Type 2 diabetes mellitus: medicines optimisation priorities

Key therapeutic topic
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Options for local implementation

- The NICE guideline on type 2 diabetes in adults recommends adopting an individualised approach to diabetes care. Involve people with type 2 diabetes in decisions about their individual glycated haemoglobin (HbA1c) target, and reassess their individual needs and circumstances at each review. Consider stopping any medicines that are not effective.

- Consider carefully, with an individualised approach, the benefits and risks of controlling blood glucose and the use of blood glucose lowering medicines. Review and, if appropriate, optimise prescribing to ensure that it is in line with NICE guidance taking into account the person's preferences, comorbidities, risks from polypharmacy, and their life expectancy and consequent chances of benefiting from long-term interventions.

- When choosing and reviewing medicines, take into account the person's individual clinical circumstances, preferences and needs; the medicines' efficacy (based on metabolic response), safety and tolerability; and the licensed indications or combinations available. Consider also the cost of medicines: the NICE guideline recommends choosing medicines with the lowest acquisition cost if 2 in the same class are appropriate.

- The NICE guideline recommends that self-monitoring of blood glucose levels for adults with type 2 diabetes should not routinely be offered. See the guideline for details on when self-monitoring is appropriate.
Evidence context

Type 2 diabetes is a chronic metabolic condition characterised by insulin resistance and insufficient pancreatic insulin production, resulting in high blood glucose levels. Type 2 diabetes is commonly associated with obesity, physical inactivity, raised blood pressure and disturbed blood lipid levels, and therefore is recognised to increase cardiovascular risk. It is associated with long-term microvascular and macrovascular complications, together with reduced quality of life and life expectancy. The NICE guideline on type 2 diabetes in adults recommends adopting an individualised approach to diabetes care, which takes into account personal preferences, comorbidities, risks from polypharmacy, and the ability to benefit from long-term interventions because of reduced life expectancy. Such an approach is especially important in the context of multimorbidity. See also the key therapeutic topic on multimorbidity and polypharmacy for further information on reviewing polypharmacy and de-prescribing.

The guideline recommends that the person's needs and circumstances should be reassessed at each review and consideration given to stopping any medicines that are not effective. Controlling blood glucose levels requires a careful balance between the intensity of the treatment regimen and avoiding hypoglycaemia. This key therapeutic topic focusses on blood glucose management; however, the NICE guideline also has recommendations on patient education, dietary advice, blood pressure management, antiplatelet therapy and management of complications. Recommendations on the management of blood lipids in people with type 2 diabetes are given in the NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification. All these components should be given due consideration in the care of people with type 2 diabetes.

The NICE guideline on type 2 diabetes in adults is being partially updated, to consider specifically: the clinical effectiveness of sodium-glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) mimetics on cardiovascular outcomes, and the differences between the assumptions used in the health economic model that informed the guideline and the empirical evidence from randomised controlled trials (RCTs).

The relevant RCTs are discussed below.

The NICE Pathway on diabetes brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams. NICE has also published a quality standard on diabetes in adults, which provides a concise set of prioritised statements designed to drive measurable quality improvements within this area. In September 2016, the Care Quality Commission published My diabetes, my care: a community diabetes care review that considers how well care services work together to deliver high-quality diabetes care. The review makes a number of recommendations for
how health and social care commissioners, providers and professionals could work together to improve diabetes care and prevention.

**Target blood glucose levels**

The NICE guideline on type 2 diabetes in adults recommends that people with type 2 diabetes should be involved in decisions about their individual glycated haemoglobin (HbA1c) target and be supported to achieve and maintain this. For adults with type 2 diabetes that is managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycaemia, the guideline recommends supporting the person to aim for an HbA1c level of 48 mmol/mol (6.5%). For adults on a drug associated with hypoglycaemia, the recommended aim is an HbA1c level of 53 mmol/mol (7.0%). If HbA1c levels are not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher, advice about diet, lifestyle and adherence to drug treatment should be reinforced, the person should be supported to aim for an HbA1c level of 53 mmol/mol (7.0%) and drug treatment should be intensified (taking into account principles of individualised care). When intensification of drug treatment is required the guideline recommends that additional treatments should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug.

