REVIEW ARTICLE

Role of metformin in the management of type 2 diabetes: recent advances

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KEY WORDS

glucagon-like peptide-1 receptor agonist, guideline, sodium-glucose cotransporter-2 inhibitors, type 2 diabetes

ABSTRACT

Metformin is one of the oldest antidiabetic medications, commonly used in the management of type 2 diabetes. Its mechanism of action is based on reducing glucose production in the liver, decreasing insulin resistance, and increasing insulin sensitivity. The drug has been studied extensively and has been shown to be effective in lowering blood glucose levels without increasing the risk of hypoglycemia. It has been used for the treatment of obesity, gestational diabetes, and polycystic ovary syndrome. According to current guidelines, metformin can be used as the first-line agent in the management of diabetes; however, in individuals with type 2 diabetes who would benefit from cardio-renal protection, newer agents, such as sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists, are favored as the first-line therapy. The novel classes of antidiabetic medications have demonstrated significant positive effects on glycemia with added benefits in patients with obesity, renal disease, heart failure, and cardiovascular disease. The emergence of these more effective agents has significantly altered the way diabetes is managed, thus prompting re-evaluation of metformin as the initial therapy for all patients with diabetes.

Introduction Metformin (1,1-dimethylbiguanide) has been the cornerstone of type 2 diabetes mellitus (T2DM) management for decades. The drug is derived from *Galega officinalis*, otherwise known as the French lilac, and was first found to have glucose-lowering activity in 1918.[1] It belongs to the class of drugs called biguanides. This class of medications was first used to treat T2DM in 1957, with the advent of phenformin.[1] Metformin was approved by the United States Food and Drug Administration (FDA) on December 29, 1994 and, based on promising trial data, it became the first-line therapy for the management of T2DM in 2005,[2] after the publication of the International Diabetes Federation guidelines.[1] In recent years, sodium-glucose cotransporter-2 inhibitors (SGLT-2is) have been studied in the context of T2DM management. In addition to treating diabetes, these agents have been shown to have strong beneficial effects on heart failure, as well as vascular and renal outcomes.[3] Large trials on glucagon-like peptide-1 receptor agonists (GLP-1RAs) have shown their efficacy in glycemic management, with simultaneous lowering of the risk for hypoglycemic events. The benefits of these drugs extend to managing obesity, vascular risk, and fatty liver disease. With the arrival of the dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist (GIP/GLP-1 RA), the management of T2DM continues to evolve. The addition of these new agents to glycemic treatment regimens led to major changes in the guidelines of major medical societies, and to re-evaluation of metformin's role in glycemic management.

Mechanism of action Metformin has multiple reported mechanisms of action in different tissues. It inhibits hepatic gluconeogenesis, increases insulin-related glucose uptake in muscles, and increases glucose uptake and utilization in intestinal tissue.[4-6] It has an oral bioavailability of 50% to 60% and, following intestinal absorption, enters the portal vein and accumulates in the liver.[4] Metformin has also been linked to weight loss and appetite suppression by modulating serum growth differentiating factor-15 in mouse models[7,8] and hypothalamic appetite-regulatory centers[9,10] in healthy individuals. In a study involving 154 nondiabetic patients with obesity

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who were followed for 6 months, the mean (SD) weight loss in the metformin-treated group was 5.8 (7.0) kg (5.6% [6.5%]), whereas the untreated controls gained a mean (SD) of 0.8 (3.5) kg (0.8% [3.7%]).[11] Metformin does not increase insulin concentrations, and thus does not put patients at risk of hypoglycemia.[5,12] Recent studies have linked the clinical benefits of metformin to alterations in the gut microbiome composition[4,13,14] and delayed gastric emptying.[15] Studies investigating the effect of metformin on GLP-1 secretion have yielded conflicting results, reporting a direct effect of metformin on the GLP-1 expression, indirect effects through dipeptidyl peptidase-4 activity, or no effect on GLP-1.[4,15,16]

Efficacy of metformin in patients with type 2 diabetes In 1995, the first major trial evaluating the efficacy of metformin was published.[17] The participants were randomized to receive glyburide or metformin or a combination of both drugs. A total of 921 individuals were randomized to either metformin vs placebo (protocol 1; n = 289) or combined therapy with metformin and glyburide vs metformin monotherapy vs glyburide monotherapy (protocol 2; n = 632). All participants had poorly controlled T2DM with the glycated hemoglobin concentration greater than 8%. At the end of the study, the metformin-treated individuals included in protocol 1 had a lower mean (SD) fasting plasma glucose concentration (189 [5] vs 244 [6] mg/dl; 10.6 [0.3] vs 13.7 [0.3] mmol/l; P <0.001) and glycated hemoglobin values (7.1% [0.1%] vs 8.6% [0.2%]; P <0.001) than the placebo arm.[17] Among the patients included in protocol 2, those treated with metformin and glyburide dual therapy had lower mean (SD) fasting plasma glucose concentrations (187 [4] vs 261 [4] mg/dl; 10.5 [0.2] vs 14.6 [0.2] mmol/l; P <0.001) and glycated hemoglobin values (7.1% [0.1%] vs 8.7% [0.1%]; P <0.001), as compared with the glyburide monotherapy arm.[17] This effect was not significant when the groups treated with metformin monotherapy vs glyburide monotherapy were compared. Adverse events included diarrhea and nausea in the groups receiving metformin, and the frequency and severity of hypoglycemia were similar in the metformin monotherapy, glyburide monotherapy, and placebo groups (<2%–3%). However, the rate of hypoglycemia increased to 18% in the patients receiving the combination therapy with metformin and glyburide.[17] The results of this groundbreaking study revealed that metformin monotherapy and a combination therapy with metformin and sulfonylurea were well tolerated and dramatically improved glycemic control in the patients with non–insulin-dependent diabetes, drastically reducing the risk of hypoglycemia. These findings revolutionized the pharmacotherapy of T2DM, ushering in a new era of treatment options beyond insulin- and sulfonylurea-based therapies.

