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Dipeptidyl Peptidase-4 Inhibitors and Cardiovascular Risk in Patients with Diabetes: Fact or Fiction?

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I. INTRODUCTION

Diabetes is a metabolic disease in which the body is unable to produce enough insulin, or when body cells cannot use the produced insulin sufficiently (insulin resistance) which consequently causes an elevation of blood glucose (1).Diabetes affects large population worldwide. According to American Diabetes Association (ADA), diabetes considered the 7th leading cause of death in US and it accounts for 8.3% of the cases (2). In addition, It has been reported that there are around 3.5 million people who have been diagnosed with diabetes in UK in 2015 (3). Diabetes can lead to several complications including macrovascular (neuropathy, nephropathy and retinopathy) and macrovascular complications (cardiovascular disease, stroke, coronary artery diseases …etc.) (4). In order to treat diabetes and prevent those complications, several interventions have been recommended by different guidelines. Patients start with weight loss program, physical activities and specific health diet to control blood glucose as cornerstone for the treatment. When glucose level is not controlled, pharmacological therapy is added; and the first line therapy is metformin according to the American Diabetic Association (5). However, when metformin fails to improve the HbA1c level, other additional therapies are recommended in this case. Several second line medications are developed for the treatment of diabetes; these include sulfonylureas, thiazolidinedione, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose transporter-2 (SGLT2) antagonist and dipeptidyl peptidase-4 (DPP-4) inhibitors (6). The new group of medication (DPP-4 inhibitors) lowers blood glucose by blocking the degradation of incretin hormone GLP-1. This group shows distinctive advantages over other classes of medication. First, they are less likely to cause hypoglycemia. In addition, they lack the gastrointestinal side effects and weight gain that are observed in other agents. Moreover, they are given through oral rout and have lower risk of drug-drug interactions (7). Some studies showed a relation between the use of DPP-4 inhibitors and the increase in cardiovascular risk, however, this relation still uncertain. Therefore, this study aims to review this anti-diabetic class and explore the recent studies regarding its effect andsafety in relation to cardiovascular risks.

II. METHOD

atabases including Cochrane library database, Academic Search Complete, and PubMed were conducted using different MeSH terms (linagliptin (MeSH Terms]) OR saxagliptin [MeSH Terms] OR sitagliptin [MeSH Term] OR alogliptin [MeSH Term]) AND (cardiovascular safety [MeSH Term]).

The search was limited to studies conducted on humans, randomized or observational trials, and written in English language. Articles were excluded if the primary outcome did not include the cardiovascular safety for DPP-4 inhibitors. Other data extracted were the study design, patients profile, demographics, overall survival and other hemodynamic parameters.

III. RESULTS

Several studies have been conducted to evaluate the efficacy and safety of each DPP-4 inhibitors especially in relation to their cardiovascular risks and benefits. Most of the data currently available for the safety of alogliptin are results of randomized controlled trials (RCTs) and pooled analysis. Similarly, the data for linagliptin are mostly resulted from the pooled analysis trials. However, the data for both saxagliptin and

sitagliptin are results from different trials including RCTs, cohort studies, retrospective designs and post-hoc analysis. These studies will be discussed in details for each member of this class.

Alogliptin:

It is considered the newest member of DPP-4 inhibitors. In order to identify its cardiovascular risk, different trials including RCTs and pooled analysis were conducted. The recent RCT which is SPEAD-A trial published in 2016 (8) is a randomized, blinded, open-label, multicenter trial. It included around 341 patients with type 2 diabetes with no previous cardiovascular diseases. The patients were allocated into two arms, first is the treatment (alogliptin 25 mg orally) and the second arm was the placebo (or conventional treatment) for 24 months treatment period. The main primary outcome was the change in mean common and maximum intima-media thickness (IMT) of the carotid artery measured by atrial echography. The result of this study showed that alogliptin reduces the glucose level more than other conventional treatments. In addition, the changes in the mean IMT of carotid artery were significantly greater with alogliptin compared to other treatment (P=0.02). Therefore, alogliptin was successful in reducing the progression of carotid artery, thus it helped in improving cardiovascular safety as compared to other treatment.

