Glucagon-Like Peptide-1 Receptor Agonists for the Treatment of Type 2 Diabetes Mellitus: A Position Statement of the Korean Diabetes Association

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The glucagon-like peptide-1 receptor agonists (GLP-1RAs) were recommended as a monotherapy or combination therapy with oral hypoglycemic agents or basal insulin in the position statement of the Korean Diabetes Association 2017 for pharmacological therapy. Many randomized clinical trials and systematic reviews report that GLP-1RAs have considerable glucose-lowering effect and lead to weight reduction and low risk of hypoglycemia when used as a monotherapy or combination therapy. The cardiovascular safety of GLP-1RAs has been assessed in several randomized clinical trials and systematic reviews. The results of cardiovascular outcome trials of long-acting GLP-1RAs (liraglutide, semaglutide) demonstrated cardiovascular benefits in subjects with type 2 diabetes mellitus and a high risk of cardiovascular disease. The GLP-1RA may be a choice of therapy when weight control and avoidance of hypoglycemia are important, and patients with high risk of cardiovascular disease might also favor choosing GLP-1RA.

Keywords: Cardiovascular benefit; Clinical practice guideline; Combination therapy; Glucagon-like peptide-1 receptor agonist; Hypoglycemia; Monotherapy

INTRODUCTION

Incretin hormone includes glucagon-like peptide-1 (GLP-1) from L-cells and glucose-dependent insulinotropic polypeptide from K-cells of the small intestine. GLP-1 stimulates glucose-dependent insulin release, inhibits glucagon release, delays gastric emptying, and suppresses the appetite through GLP-1 receptor binding. However, GLP-1 has a short half-life of 1 to 2 minutes due to degradation by dipeptidyl peptidase-4 (DPP-4), which has been a limitation for its use as an anti-hyperglycemic agent. GLP-1 receptor agonists (GLP-1RAs) are synthetic analogues that are resistant to DPP-4 degradation and have more stable pharmacodynamic profiles [1,2]. The GLP-1RAs are effective in improving glycemic control with reduction in body weight and a low risk of hypoglycemia. Recently, there have been many clinical trials and system-
atic reviews to determine the efficacy, safety, and cardiovascular effects of GLP-1RAs [3-10].

In the position statement of the Korean Diabetes Association (KDA) 2017 for pharmacological therapy in non-pregnant adult patients with type 2 diabetes mellitus (T2DM), the Committee of Clinical Practice Guidelines of KDA updated the previous recommendations published in 2015 after extensive review of the scientific evidence. In particular, GLP-1RAs were recommended as a monotherapy or combination therapy with oral hypoglycemic agents or basal insulin, which was unlike the previous guideline that recommended them only as a combination therapy.

In this article, we will review the glycemic and metabolic effects and cardiovascular outcome trials and provide the rationale for the recommendation of GLP-1RAs in the position statement of the KDA 2017.

GLYCEMIC AND METABOLIC EFFECTS

GLP-1RAs reduce fasting glucose concentrations, by up to 50 mg/dL, and glycosylated hemoglobin (HbA1c) by 0.5% to 1.3% with a lower risk of hypoglycemia due to a glucose-dependent mechanism of modulating insulin and glucagon secretion (Table 1) [3-6,11]. The short-acting GLP-1RAs have more pronounced effects on gastric emptying time and a greater effect on postprandial glucose, whereas the longer-acting agents result in greater effect on fasting glucose and HbA1c concentrations [3-6]. The risk of hypoglycemia with GLP-1RAs is low due to the glucose-dependent mechanism. In addition to their effects on HbA1c, the GLP-1RAs are associated with the reduction of appetite and food intake resulting in weight loss of between 2 and 4 kg on average [3-6,12,13]. In clinical trials, increased concentration of high-density lipoprotein cholesterol by 0.01 to 0.02 mmol/L and decreased concentration of triglyceride by 0.15 to 0.7 mmol/L were shown after treatment with GLP-1RAs [5]. The other characteristics, side effects and caution, were introduced in Table 1.