The United Kingdom Prospective Diabetes Study The United Kingdom Prospective Diabetes Study (UKPDS)[18,19] was a series of large trials seeking to evaluate the effects of intensive blood glucose control on the risk of microvascular and macrovascular complications in patients with T2DM. Over the years, the results of these trials have provided significant insight into the management of and complications in individuals with T2DM. In the UKPDS 33,[18] a total of 3867 patients with newly diagnosed T2DM were randomized to intensive treatment with a sulfonylurea monotherapy or insulin vs conventional therapy with diet. The goal in the intensive treatment group was a fasting plasma glucose level lower than 6 mmol/l. In the conventional therapy group, the goal was the best achievable fasting plasma glucose level with diet alone. Three aggregate end points were used to assess differences between the conventional and intensive treatments: any diabetes-related end point, diabetes-related death, and all-cause mortality.[18] Over the 10 years of follow-up, the median glycated hemoglobin concentration was 7% (interquartile range [IQR], 6.2%–8.2%) in the intensive group, as compared with 7.9% (IQR, 6.9%–8.8%) in the conventional group—a reduction by 11% as compared with the baseline for the intensive group and the conventional group, respectively.[18] As compared with the conventional treatment group, the risk in the intensive treatment group was lower by 12% (95% CI, 1–21; P = 0.03) for any diabetes-related end point, by 10% (95% CI, –11 to 27; P = 0.34) for diabetes-related death, and by 6% (95% CI, –10 to 20; P = 0.44) for all-cause mortality.[18] However, there were more hypoglycemic episodes in the intensive treatment than in the conventional treatment group (P <0.001).[18] These results proved an important concept that remains a pillar of today's medicine; namely, that intensive blood glucose control substantially decreases the risk of microvascular complications in individuals with T2DM.[18]

The UKPDS 34[19] sought to evaluate whether intensive glucose control with metformin has any specific advantages or disadvantages. This randomized controlled trial included 753 overweight (>120% ideal body weight) patients with newly diagnosed T2DM. They were treated with either conventional therapy, primarily with diet alone (n = 411; median follow-up, 10.7 years) or intensive blood glucose control therapy with metformin, aiming for a fasting plasma glucose level below 6 mmol/l (n = 342). Similarly to the UKPDS 33[18], the primary aggregate outcome measures were any diabetes-related clinical end point, diabetes--related death, and all-cause mortality.[19] The results of this trial highlighted the effectiveness of metformin therapy, as the median glycated hemoglobin concentration was 7.4% in the metformin group vs 8.0% in the conventional treatment group.[19] In comparison with the conventional treatment group, the patients assigned to the metformin arm had risk reduction by 32% (95% CI, 13–47; P = 0.002) for any diabetes--related end point, by 42% for diabetes-related

death (95% CI, 9–63; $P = 0.017$), and by 36% for all-cause mortality (95% CI, 9–55; $P = 0.011$).[19] The UKPDS 34 also included a secondary analysis evaluating the effects of metformin in addition to sulfonylureas. It was found that early addition of metformin in sulfonylurea-treated patients was associated with an increased risk of diabetes-related death (risk increase by 96% [95% CI, 2–275; $P = 0.039$]), as compared with continued treatment with sulfonylureas alone.[19] This study was a landmark for metformin therapy, as it was noted that this drug appeared to decrease the risk of diabetes-related end points in overweight diabetic patients.

The Subsequent UKPDS studies[19] analyzed the differences between treatment outcomes in the 10-year follow-up and, to our interest, the effect of metformin treatment in these patients. The participants were of a median age of 53 years, had a median body max index (BMI) of 28 kg/m^2, and a median fasting plasma glucose level of 11.3 mmol/l, and they were randomized to lifestyle changes (diet), sulfonylureas, insulin, or metformin. Metformin was only assigned to individuals with obesity, who constituted less than 10% of the study population. The treatments were combined if a single treatment failed. The primary outcome was the incidence of microvascular and macrovascular complications of T2DM. The secondary outcome were differences in complication rates between the treatment regimens. The sulfonylurea–insulin group was found to have 10-year relative risk reduction by 9% for T2DM-related complications ($P = 0.04$), by 24% for microvascular disease ($P = 0.001$), by 15% for myocardial infarction ($P = 0.01$), and by 13% for all-cause mortality ($P = 0.007$). In the metformin group, at 10 years, the risk reduction for any diabetes-related end point was 21% ($P = 0.01$), for myocardial infarction it was 33% ($P = 0.005$), and for death from any cause, 27% ($P = 0.002$).[18] This study redefined the therapeutic strategy for T2DM. Shortly after its release, in 2006, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommended—in a joint statement—the use of metformin, along with diet and exercise, as the initial pharmacologic intervention in individuals with T2DM.[19]

Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study The Diabetes Prevention Program (DPP; 1996–2001) was a randomized controlled trial designed to evaluate the efficacy of intensive lifestyle intervention vs metformin on preventing or delaying the development of T2DM in high-risk individuals, identified by impaired glucose tolerance. The trial included 3234 participants assigned to intensive lifestyle intervention, metformin, or placebo. The mean (SD) patient age at randomization was 50.6 (10.7) years. Among the participants, 68% were women, and 45% belonged to a United States racial or ethnic minority group.[20] The participants were followed for an average of 2.8 years. The primary outcome was development of diabetes, defined as an elevated fasting plasma glucose level (≥126 mg/dl) or an abnormal glucose tolerance test result (2-hour plasma glucose ≥200 mg/dl in the 75-g oral glucose tolerance test [OGTT]). The secondary outcomes included development of cardiovascular disease (CVD; changes in carotid intima-media thickness, arm blood pressure, and ankle-brachial systolic blood pressure) or its risk factors, assessed based on changes in glycemia, B-cell function insulin sensitivity (measurement of insulin and glucose during the OGTT), obesity (body composition measurements), diet (standardized questionnaire assessments), physical activity (standardized questionnaire assessments), and health-related quality of life (standardized questionnaire assessments), as well as occurrence of adverse events.[21] This was the first major diabetes prevention trial using metformin. The primary findings of the DPP showed that the intensive lifestyle modification and metformin groups had a lower incidence of diabetes, respectively, by 58% (95% CI, 48–66; $P < 0.05$) and by 31% (95% CI, 17–43; $P < 0.05$), as compared with the placebo group.[22] Of note, the participants with obesity (BMI ≥35 kg/m^2), higher fasting plasma glucose levels, and younger age were more responsive to metformin, although the trial was not adequately powered to assess the significance of effects within subgroups.[23] There were no significant differences related to sex, race, or ethnicity. The most common adverse events observed in the metformin group were gastrointestinal symptoms.