Another recent trial (EXAMINE) (9) was conducted in 2016 and included 5380 patients. It is a randomized controlled trial which aimed to evaluate the risk of cardiovascular death with alogliptin versus a standard therapy. Patients with type IIdiabetes were randomly assigned to receive either alogliptin or placebo within 15 to 19 days of acute coronary syndrome. Patients were monitored and followed until death or censoring. The result showed that the rate of death due to cardiovascular situations was 4.1% with alogliptin versus 4.9% with placebo ([HR] 0.85; 95% CI 0.66- 1.10) which is a non-significant difference. In addition, the mortality rates after cardiovascular events were similar between the two groups. Therefore, this study provide a conclusion that alogliptin was not associated with either an increase or decrease in cardiovascular risk.

The last study for alogliptin is a pooled analysis published in 2013 which aimed to evaluate the cardiovascular profile for alogliptin and determine its safety in relation to any cardiovascular event (10). The trials included in the analysis were randomized controlled trials whichmust include parallel double arms, one with alogliptin and the other with placebo or other comparator medication. The analysis included 4168 patients received alogliptin at the doses of 12 to 25 mg daily for 2023 patients-years, around 691 patients received placebo for 263 patient-years and 1169 patients treated with other standard treatment for 703 patient-years. The primary outcome was a composite endpoint (MACE) which included cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. The result of this analysis showed that the difference in the occurrence of composite endpoints was similar between the groups and it was not statistically significant (HR=0.635, 95% CI 0.0 - 1.41). In addition, other serious cardiovascular event rateswere not different between the groups. Therefore, alogliptinwas not associated with increased cardiovascular risk.

Linagliptin:

It is a member of DPP-4 inhibitors that was approved by the FDA on May 2011 (11). Its effect in reducing blood glucose has been confirmed by many trials. Regarding its cardiovascular safety, there are several studies conducted for this purpose. The first study is a pooled analysis published in 2015 which aimed to evaluate the cardiovascular profile for linagliptin in patients with type IIdiabetes (12). The analysis contains 19 randomized, double-blinded, controlled trials which involve in total about 9459 patients. These studies enrolled diabetic patients into two arms, one with linagliptin 5-10 mg and the other one with placebo or other active therapy. The primary outcomes were the occurrence of composite endpoints including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization due to unstable angina and hospitalization due to congestive heart failure. The result indicated that the difference in cardiovascular risk betweenlinagliptin and other comparator treatment or placebo was not significant. In more details, linagliptin caused 60 events, compared to the comparator medications which caused 62 events (HR 0.78, 95% CI, 0.55-1.12). In addition, for

placebo-controlled trials, linagliptin resulted in 43 events and placebo caused 30 events (HR 1.09, CI 0.68-1.75). As a result of that, it can be clearly seen that linagliptin didn't cause an increase in cardiovascular risks compared to other treatments or placebo in patients with type IIdiabetes.

Another recent study which is a post-hoc analysis published in 2016 was aimed to evaluate the efficacy and cardiovascular safety as an add-on therapy to insulin in patients with type IIdiabetes (13). The data for patients receiving insulin (either basal insulin or basal-bolus one) were extracted from different randomized, double-blinded trials (n=4). In those trials, patients received either linagliptin 5 mg once daily or placebo as add on to insulin therapy. Several factors were assessed including the HbA1cand the cardiovascular adverse effects. The primary endpoint was a composite of different events including cardiovascular death, myocardial infarction and non-fatal stroke. Linagliptin was associated with multiple advantages including weight reduction, minimizing the need for frequent insulin therapy and it didn't cause negative effect on other parameters including blood pressure and lipid profile. In addition, the incidence of the endpoint was similar between placebo and linagliptin(HR 1.06, 95% CI 0.62-1.85). As a conclusion, linagliptinadded to an insulin therapy didn't cause an increase in cardiovascular events.

