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**Key points**

* Control blood glucose, blood pressure, and lipids aggressively to reduce macrovascular and microvascular complications1-3
* Aim for:
	+ Haemoglobin A1c (HbA1c): 6.5-7.0%
	+ Blood pressure: <130/80 mm Hg
	+ Fasting plasma glucose: 4.4-6.1 mmol/l
	+ Total cholesterol: <4.0 mmol/l
	+ Low density lipoprotein: <2.0 mmol/l
	+ Triglycerides: <1.7 mmol/l.

**Advances**

Many advances have been made in the drug treatment of type 2 diabetes in recent years. New drugs that have become available include:

* Dipeptidyl peptidase 4 (DPP-4) inhibitors
* Glucagon-like peptide 1 (GLP-1) analogues.

**Clinical tip**

* The most important lifestyle advice is to stop smoking and to stick to the diet as closely as possible and to exercise regularly

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**How should I treat it?**

**Principles of management**

* Patients should receive ongoing structured care to evaluate microvascular and cardiovascular risk
* All patients should be entered into practice disease registers to allow patient call and recall
* All clinical information that relates to diabetes should be collected in electronic templates with locally or nationally agreed READ code datasets. This will help you achieve care standards and the quality targets in the general medical services contract
* Targets should be tailored to the individual patient, according to what it is possible to achieve. Overambitious targets can be counterproductive and risk severe hypoglycaemia
* The impact of other cardiovascular risk factors should be taken into consideration when agreeing targets

**Treatment targets**

Table 1 sets out recommended targets for controlling glucose, blood pressure, and lipids.2 3

|  |
| --- |
| **Table 1. Targets for controlling diabetes and cardiovascular risk factors in people with diabetes.**  |
| **Risk factor**  | **Optimal**  | **Borderline**  | **Poor**  |
| Values are mmol/l unless otherwise specified |
| **Plasma glucose**  |
| Fasting | 4.4-6.1 | 6.2-7.8 | >7.8 |
| Postprandial | 4.4-8.0 | 8.1-10.0 | >10.0 |
| Total cholesterol | <4.0 | 4.0-5.5 | >6.5 |
| High density lipoprotein cholesterol | >1.1 | 0.9-1.1 | <0.9 |
| Fasting triglycerides | <1.7 | 1.7-2.2 | >2.2 |
| **Body mass index (kg/m2)**  |
| Men | 20-25 | 26-27 | >27 |
| Women | 19-24 | 25-26 | >26 |
| Blood pressure (mm Hg) | <130/80\* | 130/80-140/80 | >140/80 |
| Smoking | Non-smoker |   | Pipe/cigarettes |
| \*Stricter targets are needed in younger people and in people with early nephropathy who have a good life expectancy. |

**Evidence for treatment targets**

**Blood glucose**

The ADVANCE trial (2008), assessed the benefits of improved glucose control on the development of microvascular and macrovascular complications in type 2 diabetes. Over a 5.5 year period intensive blood glucose control (HbA1c 6.5% *v* 7.3%) resulted in:

* A 14% reduction in microvascular complications
* A non-significant reduction in cardiovascular morbidity and mortality.4

In contrast, for a population of patients with type 2 diabetes at high risk for CVD and an HbA1C of ≥7.5%, a therapeutic strategy that targets HbA1C <6% *v* 7.0-7.9% increased mortality over 3.5 years in the ACCORD study.5 This outcome is probably consequent to cardiovascular complications of severe hypoglycaemia and highlights the importance of individual treatment targets for patients with type 2 diabetes.

A 2011 Cochrane Review6 of 20 trials assessed the benefit of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in patients with type 2 diabetes. This demonstrated:

* No significant difference between intensive and conventional glycaemic control for all cause mortality (RR 1.01, 95% CI 0.90 to 1.13) or cardiovascular mortality (RR 1.06, 95% CI 0.90 to 1.26)
* Targeting intensive glycaemic control reduced the risk of amputation (RR 0.64, 95% CI 0.43 to 0.95; P = 0.03), the risk of retinopathy (RR 0.79, 95% CI 0.68 to 0.92; P = 0.002; 10,986 participants, 8 trials) and nephropathy (RR 0.78, 95% CI 0.61 to 0.99; P = 0.04).

Three other comprehensive meta-analyses of intensive glucose lowering also conclude7-9:

* There is no benefit of intensive glucose lowering treatment on all cause mortality or death from cardiovascular causes in adults with type 2 diabetes7-9
* And compared with standard treatment, the risk of severe hypoglycaemia is more than twice as high in the intensive treatment group (RR 2.33, 95% CI 1.62 to 3.36).7

**Picture 1: Example of a glucometer**



**Hypertension**

Hypertension is:

* Defined by the British Hypertension Society as blood pressure ≥140/90 mm Hg
* 1.5-3.0 times more prevalent in patients with type 2 diabetes than in controls.