The target HbA1c level can be relaxed on a case-by-case basis, with particular consideration for people who are older or frail, those with a reduced life expectancy, those for whom tight blood glucose control poses a high risk of the consequences of hypoglycaemia, and those for whom intensive management would not be appropriate, such as people with significant comorbidities. The NICE patient decision aid for adults with type 2 diabetes can support the implementation of the guideline recommendations on the individualised agreement of HbA1c targets.

The Quality and Outcomes Framework (QOF) allocates points for achieving 3 levels of glucose control in people with type 2 diabetes: HbA1c of 75 mmol/mol (9%) or less, 64 mmol/mol (8%) or less and 59 mmol/mol (7.5%) or less.

**What are the benefits and risks of controlling blood glucose?**

The NICE guideline included a review question comparing intensive glycaemic control with conventional glycaemic control in people with type 2 diabetes (see the full guideline for details). This used a Cochrane review (Hemmingsen et al. 2013 [CD008143]) as the primary source of evidence because it included all relevant RCTs. The Cochrane review included 28 RCTs in 34,912 people with type 2 diabetes; the NICE guideline excluded 8 RCTs in which intensive and
conventional glycaemic control groups had significant baseline differences in adjunctive treatment for cardiovascular risk factors.

Compared with conventional control, the NICE guideline found that intensive glycaemic control did not statistically significantly reduce death from any cause (relative risk [RR] 0.98, 95% confidence interval [CI] 0.88 to 1.09; 16 RCTs, n=6,504) or death from cardiovascular causes (RR 1.15, 95% CI 0.98 to 1.35; 14 RCTs, n=6,356). No statistically significant effect of targeting intensive glycaemic control was found on the composite of macrovascular complications (RR 0.98, 95% CI 0.74 to 1.30; 8 RCTs, n=5,334), non-fatal myocardial infarction (RR 0.92, 95% CI 0.78 to 1.09; 9 RCTs, n=5,902), congestive heart failure (RR 0.82, 95% CI 0.62 to 1.08; 8 RCTs, n=5,460), non-fatal stroke (RR 1.06, 95% CI 0.80 to 1.41; 8 RCTs, n=5,488) or amputation of lower extremity (RR 0.73, 95% CI 0.42 to 1.25; 7 RCTs, n=5,079).

Intensive glycaemic control did reduce the risk of the composite of microvascular complications (RR 0.75, 95% CI 0.61 to 0.92; 3 RCTs, n=4,376), but no statistically significant reductions in risk were seen for the individual end points of nephropathy (RR 0.64, 95% CI 0.32 to 1.29; 7 RCTs, n=4,754), progression to end-stage renal disease (RR 0.94, 95% CI 0.47 to 1.89; 4 RCTs, n=4,803) or retinopathy (RR 0.79, 95% CI 0.56 to 1.11; 5 RCTs, n=4,614).

Intensive glycaemic control increased the risk of severe hypoglycaemia (RR 2.23, 95% CI 1.22 to 4.08; 13 RCTs, n=5,452) and mild hypoglycaemia (RR 1.85, 95% CI 1.53 to 2.25; 12 RCTs, n=6,320). The guideline development group agreed overall that there was evidence to support the setting of target values, but considered it important to ensure that a person’s risk of hypoglycaemia is evaluated when setting appropriate target levels.

**Self-monitoring of blood glucose**

The NICE guideline on [type 2 diabetes in adults](https://www.nice.org.uk/guidance/ng36) recommends that self-monitoring of blood glucose levels for adults with type 2 diabetes should not routinely be offered unless:

- the person is on insulin treatment or
- there is evidence of hypoglycaemic episodes or
- the person is on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery or
- the person is pregnant, or is planning to become pregnant (see the NICE guideline on [diabetes in pregnancy](https://www.nice.org.uk/guidance/ng36) for more information).
Healthcare professionals should also take the Driver and Vehicle Licensing Agency (DVLA) guidance Assessing fitness to drive guide into account when offering self-monitoring of blood glucose levels to people with type 2 diabetes and advise them about their own particular requirements.

