RESEARCH PAPER

# The Evolving Role of Metformin and Glimepiride in Type 2 Diabetes Management: Efficacy, Safety, and Clinical Relevance in the Era of Newer Antidiabetic Agents

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**ABSTRACT**
Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder characterized by insulin resistance, pancreatic β-cell dysfunction, and persistent hyperglycemia. Metformin and glimepiride have remained important components of oral antidiabetic pharmacotherapy for decades because of their established glucose-lowering efficacy, affordability, and widespread availability. However, the emergence of sodium–glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonists has transformed therapeutic priorities beyond glycemic control toward cardiovascular protection, kidney preservation, and weight management. This narrative review critically evaluates the evolving therapeutic roles of metformin and glimepiride in contemporary T2DM management, focusing on their mechanisms of action, clinical effectiveness, safety, combination therapy, and comparative relevance alongside newer antidiabetic agents. Published mechanistic studies, randomized controlled trials, comparative-effectiveness investigations, cardiovascular and kidney outcome trials, and contemporary diabetes treatment recommendations were synthesized, with particular emphasis on direct comparisons involving metformin and glimepiride. Metformin remains a widely applicable glucose-lowering therapy owing to its effectiveness, low intrinsic hypoglycemia risk, relatively favorable weight profile, low acquisition cost, and extensive clinical experience. Glimepiride provides substantial glucose lowering, particularly as an add-on to metformin, but its use is constrained by hypoglycemia, weight gain, and limitations in long-term glycemic durability. Direct comparisons with DPP-4 inhibitors and SGLT2 inhibitors demonstrate important advantages of selected newer therapies in safety and weight-related outcomes. Meanwhile, newer agents with demonstrated cardiovascular and kidney benefits have shifted treatment selection toward outcomes that extend beyond HbA1c reduction. Recent clinical evidence also supports the selective incorporation of established medications into contemporary multidrug regimens. The persistence of metformin and glimepiride in diabetes management reflects their continued therapeutic utility rather than universal superiority over newer agents. Metformin retains a broad role, whereas glimepiride is increasingly positioned as a selective, cost-sensitive glucose-lowering option. Evidence-based prescribing requires balancing effectiveness, hypoglycemia risk, cardiovascular and kidney outcomes, weight-related goals, affordability, accessibility, and patient preferences.

**Keywords**: Metformin; Glimepiride; Type 2 diabetes mellitus; Combination therapy; Antidiabetic
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## INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic, progressive metabolic disorder characterized by impaired insulin sensitivity, inadequate pancreatic β-cell compensation, dysregulated hepatic glucose production, and persistent hyperglycemia. The disease is associated with microvascular complications, including retinopathy, nephropathy, and neuropathy, as well as macrovascular complications such as coronary artery disease, cerebrovascular disease, and peripheral arterial disease. The increasing global prevalence of T2DM, together with population ageing, urbanization, obesity, and lifestyle-related metabolic disturbances, represents a substantial challenge for healthcare systems worldwide[1,2,3]. The pharmacological management of T2DM has evolved considerably over the past several decades. Historically, therapeutic strategies predominantly focused on reducing fasting plasma glucose, postprandial glucose, and glycated hemoglobin (HbA1c), with the expectation that sustained glycemic improvement would reduce diabetes-related complications. Metformin and sulphonylureas consequently became widely used therapies because of their effectiveness, oral administration, affordability, and extensive clinical experience[2,4]. Metformin primarily reduces endogenous glucose production and modifies cellular energy metabolism, whereas sulphonylureas, including glimepiride, stimulate pancreatic insulin secretion. Their complementary pharmacological mechanisms provide a rationale for combination treatment when glycemic control is inadequate with monotherapy[5,6,7]. Evidence supporting metformin emerged prominently from the United Kingdom Prospective Diabetes Study (UKPDS), which demonstrated important long-term benefits of intensive glucose management in patients with newly diagnosed T2DM. In overweight participants, metformin-based treatment was associated with favorable diabetes-related outcomes, helping establish its importance in glucose-lowering therapy[8]. Further studies examining glycemic durability, long-term metabolic outcomes, and medication safety contributed to the widespread adoption of metformin as a commonly prescribed initial pharmacological treatment[9].

Glimepiride, a second-generation sulphonylurea, has similarly demonstrated meaningful glucose-lowering efficacy, either alone or in combination with metformin. Compared with some earlier insulin secretagogues, its pharmacological and dosing characteristics contributed to its incorporation into routine treatment. Nevertheless, hypoglycemia, weight gain, and dependence on residual pancreatic β-cell function remain important limitations. These concerns have become increasingly relevant as newer treatment options offer effective glycemic control with different safety profiles and additional metabolic advantages[6,7,10]. Over the past two decades, antidiabetic treatment has undergone a paradigm shift following the introduction of incretin-based therapies, SGLT2 inhibitors, and dual incretin receptor agonists. Cardiovascular outcome trials have demonstrated that selected newer medications reduce major adverse cardiovascular events, hospitalization for heart failure, or progression of chronic kidney disease (CKD), often through mechanisms extending beyond their glucose-lowering effects[11,12,13,14,15]. More recent clinical investigations have demonstrated substantial improvements in weight-related outcomes and have expanded the potential therapeutic applications of incretin-based treatments[20,21,22,23]. Consequently, contemporary diabetes management no longer considers HbA1c reduction the sole determinant of therapeutic success. Treatment selection increasingly incorporates cardiovascular disease, heart failure, kidney impairment, excess body weight, hypoglycemia risk, adverse effects, treatment burden, patient preferences, and medication accessibility. The 2026 American Diabetes Association (ADA) Standards of Care reflect this individualized approach, recommending therapies with demonstrated cardiovascular or kidney benefits in appropriate high-risk populations irrespective of the need for additional glucose lowering[1].

Large comparative-effectiveness investigations have provided important evidence for reassessing the clinical roles of older medications. The GRADE trial directly evaluated glimepiride alongside liraglutide, sitagliptin, and insulin glargine as additional therapy in patients receiving metformin, demonstrating clinically meaningful differences in glycemic durability and safety[24,25]. The CAROLINA trial compared cardiovascular outcomes between glimepiride and linagliptin, providing reassurance regarding the cardiovascular safety of glimepiride within the studied population while highlighting its greater hypoglycemia burden[10]. Additional trials comparing glimepiride with SGLT2 inhibitors and DPP-4 inhibitors have further clarified differences in weight, treatment persistence, and adverse-event profiles[27,28,29,30,31,32]. Although the mechanisms, clinical efficacy, and adverse effects of metformin and glimepiride have been individually examined in numerous publications, their continuing roles require renewed assessment within a therapeutic landscape increasingly defined by cardiovascular, kidney, and metabolic outcomes. The present narrative review critically synthesizes the pharmacological, clinical, and comparative evidence concerning metformin and glimepiride, emphasizing the distinction between glucose-lowering efficacy and broader patient-centered therapeutic benefit. It also evaluates whether the continued use of these agents is supported by clinical effectiveness, affordability, and individualized treatment considerations, or whether their positions should be reconsidered in light of newer therapeutic alternatives.

