**Metformin in the treatment of adults with type 2 diabetes mellitus**

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**INTRODUCTION** — Two classes of oral hypoglycemic drugs directly improve insulin action: biguanides (only metformin is currently available) and thiazolidinediones (TZDs). In the absence of contraindications, metformin is considered the first choice for oral treatment of type 2 diabetes (table 1). A 2006 consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), updated regularly, proposed that metformin therapy (in the absence of contraindications) be initiated, concurrent with lifestyle intervention, at the time of diabetes diagnosis [[1-3](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/1-3)].

The pharmacology, efficacy, and side effects of metformin for the treatment of diabetes will be reviewed here. A general discussion of initial treatment of type 2 diabetes and the role of metformin in the prevention of diabetes, in the treatment of polycystic ovary syndrome, and in gestational diabetes are reviewed separately.

●(See "Initial management of blood glucose in adults with type 2 diabetes mellitus".)

●(See "Prevention of type 2 diabetes mellitus", section on 'Metformin'.)

●(See "Metformin for treatment of the polycystic ovary syndrome".)

●(See "Gestational diabetes mellitus: Glycemic control and maternal prognosis", section on 'Metformin'.)

**MECHANISM OF ACTION** — Metformin's major effect is to decrease hepatic glucose output by inhibiting gluconeogenesis [[4-7](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/4-7)]. In addition, metformin increases insulin-mediated glucose utilization in peripheral tissues (such as muscle and liver), particularly after meals, and has an antilipolytic effect that lowers serum free fatty acid concentrations, thereby reducing substrate availability for gluconeogenesis [[4,8,9](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/4,8,9)]. As a result of the improvement in glycemic control, serum insulin concentrations decline slightly [[10,11](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/10,11)]. Metformin has also been shown to decrease food intake and body weight [[12,13](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/12,13)].

Metformin suppresses gluconeogenesis by inhibiting a specific mitochondrial isoform of glycerophosphate dehydrogenase (mGPD), an enzyme responsible for converting glycerophosphate to dihydroxyacetone phosphate, thereby preventing glycerol from contributing to the gluconeogenic pathway [[14,15](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/14,15)]. In addition, inhibition of mGPD leads to accumulation of cytoplasmic NADH and a decrease in the conversion of lactate to pyruvate, limiting lactate contributions to hepatic gluconeogenesis. Excess glycerol and lactate are released into the plasma.

Metformin also activates the enzyme AMP-activated protein kinase (AMPK) in hepatocytes, which appears to be the mechanism by which metformin lowers serum lipid concentrations [[16-18](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/16-18)]. AMPK-dependent inhibitory phosphorylation of acetyl-CoA carboxylases Acc1 and Acc2 suppresses lipogenesis and lowers cellular fatty acid synthesis in liver and muscle [[19,20](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/19,20)]. Metformin works through the Peutz-Jeghers protein, LKB1, to regulate AMPK [[21](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/21)]. LKB1 is a tumor suppressor, and activation of AMPK through LKB1 may play a role in inhibiting cell growth [[22](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/22)]. (See 'Cancer incidence' below.)

**INDICATIONS** — Initial treatment of patients with type 2 diabetes mellitus includes education, with emphasis on lifestyle changes including diet, exercise, and weight reduction when appropriate (table 1). In the absence of specific contraindications, metformin is considered initial pharmacologic therapy for most patients with type 2 diabetes because of glycemic efficacy, absence of weight gain and hypoglycemia, general tolerability, and favorable cost [[2,3,23-25](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/2,3,23-25)]. It can be initiated at the time of diabetes diagnosis, along with consultation for lifestyle intervention. For highly motivated patients with glycated hemoglobin (A1C) near target (<7.5 percent), a three- to six-month trial of lifestyle modification before initiating metformin is reasonable. Other options for initial therapy are discussed elsewhere. (See "Initial management of blood glucose in adults with type 2 diabetes mellitus", section on 'Choice of initial therapy'.)

After a successful initial response to metformin, the majority of patients fail to maintain glycemic targets and require the addition of a second oral or an injectable agent. For patients who fail initial therapy, there are a number of agents that are available and can be used in combination with metformin. (See "Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'Treatment options'.)

