Editorial
Others

Diabetes Metab J 2015;39:204-206
http://dx.doi.org/10.4093/dmj.2015.39.3.204
pISSN 2233-6079 · eISSN 2233-6087

dmj
DIABETES & METABOLISM JOURNAL

Dipeptidyl Peptidase-4 Inhibitor Alarms: Is Heart Failure Caused by a Class Effect?

Yong-ho Lee

Division of Endocrinology and Metabolism, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Since the rosiglitazone controversy aroused in 2007 [1], US Food and Drug Administration and most other regulatory agencies have requested to perform cardiovascular safety assessments for upcoming antidiabetic medications [2]. Dipeptidyl peptidase-4 (DPP4) inhibitors belong to a new class of oral antidiabetic drugs which can ameliorate hyperglycemia by increasing endogenous concentration of glucagon-like peptide-1, a gut-derived hormone that stimulates insulin secretion and delays gastric emptying. However, despite its popularity in the diabetes market, the cardiovascular safety of DPP4 inhibitors has not been investigated following the two large, randomized, placebo-controlled trials (RCTs), saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus-thrombolysis in myocardial infarction (SAVOR-TIMI 53) [3] with saxagliptin and Examination of Cardiovascular Outcomes with Alogliptin vs. Standard of Care (EXAMINE) [4] with alogliptin, which recently published the results of cardiovascular outcomes in 2013.

Unexpectedly, SAVOR-TIMI 53 showed that the rate of hospital admission for heart failure was significantly increased by 27% in subjects treated with saxagliptin, while EXAMINE did not report any outcome related to heart failure. A subsequent paper based on EXAMINE trial reported that alogliptin was not associated with the increased risk of heart failure outcomes, such as hospital admission for heart failure, compared with placebo group [5]. However, both studies observed that hospital admission for heart failure occurred more frequently in subjects treated with saxagliptin or alogliptin who had no history of this disease condition (SAVOR-TIMI 53: hazard ratio [HR], 1.30, 95% confidence interval [CI], 1.03 to 1.65; EXAMINE: HR, 1.76, 95% CI, 1.07 to 2.90). According to the additional report from SAVOR-TIMI 53, the high-risk patients for heart failure hospitalization were those who had a prior history of heart failure, elevated baseline levels of N-terminal pro-brain natriuretic peptide, or chronic kidney disease [6].

To date, several studies demonstrated conflicting results regarding the safety of DPP4 inhibitors on heart failure. A nested case-control study based on a large insurance claimed that the database from United States showed that sitagliptin was associated with heart failure admissions in patients recently diagnosed with heart failure (adjusted odds ratio [OR], 1.84; 95% CI, 1.16 to 2.92; $P=0.01$) [7]. A propensity-matched analysis using Taiwan National Health Insurance research database with a total of 16,576 subjects reported that sitagliptin users were hospitalized for heart failure more frequently than patients that were never exposed to a DPP4 inhibitor (HR, 1.21; 95% CI, 1.04 to 1.42; $P=0.017$) [8]. In this study, patients with the highest adherence to sitagliptin had the greatest risk of developing heart failure (HR, 2.56; 95% CI, 2.10 to 3.12) compared with never users. In addition, similar findings were derived from a recent meta-analysis of 82 randomized controlled clinical trials with various DPP4 inhibitors treated for at least 24 weeks. The overall risk of acute heart failure was significantly elevated in the DPP4 inhibitor group compared with placebo/active comparators ($n=69,615$; Mantel-Haenszel OR, 1.19; 95% CI, 1.03 to 1.37; $P=0.015$) [9]. In Vildagliptin in Ventricu-

Corresponding author: Yong-ho Lee
Division of Endocrinology and Metabolism, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea
E-mail: yholee@yuhs.ac

lar Dysfunction Diabetes (VIVIDD) trial, 254 subjects with type 2 diabetes and New York Heart Association functional classes I through III heart failure were randomized to vildagliptin or placebo for 12 months [10]. Although there was no difference in left ventricular ejection fraction between two groups, patients treated with vildagliptin had an increase in left ventricular end-diastolic volumes, suggesting that vildagliptin could possibly increase the risk of heart failure.

However, a recent population-based study from United Kingdom showed that incretin-based drugs were not associated with an increased risk of heart failure among patients with type 2 diabetes (OR, 0.85; 95% CI, 0.62 to 1.16) [11]. Although five drugs (sitagliptin, vildagliptin, saxagliptin, exenatide, and liraglutide) were included in the analysis, majority of patients were prescribed sitagliptin. A non-randomized, observational real-world study from Germany (DiaRegis registry) enrolled patients with prior metformin monotherapy who then received either DPP4 inhibitors or sulfonylurea [12]. Similarly, there was no difference in event rates of heart failure between two groups (1.7% in the DPP4 inhibitor group vs. 2.0% in the sulfonylurea group, P=0.85), while subjects with DPP4 inhibitors showed significantly lower rates of stroke and transitory ischemic attack.

