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REVIEW ARTICLE

DPP-4 inhibitors for the treatment of type 2 diabetes: a methodology overview of systematic reviews

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Abstract

Aims To evaluate the methodological quality of systematic reviews (SRs), and summarize evidence of important outcomes from dipeptidyl peptidase-4 inhibitors (DPP4-I) in treating type 2 diabetes mellitus (T2DM).

Methods We included SRs of DPP4-I for the treatment of T2DM until January, 2018 by searching the Cochrane Library, PubMed, EMBASE and three Chinese databases. We evaluated the methodological qualities with the AMSTAR (Assessing the Methodological Quality of Systematic Reviews) tool and the GRADE (The Grading of Recommendations Assessment, Development and Evaluation) approach.

Results Sixty-three SRs (a total of 2,603,140 participants) receiving DPP4-I for the treatment of T2DM were included. The results of AMSTAR showed that the lowest quality was "a list of studies (included and excluded) item" with only one (1.6%) study provided, followed by the "providing a priori design" item with only four (6.3%) studies conforming to this item, the next were "the status of publication (gray literature) used as an inclusion criterion item", with only 18 (28.9%) studies conforming to these items. Only seven (11.1%) studies scored more than nine points in AMSTAR, indicating high methodological quality. For GRADE, of the 128 outcomes, high quality evidence was provided in only 28 (21.9%), moderate in 70 (54.7%), low in 27 (21.1%), and very low in three (2.3%).

Conclusions The methodological quality of SRs of DPP4-I for type 2 diabetes mellitus is not high and there are common areas for improvement. Furthermore, the quality of evidence level is moderate and more high quality evidence is needed.

Keywords Dipeptidyl peptidase 4 inhibitors · Systematic reviews · Type 2 diabetes mellitus · AMSTAR · GRADE

Introduction

In 2015, more than 415 million people worldwide had diabetes, with 90.2% living in low- or middle-income countries [1] and the majority having T2DM. Furthermore,

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as 52.1% of cases of diabetes remain undiagnosed, diabetes is grossly underreported as a cause of death. In China, increasing affluence and lifestyle changes have led to dramatic increases in the prevalence of T2DM. The International Diabetes Federation (IDF) has indicated that, of 1.9 million deaths among adults in China in 2015, 1.3 million were due to diabetes, with 40.8% of these deaths occurring in people under 60 [1]. As a result, T2DM places a huge financial and social burden on society.

DPP4-I are a new class therapeutic class of oral anti-hyperglycemic drug for T2DM. These agents are apparently well tolerated with few side effects and induce clinically meaningful reductions in blood glucose and HbA1c levels, with minimal risk of hypoglycemia and without weight gain [2]. The use of DPP4-I as a T2DM therapy [3] is now firmly established, and numerous inhibitors are in varying stages of clinical development. Four DPP4-I (sitagliptin [4], saxagliptin [5], linagliptin [6], and alogliptin [7]) are already approved for this indication by the US Food and Drug Administration.

Many SRs of randomized controlled trials (RCTs) have revealed the effectiveness of DPP4-I for the treatment of T2DM and clinical practice guidelines recommend that DPP4-I should be used as either second- or third-line therapies after the failure of other anti-hyperglycemic regimens, particularly metformin as a monotherapy [8]. There are numerous systematic reviews of DPP4-I for the treatment of T2DM, but these vary in their quality, design and applicability to practice [9]. Therefore, an overview of systematic reviews is needed to (1) evaluate the methodological quality of these SRs, (2) summarize the evidence of important outcomes from included SRs using the GRADE approach and (3) state the conclusions of these SRs.

Methods

Sources of literature and search strategy

We searched the following databases from their inception to January, 2018 for SRs: The Cochrane Library, PubMed, EMBASE, Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), and the Wanfang Database. Text words and MeSH terms for DPP4-I were entered depending on the characteristics of databases. No language restriction was applied. Search strategies used in each English electronic database are listed in "Online Appendix 1", and were adapted appropriately with Chinese terms for Chinese electronic databases. We did not consider on-going SRs.

Eligibility criteria

The following inclusion criteria were applied: (1) type of studies: SRs (overviews, reviews and protocols of SRs were excluded); (2) types of participants: participants of any age, sex or ethnic origin with T2DM; (3) interventions: DPP4-I (including sitagliptin, linagliptin, saxagliptin, vildagliptin and alogliptin) for the treatment of T2DM; (4) comparators: placebo or other antidiabetic drugs (OADs) for the treatment of T2DM; (5) outcomes: the primary outcomes are HbA1c, the secondary outcomes are adverse events, including hypoglycemia, gastrointestinal side effects (diarrhea, nausea), infectious effects, cardiovascular events (CV events), heart failure and cardiovascular mortality. This article is based on previously conducted studies and does not contain any animal studies performed by any of the authors.

Study selection

Two reviewers (J Ling & L Ge) independently screened titles and abstracts of all citations identified by our search strategy. The full texts of potentially eligible articles were retrieved for further identification in accordance with the eligibility criteria. Disagreements were resolved by discussion to reach a consensus.

Data extraction

Two authors independently extracted data from included SRs according to a pre-designed Excel spreadsheet (version 2007) for assessment of quality and data analysis. The data extraction spreadsheet summarized key characteristics, including information on the number of included trials and participants, details of interventions and controls, and quality assessment and outcomes. Discrepancies were identified and resolved by discussion. Additional information was obtained from the original RCT reports when necessary. We summarized the outcomes using STATA 12.0 software (Stata Corporation, College Station, TX, USA) [10].

Quality assessment

Methodological quality

Two independent reviewers assessed the methodological quality of included SRs using the AMSTAR tool (details are shown in Online Appendix 2) [11]. The AMSTAR tool was used to assess the appropriate conduct of SRs; for example, duplicate study selection, data extraction and provision of characteristics of included studies. These items were judged as follows: "Yes" (when the criterion

is explicitly met), "No" (when the criterion is explicitly not met), and "Can't answer" (when the item is relevant but not described completely) and "Not applicable". In this study, the total AMSTAR score was calculated by summing one point for each "yes" and no points for others, including "no", "can't answer", and "not applicable", resulting in summary scores from 0 to 11. We considered the reviews as low quality if the total score was 4 or lower, moderate quality if the score was between 5 and 8, and high quality if the score was between 9 and 11 [12, 13].

Quality of evidence

The GRADE approach was used to evaluate the overall quality of the evidence for each main finding [14]. RCTs were downgraded based on the assessment of the following factors: risk of bias, inconsistency, indirectness, imprecision and publication bias. For each downgrading factor, a judgment of "not serious" or "serious" (downgraded by 1 level) was assigned. After rating, the quality of evidence for each outcome in comparisons of each SR was graded as "High" (we are very confident that the true effect lies close to that of the estimate of the effect), "Moderate" (we are moderately confident of the effect estimate; the true effect is likely to be close to the estimate of the effect, although there is a possibility that it is substantially different), "Low" (our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect), or "Very low" (we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect). As for the factor for risk of bias, if included studies in our study did not use the Cochrane's Collaboration Tool (they used the Jadad scale or other tools) or did not assess the quality of included RCTs, we traced back to the original RCTs and evaluated the quality with the Cochrane Collaboration's risk-of-bias assessment tool [15].

Statistical analysis and subgroup analysis

A descriptive analysis of the results was conducted, and the characteristics of the systematic reviews were summarized according to the class of DPP4-I and the outcomes assessed. We tabulated the number of SRs and the number of pooled estimates of treatment effect for all placebo and active DPP4-I treatment comparisons. In addition, when we grouped the interventions by comparators of multiple SRs, there are many same PICOs, therefore, we conducted the subgroup analysis. All analyses were performed using STATA 12.0 software [10].

Results

Study identification

A total of 1,621 records were identified in our search. Of these, 894 were screened after the removal of duplicates. After screening titles and abstracts, 383 records were excluded. The full text of the remaining 128 records was retrieved for further scrutiny. Of these, 65 were excluded because they did not fulfill the eligibility criteria. Finally, 63 SRs were included in this overview. The study selection process is summarized in Fig. 1.

Characteristics of included SRs

General characteristics of the population, interventions, and comparison groups included in the 63 SRs are summarized in Table 1. Of the 63 SRs, 53 (53/63, 84.1%) articles were published in English, the remaining 10 (10/63, 15.9%) were published in Chinese. The year of publication of the 63 SRs ranged from 2007 to 2017. All reviews were published in peer-reviewed journals.

Of the 63 SRs, 34 (54%) reported DPP4-I compared with placebo or other antidiabetic drugs; 14 reported DPP4-I compared with placebo and nine reported DPP4-I compared with other antidiabetic drugs. Of the 63 SRs, 55 (87.3%) assessed the methodological quality of the included trials. The Cochrane Collaboration's risk of bias tool (41/63, 65.1%) was the most commonly used tool for the assessment of methodological quality of the SRs and there were eight studies [17, 24, 34, 49, 53, 60, 72, 75] (8/63, 12.7%) did

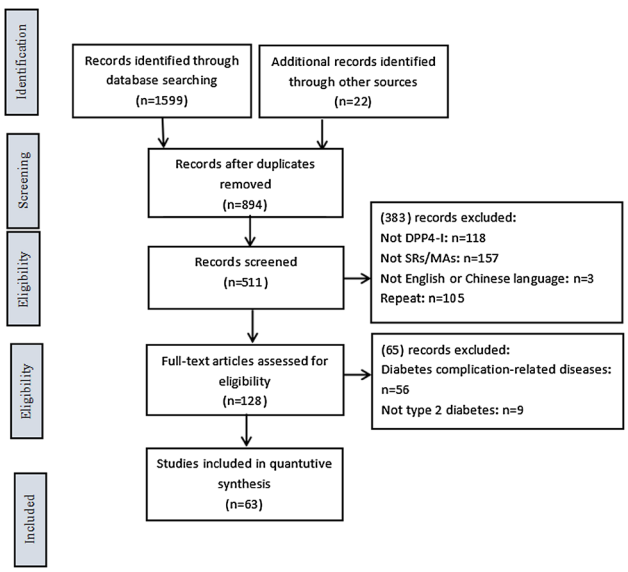


Fig. 1 The flow chart of the trial selection

Table 1 Characteristics of included systematic reviews ($n = 63$)