The UKPDS's hypertension in diabetes study compared "tight" blood pressure control (144/82 mm Hg) with "less tight" control (154/87 mm Hg).10 Tight blood pressure control reduced the incidence of myocardial infarction (14% in the tight control group *v* 21% in the less tight group) and stroke (5% in the tight control group *v* 8.7% in the less tight group).

The trial found that tight blood pressure control in patients with hypertension and type 2 diabetes achieved a clinically important reduction in the risk of deaths related to diabetes, complications related to diabetes, progression of diabetic retinopathy, and deterioration in visual acuity.

The Hypertension Optimal Treatment (HOT) trial compared an intensive treatment group, whose target diastolic was 80 mm Hg, with a conventional treatment group, whose target blood pressure was 90 mm Hg.11

* Intensive treatment reduced the incidence of all cardiovascular events (4.4% in the intensive treatment group *v* 9% in the conventional treatment group).

**Lipids**

The Heart Protection Study looked at the role of simvastatin 40 mg in the primary prevention of cardiovascular disease.12 It included 3985 patients aged 40-80 with type 1 or type 2 diabetes with no previous history of cardiovascular disease and total cholesterol >3.5 mmol/l.

* In total, 9.1% of patients who received simvastatin experienced a coronary event, stroke, or revascularisation procedure compared with 13.5% of those who received placebo.

In June 2004, results from the Collaborative Atorvastatin Diabetes Study (CARDS) were presented at the annual meeting of the American Diabetes Association. This primary prevention study investigated the benefit of treatment with atorvastatin 10 mg in patients with:

* Type 2 diabetes
* A low-density lipoprotein cholesterol ≤4.14 mmol/l
* One other cardiovascular risk factor (hypertension, smoking, retinopathy, microalbuminuria).

Atorvastatin reduced the incidence of major cardiovascular events by 37% compared with placebo (this is a relative risk reduction).

The Joint British Societies (JBS) Guideline recommends that all patients who have had type 2 diabetes for more than 10 years and all patients with type 2 diabetes who are older than 40 years, have a sufficient level of cardiovascular risk to benefit from statin therapy, unless they have specific contraindications to its use.

**Picture 2: Xanthomata on the knee from severe hyperlipidaemia. This typically occurs in patients with familial hypercholesterolaemia, but it may occur in patients with diabetes**



**Aspirin**

Current JBS guidelines recommended low dose aspirin (75 mg) is prescribed for patients who have had type 2 diabetes for more than 10 years and all patients with type 2 diabetes who are older than 50 years.

However, a meta-analysis of the primary prevention of cardiovascular events in people with diabetes in 200913 demonstrates any CV benefit is offset by an increased risk of cerebral and gastrointestinal bleeding. The Medicines and Healthcare products Regulatory Authority (MHRA) Drug safety update (Volume 3, Issue 3, October 2009) recommends if aspirin is used in primary prevention, the balance of benefits and risks should be considered for each individual, particularly the presence of risk factors for vascular disease and the risk of gastrointestinal bleeding.

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**Non-drug measures**

The most important lifestyle advice for patients is to stop smoking and to stick to an appropriate diet.

**Education**

* Tailor patients' educational needs to their beliefs and culture
* Listen and respond to preconceived ideas and anxieties
* Explain the aims of treatment and the relationship between blood glucose and diet and exercise
* Explain the consequences of poor glucose control for the development of complications
* Explain the importance of screening for complications
* Explain the importance of a healthy lifestyle, especially physical activity and stopping smoking
* Explain the role and importance of self monitoring (for example, monitoring glucose concentrations at home)
* Explain the importance of regular foot care

**Dietary advice**

* Eat regular meals planned around starchy food such as bread, potatoes, rice, and pasta
* Reduce consumption of fried and fatty foods
* Use skimmed or semi skimmed milk, rather than full fat milk
* Eat at least five portions of fruit, vegetable, or pulses a day
* Avoid eating chocolate and sweets
* Reduce consumption of salt
* Drink alcohol only in moderation

**Other lifestyle advice**

Other lifestyle advice includes:

* Reduce weight to a realistic target - body mass index of 25 (80-90% of patients with type 2 diabetes are overweight)
* Encourage 30 minutes of moderate physical exercise or activity on at least five days of the week

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**Drug management**

The principles of managing type 2 diabetes are1 14-16:

* All patients should be encourage to modify lifestyle (good diet, lose weight, exercise, and stop smoking)
* Metformin is first line drug therapy for most patients. Recommendations from both the European Association for the Study of Diabetes and the American Diabetes Association state that metformin should be prescribed alongside lifestyle modification from the time of diagnosis of type 2 diabetes. It is no longer advised that patients are given a "trial of lifestyle change" without metformin therapy
* Add a sulphonylurea to metformin if glucose control is inadequate.

