

SPECIAL ISSUE ARTICLE

Triple oral therapy with metformin, DPP-4 inhibitor, and SGLT2 inhibitor for adults with type 2 diabetes: Consensus recommendations of a Chinese expert panel (version 2025)

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Abstract

Type 2 diabetes mellitus (T2DM) is a progressive disease involving multiple patho-physiologic defects, and combination therapy is often required to achieve and sustain glycaemic control. Triple oral therapy with metformin, dipeptidyl peptidase-4 inhibitors (DPP-4i), and sodium-glucose cotransporter-2 inhibitors (SGLT2i) has demonstrated high and durable glycaemic-lowering efficacy, favourable safety and tolerability, and additional metabolic benefits in T2DM patients with diverse background therapies, including those who are treatment-naïve and those with

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inadequate control on monotherapy or dual therapy. In light of the increasing clinical use of this triple regimen and the absence of established consensus to guide its use, the Diabetes Committee of the Chinese Research Hospital Association convened an expert panel comprising endocrinologists and evidence-based experts. Through a systematic literature review and a Delphi process, the panel formulated 11 consensus recommendations (8 strong and 3 weak recommendations) on the clinical use of metformin + DPP-4i + SGLT2i, including fixed-dose combination formulations. Safety considerations regarding its use were also described. This consensus aimed to provide clinicians with practical guidance to optimize the effective and safe use of metformin + DPP-4i + SGLT2i in T2DM management.

KEYWORDS

DPP-IV inhibitor, metformin, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

In 2024, an estimated 589 million adults aged 20–79 years are living with diabetes worldwide.¹ China has the largest number of people with diabetes, driven partly by population aging, increasing prevalence of overweight and obesity, and unhealthy lifestyle changes.^{1,2} Type 2 diabetes mellitus (T2DM) accounts for over 90% of all diabetes cases and is at high risk of serious complications such as cardiovascular diseases, kidney damage, and cognitive decline.¹ Despite advances in therapy, effective management of T2DM remains challenging.

Since T2DM is a progressive disease involving at least 12 distinct pathophysiologic defects,³ combination therapy is often required to achieve and sustain glycaemic goals. Traditionally, stepwise intensification starting with metformin is recommended. Accumulating evidence has shown that early intensive glycaemic control reduces the risk of diabetic complications and death.^{4,5} Current guidelines therefore support consideration of initial combination therapy in selected adults with T2DM to facilitate early achievement of individualized glycaemic goals.^{2,6}

Currently, at least 11 metformin-based triple oral regimens are available (Table 1). Among these, the combination of metformin, DPP-4i, and SGLT2i (metformin + DPP-4i + SGLT2i) provided high and durable glycaemic-lowering efficacy with a low risk of hypoglycaemia, along with improvements in weight loss and potential cardiorenal benefits (Table 1). These three medications have complementary mechanisms of action that target multiple pathophysiologic defects in T2DM (Figure S1). Clinical studies have demonstrated that metformin + DPP-4i + SGLT2i was effective and safe in improving glycaemic control in T2DM patients with diverse background therapies, including treatment-naïve patients and those inadequately controlled on monotherapy or dual therapy.⁷ It is important to note that, in clinical practice, poor adherence and delays in treatment intensification are common barriers to achieving glycaemic control.^{8,9} Fixed-dose combinations (FDCs) of metformin, DPP-4i, and SGLT2i are available and may improve adherence and support timely treatment intensification.

Despite the growing use of metformin + DPP-4i + SGLT2i in clinical practice, no evidence-based consensus currently exists to guide its use in T2DM management. To address this gap, the present consensus was developed using a Delphi process and systematic literature review to provide evidence-informed recommendations for clinical use.

2 | METHODOLOGY

This expert consensus was developed to provide evidence-based recommendations on the clinical use of triple oral therapy with metformin + DPP-4i + SGLT2i in adults with T2DM. It was intended for use by endocrinologists across all tiers of healthcare institutions and may also be relevant to diabetes specialist nurses, clinical pharmacists, hospital administrators, and public health experts. The consensus has been registered on the International Practice Guideline Registration and Transparency Platform (<http://www.guidelines-registry.cn>; registration number: PREPARE-2025CN762). The development process followed the WHO Handbook for Guideline Development¹⁰ and the Chinese Principles for Developing/Revising Clinical Diagnosis and Treatment Guidelines (2022 edition). Reporting followed the Reporting Items for Practice Guidelines in Healthcare checklist.¹¹

2.1 | Expert panel generation

The initiative was led by the Diabetes Committee of the Chinese Research Hospital Association. An expert panel comprising experienced endocrinologists and leading evidence-based experts in China was established. Numerous panel members had rich experience in developing clinical guidelines or expert consensus statements. The expert panel included three core groups: (1) Steering committee (3 members): defined the scope and objectives, appointed panel members, and supervised the methodological process, including literature

TABLE 1 Metformin-based triple oral glycaemic-lowering regimens.