Study ID	Sample size	Included trials (size)	Intervention		Quality assessment tools	Published journals
			Treatment group	Control group		
Zhou (2016) [17]	13,234	14	DPP4-I	SU	NR	Clinical Practice
Loh (2016) [18]	4276	9	DPP4-I	SU	CCT	Primary Care Diabetes
Li (2015) [19]	2337	4	DPP4-I	GLP-1RA	CCT	Chinese Journal of Critical Care Medicine
Zhou (2014) [20]	1434	4	DPP4-I	GLP-1RA	CCT	Chinese Journal of Evidence-Based Medicine
Zhang (2014) [21]	10,982	12	DPP4-I	SU	Jadad	Diabetes/Metabolism Research and Reviews
Park (2012) [22]	30,563	62	DPP4-I	Placebo/OADs	Jadad	Annals of Pharmacotherapy
Gooßen (2012) [23]	23,456	67	DPP4-I	Placebo	CCT	BMJ
Aroda (2012) [24]	22,843	77	DPP4-I	GLP-1RA	NR	Clinical Therapeutics
Monami (2010) [25]	15,642	41	DPP4-I	Placebo/OADs	Jadad	Nutrition, Metabolism & Cardiovascular Diseases
Li (2015) [26]	3284	9	Sitagliptin	Placebo	CCT	Journal of Evidence-Based Medicine
Wang (2014) [27]	2048	4	Sitagliptin	GLP-1RA	CCT	PLoS ONE
Wan (2013) [28]	10,650	25	Sitagliptin	GLP-1RA	Jadad	Drugs Aging
Du (2013) [29]	1881	7	Sitagliptin	Met	CCT	Current Medical Research and Opinion
Zhan (2012) [30]	8565	18	Sitagliptin	Placebo	CCT	Journal of Evidence-Based Medicine
Wang (2014) [31]	5154	10	Alogliptin	Placebo/OADs	CCT	Chinese Journal of Hospital Pharmacy
Berhan (2013) [32]	10,515	10	Alogliptin	Placebo/OADs	CCT	BMC Endocrine Disorders
Bekiari (2016) [33]	28,006	69	Vildagliptin	Placebo/OADs	CCT	BMC Endocrine Disorders
Cai (2012) [34]	18,246	37	Vildagliptin	Placebo/OADs	NR	Journal of Clinical Pharmacy and Therapeutics
Zhan (2011) [35]	16,645	16	Vildagliptin	Placebo/OADs	CCT	Chinese Hospital pharmacy Journal
Zang (2015) [36]	8651	20	Linagliptin	Placebo/OADs	CCT	Chinese Journal of Clinical Pharmacology and Therapeutics
Yang (2013) [37]	3977	10	Linagliptin	Placebo	CCT	Drug Evaluation
Yao (2016) [38]	10,085	19	Saxagliptin	Placebo	CCT	Journal of Chinese Pharmaceutical Sciences
Zhan (2012) [39]	4922	7	Saxagliptin	Placebo/OADs	CCT	Chinese Journal of Evidence-Based Medicine
Rehman (2017) [40]	54,664	36	DPP4-I	Placebo	CCT	Diabetes Metab
Kamiya (2017) [41]	1893	5	DPP4-I	Placebo/OADs	CCT	Hemodial Int
Guo (2017) [42]	107,684	50	DPP4-I	Placebo/OADs	CCT	Value Health
Elgendy (2017) [43]	66,730	90	DPP4-I	Placebo	CCT	Am J Cardiovasc Drugs
Bundhun (2017) [44]	2396	5	Vildagliptin	Pioglitazone/rosiglitazone	CCT	BMC Pharmacology and Toxicology

Table 1 (continued)

Study ID	Sample size	Included trials (size)	Intervention		Quality assessment tools	Published journals
			Treatment group	Control group		
Yang (2016) [45]	2181	157	DPP4-I	Placebo/OADs	CCT	Diabetes Metab Res Rev
Wang (2016) [46]	54,758	100	DPP4-I	GPL-1RA/OADs	CCT	Diabetes Metab Res Rev
Singh-Franco (2016) [47]	2261	14	DPP4-I	Placebo	CCT	Diabetes Ther
Li (2016) [48]	68,775	12	DPP4-I	Placebo	CCT	BMJ
Kundu (2016) [49]	36,543	3	DPP4-I	Placebo	NR	Int J Cardiol
Kongwatcharapong (2016) [50]	74,737	54	DPP4-I	Placebo/OADs	Jadad, CCT	Int J Cardiol
Howse (2016) [51]	6384	13	DPP4-I	Placebo/OADs	CCT	Am J Kidney Dis
Cai (2016) [52]	12,975	30	DPP4-I + OADs	Placebo	CCT	Diabetes Technol Ther
McInnes (2015) [53]	17,000	40	Vildagliptin	Placebo/OADs	NR	Diabetes Obes Metab
Hou (2015) [54]	3585	6	Sitagliptin + Met	SU + Met	Jadad	Exp Ther Med
Esposito (2015) [55]	24,163	98	DPP4-I	Placebo/OADs	CCT	BMJ Open
Zhao (2014) [56]	8891	30	Sitagliptin	Placebo	Jadad	Drug Des Devel Ther
Esposito (2014) [57]	14,829	12	DPP4-I	Placebo/GLP-1RA	CCT	BMJ Open
Singh-Franco (2012) [58]	4246	9	Linagliptin	Placebo/OADs	CCT	Diabetes Obes Metab
Patil (2012) [59]	10,921	18	DPP4-I	Placebo/OADs	Jadad	Am J Cardiol
Johansen (2012) [60]	5239	8	Linagliptin	Placebo/OADs	NR	Cardiovasc Diabetol
Gerrald (2012) [61]	15,083	21	Sitagliptin, Saxagliptin	Placebo/OADs	USPSTF/Task Force	Diabetes Obes Metab
Amori (2007) [62]	5612	29	DPP4-I	Placebo/OADs	Jadad	JAMA
Richter (2008) [63]	12,864	25	DPP4-I	Placebo/OADs	CCT	CCT Database of Systematic Reviews
Karagiannis (2012) [64]	13,881	27	DPP4-I	Placebo/OADs	CCT	BMJ
Cheng (2014) [65]	1915	13	DPP4-I	Placebo/OADs	CCT	PLoS ONE
Tricco (2014) [66]	2967	10	DPP4-I	Placebo/OADs	CCT	BMJ Open
Wu (2014) [67]	8878	8	DPP4-I/DPP4-I + Met	Placebo/OADs	Jadad	Diabetes Obes Metab
Pérez (2014) [68]	4582	55	DPP4-I + Met	Placebo/OADs	Jadad	Value in Health the Journal of the International Society for Pharmacoeconomics & Outcomes Research
Liu (2014) [69]	18,980	23	DPP4-I/DPP4-I + Met	Placebo/OADs	Jadad	Pharmacoepidemiology & Drug Safety
Fei (2017) [70]	62,268	7	DPP4-I	Placebo/OADs	CCT	International Journal of Cardiology
Chen (2017) [71]	6987	8	DPP4-I	SU	CCT	Diabetes Obesity & Metabolism
Ayers (2017) [72]	5032	38	DPP4-I	Liraglutide	NR	Curr Med Res Opin
Verma (2017) [73]	97,867	100	DPP4-I	Placebo/OADs	CCT	CMAJ
Kay (2017) [74]	2186	8	Alogliptin + Met + SU	Placebo/OADs	STA	Diabetes Ther
Mannucci (2016) [75]	1,458,795	36	DPP4-I	Placebo/OADs	NR	Advances in Therapy
Xu (2017) [76]	36,895	3	DPP4-I	Placebo/OADs	CCT	Postgrad Med
Li (2017) [77]	1440	5	Sitagliptin + Met	Liraglutide + Met	CCT	Medicine
Min (2017) [78]	6980	14	DPP4-I/SGLT2	Placebo/OADs	CCT	Diabetes Metab Res Rev

Table 1 (continued)

Study ID	Sample size	Included trials (size)	Intervention		Quality assessment tools	Published journals
			Treatment group	Control group		
Min (2017) [79]	1677	5	DPP4-I + AGIs	AGI + placebo	CCT	JDI

DPP4-I2 dipeptidyl peptidase IV inhibitor, *CCT* Cochrane collaboration's tool, *STA* single technology appraisal, *GLP-1RA* glucagon-like peptide 1 receptor agonists, *AGI* α-glucosidase inhibitors, *SU* sulphonylureas, *SGLT2* sodium glucose cotransporter 2, *USPSTF/Task Force* U.S. Preventive Services Task Force, *OADs* other antidiabetic drugs, *Met* metformin

not report the tools used to assess the risk of bias of related outcomes and Gerrald KR's study used the U.S. Preventive Services Task Force (USPSTF/Task Force) [16].

Assessment of quality of included SRs

Methodological quality of included SRs

The AMSTAR tool was used to evaluate the methodological quality of the 63 SRs included in this overview, and Table 2 shows the results. Median AMSTAR scores were 7 (1–9). The number of individual items reported in the SRs varied widely, although six were fulfilled in over 70% of the SRs: item 2 (58/63, 92.1%), item 3 (57/63, 90.5%), item 6 (56/63, 88.9%), item 7 (56/63, 88.9%), item 8 (52/63, 82.5%), and item 9 (59/63, 93.7%). The methodological quality of SRs varied considerably, and many had some limitations. For example, only one [44] (1/63, 1.6%) study provided a list of studies (included and excluded); only four studies [19, 43, 52, 66] were conducted using an "a priori" design; 40 articles (40/63, 63.5%) did not report whether gray literature was included; 29 articles (29/63,46.0%) did not assess publication bias and 22 articles (22/63, 34.9%) did not state conflict of interest. Only seven SRs [18, 23, 41, 44, 52, 56, 66] (7/63, 11.1%) were found to be of high quality, achieving a score of nine points. Forty-nine SRs (49/63, 77.8%) were of moderate quality, scoring between 5 and 8 points, and seven studies [28, 34, 37, 49, 53, 60, 68] (7/63, 1.11%) were of low quality scoring less than four points.

