Diabetes Drugs and Cardiovascular Safety

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Diabetes is a well-known risk factor of cardiovascular morbidity and mortality, and the beneficial effect of improved glycemic control on cardiovascular complications has been well established. However, the rosiglitazone experience aroused awareness of potential cardiovascular risk associated with diabetes drugs and prompted the U.S. Food and Drug Administration to issue new guidelines about cardiovascular risk. Through postmarketing cardiovascular safety trials, some drugs demonstrated cardiovascular benefits, while some antidiabetic drugs raised concern about a possible increased cardiovascular risk associated with drug use. With the development of new classes of drugs, treatment options became wider and the complexity of glycemic management in type 2 diabetes has increased. When choosing the appropriate treatment strategy for patients with type 2 diabetes at high cardiovascular risk, not only the glucose-lowering effects, but also overall benefits and risks for cardiovascular disease should be taken into consideration.

Keywords: Diabetes mellitus; Cardiovascular diseases; Heart failure; Hypoglycemic agents

INTRODUCTION

Cardiovascular (CV) disease is a highly prevalent complication and the major cause of premature death in patients with type 2 diabetes [1]. The effect of improved glycemic control on CV complication has been well established through clinical trials and meta-analyses [2-5]. However, several studies have suggested that some antidiabetic drugs increase CV risk, despite being effective at lowering blood glucose in type 2 diabetes [6-9]. For this reason, new diabetes agents are required to demonstrate CV safety, showing robust CV outcome data from randomized, controlled trials in order to grant approvals. On the other hand, these regulatory requirements might also provide the opportunity for some of drugs in CV outcome trials to be tested for CV benefits [1].

We will discuss the evidence of the CV risk associated with thiazolidinedione (TZD) use, which aroused awareness of potential CV risk associated with diabetes agents and prompted the U.S. Food and Drug Administration (FDA) to issue new guidelines about CV risk [10]. This study will also review the published or currently ongoing CV safety trial of the dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonist, and sodium glucose cotransporter 2 (SGLT2) inhibitor.

THIAZOLIDINEDIONES

Rosiglitazone

Adverse data from a meta-analysis published in New England Journal of Medicine in 2007 evoked concern about a possible...
increased CV risk associated with rosiglitazone use [7,10]. Using a fixed-effects analytic model with data from 42 randomized clinical trials, this analysis concluded that rosiglitazone was associated with an approximately 43% increased risk of myocardial infarction (odds ratio [OR], 1.43; 95% confidence interval [CI], 1.03 to 1.98) and an approximately 64% increased risk of CV death (OR, 1.64; 95% CI, 0.98 to 2.74) [7].

The interpretation of these study results have been debated extensively [11,12]. These meta-analyses consisted of predominantly small, short-term, nonadjudicated treatment trials in lower-risk populations [7,13]. Nissen’s analysis used the number of events rather than time to event without consideration of follow-up, and some trials with no events were excluded. None of the trials included in the reports focused primarily on CV safety in patients treated with rosiglitazone [11-13]. Furthermore, studies were combined on the basis of a lack of statistical heterogeneity, despite substantial variability in control groups, inclusion criteria, follow-up, and outcome assessment. Indeed, other researchers have analyzed the same group of studies using different statistical methods and found no link between heart attack and rosiglitazone [11].

Nevertheless, additional meta-analyses suggested an increased risk of adverse CV events among patients with type 2 diabetes treated with rosiglitazone [6,14,15]. Due to this possible association with myocardial infarction, rosiglitazone was withdrawn from the European market by the European Medicines Agency in 2010 [16]. At the same time, the FDA imposed restrictions on the prescription and use of the diabetes drug rosiglitazone [17]; the drug has also been removed from the Korean market.

In 2013, the FDA lifted restrictions on the prescription and use of rosiglitazone after re-evaluation of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial, which showed no increase in the risk of CV morbidity or mortality attributable to rosiglitazone [18,19]. The RECORD trial is the only completed prospective trial to evaluate CV safety in patients treated with rosiglitazone [13].