The guideline development group discussed the evidence for self-monitoring of blood glucose and concluded that overall, while a statistically significant difference was observed in HbA1c levels in favour of self-monitoring, this was not clinically meaningful and was unlikely to be cost-effective. The reduction in HbA1c levels with self-monitoring was 2 mmol/mol (0.22%), which was less than 5 mmol/mol (0.5%), the agreed threshold for minimal important difference.

The guideline recommends considering short-term self-monitoring of blood glucose levels in adults with type 2 diabetes (and reviewing treatment as necessary) when starting treatment with oral or intravenous corticosteroids or to confirm suspected hypoglycaemia. It is also recommended for health professionals to be aware that adults with type 2 diabetes who have acute intercurrent illness are at risk of worsening hyperglycaemia, and reviewing treatment as necessary.

The guideline recommends that if adults with type 2 diabetes are self-monitoring their blood glucose levels this should be assessed in a structured way at least annually, assessing various issues including the impact on the person's quality of life and the continued benefit of self-monitoring.

**Blood glucose lowering therapy**

The NICE guideline on type 2 diabetes in adults recommends that the choice of medicine for managing blood glucose levels should be made following a discussion with the individual person about the benefits and risks of drug treatment, and the options available. The guideline recommends an individualised approach to treatment choice taking into account the person's individual preferences and needs, and their individual clinical circumstances, for example, comorbidities and risks from polypharmacy. Choice should also take into account the medicine's efficacy (based on metabolic response), safety and tolerability; and the licensed indications or combinations available. Cost should be taken into account and the guideline recommends choosing medicines with the lowest acquisition cost if more than 1 in the same class are appropriate. NICE's patient decision aid for adults with type 2 diabetes can support the implementation of the guideline recommendations on the pharmacological management of blood glucose.
Efficacy

Although all blood glucose lowering medicines are effective (at a population level) in reducing HbA1c levels, clinical outcome data, particularly around cardiovascular outcomes, are limited. Improvements in surrogate markers (including HbA1c levels) do not automatically confer benefits on mortality or morbidity, and risks may only become apparent over time when medicines are used widely in a diverse population.

Metformin, sulfonylureas and insulin have outcome data from the UK Prospective Diabetes Study (UKPDS). In UKPDS 33 (UKPDS Group 1998), intensive glycaemic control with sulfonylureas or insulin compared with conventional control (median HbA1c after 10 years follow up: 53 mmol/mol [7.0%] compared with 63 mmol/mol [7.9%]) reduced the risk of microvascular complications, but not macrovascular disease. In UKPDS 34 (UKPDS Group 1998) in people who were overweight or obese, intensive glycaemic control with metformin compared with conventional control (median HbA1c after 10.7 years follow up: 57 mmol/mol [7.4%] compared with 64 mmol/mol [8.0%]) reduced the risk of MI and death from any cause. Long-term follow-up of UKPDS (Holman et al. 2008) found a continued reduction in microvascular risk and emergent risk reductions for MI and death in the sulfonylurea-insulin group and a continued benefit for risk of MI and death in the metformin group.

Other blood glucose lowering medicines have not shown such cardiovascular benefits in people with type 2 diabetes. For example, in PROACTIVE (Dormandy et al. 2005), pioglitazone did not reduce the composite primary end point of death from any cause, non-fatal MI, stroke, acute coronary syndrome, major leg amputation, coronary revascularisation and leg revascularisation in people with type 2 diabetes and pre-existing major macrovascular disease, but did increase the incidence of oedema, weight gain and heart failure. In SAVOR-TIMI 53 (Scirica et al. 2013), saxagliptin did not reduce the composite primary end point of cardiovascular death, MI, or ischemic stroke, but did increase the risk of admission to hospital because of heart failure in people with type 2 diabetes who had established cardiovascular disease, or were current smokers, or had dyslipidaemia or hypertension. (See NICE’s medicines evidence commentary on type 2 diabetes: study finds no benefit from saxagliptin on cardiovascular outcomes.) In EXAMINE (White et al. 2013) alogliptin did not reduce the composite primary end point of death from cardiovascular causes, non-fatal MI or non-fatal stroke in people with type 2 diabetes who had had a recent acute coronary syndrome. (See NICE’s medicines evidence commentary on type 2 diabetes: study finds no benefit from alogliptin on cardiovascular outcomes in people with a recent acute coronary syndrome). Similarly, in TECOS (Green et al. 2013) sitagliptin did not reduce the composite primary end point of death from cardiovascular causes, non-fatal MI, non-fatal stroke, or hospital admission for unstable angina in people with type 2 diabetes who had established cardiovascular disease.
The ORIGIN study found that, compared with standard care (non-insulin therapy), the early use of basal insulin glargine for a median of 6 years had no effect on cardiovascular outcomes in people with impaired fasting glucose, impaired glucose tolerance or early type 2 diabetes who also had cardiovascular risk factors. As perhaps expected, episodes of severe hypoglycaemia were more common in people receiving insulin glargine. The incidence of a first episode of severe hypoglycaemia was 1.00 per 100 patient-years with insulin glargine and 0.31 per 100 patient-years with standard care (p<0.001) (see NICE’s medicines evidence commentary on insulin glargine: no effect on cardiovascular outcomes in early type 2 diabetes for details).

