

Updated NICE guidance on type 2 diabetes management

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Article points

1. The NICE guidelines on the management of type 2 diabetes have been updated and published in their final form following two rounds of consultation.
2. The algorithm in the new guideline incorporates all the available medicine classes to people with type 2 diabetes.

Key words

- Guidelines
- NICE
- Type 2 diabetes

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After consultation of two draft versions, NICE published the final version of the updated type 2 diabetes management guidelines entitled *Type 2 diabetes in adults: management in December 2015*. In this article, the author presents recommendations from the updated guidance and how they might affect clinical care from the primary care perspective.

Although NICE guidelines only apply within England, Wales and Northern Ireland, they are widely studied across the English-speaking World and generally maintain a high reputation. NICE guideline development groups are made up of practising clinicians and academics, health economists and patient representatives, which allows for the sometimes-conflicting priorities of each interest group to be brought together alongside the best available evidence to produce an authoritative guideline to best practice.

Guidelines, guidelines, guidelines

Originally expected in June 2015 but delayed by considerable revisions, the updated NICE guidelines for the management of type 2 diabetes in adults were published in December 2015 and replace clinical guidelines (CG)87 (NICE, 2009). Some readers may remember that CG87 was itself a swift revision of CG66 (NICE, 2008) because of the frequent drug launches at the time.

When considering the requirements of guidelines in general, we would expect them to be clear, credible, practical, consistent and, ideally, resistant to the need for revision for a reasonable length of time (*Box 1*). It is also important to realise the scope of NICE guidelines for diabetes care in particular (*Box 2*). The updated type 2 diabetes guidance known as NICE guideline (NG)28 (2015f) deals with the management of type 2 diabetes in adults. It does not include diabetes diagnosis, as this is covered elsewhere, but it does cross-reference to other guidelines on the management of cardiovascular disease, hypertension and lipids (CG181; NICE, 2014b) and chronic kidney disease

(CG182; NICE, 2014c). There are also specific NICE guidelines that focus on the management of type 1 diabetes (NG17; NICE, 2015e), diabetes in pregnancy (NG3; NICE, 2015b) and diabetes in children and adolescents (NG18; NICE, 2015a).

Why do we have a new guideline?

Since the publication of CG87 (NICE, 2009), probably the most significant developments in the clinical management of type 2 diabetes in primary care relate to an increasing familiarity with new classes of both oral and injectable medications. There has also been a progressive accumulation of evidence regarding type 2 diabetes management to be taken into account. For example, the update clarifies the recommendations regarding the use of antiplatelet agents aspirin and clopidogrel for “primary prevention” of cardiovascular disease (i.e. do not offer antiplatelet therapy for adults with type 2 diabetes who do not have cardiovascular disease), and it also addresses concerns around the risks of hypoglycaemia associated with some treatments.

History of NG28

Before its final publication, NG28 was published in draft in January and June 2015. Both drafts were widely criticised by the Primary Care Diabetes Society (PCDS) and other stakeholder organisations (O’Hare et al, 2015a; 2015b). In particular, clinicians criticised the prominence afforded to repaglinide, a drug of the meglitinide group, which will be familiar to few practitioners in primary care.

Repaglinide works as a short-acting insulin secretagogue – a short-acting version of a sulfonylurea. First produced in the 1990s as

“Novonorm”, it never achieved widespread usage in the UK perhaps because it was thought to offer insufficient benefit to justify its price premium against sulfonylureas. Now the drug is off patent and inexpensive, and its inclusion in the draft guideline was most likely a response to the widespread increase in awareness of the dangers of hypoglycaemia. Whilst particularly related to the use of insulin, hypoglycaemia is also an important possibility with sulfonylurea usage. A shorter-acting insulin secretagogue, such as repaglinide, might be expected to be a safer option than a sulfonylurea but the PCDS and others protested that it was impractical to include such a relatively obscure drug as a mainstay of the guideline, and also that the evidence-base for its effectiveness and safety is relatively poor. It might also be noted that the permanent inclusion of repaglinide would leave the NICE guideline significantly out of step with other international guidance, such as those from the Scottish Intercollegiate Guidelines Network in Scotland, the European Association for the Study of Diabetes and American Diabetes Association. To their great credit, NICE took these points and others on board, and the final version of NG28, whilst inevitably not satisfying all opinion holders, should be widely supported and followed.

