EDITORIAL

Cardiovascular effects of dipeptidyl peptidase-4 inhibitors

Papagianni M, Tziomalos K

1st Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, Thessaloniki, Greece

Abstract

Dipeptidyl peptidase-4 (DPP-4) inhibitors are effective glucose-lowering agents that do not increase body weight and are associated with a low risk for hypoglycemia. Also, they appear to exert beneficial effects on other established cardiovascular risk factors, including dyslipidemia and hypertension. Moreover, DPP-4 inhibitors exert antiinflammatory and antioxidant actions, improve endothelial function and reduce urinary albumin excretion. In contrast to these favorable cardiovascular effects, three recent large, randomized, placebo-controlled trials in patients with type 2 diabetes mellitus (T2DM) and established cardiovascular disease or multiple cardiovascular risk factors showed that DPP-4 inhibitors do not affect the risk of myocardial infarction or ischemic stroke and might increase the risk of heart failure. The findings of the former randomized studies highlight the limitations of surrogate markers and show that beneficial effects on cardiovascular risk factors do not necessarily translate into reductions in hard clinical endpoints. Ongoing trials will shed more light on the safety profile of DPP-4 inhibitors and will clarify whether they will improve the cardiovascular outcomes of patients with T2DM. Hippokratia 2015; 19 (3): 195-199.

Keywords: Type 2 diabetes mellitus, dipeptidyl peptidase-4 inhibitors, heart failure, cardiovascular disease, safety

Corresponding author: Konstantinos Tziomalos, 1st Propedeutic Department of Internal Medicine, AHEPA Hospital, Thessaloniki 54636, Greece, tel: +302310994621, fax: +302310994773, e-mail: ktziomalos@yahoo.com

Type 2 diabetes mellitus (T2DM) is a major public health problem and currently affects 382 million people worldwide[1]. The aging of the population, urbanization and the rising prevalence of obesity are estimated to lead to a 55% increase in the worldwide prevalence of T2DM by 2035[1]. Even though the highest prevalence of T2DM is currently observed in North America, most patients with T2DM live in low- and middle-income countries and these areas are expected to exhibit the largest increase in T2DM prevalence[1]. In low- and middle-income countries, the increase in life expectancy and the process of urbanization, followed by unhealthy lifestyle changes, are important factors contributing to the rising prevalence of T2DM[2].

It is well-established that T2DM is independently associated with increased cardiovascular risk[3,4]. Both antihypertensive treatment and lipid-lowering treatment – primarily with statins – substantially reduce cardiovascular morbidity in patients with T2DM[5,6]. In contrast, it is unclear whether antidiabetic treatment decreases cardiovascular risk. In the UK Prospective Diabetes Study (UKPDS), metformin reduced cardiovascular morbidity in overweight patients with newly diagnosed T2DM[7] and thus metformin currently represents the first-line antidiabetic treatment[8]. Among the other classes of antidiabetic agents, pioglitazone reduced cardiovascular events in patients with long-standing T2DM and established cardiovascular disease in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROACTIVE)[9]. However, pioglitazone has several adverse effects, including edema, heart failure and hip fractures that limit its use[9,10]. Very recently, empagliflozin, an inhibitor of sodium-glucose co-transporter 2, reduced cardiovascular and all-cause mortality in patients with T2DM and established cardiovascular disease in the EMPA-REG OUTCOME trial[11]. However, the incidence of non-fatal myocardial infarction and stroke was not reduced by empagliflozin, suggesting that mechanisms other than the prevention or delay of progression of atherosclerosis might underpin these benefits[11]. Moreover, rates of genital infections were considerably higher in patients treated with empagliflozin[11]. Accordingly, current guidelines recommend that the choice of the antidiabetic agent in patients who do not achieve HbA_{1c} targets despite treatment with metformin should be individualized based on safety, efficacy and patient's preferences[8].