More recently 4 studies of SGLT-2 inhibitors and GLP-1 mimetics have shown cardiovascular benefits with some, but not all, of these medicines. These studies are being considered in the partial update to the NICE guideline on type 2 diabetes.

In EMPA-REG OUTCOME (Zinman et al. 2015), adding the SGLT-2 inhibitor empagliflozin to standard care in people with type 2 diabetes and established cardiovascular disease reduced the risk of cardiovascular outcomes over a median follow-up of 3.1 years. Empagliflozin reduced the risk of the composite end point of death from cardiovascular causes, non-fatal MI or non-fatal stroke (hazard ratio 0.86; 95% CI 0.74 to 0.99). However, when analysed individually, only the reduction in risk of death from cardiovascular causes was statistically significant (hazard ratio 0.62; 95% CI 0.49 to 0.77), not the reduction in risk of non-fatal MI or non-fatal stroke. Empagliflozin also reduced the risk of death from any cause (hazard ratio 0.68; 95% CI 0.57 to 0.82). See NICE’s medicines evidence commentary on type 2 diabetes: study finds empagliflozin reduces adverse cardiovascular outcomes, which discusses this study in more detail.

The cardiovascular effects of the SGLT-2 inhibitor canagliflozin added to usual care were evaluated in the CANVAS Program (Neal et al. 2017) in people with type 2 diabetes and a history of cardiovascular disease or at high risk of developing it over a median follow-up of 3.6 years. Canagliflozin reduced the risk of the composite end point of death from cardiovascular causes, non-fatal MI or non-fatal stroke (hazard ratio 0.86; 95% CI 0.75 to 0.97). However, it did not statistically significantly reduce the risk of any of these end points individually, nor reduce the risk of death from any cause.

LEADER (Marso et al. 2016) assessed the cardiovascular effects of the GLP-1 mimetic liraglutide as an add-on to standard care in people with type 2 diabetes who had established cardiovascular disease or were at high risk of developing it over a median follow-up of 3.5 years. Liraglutide reduced the composite end point of death from cardiovascular causes, non-fatal MI or non-fatal stroke (hazard ratio 0.87; 95% CI 0.78 to 0.97). However, when these outcomes were analysed individually, only the reduction in risk of death from cardiovascular causes was statistically
significant (hazard ratio 0.78; 95% CI 0.66 to 0.93), not the reduction in risk of non-fatal MI or non-fatal stroke. Liraglutide also reduced the risk of death from any cause (hazard ratio 0.85; 95% CI 0.74 to 0.97). See NICE’s medicines evidence commentary on type 2 diabetes: liraglutide reduces cardiovascular risk in people at high risk of having a cardiovascular event for more details.

In contrast, another study with the GLP-1 mimetic lixisenatide in people with recent acute coronary syndrome (ELIXA, Pfeffer et al. 2015), did not show a reduction in cardiovascular events (including death from cardiovascular causes) or death from any cause over a median follow-up of 2.2 years.