Subsequently, the Diabetes Prevention Program Outcomes Study (DPPOS; 2002–2008) addressed the longer-term effects of metformin, showing a decline in risk reduction by 18% (hazard ratio [HR], 0.82; 95% CI, 0.72–0.93; $P = 0.001$), as compared with placebo, 10 and 15 years after randomization.[24,25] Diabetes incidence rates during the DPP were 7.8 cases per 100 person-years in the metformin group and 11 cases per 100 person-years in the placebo group,[23] and they decreased in the DPPOS to 4.9 cases per 100 person-years for metformin and 5.6 cases per 100 person-years for placebo,[24] remaining stable thereafter. Metformin also had favorable effects on several cardiovascular risk factors, including lipoprotein subfractions,[23,26] C-reactive protein, and tissue plasminogen activator levels[23,27]; however, in a long-term follow-up (10 years), there was no significant difference in the prevalence of traditional cardiovascular risk factors in comparison with the placebo groups.[23,27] The impact of metformin use on the cardiovascular system remains uncertain. Its antidiabetic effect is partially attributed to weight loss, which was persistent over time in the DPP/DPPOS.[24,25] Weight loss associated with metformin use explained 64% of its beneficial effect on diabetes risk at the end of the DPP.[28] Improvements in fasting plasma glucose levels and estimated insulin sensitivity associated with metformin treatment may be due

to a combination of weight loss and other direct effects on the liver,[23] which include the reduction in the rates of hepatic glucose production by decreasing hepatic gluconeogenesis.[4] These findings revolutionized the treatment of T2DM by offering a cost-effective agent not carrying the added risk of hypoglycemia.

Metformin safety and tolerability Metformin is generally a safe and well-tolerated drug. Long-term data on the use of metformin from the DPP provided information on its safety and tolerability. The side effects are generally gastrointestinal in nature, mild, and transient. They include, for example, nausea, diarrhea, and abdominal discomfort. In the group randomized to metformin during the DPP, 9.5% of the patients reported minor gastrointestinal symptoms (as compared with 1.1% in the placebo group); however, these were generally mild and subsided over time.[23,29,30] The adverse symptoms are dose-related and remit if the dose is reduced; sometimes an increase in the dose can later be tolerated.[31] More than half of the patients tolerate the maximal dose but about 5% cannot tolerate any dose of metformin.[31] Overall, patients starting metformin therapy should be advised that they may experience minor gastrointestinal side effects.[31]

In rare cases, metformin was associated with a serious side effect called lactic acidosis. The pathophysiology of lactic acidosis induced by metformin is likely due to the inhibition of gluconeogenesis by blocking pyruvate carboxylase, the enzyme catalyzing the first step of gluconeogenesis, that is, a conversion of pyruvate to oxaloacetate. Blocking this enzyme leads to the accumulation of lactic acid. In addition, metformin decreases the hepatic metabolism of lactate and has a negative ionotropic effect on the heart, both of which lead to the elevation of lactate levels.[32] Manifestations of lactic acidosis include nausea, abdominal pain, tachycardia, tachypnea, and hypotension, which require immediate medical intervention. However, recently, the risk of lactic acidosis induced by metformin use has been demonstrated to be much lower than previously estimated, with no reported cases in over 15 000 person-years of exposure to metformin in the DPP/DPPOS.[23] In a recent study[33] involving 2 large retrospective cohorts of patients with T2DM, metformin use in those with estimated glomerular filtration rate (eGFR) of 30 ml/min/1.73 m^2 or greater was not associated with incident hospitalization for acidosis. The FDA and other regulatory bodies now suggest that metformin can be used when eGFR ranges between 45 and 59 ml/min/1.73 m^2, and caution should be exercised in individuals with an eGFR range of 30 to 44 ml/min/1.73 m^2.[33,34]

Metformin use has also been associated with impaired intestinal absorption of vitamin B_{12} and increased risk of its deficiency.[23] In the DPP and DPPOS, annual testing of the participants was performed, and the levels of this vitamin were directly measured at 2 time points. Results showed an increased risk of B_{12} deficiency in the metformin group at 5 years (4.3% vs 2.3%; $P = 0.02$) and at 13 years (7.4% vs 5.4%; $P = 0.12$), as compared with the placebo group. A multivariate model associated longer metformin use with increased risk of B_{12} deficiency (odds ratio, 1.13; 95% CI, 1.06–1.20). Guidelines now recommend periodic measurements of vitamin B_{12} levels and supplementation as needed for patients taking metformin; however, there are no recommendations regarding the dose or duration of supplementation, rendering this an area warranting future research.

The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study The DPP/DPPOS provided significant insight on the effect of metformin on glycemia, as well as on the safety, side effect profile, and cost-effectiveness of the drug. Over 10 years, the cumulative, undiscounted direct medical costs of the interventions per capita, as incurred during the DPP, were greater for lifestyle intervention (USD 4601) than for metformin (USD 2300) or placebo (USD 769).[35] The cumulative direct medical costs of care outside the DPP/DPPOS were the lowest for lifestyle intervention (USD 24 563 for lifestyle intervention vs USD 25 616 for metformin vs USD 27 468 for placebo).[35] The cumulative, combined total direct medical costs were the highest for lifestyle intervention and the lowest for metformin (USD 29 164 for lifestyle intervention vs USD 27 915 for metformin vs USD 28 236 for placebo).[35] The authors concluded that both lifestyle intervention and metformin therapy are cost-effective strategies for diabetes prevention, particularly in populations at a high risk for developing the disease.[35]

