Int J Clin Exp Med 2016;9(10):18816-18823
www.ijcem.com /ISSN:1940-5901/IJCEM0031236

Review Article

Efficacy and safety of saxagliptin and metformin as initial combination therapy in patients with type 2 diabetes: a meta-analysis

Xue-Ying Tan[1], Yang Lu[1], Li-Ping Xuan[1], Yong-Min Huang[1], Jing-Bo Hu[2]

[1]*Department of Endocrinology, Ningbo University Affiliated Yuyao Yangming Hospital, Yuyao 315400, China;* [2]*College of Pharmaceutical Science, Zhejiang University, 866 Yuhangtang Road, Hangzhou 310058, China*

Received April 26, 2016; Accepted July 30, 2016; Epub October 15, 2016; Published October 30, 2016

Abstract: Purpose: This meta-analysis was performed to evaluate the efficacy and safety of saxagliptin and metformin as initial combination therapy in patients with type 2 diabetes. Methods: A meta-analysis was performed to identify randomized controlled trials (RCTs) of saxagliptin plus metformin as combination therapy in patients with type 2 diabetes whose glycaemic control was insufficient after metformin monotherapy. RCTs were retrieved from PubMed, Embase, the Cochrane Library and Clinical Trials Gov through May 2015. Two people independently extracted data, including haemoglobin A1C (HbA_{1c}), fasting plasma glucose (FPG), weight, and adverse events, assessed search results and appraised risk of bias. Results: Five RCTs were included in this meta-analysis. Compared with metformin monotherapy, saxagliptin combined with metformin could significantly reduce HbA_{1c} [MD=-0.44, 95% CI (-0.71, -0.17), P<0.00001] and FPG level [MD=-0.62, 95% CI (-1.09, -0.15), P<0.00001]. Meanwhile, this combination therapy did not further decreased cardiovascular events [MD=0.96, 95% CI (0.31, 2.92), P=1.00] and increased incidence risk of hypoglycaemia [MD=3.22, 95% CI (1.10, 9.40), P=0.75]. Conclusions: Saxagliptin combined with metformin can be effective in improving glycemic control in patients with type 2 diabetes and decreasing incidence of hypoglycemia.

Keywords: Saxagliptin, metformin, type 2 diabetes, meta-analysis

Introduction

Type 2 diabetes is believed to be a chronic, progressive, and multifactorial metabolic disease defined by the presence of chronic hyperglycemia [1]. Long-term elevated blood glucose levels will cause complications of various organs, including retinopathy [2], nephropathy [3], and peripheral neuropathy [4]. Control of blood glucose is fundamental to the management of diabetes. The American Diabetes Association recommends a glycemic target of a glycosylated hemoglobin (HbA_{1c})<7% [5]. Lifestyle changes such as diet, exercise, and weight loss are typically recommended for patients with type 2 diabetes, but most patients still require pharmacotherapy to achieve glycemic goals.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin, linagliptin, vildagliptin, saxagliptin, and alogliptin) provide new choices for oral pharmacological therapy [6, 7]. The incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) released from the small intestine, are released in a glucose-dependent manner after food intake [8, 9]. The enhancement of GLP-1 and GIP stimulates the pancreas to secrete insulin, as well as reduces glucagon secretion and glucose production in liver [10, 11]. Saxagliptin, a DPP-4 inhibitor, improves glucose control in patients with type 2 diabetes through contributing to the increased concentration of GLP-1 and GIP [9]. Metformin is used in the clinic more than 60 years and is still recommended as the first line therapy for patients with type 2 diabetes [12-15]. Metformin lowers glucose levels through suppressing hepatic glucose production [16]. Besides, it can reduce the absorption of glucose from the gastrointestinal tract (GIT), enhance peripheral glucose uptake and increase insulin sensitivity [17, 18].