CARDIOVASCULAR OUTCOME TRIALS

The cardiovascular safety of GLP-1RAs has been assessed in several randomized clinical trials (RCTs) and systematic reviews [4-10]. In the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial, 6,068 patients with T2DM who had experienced a myocardial infarction or who had been hospitalized for unstable angina in the past 180 days were randomized and assigned to a lixisenatide group or placebo group. There was no reduction in overall cardiovascular risk and no difference in heart failure or serious adverse events between the two groups [7]. In contrast, the long-acting liraglutide and semaglutide reduced the cardiovascular events. In the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial, 9,340 patients with T2DM and high cardiovascular risk were randomized and assigned to either a liraglutide or placebo group, which was added to standard care. Liraglutide reduced the risk for the combined primary outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke by 13%, versus 14.9% in the placebo group (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.78 to 0.97). The rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure were not significantly lower in the liraglutide group than in the

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| Table 1. Glucagon-like peptide 1 receptor agonists for patients with type 2 diabetes mellitus |
|---|---|---|---|---|
| GLP-1 receptor agonist (exenatide, liraglutide, albiglutide, lixisenatide, dulaglutide) | ↑Glucose-dependent insulin secretion, ↓postprandial glucagon secretion, ↓postprandial hyperglycemia, delay gastric emptying, ↑satiety | No | No | 0.6–1.9 | GI side effects (nausea, vomiting, diarrhea) | Acute pancreatitis, C-cell hyperplasia, MEN2/MTC family or past history, severe renal or severe bowel disease |
| **Mechanism and common use** | **Weight gain** | **Hypoglycemia** | **HbA1c reduction, %** | **Side effects** | **Caution** |
| **Adapted from Ko et al. [11].** | **HbA1c**, glycosylated hemoglobin; **GLP-1**, glucagon-like peptide 1; **SC**, subcutaneous; **GI**, gastrointestinal; **MEN2**, multiple endocrine neoplasia 2; **MTC**, medullary thyroid cancer. | **Monotherapy.** |
| **Table 1. Glucagon-like peptide 1 receptor agonists for patients with type 2 diabetes mellitus** |

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placebo group [8]. The Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in patients with T2DM (SUSTAIN-6) (semaglutide is not currently marketed in Korea) was designed as a noninferiority safety study and randomized 3,297 patients with T2DM who were at high risk of cardiovascular disease. The primary composite outcome (the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) occurred in fewer patients in the semaglutide group, 6.6% versus 8.9% in the placebo group (HR, 0.74; 95% CI, 0.58 to 0.95) [9]. The difference of results in cardiovascular outcome trials may be related to the pharmacokinetics and potency of the glucose-lowering effect of the respective agents. Differences in study design including duration, patient risk profile, and study size may also influence the results of trials. However, the cardiovascular safety trials have been performed in very high risk populations aiming at capturing cardiovascular safety issue, and the study duration is relatively short. There are few data on cardiovascular disease safety or benefits in lower-risk patients. Several systematic reviews and meta-analyses summarizing the effect of GLP-1RAs did not show an increased risk for hospitalization for heart failure. This was unlike administration of DPP-4 inhibitors, the other incretin-based therapy [4,5,10].

Microvascular outcomes
There is no trials assessing the effect of GLP-1RA on microvascular complication as the primary outcome. In trials designed to assess cardiovascular outcomes, LEADER, SUSTAIN-6, liraglutide and semaglutide reduced the risk of nephropathy [8,9]. In SUSTAIN-6 study, rates of diabetic retinopathy (vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photoagulation) were higher significantly in semaglutide group compared to placebo group (HR, 1.76; 95% CI, 1.11 to 2.78) [9]. However, we cannot conclude yet because these trials were not designed and were of short duration to assess microvascular outcomes and there was no evaluation for retinopathy at baseline of study. Further studies about the effects of GLP-1RA on microvascular complications in lower-risk patients are needed.

RECOMMENDATION

GLP-1RAs
1. A GLP-1RA can be used as a monotherapy or combination therapy with oral antihyperglycemic agents or basal insulin [A].

