Chinese Expert Consensus Statement on Metformin in Clinical Practice

Preamble
Metformin, one of the most widely used oral hypoglycemic agents in the world, plays an important role for treating type 2 diabetes mellitus (T2DM) for decades, and it has been recommended as a first-line drug in diabetes guidelines around the world because of the good efficacy and safety for monotherapy and combination therapy, evidence of health economic benefits, and definite clinical evidence in the prevention of cardiovascular complications.

Metformin has been used in China for more than 30 years. However, some clinicians and patients still have some misunderstandings about the use of metformin, which makes some patients, who could formally benefit from metformin therapy, miss the treatment opportunities. Therefore, the Chinese Expert Consensus Statement on Metformin in Clinical Practice was jointly formed by endocrinologists and pharmaceutical experts with the aim of guiding clinicians and patients to correctly understand and rationally use metformin.

By using a question-and-answer format, this consensus addressed the clinical status and initial treatment opportunity, mechanism, drug dose and clinical efficacy, drug use in special diabetic populations, safety, effects on cardiovascular system, which included six modules and seventeen main recommendations about combination medication of metformin (Figure 1).

1. Clinical status and initial treatment opportunity

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>If there is no contraindication and intolerance, metformin is the first choice and full-course drug for the treatment of T2DM and should always be retained in the treatment regimen of diabetes mellitus.</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
<td>Metformin is not only the first-choice drug for T2DM patients with overweight or obesity, but also applicable for T2DM patients with normal weight. The efficacy and adverse reactions of metformin are not related to the BMI of patients.</td>
</tr>
<tr>
<td>IIb</td>
<td>C-EO</td>
<td>Metformin can effectively reduce the risk of T2DM in the pre-diabetic population, but Metformin has not yet been approved for the prevention of diabetes mellitus in China.</td>
</tr>
</tbody>
</table>

T2DM: Type 2 diabetes mellitus; BMI: Body Mass Index.

1.1 Why Metformin is recommended as the first-line and full-course drug for treating T2DM?
Metformin has reliable short-term and long-term hypoglycemic effects. Metformin monotherapy can effectively reduce fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels of T2DM patients, and can reduce hemoglobin A1c (HbA1c) by 1.0–2.0% (after removing the placebo effect), as well as reduce HbA1c by 1.8% (including the placebo effect) in Chinese patients with newly diagnosed T2DM, without being affected by body weight. Under similar baseline HbA1c conditions, the optimal effective dose (2000 mg/d) of metformin was superior to other oral hypoglycemic agents in terms of their hypoglycemic effects. The efficacy of metformin extended-release tablets was similar to that of conventional tablets.
Combination therapy with metformin and other oral anti-diabetic agents can further significantly improve the blood glucose control for the patients with poor efficacy following metformin monotherapy. Metformin, compared with other oral anti-diabetic drugs as the first-line treatment was associated with the latest time for adding the second oral hypoglycemic drug or insulin combination treatment, and with the lowest probability of treatment plan adjustment. Metformin combined with insulin versus insulin alone induce favorable reductions in weight, HbA1c, and insulin levels and hypoglycemic risk. Metformin has cardiovascular protective effects. In the United Kingdom Prospective Diabetes Study, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed in patients treated with metformin, and a continued benefit after metformin therapy was evident among overweight patients. A meta-analysis has shown that diabetics...
taking metformin have a lower rate of all-cause mortality than non-diabetic individuals and the general population.\textsuperscript{18}

Metformin has good safety profiles and tolerance. It should be noted that use of the drug alone displayed the following characteristics: metformin alone did not increase the risk of hypoglycemia occurrence; most of the gastrointestinal reactions were transient, did not cause renal impairment, and long-term use of the drug in the patients without chronic kidney disease (CKD) and hypoxia did not increase the risk of hyperlacticemia or lactic acidosis.\textsuperscript{19-21} Compared with other hypoglycemic drugs, metformin had a good cost-benefit ratio.\textsuperscript{22}

Therefore, recent diabetes mellitus guidelines in China and other countries\textsuperscript{2, 23, 24} have recommended that metformin was the first choice drug and the initial drug of choice in combination therapy for overweight or normal-weight T2DM patients without contraindications and intolerance, and it should be retained in the treatment regimen of diabetes mellitus.

1.2 Is Metformin the first choice for T2DM without weight restriction?

The results of retrospective and prospective clinical studies\textsuperscript{25-27} showed that metformin had the same effect in T2DM patients with overweight, obese and normal weight. Therefore, body weight should not influence whether metformin should be used. Diabetes mellitus guidelines in China and other countries\textsuperscript{2,23,24,28} have recommended metformin as the initial pharmacologic agent in treating T2DM, if it is not contraindicated, and is tolerated.

1.3 Can Metformin prevent diabetes mellitus?

Metformin can reduce the risk of diabetes mellitus in prediabetic population, and had good tolerance and long-term effectiveness \textsuperscript{2,29}

The Diabetes Prevention Program (DPP)\textsuperscript{30} is a randomized controlled study of a diabetes prevention program, the results showed that the incidence of diabetes reduced by 58% with the lifestyle intervention, and by 31% with metformin (850 mg twice daily), as compared with placebo. A DPP follow-up study\textsuperscript{31} showed that the incidence of diabetes in the 10 years since DPP randomization had decreased by 34% (24–42%) in the lifestyle group and by 18% (7–28%) in the metformin group as compared with the placebo.

