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Review Article

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# EMPAGLIFLOZIN AND METFORMIN COMBINATION THERAPY IN TYPE 2 DIABETES MELLITUS: A REVIEW OF CARDIOVASCULAR AND RENAL PROTECTION BASED ON THE 2026 CLINICAL GUIDELINES

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**Abstract:** Type 2 diabetes mellitus (T2DM) is a major risk factor for cardiovascular disease (CVD) and chronic kidney disease (CKD), contributing to substantial morbidity, mortality, and healthcare expenditure. The combination of empagliflozin, a sodium–glucose cotransporter 2 (SGLT2) inhibitor, and metformin, a biguanide, is an established pharmacological approach for improving glycaemic control in patients with T2DM. Metformin primarily reduces hepatic glucose production and improves insulin sensitivity, whereas empagliflozin promotes urinary glucose excretion and produces additional haemodynamic, metabolic, cardiovascular, and renal effects. The American Diabetes Association (ADA) Standards of Care in Diabetes—2026 recommend SGLT2 inhibitors with demonstrated clinical benefits for eligible patients with T2DM and CKD or cardiovascular risk, independently of baseline glycated haemoglobin (HbA1c) and, importantly, irrespective of whether metformin is being used. Clinical evidence from EMPA-REG OUTCOME and EMPA-KIDNEY supports the cardiovascular and kidney-protective effects of empagliflozin. Metformin remains useful for glycaemic management but has no established direct kidney-protective effect comparable to that demonstrated for SGLT2 inhibitors. Combination therapy may improve glycaemic control, reduce treatment burden when a fixed-dose formulation is appropriate, and address multiple metabolic abnormalities. However, the cardiovascular and renal benefits of empagliflozin should not be interpreted as proof that the combination is superior to empagliflozin alone for preventing these outcomes. This review discusses the mechanisms of action, clinical evidence, 2026 guideline recommendations, safety considerations, and clinical implications of empagliflozin–metformin therapy.

***Keywords:*** *Empagliflozin, metformin, type 2 diabetes mellitus, chronic kidney disease, cardiovascular disease, SGLT2 inhibitors, renal protection, 2026 guidelines.*

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## 1. INTRODUCTION

Type 2 diabetes mellitus is a chronic metabolic disorder characterised by insulin resistance, progressive pancreatic beta-cell dysfunction, and persistent hyperglycaemia. Long-term diabetes is associated with microvascular complications, including diabetic nephropathy and retinopathy, and macrovascular complications, including coronary artery disease, stroke, peripheral arterial disease, and heart failure.

Chronic kidney disease is particularly important in patients with diabetes because declining kidney function increases cardiovascular risk, complicates glucose-lowering treatment, and may ultimately lead to kidney failure. Therefore, contemporary diabetes management aims not only to achieve glycaemic targets but also to prevent cardiovascular events, preserve kidney function, and improve survival.

Metformin has traditionally been used as an initial glucose-lowering treatment because of its efficacy, low risk of hypoglycaemia when used alone, affordability, and extensive clinical experience. Empagliflozin has expanded the therapeutic approach by demonstrating cardiovascular and renal benefits beyond its glucose-lowering effect.

The combination of empagliflozin and metformin provides complementary mechanisms for managing hyperglycaemia. According to the ADA Standards of Care in Diabetes—2026, however, the selection of an SGLT2 inhibitor for cardiovascular and renal protection should be based on the patient's clinical indications rather than solely on the need for additional glucose lowering or the use of metformin.

This review evaluates the scientific evidence supporting the combination, with particular emphasis on cardiovascular disease, chronic kidney disease, safety, and contemporary clinical recommendations.

## 2. OBJECTIVES

The objectives of this review are:

1. To describe the pharmacological mechanisms of empagliflozin and metformin.
2. To evaluate their complementary effects on glycaemic control.
3. To review evidence concerning cardiovascular outcomes and kidney disease progression.
4. To summarise relevant recommendations from the 2026 ADA Standards of Care and contemporary cardiovascular–kidney–metabolic guidance.
5. To discuss adverse effects, precautions, monitoring, and clinical implications.
6. To identify evidence gaps concerning the cardiovascular and renal effects of the combination compared with empagliflozin alone.

