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ORIGINAL RESEARCH ARTICLE

Cardiovascular Safety of Dipeptidyl-Peptidase IV Inhibitors: A Meta-Analysis of Placebo-Controlled Randomized Trials

Islam Y. Elgendy[1] · Ahmed N. Mahmoud[1] · Amr F. Barakat[2] · Akram Y. Elgendy[1] · Marwan Saad[3] · Ahmed Abuzaid[4] · Siddarth A. Wayangankar[1] · Anthony A. Bavry[1,5]

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Abstract

Background Large randomized trials have shown conflicting evidence regarding the cardiovascular safety of dipeptidyl-peptidase 4 (DPP-4) inhibitors. Systematic reviews have been limited by incomplete data and inclusion of observational studies. This study aimed to systematically evaluate the cardiovascular safety of DPP-4 inhibitors in patients with type 2 diabetes.

Methods Electronic databases were searched for randomized trials that compared DPP-4 inhibitors versus placebo and reported cardiovascular outcomes. The main outcome assessed in this analysis was heart failure. Other outcomes included all-cause mortality, cardiovascular mortality, myocardial infarction, and ischemic stroke. Summary odds ratios (ORs) were primarily constructed using Peto's model.

Results A total of 90 trials with 66,730 patients were included. Compared with placebo, DPP-4 inhibitors were associated with a non-significant increased risk of heart failure [OR 1.11, 95% confidence interval (CI) 0.99–1.25, $P = 0.07$] at a mean of 108 weeks. The risk of all-cause mortality (OR 1.03, 95% CI 0.94–1.12, $P = 0.53$), cardiovascular mortality (OR 1.02, 95% CI 0.92–1.14, $P = 0.72$), myocardial infarction (OR 0.98, 95% CI 0.88–1.09, $P = 0.69$), and ischemic stroke (OR 0.99, 95% CI 0.85–1.15, $P = 0.92$) was similar between both groups.

Conclusion In patients with type 2 diabetes, the safety profile of DPP-4 inhibitors is similar to placebo. As a class, there is only weak evidence for an increased risk of heart failure.

Key Points

Large randomized trials have shown conflicting evidence regarding the cardiovascular safety of dipeptidyl-peptidase 4 (DPP-4) inhibitors.

This meta-analysis demonstrated that the safety profile of DPP-4 inhibitors is similar to placebo.

Patients and providers can feel reassured that DPP-4 inhibitors are well tolerated and can represent a valuable component in the armamentarium of antiglycemic therapy.

1 Introduction

In the USA, diabetes mellitus affects approximately 21 million adults [1]. Dipeptidyl-peptidase 4 (DPP-4) inhibitors have emerged as a new class of incretin-based

I. Y. Elgendy and A. N. Mahmoud equally contributed to the paper.

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✉ Islam Y. Elgendy
islam.elgendy@medicine.ufl.edu

[1] Division of Cardiovascular Medicine, Department of Medicine, University of Florida, 1600 SW Archer Road, Gainesville, FL 32610, USA

[2] Department of Medicine, Cleveland Clinic, Cleveland, OH, USA

[3] Department of Medicine, University of Arkansas, Little Rock, AR, USA

[4] Division of Cardiovascular Medicine, Jefferson University Hospital/Christiana Care Health System, Newark, DE, USA

[5] North Florida/South Georgia Veterans Health System, Gainesville, FL, USA

medications for the management of type 2 diabetes mellitus [2]. They improve glucose control without inducing hypoglycemia or weight gain [3]. Some authors had suggested that these medications might exert a cardiovascular protective effect [4]. The American Diabetes Association and the European Association for the Study of Diabetes recommend this class as a second-line agent in patients with type 2 diabetes [5]. In the largest randomized trial designed to explore the cardiovascular safety of this class of medications, there was a 27% relative increased risk for heart failure hospitalizations with saxagliptin compared with placebo [6]. In two other large randomized trials testing alogliptin and sitagliptin, the risk of heart failure was similar compared with placebo [7, 8]. Furthermore, data from real world registries have yielded inconsistent results regarding the risk of heart failure with this class of medications [9–13]. Previous meta-analyses were limited by incomplete evaluation of cardiovascular safety outcomes [14–16], non-comprehensive evaluation of data [17–21], or inclusion of data from observational studies [22]. Given the uncertainty about the cardiovascular safety of this class of medications, we aimed to conduct a comprehensive meta-analysis of placebo-controlled randomized trials to test the cardiovascular safety of this class of medications.

2 Methods

We searched the MEDLINE database without language restriction from inception until August 2015 using the keywords and Medical Subject Headings illustrated in Fig. 1. We also searched the Web of Science and the Cochrane Register of Controlled Trials databases using similar keywords. This meta-analysis was registered at the PROSPERO international prospective register of systematic reviews (CRD42015024674) [23].

