Improving outcomes in type 2 diabetes

Type 2 diabetes is a major public health issue.[1–3] The prevalence of diabetes in England has increased from 3.3% in 2004/5 to 4.1% in 2008/9.[1] The management of these patients is complex, requiring management of blood glucose, blood lipids, blood pressure, and lifestyle issues. The health and resource burden of managing type 2 diabetes is huge, and contributes to the increasing prescribing costs in the management of blood glucose in primary care in England, from £458.6 million in 2004/5 to £649.2 million in 2009/10.[1]

An individualised approach to the care of people with type 2 diabetes is recommended by NICE.[4] Blood glucose control is one of the many important aspects of that care, and this Bulletin focusses on how to best manage blood glucose in the overall context of preventing both macrovascular and microvascular diabetic complications. More information on other important aspects of the condition — patient education, managing lifestyle, smoking cessation, controlling blood pressure and blood lipids, are available in NPC e-learning materials on type 2 diabetes, and there are ongoing additions to our portfolio of MeReC Rapid Reviews on type 2 diabetes. This Bulletin is aimed at GPs, nurses, pharmacists, prescribing managers and other professionals involved in the care of people with type 2 diabetes.

Summary

- The management of type 2 diabetes is complex. There are many issues to consider when prioritising the needs of an individual patient. Clinicians need to take account of clinical, physical, psychological and social needs, and the individual's own preferences for care.

- Controlling blood glucose requires a careful balance. There are no arguments in favour of poor blood glucose control. However, achieving good blood glucose control, while addressing lifestyle, blood pressure, and blood lipids seems likely to prevent more complications, than a narrower approach focused on intensive blood glucose control.

- If appropriate and achievable in an individual, reducing blood glucose to HbA1c levels of around 7.5% (59mmol/mol) would seem optimal based on current evidence. Lower levels may be appropriate for individuals with early disease.

- The preferred hypoglycaemic drugs recommended by NICE are metformin, a sulfonylurea and human NPH insulin — these interventions have been shown in randomised controlled trials to help patients live longer or better lives.

- Newer hypoglycaemic drugs may have a role in some individuals, but their long term safety is not known and robust evidence that they help patients live longer or better lives is not yet available.

- Progression to triple blood glucose lowering therapy should not be automatic — clinicians should discuss adherence and the risks and benefits of this approach with individual patients.

- In type 2 diabetes, long-acting insulin analogues have few advantages over human NPH insulin, and are expensive. Therefore, they should be targeted for use in specific individual patients. Their widespread use for type 2 diabetes may not represent the best use of resources.

- The NPC QIPP document includes oral hypoglycaemic drugs, long-acting insulin analogues and blood glucose testing strips as key current priorities for medicines management.

All information was correct at the time of publication (June 2011)

Figure 1. Multifactorial management of type 2 diabetes
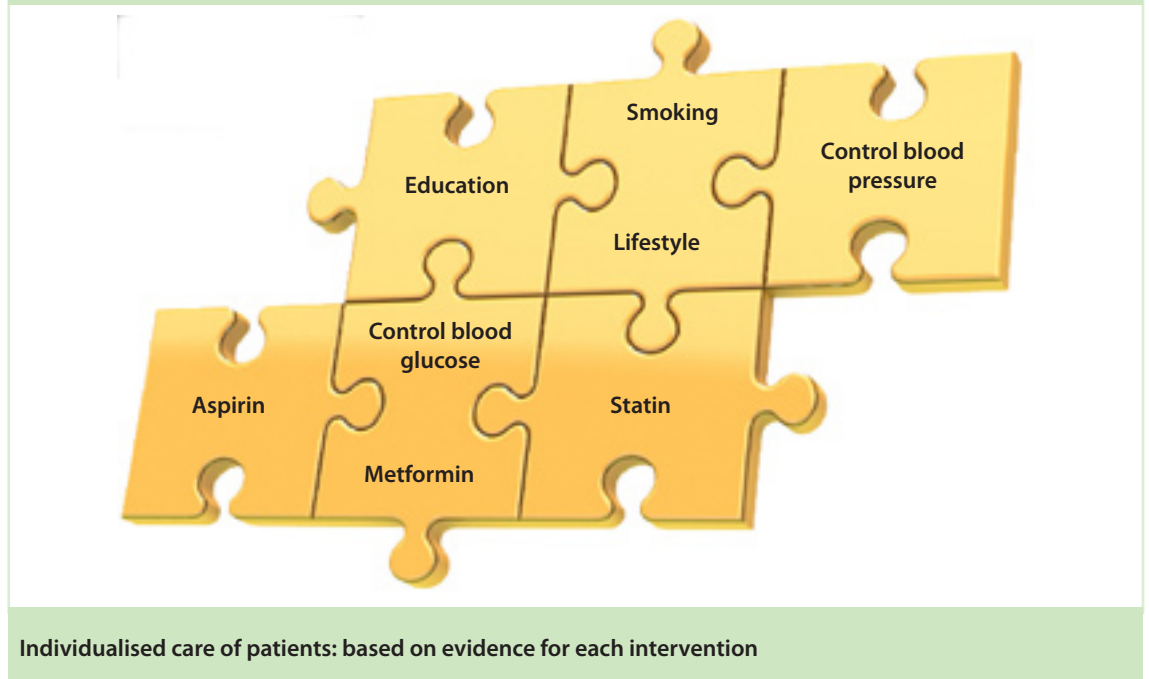
Individualised care of patients: based on evidence for each intervention