Key priorities of NG28

Management of blood glucose

Individualised care

The setting of individualised targets appropriate to each patient is specifically advocated in the updated guidance:

“Involve adults with type 2 diabetes in decisions about their individual HbA_{1c} target. Encourage them to achieve the target and maintain it unless any resulting adverse effects (including hypoglycaemia), or their efforts to achieve their target, impair their quality of life.” (NG28; NICE, 2015f)

This is alongside specific advice to consider the benefits of tighter HbA_{1c} targets for individuals towards the end of their lives. We are rightly encouraged to be holistic in our approach, and whilst this encourages “early intensive management of blood glucose” in those with potentially long life-spans, it also facilitates a more flexible approach

when tight targets are achievable or futile.

Blood glucose monitoring

Advice regarding the provision of blood glucose monitoring is also little changed. It is advocated only for those who are using insulin and those experiencing hypoglycaemia or at specific risk of doing so whilst driving, using machinery or engaging in other activities. In addition those who are, or are considering becoming, pregnant should test according to these guidelines.

The precise interpretation of this advice is likely to vary between practitioners and commissioners. Practitioners denying the use of glucose monitoring to individuals using sulfonylureas need their patients and themselves to be well aware of the potential risks of hypoglycaemia and its possible consequences. From the medical point of view, we know that those most at risk of hypoglycaemia include the elderly, people with poorly controlled diabetes of longer duration and people with renal impairment. Regarding lifestyle and diet, we must be aware of individuals with erratic or irregular eating habits and of the effects of physical activity, intercurrent illness and other physical and emotional influences on glucose control. Frankly, I doubt that any readers of this article, even if they do not drive, would feel confident aiming for optimal glucose control in the absence of blood glucose monitoring when using a sulfonylurea.

My own position is this: I believe that sulfonylureas at modest doses may be used safely and effectively if patients are well-informed and we exclude those in the risk groups mentioned above. In clinic, I offer the most cost-effective available blood glucose monitoring and urge its use before and during prolonged driving or other activities where hypoglycaemia would be dangerous. In addition, I advocate glucose monitoring during intercurrent illness, and following changes to medication, which might potentially trigger hypoglycaemia. Beyond that, individuals may choose to test in order to inform themselves of the effects of their activities and diet; however, this need not be regular or intrusive and should only be undertaken if the results are to be acted upon. Too often tens or hundreds of tests are performed only to be ignored by both patients and clinicians and it is here that sensible economies can be made. I believe my

Box 1. Essential guideline attributes.

- Clarity.
- Consistency.
- Credibility.
- Practicality.
- Longevity.

Box 2. Attributes of NICE guidelines for type 2 diabetes care.

- Diagnosis.
- Blood pressure.
- Lipids.
- Glycaemia.
- Lifestyle.
- Complications.
- Delivery and application.

Box 3. Guidelines on blood glucose targets available from www.nice.org.uk/NG28 (NICE, 2015f), reproduced with permission from NICE.

- For adults with type 2 diabetes managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycaemia, support the person to aim for an HbA_{1c} level of 48 mmol/mol (6.5%). For adults on a drug associated with hypoglycaemia, support the person to aim for an HbA_{1c} level of 53 mmol/mol (7.0%).
- In adults with type 2 diabetes, if HbA_{1c} levels are not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher: reinforce advice about diet, lifestyle and adherence to drug treatment and support the person to aim for an HbA_{1c} level of 53 mmol/mol (7.0%) and intensify drug treatment.
- Consider relaxing the target HbA_{1c} level (see recommendations above) on a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes:
 - who are unlikely to achieve longer-term risk-reduction benefits, for example, people with a reduced life expectancy
 - for whom tight blood glucose control poses a high risk of the consequences of hypoglycaemia, for example, people who are at risk of falling, people who have impaired awareness of hypoglycaemia, and people who drive or operate machinery as part of their job
 - for whom intensive management would not be appropriate, for example, people with significant comorbidities.
- If adults with type 2 diabetes achieve an HbA_{1c} level that is lower than their target and they are not experiencing hypoglycaemia, encourage them to maintain it. Be aware that there are other possible reasons for a low HbA_{1c} level, for example, deteriorating renal function or sudden loss of weight.

approach is in the spirit, if not the exact wording, of this guideline.

What is the guidance on HbA_{1c} targets?

Here I can do no better than to reproduce the

guideline advice (*Box 3*); however, I have visualised the HbA_{1c} target guidelines into an “archery target” which you may find useful (see *Figure 1*).

What agents to use?