Study (DPPOS) results\textsuperscript{32, 33} showed that metformin decreased the incidence of diabetes mellitus, reduced body weight and waist circumference, and was cost-saving in 10 years, as compared with lifestyle treatment. An Indian DPP (IDPP)\textsuperscript{34} has shown that the relative risk reduction of diabetes mellitus was 28.5% with lifestyle modification (95% CI 20.5–37.3; \(P=0.018\)), 26.4% with metformin (95% CI 19.1–35.1; \(P=0.029\)) and 28.2% with lifestyle modification plus metformin (95% CI 20.3–37.0; \(P=0.022\)), as compared with the control group. An Indian Diabetes Community Lifestyle Improvement Program (D-CLIP)\textsuperscript{35} has shown expert recommendations of adding metformin in a stepwise manner to lifestyle education is an effective method for preventing or delaying diabetes in adults with prediabetes, even in a resource-challenged setting like low- and middle-income countries (LMICs).

At present, metformin has not yet been approved for the prevention of diabetes mellitus in China.
2. Mechanism

**Recommendation**

Metformin reduces blood glucose mainly by reducing hepatic glucose output, improving insulin resistance, reducing small intestinal glucose uptake and activating AMPK.

AMPK: Adenosine monophosphate-activated protein kinase.

### 2.1 What is the hypoglycemic mechanism of metformin?

The main mechanisms of metformin in improving hyperglycemia include: (1) acting on the liver, inhibiting gluconeogenesis and reducing hepatic glucose output; (2) acting on peripheral tissues (muscle, fat), improving muscle glycogen synthesis, reducing free fatty acids, increasing insulin sensitivity, and increasing glucose uptake and utilization; (3) acting on the intestinal tract, inhibiting glucose uptake in intestinal parietal cells and improving the glucagon-likepeptide1 (GLP-1) levels; and (4) activating adenosine monophosphate-activated protein kinase (AMPK), and improving the energy metabolism of muscle, fat and liver.

### 3. Drug dose and clinical efficacy

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<tbody>
<tr>
<td>I</td>
<td>C-Eo</td>
<td>The minimum effective dose of metformin is 500 mg/d, the optimal effective dose is 2000 mg/d, and the maximum recommended dose for adults is 2550 mg/d. The efficacy of metformin is dose-dependent. When patients tolerate metformin, it is recommended that drug dosing be gradually increased to the optimal effective dose (2000 mg/d), so that the blood glucose of patients can reach the standard and be well controlled for an extended period of time.</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
<td>Metformin has a reliable hypoglycemic effect. Metformin monotherapy can reduce HbA1c by 1.0–2.0% (after removing the placebo effect)</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
<td>Metformin can be used in combination therapy with any other non-insulin hypoglycemic agents; after patients with poor glycemic control are treated with full-dose metformin monotherapy for three months, blood glucose can be significantly improved after adding other hypoglycemic agents.</td>
</tr>
<tr>
<td>Iia</td>
<td>B-R</td>
<td>Combination therapy with Metformin and insulin can further improve glycemic control and reduce insulin dose, as well as reduce the risks of weight gain and hypoglycemia caused by insulin therapy.</td>
</tr>
<tr>
<td>Iia</td>
<td>C-Eo</td>
<td>If T1DM patients need glycemic control, metformin can be added to insulin therapy.</td>
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</table>

T1DM: Type 1 diabetes mellitus.

### 3.1 What are the minimum, maximum and optimal doses of metformin, respectively?

Clinical studies have shown that the hypoglycemic effect of metformin is positively correlated with drug dose over a range of 500–2000 mg/d. Further, a 500 mg/d dose of metformin can reduce HbA1c by 0.6% (after removing the placebo effect) and a dose of 2000 mg/d metformin can reduce HbA1c by 2.0%; and there was no significant difference in gastrointestinal reactions when used at a dose of between 1000–1500 mg. The UK Prospective Diabetes Study (UKPDS) has shown that the median metformin dose in the intensive glucose control therapy study...
was 2550 mg/d. Thus, the recommended minimum effective dose of metformin was 500 mg/d, and the optimal effective dose was 2000 mg/d. The maximum dose for conventional tablets was 2550 mg/d, and the maximum recommended dose for extended-release formulations was 2000 mg/d.

3.2 How to adjust the dose of metformin?
The principle of metformin dose adjustment is to "Start with a small dose and then gradually increase the dose". A dose of 500–1000 mg/d metformin is recommend at the beginning of therapy, and the drug dose should be added at an optimal effective dose of 2000 mg/d or at the maximum tolerated dose 1–2 weeks later. Metformin can be taken with meals or immediately after meals. Considering the clinical efficacy and patient compliance, a simplified drug dose regimen can be adopted: It is recommended to start with 500 mg, twice a day, and if no adverse reactions of the gastrointestinal tract are seen, the drug dose is gradually increased to 1000 mg, twice a day. The plasma half-life of metformin is 5.1 hours, but the drug is also distributed in the red blood cell volume, which increases the elimination half-life of 17.6 hours. A dose of 1000 mg metformin, twice a day, can maintain an effective blood concentration for 24 hours. Individualized treatment can be given according to the patient's condition. Generally, the daily dose is 1500–2000 mg, 2–3 times a day. The same dose is recommended for converting conventional tablets to extended-release tablets. It is worth noting that drug dose adjustment is needed for the elderly population and in patients with hepato-renal insufficiency. The specific methods of drug dose adjustment can be found in Section IV describing the use of metformin in special sub-populations.

3.3 What are the dosage forms of metformin?
At present, there are mainly single component metformin tablets (250, 500 or 850 mg/tablet), metformin extended-release tablets or capsules (500 mg/tablet or 500 mg/capsule), metformin enteric-coated tablets or capsules (250 mg/tablet or 250 mg/capsule), metformin powder, and other oral hypoglycemic agents (including sulfonyl-ureas or dipeptidyl peptidase-4 [DPP-4] inhibitors).

