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Editorial

Present Views on Oral Hypoglycemic Drugs with Clinical Support from More Extensive Research

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ABSTRACT

Current reports for oral hypoglycemic agents (OHAs) are described. As to the association of dipeptidyl peptidase-4 inhibitors (DPP-4i) and bullous pemphigoid (BP), odds ratio (OR) was vildagliptin 5.08, linagliptin 2.87, sitagliptin 1.29 (not significant). Regarding the comparative study between SGLT2i and DPP-4i, SGLT2i group showed lower hazard ratio (HR) as MACE 0.76, myocardial infarction 0.82, cardiovascular death 0.60, heart failure 0.43, all-cause mortality 0.60. Semaglutide showed reduced OR for cardiovascular death than exenatide 0.47, dulaglutide 0.46, albiglutide 0.45, lixisenatide 0.43. SGLT2i showed reduction risk of HR for MACE 0.90, hospitalization for heart failure (HHF)/cardiovascular death 0.78, renal outcomes 0.62.

Keywords
Oral hypoglycemic agents (OHAs); Sodium glucose cotransporter-2 inhibitor (SGLT-2i); Semaglutide; Bullous pemphigoid (BP); Hospitalization for heart failure (HHF); Major adverse cardiovascular event (MACE).

INTRODUCTION

Standard guideline for diabetes mellitus in 2021 was presented by American Diabetes Association (ADA).[1] Recent topics for oral hypoglycemic agents (OHAs) will be introduced here with clinical evidence of larger studies. The episodes of hypoglycemia are risk factors for cardiovascular prognosis. A cohort study examining the prognosis of 74,610 patients for type 2 diabetes mellitus (T2DM) was reported.[2] After follow-up of 7.1-years in median, the absolute 5-year risk of death was 6.6% for cardiovascular death, 1.1% for cancer deaths, and 13.1% for other deaths in hospitalized group (n=388) for severe hypoglycemia, respectively. In contrast, the group who was not hospitalized for severe hypoglycemia had cardiovascular deaths 4.7%, cancer deaths 1.4%, and other deaths 11.1%, which were lower than those who experienced hypoglycemia, respectively.

Dipeptidyl peptidase-4 inhibitors (DPP-4i) has been recently prevalent. A systematic review was reported on the efficacy of DPP-4i for cardiovascular disease, and 18 randomized controlled trials (RCTs) and meta-analyses were analyzed.[3] As a result, no additional benefit to cardiovascular risk could be expected when DPP-4i was added to standard treatment. Some studies are found concerning DPP-4i and bullous pemphigoid (BP). For 138 RCTs, including 61514 DPP-4 inhibitor users and 59661 subjects were analyzed.[4] Among them, only 6 studies reported BP. As a result of meta-analysis, an odds ratio (OR) of 4.44 was found to be significantly associated with this risk. Meta-analysis study was conducted for evaluating the risk of BP and skin-related adverse events (AEs). Totally, 46 randomized placebo-controlled trials (n=59332) were included.[5] Among them, 3 studies revealed BP (n=38011), which included AEs. Comparison with control group, DPP4i group showed significantly higher-risk (OR 7.38). Moreover, DPP-4i therapy revealed increased overall risk of AEs (OR 1.22 p=0.03). To evaluate the relationship for BP, 5 studies for different kinds of DPP-4i were analyzed.[6] From adjusted meta-analysis, significant association between them were observed as OR 2.13. The OR was 5.08 in vildagliptin, 2.87 in linagliptin, while OR 1.29 (not significant p=0.31) in sitagliptin. By subgroup analysis, the OR in male was 2.35 and 1.88 in female. Consequently, the adjusted analysis can support a significant association of DPP-4i use and BP.

Comparative study was performed between sodium/glu-

cose cotransporter-2 inhibitors (SGLT2i) and DPP-4i. A retrospective cohort study for cardiovascular risk was reported using large databases in Canada and UK.[7] Subjects included matched 209,867 cases each for users of SGLT2i and DPP-4i. The primary outcome was major adverse cardiovascular events (MACE) and secondary outcomes were individual MACE, heart failure, and mortality of all causes. SGLT2i group for 0.9-years showed lower hazard ratio (HR) as MACE 0.76, myocardial infarction 0.82, cardiovascular death 0.60, heart failure 0.43, all-cause mortality 0.60, ischemic stroke 0.85. Similar beneficial effect for MACE were found with canagliflozin (0.79), dapagliflozin (0.73), and empagliflozin (0.77). Thus, the short-term use of SGLT2i can reduce the cardiovascular risks, compared with DPP-4i.