Saxagliptin:

It isanoral anti-diabetic therapy and a very selective member of DPP-4 inhibitors. It was approved by FDA on July 2009 (14). In order to assess its cardiovascular profile, several studies were conducted for this purpose. The first trial (SAVOR-TIMI 53) is a large randomized, double-blinded, placebo-controlled trial which was published in 2013 and leads to some changes by the FDA. This trial aimed to evaluate the efficacy and cardiovascular safety profile for saxagliptin in patients with diabetes (15). Patients were included if they have diabetes, above 40 years of age, and had a history of any cardiovascular events. Around 16,492 patients were randomly assigned in 1:1 ratio to receive either saxagliptin 5 mg once daily or a placebo. Patients were followed accordingly for 2.1 years. The main primary outcome was a composite of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke. The secondary outcomes were the primary endpoints in addition to hospitalization due to heart failure, unstable angina or coronary revascularization. The result showed that there was no significant difference in the occurrence of primary endpoint. The composite endpoint occurred in 613 patients in saxagliptin group and 609 patients in placebo group (HR 1.0, 95% CI 0.89-1.12, P=0.99). However, the difference was significant with secondary endpoints. Hospitalization due to heart failure occurred more in saxagliptin group compared to placebo (3.5% vs. 2.8%; HR, 1.27; 95% CI, 1.07 to 1.51; P = 0.007). The main conclusion out of this trial is that saxagliptin didn't associate with either increase or decrease in the occurrence of cardiovascular events. However, itresulted in higherhospitalization rate due to heart failure. Based on this trial, the FDA added a warning regarding the cardiovascular safety of saxagliptin which was introduced in April 2016 (16).

Another recent study was published in 2016 based on the previous RCT that concluded the risk of saxagliptin in causing hospitalization due to heart failure. This study has retrospective cohort design which aimed toevaluate whether this risk is significant and determine whether it is a drug specific or a class effect of all DPP-4 inhibitors (17). The data for patients with diabetes who have been receiving saxagliptin, sitagliptin or vildagliptin were identified (n=159,330) from the National Health Insurance database for two years. The main outcome of interest was the hospitalization due to heart failure. The patients were followed for one year from initiating the drug until the occurrence of the outcome, death or getting out of the study. The data were analyzed by different statistical methods. The result of this study showed that the incidence rate of heart failure was 2.63 for saxagliptin, 2.77 for sitagliptin and 1.91 for vildagliptin for 100 person–years. Bothsaxaglipton and sitagliptin had similar risk which is not significant (HR 0.98, 95% CI 0.91-1.06). In addition, an auxiliary analysis using Acarbose as a reference group showed no increased risk of heart failure with DPP-4 inhibitors. Therefore, the result of this study was in reverse to the previous one since it showed that the three DPP-4 inhibitors including saxagliptin is safe in regards to increasing the occurrence of heart failure.

The last recent study which was published in June 2016 and funded by the U.S FDA is a population-based, large retrospective cohort study (18). The aim of this study was to verify theproposed associationbetween hospitalization due to heart failure and the use of saxagliptin/ sitagliptin. Data for patients 18 years and above

with type 2 diabetes who were receiving saxagliptin or sitagliptin and other anti-diabetic medications include sulfonylurea and long-acting insulin product were collected from 18 health insurance and health system database. The main outcome was the hospitalization due to heart failure. The result showed that the risk was not higher with saxagliptin or withDPP-4 inhibitors in general as compared to other medications. The hazard ratios were 0.83 (95% CI, 0.70-0.99) for saxagliptin versus sitagliptin, 0.63 (CI, 0.47 to 0.85) for saxagliptin versus pioglitazone, 0.69 (CI, 0.54 to 0.87) for saxagliptin versus sulfonylureas, and 0.61 (CI, 0.50 to 0.73) for saxagliptin versus insulin. Therefore, this study showed that the risk of hospitalization from heart failure is not larger with DPP-4 inhibitors (saxagliptin) as compared to other therapies.

Sitagliptin:

It is a member of DPP-4 inhibitor which was developed and marketed by Merck&Co (19). Recent randomized, double-blinded, placebo-controlled trial which was published in 2015 addressed the relation between sitagliptin and its cardiovascular risk (20).Around 14,671 patients were enrolled into the study. Those patients, who have type IIdiabetes with established cardiovascular diseasewere at least 50 years of age and were treated with one or two of other anti-diabetic medications. Patients were randomly assigned in 1:1 ratio to receive either sitagliptin 100 mg daily or matching placebo. The primary outcome was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke or hospitalization due to unstable angina. The result showed that the composite outcome occurred in 839 patients in sitagliptin group and 851 patients in placebo group. Therefore, sitagliptin showed to be non-inferior to placebo (HR 0.98, 95% CI 0.88-1.09). In addition, there were no differences in term of hospitalization for heart failure or angina (HR 1.00, 95% CI 0.83-1.20).Adding sitagliptin to other therapies didn't cause an increase of cardiovascular adverse events.