## HISTORICAL EVOLUTION OF T2DM PHARMACOTHERAPY

### The conventional glucose-centered treatment approach

The early pharmacological management of T2DM was largely centered on insulin replacement or stimulation and the reduction of hyperglycemia. Sulphonylureas offered an oral approach to increasing endogenous insulin secretion, while metformin addressed increased hepatic glucose production and insulin resistance through mechanisms distinct from those of insulin secretagogues[5,6,7]. Early landmark investigations, particularly UKPDS, established the importance of improving glycemic control for reducing diabetes-related complications. UKPDS 34 provided important evidence concerning the clinical benefits of metformin among overweight individuals with newly diagnosed T2DM[8]. These findings contributed to a treatment paradigm in which metformin was commonly prioritized and sulphonylureas were frequently used as additional therapy. However, as T2DM progresses, declining pancreatic β-cell function may limit the durability of some glucose-lowering strategies. The ADOPT trial demonstrated that monotherapy failure differs among oral antidiabetic medications, indicating that initial glucose-lowering effectiveness does not necessarily predict long-term therapeutic durability[9].

### Emergence of incretin-based therapies

Recognition of the role of the incretin system in glucose homeostasis contributed to the development of DPP-4 inhibitors and GLP-1 RAs. These agents offered new opportunities to improve glucose regulation while reducing reliance on glucose-independent insulin secretion. DPP-4 inhibitors generally provide modest to intermediate glucose-lowering effects with a low intrinsic risk of hypoglycemia and relatively neutral effects on body weight. GLP-1 RAs achieve stronger glucose lowering and clinically meaningful weight reduction, although tolerability and drug-specific characteristics influence treatment selection[2,33,34,35]. The development of these therapies challenged the widespread use of sulphonylureas as routine second-line treatment, especially where avoiding hypoglycemia and weight gain became important clinical priorities.

### Emergence of cardiovascular and kidney protection

The introduction of SGLT2 inhibitors further transformed T2DM management. EMPA-REG OUTCOME trial demonstrated reductions in major cardiovascular outcomes and mortality in patients with T2DM and established cardiovascular disease[11]. Subsequent trials involving canagliflozin and dapagliflozin provided additional evidence of cardiovascular and kidney-related benefits[13,14,16,17]. Similarly, GLP-1 RA trials involving liraglutide, semaglutide, and dulaglutide demonstrated cardiovascular benefits in relevant patient populations[12,15,18]. Importantly, these observations

expanded the concept of antidiabetic efficacy beyond changes in HbA1c alone.

**The contemporary outcome-oriented treatment paradigm**

More recent evidence has strengthened the emphasis on weight management, cardiorenal protection, and long-term clinical outcomes. Trials evaluating tirzepatide demonstrated major improvements in glucose and body-weight outcomes, while cardiovascular outcome studies of newer incretin therapies further expanded their evidence base[20,21,22,23]. The SOUL trial, published in 2025, demonstrated cardiovascular benefit with oral semaglutide in patients with T2DM at high cardiovascular or renal risk[22]. In SURPASS-CVOT, published in December 2025, tirzepatide demonstrated noninferiority, but not statistically established superiority, to dulaglutide for major adverse cardiovascular events in patients with T2DM and established atherosclerotic cardiovascular disease[23]. These developments reinforce the importance of evidence-based selection among established and newer medications rather than assuming that newer drugs are universally superior or that older treatments should automatically be discontinued.

## METFORMIN: MOLECULAR MECHANISM, CLINICAL BENEFITS, AND THERAPEUTIC RELEVANCE

**Molecular and metabolic mechanisms**

Metformin remains one of the most extensively studied oral glucose-lowering agents. Although its therapeutic effectiveness has been recognized for decades, the precise molecular mechanisms responsible for its actions continue to be investigated. Its principal clinical effect is a reduction in hepatic glucose production, with additional contributions from intestinal metabolism, cellular energy regulation, and altered glucose utilization[5,36,37]. One frequently investigated mechanism involves modulation of mitochondrial energy metabolism. Experimental investigations have suggested that metformin may inhibit mitochondrial respiratory-chain complex I under certain conditions, altering the cellular AMP/ATP ratio and promoting activation of AMP-activated protein kinase (AMPK). AMPK functions as an important regulator of cellular energy homeostasis, influencing hepatic gluconeogenesis, lipid metabolism, and multiple intracellular signalling pathways[5]. However, metformin-induced suppression of hepatic glucose production cannot be explained exclusively through AMPK activation. Experimental studies have identified AMPK-independent mechanisms, including altered mitochondrial redox metabolism and effects on glucagon-mediated signalling. The relative contribution of these pathways may vary with metformin concentrations, experimental models, and tissue-specific drug distribution[5,36,37]. The gastrointestinal tract has also emerged as an important contributor to metformin activity. Intestinal glucose uptake and utilization, changes in gut hormone signalling, and alterations in intestinal microbial communities may participate in the drug's overall glucose-lowering effects. These findings suggest that metformin functions through multiple interconnected mechanisms rather than through a single molecular target[36,37]. This mechanistic complexity remains scientifically relevant because it may explain differences in tolerability and treatment response among individuals. Nevertheless, findings from cellular or animal models must be distinguished from mechanisms conclusively demonstrated to contribute to clinical outcomes in humans.

**Glucose-lowering effectiveness and durability**

The clinical effectiveness of metformin is well established. It reduces fasting glucose and HbA1c without directly inducing glucose-independent insulin secretion, which contributes to its relatively low intrinsic hypoglycemia risk. The magnitude of HbA1c reduction varies according to baseline glycemia, adherence, dosing, disease duration, and concurrent treatment[1,2]. The UKPDS 34 trial provided historical evidence supporting metformin-based treatment in overweight individuals with newly diagnosed T2DM[8]. The ADOPT trial subsequently demonstrated differences in the durability of oral glucose-lowering therapies. The cumulative incidence of monotherapy failure at five years was approximately 21% with metformin, compared with 34% with glyburide and 15% with rosiglitazone[9]. These findings highlight two important considerations. First, metformin provides clinically relevant and reasonably durable glycemic control. Second, T2DM progression may eventually require additional treatment regardless of initial therapeutic effectiveness. The historical cardiovascular benefits associated with metformin should be interpreted cautiously. UKPDS was conducted in a substantially different treatment era, and its findings should not be considered direct proof that metformin offers the same cardiovascular protection demonstrated in contemporary placebo-controlled outcome trials of selected SGLT2 inhibitors and GLP-1 RAs[8,11,12,13,14,15].