Quality of evidence in included SRs

According to the GRADE approach, the overall quality of evidence for the main findings in the SRs was limited (range "very low" to "high"). A summary of evidence is presented in Table 3. We report the pooled effect sizes or other data that were directly reported in the original SR. In this overview, we summarize the quality of evidence of the primary and secondary outcomes with the effect estimate 95% confidence intervals from each of the SRs. We used the Cochrane's Collaboration Tool to assess risk of bias for the related outcomes in included studies which did not use the Cochrane's Collaboration Tool or did not assess the quality of included RCTs. There were six studies [17, 34, 49, 53, 60, 75] (6/63, 9.5%) did not report the tools used to assess the risk of bias about related outcomes; twelve studies [21, 22, 25, 28, 50, 54, 56, 59, 62, 67–69] (12/63, 19%) used the Jadad score to assess the quality of included RCTs and Gerrald KR's study used the U.S. Preventive Services Task Force (USPSTF/Task Force) [16], we used the Cochrane's Collaboration Tool to assess the 38 outcomes (38/128, 29.7%) in total. Of 128 outcomes, 70 (70/128, 54.7%) outcomes provided moderate quality evidence, 27 (27/128, 21.1%) provided low quality evidence, 28 (28/128, 21.9%) provided high quality evidence and only three [30, 39, 47] (2.3%) outcomes provided very low quality evidence. Risk of bias (n = 74, 54.8%) was the most common of the downgrading factors in the included reviews, followed by inconsistency (n = 43, 33.6%), imprecision (n = 8, 6.3%), publication bias (n = 6, 4.7%) and indirectness (n = 0). According to GRADE, the inconsistency (defined by confidence intervals [Cis]) showed minimal or no overlap, while the statistical test for heterogeneity (defined by the I^2 value) quantifies the proportion of the variation in point estimates due to inter-study differences.

Effect of interventions

Reducing HbA1c effect

Thirty-nine SRs provided sufficient data for comparison between DPP4-I and placebo or other antidiabetic drugs (Fig. 2). The results showed that the effects of all DPP4-I lowered HbA1c significantly more than the placebo and they showed similar ability to metformin in reducing HbA1c. In addition, DPP4-I were less effective in reducing HbA1c compared with GLP-1RA and sulfonylureas. Among the studies, the two studies [24, 72] did not provide available data for comparison of DPP4-I and GLP-1RA; therefore, we did not present the results of these studies in the DPP4-I versus GLP-1RA subgroup analysis.

Table 2 AMSTAR Score for methodological quality of included systematic reviews

Included studies	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Total score
Zhou (2016) [17]	N	Y	Y	N	CA	Y	N	N	CA	Y	Y	5
Loh (2016) [18]	N	Y	Y	Y	CA	Y	Y	Y	Y	Y	Y	9
Li (2015) [19]	Y	Y	Y	CA	CA	Y	Y	Y	Y	N	Y	8
Zhou (2014) [20]	N	Y	Y	N	CA	Y	Y	Y	Y	N	Y	7
Zhang (2014) [21]	N	Y	CA	Y	CA	Y	Y	N	Y	N	Y	6
Park (2012) [22]	N	Y	Y	Y	CA	Y	Y	Y	Y	Y	N	7
Gooßen (2012) [23]	N	Y	Y	Y	CA	Y	Y	Y	Y	Y	Y	9
Aroda (2012) [24]	N	Y	Y	CA	CA	Y	N	Y	Y	Y	Y	7
Monami (2010) [25]	N	Y	Y	N	CA	Y	Y	N	Y	Y	Y	7
Li (2015) [26]	N	Y	Y	Y	CA	Y	Y	Y	Y	N	N	7
Wang (2014) [27]	N	Y	Y	Y	CA	Y	Y	Y	Y	Y	N	8
Wan (2013) [28]	N	Y	CA	N	CA	Y	Y	N	Y	N	N	4
Du (2013) [29]	N	Y	Y	N	CA	Y	Y	Y	Y	N	Y	7
Zhan (2012) [30]	N	Y	Y	CA	CA	Y	Y	Y	Y	N	N	6
Wang (2014) [31]	N	Y	Y	CA	CA	Y	Y	Y	Y	N	N	6
Berhan (2013) [32]	N	Y	Y	Y	CA	CA	Y	Y	Y	Y	Y	8
Bekiari (2016) [33]	N	Y	Y	Y	CA	Y	Y	Y	Y	N	Y	8
Cai (2012) [34]	N	Y	Y	CA	CA	Y	N	N	Y	N	N	4
Zhan (2011) [35]	N	Y	Y	N	CA	Y	Y	CA	Y	N	N	5
Zang (2015) [36]	N	Y	Y	Y	CA	Y	Y	N	Y	Y	N	7
Yang (2013) [37]	N	Y	CA	N	CA	Y	Y	N	Y	N	N	4
Yao (2016) [38]	N	Y	Y	Y	CA	Y	Y	N	CA	N	N	5
Zhan (2012) [39]	N	Y	Y	CA	CA	Y	Y	N	Y	N	N	5
Rehman (2017) [40]	N	Y	Y	N	CA	Y	Y	Y	Y	Y	Y	8
Kamiya (2017) [41]	N	Y	Y	Y	CA	Y	Y	Y	Y	Y	Y	9
Guo (2017) [42]	N	Y	Y	N	CA	Y	Y	Y	Y	Y	Y	8
Elgendy (2017) [43]	Y	Y	Y	N	CA	Y	Y	Y	Y	Y	N	8
Bundhun (2017) [44]	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	9
Yang (2016) [45]	N	Y	Y	N	CA	Y	Y	Y	Y	Y	Y	8
Wang (2016) [46]	N	Y	Y	N	CA	Y	Y	Y	Y	Y	Y	8
Singh-Franco (2016) [47]	N	Y	Y	Y	CA	CA	Y	Y	Y	Y	Y	8
Li (2016) [48]	N	Y	Y	N	CA	Y	Y	Y	Y	Y	Y	8
Kundu (2016) [49]	N	CA	Y	N	CA	CA	N	Y	Y	N	Y	4
Kongwatcharapong (2016) [50]	N	Y	Y	Y	CA	Y	Y	Y	Y	N	Y	8
Howse (2016) [51]	N	Y	Y	N	CA	Y	Y	Y	Y	Y	Y	8
Cai (2016) [52]	Y	Y	Y	N	CA	Y	Y	Y	Y	Y	Y	9
McInnes (2015) [53]	N	CA	N	N	N	CA	N	CA	CA	N	Y	1
Hou (2015) [54]	N	Y	Y	N	CA	Y	Y	Y	Y	N	N	6
Esposito (2015) [55]	N	Y	Y	Y	CA	Y	Y	Y	Y	N	Y	8
Zhao (2014) [56]	N	Y	Y	Y	CA	Y	Y	Y	Y	Y	Y	9
Esposito (2014) [57]	N	Y	Y	N	CA	Y	Y	Y	Y	N	Y	7
Singh-Franco (2012) [58]	N	Y	Y	Y	CA	Y	Y	Y	Y	N	Y	8
Patil (2012) [59]	N	Y	Y	N	CA	Y	Y	Y	Y	Y	N	7
Johansen (2012) [60]	N	N	N	N	CA	CA	N	Y	N	N	Y	2
Gerrald (2012) [61]	N	CA	Y	N	CA	Y	Y	Y	Y	Y	Y	7
Amori (2007) [62]	N	Y	Y	N	CA	CA	Y	Y	Y	N	Y	6
Richter (2008) [63]	N	Y	Y	Y	CA	Y	Y	Y	Y	Y	N	8
Karagiannis (2012) [64]	N	Y	Y	N	CA	Y	Y	Y	Y	Y	Y	8
Cheng (2014) [65]	N	Y	Y	N	CA	Y	Y	Y	Y	Y	N	7
Tricco (2014) [66]	Y	Y	Y	N	CA	Y	Y	Y	Y	Y	Y	9

Table 2 (continued)

Included studies	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Total score
Wu (2014) [67]	N	Y	Y	N	CA	Y	Y	Y	Y	N	N	6
Pérez (2014) [68]	N	Y	N	N	CA	CA	Y	Y	Y	N	N	4
Liu (2014) [69]	N	Y	Y	N	CA	Y	Y	Y	Y	Y	Y	8
Fei (2017) [70]	N	Y	Y	N	CA	Y	Y	Y	Y	Y	Y	8
Chen (2017) [71]	N	Y	Y	N	CA	Y	Y	Y	Y	Y	Y	8
Ayers (2017) [72]	N	Y	Y	N	CA	Y	N	Y	Y	N	Y	6
Verma (2017) [73]	N	Y	Y	N	CA	Y	Y	Y	Y	N	Y	7
Kay (2017) [74]	N	Y	Y	N	CA	Y	Y	Y	Y	N	Y	7
Mannucci (2016) [75]	N	CA	Y	N	CA	Y	N	Y	Y	Y	N	5
Xu (2017) [76]	N	Y	Y	Y	CA	Y	Y	Y	Y	N	N	7
Li (2017) [77]	N	Y	Y	N	CA	Y	Y	Y	Y	Y	N	7
Min (2017) [78]	N	Y	Y	N	CA	Y	Y	Y	Y	Y	Y	8
Min (2017) [79]	N	Y	Y	N	CA	Y	Y	Y	Y	Y	N	7

Y when the criterion is explicitly met; adequate, *N* when the criterion is explicitly not met, *CA (cannot answer)* when the item is relevant but not described completely. *Item 1* Was an a priori design provided? *Item 2* Was there duplicate study selection and data extraction? *Item 3* Was a comprehensive literature search performed? *Item 4* Was the status of publication (i.e., gray literature) used as an inclusion criterion? *Item 5* Was a list of studies (included and excluded) provided? *Item 6* Were the characteristics of the included studies provided? *Item 7* Was the scientific quality of the included studies assessed and documented? *Item 8* Was the scientific quality of the included studies used appropriately in formulating conclusions? *Item 9* Were the methods used to combine the findings of studies appropriate? *Item 10* Was the likelihood of publication bias assessed? *Item 11* Was a conflict of interest stated?

Adverse events effect

Hypoglycemia

The results of 33 studies that addressed the issue of hypoglycemia are listed in Fig. 3. There was no statistical significance between DPP4-I and placebo as well as GLP-1RA. In addition, compared with sulfonylureas [17, 18, 21, 54], the incidence of hypoglycemia was lower with DPP4-I [RR: 0.24 (0.21, 0.27), high quality of evidence], [RR: 0.46 (0.30, 0.70), very low quality of evidence], [RR: 0.13 (0.11, 0.16), low quality of evidence] and [RR: 0.20 (0.13, 0.30), low quality of evidence], respectively.

Gastrointestinal side effects

The results of 22 studies that addressed the issue of gastrointestinal side effects, including diarrhea and nausea, are listed in the Fig. 4a, b. The results showed that DPP4-I have similar effects in reducing the incidence of diarrhea and nausea compared with the placebo and other antidiabetic drugs. As for diarrhea, DPP4-I were associated with fewer diarrhea events than GLP-1RA [19, 27, 28, 77] [(RR: 0.29 (0.18, 0.47), low quality of evidence, RR: 0.38 (0.27, 0.54), moderate quality of evidence); RR: 0.55 (0.27, 0.54), high quality of evidence; RR: 0.45 (0.24, 0.84), moderate quality of evidence, respectively]. In terms of nausea, DPP4-I were associated with fewer nausea events than GLP-1RA [19, 27, 28, 77] [RR: 0.16 (0.11, 0.23), low quality of evidence, RR: 0.27 (0.23, 0.32), high quality of evidence, RR: 0.32 (0.22, 047), moderate quality of evidence, RR: 0.42 (0.32, 0.55), low quality of evidence, respectively].