We selected randomized controlled clinical trials that compared any of the DPP-4 inhibitors (i.e., anagliptin, alogliptin, dutogliptin, linagliptin, omarigliptin, sitagliptin, saxagliptin, teneligliptin, and vildagliptin) with placebo in patients with type 2 diabetes. We required that the published report for the study explicitly reported any cardiovascular outcome (namely, heart failure, all-cause mortality, cardiovascular mortality, myocardial infarction, or ischemic stroke). We excluded trials that compared DPP-4 inhibitors with any other comparator agent (e.g., metformin, sulfonylurea, or thiazolidinediones) in order to test the relative safety of DPP-4 inhibitors with placebo. We also excluded trials that had unequal distribution of a second oral hypoglycemic agent in either arm. For trials with multiple comparison arms, we combined the DPP-4 inhibitor arms irrespective of the doses. For trials that had a second phase with an active agent (i.e., another oral hypoglycemic agent), we reported outcomes only for the placebo-controlled phase. For these trials, we excluded the ones that reported cardiovascular outcomes only at the end of the second phase.

Teams of two paired reviewers extracted data on general study data, study design, sample size, patient characteristics, interventional strategies, and cardiovascular outcomes from the included studies. Two reviewers further reviewed the extracted data to ensure accuracy. Reviewers resolved any discrepancies by discussion. For all clinical outcomes, we tabulated the number of events that occurred in each arm. Since it is mandated that parties submit a summary of the results including serious adverse events to clinicaltrial.gov, we searched this registry for each of the included studies to ensure that we collected any possible cardiovascular outcome. We evaluated the quality of the included trials on the basis of adequate description of treatment allocation, blinded outcome assessment, and description of losses to follow-up [24].

The main outcome evaluated in this analysis was heart failure. We defined heart failure as any reported case of "heart failure," "cardiac failure," or "hospitalization for heart failure." We also evaluated all-cause mortality, cardiovascular mortality, myocardial infarction, and ischemic stroke (defined as ischemic stroke or transient ischemic attack). If a study reported outcomes at different follow-up periods, we preferentially extracted data for the longest reported follow-up.

We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines to conduct a high-quality meta-analysis [25]. We analyzed the outcomes with an intention-to-treat analysis. Since we anticipated that the outcomes are rare [26], we constructed the summary estimate odds ratios (ORs) primarily with Peto's model [27]. We performed a secondary analysis using random effects summary risk ratios (RRs) with a DerSimonian and Laird model [28]. We performed the overall analysis for each outcome using the data reported from the longest follow-up period. We examined the statistical heterogeneity using I^2 statistic [29]. We evaluated publication bias with Egger's method [30]. All P values were two-tailed, with statistical significance set at 0.05, and confidence intervals (CIs) were calculated at the 95% level for the overall estimate effect. We conducted all analyses with STATA software version 14 (STATA Corporation; College Station, TX, USA).

For the outcome of heart failure, we further performed a pre-specified sensitivity analysis including only the high-quality trials, and another sensitivity analysis including only trials that enrolled >1000 subjects. We conducted subgroup analyses according to the follow-up time (i.e., ≤24 weeks, 24–52 weeks, >52–104 weeks, and >104

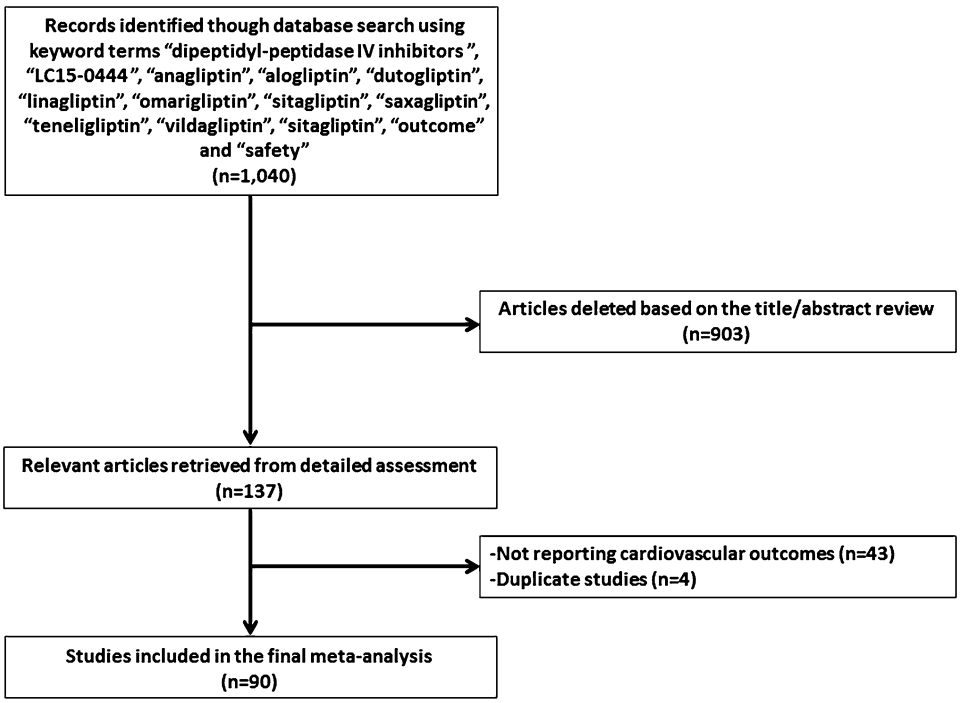

Fig. 1 Summary of how the systematic search was conducted and eligible studies were identified (PRISMA flow diagram)

weeks). Random effects meta-regression analyses were pre-specified for the outcome of heart failure with the type of DPP-4 inhibitor, age, male gender, hemoglobin A1c (HbA1c) level, duration of diabetes, and body mass index (BMI).