Although metformin is being evaluated as an adjunct to insulin therapy in type 1 diabetes, there are insufficient data to recommend metformin for patients with type 1 diabetes. This topic is reviewed separately. (See "Management of blood glucose in adults with type 1 diabetes mellitus", section on 'Adjunctive therapy'.)

**GLYCEMIC EFFICACY**

**Monotherapy** — Metformin typically lowers fasting blood glucose concentrations by approximately 20 percent and A1C by 1.5 percent, a response similar to that achieved with a sulfonylurea [[10,11,26-28](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/10,11,26-28)]. The United States Multicenter Metformin Study Group, for example, randomly assigned obese patients with type 2 diabetes who were inadequately controlled on diet alone to either metformin or placebo [[29](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/29)]. After 29 weeks, the mean A1C concentration was 7.1 percent in the metformin group as compared with 8.6 percent in the placebo group.

**Combination therapy** — Combinations of drugs are often necessary to achieve optimal glycemic control. Metformin can be given in combination with sulfonylureas, insulin, glinides, alpha-glucosidase inhibitors, thiazolidinediones (TZDs), sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors. In meta-analyses of placebo-controlled trials evaluating different drugs (sulfonylureas, TZDs, meglitinides, alpha-glucosidase inhibitors, GLP-1 agonists, DPP-4 inhibitors) as add-on therapy to metformin, reductions in A1C with different classes of drugs ranged from 0.42 to 1.0 percentage points [[30,31](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/30,31)]. Combination therapy is discussed in detail in separately. (See "Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'Combination with metformin' and "Sulfonylureas and meglitinides in the treatment of diabetes mellitus" and "Thiazolidinediones in the treatment of diabetes mellitus", section on 'Combination therapy' and "Alpha-glucosidase inhibitors and lipase inhibitors for treatment of diabetes mellitus" and "Glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes mellitus" and "Dipeptidyl peptidase-4 (DPP-4) inhibitors for the treatment of type 2 diabetes mellitus" and "Amylin analogs for the treatment of diabetes mellitus".)

**WEIGHT LOSS** — In those who are obese, metformin promotes modest weight reduction or at least weight stabilization (figure 1) [[10,32](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/10,32)]. This is in contrast to the weight gain often associated with insulin or sulfonylurea treatment [[10,32](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/10,32)]. In one large study, for example, patients treated with glyburide gained an average of 1.6 kg, whereas those receiving metformin lost 2.9 kg [[33](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/33)]. In a trial comparing metformin with a long-acting glucagon-like peptide-1 (GLP-1)-receptor agonist, weight loss at 52 weeks was similar in the two groups (-2.29 and -2.22 kg for dulaglutide 1.5 mg and metformin, respectively) [[34](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/34)].

**CARDIOVASCULAR EFFECTS** — Metformin does not have adverse cardiovascular effects, and it appears to decrease cardiovascular events in certain populations [[35-38](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/35-38)]. As examples:

●In the United Kingdom Prospective Diabetes Study (UKPDS), obese patients who were assigned initially to receive metformin rather than sulfonylurea or insulin therapy had a decreased risk of the aggregate diabetes-related endpoint (endpoints included both macrovascular and microvascular complications) and all-cause mortality [[38](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/38)]. During the post-interventional observation period of the UKPDS, reductions in the risk of macrovascular complications were maintained in the metformin group. (See "Glycemic control and vascular complications in type 2 diabetes mellitus", section on 'UKPDS'.)

●In another trial, 390 patients treated with insulin were randomly assigned to metformin versus placebo [[35](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/35)]. After four years, mean A1C (7.5 versus 7.9 percent) and body weight (85 versus 90 kg) were significantly lower in the metformin group. In addition, there was a decrease in the risk of the secondary macrovascular endpoint, which was a composite of 13 vascular events including myocardial infarction (MI), heart failure, stroke, amputation, and sudden death (event rates 15 versus 18 percent, adjusted hazard ratio [HR] 0.6, 95% CI 0.4-0.9).