The following drugs can also be used under specific circumstances:

* Thiazolidinediones
* DPP-4 inhibitors
* GLP-1 analogues
* Postprandial glucose regulators
* Acarbose
* Insulin.

**Conventional drug treatment**

**Metformin**

Metformin reduces output of glucose from the liver. It also enhances uptake and use of glucose by muscle cells.

**Benefits**

Metformin reduces the risk of microvascular and macrovascular complications.

**Side effects**

Metformin can cause anorexia, nausea, and diarrhoea. Rarely, it can cause lactic acidosis (the extremely rare cases of lactic acidosis with metformin are normally seen in association with renal impairment).

Metformin is contraindicated in patients with:

* Renal impairment (where the eGFR is <30 ml/min)
* Liver failure
* Alcoholism
* Diabetic ketoacidosis
* Major surgery
* Sepsis.

For patients undergoing radiological intravascular contrast investigations metformin should be suspended prior to the test and restarted after 48 hours, provided renal function has returned to baseline.

**Evidence**

Metformin reduces the risk of microvascular and macrovascular complications. A substudy of the United Kingdom Prospective Diabetes Study looked at the use of metformin as intensive therapy in overweight people with type 2 diabetes. These patients had fewer hypoglycaemic episodes and less weight gain on metformin than on other drug therapies.16

**Patients likely to benefit**

Patients should be offered metformin as first line treatment from the point of diagnosis of type 2 diabetes. Overweight patients especially are likely to benefit.

Metformin can be used as monotherapy or in combination with sulphonylureas.

**Dose**

Patients should start with 500 mg metformin daily. The dose should be increased gradually to 1 g twice daily or the maximum tolerated dose over the course of 2-3 months.

**Sulphonylureas**

Sulphonylureas stimulate insulin release from the pancreas.

**Benefits**

Sulphonylureas control blood sugar and reduce the incidence of long term microvascular complications.

**Side effects**

Weight gain with sulphonylureas is variable and may be up to 4 kg. Hypoglycaemia can be a problem, especially in:

* Older people
* People with poor hepatic or renal function
* People with erratic meal schedules.

Alcohol can also contribute to hypoglycaemia. Long acting sulphonylureas can cause delayed hypoglycaemia, which may be prolonged.

**Evidence**

Sulphonylureas cause a mean decrease in HbA1c of about 1-2% compared with placebo.17

Sulphonylurea treatment reduces the incidence of long term microvascular complications.18

**Patients likely to benefit**

Sulphonylureas should be used with metformin when glucose control deteriorates. They should be considered as an option for first line treatment if metformin is not tolerated or is contraindicated, or if the patient is not overweight.

Sulphonylureas can also be used with acarbose, thiazolidinediones, GLP-1 analogues, DPP-4 inhibitors, or insulin.

**Dose**

All sulphonylureas should be started at the lowest dose and the dose should be titrated upwards according to response.

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**Postprandial glucose regulators**

Postprandial glucose regulators stimulate a rapid, short duration release of insulin from the pancreas. This helps to restore the normal physiological insulin response to meals.

**Benefits**

Postprandial glucose regulators control blood glucose and reduce HbA1c.

**Side effects**

Side effects of postprandial glucose regulators include weight gain and hypoglycaemia.

Be careful with these drugs in patients with impaired renal and hepatic function.17

**Evidence**

Postprandial glucose regulators effectively control blood glucose concentrations and reduce HbA1c by up to 2%.17 18

**Patients likely to benefit**

Postprandial glucose regulators are particularly effective for patients with:

* Erratic lifestyles
* Recurrent hypoglycaemia with sulphonylureas
* Postprandial hyperglycaemia.

**Dose**

Repaglinide and nateglinide should be started at the lowest dose and the dose should be adjusted according to response.

**Acarbose**

Acarbose decreases the absorption of carbohydrates from the gut.

**Benefits**

Acarbose decreases concentrations of HbA1c by about 0.5% compared with placebo.

**Side effects**

Acarbose frequently causes gastrointestinal side effects (for example, flatulence and abdominal bloating). It should not be given to patients with:

* Inflammatory bowel disease
* Malabsorption
* Other similar gastrointestinal disorders.

**Evidence**

Acarbose is less effective at lowering concentrations of HbA1c than metformin or sulphonylureas. The average decrease in concentrations of HbA1c with alpha glucosidase inhibitors is about 0.5-1% compared with placebo.17

**Patients likely to benefit**

Acarbose may be considered as an alternative glucose lowering treatment in people unable to use other oral drugs.

**Dose**

Acarbose should be started at 50 mg daily and increased to 50 mg three times daily. It can be increased, if necessary, after 6-8 weeks to 100 mg three times daily.