3.4 Does the efficacy of different dosage forms of metformin differ?
For qualified pharmaceutical preparations, different dose forms should have bioequivalence at the same administered dosage. The main difference among different dosage forms of metformin is that the dissolution and release behavior of metformin is different after administration: conventional tablets are disintegrated and released in the stomach; enteric-coated tablets and capsules are disintegrated and released in the intestinal tract; extended-release tablets and capsules are dissolved and released slowly in the gastrointestinal tract. Extended-release metformin is associated with increased compliance as compared with the immediate release form of metformin. Studies have shown that metformin extended-release tablets given once daily were not inferior to metformin immediate release when determining the least squares mean (LSM) change in HbA1c levels from baseline. A retrospective observational study has shown an increased compliance in those use the extended release formulation (XL, Glucophage SR) as compared those use the standard immediate release formulation of metformin.

3.5 What is the hypoglycemic effect of metformin monotherapy?
A randomized, double-blind, parallel controlled study has shown that after subtracting the placebo effect, 29 weeks of metformin monotherapy can reduce FPG by 3.2 mmol/L, PPG by 4.0 mmol/L and HbA1c by 1.8%. In a
placebo-controlled clinical study conducted in the Chinese population, metformin monotherapy 1000 mg or 1700 mg daily can reduce HbA1c by 0.7% and 1.0% (after removing the placebo effect), respectively. A prospective, randomized controlled study has shown that the effects of metformin-based oral anti-diabetic drug therapy on glycemic control were not inferior to glargine in newly diagnosed T2DM patients presenting with severe hyperglycemia after short-term insulin therapy. A prospective, randomized controlled study has also shown that metformin (1500 mg/d) was similar with acarbose (300 mg/d) in terms of efficacy, and metformin is thus a viable choice for initial therapy in Chinese patients with newly diagnosed T2DM.

3.6 What is the efficacy of metformin in combination with sulfonylureas?
Metformin can improve insulin resistance and reduce hepatic glucose output, while sulfonylureas can promote insulin secretion. The combination therapy with both drugs can complement each other in terms of their mechanisms of action, which has a more comprehensive characteristic of targeting the pathophysiological defects of T2DM. However, attention should be paid to the risk of hypoglycemia to the combination therapy of both drugs.

The combination of metformin and glibenclamide can achieve more ideal control of FPG and HbA1c than monotherapy with either agent. After 18 weeks of treatment with sulfonylureas in patients with poor glycemic control, an HbA1c level < 7.0% was achieved in four-fold more patients than those that were treated with glipizide/metformin (36.3%) as compared with glipizide (8.9%) or metformin (9.9%) monotherapies. The level of HbA1c decreased significantly more in the metformin plus gliquidone group (1.7%) than in the metformin plus acarbose (0.9%) group, and there was no significant difference in hypoglycemia or weight gain between the two treatment groups.

3.7 What is the efficacy of metformin in combination with thiazolidinediones?
Combination treatment with once-daily metformin-rosiglitazone improves glycemic control, insulin sensitivity, and β-cell function more effectively than treatment with metformin alone; however, adverse reactions (weight gain, and elevated low-density lipoprotein-C (LDL-C) levels) of the combination therapy were higher than that of metformin monotherapy. In addition, patients with T2DM treated with the Rosiglitazone/metformin (8 mg/2 g per day) at a fixed-dose combination had a significantly improvement of HbA1c levels, and a greater proportion of patients achieved their glycemic targets as compared those treated with high-dose metformin (3 g/d). Thus, patients with severe insulin resistance might consider the treatment regimen of metformin combined with thiazolidinediones.

3.8 What is the efficacy of metformin in combination with meglitinides?
Meglitinide is a kind of insulin secreting agent that is used at meal times, which has a synergistic effect when combined with metformin. In newly diagnosed T2DM patients with high blood glucose levels (HbA1c level close to 11.0%), repaglinide plus metformin and repaglinide alone provided significant improvements in glycemic control and were well tolerated in Chinese patients naive to treatment with oral anti-diabetic agents. Combination therapy with repaglinide plus metformin showed superiority to repaglinide monotherapy in this population, but the incidence of hypoglycemia did not increase significantly. Thus, when metformin is combined with sulfonylureas and the incidence of hypoglycemia is higher, metformin combined with repaglinide should be considered. Combination therapy with metformin and meglitinide showed a greater reduction in HbA1c, FPG and PPG levels,
increased the target HbA1c value of <7%, and no difference was found in adverse event rates between the combination therapy and metformin monotherapy groups.\textsuperscript{57}

3.9 What is the efficacy of metformin in combination with combat-glycosidase inhibitors?
Metformin in combination with combat-glycosidase inhibitors can well control both FPG and PPG. The addition of acarbose to metformin monotherapy provides an efficacious and safe alternative for glycemic improvement in overweight T2DM patients that are otherwise inadequately controlled by metformin alone.\textsuperscript{58} A randomized, controlled study in the Chinese population with T2DM has shown that combined therapy with metformin and gliquidone was superior to metformin plus acarbose in improving glycemic control.\textsuperscript{53} Both drugs have certain gastrointestinal adverse reactions, and the combination therapy of both agents might increase gastrointestinal adverse reactions.

3.10 What is the efficacy of metformin in combination with DPP-4 inhibitors?
Combined therapy with metformin and DPP-4 inhibitors can reduce blood glucose by exerting a complementarity of mechanisms and synergistic effects according to different pathophysiological defects seen in T2DM. The addition of DPP-4 inhibitors to ongoing metformin treatment in T2DM patients was well tolerated and resulted in significant and clinically relevant improvements in glycemic control.\textsuperscript{59} If the patient has no contra-indications or intolerance, it is suggested that metformin in combination with DPP-4 inhibitors is considered when the efficacy of three-month metformin monotherapy is unsatisfactory.