3 Results

The electronic search yielded 1040 articles, which we screened by reviewing the title and/or abstract; 137 articles were deemed potentially eligible. Upon further review of the full article, 90 trials with 66,730 patients were included in the final analysis (Fig. 1) [6–8, 31–117]. Table 1 summarizes the baseline characteristics of the included trials. Sitagliptin was the most frequent medication tested (i.e., in 24 trials), while 15 trials evaluated saxagliptin. All of the included studies were multicenter and double blinded. The follow-up time ranged from 2 to 156 weeks. Supplemental Table 1 reports the quality of the included studies (see the electronic supplementary material, online resource 1). The primary outcome for most of the included studies was the change in the HbA1c level at the end of the follow-up period. Only three trials evaluated cardiovascular outcomes as the primary outcome [6, 8, 50].

Twenty-five trials evaluated the outcome of heart failure (nine of these studies had zero events in both arms). The mean follow-up was 108 ± 45 weeks (median follow-up time 109 weeks). We utilized data regarding heart failure events for the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial from the pre-specified analysis that evaluated heart failure [7]. Compared with placebo, DPP-4 inhibitors were associated with a non-significant increase in the risk of heart failure using both Peto's method (OR 1.11, 95% CI 0.99–1.25, $P = 0.07$) (Fig. 2) and the DerSimonian and Laird model (RR 1.11, 95% CI 0.99–1.24, $P = 0.09$, $I^2 = 0\%$). There was no evidence of publication bias with Egger's test ($P = 0.23$). The pre-specified sensitivity analysis including only high-quality studies yielded similar results (OR 1.13, 95% CI 0.99–1.28, $P = 0.07$, $I^2 = 27\%$), as well as the pre-specified analysis limited to trials that enrolled >1000 subjects (OR 1.12, 95% CI 1.00–1.26, $P = 0.06$, $I^2 = 42\%$) (Supplemental Figure 1). Subgroup analyses according to the follow-up time showed that the risk of heart failure was comparable to placebo at ≤24 weeks (OR 0.48, 95% CI 0.13–1.73), at 24–52 weeks (OR 2.64, 95% CI 0.54–12.87), and at >52–104 weeks (OR 0.35, 95% CI 0.02–7.60), but a non-significant increase in heart failure at >104 weeks (OR 1.12, 95% CI 0.99–1.26) (P for interaction = 0.27). Meta-regression analysis did not identify a difference in treatment effect based on the type of DPP-4 inhibitors, age, male gender, HbA1c level, duration of diabetes, and BMI ($P = 0.76$, 0.34, 0.24, 0.23, 0.66, and 0.10, respectively).

Compared with placebo, DPP-4 inhibitors were associated with a similar risk of all-cause mortality (OR 1.03, 95% CI 0.94–1.12, $P = 0.53$, $I^2 = 0\%$) (Fig. 3), cardiovascular mortality (OR 1.02, 95% CI 0.92–1.14, $P = 0.72$, $I^2 = 0\%$) (Supplemental Figure 2), myocardial infarction