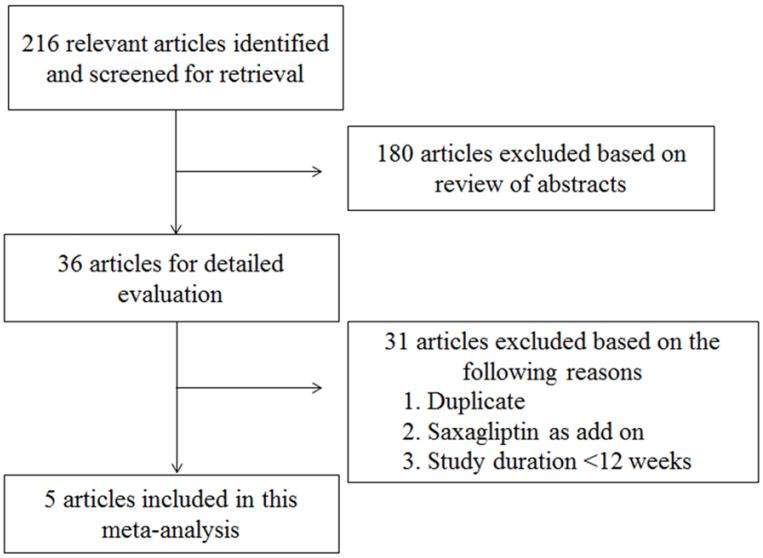

Figure 1. Flow diagram of citations.

By combining their different, complementary glucose-lowering activity, saxagliptin and metformin synergistic treatment benefits patients to achieve glucose target than individual component [19-21]. Hence, we conducted a meta-analysis to assess comparative change in HbA_{1c}, FPG and risk of hypoglycaemia of saxagliptin as add-on therapy to metformin in patients with type 2 diabetes inadequately controlled with metformin monotherapy.

Methods

Information sources and search strategy

We identified eligible studies through electronic databases, including Medline, Embase, the Cochrane Library, and Clinical Trials Gov, from inception to March 2015 using pertinent terms (saxagliptin, metformin, dipeptidyl peptidase-4 inhibitors, DPP-4 inhibitors). In addition, we hand-searched abstracts of major scientific meetings in the field of diabetes along with any associated e-posters (American Diabetes Association, Canadian Diabetes Association, European Association for the Study of Diabetes, American Association of Clinical Endocrinologists and International Diabetes Federation) from 2010 to 2015.

Study selection

In this meta-analysis, we included randomized controlled trials (RCTs) with the follow-up duration ≥12 weeks (trials with follow-up duration <12 weeks excluded), enrolling subjects with type 2 diabetes, and comparing saxagliptin plus metformin as combination therapy to metformin monotherapy. The changes in HbA_{1c}, FPG, body weight and adverse events, including cardiovascular events, hypoglycaemia and gastrointestinal events, were investigated. Eligible studies included were no limitation with respect to language, years of publication or publication status. Studies without a control group, non-randomized grouping and retrospective trials were excluded.

Data extraction and risk of bias assessment

Trial data were independently abstracted by two reviewers and any resulting discrepancies were resolved by discussion. For each eligible trial included, we extracted data on study characteristics, baseline characteristics of participants and key efficacy and safety outcomes. The quality of included trials was assessed through Jadad criteria [22]. Assessment included the following domains: random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting.

Data synthesis and analysis

During the study, Cochrane Collaboration's method was used for meta-analysis. Significant heterogeneities among the studies were resolved with the random-effects model (DerSimonian-Laird method) [23]. Otherwise, the fixed-effects model (Mantel-Haenszel method) was applied [24]. The mean difference (MD), pooled odds ratio (OR) and their 95% confidence intervals (CI) were calculated for each outcome. Cochran's chi-squared test was used to examine heterogeneity among the included studies and I^2, which is the proportion of the total variation due to heterogeneity between studies, was computed to determine the degree of inconsistency across studies. Heterogeneity was assessed by using I^2 statistics, with results