3.11 What is the efficacy of metformin combined with sodium-glucose co-transporter-2 (SGLT-2) inhibitors?
Current SGLT-2 inhibitors available in China include dapagliflozin, empagliflozin and canagliflozin. SGLT-2 inhibitors can effectively inhibit SGLT-2 activity in renal proximal convoluted tubules, reduce glucose reabsorption by renal tubular epithelial cells, and increase glucose excretion in the urine, thus reducing blood glucose. Randomized controlled trials\textsuperscript{60, 61} and a meta-analysis\textsuperscript{62} have shown that adding SGLT-2 inhibitors to metformin monotherapy significantly improved glycemic parameters with the added benefits of weight loss and systolic blood pressure reduction in T2DM patients with poor control of metformin monotherapy.

3.12 What is the efficacy of metformin in combination with glucagon-like peptide-1 (GLP-1) receptor agonist?
Metformin in combination with the GLP-1 receptor agonist can further reduce FPG and HbA1c levels, increase the target rate of blood glucose, improve islet β-cell function, improve insulin resistance, and reduce body weight and systolic blood pressure, and importantly do not increase the incidence of severe hypoglycemia.\textsuperscript{63-65} A randomized and controlled study in the Chinese population with T2DM\textsuperscript{64} showed that liraglutide combined with metformin improved glycemic control similar to that seen with glimepiride combined with metformin, but with less frequent major and minor hypoglycemia. Liraglutide combined with metformin also induced a significant weight loss and reduced the systolic blood pressure, while with poor gastrointestinal tolerance.

3.13 What is the efficacy of metformin in combination with insulin?
Metformin can enhance insulin sensitivity in liver and muscle tissues. For T2DM patients with poor glycemic
control after combination therapy with metformin and oral hypoglycemic agents, metformin should be retained when initiating insulin therapy. Compared with insulin monotherapy, metformin in combination with insulin can favorably reduce weight, HbA1c, and insulin dose and hypoglycemic risk; moreover, the combination of both agents might also be associated with decreased risk of cardiovascular disease and cancer. 12-15, 66, 67

The Hyperinsulinemia Outcome of its Metabolic Effects (HOME) trial 14 has shown that the addition of metformin resulted in improvements in weight, glycemic control, and insulin requirements (average daily dose of insulin reduced by 19.63 IU) in patients with T2DM treated with insulin, which were maintained after 4.3 years of treatment. Analysis of the secondary endpoints of this HOME trial has shown that metformin treatment was associated with a 40% reduction in the relative risk of macrovascular events. The Merit study 15 has shown that when compared with insulin as part 30 treatment, biphasic insulin as part 30 plus metformin, was not only superior in terms of its glycemic control, but it also did not increase the incidence of hypoglycemia and gastrointestinal reactions, with decreased insulin dose and a lower weight gain being seen. A retrospective observational study 68 has shown that when metformin was added to initial continuous subcutaneous insulin infusion or multiple daily injections, the regimen was associated with decreased glucose fluctuation and nocturnal hypoglycemic risk in patients with T2DM.

3.14 Can newly diagnosed T2DM patients with initial high HbA1c be treated with Metformin-based oral hypoglycemic agents after short-term intensive insulin therapy?
A Chinese study 49 randomly divided T2DM patients treated with short-term insulin into a glargine group and a metformin-based oral antidiabetic drug group. After 24 weeks of treatment, HbA1c was similarly reduced in both groups. Thus, considering the superiority of metformin in terms of its safety, cost, and convenience, metformin-based oral anti-diabetic (OAD) therapy is strongly recommended for these patients.

A 2-year open-label, parallel-group, controlled clinical trial 69 randomized T2DM patients to three weeks of induction intensive insulin therapy (IIT) followed by either repeat induction intermittently for up to two weeks every three months or daily metformin. The results showed that after induction IIT, metformin was superior to intermittent IIT for maintaining β-cell function and glycemic control over a period of two years. Therefore, after hyperglycemia symptoms are improved in newly diagnosed T2DM patients that are receiving short-term insulin therapy, metformin-based oral hypoglycemic therapy may be considered.

3.15 Should metformin be used in sufficient quantities as soon as possible to maintain a longer target time?
Within the drug dose range of 500–2000 mg/d, the anti-hyperglycemic activity of metformin is generally dose-dependent. 3 Compared with other hypoglycemic agents, metformin had a better cost-effectiveness ratio. 22 A Diabetes Outcome Progression Trial (ADOPT) 70 has shown that in patients with newly diagnosed T2DM, metformin monotherapy (2000 mg/d) could maintain the average HbA1c level below 7% within 45 months. A 104-week controlled clinical trial 71 showed that when compared with sitagliptin monotherapy (100 mg/d), metformin monotherapy (2000 mg/d) extended by 24 weeks a maintained HbA1c level of <7% in treated patients. Therefore, when patients can tolerate metformin, the optimal dose of the drug (2000 mg/d) not only makes the blood glucose level reach the standard as soon as possible, but it can also achieve better glycemic control for longer periods of time.
3.16 Can metformin be added in insulin therapy for T1DM patients?

Metformin can be added to insulin therapy for T1DM patients, especially for those with high insulin dose and obvious weight gain. However, metformin is prohibited in patients with diabetic ketoacidosis, hyperglycemic hyperosmolar syndrome and diabetic lactic acidosis.

A clinical study found that metformin combination therapy in T1DM patients can decrease cholesterolemia, body weight and insulin dose, especially the LDL-C levels. For T1DM patients with poor glycemic control after insulin monotherapy, combination metformin therapy was associated with sustained reductions in insulin dose and body weight. A meta-analysis has shown that metformin was associated with reduced daily insulin dose, body weight, total cholesterol level, LDL and high-density lipoprotein levels, without increased risk of hypoglycemia and diabetic ketoacidosis.