Table 1 Baseline characteristics of the included trials

Study (Ref.)	Year	Patients, n	Intervention arm	Background therapy	Age, %	Men, %	HbA1c, %	DM duration, years	BMI, kg/m^2
Matthaei et al. [31]	2015	153/162	Saxagliptin	Dapagliflozin	55/55	48/47	8.0/7.9	8.1/7.4	31/31
Mathieu et al. [32]	2015	329/329	Sitagliptin	Insulin/metformin	59/58	46/50	8.7/8.8	13.2/13.7	32/32
Green et al. [8]	2015	7332/7339	Sitagliptin	Multiple drugs	65/66	71/71	7.2/7.2	11.6/11.6	30/30
Yang et al. [33]	2015	70/39	Anagliptin	None	56/57	50/63	7.1/7.1	3.3/4.1	25/25
Wang et al. [34]	2015	205/100	Linagliptin	Metformin	55/57	50/50	8.0/8	NR/NR	26/26
Yang et al. [35]	2015	143/136	Vildagliptin	Sulfonylurea	58/59	55/58	8.6/8.7	6.9/6.9	25/25
Sheu et al. [36]	2015	571/114	Omarigliptin	None	55/56	56/57	8.0/8.1	5.3/5.8	30/30
Ning et al. [37]	2015	146/147	Vildagliptin	Insulin	58/58	42/45	8.6/8.7	11.2/11.4	26/26
Bajaj et al. [38]	2014	182/89	Linagliptin	Thiazolidinedione/metformin	53/55	45/55	8.4/8.5	NR/NR	28/28
Thrasher et al. [39]	2014	106/120	Linagliptin	Metformin/sulfonylurea	54/54	57/51	8.7/8.8	NR/NR	32/33
Pratley et al. [40]	2014	225/109	Alogliptin	None	53/53	49/51	8.5/8.5	3.8/4.3	31/31
White et al. [41]	2014	74/86	Saxagliptin	Metformin	54/57	54/52	7.9/8.0	5.8/6.2	34/33
Odawara et al. [42]	2014	69/70	Vildagliptin	Metformin	59/58	64/69	8.0/8.0	7.2/7.0	25/26
Ahrén et al. [43]	2014	313/104	Sitagliptin	Metformin	54/56	46/50	8.2/8.2	NR/NR	NR/NR
Kadowaki et al. [44]	2014	96/98	Teneligliptin	Sulfonylurea	58/60	65/67	8.4/8.4	NR/NR	NR/NR
Moses et al. [45]	2014	129/128	Saxagliptin	Metformin/sulfonylurea	57/57	62/58	8.4/8.2	NR/NR	29/29
Lukashevich et al. [46]	2014	158/160	Vildagliptin	Metformin/sulfonylurea	55/55	51/45	8.7/8.8	7.1/7.5	28/28
Hage et al. [47]	2013	39/40	Sitagliptin	None	69/66	85/78	40/40[a]	0/0	27/27
Barnett et al. [48]	2013	304/151	Saxagliptin	Insulin/metformin	57/57	40/45	8.7/8.6	11.8/12.2	33/32
Barnett et al. [49]	2013	162/79	Linagliptin	Multiple	75/75	72/62	7·8/7·7	NR/NR	30/30
White et al. [7, 50]	2013	2701/2679	Alogliptin	Multiple	61/61	68/68	8.0/8.0	7.3/7.1	29/29
Strain et al. [51]	2013	139/139	Vildagliptin	Sulfonylurea	75/74	53/38	7.9/7.9	12.2/10.6	29/31
Kothny et al. [52]	2013	228/221	Vildagliptin	Insulin/metformin	59/59	48/52	8.8/8.8	12.9/13.2	29/29
McGill et al. [53]	2013	68/65	Linagliptin	Multiple	64/65	66/54	8.2/8.2	NR/NR	32/32
Scirica et al. [6]	2013	8280/8216	Saxagliptin	Multiple	65/65	67/67	8.0/8.0	10.3/13.3	31/31
Yki-Järvinen et al. [54]	2013	631/630	Linagliptin	Multiple	60/60	52/52	8.3/8.3	84/87 (>5 years)[b]	31/31
Dobs et al. [55]	2013	170/92	Sitagliptin	Thiazolidinedione/metformin	54/55	56/60	8.8/8.7	9.3/9.4	30/31
Kadowaki and Kondo [56]	2013	103/101	Teneligliptin	Thiazolidinedione	60/61	66/75	8.1/7.9	7.2/7.7	26/26
Rosenstock et al. [57]	2013	564/179	Saxagliptin	Metformin	55/55	50/54	8.1/8.1	6.5/6.7	31/32
Lavalle-González et al. [58]	2013	366/183	Sitagliptin	Metformin	55/56	47/51	7.9/8.0	6.8/6.8	32/31
Alba et al. [59]	2013	52/53	Sitagliptin	NR	55/53	54/60	7.7/8.0	2.4/2.3	31/30
Kadowaki and Kondo [60]	2013	244/80	Teneligliptin	NR	58/59	67/64	7.8/8.0	6.3/5.8	24/25
Kadowaki et al. [61]	2013	77/72	Sitagliptin	Metformin	60/57	71/68	8.2/8.4	7.7/7.3	25/25
Fonseca et al. [69]	2013	157/156	Sitagliptin	Thiazolidinedione/metformin	56/56	62/63	8.8/8.7	9.4/10.2	30/30
Seino et al. [62]	2012	209/103	Alogliptin	Sulfonylurea	60/60	66/69	8.6/8.6	10.0/9.0	25/25
Ross et al. [63]	2012	447/44	Linagliptin	Metformin	59/60	58/48	8.0/7.9	52/56 (>5 years)[b]	30/29