COMMENTS ON RECOMMENDATIONS

GLP-1RAs as monotherapy
In accordance with other guidelines, metformin monotherapy is recommended as an initial therapy for patients with T2DM in the position statement of the KDA 2017 for pharmacological therapy [14-18]. However, if metformin is not tolerated or is contraindicated, then another class of antihyperglycemic agent including GLP-1RA can be chosen according to the patient’s circumstances, with the goal of controlling blood glucose levels with fewer side effects. There are many studies demonstrating that GLP-1RAs have a considerable glucose-lowering effect leading to weight reduction and a low risk of hypoglycemia when used as a monotherapy [19-21]. Weight control and avoidance of weight gain are important factors in T2DM management. Therefore, GLP-1RA may be appropriate when weight loss and avoidance of hypoglycemia is a primary consideration. In addition, patients with a high risk of cardiovascular disease might also favor choosing GLP-1RA based on the results of cardiovascular outcome studies.

GLP-1RAs as combination therapy with basal insulin
When basal insulin has been titrated to an acceptable fasting glucose level but satisfactory HbA1c levels have not been achieved, GLP-1RA can be added to basal insulin therapy. Many RCTs and systematic reviews have demonstrated that a combination of GLP-1RA with basal insulin showed equal or slightly superior efficacy of HbA1c reduction and less hypoglycemia and better weight control compared to combination therapy of prandial insulin and basal insulin [22-26]. In another study, the Basal Insulin Glargine plus Exenatide twice daily versus Basal Insulin Glargine plus Bolus Insulin Lispro (4B) study, exenatide twice daily or mealtime insulin lispro was given to patients with T2DM and insufficient glycemic control receiving titrated insulin glargine and resulted in comparable reductions in HbA1c. Exenatide was associated with weight loss and less hypoglycemia, but more gastrointestinal adverse effects, including nausea, vomiting, and diarrhea [23]. Subgroup analysis for Korean patients in the 4B study reported that exenatide twice daily and prandial insulin lispro both reduced HbA1c effectively [24]. In a 26-week trial, compared the addition of liraglutide versus a single daily dose of insulin aspart to insulin degludec in patients who were already treated with metformin (BEGIN: VICTOZA ADD-ON), liraglutide reduced HbA1c levels significantly more than insulin aspart, and
it was also associated with more weight loss and less hypoglycemia [25]. In the AWARD (Assessment of Weekly Administration of Dulaglutide)-9 trial, weekly dulaglutide added to basal insulin glargine was efficient for glucose control and well-tolerated by patients [26].

**GLP-1RAs as combination therapy with oral hypoglycemic agents**

GLP-1RAs have been studied in combination with one or two oral hypoglycemic agents. Liraglutide was effective when used in combination with one (metformin, sulfonylurea) or two (sulfonylurea plus metformin, thiazolidinedione plus metformin) oral hypoglycemic agents [27-30]. In a 26-week randomized study, exenatide weekly therapy resulted in a greater reduction of HbA1c and more frequent weight loss compared with insulin glargine therapy [31]. In HARMONY 4: an RCT comparing once-weekly albiglutide and insulin glargine, albiglutide was noninferior to insulin glargine at reducing HbA1c at week 52, and produced modest weight loss and less hypoglycemia [32]. Dulaglutide has been evaluated in combination with one or two oral hypoglycemic agents (metformin, sulfonylurea, pioglitazone) and showed good glucose-lowering effect and weight loss but with gastrointestinal adverse events [33, 34]. Combined use of the most recently approved antihyperglycemic agent classes, GLP-1RA (exenatide weekly) and sodium-glucose co-transporter-2 inhibitors (dapagliflozin), improved glycemic control and were well-tolerated in patients with T2DM which was inadequately controlled by metformin monotherapy [35]. Recently a meta-analysis comparing the clinical effects of short- or long-acting GLP-1RAs versus insulin treatment in head-to-head studies reported that GLP-1RAs achieved better glycemic control with benefits regarding hypoglycemia, body weight, blood pressure, and lipoprotein when added on oral hypoglycemic agents [36].

**CONCLUSIONS**

GLP-1RAs have benefits as antihyperglycemic agents which can achieve reduction of glucose levels and body weight with a low risk of hypoglycemia. In the position statement of the KDA 2017, GLP-1RAs were recommended as a monotherapy or combination therapy with oral hypoglycemic agents or basal insulin based on sufficient clinical evidence. Table 2 shows compounds and dosing of currently available GLP-1 RAs in Korea [37]. We can choose a GLP-1 RA according to the patient's status, for example, level and pattern of hyperglycemia and life style.