Metformin in combination therapy Metformin for the treatment of T2DM can be used in monotherapy or in combination with other antidiabetic medications. Metformin monotherapy can reduce the level of glycated hemoglobin and body weight.[36] However, using metformin in combination with other medications may provide even greater benefits.[33,34,36] A systematic review and meta-analysis[36] showed that metformin-based combination therapy was associated with a greater reduction in glycated hemoglobin levels and body weight than metformin monotherapy, as well as with a lower risk of hypoglycemia, heart failure, and cardiovascular outcomes, particularly when used in combination with GLP-1RAs and SGLT-2is. Furthermore, the use of metformin in combination with insulin in individuals with type 1 diabetes with excess body fat improves metabolic control.[37] Therefore, combining metformin with other medications may result in better glycemic control and improved safety outcomes for patients with T2DM.[33,34]

Metformin beyond the management of type 2 diabetes Metformin use in patients with gestational diabetes mellitus (GDM) may improve maternal and perinatal outcomes.[38-40] A meta-analysis of 8 clinical trials involving 1712 pregnant women with GDM has proven that metformin and insulin therapy have a similar effect on glycemic control. Interestingly, metformin treatment was associated with a lower incidence of neonatal hypoglycemia and neonatal intensive care admission.[39] Metformin is classified as a category B medication, whereas all other antiglycemic medications, barring insulin, are classified as category C medications and are contraindicated for the treatment of GDM and T2DM in pregnancy due to the risk of serious adverse effects.[27] However, in light of the lack of unequivocal long-term results in children with intrauterine exposure to metformin, insulin remains the treatment of choice for the management of hyperglycemia in pregnancy. According to the current position of Diabetes Poland issued in 2022, insulin is the only antidiabetic drug recommended in pregnancy.[41] In women with polycystic ovary syndrome (PCOS) treated with metformin either for insulin resistance or to induce ovulation, the drug should be discontinued by the end of the first trimester of pregnancy.[41]

Metformin is used in women with PCOS for the treatment of metabolic derangements.[27] By increasing insulin sensitivity in target organs, metformin can, to some extent, correct the metabolic abnormalities and reduce the risk of glucose intolerance, as well as contribute to reducing the level of androgens and controlling the menstrual cycle.[42]

Lastly, a prothrombotic state is typical of T2DM. Metformin has been reported to improve fibrin properties and accelerate fibrinolysis in T2DM by decreasing platelet activity and concentrations of fibrinogen, reducing oxidative stress, and improving endothelial function as well as fibrin clot properties.[43] Therefore, metformin may also be considered as a potential treatment for CVD and other panvascular diseases in which endothelial dysfunction plays a fundamental role.

Trials evaluating cardiovascular outcomes in patients treated with sodium-glucose cotransporter-2 inhibitors The advent of SGLT-2is as antidiabetic medications has demonstrated their renoprotective effects as well as cardiovascular benefits, as noted in 3 major trials: the EMPA-REG OUTCOME study,[44] the CANVAS (Canagliflozin Cardiovascular Assessment Study),[45] and the DECLARE-TIMI 58 study.[46] In the EMPA-REG OUTCOME trial,[44] a total of 7020 patients were treated with either 10 mg or 25 mg of empagliflozin or placebo once daily. The median follow-up was 3.1 years. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.[44] The primary outcome occurred in 490 of 4687 patients (10.5%) in the empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (HR, 0.86; 95% CI, 0.74–0.99; P = 0.04 for superiority). There were no significant intergroup differences in the rates of myocardial infarction or stroke, but in the empagliflozin group there was a relative risk reduction by 37% for cardiovascular mortality (HR, 0.62; 95% CI, 0.49–0.77; P <0.001), and by 35% for hospitalization for heart failure (HR, 0.65; 95% CI, 0.50–0.85; P = 0.002).[44]

CANVAS[45] confirmed the benefits of SGLT-2i use, as it showed that participants with diabetes and atherosclerotic cardiovascular disease (ASCVD) or cardiovascular risk factors had a 14% reduction in major adverse cardiovascular event (MACE) incidence while on canagliflozin, as compared with those on placebo (26.9 vs 31.5 participants per 1000 patient-years; HR, 0.86; 95% CI, 0.75–0.97; P <0.001 for noninferiority; P = 0.02 for superiority).[45]

The DECLARE-TIMI 58 study[46] was a randomized controlled trial involving a total of 17 160 participants with T2DM who were either diagnosed with or at a risk for ASCVD. The patients were assigned to either 10 mg of dapagliflozin or placebo daily. They were followed for a median of 4.2 years. The mean (SD) glycated hemoglobin level was 8.3% (1.2%), and the median duration of diabetes was 11 years (interquartile range, 6–16). The mean eGFR was 85.2 ml/min/1.73 m^2; 45% of the patients had an eGFR between 60 and 90 ml/min/1.73 m^2.[46] The primary safety outcome was the occurrence of MACEs (defined as cardiovascular death, myocardial infarction, or ischemic stroke). The 2 primary efficacy outcomes were MACEs and a composite of cardiovascular death or hospitalization for heart failure.[46] The use of dapagliflozin resulted in a 17% lower rate of cardiovascular death or hospitalization for heart failure (4.9% vs 5.8%; HR, 0.83; 95% CI, 0.73–0.95; P = 0.005), which reflected a 27% lower rate of hospitalization for heart failure (HR, 0.73; 95% CI, 0.61–0.88), as compared with placebo. A recent meta-analysis[47] examined the cardiovascular and renal outcomes associated with SGLT-2i use in patients with T2DM. It was found that SGLT-2i use was associated with a lower risk of MACEs (HR, 0.90; 95% CI, 0.85–0.95; P = 0.27), hospitalization for heart failure or cardiovascular death (HR, 0.78; 95% CI, 0.73–0.84; P = 0.09), and kidney outcomes (HR, 0.62; 95% CI, 0.56–0.70; P = 0.09),[47] as compared with other glucose-lowering therapies. Moreover, the patients treated with SGLT-2is had lower risk of hospitalization for heart failure (HR, 0.68; 95% CI, 0.61–0.76; I^2 = 0.0%) and renal replacement therapy. These findings suggest that SGLT-2is may provide additional benefits to patients with T2DM.[47]