**Metformin and body-weight regulation**

Metformin is generally considered weight neutral or modestly weight reducing, distinguishing it from medications such as sulphonylureas and insulin, which may promote weight gain[1,2]. Its potential effects on body weight may involve improvements in insulin sensitivity, intestinal metabolic signalling, and changes in appetite-related pathways. However, weight reduction with metformin is typically much less pronounced than that achieved with newer incretin-based therapies in populations selected for weight-related treatment outcomes[20,21]. Therefore, metformin remains relevant in patients with insulin resistance and excess body weight, but it should not be regarded as an alternative providing equivalent weight-loss efficacy to high-potency GLP-1-based treatments.

**Gastrointestinal tolerability and formulation considerations**

Gastrointestinal adverse effects, particularly diarrhoea, nausea, abdominal discomfort, and bloating, remain major contributors to metformin intolerance. Such adverse effects may occur during treatment initiation or dose escalation and can interfere with adherence[1,38]. Prolonged-release formulations have been developed to modify drug delivery and may improve gastrointestinal tolerability and dosing convenience in some patients. However, improvements are not universal, and the magnitude of benefit can depend on the formulation,

dose, patient characteristics, and treatment history. This distinction is particularly relevant for patients requiring prolonged treatment. The choice between immediate-release and prolonged-release metformin should be informed by tolerability, adherence, availability, cost, and the ability to achieve the intended glycemic response.

**Vitamin B12 deficiency and renal safety**

Long-term metformin treatment has been associated with reductions in circulating vitamin B12. In a randomized placebo-controlled study, de Jager et al. [39] demonstrated an increased risk of vitamin B12 deficiency among patients receiving prolonged metformin therapy[39]. This adverse effect is clinically important because vitamin B12 deficiency may contribute to anaemia and neurological symptoms, potentially complicating the evaluation of diabetic peripheral neuropathy. Periodic assessment is therefore appropriate, particularly in patients with anaemia, neuropathy, or prolonged exposure[1]. Metformin elimination is dependent largely on renal function. Reduced kidney function may increase systemic exposure, particularly in the presence of acute illness or other conditions affecting drug clearance. Metformin is generally contraindicated at an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m², while continued treatment at moderately reduced eGFR requires individualized consideration[1,40]. Although metformin-associated lactic acidosis is rare, the possibility of serious adverse outcomes emphasizes the need for appropriate patient selection and reassessment during acute kidney injury, severe hypoxia, or major intercurrent illness.

**Contemporary therapeutic positioning of metformin**

The continuing importance of metformin is supported by the combination of efficacy, safety, low acquisition cost, oral administration, and extensive experience across heterogeneous populations. Nevertheless, its position has evolved from being routinely regarded as an obligatory first step toward being one of several foundational treatment options selected according to individual clinical needs. For patients with established cardiovascular disease, heart failure, or CKD, the use of medications with demonstrated cardiorenal benefits may be prioritized irrespective of whether metformin has already been initiated[1,2].

## GLIMEPIRIDE: CLINICAL EFFECTIVENESS AND THE CHANGING POSITION OF SULPHONYLUREAS

**Pharmacological mechanism of action**

Glimepiride is a second-generation sulphonylurea that lowers blood glucose primarily by stimulating insulin secretion from pancreatic β-cells. It binds to the sulphonylurea receptor component of ATP-sensitive potassium channels, promoting channel closure, membrane depolarization, calcium influx, and insulin exocytosis[6,7]. The resulting increase in circulating insulin can effectively reduce blood glucose in individuals with residual β-cell function. Unlike incretin-based therapies, however, sulphonylurea-induced insulin secretion is not strictly dependent on ambient glucose concentration. This mechanism contributes to both the glucose-lowering effectiveness and the principal safety limitations of glimepiride. Increased insulin secretion may produce hypoglycemia, particularly when food intake is reduced, physical activity changes, or drug elimination is impaired.

**Clinical glucose-lowering effectiveness**

Glimepiride has demonstrated substantial glucose-lowering effectiveness as monotherapy and as an additional medication in patients receiving metformin. The GRADE trial provides particularly important evidence regarding its contemporary clinical performance. In this multicentre randomized investigation, approximately 5,000 patients with T2DM receiving metformin were assigned to glimepiride, sitagliptin, liraglutide, or insulin glargine[24]. Although all four medications improved glucose control, insulin glargine and liraglutide provided more favourable maintenance of glycemic targets than glimepiride and sitagliptin over the observation period. These differences demonstrate that effective initial HbA1c lowering does not necessarily establish equivalent long-term durability[24]. Consequently, the clinical value of glimepiride should be considered through both its immediate glucose-lowering effect and its ability to maintain individualized glycemic targets without unacceptable treatment-related risks.

**Hypoglycemia and associated clinical consequences**

Hypoglycemia is a major limitation of glimepiride treatment. Its incidence is influenced by dose, age, kidney function, dietary patterns, concomitant therapies, and residual endogenous insulin secretion. In the GRADE trial, severe hypoglycemia was more frequent among patients receiving glimepiride than among those assigned to liraglutide or sitagliptin[24]. Similarly, the CAROLINA trial demonstrated a substantially greater frequency of hypoglycemic events with glimepiride than with linagliptin despite broadly comparable cardiovascular outcomes[10]. The clinical significance of hypoglycemia extends beyond acute symptoms. Recurrent episodes may contribute to falls, accidents, emergency healthcare use, medication nonadherence, anxiety concerning treatment, and reduced quality of life. Although the probability and severity of these outcomes vary considerably, hypoglycemia risk is an important consideration when selecting therapy for older adults, patients with CKD, individuals with irregular meal patterns, and patients receiving multiple glucose-lowering drugs[1,2,26].

**Weight gain and metabolic limitations**

Glimepiride treatment may be associated with modest weight gain, primarily because of increased endogenous insulin secretion and changes in energy storage. This characteristic has become increasingly important because contemporary T2DM management often includes weight reduction as a central therapeutic objective. In direct comparative investigations, SGLT2 inhibitors and some incretin-based treatments have demonstrated more favorable body-weight effects than glimepiride[27,28,29,30,31]. Therefore, while glimepiride remains effective for reducing HbA1c, its overall metabolic profile may be less suitable for individuals with obesity or for patients prioritizing substantial weight reduction.