Triple-combination regimens	Glycaemic-lowering efficacy ^a	Hypoglycaemia risk ^b	Weight changes ^c	Potential organ-protective benefits (ASCVD/HF/CKD) ^d	Safety risk ^e
Metformin + DPP-4i + SGLT2i	High and durable ^{31,45,49,78}	Low ⁷⁸	Loss ^{31,45,78}	+++ ⁷⁹	Genital mycotic infections ^{49,78,80}
Metformin + DPP-4i + SU/GLN	High ⁸¹⁻⁸⁴	Intermediate ^{82,83}	Gain ⁸¹	++ ^{82,85,86}	Weight gain ⁸¹
Metformin + DPP-4i + TZD	Intermediate ⁸⁷⁻⁹⁰	Low ⁹¹	Gain ⁸⁹	++ ^{85,90}	Weight gain, risk of HF ⁹²
Metformin + DPP-4i + AGI	Intermediate ^{84,91}	Low ^{84,93}	Loss ^{84,93}	++ ^{85,86,90}	Gastrointestinal intolerance ⁹⁴
Metformin + SGLT2i + oral GLP-1RA	High and durable ⁹⁵⁻⁹⁷	Low ⁹⁷	Loss ⁹⁵⁻⁹⁷	+++ ^{79,95}	Gastrointestinal intolerance ^{96,97}
Metformin + SGLT2i + SU/GLN	High ⁹⁸	Intermediate ⁹⁸	Neutral ⁹⁸	+ ⁷⁹	Genital mycotic infections ⁹⁹
Metformin + SGLT2i + TZD	High ^{100,101}	Low ^{100,101}	Gain ^{100,101}	+ ⁷⁹	Weight gain, edema ^{100,101}
Metformin + SGLT2i + AGI	High ¹⁰²	Low ¹⁰²	Loss ¹⁰²	+ ⁷⁹	Vulvovaginal pruritus ¹⁰²
Metformin + SU/GLN + oral GLP-1RA	High and durable ¹⁰³	Intermediate ¹⁰³	Loss ¹⁰³	+ ^{104,105}	Gastrointestinal intolerance ¹⁰³
Metformin + SU/GLN + TZD	High ^{88,89,106}	High ^{88,89}	Gain ^{88,89,106,107}	- ⁹⁰	Weight gain, edema ¹⁰⁷
Metformin + SU/GLN + AGI	High ¹⁰⁸	Intermediate ¹⁰⁸	Gain ¹⁰⁸	- ⁹⁰	Weight gain ¹⁰⁸

Abbreviations: AGI, α -glucosidase inhibitor; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLN, glnide; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

^aGlycaemic-lowering efficacy: "High"—Better glycaemic control than dual therapy and either superior or non-inferior to other glucose-lowering regimens. "Intermediate"—Better glycaemic control than dual therapy or non-inferior to glucose-lowering regimens. "Durable"—Glycaemic effects maintained for ≥ 52 weeks.

^bHypoglycaemia risk: "Low"—Significantly reduced risk of hypoglycaemia or no reported cases of severe or symptomatic hypoglycaemia. "Intermediate"—No significant increase in hypoglycaemia risk. "High"—Significantly increased risk. Both were relative to dual therapy or other glucose-lowering regimens.

^cWeight change: "Gain"—Significant increase in body weight. "Loss"—Significant decrease in body weight. "Gain"—Significant increase in body weight than dual therapy or other regimens. Both were relative to dual therapy or other glucose-lowering regimens.

^dPotential organ-protective benefits: "+++"—Benefits from both dual-combination therapy and monotherapy. "++"—Benefits from both dual-combination therapy. "+"—Benefits from monotherapy. "-"—Lack of evidence or potential harm.

^ePotential safety risks—Adverse events with an obviously higher incidence than control regimens.

review and evidence grading. (2) Development group (38 members): drafted clinical questions, conducted systematic literature research, summarized and synthesized evidence, formulated recommendations, participated in consensus discussions and voting, and drafted and revised the manuscript. (3) Methodology group (one member): provided methodological training to the panel, graded the quality of evidence, ensured methodological rigor and adherence to standard procedures, and provided inputs to the consensus draft.

2.2 | Procedure for recommendations formulation

2.2.1 | Selection of clinical questions

The development group conducted a systematic literature research of all relevant publications on the efficacy, safety, or clinical use of metformin + DPP-4i + SGLT2i in T2DM from database inception to 30 June 2025. The searched databases included PubMed, Cochrane Library, Web of Science, CNKI, and Wanfang. After a face-to-face discussion on the results of the literature review, the development group raised 11 important clinical questions that required the formulation of recommendations.

2.2.2 | Recommendations formulation and evidence grading

Based on the literature review and clinical experience, the development group drafted 11 recommendations. Evidence was graded to four levels (Grade A, B, C, and E) according to the 2025 American Diabetes Association grading system (Table S1).

2.2.3 | Delphi consensus process

Two Delphi survey rounds were conducted. In the first round (30 April to 8 May 2025), 34 online questionnaires were sent to panel members and 31 were returned (response rate: 91%); the expert authority coefficient (Cr) was 0.827. Of the 11 drafted recommendations, 6 achieved >90% of agreement, 4 achieved 75%–90% of agreement, and one achieved <75% of agreement. Recommendations with ≤90% agreement were revised and re-evaluated in the second round (2–13 June 2025); 34 online questionnaires were sent to panel members and 30 were returned (response rate: 88%); Cr was 0.782. After two Delphi rounds, consensus was achieved on all 11 recommendations (Table 2).

2.2.4 | Draft review and approval

The manuscript draft was reviewed by 38 expert panel members. After two rounds of revisions, the final version of the manuscript was approved by all panel members.

3 | RESULTS

3.1 | Recommendations on triple oral therapy with metformin, DPP-4i, and SGLT2i

Q1. Should triple therapy be initiated in patients with T2DM and HbA1c ≥ 7.0% after 3 months of dual therapy?

Recommendation 1: In patients with T2DM who have HbA1c ≥ 7.0% after 3 months of dual therapy with metformin + DPP-4i or SGLT2i, triple therapy with metformin + DPP-4i + SGLT2i should be initiated promptly (Grade A; strong recommendation [agreement: 100%]).