Semaglutide has been a topic for oral agent of GLP-1a. Systematic review for the effect of semaglutide was conducted in 11 RCTs with 9890 cases.[8] The results showed that hemoglobin A1C (HbA1c) decreased 0.89% and body weight decreased 2.99 kg, respectively. Semaglutide showed superiority of decreased HbA1c/weight as -0.35%/-1.48 kg, compared with sitagliptin, empagliflozin and liraglutide. Furthermore, semaglutide decreased all-cause mortality (OR 0.58) and cardiovascular mortality (OR 0.55), and showed the neutral efficacy for stroke, myocardial infarction, diabetic retinopathy and hypoglycemia. Seven cardiovascular outcome trials (CVOTs) were conducted including 56004 patients using network meta-analysis (NMA).[9] Semaglutide showed reduced OR of cardiovascular death statistically than exenatide 0.47, dulaglutide 0.46, albiglutide 0.45, lixisenatide 0.43. In contrast, significant differences were not detected for reducing death from any case, stroke and MI events. Consequently, GLP-1RAs revealed significant benefits for cardiovascular safety.

Regarding SGLT2i, several recent reports are found. The cardiovascular efficacy of ertugliflozin was evaluated for the study of VERTIS CV. T2DM cases (n=8246) received ertugliflozin or placebo, and a major adverse cardiovascular event (MACE) was analyzed for 3.5-years.[10] OR were 0.97 for MACE, 0.88 for death or hospitalization for heart failure (HHF). Hazard ratio (HR) for death from cardiovascular causes was 0.92, and death from renal causes was 0.81. Thus, ertugliflozin was proved to be non-inferior to placebo for MACE. In order to assess the renal and cardiovascular outcomes of T2DM for SGLT2i agents, analysis of systematic literature search was conducted.[11] The data were from 46969 T2DM cases including 31116 cases of cardiovascular disease. The results showed reduction risk of MACE (HR 0.90), HHF/cardiovascular death (HR 0.78), renal outcomes (HR 0.62). Consequently, SGLT2i showed reduced risk of MACE, HHF and renal outcomes, associated with beneficial effects of HHF risk that is consistent findings across the trials.

Chronic kidney disease (CKD) patients have elevated risk of adverse cardiovascular and renal outcomes. Clinical efficacy of dapagliflozin was studied for CKD patients as dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial.[12] Randomly assigned 4304 cases with estimated glomerular filtration rate (eGFR) 25-75 mL/min/1.73 m^2 and urinary Alb/Cre ratio (200-5000) were investigated and provided dapagliflozin or placebo. The primary outcome included a sustained eGFR decline, end-stage kidney disease (ESKD) or death from kidney or cardiovascular causes. HRs were primary outcome event 0.61, sustained eGFR decline 0.56 and death for various cause 0.69. The results were similar for patients with/without T2DM. Consequently, safer profile of dapagliflozin was confirmed. The study was apparently effective and then discontinued early, for 2.4-years in median.

SGLT2i may reduce the risk of HHF. For 3730 patients with heart failure with class II, III, IV and <40% of ejection fraction, double-blind trial was conducted by providing empagliflozin 10 mg a day or control as EMPEROR-Reduced Trial.[13] Primary outcome was HHF or cardiovascular death. During 16-months, primary outcome event was observed in 19.4% in empagliflozin group, and 24.7% in control group (HR 0.75). The total number of HHF was lower in empagliflozin group (HR 0.70). Annual decline of eGFR was slower in empagliflozin group (-0.55 *vs.* -2.28 ml/min/1.73 m^2/year, $p<0.001$). Consequently, patients in the empagliflozin group showed lower risk of cardiovascular death or HHF, irrespective of the presence or absence of diabetes.

Concerning the relationship between SGLT2i and lower extremity amputation outcomes, 12 RCTs and 18 observational studies were investigated.[14] Meta-analysis of 7 RCTs has brought absence of significant association as RR 1.28. From sub-group analysis, canagliflozin showed significantly increased risk in meta-analysis (RR 1.59) (2 RCTs), while dapagliflozin or empagliflozin did not show a significantly increased risk (2 RCTs each). Generally, no consistent evidence of increased risk was not found. Another study of adverse limb event was performed from 6 reports.[15] They include canagliflozin (CANVAS, CREDENCE), empagliflozin (EMPA-REG OUTCOME), ertugliflozin (VERTIS CV) and dapagliflozin (DECLARE-TIMI 58, DAPA-HF trials). Out of 51713 cases, 858 had amputation operations. The amputation ratio was 2.0/1.3% in SGLT-2i/control group, as pooled risk ratio of 1.24. From this analysis, SGLT-2i is not statistically associated with increased risks of amputation operations.

CONCLUSION

In summary, recent meaningful reports were introduced. The information will be hopefully useful for future research and practice for diabetes mellitus.

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