Large studies evaluating the cardiovascular effects of other medicines in these classes are in progress or have been completed but not yet published. DECLARE-TIMI58, evaluating the SGLT-2 inhibitor dapagliflozin, is expected to be competed in April 2019. EXSCEL, evaluating the GLP-1 mimetic exenatide, has been completed but has not yet been published. HARMONY Outcomes, evaluating the GLP-1 mimetic albiglutide, is expected to be completed in February 2018; and REWIND, evaluating the GLP-1 mimetic dulaglutide, is expected to be competed in July 2018.

Safety

The MHRA has highlighted several safety concerns with blood glucose lowering medicines and these are cross referenced in the NICE guideline on type 2 diabetes in adults. For example, warnings about pioglitazone and risks of heart failure, bladder cancer and use in older people have been incorporated into the summaries of product characteristics, and the guideline recommends that pioglitazone should not be offered or continued in adults with heart failure, hepatic impairment, diabetic ketoacidosis, bladder cancer or uninvestigated macroscopic haematuria. The MHRA reported in the January 2011 edition of Drug Safety Update that cases of heart failure have been reported when pioglitazone was used in combination with insulin (especially in people with pre-existing risk factors for developing heart failure). If the combination is used, people should be observed for signs and symptoms of heart failure, weight gain, and oedema; and pioglitazone discontinued if any deterioration in cardiac status occurs.

All the GLP-1-based therapies – that is, GLP-1 agonists and dipeptidylpeptidase-4 (DPP-4) inhibitors (gliptins) – have warnings in their summaries of product characteristics about a risk of developing acute pancreatitis. In the March 2009 edition of Drug Safety Update, the MHRA drew attention to reports of severe pancreatitis and renal failure associated with exenatide (Byetta), and in the September 2012 edition of Drug Safety Update, reports of acute pancreatitis associated with gliptins.
In the April 2016 edition of Drug Safety Update, the MHRA warned about the risk of diabetic ketoacidosis (DKA) with the SGLT-2 inhibitors canagliflozin, dapagliflozin and empagliflozin. Serious and life-threatening cases of DKA have been reported in people taking SGLT-2 inhibitors and, in several cases, blood glucose levels were only moderately elevated, which is atypical for DKA. When treating people who are taking an SGLT-2 inhibitor the MHRA recommends testing for raised ketones in people with ketoacidosis symptoms, even if plasma glucose levels are near-normal. It advises informing people who are being treated with SGLT-2 inhibitors of the signs and symptoms of DKA and advising them to seek immediate medical advice if they develop any of these. SGLT-2 inhibitors should be discontinued immediately if DKA is suspected or diagnosed. Treatment with SGLT-2 inhibitors should also be interrupted in people who are hospitalised for major surgery or acute serious illnesses.

In the March 2017 edition of Drug Safety Update, the MHRA warned that canagliflozin may increase the risk of lower-limb amputation (mainly toes) in people with type 2 diabetes. In the CANVAS Program, the risk of amputation of toes, feet or legs with canagliflozin was 6.3 per 1,000 patient-years, compared with 3.4 per 1,000 patient-years in the control group (hazard ratio 1.97; 95% CI 1.41 to 2.75). In 71% of affected participants the highest level of amputation was the toe or metatarsal. An increased risk of amputation was not seen in studies of dapagliflozin and empagliflozin. However, data are limited and the MHRA advises that the risk could also apply to these other medicines. Preventive foot care, in line with NICE guidance, is important for everyone who has diabetes.

One possible side effect of blood glucose lowering medicines is hypoglycaemia, and controlling blood glucose needs a careful balance between the intensity of the treatment regimen and avoiding hypoglycaemia. NICE's medicines evidence commentary on type 2 diabetes: increased risk of hypoglycaemia with combined use of dipeptidyl peptidase-4 (DPP-4) inhibitors and sulfonylureas discusses a systematic review and meta-analysis which found that adding a DPP-4 inhibitor to a sulfonylurea increased the risk of hypoglycaemia by around 50%. Many of the summaries of product characteristics for blood glucose lowering medicines warn about the increased risk of hypoglycaemia when combining treatments, particularly with a sulfonylurea or insulin, and a lower dose of insulin or a sulfonylurea may be needed.