In a subsequent meta-analysis of 170 trials and 25 observational studies evaluating the effects of oral or injectable diabetes medications as monotherapy and in combination with other oral agents or insulin on cardiovascular mortality, intermediate outcomes (A1C, body weight, lipid profiles), and adverse events, metformin was associated with lower long-term cardiovascular mortality compared with sulfonylurea monotherapy (based upon findings from two randomized trials and three observational studies) [[37](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/37)]. As an example:

●In one trial, 304 Chinese patients with established coronary heart disease and type 2 diabetes were randomly assigned to metformin versus glipizide [[36](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/36)]. Lifestyle intervention and other treatment for coronary heart disease were similar in both groups. After three years, the mean achieved A1C level was similar (7.0 and 7.1 percent) in the two groups. However, body weight, waist circumference, and body mass index (BMI) were significantly lower in the metformin group. A similar proportion of patients in each group received insulin (30 and 25 patients in metformin and glipizide groups, respectively). After a median follow-up of five years, there were fewer cardiovascular events (composite of nonfatal MI [five versus six], stroke [10 versus 15], arterial revascularization [21 versus 25], or death from cardiovascular or any cause [7 versus 14]) in the metformin group (total events 43 versus 60; HR 0.54, 95% CI 0.3-0.9). The main limitation of this trial was the small number of events. In addition, it is not possible to distinguish the potential beneficial effect of metformin from the putative adverse effect of sulfonylurea. However, the results support the use of metformin, particularly in patients with coronary heart disease.

Metformin has lipid-lowering activity, resulting in a decrease in serum triglyceride and free fatty acid concentrations, a small decrease in serum low-density lipoprotein (LDL) cholesterol concentrations, and a very modest increase in serum high-density lipoprotein (HDL) cholesterol concentrations [[11,26,27](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/11,26,27)].

An unexpected finding in a UKPDS substudy was that the early addition of metformin in patients already receiving a sulfonylurea was associated with a 96 percent increase in the risk of diabetes-related death compared with continuation of the sulfonylurea alone (p = 0.04) [[38](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/38)]. It is not clear how to interpret these data as the analyses are secondary and not internally consistent. On the one hand, metformin appears to be beneficial as initial monotherapy in overweight patients with type 2 diabetes. However, the evidence of an adverse effect with the early addition of metformin to sulfonylurea therapy is troubling.

The results of larger trials are reassuring, although they were not specifically designed to address this issue [[39-41](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/39-41)]. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial, the majority of subjects were taking metformin, regardless of treatment assignment (74 and 67 percent of those assigned to intensive versus conventional therapy, respectively). However, a sulfonylurea (gliclazide) was used, by design, by a significantly greater proportion of subjects in the intensive group (90 versus 16 percent). There was no difference in mortality between intensive and conventionally treated subjects in the ADVANCE trial.

**CANCER INCIDENCE** — Observational data suggest that use of metformin decreases cancer incidence [[42-44](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/42-44)]. In meta-analyses of predominantly case-control and cohort studies in patients with type 2 diabetes, use of metformin compared with nonuse or with use of other diabetes treatment was associated with a reduced risk of all cancers (relative risk [RR] 0.61, 95% CI 0.54-0.70) [[45,46](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/45,46)], colorectal cancer (RR 0.64, 95% CI 0.54-0.76) [[45-47](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/45-47)], and lower cancer mortality (RR 0.66, 95% CI 0.49-0.88) [[45,48](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/45,48)]. Among the meta-analyses, the summary effect estimates were similar. With the exception of colorectal cancer, there was significant heterogeneity among the individual studies.

In contrast to the observational data, a meta-analysis of randomized trials comparing metformin with a comparator (thiazolidinedione [TZD], sulfonylurea, dipeptidyl peptidase-4 [DPP-4] inhibitor, or placebo) did not show a reduction in cancer incidence [[49](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/49)]. The majority of the trials were not designed to explore cancer outcomes, which were not uniformly collected or adjudicated; therefore, malignancies were noted as serious adverse events. In addition, average follow-up for cancer outcomes was only four years. A longer interval may be required to adequately assess cancer outcomes. Thus, prospective clinical trial data are required to confirm or refute this protective effect.