Table 1. Characteristics of RCTs included in this meta-analysis

Study	Mean age (years)	Study size	Combination therapy	Monotherapy	Study duration (weeks)	Quality score (max 5)
White [27]	55	160	Saxagliptin 2.5 mg+Metformin ≥1500 mg	Metformin ≥1500 mg	12	4
Hermans [28]	58	286	Saxagliptin 5 mg+Metformin 1500 mg	Metformin 2500 mg	24	3
Yang [29]	54	570	Saxagliptin 5 mg+Metformin 1500 mg	Metformin ≥1500 mg	24	5
Deffronzo [30]	54	371	Saxagliptin 2.5 mg+Metformin1500~2000 mg	Metformin 1500~2000 mg	24	4
Fonseca [31]	55	282	Saxagliptin 5 mg+Metformin 1500 mg	Metformin 2000 mg	18	4

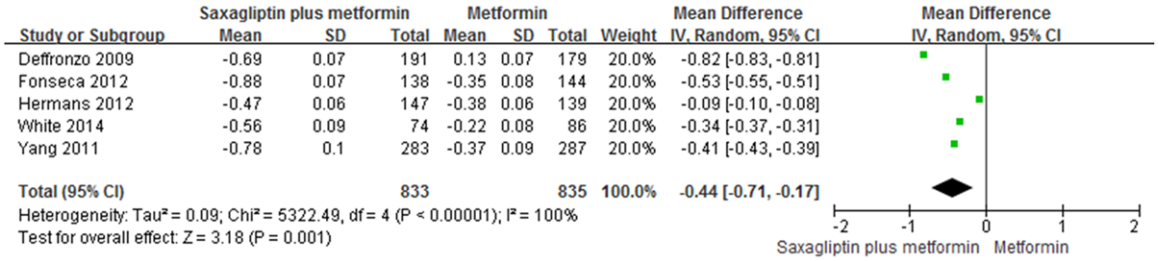

Figure 2. Meta-analysis for HbA1c change from baseline between saxagliptin plus metformin as combination therapy and metformin monotherapy.

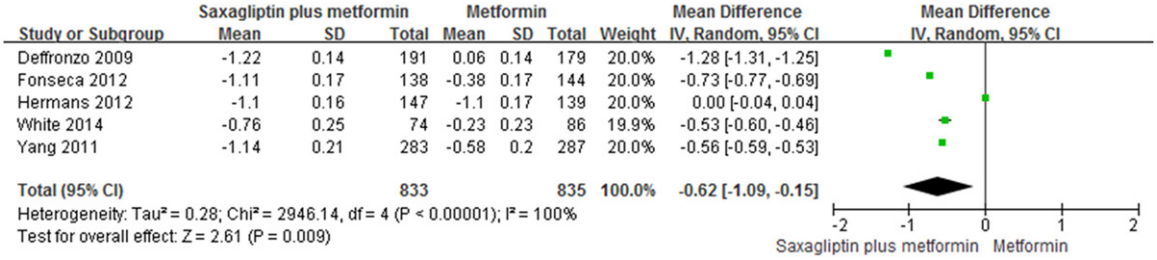

Figure 3. Meta-analysis for FPG change from baseline between saxagliptin plus metformin as combination therapy and metformin monotherapy.