In this issue of *Diabetes and Metabolism Journal*, Seo et al. [13] provided additional concerns about the safety of DPP4 inhibitors on heart failure in Korean type 2 diabetes. Based on Korean Health Insurance claims database, they used pioglitazone as a positive control for increasing risk of heart failure [14] and compared the incidence rate of hospital admission for heart failure with DPP4 inhibitors. Compared with pioglitazone group, sitagliptin and vildagliptin users did not show any significant difference in hospitalization rate for heart failure, indicating the comparable effects on the development of heart failure between DPP4 inhibitors and pioglitazone. Despite the large number of subjects, the potential for confounding in this study cannot be ruled out because of the limitation of the nature of claim database. Furthermore, there is no information regarding compliance of medications and comorbidities in the study population which should be adjusted in the analysis. Regardless of drug types, the hospitalization rate for heart failure was greatest in the first 30 days after starting to take the medication, when compared with days 31 to 360 days. Similar to their findings, Scirica et al. [6] reported that the risk of heart failure hospitalization was most pronounced in the first 12 months of treatment with saxagliptin. These two findings suggest that DPP4 inhibitors may trigger heart failure in vulnerable but unidentified or subclinical subjects who are likely to develop heart failure. On the contrary to thiazolidinediones, DPP4 inhibitors are not associated with edema or fluid retention, therefore the mechanism for heart failure might be different, which should be elucidated by further research.

In summary, inconsistent findings from various studies, including meta-analyses, large randomized trials, observational studies, and analysis of insurance claim database, indicate that we still cannot draw any definite conclusion in terms of the safety of DPP4 inhibitors on heart failure in patients with type 2 diabetes. We should wait with prudence for the upcoming reports from Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) trial [15], another large RCT with Sitagliptin including 14,724 subjects with type 2 diabetes and Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial [16], to fully address all the concerns related to the safety issues of incretin-based drugs on heart failure.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457-71.
2. Goldfine AB. Assessing the cardiovascular safety of diabetes therapies. N Engl J Med 2008;359:1092-5.
3. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317-26.
4. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327-35.
5. Zannad F, Cannon CP, Cushman WC, Bakris GL, Menon V, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Lam H,

White WB; 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 Mar 9 [Epub]. http://dx.doi.org/10.1016/S0140-6736(14)62225-X.
6. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, Udell JA, Mosenzon O, Im K, Umez-Eronini AA, Pollack PS, Hirshberg B, Frederich R, Lewis BS, McGuire DK, Davidson J, Steg PG, Bhatt DL; SAVOR-TIMI 53 Steering Committee and Investigators. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation 2014;130:1579-88.
7. 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;2:573-82.
8. Wang KL, Liu CJ, Chao TF, Huang CM, Wu CH, Chen SJ, Yeh CM, Chen TJ, Lin SJ, Chiang CE. Sitagliptin and the risk of hospitalization for heart failure: a population-based study. Int J Cardiol 2014;177:86-90.
9. Monami M, Dicembrini I, Mannucci E. Dipeptidyl peptidase-4 inhibitors and heart failure: a meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis 2014;24:689-97.
10. McMurray J. Effect of vildagliptin on left ventricular function in patients with type 2 diabetes and congestive heart failure. Paper presented at: heart Failure Congress 2013; 2013 May 25-28; Lisbon.
11. Yu OH, Filion KB, Azoulay L, Patenaude V, Majdan A, Suissa S. Incretin-based drugs and the risk of congestive heart failure. Diabetes Care 2015;38:277-84.
12. Gitt AK, Bramlage P, Binz C, Krekler M, Deeg E, Tschope D. Prognostic implications of DPP-4 inhibitor vs. sulfonylurea use on top of metformin in a real world setting: results of the 1 year follow-up of the prospective DiaRegis registry. Int J Clin Pract 2013;67:1005-14.
13. Suh S, Seo GH, Jung CH, Kim MK, Jin SM, Hwang YC, Lee BW, Kim JH. Increased risk of hospitalization for heart failure with newly prescribed dipeptidyl peptidase-4 inhibitors and pioglitazone using the Korean Health Insurance Claims Database. Diabetes Metab J 2015;39:247-52.
14. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefebvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Koranyi L, Laakso M, Mokan M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J; 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 randomised controlled trial. Lancet 2005;366:1279-89.
15. Green JB, Bethel MA, Paul SK, Ring A, Kaufman KD, Shapiro DR, Califf RM, Holman RR. Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. Am Heart J 2013;166:983-9.e7.
16. Marso SP, Poulter NR, Nissen SE, Nauck MA, Zinman B, Daniels GH, Pocock S, Steinberg WM, Bergenstal RM, Mann JF, Ravn LS, Frandsen KB, Moses AC, Buse JB. Design of the liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (LEADER) trial. Am Heart J 2013;166:823-30.e5.