Serious adverse events associated with the use of SLGT2is include the risk of lower limb amputations and increased risk of bone fractures, as seen in CANVAS[45]; however, the elevated fracture risk has not been observed in other trials involving canagliflozin. A meta-analysis of clinical trials revealed no imbalance in fracture rates

between individuals treated with empagliflozin and those receiving placebo.[48] Diabetic ketoacidosis is another serious adverse event that has been encountered in trials on various SGLT-2i therapies. The rates of this adverse event were numerically higher among those receiving active treatment in the CANVAS program (0.6 vs 0.3 events per 1000 person-years),[49] as well as in a meta-analysis of clinical trials on SGLT-2is (OR, 1.96; 95% CI, 0.77–4.98).[50] In addition, higher rates of diabetic ketoacidosis have been observed among individuals receiving SGLT-2is in trials that included patients with type 1 diabetes.[51]

Data from trials assessing cardiovascular outcomes demonstrate important and significant benefits of SGLT-2i use in patients with diabetes who have comorbidities such as kidney disease, CVD, and heart failure. Lastly, in addition to cardiorenal protection, SGLT-2is can induce weight loss of approximately 1.5 to 2 kg[52] in a dose-dependent manner, which is maximized when a SGLT-2i is combined with other types of antidiabetic drugs, especially GLP-1RAs.[52] Weight loss secondary to SGLT-2i use is due to their glucosuric effects, interference with excess adipose tissue, and polarization toward the M2 phenotype of macrophages.[52] Other studies have highlighted the efficacy of SGLT-2is in the treatment of nonalcoholic fatty liver disease and PCOS.[52] However, additional research needs to be conducted to further confirm these observations. Currently, there are ongoing studies on the benefits of these medications when used for the treatment of fatty liver disease, amongst other complications of T2DM. Overall, this class of medications (similarly to metformin in the past) has revolutionized the management of diabetes.

Trials evaluating cardiovascular outcomes in patients treated with glucagon-like peptide-1 receptor agonists To date, there have been 7 trials assessing cardiovascular outcomes in patients treated with GLP-1RAs: ELIXA, LEADER, SUSTAIN-6, EXSCEL, Harmony outcomes, REWIND, and PIONEER 6, all of which have shown noninferiority of GLP-1RAs to metformin.[53] In addition, liraglutide, subcutaneous semaglutide, albiglutide, and dulaglutide have been shown to significantly reduce the rate of composite cardiovascular outcomes.[54] This class of medications has been clinically proven to reduce glucose levels without increasing the risk of hypoglycemia, while adding a cardiovascular benefit. Furthermore, they have been shown to have beneficial effects in patients with obesity and nonalcoholic steatohepatitis.[55]

A GIP/GLP-1 RA, tirzepatide, is a synthetically produced peptide molecule that acts on both GIP and GLP-1.[56] In the SURPASS-2 trial,[57] tirzepatide at all doses was noninferior and superior to semaglutide (P = 0.02, P <0.001, and P <0.001). Reductions in body weight were greater with tirzepatide than with semaglutide.[57] Tirzepatide had a side effect profile similar to that of semaglutide, with gastrointestinal effects being the most common. Studies have shown a favorable profile in individuals with diabetes and obesity, and there are ongoing trials on its use in the pediatric population and in individuals with heart failure with preserved ejection fraction.[58]

Kidney and cardiovascular guidelines In 2019, the ADA recommended metformin as the first-line therapy for diabetes; however, further recommendations were added to tailor additional treatment based on patient comorbidities; specifically established CVD or chronic kidney disease (CKD).[34] The new guidelines released in 2023[59] highlight the importance of reducing the cardiorenal risk in patients with T2DM and established ASCVD, heart failure, and/or CKD or with risk factors for these conditions. The guidelines suggest adopting a new approach to the choice of glucose-lowering therapy, whereby pharmacologic therapy should be guided by patient-centered factors, including comorbidities and treatment goals.[59] Although not specifically the first treatment choice in these high-risk individuals, metformin is still recommended to achieve a target glycemic goal, in addition to GLP-1RAs and SGLT-2is.

The 2019 guidelines of the European Society of Cardiology (ESC) recommended GLP-1RAs or SGLT-2is to be considered as the first-line therapy in T2DM patients with known CVD or at a high risk of the disease.[60] The ESC guidelines also recommend the use of SGLT-2is and GLP-1RAs as the first-line therapy in individuals with T2DM and ASCVD or at a high risk of the disease,[61,62] with metformin as a possible, albeit not mandatory, first-line treatment option.[62]

The New Kidney Disease: Improving Global Outcomes (KDIGO) guidelines,[33] released in 2022, also adopted a comprehensive approach to the management of T2DM. In contrast to the ESC guidelines, the recommended first-line therapy is a combination of metformin (if eGFR ≥30 ml/min/1.73 m^2) and an SGLT-2i (if GFR ≥20 ml/min per 1.73 m^2), with an emphasis that once an SGLT-2i is initiated, it is reasonable to continue it even if the eGFR falls below 20 ml/min/1.73 m^2, unless it is not tolerated or kidney replacement therapy is initiated.[33] On the other hand, GLP-1RAs should be considered as a second-line therapy, if needed, to achieve an individualized glycemic target or in the case of persistent albuminuria.[33]

The 2022 Diabetes Poland guidelines on the management of patients with diabetes recommend metformin as the first-choice drug for the treatment of T2DM unless contraindicated or poorly tolerated.[41] The choice of other drugs should be individualized, considering cardiorenal risk factors, similarly to what is proposed in the KIDGO and ESC guidelines. This recommendation highlights the importance of metformin when initiating therapy for individuals with T2DM and recognizes it as a strong agent for the management of dysglycemia.

