EnM
ENDOCRINOLOGY AND METABOLISM

Review Article

Endocrinol Metab 2022;37:415-429
https://doi.org/10.3803/EnM.2022.304
pISSN 2093-596X · eISSN 2093-5978

Extra-Glycemic Effects of Anti-Diabetic Medications: Two Birds with One Stone?

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The world is suffering from a rapid increase in the number of people with diabetes due to the increased prevalence of obesity and lengthened life span. Since the development of insulin thanks to the efforts of Prof. Banting and Dr. Best in 1922, for which they won the Nobel Prize, remarkable developments in anti-diabetic medications have dramatically lengthened the lifespan of patients with diabetes. However, the control rate of hyperglycemia in patients with diabetes remains unsatisfactory, since glycemic control requires both medication and lifestyle modifications to slow the deterioration of pancreatic beta-cell function and prevent diabetic complications. From the initial "triumvirate" to the "ominous octet," and now the "egregious eleven," the number of organs recognized as being involved in hyperglycemia and diabetes has increased with the development of anti-diabetic medications. Recent unexpected results from outcome trials of anti-diabetic medications have enabled anti-diabetic medications to be indicated for the prevention of chronic kidney disease and heart failure, even in patients without diabetes. In this review, I would like to summarize the extra-glycemic effects of anti-diabetic medications.

Keywords: Diabetes mellitus; Medication therapy management; Cardiovascular diseases; Heart failure; Diabetic nephropathies; Stroke; Osteoporosis

INTRODUCTION

According to the Diabetes Atlas, 537 million adults (20 to 79 years) are living with diabetes, corresponding to 1 in 10 of the global population, and this number is predicted to rise to 643 million by 2030 and 783 million by 2045 [1]. A serious problem is that one-third of the population with diabetes worldwide is living in the Asia-Pacific area, and the incidence of young-onset diabetes is increasing in this region [2]. As the gap of years lost due to disease between individuals with and without diabetes is becoming smaller and smaller (i.e., patients with diabetes are living as long as those without diabetes), the disease burden of young people with diabetes is tremendous and is becoming larger with time [3]. The selection of proper anti-diabetic medications earlier in the course of the disease could influence the rate of deterioration of insulin secretory function and the development of diabetic complications.

Since the finding and development of insulin thanks to the efforts of Prof. Banting and Dr. Best in 1922, for which they won the Nobel Prize, remarkable developments in anti-diabetic medications have occurred, giving hope to people with diabetes [4]. From the initial "triumvirate" to the "ominous octet" and now the "egregious eleven," the number of target organs known to be involved in the pathogenesis of type 2 diabetes mellitus (T2DM)

Received: 1 June 2022, **Revised:** 7 June 2022, **Accepted:** 12 June 2022

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has increased as more anti-diabetic medications have been developed [5,6]. Since the withdrawal of rosiglitazone from the market due to a signal regarding an increased risk for myocardial infarction (MI) in 2007, the U.S. Food and Drug Administration (FDA) has requested that results from a cardiovascular (CV) safety trial should be submitted for all new anti-diabetic medications that come to the market [7]. Although this policy has incurred astronomical expenses for pharmaceutical companies, it has also enabled the discovery of unexpected effects of novel anti-diabetic medications, leading to new indications for anti-diabetic medications in diseases other than diabetes.

In this review, I would like to summarize the extra-glycemic effects of anti-diabetic medications, mainly focusing on novel drugs that came out to the market within roughly the last decade.

CARDIOVASCULAR DISEASE

Since data from meta-analyses showed that rosiglitazone had issues related to an increased risk for MI, the FDA issued guidance for industry stating that all glucose-lowering drugs submitted for approval for T2DM should be associated with an acceptable level of CV risk in post-marketing trials involving CV outcomes [8]. Since then, numerous cardiovascular outcome trials (CVOTs) have been conducted for new drugs coming to the market, such as dipeptidylpeptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs), and sodium-glucose cotransporter type 2 (SGLT2) inhibitors.

Although the designs of CVOTs are somewhat similar regarding their primary outcome, which is major adverse cardiovascular events (MACE), including nonfatal MI, nonfatal stroke, or death from cardiovascular disease (CVD), with or without hospitalization for unstable angina, and their study populations (i.e., patients with or without established CVD), the findings from these trials have been different, not only in terms of the results for CV safety but also in the superiority of specific agents with respect to CV outcomes and in whether or not there are class effects.

For conventional anti-diabetic drugs, the results of studies on CV outcomes have been inconsistent [9]. No increased risk of MI or diabetes-related death was observed among participants assigned to insulin therapy as compared with conventional treatment in the UK Prospective Diabetes Study (UKPDS) 33 [10]. In later large clinical trials, such as the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial, similar neutral effects were observed [9,11,12]. For sulfonylureas, although there were some concerns regarding a potential association between the use of the first-generation sulfonylurea tolbutamide and an increased risk of CVD, no increased risk of MI or diabetes-related death was reported in UKPDS 33 participants assigned to a sulfonylurea as compared with conventional treatment [10,13]. Later studies that included trials of second- and third-generation sulfonylureas did not suggest an overall increased risk of MI or death from CVD [14]. In the UKPDS 34, metformin treatment was shown to be beneficial for CVD protection [15]. However, a meta-analysis that included the results of this trial and other, smaller trials concluded that owing to limited data, there was uncertainty as to whether metformin reduces the risk of CVD [16].

Although rosiglitazone, a thiazolidinedione (TZD), was reported to result in significantly increased risks of MI and death from CVD in a large meta-analysis of 42 trials, prompting guidance from the FDA in 2008 regarding trials assessing CV outcomes, TZDs are conventional drugs that have promising protective effects on CVD [17,18]. Another TZD, pioglitazone, was found to reduce the risk of secondary composite endpoint events in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) trial, which included death from any cause, nonfatal MI, and stroke over 3 years (Fig. 1) [19]. Pioglitazone treatment also showed a reduction in CV risk among patients with insulin resistance (but without diabetes) and a recent history of ischemic stroke in the Insulin Resistance Intervention after Stroke (IRIS) trial [20].

DPP-4 inhibitors were shown to be noninferior or safe as compared with placebo in CVOTs, with the exception of saxagliptin, which was associated with a significantly increased risk of hospitalization for heart failure (HF) in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial [21,22]. In the Cardiovascular Outcome Study of Linagliptin vs Glimepiride in Type 2 Diabetes (CAROLINA) study, linagliptin was found to be noninferior to glimepiride with respect to the risk of major adverse CV outcomes over 6 years [23].

GLP-1RAs show diversity regarding their superiority in terms of reduction of risk for primary composite endpoints as compared with placebo in patients with T2DM and established CVD or risk factors. In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, which included patients with T2DM and established CVD, significant risk reductions for primary outcomes were reported for liraglutide (hazard ratio [HR], 0.87; 95% confidence interval