Cardiovascular-related outcomes effect

The results of 24 studies addressed the issue of cardiovascular-related outcomes, including CV events, cardiovascular mortality and heart failure, which are listed in Fig. 5a–c. The results showed that DPP4-I have the similar effects in reducing the incidence of CV events, cardiovascular mortality when compared with the placebo. In addition, they were associated with a lower risk of adverse CV events when compared with the comparator [59, 60] and sulfonylureas [21]. Furthermore DPP4-I were associated with an increased risk of heart failure when compared with placebo [40] and the comparator [73, 76].

Infections effect

The results of ten studies that addressed the issue of infections effect are listed in Fig. 6. The results showed that DPP4-I have the similar effects in reducing the incidence of infections compared with placebo and other antidiabetic drugs. One study [37] showed that linagliptin was associated with a lower risk of infections compared with placebo [RR: 0.62 (0.43, 0.90), moderate quality of evidence].

Table 3 Quality of evidence in included systematic reviews with GRADE

Study ID	Outcomes	Effect estimate 95% CI	Included RCTs (patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	GRADE quality
Zhou (2016) [17]	HbA1c	0.08 (0.03, 0.14)	11 (12,245)	Not serious[i]	Not serious	Not serious	Not serious	Not serious	Moderate
	Hypoglycaemia	0.24 (0.21, 0.27)	11 (8396)	Not serious[i]	Not serious	Not serious	Not serious	Not serious	Moderate
Loh (2016) [18]	HbA1c	−0.11 (−0.32, 0.08)	4 (398)	Not serious	Not serious	Not serious	Serious[g]	Not serious	Moderate
	Hypoglycemia	0.46 (0.30,0.70)	9 (4276)	Not serious	Serious[f]	Not serious	Serious[g]	Not serious	Low
Li (2015) [19]	HbA1c	0.43 (0.34, 0.53)	10 (2335)	Serious[a]	Not serious	Not serious	Not serious	Not serious	Moderate
	Hypoglycemia	0.94 (0.47, 1.33)	10 (1226)	Serious[a]	Not serious	Not serious	Not serious	Not serious	Moderate
	Diarrhea	0.38 (0.26, 0.53)	8 (955)	Serious[a]	Not serious	Not serious	Not serious	Not serious	Moderate
	Nausea	0.27 (0.23, 0.33)	10 (1216)	Serious[a]	Not serious	Not serious	Not serious	Not serious	Moderate
Zhou (2014) [20]	HbA1c	0.46 (0.35, 0.57)	4 (1246)	Serious[a]	Not serious	Not serious	Not serious	Not serious	Moderate
	Hypoglycemia	0.79 (0.47, 1.35)	4 (1427)	Serious[a]	Not serious	Not serious	Not serious	Not serious	Moderate
Zhang (2014) [21]	CV events	0.53 (0.32, 0.87)	4 (1553)	Not serious[i]	Not serious	Not serious	Not serious	Not serious	High
	HbA1c	0.105 (0.103, 0.107)	12 (6772)	Not serious[i]	Serious[f]	Not serious	Not serious	Not serious	Moderate
	Hypoglycemia	0.13 (0.11, 0.16)	12 (4983)	Not serious[i]	Serious[f]	Not serious	Not serious	Not serious	Moderate
Park (2012) [22]	HbA1c	−0.76 (−0.83, −0.68)	59 (16,719)	Serious[b,i]	Not serious	Not serious	Not serious	Not serious	Moderate
	Hypoglycemia	1.30 (1.00,1.68)	48 (18,101)	Serious[b,i]	Serious[f]	Not serious	Not serious	Not serious	Low
Gooßen (2012) [23]	Hypoglycemia	0.92 (0.74,1.15)	10 (4765)	Serious[b]	Serious[f]	Not serious	Not serious	Not serious	Low
	Infections	0.97 (0.83,1.14)	25 (13,451)	Serious[b]	Not serious	Not serious	Not serious	Not serious	Moderate
	CV events	0.93 (0.80,1.08)	11 (9335)	Serious[b]	Not serious	Not serious	Not serious	Not serious	Moderate
Monami (2010) [25]	HbA1c	−0.7 (−0.8, −0.6)	38 (6609)	Serious[a,b,i]	Not serious	Not serious	Not serious	Not serious	Moderate
	Hypoglycemia	−0.7 (−0.8, −0.6)	33 (5674)	Serious[a,b,i]	Not serious	Not serious	Not serious	Not serious	Moderate
	CV events	0.76 (0.46,1.28)	25 (8796)	Serious[a,b,i]	Not serious	Not serious	Not serious	Not serious	Moderate
	Diarrhea	0.80 (0.56,1.15)	22 (6794)	Serious[a,b,i]	Not serious	Not serious	Not serious	Not serious	Moderate
	Nausea	0.77 (0.57,1.04)	19 (9973)	Serious[a,b,i]	Not serious	Not serious	Not serious	Not serious	Moderate
Li (2015) [26]	Diarrhea	0.95 (0.69,1.29)	9 (2379)	Serious[b]	Not serious	Not serious	Not serious	Not serious	Moderate
Wang (2014) [27]	HbA1C	0.41 (0.31,0.51)	4 (1111)	Not serious	Not serious	Not serious	Not serious	Not serious	High
	Nausea	0.32 (0.22,0.47)	3 (1321)	Not serious	Not serious	Not serious	Not serious	Not serious	High
	Diarrhea	0.55 (0.37,0.81)	3 (1284)	Not serious	Not serious	Not serious	Not serious	Not serious	High
	Hypoglycemia	0.74 (0.39,1.41)	4 (1885)	Not serious	Not serious	Not serious	Not serious	Not serious	High
Wan (2013) [28]	Hypoglycemia	1.11 (0.89,1.39)	17 (8111)	Serious[a,i]	Not serious	Not serious	Not serious	Not serious	Moderate
	Nausea	0.42 (0.32,0.55)	3 (408)	Serious[a,i]	Not serious	Not serious	Serious[g]	Not serious	Low
	Diarrhea	0.45 (0.24,0.83)	4 (563)	Serious[a,i]	Not serious	Not serious	Serious[g]	Not serious	Low
Du (2013) [29]	HbA1C	0.13 (−0.05,0.30)	7 (1881)	Serious[c]	Serious[f]	Not serious	Not serious	Not serious	Low

Table 3 (continued)

Study ID	Outcomes	Effect estimate 95% CI	Included RCTs (patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	GRADE quality
Zhan (2012) [30]	HbA1C	−0.66 (−0.82, −0.50)	6 (482)	Serious[d]	Not serious	Not serious	Serious[g]	Serious[h]	Very Low
	Nausea	1.01 (0.95,1.07)	6 (2223)	Serious[d]	Not serious	Not serious	Not serious	Serious[h]	Low
	Hypoglycemia	1.03 (0.93,1.14)	5 (1584)	Serious[d]	Not serious	Not serious	Not serious	Serious[h]	Low
	Diarrhea	1.04 (0.96,1.12)	4 (1334)	Serious[d]	Not serious	Not serious	Not serious	Serious[h]	Low
Wang (2014) [31]	HbA1C	−0.73 (−0.84, −0.61)	10 (1212)	Not serious	Serious[f]	Not serious	Not serious	Not serious	Moderate
	Hypoglycemia	1.08 (0.81,1.43)	10 (2664)	Not serious	Not serious	Not serious	Not serious	Not serious	High
	Infections	0.70 (0.45,1.07)	8 (2209)	Not serious	Not serious	Not serious	Not serious	Not serious	High
Berhan (2013) [32]	HbA1C	−0.81 (−0.11, −0.51)	8 (2233)	Not serious	Serious[f]	Not serious	Not serious	Not serious	Moderate
Bekiari (2016) [33]	HbA1C	−0.69 (−0.83, −0.56)	18 (4985)	Serious[c]	Serious[f]	Not serious	Not serious	Not serious	Low
	Hypoglycemia	0.83 (0.59.1.16)	17 (1034)	Serious[c]	Not serious	Not serious	Not serious	Not serious	Moderate
	Infections	0.94 (0.57,1.56)	8 (1584)	Serious[c]	Not serious	Not serious	Not serious	Not serious	Moderate
Cai (2012) [34]	HbA1C	−0.32 (−0.44, −0.19)	37 (17,717)	Serious[e,i]	Serious[f]	Not serious	Not serious	Not serious	Low
	Hypoglycemia	0.85 (0.49,1.47)	30 (22,733)	Serious[e,i]	Not serious	Not serious	Not serious	Not serious	Moderate
	Infections	1.07 (0.90,1.27)	12 (9225)	Serious[e,i]	Serious[f]	Not serious	Not serious	Not serious	Low
	Nausea	0.70 (0.39,1.23)	17 (16,274)	Serious[e,i]	Not serious	Not serious	Not serious	Not serious	Moderate
Zhan (2011) [35]	Hypoglycemia	0.66 (0.39,1.10)	3 (1383)	Not serious	Not serious	Not serious	Not serious	Not serious	High
Zang (2015) [36]	HbA1C	−0.72 (−0.82.−0.62)	6 (1335)	Serious[b]	Not serious	Not serious	Not serious	Not serious	Moderate
	Hypoglycemia	0.97 (0.69,1.36)	11 (4864)	Serious[b]	Serious[f]	Not serious	Not serious	Not serious	Low
	Diarrhea	0.90 (0.69, 1.19)	6 (1370)	Serious[b]	Not serious	Not serious	Not serious	Not serious	Moderate
Yang (2013) [37]	Infections	0.62 (0.43, 0.90)	6 (3081)	Not serious	Not serious	Not serious	Not serious	Not serious	High
	Hypoglycemia	0.86 (0.34,2.17)	5 (2847)	Not serious	Not serious	Not serious	Not serious	Not serious	High
	Diarrhea	0.94 (0.55,1.62)	5 (2415)	Not serious	Not serious	Not serious	Not serious	Not serious	High
Yao (2016) [38]	HbA1C	−0.47 (−0.58, −0.35)	10 (2377)	Not serious	Serious[f]	Not serious	Not serious	Not serious	Moderate
	Hypoglycemia	1.28 (0.72,2.27)	12 (8454)	Not serious	Not serious	Not serious	Not serious	Not serious	High
	Diarrhea	0.89 (0.76,1.05)	17 (8733)	Not serious	Serious[f]	Not serious	Not serious	Not serious	Moderate
	Infections	0.94 (0.76,1.17)	10 (6810)	Not serious	Not serious	Not serious	Not serious	Not serious	High
Zhan (2012) [39]	HbA1C	−0.20 (−0.37, −0.03)	7 (4032)	Serious[b]	Not serious	Not serious	Not serious	Serious[h]	Low
	Hypoglycemia	0.38 (0.14,1.08)	4 (1584)	Serious[b]	Serious[f]	Not serious	Not serious	Serious[h]	Very Low
Rehman (2017) [40]	Cardiovascular mortality	1.00 (0.91, 1.11)	3 (36,543)	Not serious	Not serious	Not serious	Not serious	Not serious	High
	Heart failure	1.13 (1.01,1.26)	3 (27,851)	Not serious	Not serious	Not serious	Not serious	Not serious	High