The second trial (PROLOGUE) published in 2016 aimed to examine the effect of sitagliptin on cardiovascular safety by using the intima-media thickness of the carotid artery as a surrogate marker for the cardiac health (21). The study is a prospective, randomized, open-labeled, blinded controlled trial. Patients (n=442) with type IIdiabetes were randomly assigned to receive either sitagliptin at doses of 25 to 100 mg per day or other conventional therapy. Patients were followed and they underwent carotid ultrasound accordingly to assess the primary outcome. The common carotid artery IMT after 24 months of follow up were 0.827 ± 0.007 mm for sitagliptin and 0.837 ± 0.007 mm for other comparator therapy (97.2% CI -0.028-0.011, P=0.309). In addition, the HbA1c level was significantly lower with sitagliptin as compared to other therapy. Therefore, this study concluded that sitagliptin didn't cause a risk or a benefit in terms of cardiovascular safety.

One pooled analysis was published in 2013 assessed the cardiovascular safety for sitagliptin by pooling data from 25 double blinded trials (22). The main outcome was the major cardiovascular events and death. The result of this analysis found that sitagliptin didn't cause an increase in cardiovascular risk compared to other treatment.

Vildagliptin:

It is another member of DPP-4 inhibitors which was EU approved in 2007 (23). To assess its cardiovascular safety profile, a large retrospective meta-analysis was conducted for this purpose (24). Around 17,446 patients data were collected from 40 double-blinded, randomized, controlled trials (phase III and IV). The primary outcome was the rate of major cardiovascular adverse events including myocardial infarction, stroke and cardiovascular death. Hospitalization due to cardiac issues was considered a secondary endpoint. The result of the study showed that the occurrence of cardiovascular events occurred in 83 patients in vildagliptin group and 85 in comparator therapy groups (RR 0.82, 95% CI 0.61-1.11). A non-significant difference was also found in relation to hospitalization due to heart failure. Therefore, this meta-analysis indicated that vildagliptin was not associated with an increase in the risk of cardiovascular adverse events.

IV. DISCUSSION

DPP-4 inhibitors are members of the anti-hyperglycemic medications that used widely worldwide. Their effect in reducing sugar level has been reported in many trials. Recent studies have brought a concern regarding their cardiovascular safety, although it was not evaluated initially in clinical trials. Multiple randomized trials, pooled analysis and observational studies were published for this purpose. However, the definite answer regarding its safety is still uncertain. Therefore, this study is done to review the main recent