Table 1 continued

Study (Ref.)	Year	Patients, n	Intervention arm	Background therapy	Age, %	Men, %	HbA1c, %	DM duration, years	BMI, kg/m^2
Lewin et al. [64]	2012	161/84	Linagliptin	Sulfonylurea	57/56	48/62	8.6/8.6	58/56 (>5 years)[b]	28/28
Kothny et al. [65]	2012	216/153	Vildagliptin	Multiple	65/67	55/58	7.8/7.7	16.5/17.4	31/30
Barnett et al. [66]	2012	151/76	Linagliptin	None	56/57	36/43	8.1/8.1	27/21 (>5 years)[b]	29/30
Pan et al. [67]	2012	284/284	Saxagliptin	None	50/52	56/55	8.1/8.2	0.8/1.2	26/26
Frederich et al. [68]	2012	291/74	Saxagliptin	None	55/56	46/47	8.0/7.8	1.7/1.7	30/31
Barnett et al. [70]	2012	304/151	Saxagliptin	Insulin/metformin	57/57	40/45	8.7/8.6	12.0/12.0	33/32
Kawamori et al. [71]	2012	319/80	Linagliptin	Single or multiple agents	61/60	70/71	8.1/8.0	NR/NR	25/24
Bergenstal et al. [72]	2012	185/90	Sitagliptin	Metformin	56/56	59/52	7.9/8.0	6.0/5.5	32/33
Eto et al. [73]	2012	67/32	Teneligliptin	NR	57/59	81/87	8.4/8.2	6.4/7.8	24/26
Haak et al. [74]	2012	142/72	Linagliptin	NR	56/56	56/50	8.7/8.7	25/34 (>5 years)[b]	29/29
Yang et al. [75]	2012	197/198	Sitagliptin	Metformin	54/55	47/55	8.5/8.5	6.4/7.3	25/25
Yang et al. [76]	2011	283/287	Saxagliptin	Metformin	54/54	48/48	7.8/7.9	5.1/5.1	26/26
Seino et al. [77]	2011	322/75	Alogliptin	None	59/59	72/75	7.9/7.9	6.8/6.6	25/24
Kashiwagi et al. [78]	2011	66/68	Sitagliptin	Thiazolidinedione	58/59	58/72	8.1/8.0	8.2/7.6	26/27
Hollander et al. [79]	2011	381/184	Saxagliptin	Thiazolidinedione	54/54	50/46	8.4/8.2	5.3/5.1	3030
Forst et al. [80]	2011	61/16	Linagliptin	None	63/62	92/100	7.0/7.5	NR/NR	29/29
Nowicki et al. [81]	2011	85/85	Saxagliptin	Multiple	67/66	38/48	8.5/8.1	15.0/18.0	31/30
Lukashevich et al. [82]	2011	289/226	Vildagliptin	Multiple	66/67	56/59	7.8/7.8	16.2/17.1	30/30
Kaku et al. [83]	2011	224/115	Alogliptin	Thiazolidinedione	60/60	61/66	7.9/7.9	6.7/6.7	26/26
Henry et al. [84]	2011	20/16	Saxagliptin	None	55/56	40/36	6.9/6.6	2.7/3.7	34/32
Owens et al. [85]	2011	792/263	Linagliptin	Metformin/sulfonylurea	58/58	47/48	8.2/8.1	NR/NR	28/28
Taskinen et al. [86]	2011	523/177	Linagliptin	Metformin	57/57	53/57	8.1/8.0	NR/NR	30/30
Vilsbøll et al. [87]	2010	322/319	Sitagliptin	Insulin/metformin	58/57	49/53	8.7/8.6	13/12	31/31
Pattzi et al. [88]	2010	337/86	Dutogliptin	Multiple	53/53	54/52	8.5/8.4	>4 months and <12 years	32/32
Iwamoto et al. [89]	2010	290/73	Sitagliptin	None	60/60	60/69	7.6/7.7	5.2/6.4	25/24
Stenlöf et al. [90]	2010	46/47	Saxagliptin	Metformin	55/56	57/49	NR/NR	6.1/7.6	31/32
Raz et al. [101]	2008	94/96	Sitagliptin	Metformin	54/56	51/41	9.3/9.4	8.4/7.3	30/30
Kikuchi et al. [91]	2010	102/100	Vildagliptin	Sulfonylurea	59/60	74/69	7.8/8.0	8.6/9.8	25/24
Aaboe et al. [92]	2010	12/12	Sitagliptin	Metformin	60/60	66/75	8.0/7.7	3.6/5.8	33/31
Forst et al. [93]	2010	197/71	Linagliptin	Metformin	60/60	55/62	8.4/8.4	7.5/6.2	32/32
Nauck et al. [94]	2009	423/104	Alogliptin	Metformin	55/56	51/48	7.9/8.0	6.0/6.0	32/32
Pratley et al. [95]	2009	396/97	Alogliptin	Thiazolidinedione/metformin	55/55	59/55	8.0/8.0	7.6/7.8	33/33
Rosenstock et al. [96]	2009	260/130	Alogliptin	Insulin/metformin	56/55	38/48	9.3/9.3	12.8/12.2	33/32
Heise et al. [97]	2009	36/12	Linagliptin	None	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Nonaka et al. [98]	2009	52/28	Sitagliptin	None	56/54	65/70	7.7/7.9	3.7/3.0	26/25

Table 1 continued

Study (Ref.)	Year	Patients, n	Intervention arm	Background therapy	Age, %	Men, %	HbA1c, %	DM duration, years	BMI, kg/m^2
Goodman et al. [99]	2009	248/122	Vildagliptin	Metformin	55/55	53/67	8.5/8.5	NR/NR	31/32
Pratley et al. [95]	2009	401/99	Alogliptin	Sulfonylurea	57/57	52/52	8.1/8.2	7.7/7.7	30/30
Mohan et al. [100]	2009	352/178	Sitagliptin	None	51/51	57/60	8.7/8.8	2.1/1.9	25/25
Kikuchi et al. [102]	2009	219/72	Vildagliptin	None	59/60	6864	7.4/7.4	4.6/7.1	24/25
Garcia-Soria et al. [103]	2008	133/41	Dutogliptin	Thiazolidinedione/metformin	51/53	4239	8.7/8.7	5.5/5.2	32/33
Defronzo et al. [104]	2008	264/65	Alogliptin	None	53[c]	53[c]	7.9[c]	NR/NR	NR/NR
Covington et al. [105]	2008	45/11	Alogliptin	None	56[c]	43[c]	7.8/7.7	NR/NR	32[c]
Rosenstock et al. [106]	2008	271/67	Saxagliptin	None	53/55	57/63	7.8/8.0	0.9/1.8	31/31
Garber et al. [107]	2008	264/144	Vildagliptin	Sulfonylurea	59/58	60/58	8.6/8.5	6.8/7.8	32/31
Scherbaum et al. [108]	2008	156/150	Vildagliptin	None	63/63	60/59	6.7/6.8	2.5/2.7	30/30
Rosenstock et al. [109]	2008	90/89	Vildagliptin	None	57/60	48/43	5.9/5.9	NR/NR	32/31
Nonaka et al. [110]	2007	76/76	Sitagliptin	None	56/55	60/66	7.5/7.7	4.0/4.1	25/25
Bosi et al. [111]	2007	362/182	Vildagliptin	Metformin	54/55	59/53	8.4/8.3	6.3/6.2	33/33
Garber et al. [112]	2007	305/158	Vildagliptin	Thiazolidinedione	54/55	50/51	8.7/8.7	4.7/4.8	32/32
Goldstein et al. [113]	2007	179/176	Sitagliptin	None	53/54	52/53	8.9/8.7	4.4/4.6	31/33
Hermansen et al. [114]	2007	222/219	Sitagliptin	Metformin/sulfonylurea	56/57	53/53	8.3/8.3	8.3/9.3	31/31
Hanefeld et al. [115]	2007	444/111	Sitagliptin	NR	55/56	49/63	7.7/7.6	3.8/3.3	32/31
Scott et al. [116]	2007	495/125	Sitagliptin	None	56/55	52/62	7.9/7.9	4.6/4.8	31/32
Rosenstock et al. [117]	2006	175/178	Sitagliptin	Thiazolidinedione	56/57	53/58	8.1/8.0	6.1/6.1	32/31