**Cardiovascular safety: Reassessing established concerns**

Historical concerns were influenced by observations involving earlier agents and by the potential consequences of hypoglycemia. However, it is inappropriate to assume that all sulphonylureas possess identical cardiovascular effects or that observational associations necessarily establish causation. The CAROLINA randomized trial directly evaluated linagliptin and glimepiride in patients with T2DM and increased cardiovascular risk. The primary composite cardiovascular endpoint occurred in 11.8% of patients receiving linagliptin and 12.0% receiving glimepiride, establishing noninferiority of linagliptin relative to glimepiride[10]. These findings provide clinically important reassurance regarding the cardiovascular safety of glimepiride within the studied population. Nevertheless, cardiovascular safety and cardiovascular protection are fundamentally different concepts. Demonstrating that glimepiride does not produce significantly worse cardiovascular outcomes than a comparator does not demonstrate that it reduces cardiovascular events compared with placebo or provides the organ-protective effects established for selected newer antidiabetic agents. This distinction is central to interpreting the evolving position of sulphonylureas.

**Long-term therapeutic relevance**

Glimepiride remains useful because of its effectiveness, low acquisition cost, oral administration, and broad availability. For individuals requiring additional glucose lowering who cannot access or afford newer agents, glimepiride may represent a practical and clinically effective option. However, its suitability should be reconsidered in patients with recurrent hypoglycemia, frailty, substantial kidney impairment, treatment-related weight gain, or the development of cardiovascular or kidney conditions for which other agents offer demonstrated benefits[1,2]. Its evolving role therefore reflects a shift from routine treatment intensification toward more selective application based on individual benefit–risk considerations.

## METFORMIN–GLIMEPIRIDE COMBINATION THERAPY: CLINICAL RATIONALE, EFFECTIVENESS, AND LIMITATIONS

### Complementary mechanisms and therapeutic rationale

Metformin and glimepiride exert complementary effects on glucose homeostasis. Metformin reduces excessive hepatic glucose production and influences cellular glucose metabolism, whereas glimepiride enhances insulin secretion from pancreatic β-cells[5,6,7]. Their combination can therefore address more than one metabolic defect contributing to hyperglycemia. However, complementary mechanisms should not automatically be described as pharmacological synergy. True synergy requires evidence demonstrating that the combined drug effect exceeds that predicted from the effects of the individual components. For this reason, the combination is more accurately described as a complementary glucose-lowering strategy unless a formal interaction analysis establishes synergistic activity.

### Clinical effectiveness of combination treatment

Adding a sulphonylurea to metformin can provide additional HbA1c reduction in patients whose glycemic targets are not achieved with metformin alone. The GRADE trial established that glimepiride remains an effective add-on treatment, although differences in durability and hypoglycemia influence its relative attractiveness compared with alternative agents[24]. Direct comparisons with DPP-4 inhibitors and SGLT2 inhibitors provide further evidence concerning the benefits and limitations of this combination approach[27,28,29,30,31,32]. The therapeutic value of metformin–glimepiride treatment is therefore not determined simply by its ability to reduce HbA1c, but by its capacity to achieve sustained glucose control with acceptable treatment burden and adverse-event risk. **Figure 1** illustrates the complementary glucose-lowering mechanisms of metformin and glimepiride in T2DM.

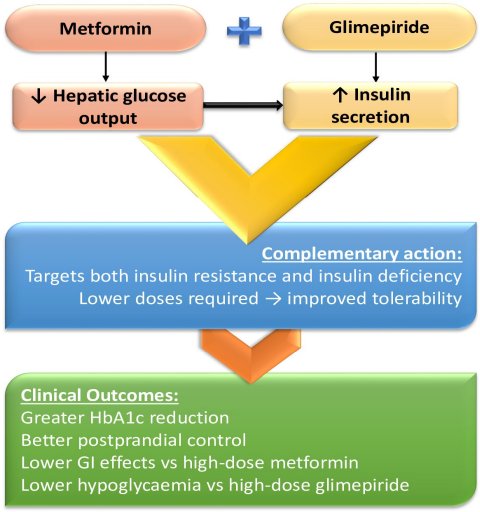



**Figure 1**: Complementary Glucose-Lowering Mechanisms of Metformin and Glimepiride in T2DM.

### Fixed-dose combination formulations

Fixed-dose combinations may simplify medication schedules and reduce the number of tablets required each day. This can be valuable when treatment complexity affects adherence. The use of prolonged-release metformin in combination regimens may also provide advantages in dosing convenience and gastrointestinal tolerability for selected patients. However, fixed-dose combinations can restrict individual dose adjustment. This may become problematic when metformin requires modification because of gastrointestinal intolerance or kidney function, or when glimepiride requires reduction because of hypoglycemia. Thus, any advantage in convenience must be balanced against the clinical need for dosing flexibility.

### Integration with newer antidiabetic therapies

The continued relevance of metformin–glimepiride therapy is also reflected in studies evaluating the addition of newer agents to established dual-drug regimens. A 2025 randomized Indian clinical investigation evaluated a fixed-dose combination incorporating dapagliflozin, glimepiride, and extended-release metformin in patients inadequately controlled with metformin and glimepiride[41]. Similarly, a 2026 randomized investigation

compared sitagliptin–metformin–glimepiride combination therapy with metformin–glimepiride treatment in Indian patients with T2DM[42]. These studies illustrate that treatment evolution does not always require complete abandonment of older medications. In selected circumstances, newer agents may be incorporated into established regimens to improve glycemic effectiveness. Nevertheless, increasing the number of glucose-lowering medications also introduces concerns about polypharmacy, drug interactions, monitoring requirements, and hypoglycemia. In particular, the need for sulphonylurea dose reduction should be considered when additional treatment improves glucose control[1].

## DIRECT COMPARATIVE EVIDENCE: GLIMEPIRIDE VERSUS NEWER ANTIDIABETIC AGENTS

Direct randomized comparisons are particularly valuable for determining the contemporary position of glimepiride because they reduce the uncertainty associated with comparing outcomes across unrelated trials.

### Glimepiride versus SGLT2 inhibitors

The CANTATA-SU trial compared canagliflozin with glimepiride in patients whose T2DM was inadequately controlled with metformin. Canagliflozin demonstrated clinically meaningful glucose lowering together with favourable effects on body weight, while glimepiride was associated with a higher frequency of hypoglycemia[28]. Similarly, Ridderstrale et al. [27] evaluated empagliflozin versus glimepiride as add-on treatment to metformin over 104 weeks. Empagliflozin demonstrated noninferior glucose-lowering efficacy at the primary assessment and a more favourable hypoglycemia and weight profile[27]. Confirmed hypoglycemic adverse events occurred in approximately 2% of patients receiving empagliflozin compared with 24% of those receiving glimepiride[27]. These findings are directly relevant because they demonstrate that the clinical advantages of newer treatments may arise from safety and weight-related outcomes even when glucose-lowering effectiveness is broadly comparable. Nevertheless, it is important to recognize differences in adverse-effect profiles. SGLT2 inhibitors may increase the risk of genital mycotic infections and require additional caution in patients vulnerable to volume depletion or ketoacidosis[1].