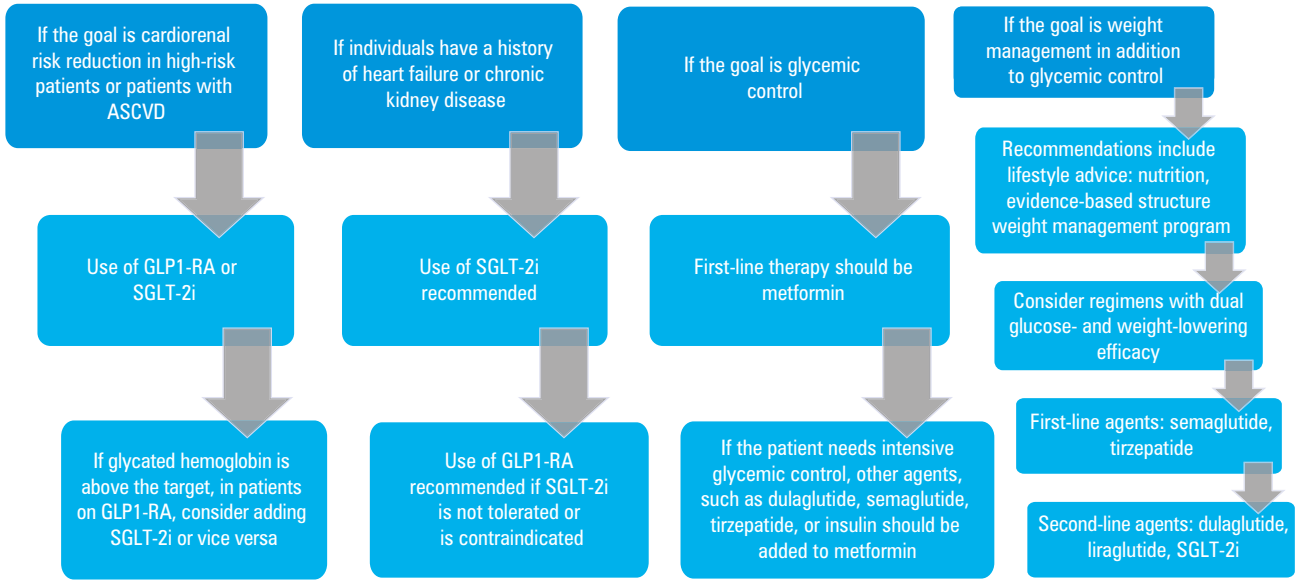

FIGURE 1 A simplified overview of the use of antidiabetic medications in individuals with T2DM based on comorbidities and the glycemic goal. ASCVD is defined according to the trials assessing cardiovascular outcomes as myocardial infarction, stroke, need for revascularization procedures, transient ischemic attack, unstable angina, and symptomatic or asymptomatic coronary artery disease. High-risk individuals are defined as those aged over 55 years, with 2 or more additional risk factors (obesity, hypertension, smoking, dyslipidemia, or albuminuria). Chronic kidney disease is defined as eGFR <60 ml/min/1.73 m^2 or albuminuria (albumin-to-creatinine ratio >3.0 mg/mmol [30 mg/g]). The ADA further recommends to consider metabolic surgery and/or medications for weight loss; however, these interventions were excluded from the analysis, as the goal was to highlight the importance of antidiabetic medications.

Abbreviations: ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP1-RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; T2DM, type 2 diabetes mellitus

All the above recommendations provide significant guidance with respect to the management of high-risk patients with T2DM, highlighting the importance of a more individualized approach. However, metformin still remains a great choice for the management of T2DM, even in the presence of high-risk factors, given its low cost, effective blood sugar control, and a favorable safety profile.

Navigating the evolving landscape: changes in diabetes guidelines in response to trials evaluating cardiovascular outcomes Newer guidelines of the ADA and EASD include additional areas of focus, such as social determinants of health, the health care system, and lifestyle behaviors, including sleep.[63] In contrast to the previous guidelines, there is greater emphasis on weight management as part of the holistic approach to the treatment of diabetes.[63] The guidelines highlight the importance of SGLT-2is and GLP-1RAs for cardiorenal protection in individuals with diabetes at a high risk for cardiorenal disease.[63] The new guidelines do not clearly state which agent should be used as the first-line therapy, but rather encourage the health care provider to adopt an individual approach when deciding which drug to use for the management of T2DM (FIGURE 1).[63]

Current use of metformin Diabetes has become a global epidemic, and studies have shown that its prevalence (including that of undiagnosed diabetes) is increasing.[64] Therefore, navigating the landscape of the available pharmacotherapies for this chronic condition is crucial. In addition, mitigating the effects of diabetes on the cardiovascular system plays a significant role in today's approach to managing diabetes. Studies have shown that individuals hospitalized for acute myocardial infarction and diabetes tend to develop significant in-hospital complications, cardiovascular complications, such as cardiogenic shock, and have the highest overall in-hospital and 3-year all-cause death rates.[65] In light of the strong evidence of renal and cardiovascular protective effects associated with the use of SGLT-2is and GLP-1RAs, choosing metformin as the first-line agent for the management of diabetes is debatable. Diabetes exacerbates the dynamics of atherosclerosis,[66] contributing to the risk for further development of CVD. It is estimated that about 52% of deaths in individuals with T2DM are due to CVD.[67,68] Initial presentations of CVD in diabetic patients most commonly include peripheral artery disease (16.2% or three times greater) and heart failure (14.7%), followed by angina and nonfatal myocardial infarction.[67] This was demonstrated by the San Antonio Heart Study,[69] including 4875 patients followed for 7 to 8 years, which showed that diabetes was significantly associated with increased all-cause mortality (relative risk [RR], 2.1; 95% CI, 1.3–3.5 in men; RR, 8.5; 95% CI, 2.8–25.2 in women). Heart failure risk can be higher by 40% in individuals with T2DM than in non-diabetics.[70] Moreover, in the NHANES (National Health and Nutrition Examination Survey) cohort, it was noted

that 26.3% of strokes were associated with diabetes.[71] Furthermore, the risk for renal impairment continues to increase in individuals with T2DM, with studies showing that 50% of individuals without a known history of proteinuria or diabetic kidney disease have some signs of CKD.[72,73] Based on the UKPDS data, more than half of the individuals with T2DM ultimately developed CKD after a median of 15 years.[74] In light of this, medical societies have changed their recommendations, and shifted them toward focusing on individual patient characteristics and presence of comorbidities, assuming that if a patient suffers from CVD or has risk factors for the disease, early implementation of SGLT-2is or GLP-1RAs should be considered to decrease the risk of MACEs or CKD.[33,59-61]

It is impossible to ignore the ground-breaking findings on the newer classes of antidiabetic drugs, mainly SGLT-2is and GLP-1RAs. However, metformin still remains an excellent first-line agent for individuals with T2DM. It has been shown to improve glycemic control and reduce the risk of hypoglycemia and weight gain,[8] as well as potentially slow the progression of CKD[75] and reduce the risk of CVD. Metformin is also an attractive option for care givers and patients due to its affordability, wide availability, and a well-documented safety profile.