Management of type 2 diabetes should not be based on a simple medical model, but requires individualisation of care

What is the impact of type 2 diabetes?

Type 2 diabetes can result in a wide range of complications, including premature death.[5] A large meta-analysis of individual patient data found that a 50-year old with diabetes died, on average, six years earlier than a counterpart without diabetes.[6] Cardiovascular disease is the most common cause of death in type 2 diabetes.[5,7] Type 2 diabetes is also associated with substantial risks of premature death from other causes (e.g. several cancers, infectious diseases).[6] Furthermore, type 2 diabetes causes microvascular complications, such as retinopathy, nephropathy and neuropathy, which can cause substantial morbidity.[4,5]

Panel 1. Case illustration of individualised care of a patient with type 2 diabetes

Susan is 62 years old and recently diagnosed with type 2 diabetes. She has no other significant past medical history. She smokes 20 cigarettes a day, and drinks 28 units of alcohol a week.

Investigations:
- Blood pressure (BP) 152/94 mmHg
- Body Mass Index (BMI) 31 kg/m^2
- High-density lipoprotein cholesterol (HDLC) 0.9 mmol/L
- Low-density lipoprotein cholesterol (LDLC) 2.2 mmol/L
- Total cholesterol (TC) 5.5 mmol/L
- HbA1c 8.1% (65mmol/mol)

What issues would you want to discuss with Susan? See **Panel 2**.

Individualisation of care

The management of type 2 diabetes should not be based on a simple medical model, but requires individualisation of care. As the case illustration in **Panels 1 and 2** shows, there are likely to be many dilemmas when deciding priorities in the care of an individual patient, and clinicians must also take account of physical, psychological and social needs, including the patient's own preferences for care. It is important that the aim of individualised, holistic care is not lost in a drive to improve specific parameters and surrogate markers.

What are the evidence-based priorities?

On a population basis, an evidence-based, multifactorial approach to the management of type 2 diabetes is recommended as illustrated by the jigsaw in **Figure 1**. The different aspects of care, such as lifestyle, smoking cessation, blood pressure, blood lipids, blood glucose etc., need to come together to complete the whole picture of care. However, as **Panels 1 and 2** show, exactly how the pieces fit together will be different for each individual. Targets for all the different aspects of the condition (blood pressure, blood lipids, and blood glucose) can be demanding to reach, and it is essential that the targets are agreed with each patient on an individual basis. Aggressive therapy of each aspect of care may not be appropriate or feasible for every individual patient.

Where does blood glucose control fit within the evidence-based priorities?

Blood glucose control is an important piece of the

Figure 2. Relationship of reductions in cholesterol, blood pressure and HbA1c with improvements in coronary heart disease (CHD)[a] and cardiovascular (CV) outcomes[9]
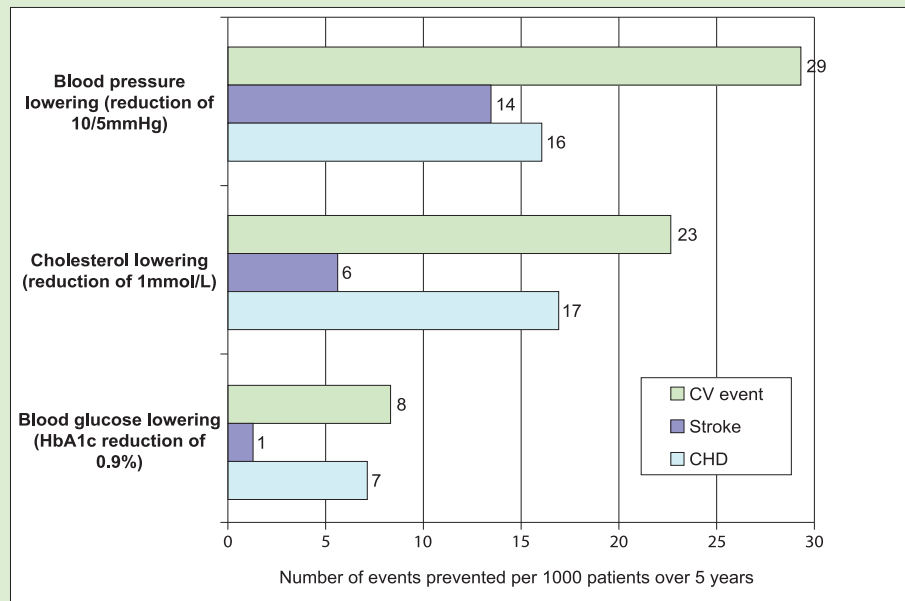