**Thiazolidinediones**

Thiazolidinediones reduce insulin resistance in adipose, skeletal, and hepatic tissues by increasing transcription of insulin sensitive genes in these cells. The only thiazolidinedione available in the UK is pioglitazone (Actos).

**Benefits**

Thiazolidinediones control blood sugar concentrations and lower the concentration of HbA1c by approximately 1.0%. Trials have shown thiazolidinediones are almost equivalent in effect to sulphonylureas, but can maintain HbA1c control <7% for a greater period than conventional therapies.17 19

**Side effects**

Hepatotoxicity has been reported rarely. Liver enzymes should be monitored before the drugs are started and periodically thereafter.

Thiazolidinediones can cause oedema and anaemia.

**Evidence**

Results from the ADOPT study demonstrate that weight gain is greater than that observed with sulphonylureas. The increase in weight is due to fat deposition peripherally rather than centrally. Patients should be advised of this effect so they may anticipate it despite efforts to lose weight as part of the overall diabetes management.

In 2007 a meta-analysis of the effect of rosiglitazone on myocardial infarction concluded that this drug increases the risk of myocardial infarction by 43%. The RECORD study investigators demonstrated in 2009 that rosiglitazone increases risk of heart failure and fracture (mainly in women).20

In September 2010, the European Medicines Agency recommended the suspension of marketing authorisations for rosiglitazone, as recent studies and accumulated data confirmed an increased cardiovascular risk.21 In July 2011, the European Medicines Agency also advised against prescribing pioglitazone in patients with a history of bladder cancer or uninvestigated macroscopic haematuria. In light of age related risks, the balance of benefits and risks should be considered carefully both before initiating and during treatment in the elderly.22

Thiazolidinediones are contraindicated in patients with a history of heart failure or at higher risk of fracture.

**Patients likely to benefit**

NICE 6 recommends adding a thiazolidinedione (pioglitazone):

* As second line therapy when control of blood glucose is inadequate (HbA1c ≥6.5%, or other higher level agreed with the individual) and the person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs (for example, those working at heights or with heavy machinery) or people in certain social circumstances (for example, those living alone)), or
* As third line therapy to first line metformin and a second line sulphonylurea when control of blood glucose is inadequate (HbA1c ≥7.5%, or other higher level agreed with the individual) and insulin is unacceptable or inappropriate
* Consider combining pioglitazone with insulin therapy for a person who has previously had a marked glucose lowering response to thiazolidinedione therapy (pioglitazone), or who is on high dose insulin therapy and whose blood glucose is inadequately controlled.

**Dose**

The starting dose of pioglitazone is 30 mg once a day.

**Advances in drug treatment**

Many advances have been made in the drug treatment of type 2 diabetes in recent years. The new drugs that have become available include:

* DPP-4 inhibitors
* GLP-1 analogues
* Insulin glargine and insulin detemir.

**Glucagon-like peptide-1 analogues**

GLP-1 analogues work through the incretin effect. Incretin hormones were first identified when it was found that glucose given orally produced a greater stimulation of insulin release than when an equivalent glucose level was achieved by intravenous infusion.

GLP-1 is secreted from the ileum when food is ingested. It has multiple sites of action with the following effects:

* Beta cells: Enhances glucose-dependent insulin secretion
* Stomach: Helps slow gastric emptying
* Liver: ↓ Glucagon which reduces hepatic glucose output
* Alpha cells: ↓ Postprandial glucagon secretion
* Promotes satiety and reduces appetite.

**Benefits**

There are two GLP-1 analogues currently available in the UK; exenatide (Byetta) and liraglutide (Victoza). Both reduce HbA1c by approximately 1% over a six month period and also effectively reduce weight - achieving weight loss of up to 5% over a six month period.23

**Side effects**

Dose dependent nausea and vomiting are the most frequently reported short term adverse events. The incidence is greater with exenatide than liraglutide and is probably related to its shorter half life of action. Provided the patient is counselled before starting treatment, nausea symptoms are not usually associated with drug withdrawal. Symptoms reduce with time in most patients.

There is some evidence to suggest GLP-1 analogue therapy may increase the risk of pancreatitis. In patients at high risk of developing pancreatitis (gallstones, alcohol dependency, hypertriglyceridaemia) exenatide and liraglutide should only be used where the benefit of use is likely to outweigh potential risk.

**Dose**

Exenatide is administered by a twice daily, fixed dose subcutaneous injection. For the first month this should be prescribed as 5 µg twice daily, increasing to 10 µg after one month. Exenatide has been available as a 2 mg once weekly preparation since June 2011 (Bydureon).

Liraglutide is administered by a once daily, fixed dose subcutaneous injection. For the first week this should be prescribed as 0.6 mg once daily, increasing to 1.2 mg after one week.