Conclusions Metformin continues to play the central role in the management of T2DM due to its efficacy and a favorable safety profile. While the drug is generally well tolerated, some patients may not respond to it or experience side effects. In such cases, other agents, such as SGLT-2is and GLP-1 RAs should be considered, especially in individuals with cardiorenal risk factors. Even though metformin is a relatively old drug, it is still a reliable and effective treatment option that is recommended by current guidelines.

ARTICLE INFORMATION

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REFERENCES

1 Bailey CJ. Metformin: historical overview. Diabetologia. 2017; 60: 1566-1576.

2 Blonde L, Dailey GE, Jabbour SA, et al. Gastrointestinal tolerability of extended-release metformin tablets compared to immediate-release metformin tablets: results of a retrospective cohort study. Curr Med Res Opin. 2004; 20: 565-572.

3 Engler C, Leo M, Pfeifer B, et al. Long-term trends in the prescription of antidiabetic drugs: real-world evidence from the Diabetes Registry Tyrol 2012-2018. BMJ Open Diabetes Res Care. 2020; 8: e001279.

4 LaMoia TE, Shulman GI. Cellular and molecular mechanisms of metformin action. Endocr Rev. 2021; 42: 77-96.

5 Inzucchi SE, Maggs DG, Spollett GR, et al. Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. N Engl J Med. 1998; 338: 867-872.

6 Rossetti L, Smith D, Shulman GI, et al. Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats. J Clin Invest. 1987; 79: 1510-1515.

7 Coll AP, Chen M, Taskar P, et al. GDF15 mediates the effects of metformin on body weight and energy balance. Nature. 2020; 578: 444-448.

8 Day EA, Ford RJ, Smith BK, et al. Metformin-induced increases in GDF15 are important for suppressing appetite and promoting weight loss. Nat Metab. 2019; 1: 1202-1208.

9 Schultes B, Oltmanns KM, Kern W, et al. Modulation of hunger by plasma glucose and metformin. J Clin Endocrinol Metab. 2003; 88: 1133-1141.

10 Yerevanian A, Soukas AA. Metformin: mechanisms in human obesity and weight loss. Curr Obes Rep. 2019; 8: 156-164.

11 Seifarth C, Schehler B, Schneider HJ. Effectiveness of metformin on weight loss in non-diabetic individuals with obesity. Exp Clin Endocrinol Diabetes. 2013; 121: 27-31.

12 Stumvoll M, Nurjhan N, Perriello G, et al. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. N Engl J Med. 1995; 333: 550-554.

13 Forslund K, Hildebrand F, Nielsen T, et al. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. Nature. 2015; 528: 262-266.

14 Wu H, Esteve E, Tremaroli V, et al. Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug. Nat Med. 2017; 23: 850-858.

15 Gontier E, Fourme E, Wartski M, et al. High and typical 18F-FDG bowel uptake in patients treated with metformin. Eur J Nucl Med Mol Imaging. 2008; 35: 95-99.

16 Migoya EM, Bergeron R, Miller JL, et al. Dipeptidyl peptidase-4 inhibitors administered in combination with metformin result in an additive increase in the plasma concentration of active GLP-1. Clin Pharmacol Ther. 2010; 88: 801-808.

17 DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. N Engl J Med. 1995; 333: 541-549.

18 Holman RR, Paul SK, Bethel MA, et al. 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008; 359: 1577-1589.

19 Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998; 352: 854-865.

20 Diabetes Prevention Program Research Group. The Diabetes Prevention Program: baseline characteristics of the randomized cohort. Diabetes Care. 2000; 23: 1619-1629.

21 Diabetes Prevention Program Research Group. The Diabetes Prevention Program. Design and methods for a clinical trial in the prevention of type 2 diabetes. Diabetes Care. 1999; 22: 623-634.

22 Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002; 346: 393-403.

23 Aroda VR, Knowler WC, Crandall JP, et al. Metformin for diabetes prevention: insights gained from the Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study. Diabetologia. 2017; 60: 1601-1611.

24 Knowler WC, Fowler SE, Hamman RF, et al; Diabetes Prevention Program Research Group. 10-Year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet. 2009; 374: 1677-1686.

25 Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. Lancet Diabetes Endocrinol. 2015; 3: 866-875.

26 Goldberg R, Temprosa M, Otvos J, et al. Lifestyle and metformin treatment favorably influence lipoprotein subfraction distribution in the Diabetes Prevention Program. J Clin Endocrinol Metab. 2013; 98: 3989-3998.

27 Drzewoski J, Hanefeld M. The current and potential therapeutic use of metformin-the good old drug. Pharmaceuticals (Basel). 2021;14: 122.

28 Lachin JM, Christophi CA, Edelstein SL, et al. Factors associated with diabetes onset during metformin versus placebo therapy in the diabetes prevention program. Diabetes. 2007; 56: 1153-1159.

29 Diabetes Prevention Program Research Group. Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study. Diabetes Care. 2012; 35: 731-737.

30 Inzucchi SE, Lipska KJ, Mayo H, et al. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. JAMA. 2014; 312: 2668-2675.

31 Bailey CJ, Turner RC. Metformin. N Engl J Med. 1996; 334: 574-579.

32 Gan SC, Barr J, Arieff AI, Pearl RG. Biguanide-associated lactic acidosis. Case report and review of the literature. Arch Intern Med. 1992; 152: 2333-2336.

33 Kidney Disease: Improving Global Outcomes Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2022; 102: S1-S127.

34 American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes – 2019. Diabetes Care. 2019; 42: S90-S102.

35 Diabetes Prevention Program Research Group. The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS. Diabetes Care. 2012; 35: 723-730.

36 Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2016; 164: 740-751.