Dipeptidyl peptidase-4 (DPP-4) inhibitors, also known as gliptins, were initially introduced in the therapeutics of T2DM in 2006. They lower blood glucose levels through their ability to inhibit the degradation of

the incretins glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), which results in reduced secretion of glucagon, increased secretion of insulin and delayed gastric emptying[12]. In head-to-head comparisons, DPP-4 inhibitors were as effective as sulfonylureas and pioglitazone in reducing HbA_{1c} levels[13]. However, DPP-4 inhibitors also appear to have beneficial effects on other cardiovascular risk factors. Indeed, these agents do not increase body weight, in contrast to sulfonylureas, pioglitazone, and insulin, which are associated with weight gain[13]. The effects of DPP-4 inhibitors on serum low- and high-density lipoprotein levels are neutral, but there is a trend for a reduction in triglyceride levels and in the more atherogenic, small-dense low-density lipoprotein particles[14-17]. In some studies, DPP-4 inhibitors reduced blood pressure[18-20] but in others they had no effect[21]. The risk of hypoglycemia is also lower during treatment with DPP-4 inhibitors compared with sulfonylureas and insulin[13]. In turn, hypoglycemia has been associated with increased cardiovascular risk in patients with T2DM[22,23].

Small and mostly uncontrolled studies also suggested that DPP-4 inhibitors exert beneficial effects on emerging cardiovascular risk factors. Indeed, these agents appear to exert antiinflammatory effects[18,24-27], mitigate oxidative stress[26,28], improve endothelial function[18,25,29,30] and reduce urinary albumin excretion[16,18,21,28]. A beneficial effect on nonalcoholic fatty liver disease, which is independently associated with increased cardiovascular risk, has also been reported in patients treated with these agents[31-33]. It was also reported that treatment with DPP-4 inhibitors improves left ventricular function and reduces postischemic stunning in patients with T2DM and coronary heart disease (CHD)[34,35]. A recent study in 96 patients with T2DM and stable CHD also reported that vildagliptin maintains ischemic preconditioning whereas repaglinide abolishes this protective mechanism[36]. In this context, animal studies suggested that DPP-4 inhibitors reduce infarct size and mortality after experimental myocardial infarction[37,38]. Moreover, small studies also reported a decrease in carotid intima-media thickness, a marker of subclinical atherosclerosis, during treatment with DPP-4 inhibitors[39,40].

The promise of a cardioprotective effect of DPP-4 inhibitors was further supported by early meta-analyses of phase 2b-3 studies, which suggested that DPP-4 inhibitors might reduce cardiovascular morbidity[41-43]. However, these results were based on very few events since the studies included in these meta-analyses were short-term and not designed to evaluate the effects of DPP-4 inhibitors on cardiovascular events and the ascertainment of these events was non-uniform and incomplete[41-43]. In a recent randomized study in 1,551 patients with T2DM, linagliptin reduced cardiovascular events more than glimepiride during the 2-year follow-up despite similar reductions in HbA_{1c}[44]. However, this benefit was again based on very few cardiovascular events (n =38)[44].

In contrast with the beneficial effects of DPP-4 inhibitors on multiple cardiovascular risk factors and the promising results of these preliminary meta-analyses of small studies, three recent large studies showed a neutral or even potentially adverse effect of these agents on cardiovascular events[45-47]. In the first trial, the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) study, 5,380 patients with T2DM and recent hospitalization for an acute coronary syndrome were randomized to receive alogliptin 25 mg/day or placebo for a median of 18 months[45]. The primary end point included death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke[45]. At the end of the study, HbA_{1c} levels were an absolute 0.36% lower in patients treated with alogliptin than in those who received placebo whereas body weight and lipid levels did not differ between the two groups[45]. Despite this reduction in HbA_{1c} levels with alogliptin treatment, the incidence of the primary end point was similar in patients treated with alogliptin and placebo (11.3 and 11.8%, respectively; hazard ratio (HR) 0.96, upper boundary of the one-sided repeated confidence interval (CI) 1.16, $p < 0.001$ for non-inferiority and $p = 0.32$ for superiority)[45]. Nevertheless, this trial was designed to evaluate the cardiovascular safety of alogliptin and had limited power (< 20%) to identify a reduction in cardiovascular events with this DPP-4 inhibitor[45]. Interestingly, subgroup analyses suggested a trend for reduction in cardiovascular events with alogliptin treatment in current smokers and patients with T2DM duration < 10 years, with normal kidney function, who were treated with metformin and who were not treated with insulin[45]. Conversely, former smokers and patients with T2DM duration ≥ 10 years, with impaired kidney function, who were not treated with metformin and who were treated with insulin showed a trend for greater cardiovascular risk when treated with alogliptin[45]. Nevertheless, these results should be considered preliminary and exploratory given the large number of subgroup analyses that were performed in the EXAMINE trial[45].