**Patients likely to benefit**

NICE recommends adding a GLP-1 mimetic as third line therapy to first line metformin and a second line sulphonylurea when control of blood glucose is inadequate (HbA1c ≥7.5%, or other higher level agreed with the individual), and the person has:

* A body mass index (BMI) ≥35.0 in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or
* A BMI <35.0, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity related comorbidities.

NICE only supports continuation of GLP-1 mimetic therapy beyond six months if the person has had a beneficial metabolic response (a reduction of at least 1.0 percentage point in HbA1c and a weight loss of at least 3% of initial body weight).

If a positive response to GLP-1 mimetic therapy is achieved, reductions in the dose of other oral medication may be required to reduce the risk of hypoglycaemia. There are no long term safety data for this drug at the current time.

**Dipeptidyl peptidase-4 inhibitors.**

An alternative strategy to improve insulin output from the pancreas via the incretin system is to block the action of DPP-4. DPP-4 inhibitors bind to the active site of the DPP-4 enzyme so that it cannot bind to and degrade GLP-1. This increases the availability of GLP-1.

**Benefits**

The DPP-4 inhibitor drugs sitagliptin, vildagliptin, saxagliptin, and linagliptin have been shown to reduce HbA1c between 0.6-1.1%. These drugs are glucose dependent and the risk of hypoglycaemia is reduced compared with other oral therapies.

**Side effects**

The DPP-4 inhibitors are generally well tolerated and importantly are weight neutral.

**Dose**

Vildagliptin, sitagliptin, saxagliptin, and linagliptin have different dose and licence indications for use in combination glucose lowering therapy. Latest guidance is available from the European Medicines Evaluation Agency.

Only saxagliptin and linagliptin are currently licensed for use in patients with renal impairment.

**Patients likely to benefit**

Consider adding a DPP-4 inhibitor as second or third line therapy to sulphonylurea or metformin when control of blood glucose is inadequate (HbA1c ≥6.5%, or other higher level agreed with the individual) if:

* The person is at significant risk of hypoglycaemia or its consequences
* Further weight gain would cause or exacerbate significant problems associated with a high body weight
* When control of blood glucose is inadequate (HbA1c ≥7.5% or other higher level agreed with the individual) and insulin is unacceptable or inappropriate.

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**Insulin**

You should consider insulin in patients who have poor glycaemic control despite oral therapy and also at times of acute illness or surgery.

You should also consider insulin in patients with obvious symptoms of hyperglycaemia despite oral therapy.

**Benefits**

Frequent, well timed insulin injections and self monitoring allow patients to fine tune blood glucose concentrations to diet and exercise.

**Side effects**

Insulin needs to be given as regular injections and can cause hypoglycaemia. Patients may be reluctant to use insulin because of:

* Fear of the increased risk of hypoglycaemia
* Fear of self injection
* Fear of weight gain
* Inconvenience of pre-meal dosing.

The following factors increase the risk of severe hypoglycaemia:

* Lack of awareness of hypoglycaemia
* Advanced autonomic neuropathy
* Altered mental state (for example dementia)
* Immobility
* Lack of social support.

Insulin treatment also causes weight gain.

**Evidence**

Intensive treatment with insulin reduces the incidence of microvascular complications in patients with type 2 diabetes.6

**Patients likely to benefit**

The reasons for needing to consider insulin include:

* Poor glycaemic control despite maximal treatment with oral anti-diabetes agents
* Weight loss without dieting in someone of low or normal weight
* Contraindications to oral hypoglycaemic agents, for example renal or hepatic failure
* Pregnancy
* Post-myocardial infarct
* Marked thirst and polyuria with high blood glucose.

**Picture 3: Examples of insulin pens**



**Important points to remember with insulin**

**Insulin regimens**

GPs should be aware of insulin formulations and how to adjust the regimen.

The choice of insulin regimen for patients should be determined by:

* Compliance or resistance to injections
* Risk of hypoglycaemia
* Lifestyle
* Age
* Complications (good control is needed to reduce the incidence of complications; however, a blind patient is unlikely to cope with injections four times a day without support from a carer).

Insulin is available in four main types (Table 3).

|  |
| --- |
| **Table 3. Types of insulin**  |
| Values are in hours unless otherwise specified. |
| **Type of action**  | **Onset of action**  | **Peak action**  | **Duration**  | **Chemical name**  | **Drug name**  |
| Rapid | 5-10 minutes | 30-90 minutes | 2-4 | Insulin lisproInsulin aspart | HumalogNovoRapid |
| Short | 30 minutes | 1-2 | 4-6 | Soluble insulin | ActrapidHumulin SVelosulin and Insuman Rapid |
| Intermediate | 2 | 3-6 | 18-24 | Human insulin zinc suspension (rDNA origin)Isophane insulin suspension/NPH | Humulin LenteMonotardInsulatardHumulin IInsuman Basal |
| Long | 4 1-3 | 8-24 Flat without a peak | 36 12-24 | Human recombinant insulinCrystalline insulin zinc suspensionInsulin glargineInsulin detemir | UltratardHumulin ZnLantusLevemir |

**Combining insulin with other drugs**

It is common for patients with type 2 diabetes to progress from oral hypoglycaemic agents to insulin. The idea of insulin therapy should be introduced at an early stage in diagnosis so that it is not perceived by patients to be a last resort.