The rosiglitazone experience aroused awareness of potential CV risk associated with diabetes agents and prompted the FDA to issue new guidelines about CV risk. The approval process for new agents must include a demonstration of no unacceptable increase in CV risk [10]. This requires a meta-analysis of important CV events in phase 2/3 to achieve an upper 95% CI <1.3 to qualify for approval without requiring a postmarketing CV trial, provided that the overall benefits and risks support drug approval. If the upper 95% CI is >1.8, additional phase 3 safety studies are required before resubmission for marketing authorization. If the overall risk-benefit balance supports drug approval but the upper CI lies between 1.3 and 1.8, then a postmarketing CV trial usually required to demonstrate an upper 95% CI <1.3 [10,20]. In practice, each sponsor of a recently approved drug has undertaken such a study, even if the phase 2/3 CV events conform to an upper 95% CI <1.3; such postmarketing studies appear to be almost obligatory [10,21].

**Pioglitazone**

Along with rosiglitazone, pioglitazone is also a member of the TZD class of drugs. Thus, there is a question of whether use of the other marketed TZD, pioglitazone, carries similar risks [15]. A large CV outcomes trial with pioglitazone, the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) trial, was performed to evaluate the effects of pioglitazone on CV morbidity and mortality in high-risk patients with type 2 diabetes. The PROactive trial was a prospective, randomized, controlled trial in 5,238 patients with type 2 diabetes who had evidence of CV disease. These patients were randomized to pioglitazone, titrated to 45 mg daily, or matching placebo with a background of usual glucose-lowering medications. In that study, treatment with pioglitazone produced a nonsignificant reduced risk of coronary and peripheral vascular events (hazard ratio [HR], 0.90; 95% CI, 0.80 to 1.02; P=0.10). As a secondary endpoint, pioglitazone reduced the composite of all-cause mortality, nonfatal myocardial infarction, and stroke (HR, 0.84; 95% CI, 0.72 to 0.98; P=0.03) [22]. More recently, in the Insulin Resistance Intervention after Stroke (IRIS) trial, which included 3,876 nondiabetic patients with insulin resistance and ischemic stroke or transient ischemic attack, patients who were assigned to the pioglitazone group showed a statistically significant 24% reduction in strokes and myocardial infarction compared with placebo recipients over 4.8 years [23]. In addition, a meta-analysis of CV outcome from 19 randomized clinical trials, with a total enrollment of 16,390 diabetic patients, showed that pioglitazone was associated with a significantly lower risk of the composite of death, myocardial infarction, and stroke (HR, 0.82; 95% CI, 0.72 to 0.94; P=0.005) [24].

However, there remains a major concern about the increase in heart failure associated with pioglitazone treatment. Serious congestive heart failure was increased by pioglitazone in both the PROactive trial and the meta-analysis, although without an associated increase in mortality [22,24].
DIPEPTIDYL PEPTIDASE-4 INHIBITORS

The DPP-4 inhibitor class of antidiabetic drugs emerged after the FDA issued new guidance about CV risk that requires new diabetes drugs to conduct postmarketing CV trials to show drug safety. In accordance with this new FDA guideline, examination of cardiovascular outcomes with alogliptin versus standard of care in patients with type 2 diabetes and acute coronary syndrome (EXAMINE), Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SA VOR-TIMI 53), and Trial Evaluating Cardiovascular Outcome with Sitagliptin (TECOS) were conducted to demonstrate CV safety or CV benefit. In the EXAMINE trial, which included a total of 5,380 patients with type 2 diabetes who had experienced either acute myocardial infarction or unstable angina within the previous 15 to 90 days, the rates of major adverse CV events were not increased with the DPP-4 inhibitor alogliptin compared with placebo [25]. In the SAVOR-TIMI trial, 16,492 patients with type 2 diabetes at high risk for CV events or who had a history of CV events were randomized to saxagliptin or placebo. Consistent with the results from EXAMINE, saxagliptin did not increase the risk of CV events [26]. The TECOS trial also produced consistent findings of no CV risk associated with sitagliptin [27]. However, none of these trials demonstrated a CV benefit of DPP-4 inhibitors [25-27].