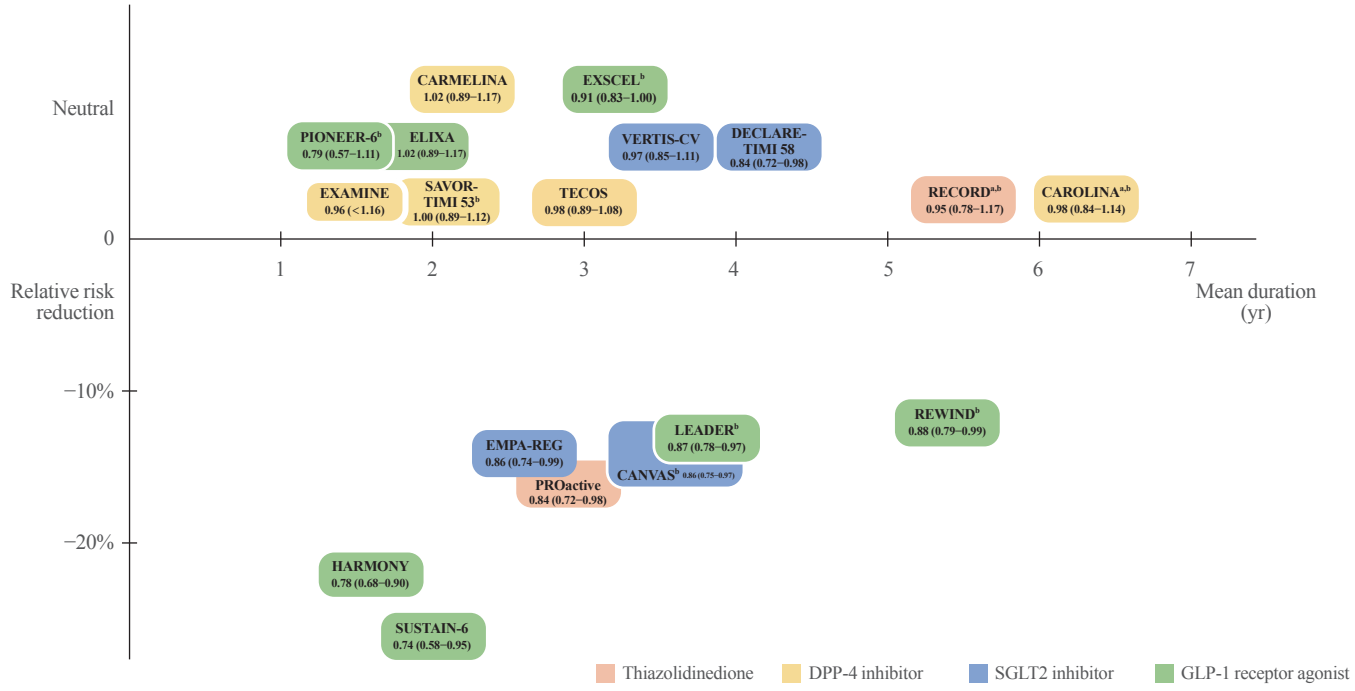

Fig. 1. Cardiovascular outcome trials of anti-diabetic drugs according to the mean duration of the trial and relative risk reduction of major adverse cardiovascular events. The numbers in boxes are hazard ratios and 95% confidence intervals of major adverse cardiovascular events, defined as the composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. PIONEER-6, Peptide Innovation for Early Diabetes Treatment 6; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; CARMELINA, Cardiovascular and Renal Microvascular Outcome Study With Linagliptin; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; SAVOR-TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53; EXSCEL, Exenatide Study of Cardiovascular Event Lowering Trial; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; DECLARE-TIMI 58, Dapagliflozin Effect on CardiovascuLAR Events-Thrombolysis in Myocardial Infarction 58; VERTIS-CV, Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial; RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes; CAROLINA, Cardiovascular Outcome Study of Linagliptin vs. Glimepiride in Type 2 Diabetes; HARMONY, Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; EMPA-REG, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; PROactive, PROspective pioglitAzone Clinical Trial In macroVascular Events; CANVAS, Canagliflozin Cardiovascular Assessment Study; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; REWIND, Dulaglutide and cardiovascular outcomes in type 2 diabetes; DPP-4, dipeptidylpeptidase-4; SGLT2, sodium-glucose cotransporter type 2; GLP-1, glucagon-like peptide-1. [a]Comparator is another anti-diabetic medication; [b]Includes primary prevention population.

[CI], 0.78 to 0.97) versus placebo on top of standard of care (Fig. 1) [24]. In the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) trial, 3,297 patients with T2DM were treated with injectable semaglutide or placebo, and semaglutide showed a significant reduction for primary three-point MACE (HR, 0.74; 95% CI, 0.58 to 0.95) [25]. In the Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND) trial, which included 9,901 T2DM patients who were largely at high risk for CVD, with only 32% having established CVD, the use of dulaglutide resulted in a significant reduction in the composite CV outcome (HR, 0.88; 95% CI, 0.79 to 0.99) [26]. However, the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial, which tested the effect of extended-release exenatide once weekly, did not show superiority for CV outcomes versus placebo treatment, and the same occurred for lixisenatide in the the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial [27,28]. To summarize, a meta-analysis summarizing these randomized controlled trials (RCTs) with GLP-1RAs showed significant reductions of MACE by 12%, CV death by 11%, stroke by 16%, MI by 9%, and all-cause death by 12% [29]. Finally, in the Peptide Innovation for Early

Diabetes Treatment 6 (PIONEER 6) trial, oral semaglutide treatment showed a non-significant 21% reduction in MACE compared with a placebo group in 1.3 years of follow-up in T2DM patients [30].

The robust effect of SGLT2 inhibitors on CV outcomes seems to be a class effect. The first trial to show CV efficacy of an SGLT2 inhibitor was Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial, which randomized 7,020 patients with T2DM and high CV risk to empagliflozin or placebo [31]. Over a median follow-up of 3.1 years, empagliflozin reduced the occurrence of the primary three-point MACE outcome by 14%; these were the first results showing a significant effect of an SGLT2 inhibitor on CVD (Fig. 1). The Dapagliflozin Effect on CardiovascuLAR Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial randomized 17,160 patients at high risk for CVD (only 40% with established CVD) to dapagliflozin versus placebo on top of standard T2DM treatment [32]. Although dapagliflozin showed noninferiority, but not superiority, to placebo for the risk of the three-point MACE primary outcome, dapagliflozin significantly reduced the incidence of the co-primary outcome of death from CVD or hospitalization for HF by 17%, which was mainly driven by a 27% reduction in the risk of HF hospitalization. In another clinical trial of an SGLT2 inhibitor, canagliflozin, the Canagliflozin Cardiovascular Assessment Study (CANVAS) trial, 10,142 T2DM patients with high CVD risk were randomized to canagliflozin versus placebo, and canagliflozin reduced the risk of the three-point MACE primary outcome by 14% [33]. Finally, the Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS-CV) trial randomized 8246 T1DM patients with CVD to ertugliflozin versus placebo; ertugliflozin treatment was noninferior, but failed to show superiority, for the three-point MACE primary outcome [34]. A meta-analysis pooling data from the EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, VERTIS-CV, and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trials showed that SGLT2 inhibitors reduced the risk of the MACE by 10%, CV death by 5% and MI by 9%, suggesting the class effect of SGLT2 inhibitors on CVD risk reduction [35].

Based on these evidences, recent guidelines recommend that SGLT2 inhibitor or GLP-1RA with proven CV benefit be preferentially prescribed for diabetic patients with atherosclerotic cardiovascular disease (ASCVD) or high risk for ASCVD [36,37].

ISCHEMIC STROKE

Not many clinical trials of anti-diabetic agents have analyzed ischemic stroke as the primary outcome. In the UKPDS, metformin treatment to overweight patients with newly diagnosed T2DM reduced stroke risk more than sulfonylurea treatment or insulin [15]. In the UKPDS, the effects of sulfonylurea on ischemic stroke showed a negative trend or less favorable outcomes than other comparators [10]. In addition, insulin treatment had no effect on the risk of ischemic stroke in the same trial. DPP-4 inhibitors have shown generally neutral effects on ischemic stroke versus placebo, with the exception that an RCT showed a lower number of nonfatal strokes in the linagliptin-treated group compared with glimepiride [38-41].