## 3. PHARMACOLOGICAL OVERVIEW:

### 3.1 Empagliflozin:

Empagliflozin is an orally administered SGLT2 inhibitor. SGLT2 proteins in the proximal renal tubules normally reabsorb a substantial proportion of filtered glucose. By inhibiting this transporter, empagliflozin reduces renal glucose reabsorption and increases urinary glucose excretion.

Its principal pharmacological effects include:

- Reduction in blood glucose and HbA1c.
- Modest reductions in body weight and blood pressure.
- Increased urinary glucose and sodium excretion.
- Improvement in intraglomerularhaemodynamics.
- Reduction in heart failure hospitalisation and slowing of CKD progression in appropriate populations.

The cardiovascular and kidney benefits of empagliflozin cannot be explained solely by glucose lowering. Proposed mechanisms include reduced intraglomerular pressure, changes in renal sodium handling, improved volume regulation, and alterations in cardiac and renal energy metabolism.

### 3.2 Metformin:

Metformin is a biguanide glucose-lowering agent. It primarily reduces hepatic glucose production and improves insulin sensitivity, thereby lowering fasting and postprandial blood glucose levels.

Its major pharmacological effects include:

- Suppression of hepatic gluconeogenesis.
- Improvement in peripheral insulin sensitivity.
- Reduction in HbA1c.
- Minimal risk of hypoglycaemia when used alone.
- Generally weight-neutral effects or modest weight reduction.

Metformin is not considered a treatment with established direct kidney-protective efficacy equivalent to empagliflozin. Its continued use in CKD depends on renal function, tolerability, and the risk of metformin accumulation and lactic acidosis.

### 3.3 Rationale for Combination Therapy:

The two drugs act through different pathways. Metformin primarily reduces endogenous glucose production, whereas empagliflozin increases urinary glucose excretion. This complementary action can improve glycaemic control without substantially increasing hypoglycaemia risk when the drugs are used without insulin or insulin secretagogues.

The combination may be useful when monotherapy does not achieve the patient's individualised glycaemic target. A fixed-dose tablet may also reduce pill burden and support adherence when its dose and formulation suit the patient.

Nevertheless, the combination's overall clinical benefit depends on patient characteristics, renal function, cardiovascular status, treatment adherence, and appropriate management of other risk factors.

## 4. MECHANISMS OF CARDIOVASCULAR AND RENAL PROTECTION

### 4.1 Cardiovascular Effects of Empagliflozin

Empagliflozin reduces the risk of hospitalisation for heart failure and has demonstrated cardiovascular benefits in appropriate populations. Potential mechanisms include:

- Reduction in plasma volume and cardiac preload.
- Modest lowering of blood pressure.
- Improved renal sodium handling.
- Reduced cardiac congestion.
- Changes in myocardial and renal energy metabolism.

The magnitude and nature of benefit depend on the underlying clinical condition. Evidence for reducing heart failure events is particularly strong; benefits should not be described as an equal reduction in every cardiovascular endpoint, such as myocardial infarction or stroke.

### 4.2 Renal Effects of Empagliflozin

SGLT2 inhibition reduces sodium and glucose reabsorption in the proximal tubule, increasing sodium delivery to the macula densa and modifying tubuloglomerular feedback. This can reduce intraglomerular pressure and help slow the decline in estimated glomerular filtration rate (eGFR).

Other effects include reduced albuminuria in many patients, modest blood-pressure lowering, and changes in renal haemodynamics. An initial, usually reversible decline in eGFR can occur after treatment initiation and does not necessarily indicate kidney injury.

### 4.3 Contribution of Metformin

Metformin improves glucose regulation and may indirectly contribute to long-term cardiovascular risk management through better metabolic control. However, evidence for direct prevention of CKD progression is not comparable to the dedicated kidney-outcome evidence for empagliflozin.

Consequently, the renal and heart failure benefits of this combination should be understood primarily in the context of empagliflozin's established effects, together with the additional glycaemic benefits of metformin.

## 5. CLINICAL EVIDENCE

### 5.1 EMPA-REG OUTCOME Trial

The EMPA-REG OUTCOME trial investigated empagliflozin in patients with T2DM and established cardiovascular disease.