Table 3 (continued)

Study ID	Outcomes	Effect estimate 95% CI	Included RCTs (patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	GRADE quality
Kamiya (2017) [41]	HbA1C	−0.42 (−0.73, −0.11)	2 (1053)	Serious[c]	Not serious	Not serious	Not serious	Not serious	Moderate
	Hypoglycemia	1.35 (0.98,1.84)	5 (1148)	Serious[c]	Not serious	Not serious	Not serious	Not serious	Moderate
	CV events	0.77 (0.42, 1.41)	4 (1564)	Serious[c]	Not serious	Not serious	Not serious	Not serious	Moderate
Guo (2017) [42]	Heart failure	2.13 (1.06,6.26)	20 (10,768)	Serious[b]	Not serious	Not serious	Not serious	Not serious	Moderate
Elgendy (2017) [43]	Heart failure	1.11 (0.99,1.25)	16 (42,031)	Serious[b]	Not serious	Not serious	Not serious	Not serious	Moderate
	Cardiovascular mortality	1.02 (0.92,1.14)	15 (44,209)	Serious[b]	Not serious	Not serious	Not serious	Not serious	Moderate
Bundhun (2017) [44]	Diarrhea	0.83 (0.48,1.44)	2 (1166)	Not serious	Not serious	Not serious	Not serious	Not serious	High
	Nausea	0.52 (0.25,1.05)	2 (1053)	Not serious	Not serious	Not serious	Not serious	Not serious	High
	Infections	0.95 (0.71,1.27)	4 (1934)	Not serious	Serious[f]	Not serious	Not serious	Not serious	Moderate
Yang (2016) [45]	Infections	0.97 (0.91,1.04)	54 (39,330)	Not serious	Serious[f]	Not serious	Not serious	Not serious	Moderate
Wang (2016) [46]	Heart failure	0.45 (0.17,1.17)	40(68,801)	Serious[a]	Not serious	Not serious	Not serious	Not serious	Moderate
	Cardiovascular mortality	0.98 (0.78,1.23)	37 (71,245)	Serious[a]	Not serious	Not serious	Not serious	Not serious	Moderate
Singh-Franco (2016) [47]	HbA1C	−0.32 (−0.52, −0.12)	14 (1964)	Serious[b]	Serious[f]	Not serious	Not serious	Not serious	Low
	Hypoglycemia	0.92 (0.71,1.19)	11 (1750)	Serious[b]	Not serious	Not serious	Not serious	Not serious	Moderate
	Infections	0.84 (0.33, 2.15)	3 (368)	Serious[b]	Serious[f]	Not serious	Serious[g]	Not serious	Very Low
Li (2016) [48]	Heart failure	0.97 (0.61,1.56)	38 (1292)	Serious[a]	Not serious	Not serious	Not serious	Not serious	Moderate
Kundu (2016) [49]	Heart failure	1.14 (0.97,1.34)	3 (36,543)	Serious[b,i]	Serious[f]	Not serious	Not serious	Not serious	Low
Kongwatcharapong (2016) [50]	Heart failure	1.11 (0.99,1.22)	54 (74,737)	Not serious[i]	Not serious	Not serious	Not serious	Not serious	High
Howse (2016) [51]	HbA1C	−0.64 (−0.68, −0.43)	11 (263)	Serious[c]	Serious[f]	Not serious	Not serious	Not serious	Low
	Hypoglycemia	1.38 (1.01,1.89)	10 (277)	Serious[c]	Not serious	Not serious	Not serious	Not serious	Moderate
Cai (2016) [52]	HbA1C	−0.99 (−1.04, −0.94)	14 (8137)	Not serious	Serious[f]	Not serious	Not serious	Not serious	Moderate
McInnes (2015) [53]	CV events	0.77 (0.45,1.31)	32 (9701)	Serious[e,i]	Not serious	Not serious	Not serious	Not serious	Moderate
	Heart failure	1.08 (0.68,1.70)	32 (9599)	Serious[e,i]	Not serious	Not serious	Not serious	Not serious	Moderate
Hou (2015) [54]	HbA1C	0.04 (−0.09,0.17)	6 (2410)	Not serious[i]	Serious[f]	Not serious	Not serious	Not serious	Moderate
	Hypoglycemia	0.20 (0.13,0.30)	6 (3612)	Not serious[i]	Serious[f]	Not serious	Not serious	Not serious	Moderate
Esposito (2015) [55]	HbA1C	−0.77 (−0.82,0.72)	94 (24,163)	Not serious	Not serious	Not serious	Not serious	Not serious	High
Zhao (2014) [56]	Diarrhea	1.10 (0.78,1.55)	15 (8891)	Not serious[i]	Not serious	Not serious	Not serious	Not serious	High

Table 3 (continued)

Study ID	Outcomes	Effect estimate 95% CI	Included RCTs (patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	GRADE quality
Esposito (2014) [57]	HbA1C	0.22 (0.15,0.29)	12 (14,829)	Serious[a]	Serious[f]	Not serious	Not serious	Not serious	Low
Singh-Franco (2012) [58]	HbA1C	−0.63 (−0.71, −0.55)	9 (3532)	Serious[e]	Not serious	Not serious	Not serious	Not serious	Moderate
Patil (2012) [59]	CV events	0.48 (0.31,0.75)	18 (8544)	Not serious[i]	Not serious	Not serious	Not serious	Not serious	High
Johansen (2012) [60]	CV events	0.34 (0.16,0.70)	8 (5239)	Not serious[i]	Not serious	Not serious	Not serious	Not serious	Moderate
Gerrald (2012) [61]	HbA1C	−0.82 (−0.95, −0.70)	8 (9765)	Serious[e,i]	Serious[f]	Not serious	Not serious	Not serious	Low
	Hypoglycemia	1.55 (0.55,4.36)	8 (9677)	Not serious	Serious[f]	Not serious	Not serious	Not serious	Moderate
Amori (2007) [62]	HbA1C	−0.97 (−1.13, −0.81)	6 (1285)	Serious[e,i]	Not serious	Not serious	Not serious	Not serious	Moderate
Richter (2008) [63]	HbA1C	−0.82 (−1.13, −0.76)	2 (592)	Serious[e]	Not serious	Not serious	Serious[g]	Not serious	Low
Karagiannis (2012) [64]	HbA1C	0.20 (−0.14, 0.54)	7 (3237)	Not serious	Serious[f]	Not serious	Not serious	Not serious	Moderate
Cheng (2014) [65]	HbA1C	−0.52 (−0.64, −0.39)	6 (993)	Serious[c]	Not serious	Not serious	Not serious	Not serious	Moderate
	Hypoglycemia	1.10 (0.92,1.32)	6 (1049)	Serious[c]	Not serious	Not serious	Not serious	Not serious	Moderate
Tricco (2014) [66]	HbA1C	−0.61 (−0.41, −0.81)	5 (1680)	Serious[b]	Serious[f]	Not serious	Not serious	Not serious	Low
	Hypoglycemia	0.69 (0.16,2.94)	2 (1310)	Serious[b]	Not serious	Not serious	Serious[g]	Not serious	Low
Wu (2014) [67]	HbA1C	−0.28 (−0.71, −0.40)	7 (3228)	Not serious[i]	Serious[f]	Not serious	Not serious	Not serious	Moderate
	CV events	0.54 (0.25,1.19)	5 (4402)	Not serious[i]	Not serious	Not serious	Not serious	Not serious	High
	Hypoglycemia	1.04 (0.72,1.50)	5 (4404[j])	Not serious[i]	Not serious	Not serious	Not serious	Not serious	High
Pérez (2014) [68]	HbA1C	−0.60 (−0.75, −0.46)	8 (987)	Serious[a,i]	Serious[f]	Not serious	Not serious	Not serious	Low
	Hypoglycemia	0.88 (0.32,2.45)	9 (1089)	Serious[a,i]	Not serious	Not serious	Not serious	Not serious	Moderate
Liu (2014) [69]	HbA1C	−0.35 (−0.51, −0.19)	14 (9149)	Not serious[i]	Serious[f]	Not serious	Not serious	Not serious	Moderate
	Hypoglycemia	0.33 (0.20, 0.56)	20 (17,473)	Not serious[i]	Serious[f]	Not serious	Not serious	Not serious	Moderate
	Nausea	0.83 (0.62,1.11)	9 (4063)	Not serious[i]	Not serious	Not serious	Not serious	Not serious	High
	Diarrhea	0.91 (0.80,1.02)	19 (15,948)	Not serious[i]	Not serious	Not serious	Not serious	Not serious	High
	Infections	0.00 (−0.01,0.01)	15 (11,529)	Not serious[i]	Serious[f]	Not serious	Not serious	Not serious	Moderate
Fei (2017) [70]	Cardiovascular mortality	1.00 (0.88,1.13)	7 (62,268)	Not serious	Serious[f]	Not serious	Not serious	Not serious	Moderate

Table 3 (continued)

