For almost all patients

Metformin, insulin secretagogues and acarbose

Patients that are overweight or obese

Offer metformin instead of a sulfonylurea or acarbose if blood glucose is inadequately controlled by lifestyle interventions alone.

**Rationale**

All or nearly all patients that are overweight or obese, with blood glucose inadequately controlled though lifestyle interventions, are likely to place a greater value on the reduced risk of death and myocardial infarction provided by metformin than the increased risk of hypoglycemia and diarrhea. The cardioprotective gains shown in the UKPDS and the Scottish study far outweigh the risk of lactic acidosis (provided adequate renal function) in people with mild to moderate hepatic and cardiac disease. The observed benefits of metformin combined with the low cost and limited burden of taking tablets underlies our strong recommendation. Patients who experience side effects while using metformin will likely prefer the suggested alternatives.

**Key info**

Continue with metformin if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication is added.

Step up metformin therapy gradually over weeks to minimize risk of gastrointestinal side effects.

Consider a trial of extended-absorption metformin when GI-tolerability prevents continuation of metformin therapy.

**Benefits and harms**

**Metformin vs diet (1000 patients over 10 years):**

- **Benefits:** Decreased incidence of death (220 deaths with diet, 140 deaths with metformin) and myocardial infarction (178 with diet, 114 with metformin). Decreased level of HbA1c (mean -1.06%). No difference in incidence of stroke, peripheral- and microvascular disease.

- **Harms:** Slightly increased incidence of hypoglycemia (27 with metformin) and increase of diarrhea (143 with metformin). No reported cases of lactic acidosis.

**Burden of treatment:** Daily medication.

**Quality of the evidence**

High. The recommendation is based on a Cochrane review.

**Values and preferences**

Almost all patients are likely to prefer treatment given the substantial reduction in death and myocardial infarction. However, preference concerning choice of drug may possibly vary based on side-effect profiles.

**Resources**

One large RCT (UKPDS 30/2) concluded that intensive blood glucose control with any pharmacological therapy, to be cost-effective compared to lifestyle interventions alone.