3.17 What is the effect of metformin on weight loss?

Metformin has the effect of weight loss. After 16 weeks of metformin treatment, the body weight of Chinese patients with newly diagnosed T2DM decreased by 2.4%, 3.9% and 3.5% in the context of normal-weight, overweight, and obese patients, respectively. The magnitude of weight loss was positively associated with the baseline weight after metformin treatment; however, baseline BMI had no impact on glycemic control, weight change or other efficacy measures with metformin monotherapy. Furthermore, the use of sulfonylureas, glitazone and insulin can increase body weight of T2DM, while combination therapy with metformin and the above drugs can reduce the effect of these drugs on weight gain. The HOME trial showed that when compared with insulin monotherapy, metformin combined with insulin prevented weight gain by 2.28–3.85 kg. The results may differ across different studies due to differences in the population and the test methods.

4. Drug use in special diabetic populations

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<tr>
<td>IIa</td>
<td>C-E0</td>
<td>Metformin is applicable in children aged 10 years or more; no age limit for the use of metformin in elderly people. However, due to the renal hypofunction in elderly patients, the dose of metformin should be adjusted according to the status of renal function before and during medication.</td>
</tr>
<tr>
<td>IIa</td>
<td>C-E0</td>
<td>Metformin should be avoided in patients whose serum transaminase is more than three times the upper limit of the normal value.</td>
</tr>
<tr>
<td>IIa</td>
<td>C-E0</td>
<td>The dose of metformin should be adjusted for patients with renal insufficiency by adjusting eGFR level:</td>
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<tr>
<td></td>
<td></td>
<td>• No dose adjustment if eGFR ≥60 ml/min per 1.73 m²</td>
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<tr>
<td></td>
<td></td>
<td>• Dose adjustment is needed if eGFR 45–59 ml/min per 1.73 m²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Avoid if eGFR&lt;45 ml/min per 1.73 m²</td>
</tr>
<tr>
<td>I</td>
<td>C-E0</td>
<td>For patients (eGFR &gt;60 ml/min per 1.73m²), metformin should be discontinued before or at the time of angiography, and it can be resumed at least 48 hours after the examination and only if renal function deteriorates again. For patients with moderate renal insufficiency (eGFR: 45–59 ml/min per 1.73m²), metformin should be temporarily discontinued for 48 hours before using contrast agents and general anesthesia, after that, metformin should be discontinued for 48–72 hours, and can be resumed after the renal function is not deteriorated.</td>
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</table>

eGFR: Estimated glomerular filtration rate.
4.1 Is heart failure an absolute contraindication of metformin?
Prescribing metformin is prohibited in patients with acute and unstable heart failure. Compared with other treatments, metformin is a safe option for glycemic control in patients with heart failure. Metformin therapy is associated with a reduced mortality of heart failure in patients with new onset diabetes mellitus, and may be associated with increased survival in diabetic patients with heart failure. The 2019 ADA Guideline has pointed out that in patients with T2DM with stable congestive heart failure, metformin may be used if estimated glomerular filtration rate remains >30 mL/min, but should be avoided in unstable or hospitalized patients with congestive heart failure. The contraindication of chronic heart failure has been removed from the European and Chinese versions of the metformin guidance instructions.

4.2 How to use metformin in elderly patients over 65 years old?
Metformin was still the first choice drug for elderly T2DM patients with normal renal function, and there was no specific age limit. Rational use of metformin in elderly patients can achieve a good hypoglycemic effect, and a lowered incidence of hypoglycemia was also beneficial to elderly patients. However, the renal function of elderly patients with renal dysfunction needed to be monitored regularly (i.e., to be examined once every 3–6 months) and the dose of metformin should be adjusted according to the eGFR. The principles are as follows: drug dose adjustment is needed if the eGFR is 45–59 ml/min per 1.73 m²; avoid using if the eGFR <45 ml/min per 1.73 m². The eGFR evaluation formula applicable for Chinese CKD patients is an eGFR (ml/min per 1.73 m²) = 175×Scr−1.234(mg/dl)×age−0.179 (female × 0.79).

4.3 Is metformin applicable to children and adolescents with diabetes mellitus?
For children with T2DM aged 10 years and over, metformin should be initiated along with promoting lifestyle changes, unless insulin is needed to reverse glucose toxicity in the case of significant hyperglycemia or ketoacidosis. Metformin can be used in children or adolescents aged 10 years or over, and the maximum daily dose should not exceed 2000 mg; furthermore, metformin is not recommended for children under 10 years of age.

4.4 Is metformin applicable to patients with gestational diabetes mellitus (GDM)?
Although many international academic organizations have recommended that metformin is applicable in the case of GDM patients, there is no indication for metformin during pregnancy in China. The Chinese Guideline for the Prevention and Treatment of T2DM in 2017 has recommended that if patients need to continue taking metformin for special reasons during pregnancy, it should be added on the basis of insulin on the premise of fully informing the advantages and disadvantages of metformin therapy during pregnancy. The 2019 ADA guideline has recommended insulin as the first choice drug for GDM treatment. Metformin and glyburide may be considered when insulin is not applicable; however, both therapeutics cross the placenta to the fetus, with metformin likely crossing to a greater extent than glyburide, and all oral agents lack long-term safety data. The ACOG (American college of obstetrics and gynecology) guideline in 2018 has recommended that when pharmacological treatment of GDM is indicated, insulin is considered the preferred treatment for diabetes in pregnancy; in women that elect to decline insulin therapy or in whom the obstetrician or other obstetric care providers believe cannot safely administer insulin, or for women that cannot afford treatment with insulin, metformin is a reasonable and alternative choice. Breastfeeding women should use metformin with caution and stop breastfeeding when they have to use it.
4.5 What should be paid attention to when metformin is used in T2DM patients with hepatic insufficiency?

Metformin is not metabolized on passing through the liver, without hepatotoxicity. A systematic review\textsuperscript{89} has shown that metformin has a number of biochemical effects that would suggest a benefit in treating chronic liver diseases, particularly in the context of insulin resistance and inflammation. A meta-analysis\textsuperscript{90} has shown that thiazolidinediones were inferior to metformin in lowering HbA1c and alkaline phosphatase levels. In addition, severe impairment of liver function can significantly limit lactic acid clearance; thus, it is suggested that metformin be avoided in patients whose serum transaminase exceeds three times the upper limit of normal values or whose liver function is severely impaired.