Study ID	Outcomes	Effect estimate 95% CI	Included RCTs (patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	GRADE quality
Chen (2017) [71]	HbA1C	0.16 (0.11,0.21)	9 (6987)	Not serious	Not serious	Not serious	Not serious	Not serious	High
Verma (2017) [73]	Heart failure	1.13 (1.01,1.26)	38 (54,540)	Not serious	Not serious	Not serious	Not serious	Not serious	High
Kay (2017) [74]	HbA1C	−0.65 (−0.96, −0.34)	8 (3261)	Not serious	Serious[f]	Not serious	Not serious	Not serious	Moderate
	Hypoglycemia	1.78 (0.60,5.29)	8 (3256)	Not serious	Serious[f]	Not serious	Not serious	Not serious	Moderate
Mannucci (2016) [75]	CV events	0.63 (0.37,1.08)	36 (90,641)	Not serious[i]	Serious[f]	Not serious	Not serious	Not serious	Low
Xu (2017) [76]	Cardiovascular mortality	1.01 (0.91,1.12)	9 (5425)	Serious[b]	Not serious	Not serious	Not serious	Not serious	Moderate
	Heart failure	1.14 (1.01,1.27)	6 (2789)	Serious[b]	Serious[f]	Not serious	Not serious	Not serious	Low
	Hypoglycemia	0.05 (0.00,0.81)	11 (6432)	Serious[b]	Serious[f]	Not serious	Not serious	Not serious	Low
Li (2017) [77]	HbA1C	0.35 (0.20, 0.51)	6 (1656)	Not serious	Serious[f]	Not serious	Not serious	Not serious	Moderate
	Diarrhea	0.29 (0.18,0.47)	4 (1203)	Not serious	Serious[f]	Not serious	Not serious	Not serious	Moderate
	Nausea	0.16 (0.11,0.23)	5 (1591)	Not serious	Serious[f]	Not serious	Not serious	Not serious	Moderate
Min (2017) [78]	HbA1C	−1.20 (−1.61, −0.8)	5 (1688)	Serious[b]	Serious[f]	Not serious	Not serious	Not serious	Low
	Hypoglycemia	1.39 (0.41,4.64)	4 (1003)	Serious[b]	Not serious	Not serious	Not serious	Not serious	Moderate
Min (2017) [79]	HbA1C	−0.58 (−0.70, −0.45)	14 (6980)	Not serious	Serious[f]	Not serious	Not serious	Not serious	Moderate
	Hypoglycemia	1.03 (0.81, 1.29)	14 (5506)	Not serious	Not serious	Not serious	Not serious	Not serious	High

CI confidence interval, *CV events* cardiovascular events

[a]The risk from blinding of participants (performance bias) was high

[b]The risk of randomization was high

[c]Incomplete accounting of patients and outcome events

[d]Selective outcome reporting bias

[e]The risk of the concealment of randomization is high

[f]Unexplained heterogeneity in the results, confidence intervals of individual studies overlap is poor, and the I^2 value is large

[g]Small sample size and wide confidence intervals (the 95% CI overlapped with no effect and CI failed to exclude important benefits)

[h]Important published articles and unpublished data were missed

[i]The studies did not report the information about risk of bias, we used the Cochrane's Collaboration Tool to assess risk of bias for the primary outcome in included studies

Discussion

Summary of evidence

Statement of main findings

The number of SRs of DPP4-I for T2DM is increasing annually. The purpose of this overview was to evaluate the methodological quality and quality of evidence from published SRs and to provide an evidence-based assessment and an objective summary on the safety and effectiveness of DPP4-I for T2DM. Overall analysis suggests that: (1) GLP-1 receptor agonists are superior to DPP4-I in reducing the levels of HbA1c, although more gastrointestinal side effects were reported. (2) There was no statistically significant difference between DPP4-I and placebo in reducing the incidence of hypoglycemia, and DPP4-I were associated with fewer hypoglycemia events than sulfonylureas. (3) DPP4-I have similar

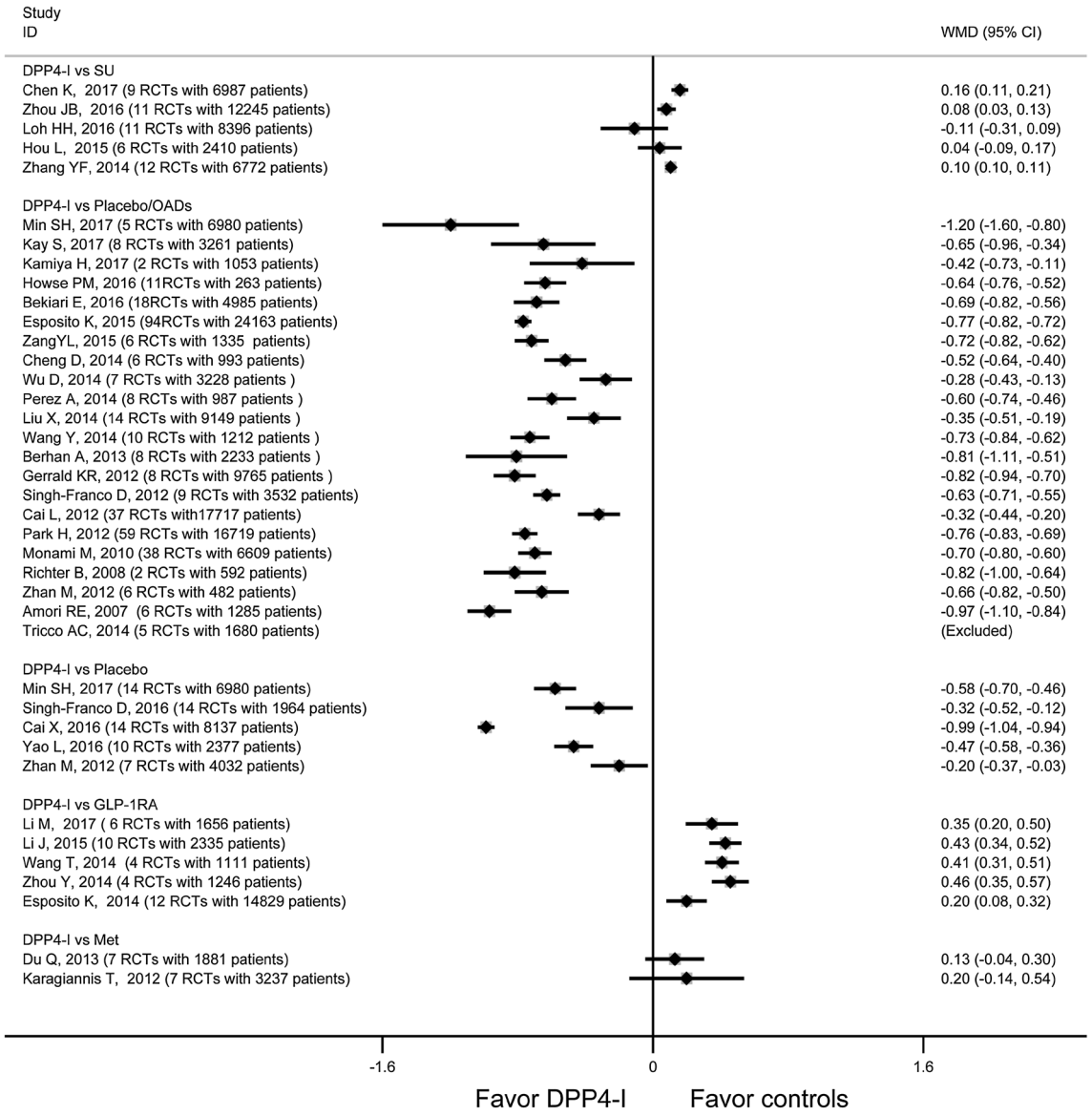


Fig. 2 Summary of findings for HbA1C outcome

effects in reducing the incidence of CV events, cardiovascular mortality, infections, diarrhea and nausea when compared with the placebo. Furthermore, patients treated with DPP4-I are less likely to experience CV events compared with those treated with sulfonylureas and DPP4-I were associated with an increased risk of heart failure when compared with placebo [40] and GLP1-RA [46]. These findings are in accordance with those reported for analysis of 67 clinical trials [80].

As for the results of subgroup analysis, we noticed that multiple SRs had the same PICO and there was homogeneity of outcomes. For example, cardiovascular event outcomes with DPP4-I versus placebo/OADs, the effects were on the same left side of the null, or some on the null. Among them, the Johansen OE's study [60] (eight RCTs with 5239 patients) had a statistically significant result which was different from the results of other studies because it used the hazard ratio (HR) for time to first event calculated using the Cox proportional hazards model with adjustments for study and treatment group, and the Patil HR's study [59] (18 RCTs with 8544 patients) was also statistically significant with effect on the left side of the null. For heart failure outcome with DPP4-I versus placebo/OADs, the effect of the Xu SS' study [76] which was different from the results of other studies because it included the diabetes patients with and without established cardiovascular disease. For heterogeneity of infections outcome with DPP4-I versus placebo, Yang T's study [37] was poor overlapping of effect because the less

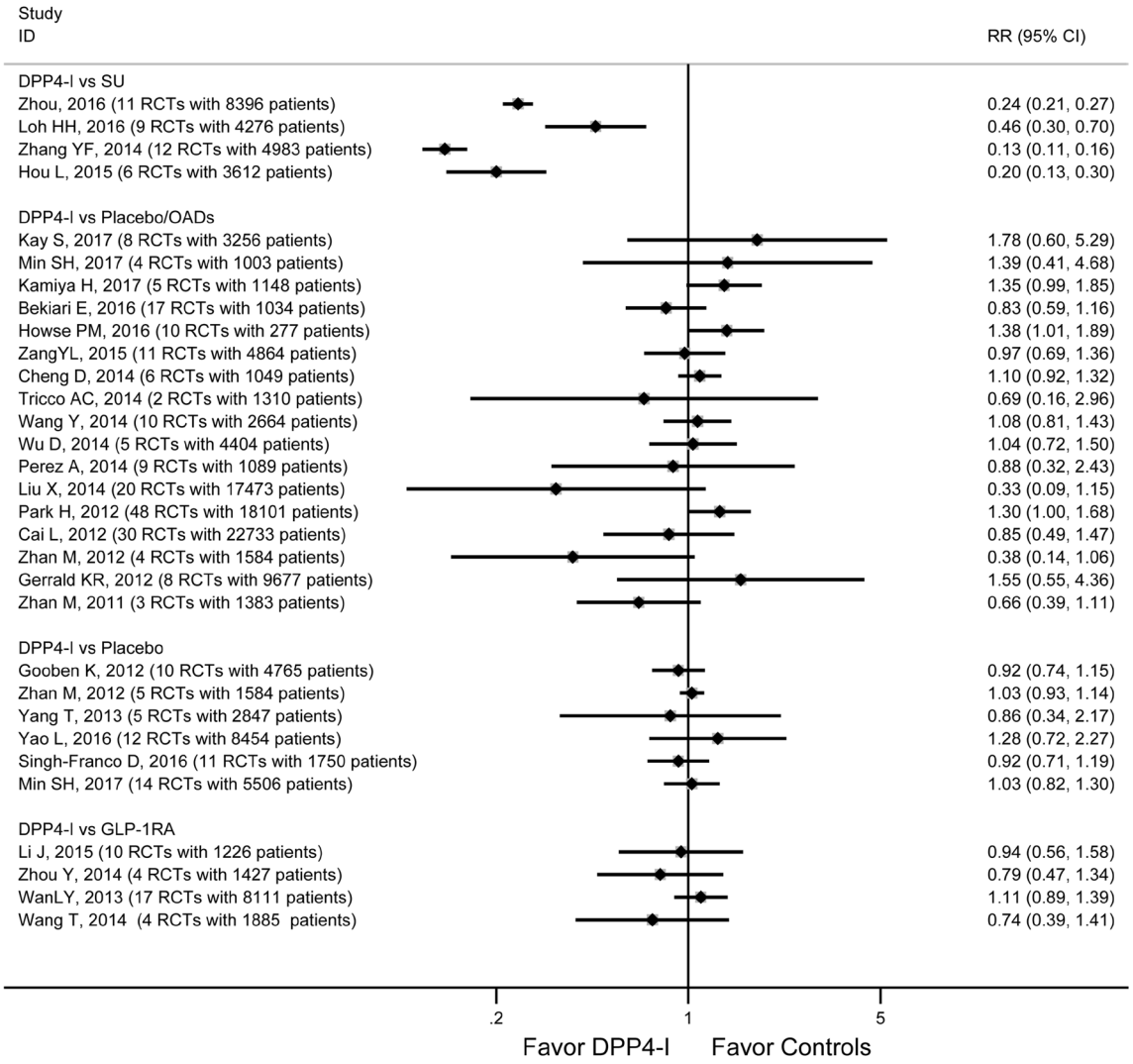


Fig. 3 Summary of findings for hypoglycemia outcome

quantity of included studies with six RCTs. Therefore, the main reasons for heterogeneity can be summarized as the methods were used as well as quantity of included studies and patients.