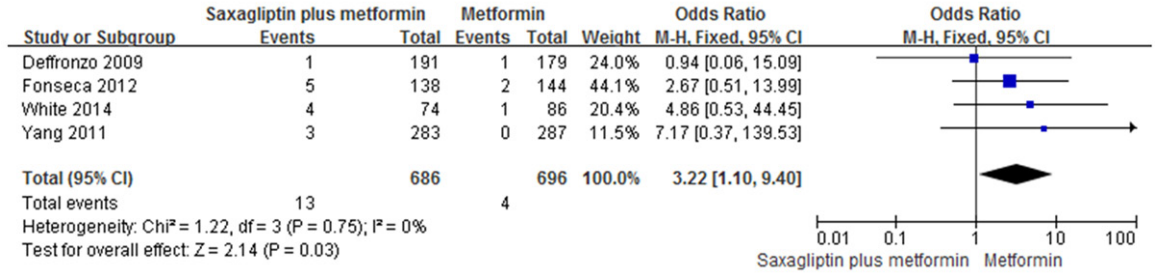

Figure 4. Meta-analysis for hypoglycaemia between saxagliptin plus metformin as combination therapy and metformin monotherapy.

ranging from 0 to 100% and values of 25, 50 and 75% representing low, moderate and high levels of heterogeneity, respectively 25. The random-effect model was used when I^2>50%, whereas the fixed-effect model was used in cases where heterogeneity was not significant (I^2<50%). A sensitivity analysis was performed, for the main analysis and for the predefined separate analyses, including also trials with zero events, using continuity correction. Publication bias was assessed using visual inspection of funnel plots and Egger's weighted regression statistics, where asymmetrical funnel plot and Egger's *p*-value <0.05 indicate potential publication bias [26]. All statistical analyses were performed by RevMan5.0 from Cochrane Collaboration.

Results

Figure 1 presented the trial flow summary. A total of 5 trials fulfilling the inclusion criteria were ultimately included in this meta-analysis [27-31]. Characteristics of the studies included in the review are presented in **Table 1**.

Compared with metformin monotherapy, saxagliptin plus metformin combination therapy could significantly reduce HbA_{1c} [MD=-0.44, 95% CI (-0.71, -17), P<0.00001; heterogeneity (I^2=100%), **Figure 2**] and FPG [MD=-0.62, 95%

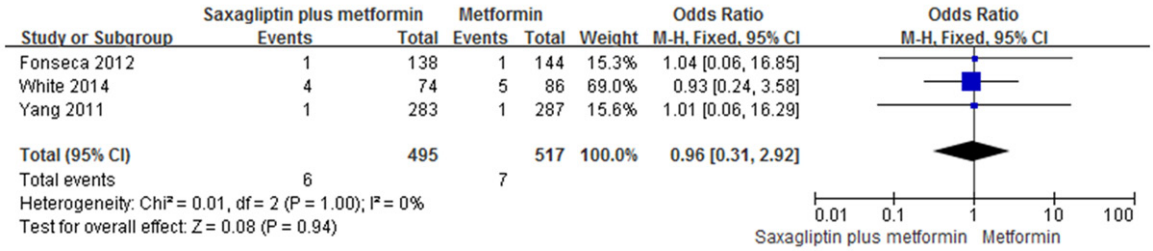

Figure 5. Meta-analysis for cardiovascular events between saxagliptin plus metformin as combination therapy and metformin monotherapy.

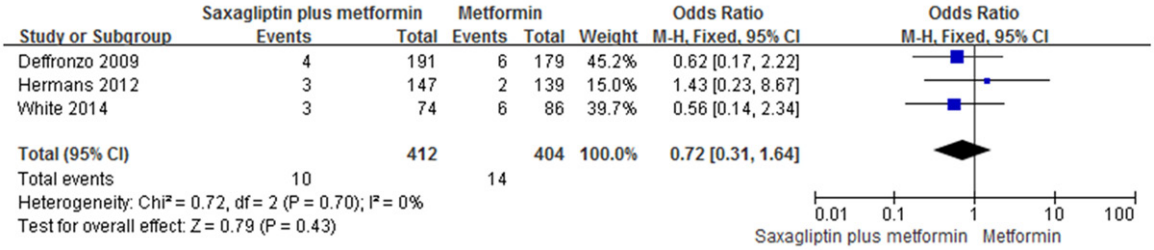

Figure 6. Meta-analysis for gastrointestinal adverse reactions between saxagliptin plus metformin as combination therapy and metformin monotherapy.