Quite reasonably, the guideline suggests making drug choices based on efficacy, safety, suitability to the individual and cost. As it is commonly the case in medicine, there is rarely a single course of action but rather a range of alternatives. The algorithm follows the almost universally accepted first use of metformin if HbA_{1c} exceeds 48 mmol/mol (6.5%) with lifestyle measures alone (*Figure 2*). It reinforces previous advice to initiate metformin treatment in a stepwise manner and to reduce dosage if estimated glomerular filtration rate (eGFR) falls to 45 mL/min/1.73 m² or below, with cessation at an eGFR of 30 mL/min/1.73 m² or worse. Modified-release metformin is allowable if standard preparations are not tolerated, and failing that, pioglitazone, a sulfonylurea or a dipeptidyl peptidase-4 (DPP-4) inhibitor can be given as first-line treatment.

Of note, a NICE technology appraisal evaluating the potential role of sodium–glucose co-transporter 2 (SGLT2) inhibitors as a monotherapy in the treatment of type 2 diabetes is due in mid-2016, which might add another option here.

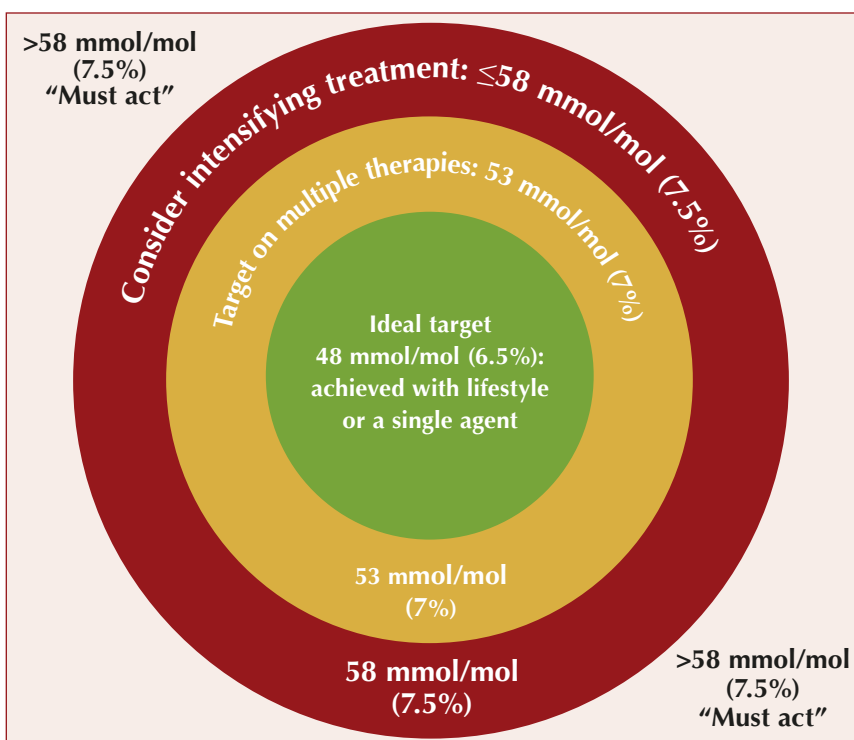


Figure 1. “Archery target” for the HbA_{1c} targets when action is required.

- Reinforce advice on diet, lifestyle and adherence to drug treatment.
- Agree an individualised HbA1c target based on: the person's needs and circumstances including preferences, comorbidities, risks from polypharmacy and tight blood glucose control and ability to achieve longer-term risk-reduction benefits. Where appropriate, support the person to aim for the HbA1c levels in the algorithm. Measure HbA1c levels at 3/6 monthly intervals, as appropriate. If the person achieves an HbA1c target lower than target with no hypoglycaemia, encourage them to maintain it. Be aware that there are other possible reasons for a low HbA1c level.
- Base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, the person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
- Do not routinely offer self-monitoring of blood glucose levels unless the person is on insulin, on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery, is pregnant or planning to become pregnant or if there is evidence of hypoglycaemic episodes.