Explanation 1: When HbA1c goals are not achieved with 3 months of dual glycaemic-lowering therapy, a new drug with complementary mechanisms of action should be added.^{2,6} Substantial literature reported that in T2DM patients with inadequate glycaemic control on metformin plus DPP-4i, the addition of SGLT2i lowered HbA1c by 0.65%–1.4%, with glycaemic goal achievement rates of 35.5%–90%.^{12–17} Similarly, in those with inadequate glycaemic control on metformin plus SGLT2i, the addition of DPP-4i lowered HbA1c by 0.36%–0.86%, with glycaemic goal achievement rates of 32.1%–66.7%.^{15,18–21} These glycaemic-lowering effects were sustained through 52 weeks, with a low risk of hypoglycaemia (0%–4.5%). Beyond glycaemic control, the triple regimen of metformin + DPP-4i + SGLT2i also demonstrated metabolic benefits such as improvements in weight loss (1.8–2.8 kg), β-cell function, and blood pressure.^{16,20–22}

In addition, real-world data from 84,915 patients with T2DM suggest that metformin + DPP-4i + SGLT2i may reduce the risk of macrovascular and microvascular complications and all-cause mortality.²³ Specifically, adding SGLT2i to DPP-4i reduced all-cause mortality by 54%, cardiovascular composite events (non-fatal myocardial infarction, stroke, or all-cause death) by 36%, and the risk of lower-limb amputation by 37%, compared with switching from DPP-4i to SGLT2i.²³

Q2. Should triple oral therapy be initiated in those with T2DM who fail to achieve HbA1c goals after 3 months of maximum-dose metformin monotherapy?

Recommendation 2: In patients with T2DM who have HbA1c ≥ 7.5% after 3 months of maximum-dose metformin monotherapy, the addition of DPP-4i and SGLT2i to metformin is recommended (Grade A; weak recommendation [agreement rate: 87%]).

Explanation 2: Current evidence supports that, in patients with T2DM and HbA1c ≥ 7.5% after 3 months of maximum-dose metformin monotherapy, the addition of DPP-4i and SGLT2i to metformin can facilitate rapid achievement and maintenance of glycaemic control. In a 24-week, randomized, double-blind, phase 3 trial of patients with HbA1c 7.5%–10.5% after metformin (≥1500 mg/day) monotherapy, triple metformin, SGLT2i (henagliflozin), and DPP-4i (retagliptin) resulted in greater HbA1c reductions (−1.54% vs. −0.95% vs. −0.98%) and higher glycaemic goal achievement rates (56.4% vs. 24.4% vs. 27.1%) compared with dual metformin plus SGLT2i or DPP-4i.²⁴ The incidences of hypoglycaemia were low (7.7%, 3.2%, and

TABLE 2 Summary of recommendations.

No.	Recommendations	Evidence grade	Strength of recommendations (agreement rate)
1	In patients with T2DM who have HbA1c $\geq 7.0\%$ after 3 months of dual therapy with metformin + DPP-4i or SGLT2i, triple therapy with metformin + DPP-4i + SGLT2i should be initiated promptly.	Grade A	Strong recommendation (100%)
2	In patients with T2DM who have HbA1c $\geq 7.5\%$ after 3 months of maximum-dose metformin monotherapy, the addition of DPP-4i and SGLT2i to metformin is recommended.	Grade A	Weak recommendation (87%)
3	In patients with newly diagnosed T2DM and HbA1c $\geq 9.0\%$ or $\geq 1.5\%$ above the individualized glycaemic goals, initial therapy with metformin + DPP-4i + SGLT2i can be considered to achieve rapid and durable glycaemic control.	Grade A	Weak recommendation (90%)
4	In some patients with newly diagnosed T2DM and $7.5\% \leq \text{HbA1c} < 9.0\%$, initial therapy with metformin + DPP-4i + SGLT2i can be considered after comprehensive consideration of glycaemic-lowering efficacy and durability, safety, and benefits beyond glycaemic control. When glycaemic goals are achieved, de-escalation can be chosen based on clinical need.	Grade C	Weak recommendation (87%)
5	In patients with T2DM who are intolerant of and/or fail to achieve HbA1c goals on high-dose metformin (≥ 1500 mg/day), triple combination of low- or intermediate-dose metformin (≤ 1000 mg/day), DPP-4i, and SGLT2i is recommended to improve glycaemic control and/or tolerability.	Grade A	Strong recommendation (94%)
6	In patients with T2DM who have achieved glycaemic goals on metformin plus insulin and have preserved islet function, switching to triple oral therapy with metformin + DPP-4i + SGLT2i is recommended to maintain glycaemic control, reduce the risk of hypoglycaemia, and/or improve weight management.	Grade A	Strong recommendation (94%)
7	In older patients with T2DM or those with overweight/obesity who are already treated with metformin plus sulfonylureas, switching to triple therapy with metformin + DPP-4i + SGLT2i is recommended to reduce the risk of hypoglycaemia and/or improve weight management.	Grade A	Strong recommendation (94%)
8	In patients with T2DM and without ASCVD who have achieved glycaemic goals on metformin plus GLP-1 RAs, when treatment is intolerable or treatment simplification is needed, switching to triple oral therapy with metformin + DPP-4i + SGLT2i can be considered to maintain comparable glycaemic and metabolic benefits.	Grade A	Strong recommendation (97%)
9	In patients with T2DM who are already treated with other triple regimens (e.g., metformin + DPP-4i + sulfonylureas), switching to triple therapy with metformin + DPP-4i + SGLT2i may be considered, as appropriate, based on the need to optimize glycaemic control, improve cardiovascular and renal outcomes, support weight management, or reduce hypoglycaemia risk.	Grade C	Strong recommendation (100%)
10	In hospitalized patients with hyperglycaemia who require outpatient antihyperglycaemic therapy following short-term insulin intensification, switching to triple oral therapy with metformin + DPP-4i + SGLT2i may be considered, as appropriate, in individuals with short disease duration, high BMI, and preserved islet function to maintain long-term glycaemic control and improve islet function.	Grade E	Strong recommendation (93%)
11	FDCs can simplify treatment and improve adherence, but they lack dosing flexibility and should be discontinued if one component is not tolerated. ⁵⁹ FDCs of metformin + DPP-4i + SGLT2i are recommended with careful consideration of their advantages and limitations. Available options include (1) triple FDCs (metformin + DPP-4i + SGLT2i), (2) dual FDCs (metformin + DPP-4i) plus SGLT2i, and (3) dual FDCs (metformin + SGLT2i) plus DPP-4i.	Grade A	Strong recommendation (100%)

Note: Evidence was graded according to the 2025 ADA evidence-grading system. Strength of recommendation was determined by a Delphi process: strong recommendation (agreement $>90\%$), weak recommendation (75%–90%), no consensus ($<75\%$). In clinical practice, individual patient factors such as treatment goals, tolerability, and economic constraints should be considered when following the consensus recommendations, particularly those classified as “weak”.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; FDCs, fixed-dose combinations; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, haemoglobin A1C; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus.