Figure based on Table 1 from Yudkin JS, et al.[9] Data are from CTT meta-analysis[10] (blood pressure lowering), Law MR, et al[11] (cholesterol lowering) and CONTROL meta-analysis[12] (blood glucose lowering). Note that the number of events prevented cannot be added together as the law of cumulative benefits (or diminishing returns) will apply.

[a] CHD is defined as fatal and non-fatal myocardial infarction (MI) and sudden death.

Blood glucose control appears to be less effective in reducing cardiovascular disease than controlling either blood pressure or blood lipids

jigsaw. There are no arguments in favour of poor glucose control, particularly if there are symptoms of hyperglycaemia. Poor glucose control is associated with increased mortality[8,9] and an increased risk of microvascular complications.[5,9] However, blood glucose control appears to be less effective in reducing cardiovascular disease than controlling either blood pressure or blood lipids (see **Figure 2**).[9] For example, for every 1,000 people similar to those recruited to major trials treated with more intensive blood glucose control (HbA1c reduction of 0.9 percentage points), only about eight would avoid a cardiovascular event, compared with about 23 in every 1,000 whose cholesterol is reduced by 1mmol/L and about 29 in every 1,000 whose blood pressure is reduced by 10/5mmHg.[9] The effectiveness of different interventions in reducing microvascular complications is less clear, but similarly, blood glucose control may be less effective than blood pressure control.[13–15]

What is optimal blood glucose control?

Although blood glucose control is very important, pursuing intensive control (HbA1c less than 6.5% [48mmol/mol]), particularly at the expense of other priorities would seem inappropriate,[8,16] and is not recommended by NICE.[4] Many experienced clinicians are now calling for a change in the emphasis of care of people with type 2 diabetes, to prioritise lifestyle interventions and cardiovascular risk reduction ahead of intensive blood glucose control alone,[9,17–19] particularly in older patients who often have other cardiovascular risk factors.[9] A holistic approach to an individual patient's care, deploying maximal lifestyle interventions (stopping smoking, losing weight, taking more exercise),

Panel 2. Potential priorities for Susan

The following areas (not in order of importance) are the traditional priorities:

- Adherence
- Blood pressure
- Cardiovascular risk assessment
- Diet
- Education about type 2 diabetes
- Exercise
- Lower HbA1c
- Self monitoring of blood glucose
- Smoking cessation
- Statin
- Weight loss

However, Susan has many different priorities. She is concerned about her grandson who is in trouble with the police. She has lost friends and social contact since retirement. Her husband is "dull" and not interested in her. How will these issues affect your discussions with Susan?

Table 1. The estimated effects of intensified blood glucose control (mean additional HbA1c reduction of 0.9 percentage points) on mortality, cardiovascular and advanced microvascular event rates[9]

Outcome	Hazard ratio (95%CI)	Reduction/increase in events per 1,000 treated patients over 4.4 years (95%CI)	NNT/NNH over 4.4 years (95%CI)
CHD[a]	↓0.90 (0.82 to 0.99)	↓6.3 (0.6 to 11.3)	NNT 159 (88 to 1599)
Stroke	0.96 (0.83 to 1.10)	No significant difference	
All-cause mortality	1.04 (0.90 to 1.20)	No significant difference	
Cardiovascular mortality	1.10 (0.84 to 1.42)	No significant difference	
Severe hypoglycaemia	↑2.48 (1.91 to 3.21)	↑41.7 (25.8 to 61.7)	NNH 24 (16 to 39)
Blindness in one eye/severe loss of vision	0.94 (0.80 to 1.10)	No significant difference	
Renal replacement therapy, renal failure or death from renal causes	0.88 (0.70 to 1.11)	No significant difference	

Table adapted from Yudkin JS, et al.[9] Data are derived from UKPDS 33,[13] ACCORD,[16,25] ADVANCE,[21] VADT[22] and CONTROL[12] meta-analysis. Absolute differences and numbers needed to treat (NNT) or numbers needed to harm (NNH) are shown for statistically significant results only.
a   Fatal and non-fatal MI and sudden death

Overall, intensive compared with conventional blood glucose control does have some benefits, but it also has harms

controlling blood pressure, taking a statin, and taking metformin, seems likely to prevent more complications than a narrow focus on attempting to achieve intensive (rather than good) blood glucose control.