### Glimepiride versus DPP-4 inhibitors

DPP-4 inhibitors have been investigated extensively as alternatives to sulphonylureas in patients receiving metformin. Gallwitz et al. [29] compared linagliptin with glimepiride over two years and reported similar overall glycemic efficacy with differences in hypoglycemia and weight-related outcomes[29]. Matthews et al. [30] similarly compared vildagliptin with glimepiride as add-on treatment to metformin, demonstrating the potential advantages of DPP-4 inhibition in reducing hypoglycemia and avoiding treatment-associated weight gain[30]. Indian comparative studies have also examined sitagliptin–metformin and glimepiride–metformin regimens, providing evidence relevant to treatment selection in settings where drug affordability and accessibility influence prescribing[31,32]. These findings indicate that DPP-4 inhibitors may offer improved tolerability and reduced hypoglycemia risk in selected patients[1,2].

### Glimepiride versus GLP-1 receptor agonists

The GRADE trial provided direct comparative evidence concerning glimepiride and liraglutide as additional therapy to metformin. Liraglutide demonstrated more favourable glycemic durability than glimepiride and was associated with a lower frequency of severe hypoglycemia[24]. Beyond glycemic control, selected GLP-1 RAs have demonstrated reductions in major cardiovascular events and clinically meaningful weight loss[12,15,18]. More recent evidence from the FLOW trial demonstrated that subcutaneous semaglutide reduced important kidney outcomes in patients with T2DM and CKD[19]. This further strengthens the argument that newer agents may provide benefits that cannot be adequately represented by HbA1c comparisons alone.

### Interpretation of comparative evidence

Direct comparative trials consistently demonstrate that glimepiride remains effective for glucose lowering. However, the evidence also identifies important differences in hypoglycemia, weight change, durability, and broader clinical outcomes.

**Table 1: Direct comparative trials relevant to the contemporary role of glimepiride**

| Study | Comparison | Main observation | Clinical interpretation |
|---|---|---|---|
| Matthews et al., 2010[30] | Vildagliptin vs. glimepiride, both added to metformin | Similar glycemic effectiveness with reduced hypoglycemia and weight-related disadvantages in the vildagliptin group | Safety may differentiate treatments with comparable glucose lowering |
| Gallwitz et al., 2012[29] | Linagliptin vs. glimepiride added to metformin | Similar overall glucose-lowering effectiveness with a more favorable hypoglycemia profile | DPP-4 inhibitors may be preferable where hypoglycemia avoidance is important |

| | | | |
|---|---|---|---|
| | | for linagliptin | |
| Cefalu et al., 2013[28] | Canagliflozin vs. glimepiride added to metformin | Effective glucose lowering with favorable weight and hypoglycemia outcomes for canagliflozin | SGLT2 inhibitors offer additional metabolic advantages |
| Ridderstrale et al., 2014[27] | Empagliflozin vs. glimepiride added to metformin | Confirmed hypoglycemic adverse events: approximately 2% vs. 24% | Strong direct evidence of different safety profiles |
| Devarajan et al., 2017[31] | Glimepiride–metformin vs. sitagliptin–metformin | Indian comparative evidence on effectiveness and tolerability | Relevant to individualized and affordability-sensitive prescribing |
| Rosenstock et al., 2019[10] | Linagliptin vs. glimepiride | Comparable major cardiovascular event rates, greater hypoglycemia burden with glimepiride | Cardiovascular safety does not eliminate other treatment limitations |
| The GRADE Study Research Group, 2022[24,25] | Glimepiride, liraglutide, sitagliptin, and insulin glargine | Differences in glycemic durability, safety and clinical outcomes | Effective HbA1c reduction alone is insufficient for ranking therapies |
| | added to metformin | | |

## CARDIOVASCULAR AND KIDNEY OUTCOMES

### Cardiovascular outcomes with established glucose-lowering therapies

Cardiovascular disease remains a major contributor to morbidity and mortality in patients with T2DM. Historically, therapeutic decisions were often based on the assumption that improving long-term glycemic control would translate into reductions in cardiovascular complications. However, evidence from major trials has demonstrated that the relationship between glucose lowering and cardiovascular protection is complex. The ACCORD trial highlighted the potential risks of intensive glucose-lowering strategies in selected high-risk populations, while ADVANCE and VADT contributed additional evidence regarding the long-term clinical consequences of intensive glycemic management[43,44,45]. These trials helped establish that the magnitude of HbA1c reduction should not be considered a substitute for directly measured cardiovascular outcomes. For metformin, the UKPDS findings remain historically important, although contemporary interpretation must account for changes in background cardiovascular treatment and diabetes management[8]. For glimepiride, CAROLINA provided reassurance concerning cardiovascular safety compared with linagliptin, but did not establish cardiovascular protection[10].

### Cardiovascular benefits of SGLT2 inhibitors

The EMPA-REG OUTCOME trial demonstrated significant cardiovascular benefits with empagliflozin in patients with T2DM and established cardiovascular disease[11]. The CANVAS Program and DECLARE–TIMI 58 trial provided additional evidence concerning the cardiovascular effects of SGLT2 inhibitors in populations with differing baseline cardiovascular risk[13,14]. The benefits of this class extend to heart failure management. EMPEROR-Preserved and DELIVER demonstrated reductions in clinically important heart failure outcomes in patients with preserved or mildly reduced ejection fraction[46,47]. These observations distinguish SGLT2 inhibitors from glucose-lowering medications whose cardiovascular value has primarily been assessed through safety comparisons rather than demonstrations of reduced heart failure or cardiovascular events.

### Kidney protection and disease progression

CKD is a major complication of T2DM, and preservation of kidney function has become an important therapeutic objective. CREDENCE demonstrated the kidney-protective effects of canagliflozin in patients with T2DM and albuminuric CKD[16]. DAPA-CKD demonstrated clinically important benefits of dapagliflozin in patients with CKD, including those without diabetes[17]. The EMPA-KIDNEY trial further expanded evidence concerning empagliflozin in CKD[48]. More recent follow-up and secondary analyses have examined sustained treatment effects and kidney disease progression[49,50]. GLP-1 RA treatment has also demonstrated kidney-related advantages in selected populations. In FLOW, semaglutide significantly reduced the risk of clinically important kidney outcomes and death from

cardiovascular causes among patients with T2DM and CKD[19]. These findings have substantially changed the positioning of medications used in patients with diabetes and CKD. Although metformin and glimepiride may continue to contribute to glycemic control in appropriately selected patients, they should not be considered substitutes for treatments with established kidney-protective efficacy.