2.6%, respectively), and no severe hypoglycaemia events were reported.²⁴ Other randomized studies and meta-analyses also confirmed the glycaemic benefits of the triple regimen in patients inadequately controlled on maximum-dose metformin monotherapy, reporting additional HbA1c reductions of 0.27%–0.65% and elevations in glycaemic goal achievement rates by 17.3%–36.2% compared with dual metformin plus DPP-4i or SGLT2i.^{24–31} These effects were sustained for at least 52 weeks. Besides, its favourable effects on β -cell function, weight loss (1.1–3.0 kg), and blood pressure were observed.

Q3. In patients with newly diagnosed T2DM and high glycaemic levels, should initial triple oral therapy or a stepwise addition of medications be used?

Recommendation 3: In patients with newly diagnosed T2DM and HbA1c $\geq 9.0\%$ or $\geq 1.5\%$ above the individualized glycaemic goals, initial therapy with metformin + DPP-4i + SGLT2i can be considered to achieve rapid and durable glycaemic control (Grade A; weak recommendation [agreement rate: 90%]).

Explanation 3: In patients with newly diagnosed T2DM, high baseline HbA1c is strongly associated with long-term adverse outcomes, such as microvascular and macrovascular complications.³² Early achievement of glycaemic control is important to reduce the risk of these complications. It has been reported that in drug-naïve patients with HbA1c $\geq 9.0\%$, initial combination of metformin, DPP-4i, and SGLT2i obviously reduced HbA1c from 12.2% to 6.3% at month 4 and improved insulin sensitivity, β -cell function, blood pressure, and body composition.³³ In patients with HbA1c $\geq 1.5\%$ above the individualized glycaemic goals ($<6.5\%$ for adults with good health and function, low treatment risks and burdens and $<7.0\%$ for most adults), the guideline recommends initial treatment with dual-combination regimens or medications with greater glucose-lowering efficacy.⁶ Recently, the TRIPLE-AXEL trial showed that in newly diagnosed patients with HbA1c 8.0%–11.0%, initial metformin + DPP-4i + SGLT2i achieved comparable HbA1c reductions to stepwise addition of medications to metformin (–2.56% vs. –2.75%), but reached HbA1c $<6.5\%$ more rapidly (median 2.88 vs. 3.19 months) and resulted in a higher proportion of patients reaching a composite endpoint of glycaemic control, tolerability, and safety (39.0% vs. 17.1%).³⁴ These benefits were sustained over 2 years.³⁴ Additionally, the incidence of the composition safety endpoint (hypoglycaemia, weight gain, or treatment discontinuation due to adverse events) was lower with initial triple therapy (16.7% vs. 62.0%).³⁴

Q4. In patients with newly diagnosed T2DM and non-high baseline HbA1c ($<9.0\%$), should triple therapy be initiated?

Recommendation 4: In some patients with newly diagnosed T2DM and $7.5\% \leq \text{HbA1c} < 9.0\%$, initial therapy with metformin + DPP-4i + SGLT2i can be considered after comprehensive consideration of glycaemic-lowering efficacy and durability, safety, and benefits beyond glycaemic control. When glycaemic goals are achieved, de-escalation can be chosen based on clinical need (Grade C; weak recommendation [agreement rate: 87%]).

Explanation 4: According to previous consensus, early dual therapy may be needed when initial HbA1c is $\geq 7.5\%$.³⁵ The VERIFY trial

showed that in newly diagnosed patients with T2DM and baseline HbA1c of 6.7%, early initiation of metformin plus DPP-4i (vildagliptin) provided greater and more durable glycaemic control than stepwise intensification.³⁶ A recent prospective study in drug-naïve patients with HbA1c $\geq 7.5\%$ and without severe hyperglycaemic symptoms found that initial triple therapy with metformin + DPP-4i + SGLT2i followed by dual therapy with metformin + DPP-4i or SGLT2i or maintenance of triple therapy at the physician's discretion achieved sustained, satisfactory, and tolerable glycaemic benefits.³⁷ At month 12, 72.5% of patients achieved HbA1c $<7.0\%$, and glycaemic control was still sustained through 24 months after de-escalation or maintenance treatment.³⁷ Additional benefits included improved β -cell function, insulin sensitivity, body composition, lipid levels, liver enzymes, and renal function, with no serious adverse events reported.³⁷ These indicate that initial metformin + DPP-4i + SGLT2i may be a viable option for patients with newly diagnosed T2DM and $7.5\% \leq \text{HbA1c} < 9.0\%$, with subsequent regimen adjustment individualized based on clinical needs.

Q5. In patients with T2DM who are intolerant of and/or fail to achieve HbA1c goals on high-dose metformin (≥ 1500 mg/day), should treatment be switched to a combination regimen with low- or moderate-dose metformin (≤ 1000 mg/day)?

Recommendation 5: In patients with T2DM who are intolerant of and/or fail to achieve HbA1c goals on high-dose metformin (≥ 1500 mg/day), a triple combination of low- or intermediate-dose metformin (≤ 1000 mg/day), DPP-4i, and SGLT2i is recommended to improve glycaemic control and/or tolerability (Grade A; strong recommendation [agreement rate: 94%]).