The second study, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53) trial, included 16,492 patients with T2DM and either established cardiovascular disease or multiple cardiovascular risk factors (age > 55 years (men) or > 60 years (women) and at least one of the following: dyslipidemia, hypertension or smoking)[46]. Patients were randomly allocated to treatment with saxagliptin 5 mg/day or placebo for a median of 2.1 years[46]. At study completion, HbA_{1c} levels were an absolute 0.2% lower in the saxagliptin group whereas body weight was similar in saxagliptin- and placebo-treated patients[46]. The incidence of the primary endpoint (cardiovascular death, nonfatal myocardial infarction and nonfatal ischemic stroke) did not differ between patients treated with saxagliptin and placebo (7.3 and 7.2%, respectively; HR 1.00, 95% CI 0.89-1.12, $p = 0.99$ for superiority and $p < 0.001$ for non-inferiority)[46]. It should be mentioned that SAVOR-TIMI 53 was designed as a superiority trial and had 85% power

to show a 17% reduction in cardiovascular events with saxagliptin[46].

In the third study, the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), 14,671 patients with T2DM and established cardiovascular disease were randomized to receive sitagliptin 100 mg/day (or 50 mg/day if the baseline estimated glomerular filtration rate was 30-50 ml/min/1.73m^2) or placebo[47]. After a median follow-up of 3.0 years, HbA_{1c} levels were 0.29% lower in patients treated with sitagliptin[47]. Again, the incidence of the primary endpoint (cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke or hospitalization for unstable angina) did not differ between patients treated with sitagliptin and placebo (11.4 and 11.6%, respectively; HR 0.98, 95% CI 0.88-1.09, $p < 0.001$ for non-inferiority)[47].

An unexpected finding of the SAVOR-TIMI 53 trial was that the incidence of hospitalization for heart failure was higher in patients who received saxagliptin compared with the placebo group (3.5 and 2.8%, respectively; HR 1.27, 95% CI 1.07-1.51, $p = 0.007$)[46]. Importantly, 26.5% of patients hospitalized for heart failure were readmitted for heart failure and 26.1% died during follow-up[48]. Patients with established heart failure, estimated glomerular filtration rate ≤ 60 ml/min or elevated levels of N-terminal pro B-type natriuretic peptide had higher absolute risk for hospitalization for heart failure[48]. However, the relative increase in the risk for hospitalization for heart failure induced by saxagliptin was independent of the clinical characteristics of the patients, including the history of heart failure and chronic kidney disease[48].

This increased risk of heart failure in patients treated with saxagliptin is difficult to explain, given the apparently beneficial effects of DPP-4 inhibitors on cardiovascular risk factors and potentially on heart function. The increased risk for hospitalization for heart failure was observed mostly during the first year of treatment with saxagliptin, suggesting an acute adverse effect[48]. However, there was no evidence of fluid retention or myocardial toxicity in patients treated with this agent[48]. In the EXAMINE trial, alogliptin did not increase the risk for hospitalization for heart failure[49,50]. Even though observational studies suggested that sitagliptin increases the risk for hospitalization for heart failure in patients with T2DM and pre-existing heart failure[51], sitagliptin did not increase the risk for hospitalization for heart failure in the TECOS trial[47]. On the other hand, DPP-4 inhibitors appear to attenuate the antihypertensive effect of angiotensin converting enzyme inhibitors (ACE-Is)[52], which are first-line agents for the management of hypertension in patients with T2DM and the management of heart failure[53,54]. Therefore, treatment with DPP-4 inhibitors might reduce the protective effects of ACE-Is against new-onset or worsening heart failure[52]. Notably, 54% of patients in the SAVOR-TIMI 53 were treated with ACE-Is[46]. DPP-4 also inactivates several vasoactive peptides, including neuropeptide Y, substance P, brain natriuretic peptide and peptide YY[30]. Therefore, DPP-4 inhibitors might increase the levels of these peptides, which in turn might have a detrimental effect on heart function[30].