Cardiovascular disease is the major cause of mortality and morbidity in patients with T2DM [38,39] and reduction of cardiovascular risk is one of the treatment goals in management of T2DM. Each therapeutic agent's capacity to modify cardiovascular risk has been investigated and is one of the important considerations for choice of an antihyperglycemic agent. Therefore, recent reports of cardiovascular outcome trials of GLP-1RAs yield informative data. We should consider the limitation; however, that these trials were performed in very high risk populations. Hypoglycemia is a major barrier to achieving good glycemic control in patients with T2DM, and the risk of hypoglycemia is an important factor for the choice of antihyperglycemic agents [40]. The percentage of those who are obese has increased among Korean patients with diabetes, and nearly half of all patients with diabetes are obese according to a Diabetes Fact Sheet in Korea [41,42]. Weight control is one of the important factors in obese diabetes. Therefore, GLP-1RA may be a choice of therapy when weight control and avoidance of hypoglycemia are important and in patients with

Table 2. Currently available glucagon-like peptide-1 receptor agonists in Korea

| Compound   | Brand name | Dosing                                                                 |
|------------|------------|----------------------------------------------------------------------|
| Short-acting | Exenatide  | Byetta 5–10 µg SC twice daily prior to meals                           |
|            | Lixisenatide | Lymuxia 10 µg SC once daily, in the hour before the same meal for 14 days –→ a fixed maintenance dose of 20 µg once daily |
| Long-acting | Liraglutide | Victoza 0.6–1.8 mg SC once daily without regard to meals               |
|            | Saxenda    | BMI ≥30 kg/m² BMI 27–30 kg/m² + prediabetes, T2DM, HTN, or dyslipidemia 3 mg daily for 12 weeks |
|            | Dulaglutide | Trulicity 0.75–1.5 mg SC once weekly without regard to meals          |

Modified from Korean Diabetes Association [37].
SC, subcutaneous; BMI, body mass index; T2DM, type 2 diabetes mellitus; HTN, hypertension.
high risk of cardiovascular disease. In addition, further studies about cardiovascular disease safety or benefits in lower-risk patients and concerning efficacy and safety in Korean patients are needed.

CONFLICTS OF INTEREST

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

ACKNOWLEDGMENTS

This position statement on antihyperglycemic-agent therapy was written by the Korean Diabetes Association Committee of Clinical Practice Guidelines. We gratefully acknowledge the following experts who provided a critical review and discussion of this update: Tae-Nyun Kim, Inje University College of Medicine, Busan; Yong-ho Lee, Severance Hospital, Yonsei University College of Medicine, Seoul; Jin-Hwa Kim, Chosun University Hospital, Chosun University College of Medicine, Gwangju; Eun-Gyoon Hong, Hallym University Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong; Bokrye Song, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul; Ji Young Kim, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; Dong Hee Yang, Inje University Ilsan Paik Hospital, Inje University College of Medicine, Goyang; Taeyoung Yang, Taeyoung 21 Hospital, Gwangju; and Hyeongjin Kim, Kim HJ Medical Clinic, Paju, Korea.