Explanation 5: When used for treating T2DM, metformin is generally started at a low dose (500 mg/day) and titrated gradually to a maximum of 2550 mg/day. Its glucose-lowering effects are dose-dependent within the range of 500–2000 mg/day.³⁸ However, many patients are unable to tolerate high-dose metformin due to significant gastrointestinal side effects.³⁸ Evidence from several randomized controlled trials showed that, in patients with T2DM who were intolerant of or had poor glycaemic control (HbA1c 8.0%–11.0%) on high-dose metformin (≥ 1500 mg/day), a triple-combination FDC containing low- or intermediate-dose metformin (≤ 1000 mg/day), DPP-4i, and SGLT2i reduced HbA1c levels by 1.45%–1.73% and increased glycaemic goal achievement rates to 27.5%–54% with good safety and tolerability.^{39–42}

Q6. In patients with T2DM who have achieved glycaemic goals on metformin plus insulin, should treatment be switched to triple oral therapy with metformin + DPP-4i + SGLT2i?

Recommendation 6: In patients with T2DM who have achieved glycaemic goals on metformin plus insulin and have preserved islet function, switching to triple oral therapy with metformin + DPP-4i + SGLT2i is recommended to maintain glycaemic control, reduce the risk of hypoglycaemia, and/or improve weight management (Grade A; strong recommendation [agreement rate: 94%]).

Explanation 6: Metformin plus insulin can effectively reduce glucose levels but is associated with an increased risk of hypoglycaemia, weight gain, and an increased injection burden, which may reduce

adherence during long-term treatment.^{43,44} Results from several studies support triple oral therapy with metformin + DPP-4i + SGLT2i as a long-term alternative to metformin plus insulin in patients who have achieved glycaemic goals. In a 52-week phase 3b trial, metformin + DPP-4i + SGLT2i resulted in greater HbA1c reductions (-1.5% vs. -1.3%) and weight loss (-1.8 kg vs. $+2.8$ kg) with a lower hypoglycaemia incidence (28.7% vs. 46.1%) than metformin plus insulin glargine in patients with T2DM.⁴⁵ In a phase 2b randomized trial involving adults with latent autoimmune diabetes and preserved endogenous insulin production, the efficacy of this triple oral therapy was non-inferior to metformin plus insulin glargine in preserving β -cell function and improving body mass index (-0.4 kg/m² vs. $+0.4$ kg/m²), with no significant differences in glycaemic control and hypoglycaemia risk between groups.⁴⁶ In an exploratory study, triple oral therapy offered similar HbA1c reductions (-1.2% vs. -0.9%) but markedly lower hypoglycaemia incidence (7.5% vs. 47.5%) compared with premixed insulin plus oral glycaemic-lowering medications.⁴⁷

Q7. In patients with T2DM who are already treated with metformin plus sulfonylureas, should treatment be switched to triple therapy with metformin + DPP-4i + SGLT2i?

Recommendation 7: In older patients with T2DM or those with overweight/obesity who are already treated with metformin plus sulfonylureas, switching to triple therapy with metformin + DPP-4i + SGLT2i is recommended to reduce the risk of hypoglycaemia and/or improve weight management (Grade A; strong recommendation [agreement rate: 94%]).

Explanation 7: Sulfonylureas exert glycaemic-lowering effects primarily by stimulating insulin secretion from pancreatic β -cell and are typically used in patients with preserved β -cell function.⁴⁸ However, metformin plus sulfonylureas is associated with an increased risk of hypoglycaemia and weight gain, so it should be used with caution in older adults, individuals with renal or hepatic impairment, and those with overweight or obesity.⁴⁸ In patients with T2DM inadequately controlled on metformin, metformin + DPP-4i + SGLT2i demonstrated improved long-term efficacy and safety outcomes compared to metformin plus sulfonylureas.⁴⁹ At week 156, metformin + DPP-4i + SGLT2i resulted in higher rates of HbA1c $<7.0\%$ (21.4% vs. 11.7%) and HbA1c $<7.0\%$ without hypoglycaemia (16.7% vs. 3.2%), reduced the need for insulin intensification (37.0% vs. 55.6%), and lowered the incidence of hypoglycaemia (22.5% vs. 47.7%) compared with metformin plus sulfonylureas.⁴⁹ Additional metabolic benefits of the triple therapy included greater reductions in liver fat content (-4.49% vs. $+0.4\%$), visceral adipose tissue volume (-0.347 L vs. $+0.058$ L), subcutaneous fat volume (-0.431 L vs. $+0.011$ L), and body weight (-4.36 kg vs. $+1.96$ kg) at week 122.⁴⁹ Similar benefits were observed in patients inadequately controlled on metformin + DPP-4i, where metformin + DPP-4i + SGLT2i showed greater reductions in fat mass (-0.7 kg vs. $+0.7$ kg), body weight (-2.0 kg vs. $+1.6$ kg), and waist circumference (-2.7 cm vs. $+2.5$ cm) at week 24 compared to metformin plus sulfonylureas.⁵⁰

Q8. In patients with T2DM who are already treated with metformin plus GLP-1 receptor agonists (GLP-1 RAs), should treatment be switched to triple therapy with metformin + DPP-4i + SGLT2i?

Recommendation 8: In patients with T2DM and without ASCVD who have achieved glycaemic goals on metformin plus GLP-1 RAs, when treatment is intolerable or treatment simplification is needed, switching to triple oral therapy with metformin + DPP-4i + SGLT2i can be considered to maintain comparable glycaemic and metabolic benefits (Grade A; strong recommendation [agreement rate: 97%]).