Empagliflozin reduced the primary composite outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke compared with placebo. The relative risk reduction for this composite outcome was approximately 14%. Cardiovascular death was reduced by approximately 38%, and hospitalisation for heart failure by approximately 35%.

These findings established empagliflozin as an important option for cardiovascular risk reduction in eligible patients with T2DM and established cardiovascular disease.

**Clinical interpretation:** This trial provides evidence for empagliflozin's cardiovascular benefits, not proof that empagliflozin plus metformin is superior to empagliflozin alone. Background glucose-lowering therapy varied among trial participants.

### 5.2 EMPA-KIDNEY Trial

The EMPA-KIDNEY trial evaluated empagliflozin in a broad population with CKD, including people with and without diabetes.

The primary composite outcome was progression of kidney disease or cardiovascular death. The outcome occurred in 13.1% of participants receiving empagliflozin and 16.9% receiving placebo during a median follow-up of approximately two years. This corresponded to a hazard ratio of 0.72 (95% confidence interval 0.64–0.82).

The findings support the use of empagliflozin to slow CKD progression in eligible patients. Because the study included people without diabetes, its findings also demonstrate that the kidney benefits are not dependent solely on lowering blood glucose.

**Clinical interpretation:**Empagliflozin has demonstrated kidney-protective effects across relevant CKD populations. Metformin may be combined with it when clinically appropriate, but metformin itself is not responsible for the trial's demonstrated kidney benefit.

### 5.3 Evidence for the Empagliflozin–Metformin Combination

Clinical studies of empagliflozin added to metformin have demonstrated improvements in glycaemic control compared with metformin alone. The combination can also produce modest reductions in body weight and blood pressure.

However, glucose-lowering studies and cardiovascular or renal outcome trials address different questions. Improvement in HbA1c does not by itself establish that the combination reduces cardiovascular events or kidney failure more than empagliflozin alone.

The most appropriate evidence-based conclusion is that empagliflozin–metformin therapy can provide complementary glycaemic benefits while incorporating an agent with independently demonstrated cardiovascular and kidney protection.

## 6. RECOMMENDATIONS BASED ON THE 2026 CLINICAL GUIDELINES

The ADA Standards of Care in Diabetes—2026 emphasise person-centred treatment and the prevention of cardiovascular and kidney complications alongside glycaemic management.

### 6.1 Patients with Type 2 Diabetes and CKD

The ADA recommends an SGLT2 inhibitor with demonstrated kidney and cardiovascular benefit for eligible patients with T2DM and CKD. Treatment can generally be initiated at an eGFR of at least 20 mL/min/1.73 $m^2$, subject to the agent's approved indications and prescribing information.

The glucose-lowering effect of SGLT2 inhibitors becomes weaker as eGFR declines, but their kidney and cardiovascular benefits may remain clinically important.

### 6.2 Patients with Established Cardiovascular Disease or Heart Failure

For patients with T2DM and established atherosclerotic cardiovascular disease, multiple cardiovascular risk factors, or CKD, the ADA recommends an SGLT2 inhibitor and/or a GLP-1 receptor agonist with demonstrated cardiovascular benefit, selected according to the clinical indication.

For patients with heart failure, including preserved or reduced ejection fraction, an SGLT2 inhibitor with established benefit is recommended to reduce worsening heart failure events and cardiovascular death.

### 6.3 Metformin Use Alongside Empagliflozin

Metformin may be used for glycaemic management when appropriate, but its use is not a prerequisite for prescribing empagliflozin for cardiovascular or renal protection. The 2026 ADA recommendations specifically support treatment decisions based on cardiovascular and kidney risk irrespective of baseline HbA1c and metformin use.

Metformin should not be initiated when eGFR is below 45 mL/min/1.73 $m^2$ under the ADA's 2026 pharmacological guidance; patients already taking it require reassessment and possible dose reduction as renal function declines, and it should be discontinued when eGFR falls below 30 mL/min/1.73 $m^2$. Local product labelling and individual clinical circumstances should also be considered.

### 6.4 Additional Risk-Reduction Measures

The combination should not replace comprehensive cardiovascular and renal care. Management may also include:

- Blood-pressure control and an ACE inhibitor or angiotensin receptor blocker when indicated.
- Lipid-lowering therapy according to cardiovascular risk.
- Smoking cessation, physical activity, and appropriate nutrition.
- Regular monitoring of eGFR and urine albumin-to-creatinine ratio.
- Consideration of additional agents, such as a GLP-1 receptor agonist or finerenone, when indicated by residual cardiovascular or renal risk.