Several new insulin products have been launched in recent years and the European Medicines Agency issued a risk minimisation strategy for high-strength and fixed-combination insulin products in October 2015. In the April 2015 edition of Drug Safety Update the MHRA issued advice to health professionals to minimise the risk of medication errors with recently launched high strength, fixed combination and biosimilar insulin products. See the key therapeutic topic on safer insulin prescribing for more information.
Blood glucose lowering therapy

Recommendations on blood glucose lowering therapy are given in the NICE guideline on type 2 diabetes in adults. These are summarised in the current algorithm for blood glucose lowering therapy in adults with type 2 diabetes. The recommendations for insulin glargine also apply to any current and future biosimilar product(s) of insulin glargine that have an appropriate marketing authorisation that allows the use of the biosimilar(s) in the same indication. For more information on the insulin glargine biosimilar, Abasaglar, see NICE’s evidence summary on diabetes mellitus type 1 and type 2: insulin glargine biosimilar (Abasaglar).

Practice examples and shared learning

There are NICE shared learning examples relating to type 2 diabetes, showing how NICE guidance and standards have been put into practice by some NHS organisations:

- Evidence-based insulin prescribing in type 2 diabetes.
- PITstop training and the use of NICE guidance and the type 2 diabetes treatment pathway.

Prescribing data, metrics or supporting resources

The selection of metrics to support key therapeutic topics is overseen by the NHS England Medicines Optimisation Intelligence Group, and work is ongoing in this area. At this point, the following prescribing data and metrics have been identified by this group to support this topic.

The NHS Digital report Prescribing for diabetes, England: 2006/07 to 2016/17 found that in the financial year 2016/17 there were 52.0 million items prescribed for diabetes at a total net ingredient cost of £983.7 million. This represents an additional 23.1 million items (80% relative increase) and an additional £411.3 million (72% relative increase) compared with 2006/07. The prescribing of 'other antidiabetic drugs' (which includes the newer blood glucose lowering drugs) has increased considerably in recent years. The number of items prescribed increased by 236% (5.7 million) from 2006/07 to 2016/17 with a growth in net ingredient cost of 213% (£219.5 million).

The net ingredient cost of all insulin therapy in primary care in 2016/17 was £349.1 million; a growth of 43% from 2006/07. In the financial year 2016/17, 1.5 million items of insulin glargine were prescribed at a cost of £82 million, 700,000 items of insulin detemir were prescribed at a cost of £43 million and 80,000 items of insulin degludec at a cost of £6 million. This compared with 600,000 items of NPH (isophane) insulin at a cost of £18 million.
A medicines optimisation key therapeutic topic (MO KTT) prescribing comparator is available – Long-acting insulin analogues.

Several diabetes metrics related to this key therapeutic topic are also included in the Medicines optimisation dashboard, which brings together a range of medicines-related metrics from across sectors. These are:

- Diabetes Mellitus (DM009) % achieving upper threshold or above, which is the percentage of practices in a clinical commissioning group (CCG) that achieve upper threshold or above (92% or more inclusive of exceptions) for quality and outcomes framework (QOF) indicator DM009.

- Diabetes Mellitus (DM009) % underlying achievement, which is the percentage underlying achievement at CCG level for QOF indicator DM009 inclusive of exceptions.

- Emergency diabetes admissions, which is the number of emergency attendances for diabetes per 100 patients on the practice QOF diabetes disease register.

The medicines optimisation dashboard helps NHS organisations to understand how well their local populations are being supported to optimise medicines use and inform local planning. The dashboard allows NHS organisations to highlight variation in local practice and provoke discussion on the appropriateness of local care. It is not intended as a performance measurement tool and there are no targets.

**Update information**

**February 2018:** This topic was retained for the 2018 update of medicines optimisation: key therapeutic topics. The evidence context has been updated in the light of new guidance and important new evidence.

**January 2017:** This topic was retained for the 2017 update of medicines optimisation: key therapeutic topics. The evidence context has been updated in the light of new guidance and important new evidence.

**About this key therapeutic topic**

This document summarises the evidence base on this key therapeutic topic which has been identified to support medicines optimisation. It is not formal NICE guidance.
For information about the process used to develop the Key therapeutic topics, see the integrated process statement.