Explanation 8: Most studies suggest that oral GLP-1 RAs are comparable to injectable GLP-1 RAs in reducing HbA1c levels, indicating that they may serve as an alternative to injectable formulations in patients who have achieved their glycaemic goals.^{51–54} However, both oral and injectable GLP-1 RAs are frequently associated with gastrointestinal adverse events.⁵¹ A meta-analysis of 25 RCTs in patients with T2DM uncontrolled on metformin reported that metformin + DPP-4i + SGLT2i versus metformin + GLP-1 RAs had similar efficacy in reducing HbA1c (-1.21% vs. -0.99%), body weight (-2.37 kg vs. -2.16 kg), and systolic blood pressure.³¹ These results support that, in patients without ASCVD who have achieved glycaemic goals on metformin + GLP-1 RAs but experience poor tolerability or require treatment simplification, switching to oral metformin + DPP-4i + SGLT2i can be considered.

Q9. In patients with T2DM who are already treated with other triple regimens, should treatment be switched to metformin + DPP-4i + SGLT2i?

Recommendation 9: In patients with T2DM who are already treated with other triple regimens (e.g., metformin + DPP-4i + sulfonylureas), switching to triple therapy with metformin + DPP-4i + SGLT2i may be considered, as appropriate, based on the need to optimize glycaemic control, improve cardiovascular and renal outcomes, support weight management, or reduce hypoglycaemia risk (Grade C; strong recommendation [agreement rate: 100%]).

Explanation 9: In a retrospective study, the effectiveness of adding SGLT2i to various dual therapies (metformin + DPP-4i, sulfonylureas, GLP-1 RAs, or insulin) was evaluated.⁵⁵ Among these triple combinations, metformin + DPP-4i + SGLT2i demonstrated the highest proportion of patients achieving HbA1c $<7.0\%$ and the greatest improvement in blood pressure, with HbA1c reductions second only to metformin + SGLT2i + insulin.⁵⁵ In a nationwide Danish registry analysis, metformin + SGLT2i + GLP-1 RAs demonstrated the lowest risk of all three events (including major adverse cardiovascular events, severe hypoglycaemia, and all-cause mortality) compared with other widely used dual or triple oral therapies (metformin + DPP-4i, sulfonylureas, SGLT2i, GLP-1 RAs, or insulin; metformin + GLP-1 RAs + insulin).⁵⁶ Notably, compared with metformin + sulfonylureas, this triple regimen obviously reduced the risk of major adverse cardiovascular events by 47% and all-cause mortality by 82%.⁵⁶ Given the overlapping mechanisms between DPP-4i (which increase endogenous GLP-1 levels) and GLP-1 RAs, substitution of GLP-1 RAs with DPP-4i (namely, metformin + DPP-4i + SGLT2i) may be appropriate in some patients, such as those wishing to reduce injection burden. The glycaemic and extra-glycaemic benefits of metformin + DPP-4i + SGLT2i versus other metformin-based triple oral therapies are provided in Table 1.

Q10. In hospitalized patients with hyperglycaemia who have completed short-term insulin intensification, should treatment be switched to triple therapy with metformin + DPP-4i + SGLT2i?

Recommendation 10: In hospitalized patients with hyperglycaemia who require outpatient antihyperglycaemic therapy following short-term insulin intensification, switching to triple oral therapy with metformin + DPP-4i + SGLT2i may be considered, as appropriate, in individuals with short disease duration, high BMI, and preserved islet function to maintain long-term glycaemic control and improve islet function. (Grade E; strong recommendation [agreement rate: 93%]).

Explanation 10: Short-term intensive insulin therapy (SIIT) refers to multiple daily insulin injections or continuous subcutaneous insulin infusion administered in hospital, aiming to rapidly achieve glycaemic control.⁵⁷ After SIIT, switching to simplified outpatient regimens is recommended to sustain long-term glycaemic control. In patients with newly diagnosed T2DM, if long-term remission is not achieved after SIIT, subsequent outpatient treatments with metformin monotherapy or metformin-based combinations are preferred.⁵⁷ In a multicenter, randomized controlled trial of patients with newly diagnosed T2DM (BMI: 22.0–35.0 kg/m²) and hyperglycaemia (HbA1c ≥8.5%), after 2–3 weeks of SIIT, patients were randomized to receive metformin + DPP-4i, DPP-4i monotherapy, metformin monotherapy, or lifestyle intervention alone (control group).⁵⁸ At week 48, the metformin + DPP-4i group demonstrated a higher proportion of patients achieving HbA1c <7.0% (80% vs. 60%), greater HbA1c reductions (−4.8% vs. −4.2%), and improved β -cell function than the control group.⁵⁸ In addition, substantial evidence has confirmed that metformin + DPP-4i + SGLT2i provided better glycaemic benefits than dual metformin plus DPP-4i or SGLT2i, with a favourable safety profile. Therefore, metformin + DPP-4i + SGLT2i represents an effective outpatient option after SIIT in patients with newly diagnosed T2DM. In patients previously treated with oral antihyperglycaemic medications before SIIT, resuming prior regimens such as metformin + DPP-4i + SGLT2i can be considered if they have a short disease duration, high BMI, and preserved islet function, as some patients can restore responsiveness to oral medications.

Q11. When using a triple regimen of metformin + DPP-4i + SGLT2i, should FDCs formulation be preferred?

Recommendation 11: FDCs can simplify treatment and improve adherence, but they lack dosing flexibility and should be discontinued if one component is not tolerated.⁵⁹ FDCs of metformin + DPP-4i + SGLT2i are recommended with careful consideration of their advantages and limitations. Available options include (1) triple FDCs (metformin + DPP-4i + SGLT2i), (2) dual FDCs (metformin + DPP-4i) plus SGLT2i, and (3) dual FDCs (metformin + SGLT2i) plus DPP-4i. (Grade A; strong recommendation [agreement rate: 100%]).

Explanation 11: FDCs combine two or more medications with different mechanisms of action at fixed doses in a single tablet. FDCs have advantages of greater efficacy and lower risk of adverse events than high-dose monotherapy, simplifying treatment, improving adherence, reducing therapeutic inertia, especially in patients with delayed initiation of combination therapy. FDCs are also cost-effective.⁶⁰ Potential disadvantages include limited dose adjustment flexibility of

TABLE 3 Metformin/DPP-4i/SGLT2i dual or triple FDCs approved in China.