Other safety concerns were also noticed in the SAVOR-TIMI 53 trial. A trend for an increase in non-cardiovascular mortality was observed in the saxagliptin group (1.7 versus 1.3% in the placebo group, HR 1.27, 95% CI 1.00-1.62, $p = 0.051$)[46]. Somehow surprisingly, hypoglycemic events (both minor and major) were also more frequent in patients treated with saxagliptin than in those given placebo even though insulin was used less frequently in the former and the use of other antidiabetic agents was similar in the two groups[46]. On the other hand, saxagliptin was associated with a reduction in urinary albumin excretion[46]. Moreover, saxagliptin had comparable safety in patients < 65 years and in elderly (≥ 65 years) and very elderly patients (≥ 75 years)[55].

The findings of the EXAMINE, SAVOR-TIMI 53 and TECOS trials highlight the limitations of surrogate markers and show that beneficial effects on cardiovascular risk factors do not necessarily translate into reductions in hard clinical endpoints. Ongoing trials will shed more light on the safety profile of DPP-4 inhibitors and will clarify whether they will improve the cardiovascular outcomes of patients with T2DM[56].

Conflict of interest

Authors declare no conflict of interest.

References

1. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract. 2014; 103: 137-149.
2. Cheema A, Adeloye D, Sidhu S, Sridhar D, Chan KY. Urbanization and prevalence of type 2 diabetes in Southern Asia: A systematic analysis. J Glob Health. 2014; 4: 010404.
3. Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010; 375: 2215-2222.
4. Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. Lancet Diabetes Endocrinol. 2015; 3: 105-113.
5. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ. 1998; 317: 703-713.
6. Cholesterol Treatment Trialists' (CTT) Collaborators, Kearney PM, Blackwell L, Collins R, Keech A, Simes J, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008; 371: 117-125.
7. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998; 352: 854-865.
8. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia 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; 35: 1364-1379.

9. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al; PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. Lancet. 2005; 366: 1279-1289.
10. Zhu ZN, Jiang YF, Ding T. Risk of fracture with thiazolidinediones: an updated meta-analysis of randomized clinical trials. Bone. 2014; 68: 115-123.
11. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015; 373: 2117-2128.
12. Mulvihill EE, Drucker DJ. Pharmacology, physiology, and mechanisms of action of dipeptidyl peptidase-4 inhibitors. Endocr Rev. 2014; 35: 992-1019.
13. Karagiannis T, Paschos P, Paletas K, Matthews DR, Tsapas A. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. BMJ. 2012; 344: e1369.
14. Bennett WL, Maruthur NM, Singh S, Segal JB, Wilson LM, Chatterjee R, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med. 2011; 154: 602-613.
15. Monami M, Vitale V, Ambrosio ML, Bartoli N, Toffanello G, Ragghianti B, et al. Effects on lipid profile of dipeptidyl peptidase 4 inhibitors, pioglitazone, acarbose, and sulfonylureas: meta-analysis of placebo-controlled trials. Adv Ther. 2012; 29: 736-746.
16. Tani S, Nagao K, Hirayama A. Association between urinary albumin excretion and low-density lipoprotein heterogeneity following treatment of type 2 diabetes patients with the dipeptidyl peptidase-4 inhibitor, vildagliptin: a pilot study. Am J Cardiovasc Drugs. 2013; 13: 443-450.
17. Zhong J, Maiseyeu A, Rajagopalan S. Lipoprotein effects of incretin analogs and dipeptidyl peptidase 4 inhibitors. Clin Lipidol. 2015; 10: 103-112.
18. Hattori S. Sitagliptin reduces albuminuria in patients with type 2 diabetes. Endocr J. 2011; 58: 69-73.
19. Bosi E, Camisasca RP, Collober C, Rochotte E, Garber AJ. Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin. Diabetes Care. 2007; 30: 890-895.
20. Lovshin JA, Zinman B. Blood pressure-lowering effects of incretin-based diabetes therapies. Can J Diabetes. 2014; 38: 364-371.
21. Groop PH, Cooper ME, Perkovic V, Emser A, Woerle HJ, von Eynatten M. Linagliptin lowers albuminuria on top of recommended standard treatment in patients with type 2 diabetes and renal dysfunction. Diabetes Care. 2013; 36: 3460-3468.
22. Hsu PF, Sung SH, Cheng HM, Yeh JS, Liu WL, Chan WL, et al. Association of clinical symptomatic hypoglycemia with cardiovascular events and total mortality in type 2 diabetes: a nationwide population-based study. Diabetes Care. 2013; 36: 894-900.
23. Khunti K, Davies M, Majeed A, Thorsted BL, Wolden ML, Paul SK. Hypoglycemia and Risk of Cardiovascular Disease and All-Cause Mortality in Insulin-Treated People With Type 1 and Type 2 Diabetes: A Cohort Study. Diabetes Care. 2015; 38: 316-322.
24. Makdissi A, Ghanim H, Vora M, Green K, Abuaysheh S, Chaudhuri A, et al. Sitagliptin exerts an antinflammatory action. J Clin Endocrinol Metab. 2012; 97: 3333-3341.
25. Matsubara J, Sugiyama S, Akiyama E, Iwashita S, Kurokawa H, Ohba K, et al. Dipeptidyl peptidase-4 inhibitor, sitagliptin, improves endothelial dysfunction in association with its anti-inflammatory effects in patients with coronary artery disease and uncontrolled diabetes. Circ J. 2013; 77: 1337-1344.
26. Rizzo MR, Barbieri M, Marfella R, Paolisso G. Reduction of oxidative stress and inflammation by blunting daily acute glucose fluctuations in patients with type 2 diabetes: role of dipeptidyl peptidase-IV inhibition. Diabetes Care. 2012; 35: 2076-2082.
27. Satoh-Asahara N, Sasaki Y, Wada H, Tochiya M, Iguchi A, Nakagawachi R, et al. A dipeptidyl peptidase-4 inhibitor, sitagliptin, exerts anti-inflammatory effects in type 2 diabetic patients. Metabolism. 2013; 62: 347-351.
28. Fujita H, Taniai H, Murayama H, Ohshiro H, Hayashi H, Sato S, et al. DPP-4 inhibition with alogliptin on top of angiotensin II type 1 receptor blockade ameliorates albuminuria via up-regulation of SDF-1α in type 2 diabetic patients with incipient nephropathy. Endocr J. 2014; 61: 159-166.
29. van Poppel PC, Netea MG, Smits P, Tack CJ. Vildagliptin improves endothelium-dependent vasodilatation in type 2 diabetes. Diabetes Care. 2011; 34: 2072-2077.
30. Desouza CV, Gupta N, Patel A. Cardiometabolic Effects of a New Class of Antidiabetic Agents. Clin Ther. 2015; 37: 1178-1194.
31. Iwasaki T, Yoneda M, Inamori M, Shirakawa J, Higurashi T, Maeda S, et al. Sitagliptin as a novel treatment agent for non-alcoholic fatty liver disease patients with type 2 diabetes mellitus. Hepatogastroenterology. 2011; 58: 2103-2105.
32. Ohki T, Isogawa A, Iwamoto M, Ohsugi M, Yoshida H, Toda N, et al. The effectiveness of liraglutide in nonalcoholic fatty liver disease patients with type 2 diabetes mellitus compared to sitagliptin and pioglitazone. ScientificWorldJournal. 2012; 2012: 496453.
33. Nakouti T, Karagiannis AK, Tziomalos K, Cholongitas E. Incretin-Based Antidiabetic Agents for the Management of Non-Alcoholic Fatty Liver Disease. Curr Vasc Pharmacol. 2015; 13: 649-657.
34. Read PA, Khan FZ, Heck PM, Hoole SP, Dutka DP. DPP-4 inhibition by sitagliptin improves the myocardial response to dobutamine stress and mitigates stunning in a pilot study of patients with coronary artery disease. Circ Cardiovasc Imaging. 2010; 3: 195-201.
35. McCormick LM, Kydd AC, Read PA, Ring LS, Bond SJ, Hoole SP, et al. Chronic dipeptidyl peptidase-4 inhibition with sitagliptin is associated with sustained protection against ischemic left ventricular dysfunction in a pilot study of patients with type 2 diabetes mellitus and coronary artery disease. Circ Cardiovasc Imaging. 2014; 7: 274-281.
36. Rahmi RM, Uchida AH, Rezende PC, Lima EG, Garzillo CL, Favarato D, et al. Effect of hypoglycemic agents on ischemic preconditioning in patients with type 2 diabetes and symptomatic coronary artery disease. Diabetes Care. 2013; 36: 1654-1659.
37. Sauvé M, Ban K, Momen MA, Zhou YQ, Henkelman RM, Husain M, et al. Genetic deletion or pharmacological inhibition of dipeptidyl peptidase-4 improves cardiovascular outcomes after myocardial infarction in mice. Diabetes. 2010; 59: 1063-1073.
38. Ye Y, Keyes KT, Zhang C, Perez-Polo JR, Lin Y, Birnbaum Y. The myocardial infarct size-limiting effect of sitagliptin is PKA-dependent, whereas the protective effect of pioglitazone is partially dependent on PKA. Am J Physiol Heart Circ Physiol. 2010; 298: H1454-H1465.
39. Barbieri M, Rizzo MR, Marfella R, Boccardi V, Esposito A, Pansini A, et al. Decreased carotid atherosclerotic process by control of daily acute glucose fluctuations in diabetic patients treated by DPP-IV inhibitors. Atherosclerosis. 2013; 227: 349-354.
40. Ishikawa S, Shimano M, Watarai M, Koyasu M, Uchikawa T, Ishii H, et al. Impact of sitagliptin on carotid intima-media thickness in patients with coronary artery disease and impaired glucose tolerance or mild diabetes mellitus. Am J Cardiol. 2014; 114: 384-388.
41. Frederich R, Alexander JH, Fiedorek FT, Donovan M, Berglind N, Harris S, et al. A systematic assessment of cardiovascular outcomes in the saxagliptin drug development program for type 2 diabetes. Postgrad Med. 2010; 122: 16-27.
42. Monami M, Ahrén B, Dicembrini I, Mannucci E. Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a meta-analysis of randomized clinical trials. Diabetes Obes Metab. 2013; 15: 112-120.