4.6 What should be paid attention to when metformin is used in T2DM patients with renal insufficiency?

Metformin itself does not affect renal function, but there is a clinical misconception that metformin should be discontinued by referring to proteinuria only. It is suggested that the dose of metformin should be adjusted according to the level of eGFR: no drug dose adjustment is necessary if eGFR $\geq$ 60 ml/min per 1.73 m$^2$, and drug dose modification is needed if the eGFR is 45–59 ml/min per 1.73 m$^2$, and drug therapy should be avoided if eGFR < 45 ml/min per 1.73 m$^2$\textsuperscript{72,91}

Recommendations of ADA guideline in 2019 on the use of metformin in patients with renal insufficiency was more radical\textsuperscript{23}. This guideline recommended that no dose adjustment is recommended if the eGFR >45 ml/min per 1.73 m$^2$, or do not initiate or assess risk/benefit if currently on metformin if the eGFR is 30–45 ml/min per 1.73 m$^2$, and to discontinue therapy if the eGFR < 30 ml/min per 1.73 m$^2$. The Chinese version of the metformin instruction\textsuperscript{72} has indicated that in the absence of other conditions that might increase the risk of lactic acidosis, metformin can be used in patients with moderate renal insufficiency of Grade 3a (CrCl 45–59 ml/min or an eGFR of 45–60 ml/min per 1.73m$^2$), and the maximum dose is 1000 mg, which is taken twice daily. A recent study showed that the appropriate daily dosing schedules were 1500 mg (0.5 g in the morning [qam] plus 1 g in the evening [qpm]) in chronic kidney disease (CKD) stage 3A, and 1000 mg (0.5 g qam + 0.5 g qpm) in CKD stage 3B, and 500 mg (qam) in CKD stage 4\textsuperscript{92}

4.7 When should metformin be discontinued before angiography or general anesthesia? How long should it be discontinued before resumption of therapy?

Patients (eGFR > 60 ml/min per 1.73 m$^2$) must cease metformin therapy before or at the time of examinations, and can resume metformin therapy at least 48 hours after examination and only if renal function has not deteriorated again.

Studies have found that intravascular injection of iodine contrast agent might lead to renal failure, thus leading to metformin accumulation and the increased risk of lactic acidosis. Metformin must be discontinued 48 hours before iodine contrast agent injection and general anesthesia in patients with moderate renal impairment (eGFR between 45 and 60 ml/min per 1.73 m$^2$), metformin must be discontinued 48 hours before administration of iodinated contrast media and not be reinstituted until at least 48 hours afterwards and only after renal function has been re-evaluated and has not deteriorated further.
5. Safety

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-R</td>
<td>The gastrointestinal reaction is the main adverse reaction of metformin, which mostly occurs 10 weeks after treatment. With the prolongation of treatment time, most patients gradually tolerate it or symptoms disappear. Starting with a small dose, the dose of metformin gradually increases and is timely adjusted. Non-extended-release preparations are taken three times a day with meals, or extended-release preparations are taken once a day, which can reduce the advent of gastrointestinal reactions.</td>
</tr>
<tr>
<td>IIa</td>
<td>C-E0</td>
<td>Metformin itself has no hepatotoxicity or nephrotoxicity</td>
</tr>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>There is no definite evidence that metformin is associated with lactic acidosis. On the premise of mastering the contraindications, long-term use of metformin does not increase the risk of lactic acidosis.</td>
</tr>
</tbody>
</table>

5.1 What are the contraindications of metformin?
Contraindications of metformin include the following: (1) Moderate (grade 3b) and severe renal failure or renal insufficiency (CrCl < 45 ml/min or eGFR < 45 ml/min per 1.73 m²); (2) Diseases that can cause tissue hypoxia (especially exacerbation of acute or chronic diseases), such as decompensated heart failure, respiratory failure, recent myocardial infarction, and shock; (3) Severe infections and trauma, major surgical operations, hypotension and so on; (4) People that have been known to be allergic to metformin hydrochloride; (5) Acute or chronic metabolic acidosis, including diabetic ketoacidosis with or without coma (diabetic ketoacidosis needs insulin therapy); (6) Alcoholics; (7) Patients receiving intravascular injection of iodine contrast agent can temporarily discontinue the product; and (8) Vitamin B12, and folic acid deficiency have not been corrected.

5.2 What are the common adverse reactions to metformin?
Common adverse reactions include diarrhea, nausea, vomiting, gastric distention, fatigue, dyspepsia, abdominal discomfort and headache. These adverse reactions often occur in the early stage of drug treatment, and most patients can tolerate them. With the prolongation of the treatment time, these adverse reactions can basically disappear. Starting with a low dose, and increasing the dose gradually or changing to metformin extended-release preparation is an effective way to reduce the occurrence of adverse reactions in the early stages of therapy.