Insulin initiation should be provided by health professionals who are experienced with this process and who are readily accessible to provide ongoing support and advice. In recent years this role has been taken on by community clinics and GP practices with extended training, in place of traditional secondary care settings.

NICE guidelines2 on the management of type 2 diabetes initially recommend human NPH insulin taken at bedtime, or twice daily, according to need. Patients who add a basal or prandial insulin based regimen to oral therapy have been shown to achieve better glycated haemoglobin control than patients who add a biphasic insulin based regimen. Fewer hypoglycaemic episodes and less weight gain also occur in patients adding basal insulin.24

**Pre-mixed insulin regimens**

Pre-mixed insulin regimens are designed to offer improved glycaemic control across the day with fewer injections. They are available with varying proportions of rapid and intermediate acting insulin. Consider twice daily biphasic human insulin (pre-mix) regimens in particular where HbA1c is elevated above 9.0%. A once daily regimen may be an option when initiating this therapy.

In the UK patients are normally initiated with 30% rapid acting and 70% intermediate acting insulin. Many people with type 2 diabetes will achieve satisfactory control with twice daily pre-mixed insulin, but some will need intensification of insulin therapy in the longer term to achieve good glycaemic control.

When you transfer a patient from a combination of metformin and other oral agents to pre-mixed insulin therapy, you should continue the metformin. In some patients it may also be appropriate to continue sulphonylurea treatment.

Simple and practical guidance to start pre-mixed insulin in patients has been determined in the INITIATE treat to target study.

Initial dosing guidelines recommend insulin-naive patients should inject 6 U pre-mixed insulin with breakfast and 6 U with evening meal. The insulin dose should be adjusted weekly according to the three previous days self monitoring blood glucose levels. The INITIATE algorithm is shown in table 4.

|  |
| --- |
| **Table 4**  |
| **Fasting or pre-dinner blood glucose**  | **Dose adjustment**  |
| mmol/l |   |
| <4.4 | -2 U |
| 4.4-6.1 | - |
| 6.2-7.8 | +2 U |
| 7.9-10 | +4 U |
| >10 | +6 U |

**Once daily long acting insulin regimens**

**Insulin analogues**

**Insulin glargine (Lantus) and insulin detemir (Levemir)**

These are long acting human insulin analogues. They can be given once a day but are commonly needed twice daily. They maintain a basal concentration of insulin in the blood.

Once daily long acting insulin regimens are particularly useful for patients when25:

* They need help from a carer to administer their insulin injections
* Lifestyle is restricted considerably by recurrent symptomatic episodes of nocturnal hypoglycaemia
* They would otherwise need twice daily injections of insulin in combination with oral hypoglycaemic drugs.

The World Health Organization (WHO) reviewed evidence for the benefit of prescribing analogue insulin in 2011.26 In type 2 diabetes, WHO concludes the difference in HbA1c achieved between patients treated with analogue (glargine and detemir) and human insulin was very small (0.03%) and not clinically important. Rates of nocturnal hypoglycaemia were reduced with analogue insulin (RR=0.56, 95% CI 0.47 to 0.68). However, many studies excluded patients with a history of recurrent major hypoglycaemia and the authors were unable to conclude if a reduction in nocturnal hypoglycaemia would be observed across all patients with type 2 diabetes.

WHO advises that analogue insulin (glargine and detemir) has no advantage over NPH human insulin.

When transferring a patient from a combination of metformin and sulphonylurea, both agents should be continued with long acting insulin. Patients taking other forms of oral hypoglycaemic agent may discontinue treatment.

If inadequate control is achieved on once daily insulin, patients may either be transferred to twice daily pre-mixed insulin or additional rapid acting insulin can be administered.

Algorithms for the addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes have been published by both the 4T27 and INITIATE study investigators.

INITIATE recommends insulin-naive patients should inject 12 U long acting insulin at bedtime. The insulin dose should be adjusted weekly according to the three previous days self monitoring blood glucose levels. The algorithm for long acting insulin is shown in table 5.

|  |
| --- |
| **Table 5**  |
| **Fasting blood glucose**  | **Dose adjustment**  |
| mmol/l |   |
| <4.4 | -2 U |
| 4.4-6.1 | - |
| 6.2-7.8 | +2-4 U |
| 7.9-10 | +4-6 U |
| >10 | +6-8 U |

The increase in daily dose should not exceed the greater of 10 U or 10% of the current insulin dose.