A possible mechanism by which metformin may decrease cancer incidence is regulation of AMP-activated protein kinase (AMPK) through LKB1 [[21](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/21)]. LKB1 is a tumor suppressor, and activation of AMPK through LKB1 may play a role in inhibiting cell growth. Studies in C. elegans have suggested that inactivation of mTORC1 with subsequent inhibition of growth through induction of ACAD10 may explain the anti-cancer effects of metformin [[50](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/50)]. (See 'Mechanism of action' above.)

**SIDE EFFECTS**

**Gastrointestinal** — The most common side effects of metformin are gastrointestinal, including a metallic taste in the mouth, mild anorexia, nausea, abdominal discomfort, and soft bowel movements or diarrhea [[27](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/27)]. These symptoms are usually mild, transient, and reversible after dose reduction or discontinuation of the drug. In clinical trials, only 5 percent of study subjects discontinue metformin because of the gastrointestinal side effects.

**Vitamin B12 deficiency** — Metformin reduces intestinal absorption of vitamin B12 in up to 30 percent of patients and lowers serum vitamin B12 concentrations in 5 to 10 percent but only rarely causes megaloblastic anemia [[51,52](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/51,52)]. In some patients with vitamin B12 deficiency, peripheral neuropathy may precede the development of megaloblastic anemia [[53](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/53)]. The dose and duration of use of metformin correlates with the risk of vitamin B12 deficiency [[52,54](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/52,54)]. In one study, this reduction appeared to be due to poor absorption of B12 in the ileum and was corrected by administration of oral calcium carbonate (1.2 g daily) [[55](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/55)]. In another study, supplementation with a daily multivitamin was associated with a lower prevalence of B12 deficiency [[56](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/56)]. (See 'Dosing and monitoring' below and "Treatment of vitamin B12 and folate deficiencies".)

**Lactic acidosis** — Biguanide therapy in type 2 diabetes with phenformin in the past or currently with metformin can lead to lactic acidosis [[57,58](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/57,58)]. Symptoms of lactic acidosis are nonspecific and may include anorexia, nausea, vomiting, abdominal pain, lethargy, hyperventilation, and hypotension. Serum lactate concentrations are usually less than 2 mmol/L in patients taking metformin, values that are not clinically important. More serious lactic acid accumulation occurs with superimposed shock or in the presence of predisposing conditions to metformin toxicity as described below [[59](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/59)]. (See 'Predisposing factors' below.)

Metformin-induced lactic acidosis can occur in patients with normal renal and hepatic function. One such setting is a purposeful metformin overdose [[60,61](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/60,61)]. In addition, patients with the genetic diabetes syndrome, maternally inherited diabetes and deafness (MIDD), are at increased risk of developing lactic acidosis with metformin therapy. (See "Classification of diabetes mellitus and genetic diabetic syndromes", section on 'Genetic defects in mitochondrial DNA' and "Causes of lactic acidosis".)

**Incidence** — The incidence of lactic acidosis in metformin users appears to be very low [[58,62-64](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/58,62-64)]. In a review of 11,800 patients treated with metformin for a mean of approximately two years, only two patients developed lactic acidosis (incidence nine cases per 100,000 person-years of exposure) [[58](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/58)]. This compares with a rate of 40 to 64 per 100,000 patient-years in those taking phenformin, a previously approved biguanide that was removed from the market because of this side effect.

The very low incidence of lactic acidosis with metformin was confirmed by a systematic review of 347 randomized trials and prospective cohort studies representing 70,490 patient-years of metformin use and 55,451 patient-years in the comparator group [[63](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/63)]. There were no cases of lactic acidosis. Almost one-half of the studies allowed inclusion of patients with a serum creatinine above 1.5 mg/dL (133 micromol/L), and almost all allowed inclusion of patients with at least one standard contraindication to metformin therapy. However, the number of patients who actually had these contraindications was not presented and, therefore, the safety of metformin in the presence of standard contraindications could not be assessed. (See 'Contraindications' below.)

**Predisposing factors** — Despite its rarity, lactic acidosis related to metformin remains a concern because of the high case-fatality rate. Most cases have occurred in patients with conditions that predispose to hypoperfusion and hypoxemia (acute or progressive renal impairment, acute or progressive heart failure, acute pulmonary decompensation, sepsis, dehydration) [[27,57,65](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/27,57,65)]. This finding has resulted in the development of standard contraindications to metformin, including impaired renal function, heart failure, liver disease, and excessive alcohol intake. (See 'Contraindications' below.)