**Cardiovascular outcome evidence with incretin-based therapies**

The LEADER, SUSTAIN-6, and REWIND trials provided important evidence of cardiovascular benefits with selected GLP-1 RAs[12,15,18]. The SOUL trial subsequently demonstrated cardiovascular benefit with oral semaglutide, highlighting that the advantages of modern incretin-based therapy are not restricted to injectable formulations[22]. SURPASS-CVOT further clarified the cardiovascular profile of tirzepatide through an active-comparator trial against dulaglutide, demonstrating noninferiority for major adverse cardiovascular events without establishing superiority on the primary endpoint[23]. The evolving evidence therefore supports a treatment strategy in which medication selection is influenced by demonstrated organ-specific benefits, not merely by glucose-lowering potency.

## THE IMPORTANCE OF WEIGHT MANAGEMENT AND METABOLIC OUTCOMES

Obesity and excess adiposity contribute substantially to insulin resistance, impaired metabolic regulation, and progression of T2DM. Consequently, weight management has become increasingly integrated into pharmacological treatment selection. Metformin is generally associated with weight neutrality or modest weight reduction, whereas glimepiride may contribute to weight gain[1,2]. These characteristics should be considered when evaluating the overall benefits of established treatment regimens. In contrast, newer incretin-based therapies have demonstrated considerably greater weight-lowering effects. SURPASS-2 demonstrated superior HbA1c and body-weight reductions with tirzepatide compared with semaglutide 1 mg once weekly[20]. SURPASS-4 further evaluated tirzepatide against insulin glargine in patients with T2DM and increased cardiovascular risk, contributing evidence concerning glycemic efficacy and metabolic outcomes[21]. These findings demonstrate that contemporary antidiabetic treatment can potentially address hyperglycemia and excess weight simultaneously. However, comparisons between agents should be interpreted in relation to their study populations, comparator doses, and intended therapeutic outcomes. Greater weight reduction does not automatically establish superiority for every clinical endpoint or every patient. For patients with limited treatment access, established oral therapies may remain practical options. Conversely, where excess body weight constitutes a major clinical priority and newer therapies are accessible and appropriate, treatment strategies based primarily on sulfonylureas may be less desirable.

## METFORMIN AND GLIMEPIRIDE REMAIN CLINICALLY RELEVANT IN THE ERA OF NEWER ANTIDIABETIC AGENTS

The continued use of metformin and glimepiride represents one of the most clinically significant questions addressed by this review. Their persistence cannot be explained by a single factor. Rather, it reflects the interaction of established effectiveness, affordability, treatment familiarity, patient-specific considerations, medication accessibility, and differences in the clinical objectives of diabetes therapy.

**Established glucose-lowering effectiveness remains valuable**

Despite substantial therapeutic innovation, maintaining adequate glycemic control remains fundamental to reducing diabetes-related complications. Metformin and glimepiride provide effective glucose lowering through established mechanisms, and their continued use can be clinically appropriate when the intended glycemic targets are achieved without unacceptable adverse effects[5,6,7,8,9,24]. However, the clinical relevance of glucose lowering must be evaluated alongside broader therapeutic outcomes. In patients with cardiovascular disease, heart failure, or CKD, an alternative agent may be preferable even when current glucose concentrations are adequately controlled[1,2].

**Affordability and equitable treatment access**

The affordability of established antidiabetic medications is particularly important in settings where patients face substantial out-of-pocket expenditure. Generic metformin and glimepiride are generally available at relatively low acquisition costs, potentially reducing financial barriers to long-term pharmacotherapy. Nevertheless, medication acquisition cost does not fully capture therapeutic value. The overall economic consequences of treatment depend on several factors, including long-term glycemic durability, hypoglycemia, adverse events, monitoring, hospitalization, cardiovascular and kidney complications, and the need for treatment intensification. Therefore, the argument for continued glimepiride use should not be limited to its low price. Instead, its cost advantages should be evaluated against its clinical effectiveness and potential downstream healthcare consequences.

**Clinical familiarity and extensive prescribing experience**

Metformin and glimepiride have been prescribed for decades, providing substantial clinical experience regarding dosing, adverse effects, and treatment response. This familiarity can facilitate routine management, particularly in healthcare environments with limited access to specialist consultation. However, clinical familiarity does not necessarily establish contemporary therapeutic superiority. When newer therapies offer clinically important benefits for patients with specific comorbidities, continued prescribing of established drugs solely because of familiarity may represent therapeutic inertia rather than individualized care.

**Oral administration, convenience, and adherence**

Oral therapy may remain preferable for patients who are unwilling or unable to use injectable medications. Both

metformin and glimepiride are orally administered, and fixed-dose combinations may reduce treatment complexity. Nevertheless, oral administration is no longer an advantage unique to traditional therapies. SGLT2 inhibitors, DPP-4 inhibitors, and oral semaglutide provide alternatives with differing efficacy and safety profiles[1,22]. Therefore, route of administration should be treated as one component of treatment selection rather than the principal justification for continued use.

**Differentiating the roles of metformin and glimepiride**

Although metformin and glimepiride are frequently discussed together, their continued relevance arises from different clinical considerations. Metformin remains a broadly applicable glucose-lowering therapy because of its efficacy, low intrinsic hypoglycemia risk, relatively favorable weight profile, and affordability. Glimepiride remains a more selective option, particularly when additional glucose lowering is required and newer treatments are inaccessible, unaffordable, contraindicated, or poorly tolerated. This distinction is essential because treating both agents as equally foundational would overlook important differences in safety and contemporary clinical positioning.

**Therapeutic inertia versus rational continuation**

Continued use of an established therapy can be appropriate when it is effective, safe, affordable, and aligned with individual treatment goals. However, treatment continuation becomes less defensible when clinically important problems arise, such as recurrent hypoglycemia, substantial weight gain, inadequate glycemic durability, or the development of conditions for which newer therapies provide demonstrated benefits. Contemporary treatment recommendations emphasize timely modification, intensification, or deintensification of therapy based on changing patient circumstances[1].

## RESEARCH GAPS AND FUTURE PERSPECTIVES

**Need for contemporary comparative-effectiveness investigations**

Although established antidiabetic medications have been extensively studied, many historical trials were conducted before the availability of newer therapies with documented cardiovascular and kidney benefits. Additional comparative-effectiveness investigations are warranted to evaluate metformin- and glimepiride-based regimens against contemporary treatment strategies in populations differing by age, diabetes duration, obesity, cardiovascular status, kidney function, and treatment affordability. Such studies should incorporate long-term clinical outcomes rather than relying exclusively on HbA1c changes.

**Evidence gaps in metformin–glimepiride combination therapy**

An important research gap concerns the comparative long-term effectiveness of metformin–glimepiride combinations against contemporary multidrug regimens. Although existing trials provide evidence concerning glycemic control and adverse effects, further investigation is needed to clarify which patient subgroups obtain the greatest net benefit from sulphonylurea-containing treatment. Particular attention should be given to the durability of glucose lowering, recurrent hypoglycemia, treatment discontinuation, and differences in body-weight trajectories.