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**When should I refer the patient?**

The following patients should be referred for specialist care28:

Patients with problems with management:

* Uncontrolled hyperglycaemia despite maximum doses of drugs
* Uncontrolled hypertension
* Persistent proteinuria
* Creatinine levels >150 µmol/l
* Retinopathy or visual impairment
* Painful neuropathy, mononeuropathy, or amyotrophy
* At risk feet (patients with foot ulcers should be referred urgently)
* Introduction of insulin therapy in patients with type 2 diabetes if no primary care service is available. (Insulin may be started in primary care if a good primary care service is in place)
* Patients with psychological problems related to the diagnosis (for example, depression)
* Women with type 2 diabetes who want to become pregnant.

Patients with the following problems should be referred as an emergency:

* Protracted vomiting or ketoacidosis
* Blood glucose concentrations >25 mmol/l, with ketones in the urine.

**What's the outlook?**

The incidence of microvascular and macrovascular complications is high, and life expectancy is reduced.

Aggressive control of glucose, blood pressure, and lipids reduces the long term morbidity and mortality associated with diabetes.1-3

**What do patients want to know?**

Patients usually want to know what the best treatment for their condition is and the side effects of treatment.

**Further information for patients and doctors can be found at the end of this module.**

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1. **Mr White is a 55 year old man with hypertension. He has no symptoms that suggest diabetes, but blood tests produced two plasma glucose results >12 mmol/l. His body mass index (BMI) is 24.5 and his baseline bloods show his HbA1c is 9.4%. Which one of the following treatment strategies should you recommend?**
	1. Start metformin and lifestyle modification
	2. Start glipizide and lifestyle modification
	3. Lifestyle modification

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1. **Four months later Mr White returns to your clinic. He has made a significant effort to improve his lifestyle. He has lost weight and his BMI is now 22.7. His fasting blood glucose readings range between 6 mmol/l and 12 mmol/l and his most recent HbA1c has improved to 7.7%. He is taking metformin 500 mg twice daily without side effects. What is next logical step in treatment?**
	1. Increase metformin to 1 g twice daily
	2. Continue with more intensive lifestyle changes
	3. 

Start glipizide

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1. **You check Mr White's blood pressure and note it is 144/82 mm Hg. His last three readings were >150/90 mm Hg. Microalbuminuria screening was negative on two separate occasions and he has not been prescribed antihypertensive medication. What should you do next?**
	1. Review in three months
	2. Start ACE inhibitor therapy
	3. 

Start bendroflumethiazide therapy

1. **Two years later Mr White comes back to your surgery. He is taking:**
	* **Metformin 500 mg three times daily**
	* **Gliclazide 120 mg once daily**
	* **Ramipril 10 mg once daily.**

**His lifestyle is still sensible. Investigations show:**

* + **Fasting plasma glucose is 18.7 mmol/l**
	+ **HbA1c is 12.4%**
	+ **Urinalysis shows 4+ glucose (negative for ketones).**

**What should you recommend to him?**

* + Start a thiazolodinedione
	+ Increase the dose of metformin and gliclazide
	+ Recommend insulin therapy

You have changed your answer. Your first answer will count.

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1. **Three months later Mr White comes to see you because he does not feel his insulin doses are correct. His fasting blood glucose is usually 8-10 mmol/l and before his evening meal they are 5-8 mmol/l.**

**His medication regimen is:**

* + **Metformin 500 mg three times daily**
	+ **NovoMix 30, 20 U with breakfast and 20 U with his evening meal.**

**What should you suggest?**

|  |  |  |
| --- | --- | --- |
|  | **Your answer** | **Correct answer** |
| **a.**  | Increase his morning Novomix dose by 2 U and his evening Novomix by 2 U |  |  |
| **b.**  | Increase his morning Novomix by 2 U and reduce his evening Novomix by 6 U |  |  |
| **c.**  | Increase his evening Novomix by 4 U and leave his morning Novomix unchanged at 20 U | http://learning.bmj.com/learning/images/blueDot.gif | http://learning.bmj.com/learning/images/blueDot.gif |

**a : Increase his morning Novomix dose by 2 U and his evening Novomix by 2 U**

The titration algorithm determined from the INITIATE study recommends the insulin dose should be adjusted weekly according to the three previous days self monitoring blood glucose levels. As morning blood glucose is 8-10 mmol/l, the evening Novomix dose should be increased by 4 U. After one week a further assessment can be made on evening and morning insulin requirements.

|  |
| --- |
| **Table 4**  |
| **Fasting or pre-dinner blood glucose**  | **Dose adjustment**  |
| mmol/l |   |
| <4.4 | -2 U |
| 4.4-6.1 | - |
| 6.2-7.8 | +2 U |
| 7.9-10 | +4 U |
| >10 | +6 U |

**b : Increase his morning Novomix by 2 U and reduce his evening Novomix by 6 U**

The titration algorithm determined from the INITIATE study recommends the insulin dose should be adjusted weekly according to the three previous days self monitoring blood glucose levels. As morning blood glucose is 8-10 mmol/l, the evening Novomix dose should be increased by 4 U. After one week a further assessment can be made on evening and morning insulin requirements.