A number of patients treated with metformin have one or more of these contraindications (most often renal impairment or heart failure). The frequency with which this occurs has varied in different series, with a range of 14 to 27 percent in most reports [[66-71](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/66-71)].

Despite the appreciable disregard of contraindications, the incidence of metformin-induced lactic acidosis is not increasing. This finding has led to a reevaluation of the standard contraindications to metformin therapy, particularly in patients with an estimated glomerular filtration rate (eGFR) above 30 mL/min [[72](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/72)]. (See 'Contraindications' below.)

**Treatment** — The role of bicarbonate therapy in patients with lactic acidosis and shock or tissue hypoxia is not well established, except in severe metabolic acidosis, because of concern about possible worsening of intracellular acidosis. (See "Bicarbonate therapy in lactic acidosis".)

However, this may not apply to metformin-associated lactic acidosis since, in patients with concurrent renal failure, bicarbonate hemodialysis can both correct the acidosis and remove metformin [[73,74](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/73,74)]. Treatment of metformin-induced lactic acidosis is discussed elsewhere. (See "Metformin poisoning".)

**CONTRAINDICATIONS** — Metformin is contraindicated in patients with factors predisposing to lactic acidosis.

These predisposing factors/contraindications are:

●Impaired renal function (estimated glomerular filtration rate [eGFR] <30 mL/min)

●Concurrent active or progressive liver disease

●Active alcohol abuse

●Unstable or acute heart failure at risk of hypoperfusion and hypoxemia

●Past history of lactic acidosis during metformin therapy

●Decreased tissue perfusion or hemodynamic instability due to infection or other causes

The precise eGFR thresholds for the safe use of metformin remain uncertain. Improved clinical outcomes with metformin have been reported in observational studies of patients with diabetes and heart failure [[75-77](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/75-77)], renal impairment (eGFR 45 to 60 mL/min) [[77-79](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/77-79)], or chronic liver disease with hepatic impairment [[77](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/77)]. In one systematic review of 17 observational studies comparing regimens with and without metformin, metformin use was associated with lower all-cause mortality among patients with heart failure, renal impairment, or chronic liver disease with hepatic impairment [[77](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/77)]. In addition, metformin use in patients with renal impairment or heart failure was associated with fewer heart failure readmissions.

On the basis of these and other studies, the US Food and Drug Administration (FDA) revised its labeling of metformin, which previously had identified metformin as contraindicated in women and men with serum creatinine levels ≥1.4 mg/dL (124 micromol/L) and ≥1.5 mg/dL (133 micromol/L),respectively [[72](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/72)]. The use of metformin is contraindicated in patients with an eGFR <30 mL/min, and the initiation of metformin is not recommended in patients with an eGFR between 30 and 45 mL/min. For patients taking metformin whose eGFR falls below 45 mL/min, the benefits and risk of continuing treatment should be assessed, whereas metformin should be discontinued if the eGFR falls below 30 mL/min.

The following is our approach to the administration of metformin:

●For patients with an eGFR <30 mL/min, we do not prescribe metformin.

●For patients with an eGFR ≥45 mL/min, we prescribe full dose.

●For patients with an eGFR of 30 to 44 mL/min and in the absence of active kidney disease (eg, a glomerulonephritis), some UpToDate authors and editors would not initiate metformin, whereas others would reduce the metformin dose by half (no more than 1000 mg per day) and increase the frequency of kidney function monitoring, although there are little or no data to support the glycemic efficacy [[71,80](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/71,80)] and safety of the latter approach. Lower doses of metformin may not produce the desired lowering of glycemia and may not be safer.

●For patients taking metformin whose eGFR falls below 45 mL/min, we reduce the metformin dose by half (no more than 1000 mg per day) with more frequent testing of eGFR, although there are few data to support the efficacy and safety of this approach.

●For patients taking metformin whose eGFR falls below 30 mL/min, we discontinue metformin.