Methodological quality of SRs

Assessment of various aspects of the methodological quality of the included SRs using the AMSTAR tool revealed common areas for improvement.

1. For item 1, only four studies provided a clear a priori design; therefore, publications may be duplicated if the inclusion criteria and exclusion criteria are only indicated in the text. Consequently, inaccurate inclusion or exclusion of clinical trials evidence from systematic reviews can result in following inaccurate recommendations in clinical practice [81]. The report of another overview of 59 SRs reported similar conclusions [82].
2. For items 4 and 5, 40 studies did not state whether gray literature was included, and only one study provided a list of excluded articles. The exclusion of gray literature from SRs may introduce bias and undermine the validity, which can result in overestimation of an intervention effect by an average of 12% [83]. Thus, to avoid publication bias, gray literature without language and nationality limitations should be researched in addition to all relevant literature published both at home and abroad.
3. For items 7 and 8, there are eight studies did not use a quality scoring tool or checklist and nine studies did not consider the methodological rigor and scientific quality in the analysis and the conclusions of the review. The quality of the included studies directly reflects the strength of the evidence of the SRs and a highly accu-

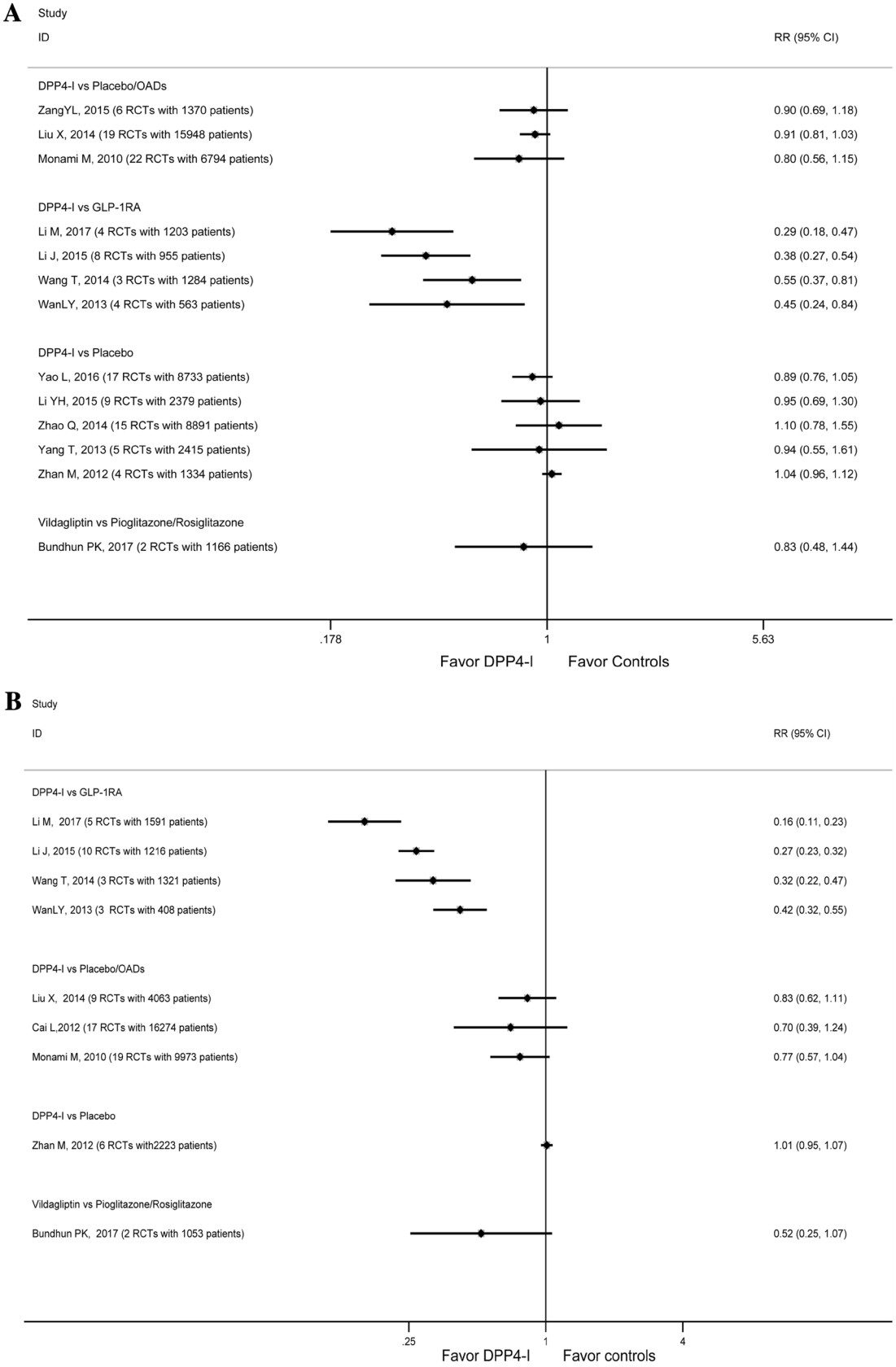
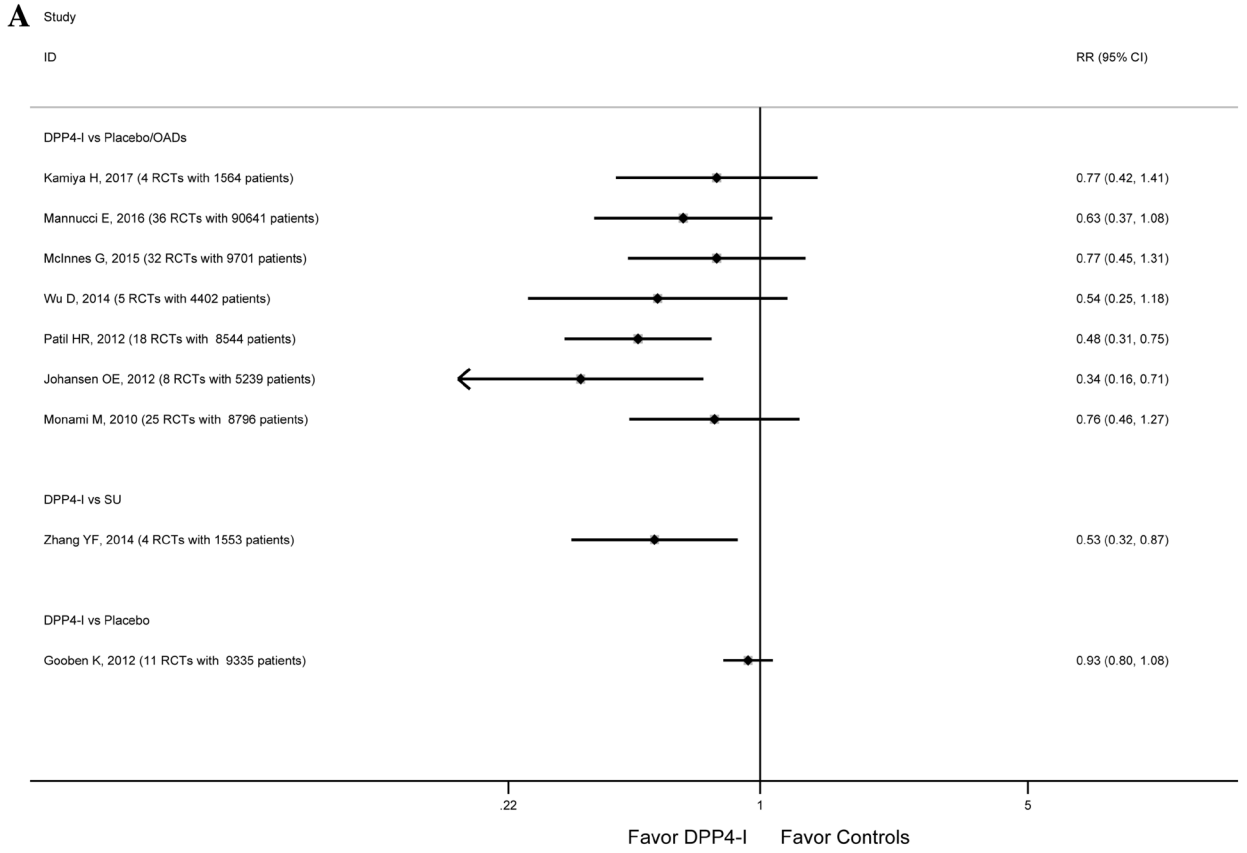


Fig. 4 **a** Summary of findings for diarrhea outcome. **b** Summary of findings for nausea outcome