37 Zawada A, Naskret D, Burchardt P, et al. Metformin added to intensive insulin therapy improves metabolic control in patients with type 1 diabetes and excess body fat. Pol Arch Intern Med. 2018; 128: 294-300.

38 Ainuddin JA, Karim N, Zaheer S, et al. Metformin treatment in type 2 diabetes in pregnancy: an active controlled, parallel-group, randomized, open label study in patients with type 2 diabetes in pregnancy. J Diabetes Res. 2015; 2015: 325851.

39 Rowan JA, Hague WM, Gao W, et al. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med. 2008; 358: 2003-2015.

40 Rowan JA, Rush EC, Plank LD, et al. Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition and metabolic outcomes at 7-9 years of age. BMJ Open Diabetes Res Care. 2018; 6: e000456.

41 Araszkiewicz A, Bandurska-Stankiewicz E, Borys S, et al. 2022 Guidelines on the management of patients with diabetes. A position of Diabetes Poland. Current Topics in Diabetes. 2022; 2.

42 Zhao J, Liu X, Zhang W. The effect of metformin therapy for preventing gestational diabetes mellitus in women with polycystic ovary syndrome: a meta-analysis. Exp Clin Endocrinol Diabetes. 2020; 128: 199-205.

43 Bryk-Wiązania AH, Undas A. Hypofibrinolysis in type 2 diabetes and its clinical implications: from mechanisms to pharmacological modulation. Cardiovasc Diabetol. 2021; 20: 191.

44 Zinman B, Lachin JM, Inzucchi SE. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2016; 374: 1094.

45 Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017; 377: 644-657.

46 Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019; 380: 347-357.

47 McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. JAMA Cardiol. 2021; 6: 148-158.

48 Kohler S, Zeller C, Iliev H, Kaspers S. Safety and tolerability of empagliflozin in patients with type 2 diabetes: pooled analysis of phase I–III clinical trials. Adv Ther. 2017; 34: 1707-1726.

49 Ueda P, Svanstrom H, Melbye M, et al. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. BMJ. 2018; 363: k4365.

50 Zhang XL, Zhu QQ, Chen YH, et al. Cardiovascular safety, long-term noncardiovascular safety, and efficacy of sodium-glucose cotransporter 2 inhibitors in patients with type 2 diabetes mellitus: a systemic review and meta-analysis with trial sequential analysis. J Am Heart Assoc. 2018; 7: e007165.

51 Umpierrez GE. Diabetes: SGLT2 inhibitors and diabetic ketoacidosis – a growing concern. Nat Rev Endocrinol. 2017; 13: 441-442.

52 Vallianou NG, Tsilingiris D, Kounatidis D, et al. Sodium-glucose cotransporter-2 inhibitors in obesity and associated cardiometabolic disorders: where do we stand? Pol Arch Intern Med. 2022; 132: 16342.

53 Iqbal AM, Imamudeen N, Basheer A, et al. Efficacy and cardiovascular safety of GLP-1 receptor analogues. Curr Drug Saf. 2021; 16: 197-206.

54 Sheahan KH, Wahlberg EA, Gilbert MP. An overview of GLP-1 agonists and recent cardiovascular outcomes trials. Postgrad Med J. 2020; 96: 156-161.

55 Mantovani A, Petracca G, Beatrice G, et al. Glucagon-like peptide-1 receptor agonists for treatment of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: an updated meta-analysis of randomized controlled trials. Metabolites. 2021; 11: 73.

56 Chavda VP, Ajabiya J, Teli D, et al. Tirzepatide, a new era of dual-targeted treatment for diabetes and obesity: a mini-review. Molecules. 2022; 27: 4315.

57 Frias JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. N Engl J Med. 2021; 385: 503-515.

58 ClinicalTrials.gov. A study of tirzepatide (LY3298176) compared with dulaglutide on major cardiovascular events in participants with type 2 diabetes (SURPASS-CVOT). https://clinicaltrials.gov/ct2/show/NCT04255433. Accessed December 30, 2022.

59 ElSayed NA, Aleppo G, Aroda VR, et al. 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes – 2023. Diabetes Care. 2023; 46: S140-S157.

60 Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020; 41: 255-323.

61 McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2022; 24: 4-131.

62 Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). Rev Esp Cardiol (Engl Ed). 2022; 75: 429.

63 Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2022; 65: 1925-1966.

64 Zieleniewska NA, Szum-Jakubowska A, Chlabicz M, et al. The prevalence of diabetes and prediabetes: a population-based study. Pol Arch Intern Med. 2023; 133: 16407.

65 Fojt A, Kowalik R, Gierlotka M, et al. Three-year mortality after acute myocardial infarction in patients with different diabetic status. Pol Arch Intern Med. 2021;131: 16095.

66 Dokken BB. The pathophysiology of cardiovascular disease and diabetes: beyond blood pressure and lipids. Diabetes Spectrum. 2008; 21: 160-165.

67 Morrish NJ, Wang SL, Stevens LK, et al. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia. 2001; 44: S14-S21.

68 Leon BM, Maddox TM. Diabetes and cardiovascular disease: epidemiology, biological mechanisms, treatment recommendations and future research. World J Diabetes. 2015; 6: 1246-1258.

69 Wei M, Gaskill SP, Haffner SM, Stern MP. Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality. The San Antonio Heart Study. Diabetes Care. 1998; 21: 1167-1172.

70 Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics - 2014 update: a report from the American Heart Association. Circulation. 2014; 129: e28-e292.

71 Ohira T, Shahar E, Chambless LE, et al. Risk factors for ischemic stroke subtypes: the Atherosclerosis Risk in Communities Study. Stroke. 2006; 37: 2493-1298.

72 Thomas MC, Cooper ME, Zimmet P. Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. Nat Rev Nephrol. 2016; 12: 73-81.

73 Parving HH, Lewis JB, Ravid M, et al. Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: a global perspective. Kidney Int. 2006; 69: 2057-2063.

74 Retnakaran R, Cull CA, Thorne KI, et al. Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. Diabetes. 2006; 55: 1832-1839.

75 Crowley MJ, Diamantidis CJ, McDuffie JR, et al. Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: a systematic review. Ann Intern Med. 2017; 166: 191-200.