**Real-world adherence, persistence, and treatment accessibility**

Randomized trials provide important evidence of efficacy under controlled conditions but may not fully represent clinical practice in resource-constrained settings. Real-world investigations are needed to evaluate medication persistence, affordability, prescribing behavior, treatment interruption, and barriers to accessing newer therapies. Such evidence could clarify whether continued glimepiride use primarily reflects rational individualized treatment, financial limitations, or persistent prescribing habits.

**Cost-effectiveness and resource-sensitive treatment strategies**

Future pharmacoeconomic studies should compare complete treatment pathways rather than acquisition costs alone. Relevant outcomes include medication expenditure, monitoring, hospitalization, severe hypoglycemia, cardiovascular events, kidney disease progression, and quality-adjusted life-years. This is particularly important because the availability and prices of newer medications may change over time, potentially altering the economic advantages of established treatment options.

**Personalized prescribing and treatment deintensification**

Greater understanding of T2DM heterogeneity may support more individualized therapeutic decisions. Clinical characteristics such as residual β-cell function, insulin resistance, kidney function, body composition, dietary patterns, and susceptibility to hypoglycemia could inform the selection of established or newer therapies. Treatment deintensification also deserves additional investigation, particularly among older adults and patients receiving multiple glucose-lowering medications. In some circumstances, reducing or discontinuing a sulphonylurea may improve safety without substantially compromising glycemic control.

**Future role of established treatments**

The future of metformin and glimepiride is unlikely to involve either universal continuation or complete replacement. Metformin is likely to remain clinically important because of its established effectiveness, safety familiarity, affordability, and broad applicability. Glimepiride may increasingly occupy a narrower position as an effective and affordable medication for appropriately selected patients, with particular attention to hypoglycemia vulnerability and treatment goals. The principal research challenge is therefore to determine where established treatments produce favorable outcomes relative to newer alternatives, rather than simply determining which medication lowers HbA1c most strongly.

## CONCLUSION

The management of T2DM has undergone a major therapeutic transition, from a predominantly glucose-centered approach toward integrated strategies emphasizing cardiovascular protection, kidney preservation, weight management, treatment safety, and individualized clinical outcomes. In this changing

environment, metformin and glimepiride remain relevant, but their contemporary roles are increasingly distinct. Metformin continues to occupy a broad position in T2DM management because of its glucose-lowering effectiveness, low intrinsic hypoglycemia risk, relatively favorable weight profile, affordability, and extensive clinical experience. Nevertheless, the increasing availability of therapies with established cardiovascular and kidney benefits challenges the traditional assumption that metformin must universally precede all other treatments. Glimepiride remains a potent and accessible insulin secretagogue capable of achieving clinically meaningful reductions in blood glucose. Direct comparative investigations, including GRADE, CAROLINA, and studies involving DPP-4 and SGLT2 inhibitors, confirm its continued efficacy while identifying important limitations relating to hypoglycemia, weight gain, and treatment durability. The emergence of newer antidiabetic medications does not necessarily render established therapies obsolete. However, it requires their clinical value to be reassessed against broader therapeutic objectives. Affordability, oral administration, and treatment familiarity remain important considerations, particularly in resource-limited settings, but should not justify continued use when safer or more clinically beneficial alternatives are indicated. The evolving role of metformin and glimepiride is therefore best understood as therapeutic repositioning rather than therapeutic replacement. Metformin remains a broadly useful component of individualized diabetes care, whereas glimepiride retains a more selective position guided by glycemic needs, hypoglycemia risk, affordability, and patient characteristics. Their continued relevance should ultimately be defined by evidence-based clinical value rather than the duration of their historical use.

**References**


1. American Diabetes Association Professional Practice Committee for Diabetes. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2026. *Diabetes Care*. 2025;49(Supplement_1):S183-S215. doi:10.2337/dc26-S009

2. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in Type 2 diabetes, 2022. A consensus Report by the American Diabetes Association (ADA) and the european association for the study of diabetes (EASD). *Diabetes Care*. 2022;45(11):2753-2786. doi:10.2337/dci22-0034

3. Genitsaridi I, Salpea P, Salim A, et al. 11th edition of the IDF Diabetes Atlas: global, regional, and national diabetes prevalence estimates for 2024 and projections for 2050. *The Lancet Diabetes & Endocrinology*. 2026;14(2):149-156. doi:10.1016/s2213-8587(25)00299-2

4. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and Treatment of Type 2 diabetes: Perspectives on the past, present, and Future. *The Lancet*. 2014;383(9922):1068-1083. doi:10.1016/s0140-6736(13)62154-6

5. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. *Diabetologia*. 2017;60(9):1577-1585. doi:10.1007/s00125-017-4342-z

6. Proks P, Reimann F, Green N, Gribble F, Ashcroft F. Sulfonylurea stimulation of insulin secretion. *Diabetes*. 2002;51 (3):S368-76. doi:10.2337/diabetes.51.2007.s368

7. Müller G, Satoh Y, Geisen K. Extrapancreatic effects of sulfonylureas — a comparison between glimepiride and conventional sulfonylureas. *Diabetes Research and Clinical Practice*. 1995;28:S115-S137. doi:10.1016/0168-8227(95)01089-V

8. 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). *The Lancet*. 1998;352(9131):854-865. doi:10.1016/s0140-6736(98)07037-8

9. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *The New England journal of medicine*. 2006;355(23):2427-2443. doi:10.1056/NEJMoa066224

10. Rosenstock J, Kahn SE, Johansen OE, 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(12):1155-1166. doi:10.1001/jama.2019.13772

11. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *New England Journal of Medicine*. 2015;373(22):2117-2128. doi:10.1056/nejmoa1504720

12. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine*. 2016;375(4):311-322. doi:10.1056/nejmoa1603827

13. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *New England Journal of Medicine*. 2017;377(7):644-657. doi:10.1056/nejmoa1611925

14. Wiviott S D, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *The New England Journal of Medicine*. 2018;380(4):347-357. doi:10.1056/NEJMoa1812389

15. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *New England Journal of Medicine*. 2016;375(19):1834-1844. doi:10.1056/nejmoa1607141

16. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *New England Journal of Medicine*. 2019;380(24):2295-2306. doi:10.1056/nejmoa1811744

17. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *New England Journal of Medicine*. 2020;383(15):1436-1446. doi:10.1056/nejmoa2024816

18. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *The Lancet*. 2019;394(10193):121-130. doi:10.1016/s0140-6736(19)31149-3

19. Perkovic V, Tuttle KR, Rossing P, et al. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. *New England journal of medicine/□The □New England journal of medicine*. 2024;391(2):109-121. doi:10.1056/nejmoa2403347

20. Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *New England Journal of Medicine*. 2021;385(6):503-515. doi:10.1056/nejmoa2107519