It is important to note that these trials have raised concerns about the increased rate of heart failure associated with DPP-4 inhibitor use, with ongoing uncertainty regarding the validity of the findings and their clinical implications [28,29]. Saxagliptin use was associated with a 27% increase in hospitalization for heart failure in the SAVOR-TIMI trial [26]. This increase in risk was highest among patients with elevated levels of natriuretic peptides, prior heart failure, or chronic kidney disease [30]. Alogliptin use was also associated with a numerically higher but not statistically significant increased risk of hospitalization for heart failure in the EXAMINE trial [25]. In a 12-month VIVIDD (Vildagliptin in Ventricular Dysfunction Diabetes) trial, which randomized 254 patients with type 2 diabetes and New York Heart Association functional class I to III heart failure to vildagliptin or placebo, there was no difference in left ventricular function and no excess of heart failure hospitalization with vildagliptin. However, despite a significant decrease in plasma level of brain natriuretic peptide, patients treated with vildagliptin had an increase in left ventricular end-diastolic volume, and there were numerically more deaths in the vildagliptin arm compared with the placebo arm, raising additional concerns about safety with DPP-4 inhibitors in patients with established heart failure [31-34]. Meta-analyses of these and other DPP-4 inhibitor studies suggest that these agents are associated with increased risk of hospitalization for heart failure [34-36].

There are no specific mechanistic reasons to attribute an increase in heart failure outcomes to the pharmacological properties of the DPP-4 inhibitor [34]. In addition, the most recent large-scale TECOS findings did not confirm the findings of increased risk of hospitalization for heart failure [37]. At this time, it is unclear whether increased risk of heart failure hospitalization is a class effect of DPP-4 inhibitor. In order to elucidate and interpret the concern about hospitalization for heart failure with DPP-4 inhibitors, further large-scale CV outcome studies need to be conducted; such work is ongoing (CAROLINA [Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes], Clinical Trial.gov number, NCT01243424) [10,34].

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

As with DPP-4 inhibitor, CV safety studies for GLP-1 receptor agonists were designed to satisfy the requirement of the 2008 FDA guidance [10]. The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial was the first completed study of GLP-1 receptor agonist and did not show a benefit on CV outcomes in the 6,068 patients with type 2 diabetes at high CV risk. There was no difference between the lixisenatide and placebo group in the primary composite outcome of CV death, myocardial infarction, stroke, or hospitalization for unstable angina [38]. Some trials and meta-analyses have raised concerns about the increased rate of heart failure associated with DPP-4 inhibitor use [25,26,31,34-36]. Along with DPP-4 inhibitor, GLP-1 receptor agonist is also a member of the incretin-based drug family [39]. However, the ELIXA study has shown a neutral effect on the incidence of hospitalization for heart failure among patients randomly assigned to lixisenatide, which was consistent in the subgroups of patients who had experienced heart failure and those who had not [38].

CV safety studies with other GLP-1 receptor agonists (LEADER [Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results], Clinical Trial.gov number, NCT01179048; EXSCEL [Exenatide Study of Cardiovascular Event Lowering Trial], NCT01144338; REWIND
[Researching Cardiovascular Events with a Weekly Incretin in Diabetes] with dulaglutide, NCT01394952; SUSTAIN 6 [Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes 6], NCT01720446) are ongoing; their results are expected to provide new information on CV safety or benefit regarding this GLP-1 receptor agonist [10]

**SODIUM GLUCOSE COTRANSPORTER-2 INHIBITORS**

EMPA-REG OUTCOME is a CV safety trial of an agent from the SGLT2 inhibitor class. This trial was performed to evaluate the effects of empagliflozin on CV morbidity and mortality in patients with type 2 diabetes at high CV risk. A total of 7,020 patients with diabetes and established CV disease were randomly assigned in a 1:1:1 ratio to receive either 10 or 25 mg of empagliflozin or placebo once daily on a background of standard care (including dyslipidemia-, hypertension-, and glucose-lowering therapy). In this study, the pooled empagliflozin group has shown a statistically significant 14% reduction in the primary composite major adverse cardiac event endpoint (death from CV causes, nonfatal myocardial infarction, or nonfatal stroke) compared with placebo recipients over a median of 3.1 years [40].