Pioglitazone, a TZD, has shown favorable effects on protection against ischemic stroke. In the PROactive study, 5238 T2DM patients with established CVD were assigned to pioglitazone or placebo [19]. Pioglitazone did not reduce the risk of the primary endpoints and did not reduce the risk of ischemic stroke in the total study population; however, pioglitazone treatment reduced the risk of recurrent stroke by 47% in the subgroup with a history of ischemic stroke or transient ischemic attack (TIA), suggesting its effect on secondary prevention of ischemic stroke [42]. Pioglitazone was also recently shown to reduce the risk of CVD in patients with insulin resistance, but not diabetes, who had a history of ischemic stroke or TIA in the IRIS trial [20]. After a median follow-up of 4.8 years, the risk of the primary outcome, MI or stroke, was reduced in the pioglitazone group by 24% compared to the placebo group, consistently showing positive effects of pioglitazone in this study population.

Newer drugs, in the GLP-1RA and SGLT2 inhibitor classes, seem not to be effective for protection against ischemic stroke or TIA. However, treatment with semaglutide, a GLP-1RA, in the SUSTAIN-6 trial reduced the risk of ischemic stroke by 39% versus placebo [25]. This effect does not seem to be a class effect.

HEART FAILURE

Some diabetes drugs are considered to have a class effect on HF despite different individual effects within the same class. As demonstrated by previous studies and meta-analyses, TZD is not indicated in patients with HF [43]. Metformin used to be contraindicated in patients with HF, although this restriction was removed in 2006 by the FDA [44]. A meta-analysis of nine

cohort studies with 34,000 patients revealed that metformin administration reduced the risk of HF by 20%, with a risk ratio (RR) of 0.80 (95% CI, 0.74 to 0.87) [45].

Although no consensus has yet been reached regarding the effect of sulfonylureas on HF, no significant increase in the risk of HF has been observed in the insulin supplement therapy group administered sulfonylureas in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) trial, which investigated CV outcomes in T2DM patients who underwent intensive medical therapy and percutaneous coronary intervention or only medical therapy [46]. In the recently published CAROLINA trial, which compared the effects of glimepiride (a sulfonylurea) and linagliptin (a DPP-4 inhibitor) on HF, no significant increase in HF-induced hospitalization was observed in the glimepiride group [23]. However, the data derived by analyzing the U.S. Veterans Affairs Hospital Database revealed that the risk of HF-induced hospitalization was 1.3-fold higher in patients with diabetes exposed to a sulfonylurea than in those exposed to metformin [47]. However, since the CAROLINA trial compared a sulfonylurea with metformin, it is difficult to determine the HF risk factors of sulfonylureas themselves.

The effect of DPP-4 inhibitors on HF is difficult to conclusively regard as a class effect. In the SAVOR-TIMI 53 trial, a saxagliptin CVOT, the risk of HF increased in the saxagliptin group [22]. However, a meta-analysis of a collection of CVOTs of DPP-4 inhibitors reported that DPP-4 inhibitors do not increase the risk of HF [48].

SGLT2 inhibitors have been reported to decrease the risk of HF in patients in three CVOTs, namely the EMPA-REG OUTCOME, DECLARE-TIMI 58, and CANVAS trials [49]. In a meta-analysis of these CVOTs, SGLT2 inhibitors were found to reduce the risk of HF by 31%. This effect was commonly manifested in patients with and without a history of HF, which leads to the assumption that the effect of SGLT2 inhibitors on HF is very strong. What is more, the effect of SGLT2 inhibitors on HF was found to be stronger in patients with more impaired kidney function, which suggests that SGLT2 inhibitors contribute to breaking the vicious cycle of the so-called "cardio-renal spectrum," in which the heart and kidney mutually affect each other in patients with T2DM [50].

The significant effect of SGLT2 inhibitors on HF in patients with T2DM raised the question of whether they would have the same effect in HF patients without diabetes. In two recently published CVOTs, the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and Reduced Ejection Fraction (EMPEROR-Reduced) and the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trials, HF patients with and without diabetes were equally administered SGLT2 inhibitors, and both studies reported a significantly reduced risk of HF in both groups of patients [51,52]. In addition, a meta-analysis of these two studies together found that SGLT2 inhibitors reduced the risk of HF by 25%, with no significant difference between patients with and without diabetes, demonstrating the potential of SGLT2 inhibitors to change the therapeutic landscape in HF patients in the future [53]. A recently published Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) study reported that dapagliflozin significantly reduced the risk of CV death and hospitalization for HF even in HF patients with retained ejection fraction [54]. In addition, treatment with sotagliflozin, an SGLT1/2 dual inhibitor, in patients with diabetes and recent worsening HF, resulted in a significantly lower total number of CV death and hospitalizations and urgent visits for HF than placebo, finalizing the class effect of SGLT2 inhibitor in protection against HF [55].

Regarding the effect of GLP-1RAs on HF, they are considered to have a positive effect on the myocardium via their anti-inflammatory effects, increased glucose utilization, improved left ventricular function, and decreased ischemic damage [56]. The GLP-1RA CVOTs conducted thus far have reported varying effects on HF. In a meta-analysis that investigated seven different GLP-1RA CVOTs together, the odds ratio for HF was 0.91 (95% CI, 0.83 to 0.99), corresponding to about a 9% risk reduction [29].

Based on the above mentioned evidences, recent guidelines recommend that SGLT2 inhibitors with proven benefit be preferentially prescribed for diabetic patients with HF [36,37].

CHRONIC KIDNEY DISEASE

The goal of renoprotection is to slow the loss of functioning nephrons, thereby preserving glomerular and tubular function to delay the onset of end-stage kidney disease and renal death. Microalbuminuria is often the earliest manifestation of diabetic kidney disease and is predictive of progression. The effects of anti-diabetic medications on the kidney could be divided into three categories: drugs that deteriorate renal function, drugs that have neutral effects on renal function, and drugs with protective effects on renal function.

Among the traditional anti-diabetic medications, metformin is a drug with a narrow safety range, so that the drug has to be prescribed with caution in patients with mild to moderate chronic

kidney disease (CKD) [57]. Sulfonylureas also need to be used with caution in patients with CKD, although some drugs in this class could be used in CKD patients [36]. TZD is a drug with neutral or a slightly better profile in patients with reduced renal function, since TZD is known to decrease microalbuminuria in patients with diabetes [58,59]. Insulin could be used safely in patients with CKD, since insulin does not affect renal function.

Most information on the renal effects of DPP-4 inhibitors comes from secondary analyses from CVOTs [60]. Among the many DPP-4 inhibitors currently available on the market, only the trials of linagliptin and saxagliptin included prespecified secondary kidney disease outcomes. In the Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) trial, in which the effects of linagliptin treatment were evaluated in 6,991 patients with T2DM and high CVD or CKD risk, a secondary kidney outcome (renal failure, renal death, or sustained estimated glomerular filtration rate [eGFR] decline of ≥40% from baseline) did not differ between linagliptin and placebo [61]. However, linagliptin treatment significantly improved albuminuria progression compared to placebo. Saxagliptin improved albumin-creatinine ratio, even in the normoalbuminuric range, without affecting eGFR in the analysis of renal outcomes of SAVOR-TIMI 53 trial [62]. Other DPP-4 inhibitors did not show any significant improvements in renal function or protection against progression of CKD in secondary analyses of their CVOTs. Gemigliptin showed an albuminuria-reducing effect in the Efficacy and safety of gemigliptin in type 2 diabetes patients with moderate to severe renal impairment (GUARD) study, which evaluated the efficacy and safety of gemigliptin in patients with moderate to severe renal impairment, although it did not show any difference compared to linagliptin in a 40-week extension study [63,64].