5.3 Does the gastrointestinal reaction to metformin relate to drug dose? How to deal with it?
Metformin-induced gastrointestinal reactions occur mostly in the early stages of treatment (most occur in the first 10 weeks of treatment). Most patients can gradually tolerate these gastrointestinal reactions or symptoms disappear with the prolongation of treatment time. A multicenter, double-blind, placebo-controlled trial has shown that the incidence of gastrointestinal reactions was 24% at the beginning of metformin treatment (1000 mg/d); there was no significant difference in the incidence of gastrointestinal reactions when the dose of metformin increased from 1000–2500 mg/d. The incidence of gastrointestinal reactions of metformin was reported to be 15% in China, and patients that reported gastrointestinal reactions in the two BMI groups experienced similar rates of GI AE severity (P = 0.5410), mean duration (P = 0.3572) and duration distribution (P = 0.1347). In addition, there was no significant difference in terms of gastrointestinal reaction severity and duration between metformin dosage groups (1500 mg/d versus 2000 mg/d).
If serious gastrointestinal reactions appeared as doses advanced, one should decrease the metformin dose to a previously lower dose and should try to advance the dose at a later time.\textsuperscript{95} Metformin extended-release formulation taken once-daily has improved gastrointestinal reaction tolerability as compared with metformin immediate-release and other oral anti-diabetics (OADs) that are taken over the long term, which result in fewer gastrointestinal reaction side-effects and treatment discontinuation.\textsuperscript{47,96}

### 5.4 Does metformin affect the absorption of vitamin B12?

Previous studies\textsuperscript{97-100} showed that long term treatment with metformin increases the risk of vitamin B-12 deficiency. A meta-analysis in China has shown that metformin use led to significantly lowered B12 levels and significantly higher risk of B12 deficiency in diabetic patients (increased by 1.09-fold).\textsuperscript{101} The mechanism might be related to the following factors: (1) Changes in small intestinal peristalsis stimulate intestinal bacterial overgrowth and competitively inhibit the absorption of Vitamin B12; (2) Changes in the levels of intrinsic factors in vitamin B12 and the interaction of cobalamin endocytosis receptors; (3) metformin can inhibit calcium-dependent absorption of intrinsic factor-Vitamin B12 complex at the end of the ileum (i.e., this inhibition can be reversed by calcium supplements).\textsuperscript{102} A previously published study\textsuperscript{103} showed that metformin treatment was associated with low serum vitamin B12 and improved intracellular vitamin B12 metabolism despite low serum vitamin B12 levels. Vitamin B12 levels for long-term metformin users can be regularly monitored, and it is necessary to supply vitamin B12 if it is insufficient.

### 5.5 Does metformin damage the liver and kidney?

Metformin is absorbed by the gastrointestinal tract and enters the blood circulation. It hardly binds to plasma albumin, is not metabolized on passing through the liver, does not compete for liver P450 enzymes, and does not degrade \textit{in vivo}. Metformin acts directly on the liver and muscle to reduce hepatic gluconeogenesis and increase muscle glycolysis. Therefore, metformin has no hepatotoxicity, and will not cause liver damage in patients with normal liver function that are treated with recommended dose ranges of the agent. However, attention should be paid to patients with impaired liver function when using metformin, since impaired liver function will significantly limit the ability of lactate removal.

Metformin is mainly excreted from urine through the renal tubule in its original form. It can be excreted quickly, and about 90% can be excreted within 12–24 hours. The renal clearance rate of metformin is about 3.5 times that of creatinine. Thus, metformin itself does not damage the kidney.\textsuperscript{104} A study\textsuperscript{105} has suggested that metformin might exhibit renal protective effects. However, in patients with renal insufficiency, the renal clearance rate of metformin decreases and the elimination half-life is prolonged, which results in increased plasma concentrations of metformin and the risk of lactic acidosis. Thus, drug dose adjustment or discontinuation is needed for patients with renal insufficiency according to their renal function. Metformin should be avoided in patients with hypoxemia.

### 5.6 What is the relationship between metformin and lactic acidosis?

There is no definitive evidence to support that the use of metformin is associated with lactic acidosis. Long-term use of metformin in patients with normal liver and kidney function does not increase the risk of lactic acidosis. The results of the Comparative Outcomes Study of metformin Intervention versus Conventional (COSMIC) have shown
that the incidence of metformin-induced lactic acidosis was insignificantly different from those induced by other hypoglycemic agents. It was shown that in patients with normal renal function, there is no evidence from prospective comparative trials or from observational cohort studies that metformin is associated with an increased risk of lactic acidosis, or with increased levels of lactate, as compared to other anti-hyperglycemic treatments.

5.7 Does metformin affect cognitive function?
The effect of metformin on cognitive function is still unclear. A study has shown that metformin recruits adult neural precursors and enhances neural function by activating an atypical protein kinase C-CBP pathway in downstream neural stem cells through the AMPK signaling pathway, thereby providing a candidate pharmacological approach for nervous system therapy. A retrospective cohort study has suggested that incident of Parkinson’s disease risk in T2DM increases 2.2-fold and sulfonylureas further increase risk by 57%, which is avoided by combination with metformin.

5.8 What interactions between metformin and non-hypoglycemic agents should we pay attention to?
(1) Close monitoring of blood glucose and dose adjustment of metformin and/or its interactive drugs is recommended: cationic drugs, such as amiloride, digoxin, morphone, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim and vancomycin, are excreted through renal tubules, which might affect renal function or the distribution of metformin; (2) Close monitoring of blood glucose is needed under the following conditions: taking thiazides or other diuretics like glucocorticoids, phenothiazine, thyroid preparations, estrogen, oral contraceptives, phenytoin, nicotinic acid, sympathomimetic drugs, calcium channel blockers and Isoniazid, which, when taking at the same time can cause increased blood glucose. After discontinuation of these drugs, close attention should be paid to the occurrence of hypoglycemia; Close monitoring of blood glucose should be performed in patients taking chlorpropamide in the first two weeks of replacing metformin, chlorpropamide has a long retention time in vivo and is prone to hypoglycemia; (3) metformin has the tendency to increase warfarin anti-coagulation; (4) Resin drugs (such as Suhexiang, Dragon’s blood, Frankincense, etc.) in combination with metformin can reduce the absorption.