REFERENCES

1. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006;368:1696-705.
2. Tahrani AA, Barnett AH, Bailey CJ. Pharmacology and therapeutic implications of current drugs for type 2 diabetes mellitus. Nat Rev Endocrinol 2016;12:566-92.
3. Madsbad S. Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists. Diabetes Obes Metab 2016;18:317-32.
4. Mannucci E, Monami M. Cardiovascular safety of incretin-based therapies in type 2 diabetes: systematic review of integrated analyses and randomized controlled trials. Adv Ther 2017;34:1-40.
5. Nauck MA, Meier JJ, Cavender MA, Abd El Aziz M, Drucker DJ. Cardiovascular actions and clinical outcomes with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. Circulation 2017;136:849-70.
6. Thrasher J. Pharmacologic management of type 2 diabetes mellitus: available therapies. Am J Med 2017;130(6S):S4-17.
7. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, Lawson FC, Ping L, Wei X, Lewis EF, Maggioni AP, McMurray JJ, Probstfield J, Riddle MC, Solomon SD, Tardif JC; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247-57.
8. Marso SP, Daniels GH, Brown-Fromans K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311-22.
9. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsboll T, SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834-44.
10. Li L, Li S, Liu J, Deng K, Busse JW, Vandvik PO, Wong E, Sohani ZN, Bala MM, Rios LP, Malaga G, Ebrahim S, Shen J, Zhang L, Zhao P, Chen Q, Wang Y, Guyatt GH, Sun X. Glucagon-like peptide-1 receptor agonists and heart failure in type 2 diabetes: systematic review and meta-analysis of randomized and observational studies. BMC Cardiovasc Disord 2016;16:91.
11. Ko SH, Hur KY, Rhee SY, Kim NH, Moon MK, Park SO, Lee BW, Kim HJ, Choi KM, Kim JH; Committee of Clinical Practice Guideline of Korean Diabetes Association. Antihyperglycemic agent therapy for adult patients with type 2 diabetes mellitus 2017: a position statement of the Korean Diabetes Association. Diabetes Metab J 2017;41:337-48.
12. Domecq JP, Prutsky G, Leppin A, Sonbol MB, Altayar O, Undavalli C, Wang Z, Elrây T, Brito JP, Mauck KF, Lababidi MH, Prokop IJ, Asi N, Wei J, Fidalhussein S, Montori VM, Murad MH. Clinical review: drugs commonly associated with weight change: a systematic review and meta-analysis. J Clin Endocrinol Metab 2015;100:363-70.
13. Monami M, Dicembrini I, Marchionni N, Rotella CM, Man-
nucci E. Effects of glucagon-like peptide-1 receptor agonists on body weight: a meta-analysis. Exp Diabetes Res 2012;2012:672658.

14. Korean Diabetes Association. 2015 Treatment guidelines for diabetes. Seoul: Korean Diabetes Association; 2015.

15. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment. Diabetes Care 2017;40(Suppl 1):S64-74.

16. McGuire H, Longson D, Adler A, Farmer A, Lewin I; Guide-line Development Group. Management of type 2 diabetes in adults: summary of updated NICE guidance. BMJ 2016;353:i1575.

17. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Harper W, Clement M, Goldenberg R, Hanna A, Main A, Retnakaran R, Sherifali D, Woo V, Yale JF. Pharmacologic management of type 2 diabetes. Can J Diabetes 2013;37 Suppl 1:S61-8.

18. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgard-en ZT, Bush MA, Dagogo-Jack S, DeFronzo RA, Einhorn D, Fonseca VA, Garber JR, Garvey WT, Grunberger G, Handelsman Y, Hirsch JB, Jellinger PS, McGill JB, Mechanick JI, Rosenblit PD, Umpierrez GE. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm: 2017 executive summary. Endocr Pract 2017;23:207-38.

19. Fonseca VA, Alvarado-Ruiz R, Raccah D, Boka G, Miossec P, Gerich JE; EFC6018 GetGoal-Mono Study Investigators. Efficacy and safety of the once-daily GLP-1 receptor agonist lixisenatide in monotherapy: a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes (GetGoal-Mono). Diabetes Care 2012;35:1225-31.

20. Garber A, Henry RR, Ratner R, Hale P, Chang CT, Bode B; LEAD-3 (Mono) Study Group. Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycaemic control and weight for 2 years as monotherapy compared with glimepiride in patients with type 2 diabetes. Diabetes Obes Metab 2011;13:348-56.

21. Umpierrez G, Tofe Povedano S, Perez Manghi F, Shurzinske L, Pechtner V. Efficacy and safety of dulaglutide monotherapy versus metformin in type 2 diabetes in a randomized controlled trial (AWARD-3). Diabetes Care 2014;37:2168-76.

22. Cimmaruta D, Maiorino MI, Scavone C, Sportiello L, Rossi F, Giugliano D, Esposito K, Capuano A. Efficacy and safety of insulin-GLP-1 receptor agonist combination in type 2 diabetes mellitus: a systematic review. Expert Opin Drug Saf 2016;15 (sup2):77-83.

23. Diamant M, Nauck MA, Shaginian R, Malone JK, Cleall S, Reaney M, de Vries D, Hoogwerf BJ, MacConell L, Wolfenbuttel BH; 4B Study Group. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. Diabetes Care 2014;37:2763-73.