**c : Increase his evening Novomix by 4 U and leave his morning Novomix unchanged at 20 U**

Increasing the evening Novomix by 4 U is consistent with the recommendations of the INITIATE study and should improve fasting self monitored blood glucose levels.

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1. **Six months later Mr White comes to see you because his blood glucose control is less consistent. His fasting blood glucose is usually 4-7 mmol/l. By 11am it measures between 11 mmol/l and 15 mmol/l and falls to 3-5 mmol/l by mid-afternoon causing mild symptoms of hypoglycaemia.**

**His medication regimen is:**

* + **Metformin 500 mg three times daily**
	+ **NovoMix 30, 20 units with breakfast and 30 units with his evening meal.**

**What should you suggest?**

* + Increase morning NovoMix to 28 units
	+ Inject six extra units of NovoMix at 10am
	+ Change morning NovoMix 30 to Humalog Mix 50
1. **A 50 year old man has had type 2 diabetes for four years. He sticks to his diet and his BMI is 33.4. He takes metformin 850 mg twice a day, but his blood glucose concentrations still range between 10 mmol/l and 12 mmol/l. He is a police officer and has an erratic shift pattern and unpredictable mealtimes. Which drug should you add to his treatment regimen?**
	1. Gliclazide
	2. Acarbose
	3. 

Vildagliptin

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You have changed your answer. Your first answer will count.

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1. **A 50 year old man has had type 2 diabetes for four years. He sticks to his diet and his BMI is 33.4. He takes metformin 850 mg twice a day, but his blood glucose concentrations still range between 10 mmol/l and 12 mmol/l. He is a police officer and has an erratic shift pattern and unpredictable mealtimes. Which drug should you add to his treatment regimen?**

|  |  |  |
| --- | --- | --- |
|  | **Your answer** | **Correct answer** |
| **a.**  | Gliclazide  |  |  |
| **b.**  | Acarbose |  |  |
| **c.**  | Vildagliptin  | http://learning.bmj.com/learning/images/blueDot.gif | http://learning.bmj.com/learning/images/blueDot.gif |

1. **a : Gliclazide**
2. Gliclazide effectively controls blood glucose. It acts directly on the pancreas to stimulate insulin release but is associated with significant weight gain and risk of hypoglycaemia. Vildagliptin has glucose dependent actions and there is a reduced risk of hypoglycaemia in this man with unpredictable meal times. Vildagliptin is weight neutral and BMI is already in the obese range.
3. **b : Acarbose**
4. Acarbose is less effective at lowering blood glucose than other drugs. It frequently causes gastrointestinal side effects. It may be considered as an alternative glucose lowering therapy in people unable to use other oral drugs.
5. **c : Vildagliptin**
6. Vildagliptin has glucose dependent actions and there is a reduced risk of hypoglycaemia compared with gliclazide in this man with unpredictable meal times. Vildagliptin is weight neutral and BMI is already in the obese range for this man. Repaglinide could be used as an alternative to vildagliptin. It acts directly on the pancreas to stimulate a rapid, short duration release of insulin. This helps to restore the normal physiological insulin response to meals, but unlike vildagliptin is likely to cause weight gain

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1. **Which one of the following risk targets is recommended by Diabetes UK and the British Hypertension Society?**
	1. Total cholesterol <5.0 mmol/l
	2. Low density lipoprotein cholesterol <2.0 mmol/l
	3. High density lipoprotein cholesterol >0.9 mmol/

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1. **Mrs Johnson is 64 years old and was diagnosed with type 2 diabetes two years ago. She had a myocardial infarct and was diagnosed with heart failure three years ago. Although she feels well, blood glucose has been consistently elevated for the last few months - recent HbA1c is 8.5%, BMI 35.6.**

**Current medications are metformin 1000 mg twice daily, gliclazide 160 mg twice daily, simvastatin 40 mg once daily, and aspirin 75 mg once daily.**

**Which of the following treatment options is most appropriate?**

* 1. 

Add pioglitazone

* 1. 

Add GLP-1 therapy

* 1. 

Refer to dietitian for weight loss advice

1. **One month later Mrs Johnson is reviewed. Blood glucose has improved with morning readings between 6-9 mmol/l. Her main complaint is nausea and she is vomiting at least once every day. These symptoms do not appear to be improving and she is not keen to continue treatment. Her weight has reduced by 3 kg in four weeks. How should you proceed?**
	1. 

Continue exenatide 5 µg twice daily

* 1. 

Increase exenatide to 10 µg twice daily

* 1. 

Stop exenatide and start a DPP-4 inhibitor