Variables are presented as DPP-4 inhibitors/placebo

BMI body mass index, *DM* diabetes mellitus, *DPP-4* dipeptidyl-peptidase 4, *HbA1c* hemoglobin A1c, *NR* not reported, *Ref.* reference

[a] Mmol/mol

[b] Reported as percentages

[c] Reported as overall percentage of both arms

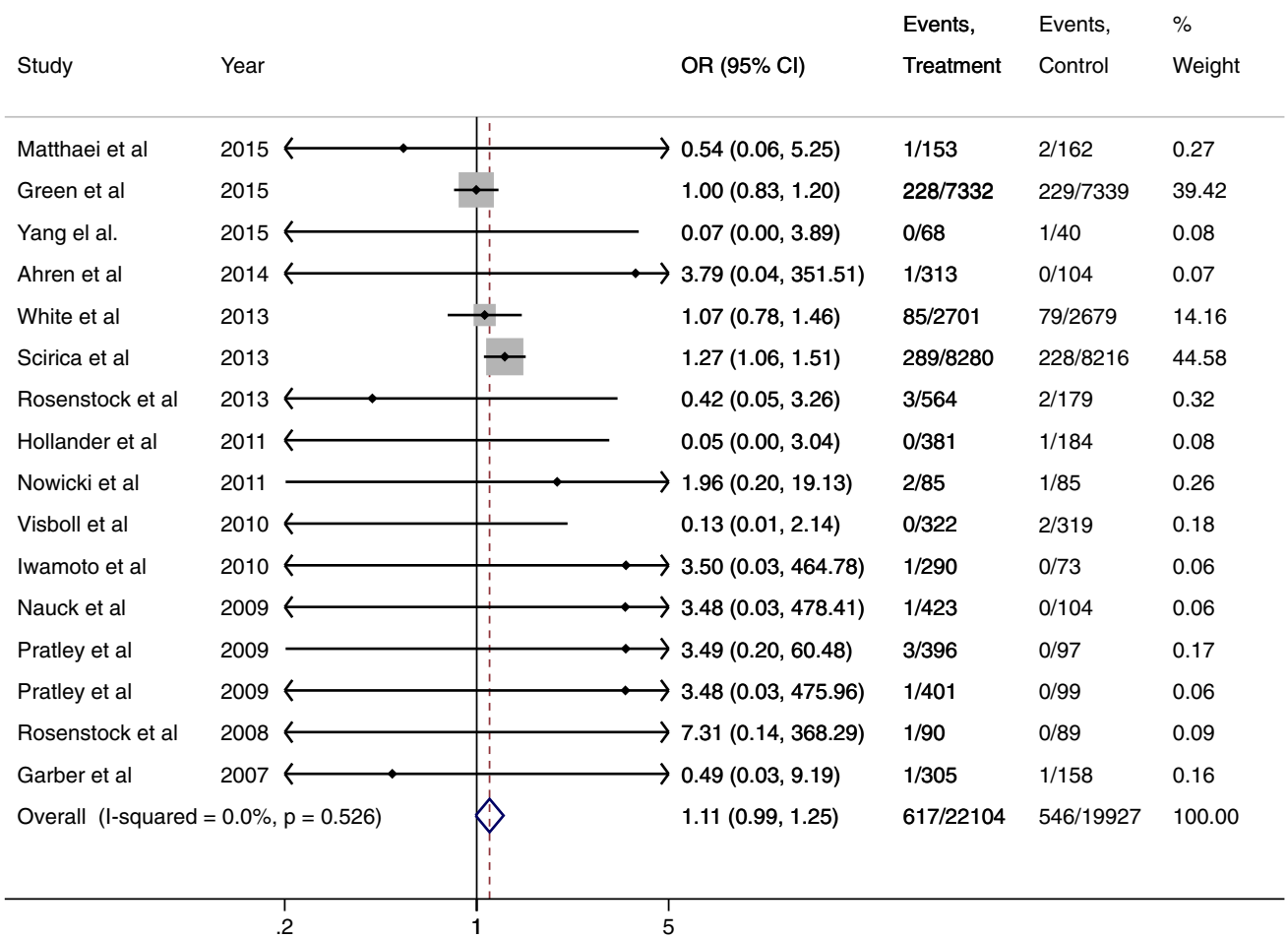

Fig. 2 Summary plot for heart failure. Trials were listed in the forest plot only if there was at least one event in either arm. The relative size of the data markers indicates the weight of the sample size from each study. *CI* confidence interval, *DPP-4* dipeptidyl-peptidase 4, *OR* odds ratio