CI (-1.09, -0.15), P<0.00001, heterogeneity (I^2=100%), **Figure 3**].

There was no statistical difference in the incidence rate of hypoglycaemia between saxagliptin plus metformin and metformin monotherapy [MD=3.22, 95% CI (1.10, 9.40), P=0.75, I^2=0%, **Figure 4**]. Consistently, saxagliptin combined with metformin did not further reduce adverse cardiovascular events [MD=0.96, 95% CI (0.31, 2.92), P=1.00, I^2=0%, **Figure 5**] compared to metformin monotherapy. Gastrointestinal adverse effects were also assessed in this meta-analysis, and it was found that no increased risk of gastrointestinal adverse reactions were seen between saxagliptin plus metformin as combination therapy and metformin monotherapy [MD=0.72, 95% CI (0.31, 1.64), P=0.70, I^2=0%, **Figure 6**].

Discussion

This meta-analysis demonstrated that saxagliptin and metformin combination therapy significantly improves glucose control in patients with type 2 diabetes compared with metformin monotherapy. Combination therapy has greater reduction in HbA_{1c} and FPG than metformin monotherapy, and does not increase the incidence of various adverse reactions.

In summary, saxagliptin, a selective DPP-4 inhibitor, is recommended as an adjuvant therapy to achieve ideal glucose targets in patients with type 2 diabetes [32]. It has demonstrated that saxagliptin is weight neutrality and low risk for hypoglycemia when used as monotherapy [33]. Saxagliptin plus metformin combination therapy provides a complementary mechanism of action. This combination therapy provides further decrease in HbA_{1c} from baseline, and permit more patients to achieve HbA_{1c} goal than the individual component [19, 20, 34]. In addition, saxagliptin probably be suitable alternative for subjects with type 2 diabetes who cannot take metformin, and reduce cardiovascular risk, especially for patients with heart disease.

One randomized, double-blind, placebo-controlled study [30] was performed to assess the efficacy of saxagliptin, with different daily dose, plus a stable dose of metformin in subjects type 2 diabetes. This trial demonstrates that the therapy of saxagliptin combined with metformin was well tolerated and significantly improved glycemic indexes in patients inadequately controlled with metformin alone. Some other trials [27-29, 31] obtained the same conclusion that saxagliptin plus metformin combi-

nation therapy was an effective and safe treatment for patients not achieving glycemic goal.

Patients with diabetes usually have high cardiovascular risks and some antidiabetic agents also probably increased incidence rate of cardiovascular events in patients [35]. Recently, in consideration of certain antidiabetic agent with additional cardiovascular risks, the Food and Drug Administration asks for all the new developed diabetes drugs to present cardiovascular risks [36]. This study demonstrated that saxagliptin combined with metformin didn't increase cardiovascular risks compared with metformin monotherapy, and even contributed to the reduced incidence of cardiovascular events. Compared with younger patients with type 2 diabetes, elderly patients usually are more likely to get hypoglycaemia [37]. DPP-4 inhibitors have good safety profile, such as low risk of hypoglycaemia [38]. Accordingly, there was no significant difference in reductions of HbA_{1c} from baseline between elderly and younger patients receiving saxagliptin [39], which demonstrated good safety and tolerance in elderly patients.

There were some potential limitations in this study. Only five trials investigating efficacy and safety of saxagliptin combined with metformin were identified in this study [27-31]. Hence, more evidence is needed to further confirm clinical value of saxagliptin and metformin combination therapy. In addition, the efficacy of saxagliptin monotherapy and in combination with other oral antidiabetic agents was not considered in this study.

Conclusion

Saxagliptin combined with metformin can be effective in improving glycemic control in patients with type 2 diabetes and decreased incidence of hypoglycemia. More high-quality RCTs are demanded to evaluate long-term safety and efficacy of saxagliptin combination with metformin in future.