trials that discuss this point and to provide a main conclusion based on the results of those trials. The members of DPP-4 inhibitors that are FDA approved arelinagliptin, alogliptin, sitagliptin and saxagliptin, while vildaglipin is approved by EU. The members of this class showed to exerta great effect in reducing glucose parameters in patients with diabetes including the glucose level and HbA1c. A meta-analysis was conducted to evaluate their effect and the result showed that patients with diabetes who received DPP-4 inhibitor achieved a great reduction in HbA1c <7% compared to placebo with no other adverse events (including hypoglycemia and weight gain) (25). Other studies indicated that using any member of DPP-4 inhibitor as add-on therapy to metformin causes an effect which is similar to that of sulfonylurea and thiazolidinedione in terms of HbA1c reduction which is considered the optimal surrogate maker for diabetes (26,27). However, some studies have brought a concern regarding the use of DPP-4 inhibitors as they might increase cardiovascular risk. Based on the studies mentioned in this review, it can be concluded that there is no increased risk of cardiovascular events with the use of all DPP-4 inhibitors (sitagliptin, saxagliptin, alogliptin, linagliptin and vildagliptin). These events includes-but not limited- to myocardial infarction, cardiovascular death and nonfatal stroke. In addition, they indicated that DPP-4 inhibitors can be safely used as additional option for diabetes in patients with high cardiovascular risks. These findings are resulted from high restricted, double-blinded, randomized controlled trials for sitagliptin, saxagliptin and alogliptin. However, the results for linagliptin and vildagliptin are taken from other designs including post-hoc analysis, pooled analysis and retrospective designs. Therefore, a well-designed randomized trial is required to confirm their safety regarding cardiovascular adverse events. Although the studies have shown that sitagliptin, saxagliptin and alogliptin are not worse than placebo, one randomized trial has showed that there is a risk of increased hospitalization due to heart failure with saxagliptin. To follow up and confirm this finding, two large retrospective cohort studies (one funded by the U.S FDA) were published recently in 2016 as mentioned above. The findings for these two trials were in contrast to the result of the RCT. These two trials indicated that saxagliptin didn't cause an increase in hospitalization rate due to heart failure as compared to placebo or any other comparator medications. This can be justified as the outcome for hospitalization in the RCT was a secondary endpoint, which means that the power of the study is not able to detect truly the statistical differences in the results. Although these two retrospective studies were large and well-designed, their results can't be guaranteed due to the lower level of evidence for the retrospective observational studies compared to clinical trials. Therefore, saxagliptin should be used in caution until there are further randomized controlled trials or long term studies that assess the risk of hospitalization due to heart failure as the main primary endpoint of the study.On the other side, some studies have shown that alogliptin and linagliptin have cardiovascular benefit in patients with type 2 diabetes. For alogliptin, this was indicated by RCT study (SPEAD-A) which assessed its cardiovascular benefit by measuring the mean common and maximum intima-media thickness of the carotid artery as a marker for its safety (8). It showed that alogliptin caused a greater change in the IMT compared to other treatment and concluded that it can have beneficial effect to diabetic patients' hearts. Although this trial provides valuable findings, other randomized trials should be done to assess other markers or outcomes including the incidence of cardiovascular mortality, stroke and other atherosclerosis related diseases.

V. CONCLUSION

The currently FDA approved DPP-4 inhibitors have not shown to increase cardiovascular adverse events and they can be considered appropriate options for patients with type II diabetes. Moreover, saxagliptin should be evaluated further by restricted randomized controlled trial to assess its risk in regards to hospitalization due to heart failure.

REFERENCES

[1] Jane Kelly. Diabetes. Center of Disease Control and Prevention (CDP)[Online]. [Cited 2016 Feb 8]. Available from: http://www.cdc.gov/media/presskits/aahd/diabetes.pdf

[2] American Diabetes Association. 2014 [cited 2016 Feb 8]. Available from: http://www.diabetes.org/diabetes-basics/statistics/?referrer=https://www.google.com/

[3] Diabetes UK. Diabetes prevalence 2015. Nov 2015 [cited 2016 Feb 8]. Available from: https://www.diabetes.org.uk/About_us/What-we-say/Statistics/2015-as-published-2016/

[4] American Diabetes Association. Diabetes complications. 2012 [cited 2016 Feb 8]. Available from:http://www.diabetes.org/living-with-diabetes/complications

[5] American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2015;38(1):1-93

[6] John P. SGLT2 Inhibitors for the Treatment of Diabetes. Medscape. 2008 [cited 2016 Feb 9]. Available from: http://www.medscape.org/viewarticle/578176

[7] Williams D, Engel S, Round E et al. Safety and tolerability of sitagliptin in clinical studies: a pooled analysis of data from 10,246 patients with type 2 diabetes. BMC Endocr Disord.2010;10:7

[8] White W, Gorelick P, Fleck P. Cardiovascular safety of the dipetidyl peptidase-4 inhibitor alogliptin in type 2 diabetes mellitus. Diabetes Obes Metab.2013; 15(7):668-673.

[9] White W, Kupfer S, Zannad F, Mehta C, Wilson C, Lei L, Bakris GL, Nissen S, Cushman W, Heller S, Bergenstal R, Fleck P, Cannon CP. Cardiovascular Mortality in Patients With Type 2 Diabetes and Recent Acute Coronary Syndromes From the EXAMINE Trial. Diabetes Care. 2016;39(7):1267-73

[10] White W, Pratley R, Fleck P, Munsaka M, Hisada M, Wilson C, Menon V. Cardiovascular safety of the dipetidyl peptidase-4 inhibitor alogliptin in type 2 diabetes mellitus. Diabetes ObesMetab. 2013;15(7):668-73

[11] Wang Y, Serradell N, RosaE, Castaner R. Drugs of the Future. 2008; 33 (6): 473–47