Abbreviations: ^{DPP-4i}Dipeptidyl peptidase-4 inhibitor, ^{GLP-1}Glucagon-like peptide-1, ^{SGLT-2}Sodium-glucose cotransporter 2 inhibitors, ^{SU}Sulfonylurea. Recommendations that cover DPP-4 inhibitors, GLP-1 mimetics and sulfonylureas refer to these groups of drugs at a class level.

a. When prescribing pioglitazone, exercise particular caution if the person is at high risk of the adverse effects of the drug. Pioglitazone is associated with an increased risk of heart failure, bladder cancer and bone fracture. Known risk factors for these conditions, including increased age, should be carefully evaluated before treatment; see the manufacturers' summaries of product characteristics for details. Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2011) advises that 'prescribers should review the safety and efficacy of pioglitazone in individuals after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated'.

b. Treatment with combinations of drugs including sodium-glucose cotransporter 2 inhibitors may be appropriate for some people at first and second intensification; see NICE technology appraisal guidance 288, 315 and 336 on dapagliflozin, canagliflozin and empagliflozin respectively. All three SGLT-2 inhibitors are recommended as options in dual therapy regimens with metformin under certain conditions. All three are also recommended as options in combination with insulin. At the time of publication, only canagliflozin and empagliflozin are recommended as options in triple therapy regimens. The role of dapagliflozin in triple therapy will be reassessed by NICE in a partial update of TA288. Serious and life-threatening cases of diabetic ketoacidosis have been reported in people taking SGLT-2 inhibitors (canagliflozin, dapagliflozin or empagliflozin) or shortly after stopping the SGLT-2 inhibitor. MHRA guidance (2015) advises testing for raised ketones in people with symptoms of diabetic ketoacidosis, even if plasma glucose levels are near normal.

c. Only continue GLP-1 mimetic therapy if the person has a beneficial metabolic response (a reduction of HbA1c by at least 1.1 mmol/mol [1.0%]) and a weight loss of at least 3% of initial body weight in 6 months) there is no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification.

d. Be aware that if metformin is contraindicated or not tolerated, repaglinide is both clinically effective and cost effective in adults with type 2 diabetes. However, discuss with any person for whom repaglinide is being considered, that there are no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification.

e. MHRA guidance (2011) notes that cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure. It advises that if the combination is used, people should be observed for signs and symptoms of heart failure, weight gain, and oedema. Pioglitazone should be discontinued if any deterioration in cardiac status occurs.

f. The recommendations in this guideline 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.

g. A consultant-led multidisciplinary team may include a wide range of staff based in primary, secondary and community care.

Figure 2. Algorithm for blood glucose-lowering therapy in adults with type 2 diabetes available from www.nice.org.uk/NG28 (NICE, 2015f), reproduced with permission from NICE.

Page points

1. NICE has provided an algorithm which includes all the available anti-diabetes medicine classes for type 2 diabetes.
2. Guidance from NICE on the management of blood pressure has not changed since 2009.
3. More in-depth guidance on the components of a patient education programme is included in NICE guideline 28.

Intensification

If HbA_{1c} rises to 58 mmol/mol (7.5%) on single agent therapy, intensification is advocated, and target HbA_{1c} is set to 53 mmol/mol (7.0%). A “trigger” to further intensify treatment is if HbA_{1c} rises again to 58 mmol/mol (7.5%) or higher. An important message here is that, in otherwise healthy individuals, we should not remain inactive once HbA_{1c} reaches or exceeds 58 mmol/mol (7.5%). The guideline allows a broad choice amongst second-line agents and gives some advice on the benefits and cautions relating to each.

The notable exclusion from the second-line options is the glucagon-like peptide-1 (GLP-1) receptor agonist class, which is only advocated when triple therapy with alternative oral agents is failing. There are alternative opinions suggesting that GLP-1 receptor agonists are better used at an earlier stage for appropriate individuals, and this is one area where I expect some practitioners and specialists to consider deviating from the guideline. Otherwise the conditions for use and continuation of GLP-1 receptor agonists remain the same. Whilst these conditions have been the subject of debate since the previous guideline, there is a very reasonable expectation that we should not continue to use any drug in the absence of benefit – though here many think that the bar has been set rather arbitrarily.

Guidance on the use of insulin is straightforward, suggesting the initial choice of human (NPH) insulin preparations; however, it also allows flexibility for the use of alternatives where justified. The concurrent use of insulin and GLP-1 receptor agonists is subject to “specialist” supervision, though the definition of this is broad enough to include those with the appropriate experience and competence to supervise this combination.