FDCs	Components
Metformin + SGLT2i	
Henagliflozin/metformin extended-release tablets	Henagliflozin 5 mg + metformin 500 mg/1000 mg
Dapagliflozin/metformin extended-release tablets	Dapagliflozin 10 mg + metformin 1000 mg
Empagliflozin/metformin tablets	Empagliflozin 5 mg + metformin 500 mg
	Empagliflozin 12.5 mg + metformin 1000 mg
Metformin + DPP-4i	
Retaglipatin/metformin tablets	Retaglipatin 50 mg + metformin 850 mg/1000 mg
Sitagliptin/metformin tablets	Sitagliptin 50 mg + metformin 500 mg/850 mg
Saxagliptin/metformin extended-release tablets	Saxagliptin 5 mg + metformin 500 mg/1000 mg
	Saxagliptin 2.5 mg + metformin 1000 mg
Linagliptin/metformin tablets	Linagliptin 2.5 mg + metformin 500 mg/850 mg
Vildagliptin/metformin tablets	Vildagliptin 50 mg + metformin 850 mg/1000 mg
Metformin + DPP-4i + SGLT2i	
Henagliflozin/retaglipatin/metformin extended-release tablets	Henagliflozin 10 mg + retaglipatin 100 mg + metformin 1000 mg
	Henagliflozin 5 mg + retaglipatin 50 mg + metformin 750 mg

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; FDCs, fixed-dose combinations; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

single medication and difficulty in attributing adverse events to a specific medication. In clinical practice, these advantages and limitations should be carefully considered to ensure the safe and effective use of FDCs.⁶¹ Table 3 summarizes currently approved dual and triple FDCs of metformin + DPP-4i + SGLT2i in China.

FDCs of metformin + DPP-4i + SGLT2i are bioequivalent to free-drug combinations.^{62,63} Landmark phase 3 trials demonstrated that, in patients with inadequate glycaemic control on metformin monotherapy, triple FDCs of Met + DPP-4i + SGLT2i achieved greater HbA1c reductions (1.45%–1.73%) compared with dual FDCs of metformin plus DPP-4i or SGLT2i (1.00%–1.33%) or dual free-drug combinations (1.28%) at week 16.^{40–42} The proportion of patients achieving HbA1c <7.0% was also higher with triple FDCs (38.5%–54%) than with dual FDCs (29.9%) or free-drug combinations (12.8%).^{40–42} In a phase 4 study, triple FDCs of Met + DPP-4i + SGLT2i reduced HbA1c by 2.0% at week 24, with 45.1% of patients reaching HbA1c <7.0%.⁶⁴ No treatment-related serious adverse events or severe hypoglycaemia were reported previously.

Treatment adherence is important for glycaemic control; a 10% increase in adherence is estimated to lower HbA1c by 0.1%.⁶⁵ Multiple studies showed that FDCs improved adherence, and thus may

TABLE 4 Dose adjustments of metformin, DPP-4i, and SGLT2i in T2DM patients with hepatic or renal impairment.

Drugs	Hepatic impairment			Renal impairment (eGFR, mL/min/1.73 m ²)				
	Mild	Moderate	Severe	ALT/ AST > 3 × ULN	≥60	45–59	30–44	<30
Metformin	No adjustment	No adjustment	Avoid use	Avoid use	No adjustment	Dose reduction	Not recommended	Contraindicated
SGLT2i								
Henagliflozin	No adjustment	Reduce to 5 mg	Reduce to 5 mg	NA	No adjustment	No adjustment	No adjustment	Not recommended
Dapagliflozin	No adjustment	No adjustment	Lack experience	NA	No adjustment	No adjustment	Not recommended	Contraindicated
Canagliflozin	No adjustment	No adjustment	Not recommended	NA	No adjustment	Max dose 100 mg/day	Max dose 100 mg/day	Contraindicated
Empagliflozin	No adjustment	No adjustment	Not recommended	NA	No adjustment	No adjustment	No adjustment	Not recommended
Ertugliflozin	No adjustment	No adjustment	Not recommended	NA	No adjustment	No adjustment	Not recommended	Contraindicated
Ipragliflozin	No data available	No data available	No data available	NA	No adjustment	Unknown	Unknown	Contraindicated
DPP-4i								
Retaglipitin	No adjustment	NA	NA	NA	No adjustment	Reduce by 50%	Reduce by 50%	Not recommended
Teneligliptin	No adjustment	No adjustment	Lack experience	NA	No adjustment	No adjustment	No adjustment	No adjustment
Omarigliptin	No adjustment	NA	NA	NA	No adjustment	No adjustment	No adjustment	No adjustment
Sitagliptin	No adjustment	No adjustment	Lack experience	NA	No adjustment	No adjustment	Reduce by 50%	Reduce to 25% of standard dose
Saxagliptin	No adjustment	No adjustment	No adjustment	No adjustment	No adjustment	No adjustment	Reduce by 50%	Reduce by 50%
Vildagliptin	Avoid use	Avoid use	Avoid use	Avoid use	No adjustment	Reduce by 50%	Reduce by 50%	Reduce by 50%
Linagliptin	No adjustment	No adjustment	No adjustment	No adjustment	No adjustment	No adjustment	No adjustment	No adjustment
Alogliptin	Use with caution if liver tests are abnormal	Use with caution if liver tests are abnormal	No adjustment	No adjustment	No adjustment	Reduce by 50%	Reduce by 50%	Reduce to 25% of standard dose

Note: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; NA, no information available; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus; ULN, upper limit of normal.

result in better glycaemic outcomes, fewer diabetic complications, and decreased healthcare cost.^{61,66,67} Currently, most economic studies of FDCs were from Western countries and suggest potential economic benefits. In an analysis of German T2DM management data, FDCs increased short-term diabetes-specific drug costs, possibly due to improved adherence or cost shifting to payers, yet total medical costs were unchanged.⁶⁸ From the patient's perspective, FDCs reduced out-of-pocket costs, making FDCs a potentially more favourable option.⁶⁸ Real-world data from the USA and Italy also associate FDCs' use with lower overall healthcare and diabetes-related costs compared with free-drug combinations.^{69–74} The cost-effectiveness data in Chinese patients remain lacking.