## 7. SAFETY AND MONITORING:

### 7.1 Adverse Effects of Empagliflozin

Potential adverse effects include genital mycotic infections, increased urination, volume depletion, and an initial eGFR decline. Rare but serious adverse effects include diabetic ketoacidosis, which may occur even without markedly elevated blood glucose.

Patients should receive advice on hydration, recognition of ketoacidosis symptoms, and temporary withholding of SGLT2 inhibitors during prolonged fasting, critical illness, or around surgery according to clinical guidance and product instructions.

### 7.2 Adverse Effects of Metformin

Common adverse effects include nausea, diarrhoea, abdominal discomfort, and other gastrointestinal symptoms. Long-term treatment may contribute to vitamin B12 deficiency.

Metformin-associated lactic acidosis is rare but serious, particularly in settings involving severe renal impairment, hypoxia, acute illness, or other factors causing drug accumulation or impaired lactate clearance.

### 7.3 Monitoring Parameters

Clinical monitoring should include renal function, HbA1c, blood pressure, volume status, tolerability, and relevant adverse effects. Urine albumin-to-creatinine ratio should be assessed in patients at risk of CKD.

Renal function should be reassessed when clinically indicated, especially during acute illness or changes in volume status. Patients should also be advised about symptoms of genital infections, dehydration, and ketoacidosis.

## 8. LIMITATIONS AND EVIDENCE GAPS:

Although empagliflozin and metformin are frequently prescribed together, several limitations should be recognised.

First, the major cardiovascular and kidney outcome trials evaluated empagliflozin against placebo on top of usual care rather than testing whether the fixed combination was superior to empagliflozin alone.

Second, cardiovascular benefits vary according to the endpoint and the patient's baseline risk. A reduction in heart failure hospitalisation should not be interpreted as equivalent evidence for reductions in all atherosclerotic events.

Third, metformin suitability is restricted by renal function and certain acute clinical conditions. The combination is therefore not appropriate for every patient with diabetes and CKD.

Finally, clinical decisions must account for the individual's cardiovascular history, degree of albuminuria, kidney function, concomitant medication, treatment goals, affordability, and local regulatory recommendations.

## 9. FUTURE PERSPECTIVES

Future studies should evaluate long-term outcomes in patients receiving empagliflozin and metformin together, including cardiovascular death, heart failure hospitalisation, sustained eGFR decline, kidney failure, and quality of life.

Comparative studies of fixed-dose combination therapy and separate tablets may clarify adherence, persistence, cost-effectiveness, and real-world clinical outcomes. Research should also investigate how combination treatment fits into

multidrug strategies incorporating renin–angiotensin system inhibitors, GLP-1 receptor agonists, and nonsteroidal mineralocorticoid receptor antagonists.

## 10. CONCLUSION

Empagliflozin plus metformin is an effective therapeutic combination for patients with T2DM who require complementary glucose-lowering mechanisms and are suitable for both agents. Metformin reduces hepatic glucose production, whereas empagliflozin increases urinary glucose excretion and has demonstrated cardiovascular and kidney-protective effects. Evidence from EMPA-REG OUTCOME and EMPA-KIDNEY supports empagliflozin's role in reducing cardiovascular risk and slowing kidney disease progression in appropriate populations. The ADA Standards of Care in Diabetes—2026 reinforce the use of SGLT2 inhibitors with proven benefits in eligible patients with T2DM and CKD or cardiovascular disease, irrespective of baseline HbA1c and whether metformin is being used. The principal conclusion is that the combination can support comprehensive diabetes management, but the proven cardiovascular and renal benefits should be attributed primarily to empagliflozin's outcome-trial evidence rather than assumed to result from a unique protective effect of the combination. Individualised prescribing, renal monitoring, safety counselling, and comprehensive risk-factor management remain essential.

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## 13. CONFLICT OF INTEREST

Nil

## 14. INFORMED CONSENT

Not applicable

## 15. ETHICAL STATEMENT

Not Applicable.

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