

Global Guideline

for Type 2 Diabetes

Chapter 9: Glucose control: oral therapy

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Recommendations

■ Standard care

OA1 Begin oral glucose-lowering drugs when lifestyle interventions alone are unable to maintain blood glucose control at target levels (see *Glucose control levels*).

Maintain support for lifestyle measures throughout the periods of use of these drugs.

Consider each initiation or dose increase of an oral glucose-lowering drug as a trial, monitoring the response in 2-6 months.

OA2 Begin with metformin unless evidence or risk of renal impairment, titrating the dose over early weeks to minimize discontinuation due to gastro-intestinal intolerance.

Monitor renal function and risk of significant renal impairment (eGFR <60 ml/min/1.73 m²) in people taking metformin.

OA3 Use sulfonylureas when metformin fails to control glucose concentrations to target levels, or as a first-line option in the person who is not overweight.

Choose a drug of low cost, but exercise caution if hypoglycaemia may be a problem to the individual, including through renal impairment.

Provide education and, if appropriate, self-monitoring (see *Self-monitoring*) to guard against the consequences of hypoglycaemia.

Once-daily sulfonylureas should be an available option where drug concordance is problematic.

Rapid-acting insulin secretagogues may be useful as an alternative to sulfonylureas in some insulin-sensitive people with flexible lifestyles.

OA4 Use a PPAR- γ agonist (thiazolidinedione) when glucose concentrations are not controlled to target levels, adding it:

- to metformin as an alternative to a sulfonylurea, or
- to a sulfonylurea where metformin is not tolerated, or
- to the combination of metformin and a sulfonylurea.

Be alert to the contra-indication of cardiac failure, and warn the person with diabetes of the possibility of development of significant oedema.

- OA5 Use α -glucosidase inhibitors as a further option. They may also have a role in some people intolerant of other therapies.
- OA6 Step up doses, and add other oral glucose-lowering drugs, at frequent intervals until blood glucose control is at target levels. Consider whether the rate of deterioration suggests insulin therapy will be needed early despite such measures.

■ Comprehensive care

- OA_c1 The principles of use of oral glucose-lowering drugs are as for *Standard care*. Metformin remains the drug of choice for first-line therapy.

■ Minimal care

- OA_M1 Metformin and a generic sulfonylurea should be the basis of oral glucose-lowering therapy. Where the costs of thiazolidinedione therapy are lower than those of basic insulin therapy, use of these drugs may be considered before transfer to insulin.
- OA_M2 Where renal function tests are not routinely available for people on metformin, such tests are nevertheless required where the likelihood of renal impairment is high.

Rationale

The evidence that elevated blood glucose levels can result in various forms of vascular damage is discussed elsewhere in this guideline (see *Glucose control levels*). Lifestyle modification (see *Lifestyle management*) by itself can only provide control of blood glucose concentrations to safe target levels in a minority of people with diabetes, and then usually only for a limited period after diagnosis. Accordingly, supplementary pharmaceutical measures are needed, and these can be oral glucose-lowering drugs and insulin injection therapy, separately or in combination.

Evidence-base

A number of systematic evidence-based reviews addressing oral glucose-lowering drugs have been published in recent years [1-4]. These nearly always use the UKPDS as the basis of a conclusion that glucose lowering with oral drugs is effective in protection against vascular complications [5]. They also conclude that the evidence on better prevention

of arterial outcomes when using metformin in the overweight sub-study of UKPDS [6] supports the primary use of that drug in all overweight people with Type 2 diabetes, and indeed probably in all people with Type 2 diabetes.

The reviews note that UKPDS in particular confirms that hyperglycaemia in people with diabetes is a progressive condition due to progressive islet B-cell failure, and thus requires continued monitoring and stepping up of therapies to maintain glucose control targets. The NICE guideline [2] notes the problem of concordance with multiple therapies (particularly as people will often be on blood-pressure-lowering, lipid-lowering, and cardiovascular medications), and suggests once-daily drugs may have advantage in many circumstances.

Review of effectiveness of glucose lowering concludes that the drugs from different classes are generally similar, except that α -glucosidase inhibitors may be less efficacious than sulfonylureas [1,2,7]. Other evidence suggests that nateglinide, a rapid-acting insulin secretagogue, is also less efficacious in this regard.

The two available PPAR- γ agonists (thiazolidinediones), while as effective as metformin and sulfonylurea in lowering glucose levels, are found to have other positive effects on risk factors associated with cardiovascular disease, but mixed effects on lipoproteins [8-10]. The former include improvements in vascular inflammation, albumin excretion rate, blood pressure, endothelial and clotting factors, and insulin insensitivity. At the time of review, no studies have confirmed that these effects give beneficial health outcomes, but some of the effects are qualitatively similar in nature, but quantitatively greater, than are found with metformin. Systematic reviews of the α -glucosidase inhibitors have not found reason to recommend them over less expensive and better tolerated drugs [1,2,7].

Lactic acidosis is a rare complication (often fatal) of metformin therapy in people with renal impairment. Gastro-intestinal intolerance of this drug is very common, particularly at higher dose levels and with fast upward dose titration. Some sulfonylureas, notably glyburide, are known to be associated with severe hypoglycaemia and rarely death from this, again usually in association with renal impairment. Thiazolidinediones can cause fluid retention and are contra-indicated in the presence of higher grades of heart failure [11].

Generic metformin and sulfonylureas are available at very low cost. Proprietary oral glucose-lowering drugs are considerably more expensive, with limited evidence of extra benefit. Thiazolidinediones are relatively new drugs and are also usually expensive.

Consideration

The outcome-based evidence from the UKPDS for the use of metformin in overweight people with Type 2 diabetes, exceeding that for any other drug, leads to its recommendation for first-line use, although the sulfonylureas also protected against vascular damage in that study. Cheap generic versions of these drugs are available, and their glucose-lowering capacity is not surpassed by any newer drug, at least on a population basis. However, tolerance and safety issues are of concern with metformin, the latter particularly if renal impairment is present. Concern over hypoglycaemia with some of the sulfonylureas is also felt to be of significance, especially with renal impairment. The evidence on the thiazolidinediones, effective in glucose-lowering and in having positive effects on some cardiovascular risk markers, would now seem to justify an early role for these drugs in combination oral agent therapy. However, they remain relatively expensive in most health-care markets.

Combination of oral glucose-lowering drugs with insulin therapy is discussed below (see *Insulin therapy*).

Implementation

Contracts should be in place for uninterrupted availability of at least one sulfonylurea, metformin and (for standard/comprehensive care) at least one thiazolidinedione. Availability is needed of an HbA_{1c} assay and visits to health-care professionals at a frequency (sometimes 3-monthly) sufficient to titrate therapy where glucose control is deteriorating. Lifestyle measures, self-monitoring where appropriate, and education, as discussed elsewhere in this guideline, are integral parts of maintaining glucose control to target, and will enhance the effectiveness of oral drugs. The recommendations should be a basis of local clinical protocols and structured records.

Evaluation

Evaluation of achieved blood glucose control should be by reference to the documented use of oral therapies and insulin in different combinations to identify appropriately early use of these drugs, and in the appropriate order. Reference to measures of renal and cardiac failure may be used to identify use where contra-indications apply. Local protocols should be identifiable.

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