The difference in this primary endpoint was mainly driven by the 38% relative risk reduction in CV death. Whereas the reduced CV death was accompanied by 35% decreased hospitalization for heart failure, treatment with empagliflozin did not reduce the risk of nonfatal myocardial infarction or stroke [40]. Also, the difference in the occurrence of the primary endpoint appeared too early in the study [40,41]. These findings suggest that this improvement was not related to atherosclerotic change, improvement in blood pressure, or glucose control but might be related to the hemodynamic effects associated with the SGLT2 inhibitor [41].

EMPA-REG OUTCOME is the first CV safety trial to show improved CV outcome in high-risk patients. Although, in PROactive and IRIS trials, pioglitazone demonstrated CV benefit in patients with type 2 diabetes at high CV risk, there remains a major concern about the increase in heart failure associated with pioglitazone treatment [22,23]. Recently, other CV safety studies with diabetes drugs including DPP-4 inhibitor or GLP-1 receptor agonist have shown only neutrality, not superiority, with regard to CV outcome [25-27,38].

EMPA-REG OUTCOME is the only trial to examine the effects of an SGLT2 inhibitor on CV events, making it difficult to draw any conclusion on the CV effects of other SGLT2 inhibitors [41]. A number of other SGLT2 inhibitor CV safety studies (DECLARE-TIMI58 [Dapagliflozin Effect on Cardiovascular Events-Thrombolysis In Myocardial Infarction 58], Clinical Trial.gov number, NCT01730534; CANVAS [Cana-gliflozin Cardiovascular Assessment Study], NCT01032629) are ongoing [42]; their results are expected to conclude whether the effects seen with empagliflozin are class effects of the SGLT2 inhibitor.

**CONCLUSIONS**

The rosiglitazone experience aroused awareness of potential CV risk associated with diabetes drugs and prompted the FDA to issue new guidelines about CV risk [10,20]. Through post-marketing CV safety trials, some drugs have demonstrated CV benefits, while some anti-diabetic drugs raised concern about a possible increased CV risk associated with drug use [23,24,28,31,40]. Patients with diabetes have various clinical presentations, different courses of disease, and different responses to therapeutic agents, which emphasize the need for individualized and patient-centered care [43]. With the development of new classes of drugs, treatment options became wider, and the complexity of glycemic management in type 2 diabetes has increased [44]. Thus, when choosing the appropriate treatment strategy in patients with type 2 diabetes at high CV risk, not only the glucose-lowering effects, but also the overall benefits and risks of CV disease should be taken into consideration.

**CONFLICTS OF INTEREST**

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

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**REFERENCES**

1. Rosenstock J, Marx N, Kahn SE, Zinman B, Kastelein JJ, Lachin JM, et al. Cardiovascular outcome trials in type 2 diabetes and the sulphonyurea controversy: rationale for the active-comparator CAROLINA trial. Diab Vasc Dis Res 2013;10:289-301.
2. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA.
10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577-89.

3. Gerstein HC, Miller ME, Ismail-Beigi F, Largay J, McDonald C, Lochnan HA, et al. Effects of intensive glycaemic control on ischaemic heart disease: analysis of data from the randomised, controlled ACCORD trial. Lancet 2014;384:1936-41.

4. Control Group, Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetesologia 2009;52:2288-98.

5. Hayward RA, Reaven PD, Wiitala WL, Bahn GD, Reda DJ, Ge L, et al. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;372:2197-206.

6. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley C, Worrall C, et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA 2010;304:411-8.

7. 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.

8. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. Lancet 2007;370:1129-36.

9. Goldfine AB. Assessing the cardiovascular safety of diabetes therapies. N Engl J Med 2008;359:1092-5.

10. Bailey CJ. Interpreting adverse signals in diabetes drug development programs. Diabetes Care 2013;36:2098-106.

11. Diamond GA, Bax L, Kaul S. Uncertain effects of rosiglitazone on the risk for myocardial infarction and cardiovascular death. Ann Intern Med 2007;147:578-81.