Disclosure of conflict of interest

None.

Address correspondence to: Xue-Ying Tan, Department of Endocrinology, Ningbo University Affiliated Yuyao Yangming Hospital, Yuyao 315400, China. E-mail: tanxueying@163.com; Jing-Bo Hu, College of Pharmaceutical Science, Zhejiang University, 866 Yuhangtang Road, Hangzhou 310058, China. E-mail: hujiaabo@zju.edu.cn

References

[1] American Diabetes Association. Standards of medical care in diabetes-2012. Diabetes Care 2012; 35: Suppl 1: S11-S63.

[2] Rosberger DF. Diabetic retinopathy: current concepts and emerging therapy. Endocrinol Metab Clin North Am 2013; 42: 721-45.

[3] Lim AKh. Diabetic nephropathy-complications and treatment. Int J Nephrol Renovasc Dis 2014; 7: 361-81.

[4] Xu Q, Pan J, Yu J, Liu X, Liu L, Zuo X, Wu P, Deng H, Zhang J, Ji A. Meta-analysis of methylcobalamin alone and in combination with lipoic acid in patients with diabeticperipheral neuropathy. Diabetes Res Clin Pract 2013; 101: 99-105.

[5] Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B; American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009; 32: 193-203.

[6] Scheen AJ. A review of gliptins in 2011. Exp Opin Pharmacother 2012; 13: 81-99.

[7] Scheen AJ. DPP-4 inhibitors in the management of Type 2 diabetes: a critical review of head-to-head trials. Diabetes Metab 2012; 38: 89-101.

[8] Shubrook J, Colucci R, Guo A, Schwartz F. Saxagliptin: A selective DPP-4 inhibitor for the treatment of type 2 diabetes mellitus. Clin Med Insights Endocrinol Diabetes 2011; 4: 1-12.

[9] Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology 2007; 132: 2131-57.

[10] Gupta R, Walunj SS, Tokala RK, Parsa KV, Singh SK, Pal M. Emerging drug candidates of dipeptidyl peptidase IV (DPP IV) inhibitor class for the treatment of Type 2 Diabetes. Curr Drug Targets 2009; 10: 71-87.

[11] Gallwitz B. New treatments in the management of type 2 diabetes: a critical appraisal of saxagliptin. Diabetes Metab Syndr Obes 2010; 10: 117-24.

[12] Ismail-Beigi F. Glycemic management of type 2 diabetes mellitus. N Engl J Med 2012; 366: 1319-27.

[13] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hy-

perglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012; 6: 1364-79.

[14] Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B; American Diabetes Association; European Association for the Study of Diabetes. Medical management of hyperglycaemia in Type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2009; 52: 17-30.

[15] Rodbard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, Grunberger G, Handelsman Y, Horton ES, Lebovitz H, Levy P, Moghissi ES, Schwartz SS. Statement by an American Association of clinical endocrinologists/American college of endocrinology consensus panel on Type 2 diabetes mellitus: an algorithm for glycemic control. Endocr Pract 2009; 15: 540-59.

[16] Hundal RS, Krssak M, Dufour S, Laurent D, Lebon V, Chandramouli V, Inzucchi SE, Schumann WC, Petersen KF, Landau BR, Shulman GI. Mechanism by which metformin reduces glucose production in type 2 diabetes. Diabetes 2000; 49: 2063-9.

[17] Stumvoll M, Haring HU, Matthaei S. Metformin. Endocr Res 2007; 32: 39-57.

[18] Collier CA, Bruce CR, Smith AC, Lopaschuk G, Dyck DJ. Metformin counters the insulin-induced suppression of fatty acid oxidation and stimulation of triacylglycerol storage in rodent skeletal muscle. Am J Physiol Endocrinol Metab 2006; 291: 182-9.

[19] Jadzinsky M, Pfützner A, Paz-Pacheco E, Xu Z, Allen E, Chen R. Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. Diabetes Obes Metab 2009; 11: 611-22.