(OR 0.98, 95% CI 0.88–1.09, $P = 0.69$, $I^2 = 10\%$) (Supplemental Figure 3), and ischemic stroke (OR 0.99, 95% CI 0.85–1.15, $P = 0.92$, $I^2 = 20\%$) (Supplemental Figure 4). There was no evidence of publication bias for the secondary outcomes. In Table 2, we summarize the summary estimates for the outcomes assessed in this meta-analysis.

4 Discussion

In this comprehensive meta-analysis of 90 double-blind, multicenter, placebo-controlled randomized clinical trials with 66,730 patients; we demonstrated that DPP-4 inhibitors were associated with a non-significant increase in the risk of heart failure at a mean of 108 weeks. We performed various sensitivity and meta-regression analyses to further explore any potential explanation for this observed finding. Our results suggested that any potential increase in the risk of heart failure was driven by one large trial [6]. Reassuringly, we also demonstrated that DPP-4 inhibitors were associated with a similar risk of all-cause mortality, cardiovascular mortality, myocardial infarction, and ischemic stroke compared with placebo.

In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 trial, saxagliptin neither increased nor decreased the composite of cardiovascular death, myocardial infarction, or ischemic stroke compared with placebo [6]. There was an unexpected 27% increased relative risk of hospitalization for heart failure in the saxagliptin arm. A post hoc analysis of this trial revealed that the risk of hospitalization for heart failure was increased among patients with elevated levels of natriuretic peptides at baseline, previous heart failure, or chronic kidney disease [118]. It remains unclear how saxagliptin might predispose to heart failure; a pooled analysis of 20 trials suggested that there was no evidence of fluid retention or weight gain with saxagliptin [21]. One plausible explanation for the increased heart failure risk in the SAVOR-TIMI 53 trial was the relatively large number of subjects with a prior history of heart failure at baseline