21. Del Prato S, Kahn SE, Pavo I, et al. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *The Lancet*. 2021;398(10313):1811-1824. doi:10.1016/s0140-6736(21)02188-7

22. McGuire DK, Marx N, Mulvagh SL, et al. Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes. *New England Journal of Medicine*. 2025;392(20):2001-2012. doi:10.1056/nejmoa2501006

23. Nicholls SJ, Pavo I, Bhatt DL, et al. Cardiovascular Outcomes with Tirzepatide versus Dulaglutide in Type 2 Diabetes. *New England Journal of Medicine*. 2025;393(24):2409-2420. doi:10.1056/nejmoa2505928

24. The GRADE Study Research Group. Glycemia reduction in type 2 diabetes — glycemic outcomes. *New England Journal of Medicine*. 2022;387(12):1063-1074. doi:10.1056/nejmoa2200433

25. The GRADE Study Research Group. Glycemia Reduction in Type 2 Diabetes — Microvascular and Cardiovascular Outcomes. *New England Journal of Medicine*. 2022;387(12):1075-1088. doi:10.1056/nejmoa2200436

26. Arechavaleta R, Seck T, Chen Y, et al. Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. *Diabetes, Obesity and Metabolism*. 2011;13(2):160-168. doi:10.1111/j.1463-1326.2010.01334.x

27. Ridderstrale M, Andersen KR, Zeller C, Kim G, Woerle HJ, Broedl UC. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. *The Lancet Diabetes & Endocrinology*. 2014;2(9):691-700. doi:10.1016/s2213-8587(14)70120-2

28. Cefalu WT, Leiter LA, Yoon KH, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. *Lancet (London, England)*. 2013;382(9896):941-950. doi:10.1016/S0140-6736(13)60683-2

29. Gallwitz B, Rosenstock J, Rauch T, 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. *The Lancet*. 2012;380(9840):475-483. doi:10.1016/s0140-6736(12)60691-6

30. Matthews DR, Dejager S, Ahren B, et al. Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycaemic risk compared with glimepiride, with no weight gain: results from a 2-year study. *Diabetes, Obesity and Metabolism*. 2010;12(9):780-789. doi:10.1111/j.1463-1326.2010.01233.x

31. Devarajan T, Venkataraman S, Kandasamy N, et al. Comparative evaluation of safety and efficacy of glimepiride and sitagliptin in combination with metformin in patients with type 2 diabetes mellitus: Indian multicentric randomized trial - START Study. *Indian Journal of Endocrinology and Metabolism*. 2017;21(5):745-750. doi:10.4103/ijem.ijem_176_17

32. Srivastava S, Saxena GN, Keshwani P, Gupta R. Comparing the efficacy and safety profile of sitagliptin versus glimepiride in patients of type 2 diabetes mellitus inadequately controlled with metformin alone. *Journal of the Association of Physicians of India*. 2012;60(3):27-30.

33. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *The Lancet*. 2006;368(9548):1696-1705. doi:10.1016/S0140-6736(06)69705-5

34. Nauck MA, Meier JJ. Incretin hormones: Their role in health and disease. *Diabetes, obesity & metabolism*. 2018;20 Suppl 1(S1):5-21. doi:10.1111/dom.13129

35. Holst JJ. The Physiology of Glucagon-like Peptide 1. *Physiological Reviews*. 2007;87(4):1409-1439. doi:10.1152/physrev.00034.2006

36. Foretz M, Guigas B, Bertrand L, Pollak M, Viollet B. Metformin: from Mechanisms of Action to Therapies. *Cell Metabolism*. 2014;20(6):953-966. doi:http://dx.doi.org/10.1016/j.cmet.2014.09.018

37. McCreight LJ, Bailey CJ, Pearson ER. Metformin and the gastrointestinal tract. *Diabetologia*. 2016;59(3):426-435. doi:10.1007/s00125-015-3844-9

38. Mohamed S. Metformin: Diverse molecular mechanisms, gastrointestinal effects and overcoming intolerance in type 2 Diabetes Mellitus: A review. *Medicine*. 2024;103(43):e40221-e40221. doi:10.1097/md.0000000000040221

39. de Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. *BMJ (Clinical research ed)*. 2010;340:c2181. doi:10.1136/bmj.c2181

40. Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in Patients With Type 2 Diabetes and Kidney Disease. *JAMA*. 2014;312(24):2668. doi:10.1001/jama.2014.15298

41. Sahay R, Dinesh Gangwani, Singh M, et al. Fixed dose combination of dapagliflozin, glimepiride and extended-release metformin tablets in patients with type 2 diabetes poorly controlled by metformin and glimepiride: A phase III, open label, randomized clinical study in India. *Diabetes Obesity and Metabolism*. 2025;27(4):2193-2205. doi:10.1111/dom.16218

42. Sahay R, Gowda A, Singh MK, et al. Sitagliptin, Metformin and Glimepiride Fixed-Dose Combination Compared to Co-Administration of Metformin and High-Dose Glimepiride in Indian Patients With Type 2 Diabetes: A Randomised, Double-Blind, Double-Dummy, Phase 3 Clinical Study. *Diabetes, Obesity and Metabolism*. 2026;28(7):6207-6216. doi:10.1111/dom.70778

43. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of Intensive Glucose Lowering in Type 2 Diabetes. *New England Journal of Medicine*. 2008;358(24):2545-2559. doi:10.1056/nejmoa0802743

44. The ADVANCE Collaborative Group. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. *New England Journal of Medicine*. 2008;358(24):2560-2572. doi:10.1056/nejmoa0802987

45. Duckworth W, Abraira C, Moritz T, et al. Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes. *New England Journal of Medicine*. 2009;360(2):129-139. doi:10.1056/nejmoa0808431

46. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *New England Journal of Medicine*. 2021;385(16):1451-1461. doi:10.1056/nejmoa2107038

47. Solomon SD, McMurray JJV, Claggett B. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *New England Journal of Medicine*. 2022;387(12):1089-1098. doi:10.1056/nejmoa2206286

48. The EMPA-KIDNEY Collaborative Group. Empagliflozin in Patients with Chronic Kidney Disease. *New England Journal of Medicine*. 2022;388(2). doi:10.1056/nejmoa2204233

49. The EMPA-KIDNEY Collaborative Group. Effects of Empagliflozin on Progression of Chronic Kidney Disease: A Pre-Specified Secondary Analysis from the Empa-Kidney Trial. *The Lancet Diabetes & Endocrinology*. 2024;12(1):39-50. doi:10.1016/S2213-8587(23)00321-2

50. EMPA-KIDNEY Collaborative Group. Long-Term Effects of Empagliflozin in Patients with Chronic Kidney Disease. *New England Journal of Medicine*. 2024;392(8):777-787. doi:10.1056/nejmoa2409183