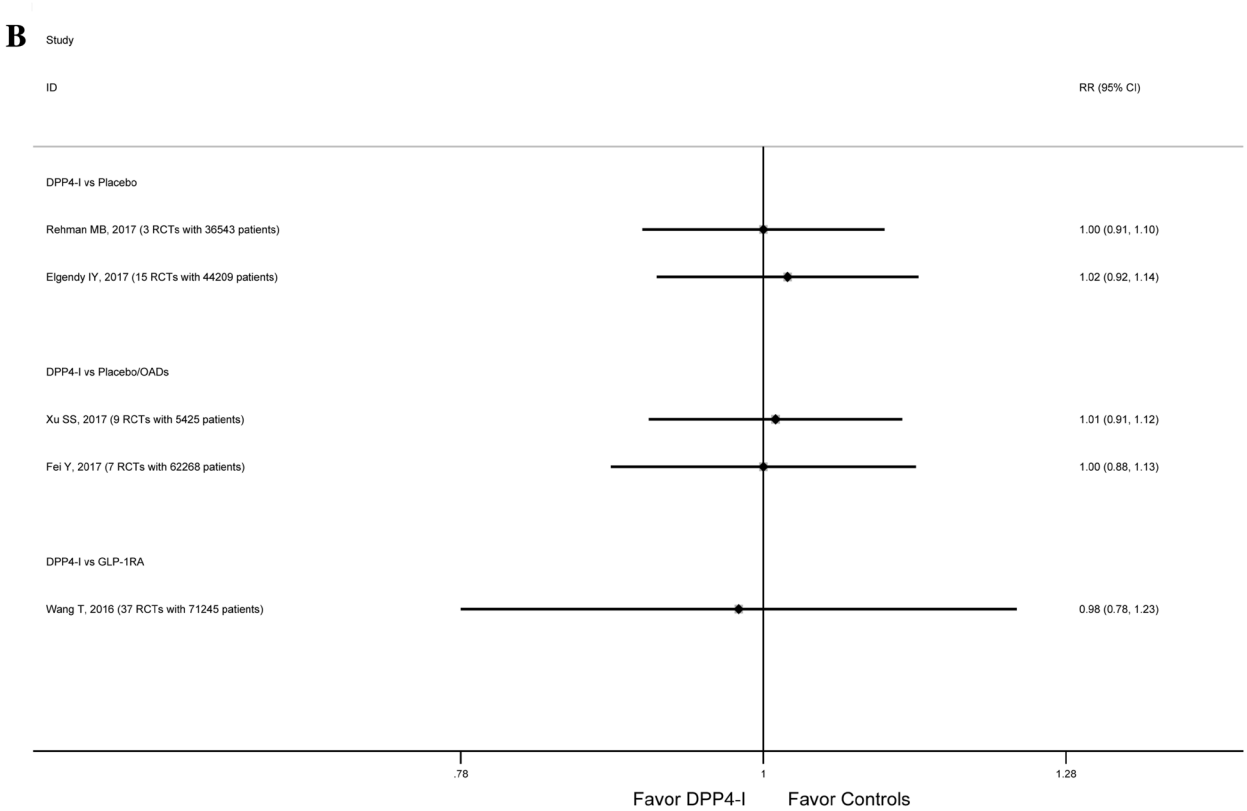


Fig. 5 **a** Summary of findings for cardiovascular events outcome. **b** Summary of findings for cardiovascular mortality outcome. **c** Summary of findings for heart failure outcome

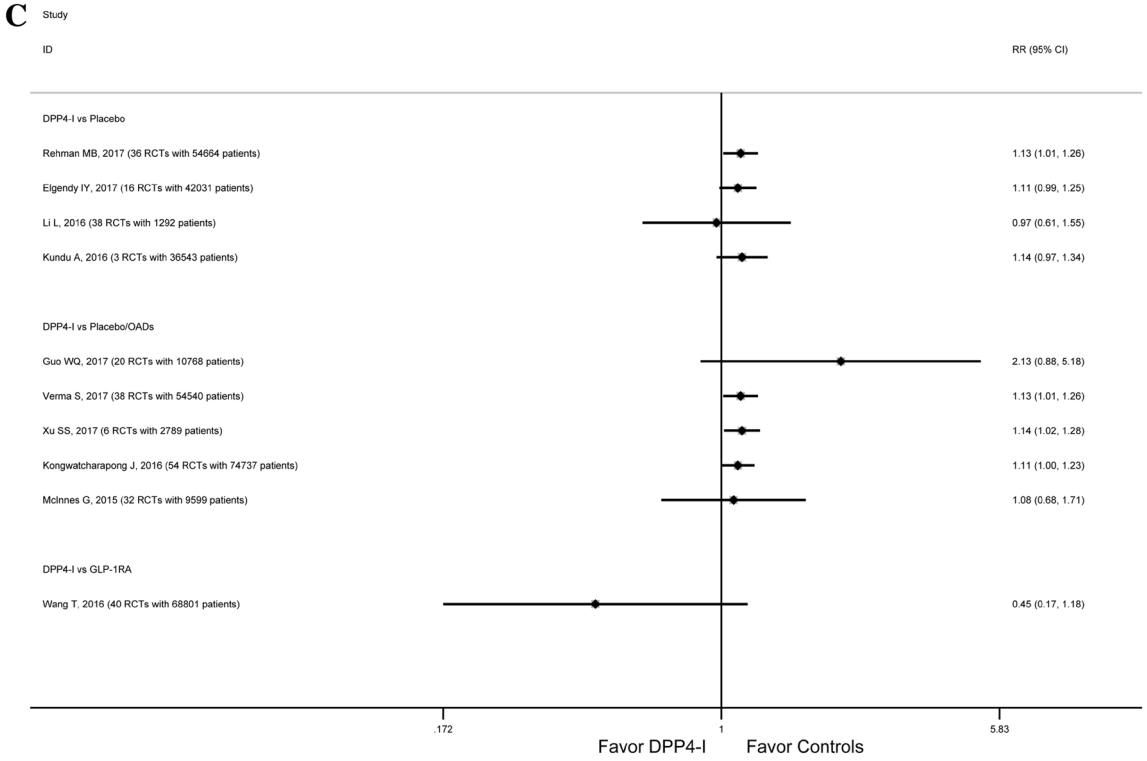


Fig. 5 (continued)

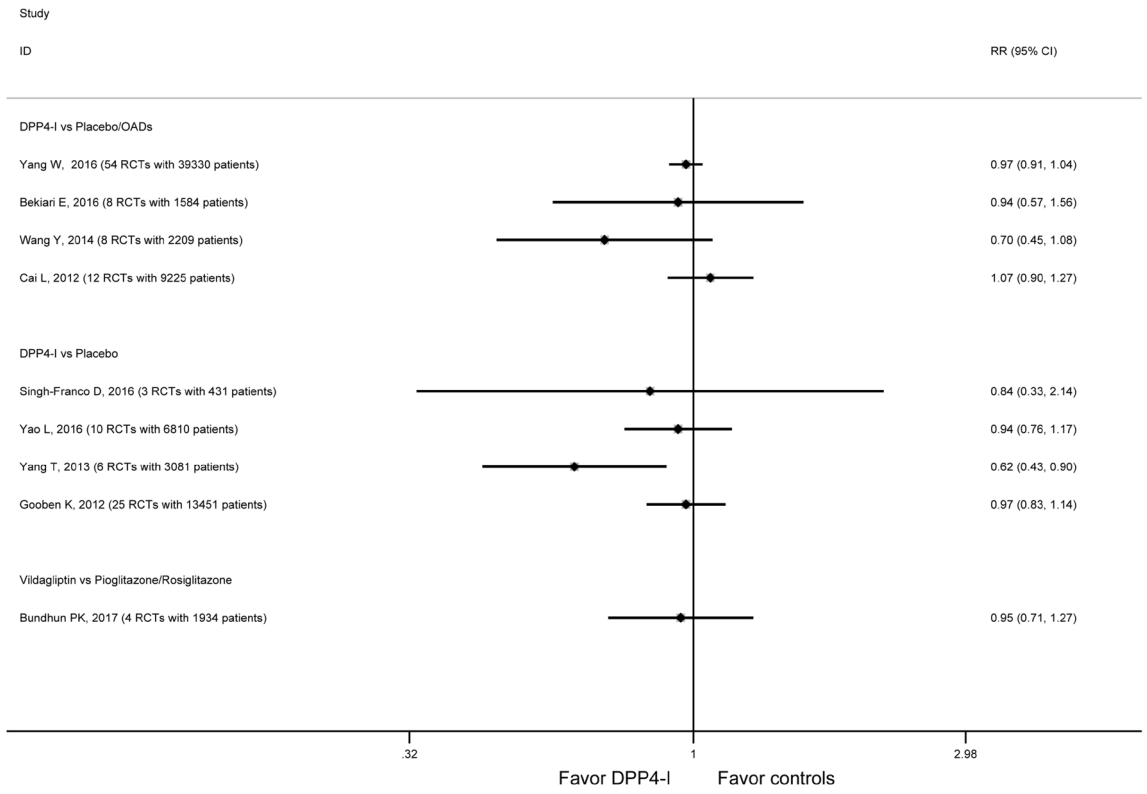


Fig. 6 Summary of findings for infections outcome

rate and valid tool is required to identify the best quality evidence [81]. Therefore, it is necessary to assess the scientific quality of included studies and apply this information in evaluation of the conclusions.

4. For item 10, 45.3% of SRs did not assess the likelihood of publication bias, while the remainder assessed the publication bias by construction of funnel plots and Begg–Mazumdar and Egger tests. Publication bias is a widespread problem in biomedical research and further evidence of the importance of this issue is reported by Dubben and Beck–Bornholdt [84].
5. For item 11, 41 studies acknowledged potential sources of support and sources of funding. Details of conflict of interest and sources of funding are important to avoid other bias [85].

Strengths and limitations

This overview is the first study to assess the methodological quality of SRs using the AMSTAR and GRADE approach to evaluate the quality of evidence for the safety and efficacy of DPP4-I in T2DM patients. However, our study has some limitations. First, in this overview, we included only SRs or meta-analyses, while the elements of DPP4-I in primary studies (such as cohort studies, observational studies and case–control studies) were not reviewed. Second, although many outcomes emerged in the included SRs, we have summarized the results of the primary and secondary outcomes in the eligibility criteria. Third, we included ten studies reported in the Chinese language based on the study by JinHui [86] showing that the methodological and reporting quality of SRs from China and the USA are similar.

Conclusion

The evidence summarized here shows the methodological quality of SRs was not high; therefore, the AMSTAR scale should be employed to improve it to provide effective Evidence-based medicine for the formulation of clinical guidance.

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Compliance with ethical standards

Conflict of interest The authors (Juan Ling, Long Ge, Ding-hua Zhang, Yong-feng Wang, Zhuo-lin Xie, Jin-hui Tian, Xiao-hui Xiao and Ke-hu Yang) have indicated that they have no conflicts of interest regarding the content of this article.

Human and animal rights This article is based on previously conducted studies and does not contain any studies with animals performed by any of the authors.

Informed consent Not applicable.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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