3.2 | Warnings and contraindications

The triple combination of metformin, DPP-4i, and SGLT2i has an overall incidence of adverse events comparable to that of metformin monotherapy or dual therapy with metformin plus DPP-4i or SGLT2i.^{12–21,24} The risk of severe hypoglycaemia is very low. No pharmacokinetic interactions are reported among the three medications.⁷⁵ However, the use of this regimen (including FDCs) is contraindicated in patients with known hypersensitivity or contraindications to any component. FDCs are not suitable for patients requiring dose adjustment of any single component.

This regimen is not recommended for patients with serum transaminase levels $>3 \times$ ULN or with clinical or laboratory evidence of liver dysfunction. Kidney dysfunction may cause metformin-associated lactic acidosis.⁷⁶ The triple regimen is contraindicated in patients with an estimated glomerular filtration rate <45 mL/min/1.73 m². Kidney function is recommended to be assessed before treatment initiation, with subsequent annual monitoring in patients with normal kidney function and 2–4 times per year in patients with impaired kidney function. Recommended dose adjustments for patients with liver or kidney dysfunction are summarized in Table 4.

For older adults with T2DM, metformin, DPP-4i, and SGLT2i are the first-recommended medication.⁷⁷ SGLT2i are preferred for older patients with atherosclerotic cardiovascular disease or those with high-risk factors, heart failure, and/or chronic kidney disease.⁷⁷ Older adults often have multiple comorbidities, and thus polypharmacy (concurrent use of ≥ 5 medications) is common, increasing the risk of drug–drug interactions and hypoglycaemia. In addition, this population has poor perception and tolerance to hypoglycaemia. Therefore, anti-diabetic regimens with a low risk of hypoglycaemia (e.g., metformin + DPP-4i + SGLT2i) and simplified regimens (e.g., FDCs) are preferred for older patients. Given the risk of vitamin B12 deficiency during long-term use of metformin, regular monitoring of vitamin B12 levels is advised, especially in older adults.

Metformin + DPP-4i + SGLT2i should be used with caution in patients with BMI <18.5 kg/m² due to the moderate weight-loss effects of SGLT2i. There is a lack of data on the safety and efficacy of this regimen in pregnant or breastfeeding women, children, and adolescents <18 years; therefore, its use is not recommended in these

populations. In addition, metformin and SGLT2i may increase the risk of ketoacidosis, and this regimen is not recommended for alcoholics. During the perioperative period, the use of SGLT2i may increase the risk of euglycaemic ketoacidosis. Metformin + DPP-4i + SGLT2i should be discontinued 3–4 days before surgery and restarted only after oral intake has resumed and renal function is stable. In patients undergoing iodinated contrast procedures, the regimen should be stopped due to the potential risk of metformin-associated lactic acidosis. Treatment can be restarted at least 48 hours post-procedure when renal function is stable.

4 | CONCLUSIONS

This consensus provided 11 evidence-based recommendations from a Chinese expert panel on the use of triple oral therapy with metformin + DPP-4i + SGLT2i, which may also inform T2DM treatment in other countries or regions. The regimen is recommended or considered in scenarios as follows: as early intensive therapy in newly diagnosed patients, especially those with high baseline HbA1c; as treatment intensification in patients inadequately controlled on monotherapy or dual therapy; as an alternative for patients who are intolerant to high-dose metformin; as treatment simplification for those transitioning from insulin therapy; and as a switch option after failure of other triple oral regimens. FDCs represent a promising option in diabetes management, and their cost-effectiveness in some countries such as China warrants further evaluation. For metformin + DPP-4i + SGLT2i, more evidence is needed to clarify the long-term cardiovascular and renal outcomes, identify patients most likely to benefit, and assess its effects on emerging outcomes such as cognitive function and non-alcoholic fatty liver disease. Overall, in clinical practice, the use of metformin + DPP-4i + SGLT2i should be tailored to patient characteristics, benefit–risk balance, and treatment preference to maximize therapeutic benefits.

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Xinhua Xiao, Lixin Guo, and Zhiguang Zhou conceived, designed, and supervised the whole project. Miao Yu and Tong Wang contributed to

the design, recruitment, implementation, data collection, and data analysis of the Delphi process. All authors contributed to the literature review and interpretation of results. Deyang Kang provided the methodological support for the consensus development. Miao Yu drafted and revised the manuscript. All authors reviewed the article and approved the final manuscript.

ACKNOWLEDGEMENTS

We thank the contributions of all participants who supported the consensus process. We are grateful to Yingying Fu, Meng Wei, Mengwen Li, and You Tian for their input and medical writing assistance, all from the Department of Medical Affairs, Jiangsu Hengrui Pharmaceuticals Co., Ltd.

FUNDING INFORMATION

The development and publication of this supplement were supported by an educational grant from Jiangsu Hengrui Pharmaceuticals Co., Ltd. The final content and decisions regarding publication were at the discretion and responsibility of the authors and editor. [Funding information added 28 Oct 2025, after original online publication]

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data relevant to this study are available upon request by contacting Xinhua Xiao (Email: xiaoxh2014@vip.163.com).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Yu M, Wang T, Xu C, et al. Triple oral therapy with metformin, DPP-4 inhibitor, and SGLT2 inhibitor for adults with type 2 diabetes: Consensus recommendations of a Chinese expert panel (version 2025). *Diabetes Obes Metab*. 2025;27(Suppl. 9):3-17. doi:[10.1111/dom.70197](https://doi.org/10.1111/dom.70197)