Technology appraisals

As new medications have become available, a number of them have individually been the subjects of NICE technology appraisals. These are directives regarding the use of specific drugs or devices issued separately from clinical guidelines. They are of great importance as their findings must be adopted by Clinical Commissioning Groups and other health service bodies, whereas guidelines are only advisory. Thus a drug recommended for NHS use in a technology

appraisal must be made available to the appropriate patients. This can lead to some apparent confusion. NICE has published technology appraisals on the SGLT2 inhibitors available (dapagliflozin – TA288 [NICE, 2013]; canagliflozin – TA315 [NICE, 2014a]; empagliflozin – TA336 [NICE, 2015d]), so readers of NG28 are directed to read these appraisals for full details of their use; however, the SGLT2 inhibitors are included in their recommended places in the glucose-lowering algorithm (*Figure 2*). It is useful to note here that a number of GLP-1 receptor agonists have also been the subjects of NICE technology appraisals. However in this guideline, NICE has admirably resisted suggesting “change for change’s sake”. Most of the key messages, and indeed much of the detail, of CG87 (NICE, 2009) have been retained. Therefore, we can concentrate on the changes, additions and new emphases within NG28.

Management of blood pressure

Guidance from NICE on the management of blood pressure has not changed since CG87 (NICE, 2009), citing the addition of treatments to obtain a blood pressure below 140/80 mmHg or below 130/80 mmHg if renal, eye or cerebrovascular damage are evident. The current algorithms for the management of blood pressure published by NICE (2011) in CG127 are to be followed to reach these targets.

Patient education

As mentioned in CG87 (NICE, 2009), information and guidance on the effects and management of diabetes should be offered to individuals at the time of diagnosis in an accessible and organised fashion. NG28 again emphasises the importance of “structured patient education”, and Quality and Outcomes Framework is now reporting that the majority of people newly diagnosed with type 2 diabetes are being referred for group education. NG28 clarifies that structured education programmes should follow the components below:

1. The programme is evidence-based and suits to the needs of the individual.
2. The programme has specific aims and learning objectives, and supports the individual and their family and carers in developing the attitudes and tools to self-manage diabetes.
3. The programme has a structured curriculum

that is theory based, evidence based and resource effective, with supportive materials, and is written down.

4. The programme is delivered by trained educators* who understand education theory appropriate to the needs and age of the person.
5. The programme outcomes are to be regularly audited.

Whilst specific educational programmes such as X-PERT and Desmond are available, their cost has dissuaded many commissioners. In my opinion, the guidelines above should, however, be achievable within any locality using available expertise and training. The inclusion of dietary advice is also integral to type 2 diabetes care, so appropriate refresher training must be made accessible and available as benefits individual.

Diabetes complications

In terms of the management of diabetes complications, this guideline generally refers to other more specific documents that exist, for example, for the management of neuropathic pain and diabetes foot complications (NG19; NICE, 2015c). There is some guidance for the management of gastroparesis, a complication perhaps under recognised in the community. Previous guidance relating to eye screening and the management of autonomic neuropathy is carried forward from CG87 (NICE, 2009). The management of erectile dysfunction is specifically discussed with a reminder to consider it as a possible presentation of peripheral vascular disease prior to offering the potentially effective phosphodiesterase type 5 inhibitors. The management of lipids is not specifically dealt with in NG28 as it is covered elsewhere under the umbrella of “cardiovascular risk”.

Antiplatelet agents for primary prevention?

The final specific guidance to mention from NG28 (NICE, 2015f) relates to the benefits or otherwise of routine prescription of antiplatelet agents, aspirin or clopidogrel, to people with type 2 diabetes. For perhaps the first time, we have guidance on this point. Meta-analyses of data regarding this suggest that there is **no benefit** from the

routine use of antiplatelet agents in people with diabetes **unless** there is evidence of established or symptomatic cardiovascular or peripheral vascular disease (Antithrombotic Trialists’ Collaboration, 2002). Further trials, such as the ASCEND (A Study of the Cardiovascular Events in Diabetes) trial in Oxford, are in progress seeking a definitive answer, but for now we have an answer, which may at least reduce the polypharmacy burden for some of our patients slightly!

Final thoughts

In summary, I might apologise for appearing to take a “glucocentric” approach to my review of NG28. However, this largely reflects the emphasis of the guideline itself, in that other priorities relevant to our management of people with diabetes have been largely covered in other guidelines. Following heavy criticism of two drafts and the changes that have been made, NG28 builds on what has gone before, but brings us up to date with new evidence and new options. It is broadly in line with worldwide expert opinion and evidence, and whilst no guideline will satisfy the hopes or opinions of us all, I commend it to you. ■

“The NICE guidelines are broadly in line with worldwide expert opinion and evidence, and whilst no guideline will satisfy the hopes or opinions of us all, I commend it to you.”

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NICE (2015c) *Diabetic foot problems: prevention and management* (NG19). NICE, London

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*The meaning of this phrase is open to hopefully common-sense interpretation.