active control (pooled estimates)	6 (4341, 1 618 295)	—	—	Pooled adjusted OR 0.85 (0.74 to 0.97)	With or without CVD
DPP-4 inhibitors *v* SU	3 (1875, 657 596)	380/202 292	1495/455 304	Adjusted HR 0.84 (0.74 to 0.96)	With or without CVD
DPP-4 inhibitors *v* pioglitazone	2 (1060, 1 031 432)	796/776 449	264/254 983	Adjusted HR 0.67 (0.57 to 0.78)	With or without CVD
DPP-4 inhibitors *v* other OADs	1 (1118, 18 744)*			Adjusted OR 0.88 (0.63 to 1.22)	With or without CVD
DPP-4 inhibitors *v* control	1 (127, 3987)	NR	NR	Adjusted HR 0.58 (0.38, 0.88)	With or without CVD
Sitagliptin use *v* no use (pooled estimates)	2 (1438, 25 638)	—	—	Pooled adjusted OR 1.41 (0.95 to 2.09)	—
Sitagliptin use *v* no use	1 (614, 16 576)	339/8288	275/8288	Adjusted HR 1.21 (1.04 to 1.42)	With or without CVD
Sitagliptin use *v* no use	1 (824, 9062)*			Adjusted OR 1.84 (1.16 to 2.92)	Heart failure at baseline

CVD=cardiovascular disease; SU=sulfonylurea; OR=odds ratio; HR=hazard ratio; NR=not reported; OADs=oral antidiabetic drugs.
*Nested case-control study.