Secondary analyses from major clinical trials of SGLT2 inhibitors have suggested that they display renal benefits, with a slower decline in the eGFR and less frequent development of end-stage renal disease [65]. The CREDENCE trial was the first renal outcome trial of an anti-diabetic medication, in which 4401 patients with diabetes and albuminuric CKD were randomized to canagliflozin (100 mg) or placebo [66]. The relative risk of the primary outcome (a composite of end-stage kidney disease, a doubling of the serum creatinine level, or death from renal or CV causes) was 30% lower in the canagliflozin group than in the placebo group, and CVD events were also less common in the canagliflozin group. The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial, which randomized 4,304 patients with albuminuric CKD with or without T2DM to dapagliflozin (10 mg) and placebo, extended the results of the CREDENCE study, with a 39% reduction in the primary endpoint of a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or CV causes in the dapagliflozin-treated group compared to the placebo group, suggesting that the renoprotective effects of SGLT2 inhibitors may be a class effect regardless of the presence of diabetes [67]. The Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY) trial, which analyzed the effects of empagliflozin in patients with CKD with or without diabetes, was stopped early due to the evidence of significant efficacy, supporting the renoprotective effects of SGLT2 inhibitors in those with or without diabetes.

Unlike SGLT2 inhibitors, there are no dedicated large clinical trials of GLP-1RAs with renal composite primary outcomes. However, favorable renal effects of GLP-1RAs could be derived from analyses of the results of secondary outcome measures from exploratory analyses in CVOTs using urinary albumin-creatinine ratio (UACR) and eGFR measurements. In the ELIXA trial, lixisenatide reduced the progression of UACR in macroalbuminuric patients and was associated with a lower risk of new-onset macroalbuminuria [68]. In the LEADER and SUSTAIN-6 trials, treatment with liraglutide and semaglutide reduced the risk of CKD development and progression; these benefits mainly derived from the reduction of new-onset macroalbuminuria [24,25]. In the Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7) trial, dulaglutide reduced the UACR and preserved renal function compared with insulin glargine in patients with macroalbuminuria and CKD stages 3b and 4 [69]. A meta-analysis analyzing kidney outcomes in the seven GLP-1RA CVOTs showed that GLP-1RA treatment reduced the incidence of a broad composite renal outcome by 17% [29]. The ongoing A Research Study to See How Semaglutide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease (FLOW) trial (NCT03819153), the first GLP-1RA trial targeting renal outcomes, which is investigating the effect of semaglutide on renal outcomes in patients with T2DM and CKD, will add further information on the renal benefits of GLP-1RAs.

Based on these evidences, recent guidelines recommend that SGLT2 inhibitor with proven benefit of reducing CKD progression or GLP-1RA with proven CVD benefit be preferentially prescribed for diabetic patients with CKD and albuminuria [36,37].

NAFLD/NASH

Nonalcoholic fatty liver disease (NAFLD) and diabetes share common metabolic abnormalities, such obesity, insulin resistance, and metabolic syndrome, and are comorbid conditions to each other [70]. The concomitant presence of both diseases predisposes affected individuals to the aggravation of each disease. The presence of NAFLD in patients with T2DM increase the risk of the macrovascular and microvascular complications of diabetes, and the presence of T2DM in patients with NAFLD exacerbates the progression from NAFLD to nonalcoholic steatohepatitis (NASH) and fibrosis. Therefore, drugs that treat diabetes might affect NAFLD status.

Metformin, which is an insulin sensitizer and the first-line therapy for T2DM, was suggested to offer histologic benefits in earlier open-label studies, but recent RCTs showed no significant effects against NAFLD [71-73]. Recent meta-analyses failed to show any histologic improvement with metformin treatment in patients with NAFLD and NASH [74,75]. Therefore, the guidelines do not recommend metformin as treatment for NAFLD [76,77]. Not enough data are available to determine the effects of DPP-4 inhibitors on NAFLD or NASH.

Pioglitazone, a TZD, is an insulin sensitizer that is known to improve insulin resistance via preventing lipolysis and reducing circulating free fatty acid levels, protecting the target organs from lipotoxicity [78]. Pioglitazone has numerous evidence supporting its ability to improve steatosis and resolve liver stiffness in patients with NAFLD. In the Pioglitazone versus vitamin E versus placebo for the treatment of non-diabetic patients with non-alcoholic steatohepatitis (PIVENS) trial, which evaluated the effects of pioglitazone and vitamin E on NAFLD, pioglitazone treatment improved steatohepatitis, ballooning necrosis, and inflammation in biopsied patients [79]. A meta-analysis showed that pioglitazone improved cases of advanced fibrosis in patients with NASH and T2DM [80]. Therefore, many guidelines recommend pioglitazone as the first-line therapy for patients with NAFLD and T2DM [76,77]. Lobeglitazone, a novel TZD developed by the ChongKunDang pharmaceutical company in Seoul, Korea, has been shown to improve hepatic steatosis in animal studies, and in a multicenter, prospective, open-label clinical trial, lobeglitazone treatment (0.5 mg daily) for 24 weeks improved liver enzymes and ameliorated hepatic fat content as assessed by liver elastography in patients with T2DM and NAFLD [81,82].

GLP-1RAs are expected to improve NAFLD and NASH, since they reduce body weight and thus help restore insulin resistance. Liraglutide showed efficacy against NAFLD in the Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN) study, which was an RCT that assessed the effect of liraglutide (1.8 mg daily) for 48 weeks in 52 patients with biopsy-proven NASH, with greater resolution of steatohepatitis and less progression of fibrosis [83]. Semaglutide, a weekly GLP-1RA, has shown efficacy against NAFLD [84]. In a 72-week phase 2 trial, semaglutide treatment with subcutaneous dose of 0.1, 0.2, or 0.4 mg in patients with biopsy-proven NASH and liver fibrosis resulted in a significantly higher percentage of patients with NASH resolution than placebo. The guidelines as yet do not recommend GLP1-RAs as treatment for NAFLD.

SGLT2 inhibitors are another class of promising drugs for treatment of NAFLD and NASH, since they promote weight loss and improve insulin resistance. In the A Study to Investigate Effects of Omega-3 Carboxylic Acids and Dapagliflozin on Liver Fat Content in Diabetic Patients (EFFECT-II) study, dapagliflozin significantly reduced liver fat content as assessed by magnetic resonance imaging (MRI)-derived proton density fat fraction (PDFF) [85]. In Effect of Empagliflozin on Liver Fat Content in Patients With Type 2 Diabetes (E-LIFT) trial, empagliflozin (10 mg) daily significantly reduced liver fat as measured by MRI-PDFF in patients with T2DM and NAFLD [86]. Pooled data from four clinical trials of canagliflozin showed significant reductions in liver enzymes compared with placebo in patients with T2DM, and in a small, prospective study, canagliflozin treatment significantly reduced hepatic fat fraction as measured by MRI in patients with T2DM and NAFLD [87]. However, the guidelines do not yet recommend SGLT2 inhibitors for the treatment of NAFLD.

CANCER

Cancer incidence appears to be increased in both patients with type 1 diabetes mellitus (T1DM) and T2DM [88]. A meta-analysis has shown that the presence of diabetes is associated with a 10% increase in the relative risk of cancer, with elevated risks for hepatocellular, hepatobiliary, pancreas, breast, ovarian, endometrial, and gastrointestinal cancers [89]. The biological mechanisms underlying the increased cancer risk in patients with diabetes cannot be explained by a single mechanism and are very diverse. Supraphysiological concentrations of insulin and glycemia expose the body to potent growth factors and energy sources for cancer [88]. Some researchers have recommended that cancer screening should be included in routine dia-

betes assessments.

As diabetes itself is associated with an increased risk of cancer development, medications that control diabetes could have diverse effects on cancer. Insulin is the mainstay treatment, both for T1DM and eventually for T2DM. There have long been concerns that exogenous insulin could increase cancer risk. The ORIGIN trial randomized 12,537 subjects with impaired glucose tolerance or T2DM to insulin glargine or standard care to examine CV outcomes and the incidence of cancer [11]. The results showed no increased CVD and cancer risk in the insulin glargine treatment group versus placebo group. At present, it is not conclusive whether exogenous insulin treatment increases malignancy risk; however, the results of the ORIGIN trial have provided more evidence on the safety of insulin in patients with T2DM regarding cancer risk.