●We do not view stable compensated heart failure as a contraindication to metformin use.

●We advise patients with an eGFR between 30 and 60 mL/min or stable heart failure to stop taking metformin if they develop hypoxemia or any condition associated with hypoxemia, dehydration, or sepsis (eg, influenza, urinary tract infection) until the condition has resolved. (See "Heart failure in diabetes mellitus", section on 'Metformin'.)

●We do not view fatty liver disease generally as a contraindication unless there are major manifestations, such as reduced synthetic function or cirrhosis.

●We prefer to hold metformin in patients who are about to receive intravenous iodinated contrast material (with potential for contrast-induced renal failure) if they are at increased risk for lactic acidosis independent of metformin. Such patients include those with vascular instability, hypotension, and potential hypoperfusion. In addition, owing to the potential for metformin accumulation in the setting of renal insufficiency and the current contraindication to using metformin in patients with eGFR <30 mL/min, metformin should be discontinued in such patients prior to any radiologic procedures with intravenous or intra-arterial contrast. Metformin should not be restarted in such patients until they are no longer at risk for lactic acidosis and demonstrated to have eGFR >30 mL/min. Serum creatinine is typically assessed two to three days after contrast administration.

The relationship among metformin use, intravenous contrast administration, and the occurrence of lactic acidosis is not well studied. The rationale for stopping metformin prior to intravenous iodinated contrast is to avoid the potential for high plasma metformin concentrations (and lactic acidosis) if the patient develops contrast-induced acute renal failure. Patient mortality in reported cases of metformin-induced lactic acidosis may be as high as 50 percent [[81](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/81)].

In a systematic review of studies and evidence-based guidelines on the use of intravenous contrast in patients taking metformin, the only available data were from case reports and case series [[82](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/82)]. The majority of cases of metformin-related lactic acidosis occurred in patients with abnormal renal function who received intravenous contrast medium. The risk of metformin-induced lactic acidosis in patients with normal renal function who receive intravenous contrast is unknown but appears to be rare.

The American College of Radiology suggests there is no need to discontinue metformin prior to or following the intravenous administration of iodinated contrast media in patients with no evidence of acute kidney injury and with eGFR ≥30 mL/min [[83](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/83)]. This recommendation was presumably predicated on the increasing uncertainty regarding the role of contrast-dye procedures in acute kidney injury [[84](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/84)] and the overall rarity of lactic acidosis in metformin-treated patients (see 'Incidence' above). Until more data are available, however, and taking into account the morbidity and mortality of metformin-associated lactic acidosis, we prefer to hold metformin in patients at increased risk for lactic acidosis (eg, vascular instability, hypotension, potential hypoperfusion) independent of metformin, as described in the bullet above. (See "Pathogenesis, clinical features, and diagnosis of contrast-induced nephropathy".)

**DOSING AND MONITORING** — Metformin is absorbed rapidly from the small intestine, with peak plasma concentrations attained in two hours. It is not bound to plasma proteins, is not metabolized, and is rapidly excreted in the urine [[27,85](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/27,85)].

Metformin is available as 500, 850, or 1000 mg tablets, and should be taken with meals. We begin with 500 mg once daily with the evening meal and, if tolerated, add a second 500 mg dose with breakfast. The dose can be increased slowly (one tablet every one to two weeks) as necessary [[27](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/27)]. The usual effective dose is 1500 to 2000 mg/day; the maximum recommended dose of 2550 mg/day (850 mg three times daily) provides only marginally better glycemic control and is often not tolerated due to gastrointestinal side effects [[1](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/1)]. For patients with estimated glomerular filtration rate (eGFR) between 30 and 45 mL/min, we typically increase the frequency of kidney function monitoring and potentially reduce the metformin dose by half (no more than 1000 mg per day), although there are little or no data to support the glycemic efficacy and safety of the latter approach. Metformin should not be used in patients with eGFR <30 mL/min. (See 'Contraindications' above.)

Extended-release tablets are also available [[86,87](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/86,87)], although patients who are doing well on immediate-release metformin should probably continue with this preparation, as there is little, if any, additional benefit documented with the long-acting preparation. Combination tablets of metformin and sulfonylureas, thiazolidinediones (TZDs), or dipeptidyl peptidase-4 (DPP-4) inhibitors are also available.