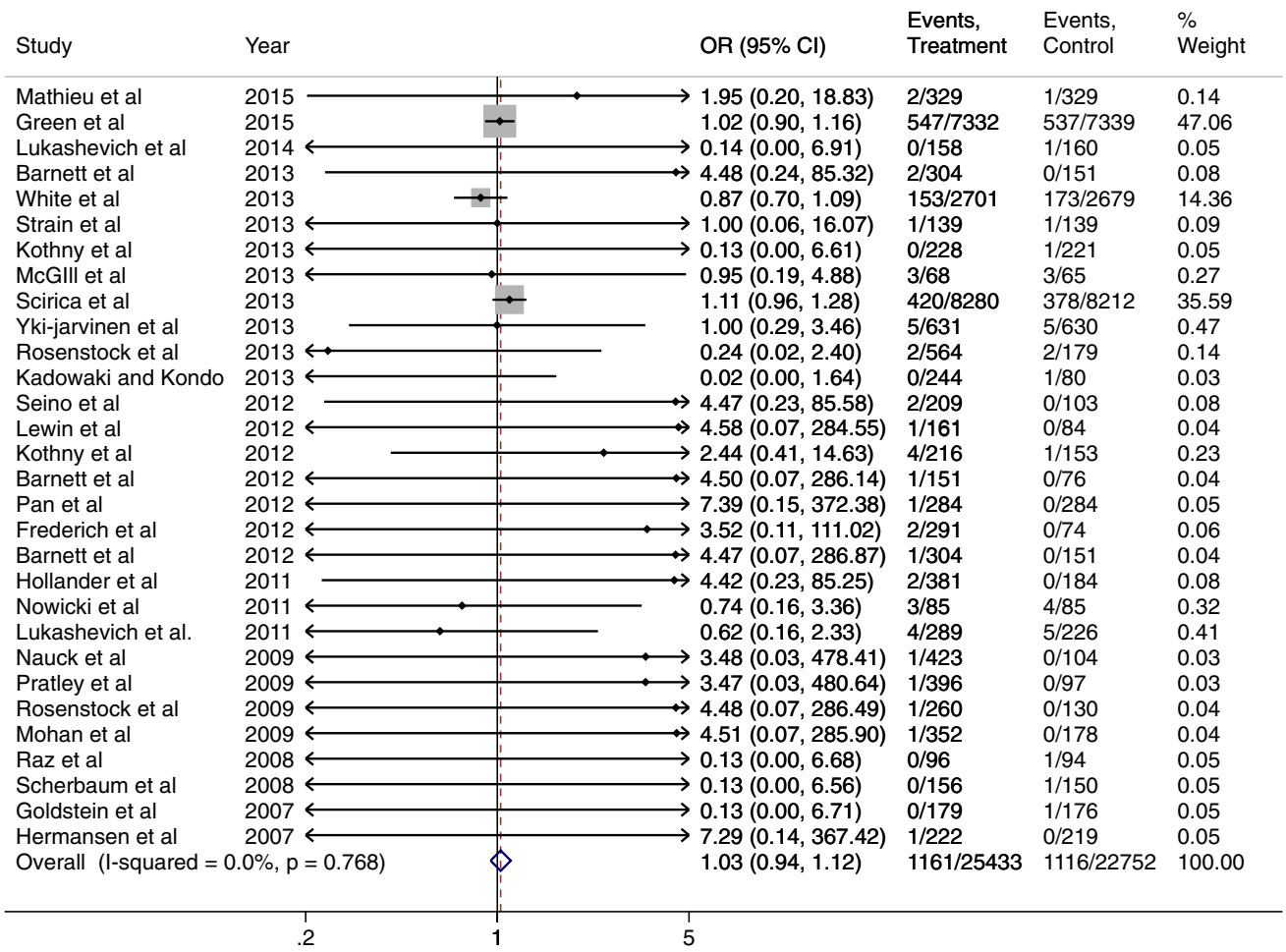

Fig. 3 Summary plot for all-cause mortality. Trials were listed in the forest plot only if there was at least one event in either arm. The relative size of the data markers indicates the weight of the sample size from each study. *CI* confidence interval, *DPP-4* dipeptidyl-peptidase 4, *OR* odds ratio

Table 2 Summary estimates for the outcomes assessed

Outcome	Model	OR[a]	95% confidence interval	*P* value	I^2 %
Heart failure	Peto	1.11	0.99–1.25	0.07	0
	DL	1.11	0.99–1.24	0.09	0
All-cause mortality	Peto	1.03	0.94–1.12	0.53	0
	DL	1.02	0.94–1.12	0.61	0
Cardiovascular mortality	Peto	1.02	0.92–1.14	0.72	0
	DL	1.01	0.91–1.12	0.83	0
Myocardial infarction	Peto	0.98	0.88–1.09	0.69	10
	DL	0.97	0.88–1.07	0.59	0
Ischemic stroke	Peto	0.99	0.85–1.15	0.92	20
	DL	0.98	0.85–1.14	0.78	0

DL DerSimonian–Laird, *OR* odds ratio, *RR* risk ratio

[a] RR was reported for DerSimonian and Laird method

(~13%). Most of the large randomized trials evaluating oral hypoglycemic agents in general had a lower number of subjects with previous heart failure history [119]. In the two other large randomized trials evaluating the cardiovascular outcomes with DPP-4 inhibitors [i.e., Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)

and EXAMINE], the risk of hospitalization for heart failure was not increased with either sitagliptin or alogliptin, respectively [7, 8, 50]. We performed a sensitivity analysis for these three large trials and found that there was a non-significant increase in the risk of heart failure, again driven by the results of the SAVOR-TIMI 53 trial. In a large multicentre cohort of 1,499,650 diabetic patients, incretin-based drugs [i.e., DPP-4 inhibitors and glucagon-like peptide-1 (GLP-1) analogs] were not associated with an increased risk of hospitalization for heart failure, as compared with oral antidiabetic drugs [120]. Our analysis of placebo-controlled randomized trials further supports that DPP-4 inhibitors as a class have only weak evidence for an increased risk of heart failure.

A recent systematic review evaluated the risk of heart failure with DPP-4 inhibitors and concluded that the risk of heart failure is uncertain with DPP-4 inhibitors [22]. However, that analysis was limited by the inclusion of observational studies that can be prone to bias. In addition, the authors used placebo and active agents in the comparator arm, which could have affected their results. In the present analysis, we included only placebo-controlled randomized trials in order to conduct a robust analysis. Furthermore, we assessed a wide spectrum of cardiovascular outcomes besides heart failure (i.e., all-cause mortality, cardiovascular mortality, myocardial infarction, and ischemic stroke), in order to provide a comprehensive analysis on the cardiovascular safety of DPP-4 inhibitors.

The present analysis has some limitations. First, the follow-up duration was variable among the included studies; thus we performed several subgroup analyses according to the follow-up time and demonstrated that the results were almost similar among these subgroups. Second, we performed our primary analysis with a fixed effects model (i.e., Peto's). We determined that Peto's model would be a good model for this particular analysis, given that the outcomes that we assessed were rare [26]. Furthermore, a secondary analysis with a DerSimonian and Laird model showed that the results were fairly robust irrespective of the methodology used. Third, the definition of heart failure was variable among the included studies; however, we observed no heterogeneity with statistical testing. Fourth, most of the included studies were small and not designed to address cardiovascular outcomes; however, all the included studies were designed to test the safety of the medication. In addition, we performed a sensitivity analysis limited to the three trials that tested cardiovascular outcomes as the primary outcome, which yielded similar results. Fifth, a considerable number of the studies had a significant drop-out rate at the end of the follow-up period; therefore we performed a sensitivity analysis excluding these low-quality studies. Finally, a lack of access to patient level data precluded a full evaluation to identify patient characteristics (e.g., renal disease, prior history of heart failure) associated with the potential risk for heart failure; however, we performed multiple meta-regression analyses using the available study-level data and found that none of the tested demographics were significant.

5 Conclusion

In patients with type 2 diabetes, DPP-4 inhibitors are relatively well tolerated compared with placebo. As a class, there is only weak evidence for an increased risk of heart failure.

Compliance with Ethical Standards

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Conflict of interest Dr. Anthony A. Bavry discloses the following relationship: honorarium from American College of Cardiology. The other authors have no conflicts of interest to declare.

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