12. Bloomgarden ZT. The Avandia debate. Diabetes Care 2007;30:2401-8.

13. Bach RG, Brooks MM, Lombardero M, Genuth S, Donner TW, Garber A, et al. Rosiglitazone and outcomes for patients with diabetes mellitus and coronary artery disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. Circulation 2013;128:785-94.

14. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. JAMA 2007;298:1189-95.

15. Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. Arch Intern Med 2010;170:1191-201.

16. European Medicines Agency. European Medicines Agency recommends suspension of avandia, avandamet and avaglim [Internet]. London: European Medicines Agency; c2016 [cited 2016 May 24]. Available from: http://ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/09/news_detail_001119.jsp.

17. Woodcock J, Sharfstein JM, Hamburg M. Regulatory action on rosiglitazone by the U.S. Food and Drug Administration. N Engl J Med 2010;363:1489-91.

18. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet 2009;373:2125-35.

19. U.S. Food and Drug Administration. FDA drug safety communication: FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines [Internet]. Silver Spring: U.S. Food and Drug Administration; 2016 [cited 2016 May 24]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm376389.htm.

20. U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for industry: diabetes mellitus-evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes [Internet]. Silver Spring: U.S. Food and Drug Administration; 2016 [cited 2016 May 24]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm376389.htm.

21. Menon V, Lincoff AM. Cardiovascular safety evaluation in the development of new drugs for diabetes mellitus. Circulation 2014;129:2705-13.

22. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. 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;366:1279-89.

23. Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, et al. Pioglitazone after ischemic stroke or transient ischemic attack. N Engl J Med 2010;363:1489-91.

24. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA 2007;298:1180-8.
25. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327-35.

26. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317-26.

27. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232-42.

28. Standl E. Saxagliptin, alogliptin, and cardiovascular outcomes. N Engl J Med 2014;370:483.

29. Standl E, Schnell O. DPP-4 inhibitors and risk of heart failure EXAMINEd. Lancet 2015;385:2022-4.

30. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, et al. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation 2014;130:1579-88.

31. 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, Portugal.

32. Fonarow GC. Diabetes medications and heart failure: recognizing the risk. Circulation 2014;130:1565-7.

33. Bhatt DL, Cavender MA. Do dipeptidyl peptidase-4 inhibitors increase the risk of heart failure? JACC Heart Fail 2014;2:583-5.

34. Wu S, Hopper I, Skiba M, Krum H. Dipeptidyl peptidase-4 inhibitors and cardiovascular outcomes: meta-analysis of randomized clinical trials with 55,141 participants. Cardiovasc Ther 2014;32:147-58.

35. Clifton P. Do dipeptidyl peptidase IV (DPP-IV) inhibitors cause heart failure? Clin Ther 2014;36:2072-9.

36. Udell JA, Cavender MA, Bhatt DL, Chatterjee S, Farkouh ME, Scirica BM. Glucose-lowering drugs or strategies and cardiovascular outcomes in patients with or at risk for type 2 diabetes: a meta-analysis of randomised controlled trials. Lancet Diabetes Endocrinol 2015;3:356-66.

37. McGuire DK, Van de Werf F, Armstrong PW, Standl E, Koglin J, Green JB, et al. Association between sitagliptin use and heart failure hospitalization and related outcomes in type 2 diabetes mellitus: secondary analysis of a randomized clinical trial. JAMA Cardiol 2016;1:126-35.

38. Pfeiffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247-57.

39. Nauck MA, Vilsboll T, Gallwitz B, Garber A, Madsbad S. Incretin-based therapies: viewpoints on the way to consensus. Diabetes Care 2009;32 Suppl 2:S223-31.

40. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.

41. Rajasekeran H, Lytvyn Y, Cherney DZ. Sodium-glucose cotransporter 2 inhibition and cardiovascular risk reduction in patients with type 2 diabetes: the emerging role of natriuresis. Kidney Int 2016;89:524-6.

42. Inzucchi SE, Zinman B, Wanner C, Ferrari R, Fitchett D, Hantel S, et al. SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. Diab Vasc Dis Res 2015;12:90-100.

43. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. 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;35:1364-79.

44. Cernea S. The role of incretin therapy at different stages of diabetes. Rev Diabet Stud 2011;8:323-38.