Among other anti-diabetic medications, preclinical studies have demonstrated antineoplastic effects of metformin, an oral biguanide, and these findings have been supported by several epidemiological studies and meta-analyses [90,91]. Metformin is known to exert anti-cancer effects via anti-angiogenic activity, antiproliferative activity achieved by LBK-dependent 5'-adenosine monophosphate-activated protein kinase activation, inhibition of signal transducer and activator of transcription 3 activation, and anti-apoptotic activity [92]. However, no randomized clinical trials of metformin have been performed on its protective effects against cancer. Although pioglitazone, a TZD, was shown to increase bladder cancer risk in initial studies, subsequent large studies failed to confirm the previous results [19,93-96].

No definitive evidence exists that anti-diabetic medications increase or decrease the risk of cancer. Retrospective cohort studies have shown that incretin-based therapies, such as DPP-4 inhibitors and GLP-1RAs, increased the risk of pancreatic cancer [97]. However, meta-analyses of 33 studies did not show any relationship between incretin-based therapies and pancreatic cancer [98,99]. In the SCALE trial, which assessed the effect of liraglutide (3 mg daily) for the treatment of obesity, the active group had a numerically higher but insignificantly increased incidence of breast cancer, suggesting a possible signal for increased risk of breast cancer in a liraglutide treatment group [100]. However, according to a recent systematic review and meta-analysis of 52 trials, GLP-1RAs treatment did not show any increase in breast cancer or benign breast neoplasms compared with comparators [101]. A recently published systematic review and meta-analysis that analyzed 46 RCTs reporting cancer events in T2DM patients treated with SGLT2 inhibitors with a mean trial duration of 61 weeks showed no significantly increased risk of overall cancer among individuals with type diabetes using SGLT2 inhibitors [102]. Future long-term prospective studies and post-marketing surveillance studies are warranted.

OSTEOPOROSIS

In 2006, an unexpected finding of increased risk of bone fractures with a TZD was first reported in the results of A diabetes outcome progression trial (ADOPT), a large-scaled trial comparing rosiglitazone with metformin and glyburide monotherapy in patients with recently diagnosed T2DM [103]. Women randomized to rosiglitazone showed a two-fold increase in the incidence of bone fractures in comparison with other treatment groups, whereas no difference was found in men. *Post hoc* analyses published after those initial results reported that pioglitazone had similar effects on fractures to those of rosiglitazone, suggesting a deleterious class effect of TZD on bone [104].

The mechanism of the deleterious effect of TZD on bone metabolism could be derived from the activity of peroxisome proliferator-activated receptor-gamma (PPAR-γ) on bone, as TZD is a PPAR-γ agonist [105]. As PPAR-γ is a nuclear receptor that acts on adipogenesis and determines the terminal differentiation of adipocytes, the activation of PPAR-γ leads to differentiation of mesenchymal stromal cells to adipocytes, but not osteoblasts. This process leads to a decrease in bone formation and an increase in bone marrow fat, and PPAR-γ activation also promotes osteoclastogenesis and increases bone resorption. The effects of TZDs on bone metabolism should be carefully monitored, and patients at high risk for bone fractures should avoid TZD or, if used, they should be strictly monitored for bone fracture risk.

As insulin is known to have anabolic effects on bone, one could expect that insulin treatment could benefit bone metabolism. However, observational studies have reported evidence showing that insulin treatment was associated with an increased risk of bone fractures [106,107]. However, from a clinical standpoint, the increased bone fracture risk in insulin-treated patients could be attributed to increased hypoglycemia in insulin-treated patients, since in the ORIGIN study with insulin glargine, in which the incidence of hypoglycemia was remarkably lower than in most other studies, there was no increase in the risk of bone fractures [11]. Insufficient data exist to support conclusions regarding the effects of other older anti-diabetic drugs on bone.

Among newer anti-diabetic medications, incretin-based

agents such as GLP-1RAs and DPP-4 inhibitors have been shown to be promising, since GLP-1RAs were shown to increase bone density in rodent models of osteopenia [108,109]. DPP-4 inhibitors showed a reduction in the incidence of fractures in a meta-analysis of short-term randomized trials [110]. However, two large-scale CVOTs with DPP-4 inhibitors failed to detect any reduction in the fracture risk [22,38]. Although GLP-1RAs have shown benefits on bone in animal models, the results of a meta-analysis of GLP-1RAs did not show any beneficial or harmful effects on bone [111].

SGLT2 inhibitors show diverse results on bone according to previous studies. A systematic review suggested that canagliflozin may be linked to an increased fracture rate [112]. However, this effect cannot be considered to be a class effect, and more studies should be performed to draw any conclusions.

In a very recent systematic review and network meta-analysis, the authors compared the effects of all available anti-diabetic medications on fracture risk in T2DM patients [113]. In 117 eligible RCTs with 221,364 participants, some drugs (omarigliptin, sitagliptin, vildagliptin, saxagliptin, empagliflozin, ertugliflozin, rosiglitazone, pioglitazone, and nateglinide) showed increased risk of fractures, whereas others (dulaglutide, exenatide, liraglutide, semaglutide, lixisenatide, linagliptin, alogliptin, canagliflozin, dapagliflozin, glipizide, gliclazide, glibenclamide, glimepiride, metformin, and insulin) showed benefits. However, to draw clear conclusions, more large-scale studies should be performed with bone fracture as an outcome.

NEURODEGENERATIVE DISEASES

Some anti-diabetic medications are known to decrease dementia risk. In a recent meta-analysis of 10 studies that analyzed the