6. Effects on cardiovascular system

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>IIa</td>
<td>C-LD</td>
<td>Metformin has a definite cardiovascular protective effect. Metformin can reduce the occurrence of cardiovascular events in newly diagnosed T2DM patients and T2DM patients with pre-existing cardiovascular disease.</td>
</tr>
</tbody>
</table>

6.1 Does metformin have cardiovascular protective effects?
Metformin plays a direct or indirect role in cardiovascular protection by effectively improving insulin resistance in diabetic and non-diabetic patients and lowering insulin levels after baseline and load. The results of UKPDS have shown that patients allocated metformin, as compared with the conventional group, had risk reductions of 36% for all-cause mortality (9–55; \( P = 0.011 \)) and a 39% lower risk (\( P = 0.010 \)) of myocardial infarction. The 10-year follow-up results of UKPDS have shown that the benefits of metformin on macrovascular complications and mortality risk had a continuing effect, and the effects on reducing mortality and myocardial infarction was
significantly superior to than those of sulfonylureas and insulin. The REACH study is a global, multicenter, randomized, double-blind trial, and the results suggested that metformin therapy is associated with a reduced mortality of heart failure patients with new onset diabetes mellitus. The “Hyperinsulinemia: the Outcome of its Metabolic Effects” (HOME) results suggested that metformin in combination with insulin can reduce the risk of macrovascular disease when compared with insulin monotherapy. An Italian multicenter cohort study included T2DM patients (with an average age of 67 years) stratified by age and eGFR, and the results suggested that compared with other hypoglycemic agents, metformin was associated with lower cardiovascular event rates. The “Study on the Prognosis and Effect of Antidiabetic Drugs” (SPREAD) is a multicenter, randomized, double-blind, placebo-controlled study that was conducted in China. The results have shown that for T2DM patients with a history of coronary heart disease, treatment with metformin substantially reduced the incidence of major cardiovascular events by 46% as compared with glipizide.

6.2 What is the cardioprotective mechanism of metformin?
Metformin might achieve cardiovascular protection by reducing the risk factors that are associated with cardiovascular disease. Risk factors of cardiovascular disease include dyslipidemia, insulin resistance, obesity, hypertension, non-alcoholic fatty liver disease (NAFLD) and so on. Risk control is an important measure aimed at reducing cardiovascular events. Metformin has been proven to reduce blood glucose, improve NAFLD and insulin resistance (especially in the liver and muscle), lose weight, and improve blood lipids (i.e., to mainly improve TG, LDL-C and TC levels, but did not affect HDL-C significantly) and anti-coagulation. In addition, metformin can directly improve endothelial function and increase blood flow.

7. Effects besides effect of hypoglycemic
7.1 What role does metformin play in improving blood lipids?
Metformin can improve fat synthesis and metabolism. Several studies have shown that metformin can significantly reduce plasma TG, LDL-C and TC levels in T2DM patients; however, it did not significantly affect HDL-C.

7.2 What effects does metformin have on non-alcoholic fatty liver disease (NAFLD)?
The Chinese National Workshop on Fatty Liver and Alcoholic Liver Disease for the Chinese Liver Disease Association promulgated the Chinese Guidelines for the Diagnosis and Treatment of Non-alcoholic Fatty Liver Disease (2010, Revised Edition), and it suggested that metformin can be safely used in NAFLD patients unless there is significant liver damage (i.e., such as serum aminotransferase levels being greater than three-fold higher than the upper limit of the normal value), liver dysfunction or decompensated cirrhosis and so on. Fourteen clinical studies have evaluated the beneficial effects of metformin on liver histology, serum enzymology and insulin resistance in NAFLD patients. All studies have shown that metformin can significantly improve the insulin resistance index, and 13 studies have shown that metformin can significantly decrease serum enzymes (i.e., alanine amino-transferase, and glutamic-oxaloacetic transaminase), and five studies have shown that metformin can prevent and reverse not only steatosis development but also liver inflammation and fibrosis.

7.3 What role does metformin play in treating polycystic ovarian syndrome (PCOS)?
Metformin has been used to treat PCOS for more than ten years in China and other countries. The American
Endocrine Society recommended metformin in women with PCOS who have T2DM or IGT, and in whom lifestyle modification has failed (i.e., as first-line therapy) or irregular menstruation without the use of contraceptives (second-line treatment). Metformin is recommended in the AACE/ACE PCOS clinical guidelines as first-line monotherapy or in combination with oral contraceptives and anti-androgen medications in adolescents with PCOS. In lean adolescent girls, a daily dose as low as 850 mg might be effective at reducing PCOS symptoms; in overweight and obese adolescents, dose escalation to 1500–2500 mg daily is likely required. Further, the guidelines mentioned that metformin in premenopausal PCOS women was associated with reduced features of metabolic syndrome.

Evidence-based medicine has shown that metformin can reduce plasma insulin levels, increase insulin sensitivity, decrease androgen levels, increase estradiol levels, improve hypertrichosis in PCOS patients, and promote a regular menstruation cycle and induction of ovulation. At the same time, metformin has been introduced to treat PCOS to manage insulin resistance and hyperglycemia, which has been shown to improve ovulation, and pregnancy rates (21–25) and live birth rates. PCOS patients can start metformin with a dose of 500 mg/d, following which, the dose can be increased by 500 mg per week until a dose of 2000 mg/d is achieved (taken twice at meals or after meals). The drug is taken for several months until ovulation and menstrual recovery, following which, the drug is discontinued when pregnancy is found. A dose of 2500 mg/d was also used in other countries, and this dose was relatively safe and well tolerated. At present, metformin has not been approved for treating PCOS by the China Food and Drug Administration.

7.4 Does metformin have anti-tumor effects?
DM might be a risk factor for a variety of tumors, such as breast cancer, pancreatic cancer, colorectal cancer, endometrial cancer and so on. Many studies have shown that the metabolic effects of metformin in subjects with T2DM might be mediated by the activation of the AMPK pathway, and activation of the AMPK pathway not only affects metabolism, but might also have a key role in cancer prevention as well as the growth and/or survival of cancer cells. Various meta-analyses have shown that metformin treatment was associated with reduced risk of lung cancer, prostate cancer, colorectal cancer, and breast cancer, among others.

References


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