43. Johansen OE, Neubacher D, von Eynatten M, Patel S, Woerle HJ. Cardiovascular safety with linagliptin in patients with type 2 diabetes mellitus: a pre-specified, prospective, and adjudicated meta-analysis of a phase 3 programme. Cardiovasc Diabetol. 2012; 11: 3.
44. Gallwitz B, Rosenstock J, Rauch T, Bhattacharya S, Patel S, von Eynatten M, et al. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. Lancet. 2012; 380: 475-483.
45. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013; 369: 1327-1335.
46. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013; 369: 1317-1326.
47. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al; TECOS Study Group. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2015; 373: 232-242.
48. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, et al; SAVOR-TIMI 53 Steering Committee and Investigators. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation. 2014; 130: 1579-1588.
49. Zannad F, Cannon CP, Cushman WC, Bakris GL, Menon V, Perez AT, et al; EXAMINE Investigators. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. Lancet. 2015; 385: 2067-2076.
50. Standl E, Schnell O. DPP-4 inhibitors and risk of heart failure EXAMINEd. Lancet. 2015; 385: 2022-2024.
51. Weir DL, McAlister FA, Senthilselvan A, Minhas-Sandhu JK, Eurich DT. Sitagliptin use in patients with diabetes and heart failure: a population-based retrospective cohort study. JACC Heart Fail. 2014; 2: 573-582.
52. Marney A, Kunchakarra S, Byrne L, Brown NJ. Interactive hemodynamic effects of dipeptidyl peptidase-IV inhibition and angiotensin-converting enzyme inhibition in humans. Hypertension. 2010; 56: 728-733.
53. American Diabetes Association. Standards of medical care in diabetes--2014. Diabetes Care. 2014; 37 Suppl 1: S14-S80.
54. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013; 128: e240-e327.
55. Leiter LA, Teoh H, Braunwald E, Mosenzon O, Cahn A, Kumar KM, et al; SAVOR-TIMI 53 Steering Committee and Investigators. Efficacy and safety of saxagliptin in older participants in the SAVOR-TIMI 53 trial. Diabetes Care. 2015; 38: 1145-1153.
56. Rosenstock J, Marx N, Kahn SE, Zinman B, Kastelein JJ, Lachin JM, et al. Cardiovascular outcome trials in type 2 diabetes and the sulphonylurea controversy: rationale for the active-comparator CAROLINA trial. Diab Vasc Dis Res. 2013; 10: 289-301.