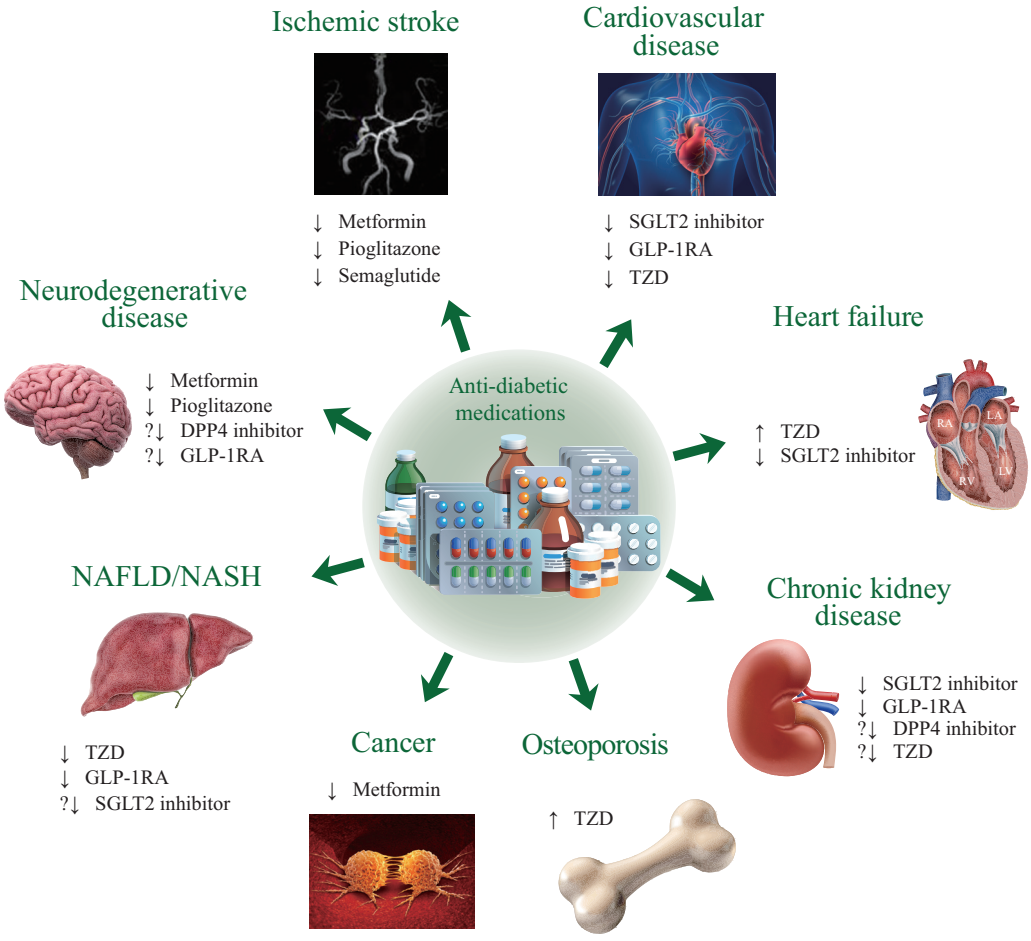

Fig. 2. Extra-glycemic effects of anti-diabetic medications. GLP-1RA, glucagon-like peptide receptor agonist; DPP-4, dipeptidyl peptidase 4; SGLT2, sodium-glucose cotransporter 2; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; TZD, thiazolidinedione.

risk of dementia with anti-diabetic agents compared to no treatment or as add-on therapy to prior care, anti-diabetic agents in general were not associated with incident dementia [114]. A slightly increased risk was observed with insulin (RR, 1.21; 95% CI, 1.06 to 1.39), and potentially protective effects with TZD exposure (RR, 0.71; 95% CI, 0.55 to 0.93). The hypothesis that PPAR-γ agonists might be useful for the treatment of Alzheimer's disease is in part linked to their positive influence on cerebral glucose metabolism, lipid metabolism, and inflammation [115,116]. However, a recent phase 3 clinical trial that evaluated the effect of low-dose pioglitazone on delaying the onset of mild cognitive impairment in at-risk participants failed to show significant efficacy [117].

There exists some evidence for the efficacy of old and new anti-diabetic medications on Parkinson's disease (PD). Metformin is known to exert protective effects on PD in T2DM patients via AMPK-mediated autophagy activation, decreased oxidative stress, and facilitation of mitochondrial function [118]. However, a recent meta-analysis failed to show any correlation between metformin therapy and PD development [119]. Although there have not yet been any clinical trials, incretin therapies, such as GLP-1RAs and DPP-4 inhibitors, have shown protective effects against PD in animal studies [120-122]. These effects should be confirmed in human studies.

CONCLUSIONS

The field of diabetes therapy is entering a new era since the development of GLP-1RAs and SGLT2 inhibitors. New evidence of the novel efficacy of these agents is pouring out every day in the literature. These drugs are providing hope for patients with renal and heart diseases, not only patients with diabetes. As mentioned above, as the age of onset of diabetes is becoming younger, the selection of appropriate anti-diabetic agents in a personalized manner is becoming extremely important for the preservation of pancreatic beta-cell function and prevention of diabetic complications.

To summarize, thanks to the tremendous number of clinical trials to date, we are fully aware that the anti-diabetic medications we are prescribing not only have anti-glycemic effects, but also protective effects against damage to other organs not directly related to diabetes (Fig. 2). Therefore, we could benefit from prescribing these drugs to our patients with diabetes with the expectation of additional benefits for protection of multiple organs in the body.

I am extremely grateful to researchers and pharmaceutical companies for producing these powerful and efficacious anti-diabetic drugs that not only lower glucose levels, but also save the lives of our patients with diabetes, since this disease is not curable—instead, it is a disease of control requiring lifelong struggle and treatment. Every day, I hope to read news describing the greater efficacy of existing anti-diabetic medications and development of novel, safe anti-diabetic medications, which could provide more hope for a healthier remaining lifetime in our patients.

CONFLICTS OF INTEREST

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

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REFERENCES

1. IDF Diabetes Atlas. Diabetes around the world in 2021 [Internet]. Brussels: International Diabetes Federation; 2022 [cited 2022 Jun 15]. Available from: https://diabetesatlas.org/.
2. Rhee EJ. Diabetes in Asians. Endocrinol Metab (Seoul) 2015;30:263-9.
3. Rhee EJ, Jung I, Kwon H, Park SE, Kim YH, Han KD, et al. Increased mortality burden in young Asian subjects with dysglycemia and comorbidities. J Clin Med 2020;9:1042.
4. Lee SH, Yoon KH. A century of progress in diabetes care with insulin: a history of innovations and foundation for the future. Diabetes Metab J 2021;45:629-40.
5. Defronzo RA. Banting lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009;58:773-95.
6. Schwartz SS, Epstein S, Corkey BE, Grant SF, Gavin JR 3rd, Aguilar RB. The time is right for a new classification system for diabetes: rationale and implications of the β-cell-centric classification schema. Diabetes Care 2016;39:179-86.
7. Hiatt WR, Kaul S, Smith RJ. The cardiovascular safety of diabetes drugs: insights from the rosiglitazone experience. N Engl J Med 2013;369:1285-7.
8. Food and Drug Administration. Guidance for industry. Diabetes mellitus: evaluating cardiovascular risk in new antidi-

abetic therapies to treat type 2 diabetes [Internet]. Silver Spring: FDA; 2008 [cited 2022 Jun 15]. Available from: https://www.fda.gov/media/71297/download.
9. Zhu J, Yu X, Zheng Y, Li J, Wang Y, Lin Y, et al. Association of glucose-lowering medications with cardiovascular outcomes: an umbrella review and evidence map. Lancet Diabetes Endocrinol 2020;8:192-205.
10. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.
11. ORIGIN Trial Investigators, Gerstein HC, Bosch J, Dagenais GR, Diaz R, Jung H, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012;367:319-28.
12. Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, et al. Efficacy and safety of degludec versus glargine in type 2 diabetes. N Engl J Med 2017;377:723-32.
13. Meinert CL, Knatterud GL, Prout TE, Klimt CR. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. Diabetes 1970;19:Suppl:789-830.
14. Varvaki Rados D, Catani Pinto L, Reck Remonti L, Bauermann Leitao C, Gross JL. The association between sulfonylurea use and all-cause and cardiovascular mortality: a meta-analysis with trial sequential analysis of randomized clinical trials. PLoS Med 2016;13:e1001992.
15. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854-65.
16. Griffin SJ, Leaver JK, Irving GJ. Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes. Diabetologia 2017;60:1620-9.
17. 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.
18. 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.
19. 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 randomised controlled trial. Lancet 2005;366:1279-89.
20. 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 2016;374:1321-31.
21. Scheen AJ. Cardiovascular effects of new oral glucose-lowering agents: DPP-4 and SGLT-2 inhibitors. Circ Res 2018;122:1439-59.
22. 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.
23. Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. JAMA 2019;322:1155-66.
24. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311-22.
25. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834-44.
26. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019;394:121-30.
27. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017;377:1228-39.
28. Pfeffer 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.
29. Kristensen SL, Rorth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol 2019;7:776-85.
30. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl

J Med 2019;381:841-51.
31. 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.
32. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347-57.
33. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57.
34. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med 2020;383:1425-35.
35. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney D, Dagogo-Jack S, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. JAMA Cardiol 2021;6:148-58.
36. American Diabetes Association Professional Practice Committee, Draznin B, Aroda VR, Bakris G, Benson G, Brown FM, et al. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2022. Diabetes Care 2022;45(Suppl 1):S125-43.
37. Hur KY, Moon MK, Park JS, Kim SK, Lee SH, Yun JS, et al. 2021 Clinical practice guidelines for diabetes mellitus of the Korean Diabetes Association. Diabetes Metab J 2021;45:461-81.
38. 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.
39. Papagianni M, Tziomalos K. Cardiovascular effects of dipeptidyl peptidase-4 inhibitors. Hippokratia 2015;19:195-9.
40. Leiter LA, Teoh H, Braunwald E, Mosenzon O, Cahn A, Kumar KM, et al. Efficacy and safety of saxagliptin in older participants in the SAVOR-TIMI 53 trial. Diabetes Care 2015;38:1145-53.
41. 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;380:475-83.
42. Wilcox R, Bousser MG, Betteridge DJ, Schernthaner G, Pirags V, Kupfer S, et al. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). Stroke 2007;38:865-73.
43. Singh S, Loke YK, Furberg CD. Thiazolidinediones and heart failure: a teleo-analysis. Diabetes Care 2007;30:2148-53.
44. Inzucchi SE, Masoudi FA, McGuire DK. Metformin in heart failure. Diabetes Care 2007;30:e129.
45. Eurich DT, Weir DL, Majumdar SR, Tsuyuki RT, Johnson JA, Tjosvold L, et al. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34,000 patients. Circ Heart Fail 2013;6:395-402.
46. BARI 2D Study Group, Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med 2009;360:2503-15.
47. Roumie CL, Min JY, D'Agostino McGowan L, Presley C, Grijalva CG, Hackstadt AJ, et al. Comparative safety of sulfonylurea and metformin monotherapy on the risk of heart failure: a cohort study. J Am Heart Assoc 2017;6:e005379.
48. Liu D, Jin B, Chen W, Yun P. Dipeptidyl peptidase 4 (DPP-4) inhibitors and cardiovascular outcomes in patients with type 2 diabetes mellitus (T2DM): a systematic review and meta-analysis. BMC Pharmacol Toxicol 2019;20:15.
49. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393:31-9.
50. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017;136:e137-61.
51. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383:1413-24.
52. McMurray J, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995-2008.
53. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. SGLT2 inhibitors in patients with heart fail-

ure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet 2020; 396:819-29.
54. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Bohm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385:1451-61.
55. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med 2021;384:117-28.
56. Drucker DJ. The cardiovascular biology of glucagon-like peptide-1. Cell Metab 2016;24:15-30.
57. Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. JAMA 2014;312:2668-75.
58. Ma Y, Shi M, Wang Y, Liu J. PPARγ and its agonists in chronic kidney disease. Int J Nephrol 2020;2020:2917474.
59. Sarafidis PA, Stafylas PC, Georgianos PI, Saratzis AN, Lasaridis AN. Effect of thiazolidinediones on albuminuria and proteinuria in diabetes: a meta-analysis. Am J Kidney Dis 2010;55:835-47.
60. Alicic RZ, Cox EJ, Neumiller JJ, Tuttle KR. Incretin drugs in diabetic kidney disease: biological mechanisms and clinical evidence. Nat Rev Nephrol 2021;17:227-44.
61. Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. JAMA 2019;321:69-79.
62. Mosenzon O, Leibowitz G, Bhatt DL, Cahn A, Hirshberg B, Wei C, et al. Effect of saxagliptin on renal outcomes in the SAVOR-TIMI 53 trial. Diabetes Care 2017;40:69-76.
63. Yoon SA, Han BG, Kim SG, Han SY, Jo YI, Jeong KH, et al. Efficacy, safety and albuminuria-reducing effect of gemigliptin in Korean type 2 diabetes patients with moderate to severe renal impairment: a 12-week, double-blind randomized study (the GUARD Study). Diabetes Obes Metab 2017;19:590-8.
64. Han SY, Yoon SA, Han BG, Kim SG, Jo YI, Jeong KH, et al. Comparative efficacy and safety of gemigliptin versus linagliptin in type 2 diabetes patients with renal impairment: a 40-week extension of the GUARD randomized study. Diabetes Obes Metab 2018;20:292-300.
65. Rhee JJ, Jardine MJ, Chertow GM, Mahaffey KW. Dedicated kidney disease-focused outcome trials with sodium-glucose cotransporter-2 inhibitors: lessons from CREDENCE and expectations from DAPA-HF, DAPA-CKD, and EMPA-KIDNEY. Diabetes Obes Metab 2020;22 Suppl 1:46-54.
66. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink H, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380: 2295-306.
67. Heerspink H, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436-46.
68. Muskiet M, Tonneijck L, Huang Y, Liu M, Saremi A, Heerspink H, et al. Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: an exploratory analysis of the ELIXA randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 2018;6:859-69.
69. Tuttle KR, Lakshmanan MC, Rayner B, Busch RS, Zimmermann AG, Woodward DB, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. Lancet Diabetes Endocrinol 2018;6:605-17.
70. Rhee EJ. Nonalcoholic fatty liver disease and diabetes: an epidemiological perspective. Endocrinol Metab (Seoul) 2019;34:226-33.
71. Bugianesi E, Gentilcore E, Manini R, Natale S, Vanni E, Villanova N, et al. A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. Am J Gastroenterol 2005;100:1082-90.
72. Loomba R, Lutchman G, Kleiner DE, Ricks M, Feld JJ, Borg BB, et al. Clinical trial: pilot study of metformin for the treatment of non-alcoholic steatohepatitis. Aliment Pharmacol Ther 2009;29:172-82.
73. Lavine JE, Schwimmer JB, Van Natta ML, Molleston JP, Murray KF, Rosenthal P, et al. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. JAMA 2011;305:1659-68.
74. Li Y, Liu L, Wang B, Wang J, Chen D. Metformin in non-alcoholic fatty liver disease: a systematic review and meta-analysis. Biomed Rep 2013;1:57-64.
75. Musso G, Gambino R, Cassader M, Pagano G. A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease. Hepatology 2010;52:79-104.
76. Cusi K, Isaacs S, Barb D, Basu R, Caprio S, Garvey WT, et al. American Association of Clinical Endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endo-