For patients taking metformin, we measure A1C every three to six months; serum creatinine annually; and hemoglobin, hematocrit, and red cell indices at diagnosis and at other times if the patient develops symptoms suggestive of anemia, neuropathy, or deteriorating renal function. If anemia is present, vitamin B12 and folate should be measured and treated accordingly. Because data suggest that anemia is not a sensitive indicator of B12 deficiency, and with a prevalence of B12 deficiency that may approach 10 percent over time in metformin-treated patients [[52](https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus/abstract/52)], routine B12 monitoring may be considered. (See "Clinical manifestations and diagnosis of vitamin B12 and folate deficiency".)

**SOCIETY GUIDELINE LINKS** — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Diabetes mellitus in adults".)

**SUMMARY AND RECOMMENDATIONS**

●Metformin typically lowers glycated hemoglobin (A1C) concentrations by approximately 1.5 percent, is not associated with weight gain, and is less likely to cause hypoglycemia than sulfonylureas and insulin. (See 'Introduction' above and 'Glycemic efficacy' above.)

●In the absence of specific contraindications, we suggest metformin as initial therapy in most patients with type 2 diabetes (**Grade 2B**) (table 1). Insulin can also be considered a first-line therapy for all patients with type 2 diabetes, particularly patients presenting with A1C >10 percent, fasting plasma glucose >250 mg/dL (13.9 mmol/L), random glucose consistently >300 mg/dL (16.7 mmol/L),or ketonuria. (See "Initial management of blood glucose in adults with type 2 diabetes mellitus" and "Insulin therapy in type 2 diabetes mellitus".)

●We suggest initiating metformin at the time of diabetes diagnosis, along with consultation for lifestyle intervention (**Grade 2C**). The dose of metformin should be titrated to its maximally effective dose (usually 1700 to 2550 mg per day in divided doses) over one to two months, as tolerated.

Alternative initial treatment for patients with contraindications or intolerance to metformin is reviewed separately. (See 'Contraindications' above and "Initial management of blood glucose in adults with type 2 diabetes mellitus", section on 'Initial pharmacologic therapy'.)

●The most common side effects of metformin are gastrointestinal, including a metallic taste in the mouth, mild anorexia, nausea, abdominal discomfort, and soft bowel movements or diarrhea. (See 'Side effects' above.)

●Lactic acidosis is an extremely uncommon side effect. However, it remains a concern because of the high case-fatality rate. Most cases have occurred in patients with conditions that predispose to hypoperfusion and hypoxemia (acute or progressive renal impairment, acute or progressive heart failure, acute pulmonary decompensation, sepsis, dehydration). (See 'Predisposing factors' above.)

●The precise serum creatinine limits and estimated glomerular filtration rate (eGFR) thresholds for the safe use of metformin remain uncertain. In clinical practice, some experts use an eGFR of ≥30 mL/min as a threshold for the safe use of metformin. For a patient with an eGFR between 30 and 45 mL/min, we typically reduce the metformin dose by half. (See 'Contraindications' above.)

We do not view stable compensated heart failure as a contraindication to metformin use. (See 'Contraindications' above.)

We advise such patients to stop taking metformin if they have any illness likely to adversely affect hydration status or kidney function or cause hypoxemia, such as influenza or urinary tract infection, until the condition has resolved.

●We prefer to hold metformin in patients who are about to receive intravenous iodinated contrast material (with potential for contrast-induced renal failure) or undergo a surgical procedure (with potential compromise of circulation), if they are at increased risk for lactic acidosis independent of metformin. Such patients include those with vascular instability, hypotension, and potential hypoperfusion. Metformin should also be discontinued in patients with eGFR <30 mL/minprior to any radiologic procedures with intravenous or intra-arterial contrast. (See 'Contraindications' above.)

●For patients taking metformin, we measure A1C every three to six months, serum creatinine annually, and hemoglobin, hematocrit, and red cell indices at diagnosis and at other times if the patient develops symptoms suggestive of anemia, neuropathy, or deteriorating renal function. (See 'Dosing and monitoring' above.)

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