[12] Rosenstock J, Marx N, Neubacher D, Seck T, Patel S, Woerle HJ, Johansen O.Cardiovascular Safety of linagliptin in type 2 diabetes: a comprehensive patient-level pooled analysis of prospectively adjudicated cardiovascular events. CardiovascDiabetol. 2015 May 21;14:57

[13] Zinman B, Ahrén B, Neubacher D, Patel S, Woerle HJ, Johansen O. Efficacy and Cardiovascular Safety of Linagliptin as an Add-On to Insulin in Type 2 Diabetes: A Pooled Comprehensive Post Hoc Analysis. Can J Diabetes. 2016;40(1):50-7

[14] Augeri D, Robl J, Betebenner D, Magnin D, Khanna A, Robertson J, Wang A, Simpkins L, Taunk P, e al. Discovery and preclinical profile of Saxagliptin (BMS-477118): a highly potent, long-acting, orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. J Med Chem. 2005;48(15):5025-37

[15] Scirica B, Bhatt D, Braunwald E, Steg P, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott S, Hoffman E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus.NEngl J Med. 2013;369(14):1317-26

[16] Safety Alerts for Human Medical Products - Diabetes Medications Containing Saxagliptin and Alogliptin: Drug Safety Communication - Risk of Heart Failure". Available at: www.fda.gov.comRetrieved 7 April 2016

[17] Chang C, Chang Y, Lin J, Caffrey J, Wu L, Lai M, Chuang L. No increased risk of hospitalization for heart failure for patients treated with dipeptidyl peptidase-4 inhibitors in Taiwan. Int J Cardiol. 2016;220:14-20

[18] Toh S, Hampp C, Reichman M, Graham D, Balakrishnan S, Pucino F, Hamilton J, Lendle S, Iyer A, Rucker M, Pimentel M, Nathwani N, Griffin M, Brown N, Fireman B. Risk for Hospitalized Heart Failure Among New Users of Saxagliptin, Sitagliptin, and Other Antihyperglycemic Drugs: A Retrospective Cohort Study. Ann Intern Med. 2016;164(11):705-14

[19] Herman G, Stevens C, Dyck K, Bergman A, Yi, De Smet M, Snyder K, Hilliard D, Tanen M, Tanaka W, Wang AQ, et al. Pharmacokinetics and pharmacodynamics of sitagliptin, an inhibitor of dipeptidyl peptidase IV, in healthy subjects: results from two randomized, double-blind, placebo-controlled studies with single oral doses. ClinPharmacol Ther.2005;78 (6): 675–88

[20] Jennifer B, Angelyn B, Armstrong W., John B, Samuel S, Jyotsna G., Robert J, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2015; 373:232-242

[21] Oyama J, Murohara T, Kitakaze M, Ishizu T, Sato Y, Kitagawa K, Kamiya H, Ajioka M, Ishihara M, et al. The Effect of Sitagliptin on Carotid Artery Atherosclerosis in Type 2 Diabetes: The PROLOGUE Randomized Controlled Trial. PLoS Med. 2016 Jun 28;13(6):e1002051

[22] Engel S, Golm G, Shapiro D, Davies M, Kaufman K, Goldstein B. Cardiovascular safety of sitagliptin in patients with type 2 diabetes mellitus: a pooled analysis. CardiovascDiabetol. 2013;12:3

[23] McIntosh C, Demuth H, Pospisilik J, Pederson R. Dipeptidyl peptidase IV inhibitors: How do they work as new antidiabeticagents. Regulatory Peptides. 2005;128 (2): 159–65

[24] McInnes G, Evans M, Del Prato S, Stumvoll M, Schweizer A, Lukashevich V, Shao Q, KothnyWCardiovascular and heart failure safety profile of vildagliptin: a meta-analysis of 17 000 patients. Diabetes ObesMetab. 2015;17(11):1085-92

[25] Esposito K, Cozzolino D, Bellastella G, Maiorino M, Chiodini P, Ceriello A, Giugliano D. Dipeptidyl peptidase-4 inhibitors and HbA1c target of <7% in type 2 diabetes: meta-analysis of randomized controlled trials.DiabetesObesMetab. 2011;13(7):594-603

[26] Phung O, Scholle J, Talwar M, Coleman C. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. JAMA.2010; 303:1410-1418

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