[20] Pfützner A, Paz-Pacheco E, Allen E, Frederich R, Chen R. Initial combination therapy with saxagliptin and metformin provides sustained glycaemic control and is well tolerated for up to 76 weeks. Diabetes Obes Metab 2011; 13: 567-76.

[21] DeFronzo RA, Hissa MN, Garber AJ, Luiz Gross J, Yuyan Duan R, Ravichandran S, Chen RS; Saxagliptin 014 Study Group. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. Diabetes Care 2009; 32: 1649-55.

[22] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17: 1-12.

[23] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-88.

[24] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective Studies of disease. Biometrics 1959; 15: 639-40.

[25] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-60.

[26] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-34.

[27] White JL, Buchanan P, Li J, Frederich R. A randomized controlled trial of the efficacy and safety of twice-daily saxagliptin plus metformin combination therapy in patients with type 2 diabetes and inadequate glycemic control on metformin monotherapy. BMC Endocr Disord 2014; 14: 17.

[28] Hermans MP, Delibasi T, Farmer I, Lohm L, Maheux P, Piatti P, Malvolti E, Jörgens S, Charbonnel B. Effects of saxagliptin added to sub-maximal doses of metformin compared with uptitration of metformin in type 2 diabetes: the PROMPT study. Curr Med Res Opin 2012; 28: 1635-45.

[29] Yang W, Pan CY, Tou C, Zhao J, Gause-Nilsson I. Efficacy and safety of saxagliptin added to metformin in Asian people with type 2 diabetes mellitus: a randomized controlled trial. Diabetes Res Clin Pract 2011; 94: 217-24.

[30] DeFronzo RA, Hissa MN, Garber AJ, Luiz Gross J, Yuyan Duan R, Ravichandran S, Chen RS; Saxagliptin 014 Study Group. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. Diabetes Care 2009; 32: 1649-55.

[31] Fonseca V, Zhu T, Karyekar C, Hirshberg B. Adding saxagliptin to extended-release metformin vs. uptitrating metformin dosage. Diabetes Obes Metab 2012; 14: 365-71.

[32] Onglyza R (saxagliptin). Full Prescribing Information, Bristol-Myers Squibb/AstraZeneca Pharmaceuticals LP, Princeton, NJ/Wilmington, DE 2011.

[33] Barnett A. DPP-4 inhibitors and their potential role in the management of type 2 diabetes. Int J Clin Pract 2006; 60: 1454-70.

[34] Boulton DW, Smith CH, Li L, Huang J, Tang A, LaCreta FP. Bioequivalence of saxagliptin/metformin extended-release (XR) fixed-dose combination tablets and single-component saxagliptin and metformin XR tablets in healthy

adult subjects. Clin Drug Investig 2011; 31: 619-30.
[35] Frederich R, Alexander JH, Fiedorek FT Donovan M, Berglind N, Harris S, Chen R, Wolf R, Mahaffey KW. A systematic assessment of cardiovascular outcomes in the saxagliptin drug development program for type 2 diabetes. Postgrad Med 2010; 122: 16-27.
[36] Goldfine AB. Assessing the cardiovascular safety of diabetes therapies. N Engl J Med 2008; 359: 1092-5.
[37] Rosenstock J. Management of type 2 diabetes in the elderly: special considerations. Drugs Aging 2001; 18: 31-44.
[38] Paolisso G, Monami M, Marfella R, Rizzo MR, Mannucci E. Dipeptidyl peptidase-4 inhibitors in the elderly: more benefits or risks? Adv Ther 2012; 29: 218-33.
[39] Doucet J, Chacra A, Maheux P Lu J, Harris S, Rosenstock J. Efficacy and safety of saxagliptin in older patients with type 2 diabetes mellitus. Curr Med Res Opin 2011; 27: 863-9.