24. Yoon KH, Hardy E, Han J. Exenatide versus insulin lispro added to basal insulin in a subgroup of Korean patients with type 2 diabetes mellitus. Diabetes Metab J 2017;41:69-74.

25. Mathieu C, Rodbard HW, Cariou B, Handelsman Y, Phili-tsikas A, Ocampo Francisco AM, Rana A, Zinman B; BEGI-N: VICTOZA ADD-ON (NN1250-3948) study group. A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin glargine in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON). Diabetes Obes Metab 2014;16:636-44.

26. Pozzilli P, Norwood P, Jodar E, Davies MJ, Ivyanti T, Jiang H, Woodward DB, Milicic Z. Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9). Diabetes Obes Metab 2017;19:1024-31.

27. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, Zdravkovic M, During M, Matthews DR; LEAD-2 Study Group. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care 2009;32:84-90.

28. Marre M, Shaw J, Brandle M, Bebakan WM, Kamaruddin NA, Strand J, Zdravkovic M, Le Th Di, Colagiuri S; LEAD-1 SU study group. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with type 2 diabetes (LEAD-1 SU). Diabet Med 2009;26:268-78.

29. Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, Antic S, Zdravkovic M, Ravn GM, Simo R; Liraglutide Effect and Action in Diabetes 5 (LEAD-5) met+SU Study Group. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. Diabetologia 2009;52:2046-55.

30. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, Hale PM, Zdravkovic M, Blonde I; LEAD-4 Study Investigators. Efficacy and safety of the human glucagon-like peptide-1
analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diabetes Care 2009;32:1224-30.
31. Diamant M, Van Gaal L, Guerci B, Stranks S, Han J, Malloy J, Boardman MK, Trautmann ME. Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3): 3-year results of an open-label randomised trial. Lancet Diabetes Endocrinol 2014;2:464-73.
32. Weissman PN, Carr MC, Ye J, Cirkel DT, Stewart M, Perry C, Pratley R. HARMONY 4: randomised clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea. Diabetologia 2014;57:2475-84.
33. Wysham C, Blevins T, Arakaki R, Colon G, Garcia P, Atisso C, Kuhstoss D, Lakshmanan M. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). Diabetes Care 2014;37:2159-67.
34. Nauck M, Weinstock RS, Umpierrez GE, Guerci B, Skrivanek Z, Milicevic Z. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). Diabetes Care 2014;37:2149-58.
35. Frias JP, Guca C, Hardy E, Ahmed A, Dong P, Ohman P, Jabbour SA. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. Lancet Diabetes Endocrinol 2016;4:1004-16.
36. Abd El Aziz MS, Kahle M, Meier JJ, Nauck MA. A meta-analysis comparing clinical effects of short- or long-acting GLP-1 receptor agonists versus insulin treatment from head-to-head studies in type 2 diabetic patients. Diabetes Obes Metab 2017;19:216-27.
37. Korean Diabetes Association: Pharmacological therapy in patient with T2DM 2017. Available from: http://www.diabetes.or.kr/pro/publish/guide.php?code=guide&number=672&mode=view (updated 2017 Oct 13).
38. Haffner SM. Coronary heart disease in patients with diabetes. N Engl J Med 2000;342:1040-2.
39. Kim JH, Kim DJ, Jang HC, Choi SH. Epidemiology of micro- and macrovascular complications of type 2 diabetes in Korea. Diabetes Metab J 2011;35:571-7.
40. Yun JS, Ko SH. Avoiding or coping with severe hypoglycemia in patients with type 2 diabetes. Korean J Intern Med 2015;30:6-16.
41. Son JW, Park CY, Kim S, Lee HK, Lee YS; Insulin Resistance as Primary Pathogenesis in Newly Diagnosed, Drug Naive Type 2 Diabetes Patients in Korea (SURPRISE) Study Group. Changing clinical characteristics according to insulin resistance and insulin secretion in newly diagnosed type 2 diabetic patients in Korea. Diabetes Metab J 2015;39:387-94.
42. Ha KH, Kim DJ. Current status of managing diabetes mellitus in Korea. Korean J Intern Med 2016;31:845-50.