crinology clinical settings: co-sponsored by the American Association for the Study of Liver Diseases (AASLD). Endocr Pract 2022;28:528-62.
77. Lee BW, Lee YH, Park CY, Rhee EJ, Lee WY, Kim NH, et al. Non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus: a position statement of the fatty liver research group of the Korean Diabetes Association. Diabetes Metab J 2020;44:382-401.
78. DeFronzo RA, Inzucchi S, Abdul-Ghani M, Nissen SE. Pioglitazone: the forgotten, cost-effective cardioprotective drug for type 2 diabetes. Diab Vasc Dis Res 2019;16:133-43.
79. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010; 362:1675-85.
80. Musso G, Cassader M, Paschetta E, Gambino R. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: a meta-analysis. JAMA Intern Med 2017;177: 633-40.
81. Choung S, Joung KH, You BR, Park SK, Kim HJ, Ku BJ. Treatment with lobeglitazone attenuates hepatic steatosis in diet-induced obese mice. PPAR Res 2018;2018:4292509.
82. Lee YH, Kim JH, Kim SR, Jin HY, Rhee EJ, Cho YM, et al. Lobeglitazone, a novel thiazolidinedione, improves nonalcoholic fatty liver disease in type 2 diabetes: its efficacy and predictive factors related to responsiveness. J Korean Med Sci 2017;32:60-9.
83. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016;387:679-90.
84. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med 2021;384:1113-24.
85. Eriksson JW, Lundkvist P, Jansson PA, Johansson L, Kvarnstrom M, Moris L, et al. Effects of dapagliflozin and n-3 carboxylic acids on non-alcoholic fatty liver disease in people with type 2 diabetes: a double-blind randomised placebo-controlled study. Diabetologia 2018;61:1923-34.
86. Kuchay MS, Krishan S, Mishra SK, Farooqui KJ, Singh MK, Wasir JS, et al. Effect of empagliflozin on liver fat in patients with type 2 diabetes and nonalcoholic fatty liver disease: a randomized controlled trial (E-LIFT Trial). Diabetes Care 2018;41:1801-8.
87. Leiter LA, Forst T, Polidori D, Balis DA, Xie J, Sha S. Effect of canagliflozin on liver function tests in patients with type 2 diabetes. Diabetes Metab 2016;42:25-32.
88. Suh S, Kim KW. Diabetes and cancer: cancer should be screened in routine diabetes assessment. Diabetes Metab J 2019;43:733-43.
89. Tsilidis KK, Kasimis JC, Lopez DS, Ntzani EE, Ioannidis JP. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. BMJ 2015;350:g7607.
90. Morales DR, Morris AD. Metformin in cancer treatment and prevention. Annu Rev Med 2015;66:17-29.
91. Rizos CV, Elisaf MS. Metformin and cancer. Eur J Pharmacol 2013;705:96-108.
92. Aljofan M, Riethmacher D. Anticancer activity of metformin: a systematic review of the literature. Future Sci OA 2019;5:FSO410.
93. Ryder RE. Pioglitazone has a dubious bladder cancer risk but an undoubted cardiovascular benefit. Diabet Med 2015; 32:305-13.
94. Jin SM, Song SO, Jung CH, Chang JS, Suh S, Kang SM, et al. Risk of bladder cancer among patients with diabetes treated with a 15 mg pioglitazone dose in Korea: a multicenter retrospective cohort study. J Korean Med Sci 2014; 29:238-42.
95. Lewis JD, Habel LA, Quesenberry CP, Strom BL, Peng T, Hedderson MM, et al. Pioglitazone use and risk of bladder cancer and other common cancers in persons with diabetes. JAMA 2015;314:265-77.
96. Mehtala J, Khanfir H, Bennett D, Ye Y, Korhonen P, Hoti F. Pioglitazone use and risk of bladder cancer: a systematic literature review and meta-analysis of observational studies. Diabetol Int 2018;10:24-36.
97. Boniol M, Franchi M, Bota M, Leclercq A, Guillaume J, van Damme N, et al. Incretin-based therapies and the short-term risk of pancreatic cancer: results from two retrospective cohort studies. Diabetes Care 2018;41:286-92.
98. Forsmark CE. Incretins, diabetes, pancreatitis and pancreatic cancer: what the GI specialist needs to know. Pancreatology 2016;16:10-3.
99. Wang H, Liu Y, Tian Q, Yang J, Lu R, Zhan S, et al. Incretin-based therapies and risk of pancreatic cancer in patients with type 2 diabetes: a meta-analysis of randomized controlled trials. Diabetes Obes Metab 2018;20:910-20.
100. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med 2015;

373:11-22.
101. Piccoli GF, Mesquita LA, Stein C, Aziz M, Zoldan M, Degobi N, et al. Do GLP-1 receptor agonists increase the risk of breast cancer? A systematic review and meta-analysis. J Clin Endocrinol Metab 2021;106:912-21.
102. Tang H, Dai Q, Shi W, Zhai S, Song Y, Han J. SGLT2 inhibitors and risk of cancer in type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. Diabetologia 2017;60:1862-72.
103. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006; 355:2427-43.
104. Dormandy J, Bhattacharya M, van Troostenburg de Bruyn AR. Safety and tolerability of pioglitazone in high-risk patients with type 2 diabetes: an overview of data from PROactive. Drug Saf 2009;32:187-202.
105. Mannucci E, Dicembrini I. Drugs for type 2 diabetes: role in the regulation of bone metabolism. Clin Cases Miner Bone Metab 2015;12:130-4.
106. Vallarino C, Perez A, Fusco G, Liang H, Bron M, Manne S, et al. Comparing pioglitazone to insulin with respect to cancer, cardiovascular and bone fracture endpoints, using propensity score weights. Clin Drug Investig 2013;33:621-31.
107. Monami M, Cresci B, Colombini A, Pala L, Balzi D, Gori F, et al. Bone fractures and hypoglycemic treatment in type 2 diabetic patients: a case-control study. Diabetes Care 2008; 31:199-203.
108. Nuche-Berenguer B, Moreno P, Portal-Nunez S, Dapia S, Esbrit P, Villanueva-Penacarrillo ML. Exendin-4 exerts osteogenic actions in insulin-resistant and type 2 diabetic states. Regul Pept 2010;159:61-6.
109. Nuche-Berenguer B, Lozano D, Gutierrez-Rojas I, Moreno P, Marinoso ML, Esbrit P, et al. GLP-1 and exendin-4 can reverse hyperlipidic-related osteopenia. J Endocrinol 2011; 209:203-10.
110. Monami M, Dicembrini I, Antenore A, Mannucci E. Dipeptidyl peptidase-4 inhibitors and bone fractures: a meta-analysis of randomized clinical trials. Diabetes Care 2011;34: 2474-6.
111. Su B, Sheng H, Zhang M, Bu L, Yang P, Li L, et al. Risk of bone fractures associated with glucagon-like peptide-1 receptor agonists' treatment: a meta-analysis of randomized controlled trials. Endocrine 2015;48:107-15.
112. Wolverton D, Blair MM. Fracture risk associated with common medications used in treating type 2 diabetes mellitus. Am J Health Syst Pharm 2017;74:1143-51.
113. Zhang YS, Zheng YD, Yuan Y, Chen SC, Xie BC. Effects of anti-diabetic drugs on fracture risk: a systematic review and network meta-analysis. Front Endocrinol (Lausanne) 2021;12:735824.
114. McMillan JM, Mele BS, Hogan DB, Leung AA. Impact of pharmacological treatment of diabetes mellitus on dementia risk: systematic review and meta-analysis. BMJ Open Diabetes Res Care 2018;6:e000563.
115. Castellani R, Hirai K, Aliev G, Drew KL, Nunomura A, Takeda A, et al. Role of mitochondrial dysfunction in Alzheimer's disease. J Neurosci Res 2002;70:357-60.
116. Corona JC, Duchen MR. PPARγ as a therapeutic target to rescue mitochondrial function in neurological disease. Free Radic Biol Med 2016;100:153-63.
117. Burns DK, Alexander RC, Welsh-Bohmer KA, Culp M, Chiang C, O'Neil J, et al. Safety and efficacy of pioglitazone for the delay of cognitive impairment in people at risk of Alzheimer's disease (TOMMORROW): a prognostic biomarker study and a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Neurol 2021;20:537-47.
118. Agostini F, Masato A, Bubacco L, Bisaglia M. Metformin repurposing for Parkinson disease therapy: opportunities and challenges. Int J Mol Sci 2021;23:398.
119. Qin X, Zhang X, Li P, Wang M, Yan L, Bao Z, et al. Association between diabetes medications and the risk of Parkinson's disease: a systematic review and meta-analysis. Front Neurol 2021;12:678649.
120. Lin TK, Lin KJ, Lin HY, Lin KL, Lan MY, Wang PW, et al. Glucagon-like peptide-1 receptor agonist ameliorates 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxicity through enhancing mitophagy flux and reducing α-synuclein and oxidative stress. Front Mol Neurosci 2021; 14:697440.
121. Ma D, Liu X, Liu J, Li M, Chen L, Gao M, et al. Long-term liraglutide ameliorates nigrostriatal impairment via regulating AMPK/PGC-1a signaling in diabetic mice. Brain Res 2019;1714:126-32.
122. Pariyar R, Bastola T, Lee DH, Seo J. Neuroprotective effects of the DPP4 inhibitor vildagliptin in in vivo and in vitro models of Parkinson's disease. Int J Mol Sci 2022;23: 2388.