What are the recommendations?

The Quality and Outcomes Framework (QOF) has changed. For 2011/12, QOF awards points for achieving three levels of glucose control — HbA1c of 7.5% or less, 8% or less, and 9% or less. The lower level of 7.5% (59mmol/mol) has replaced the previous lower level indicator of 7% (53mmol/mol), following recommendations from the NICE QOF Advisory Committee.[20] However, the committee noted that this 'audit target' may be different from the target an individual clinician may use with an individual patient.[20] NICE has also published quality standards on diabetes in adults.

NICE guidance on type 2 diabetes recommends that patients should be involved in setting their individualised HbA1c target level, **which may be above the general target of 6.5%** (48mmol/mol).[4] NICE emphasises that any reduction in HbA1c towards the agreed target level is advantageous to future health, but **pursuing highly intensive management to HbA1c levels below 6.5% (48mmol/mol) should be avoided** (see below).[4]

**What does the evidence say about intensifying blood glucose control?**

The evidence on intensive compared with conventional blood glucose control in type 2 diabetes comes from four key randomised controlled trials (UKPDS 33,[13] ACCORD,[16] ADVANCE[21] and VADT[22]), which are analysed in the CONTROL meta-analysis.[12] UKPDS 10-year follow-up data[23] are also available, although there are inherent

biases in observational follow-up data.[24] Overall, intensive compared with conventional blood glucose control does have some benefits, but it also has harms.

Taken altogether, the data show that intensive control to reduce HbA1c by an additional 0.9 percentage points over standard control significantly reduced the risk of coronary heart disease (approximately 6 fewer CHD events per 1,000 patients over 4.4 years), but the observed reduction in the risk of stroke was not statistically significant (see **Table 1**).[9] Some trials have shown a reduction in certain microvascular events with intensive blood glucose control,[13,21] but other studies have shown no such benefit, particularly with regard to advanced renal or eye complications.[21,22,25]

In terms of harms, intensive blood glucose control increased the risk of severe hypoglycaemia (approximately 42 extra events per 1,000 patients over 4.4 years).[9] In the ACCORD study, intensive blood glucose control was associated with an increased risk of death (5.01% vs. 3.96%, hazard ratio [HR] 1.22, 95% confidence interval [CI], 1.01 to 1.46, NNH 95 over an average of four years),[16] although there was no statistically significant effect on mortality in the CONTROL meta-analysis.[12]

Figure 3. Adjusted hazard ratios for all-cause mortality by HbA1c deciles in people given metformin plus a sulfonylurea (A) and insulin-based therapy (B)[8]
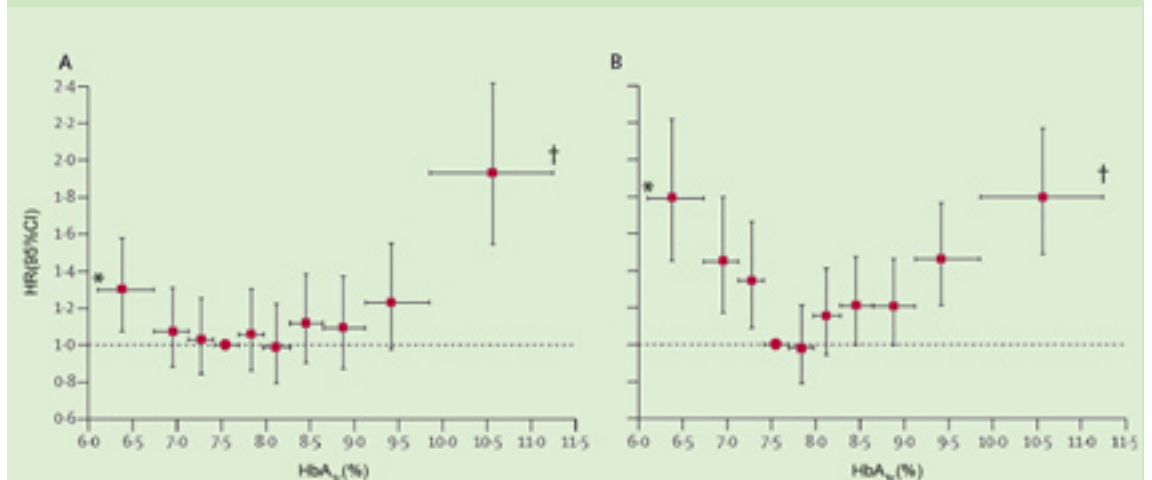
Vertical error bars show 95%CIs, horizontal bars show HbA1c range.
Red circle = reference decile. *Truncated at lower quartile. †Truncated at upper quartile

A 'keep it simple and safe' approach seems appropriate for the initial management of blood glucose

Not too little, not too much

At what point does continuing to lower HbA1c levels stop having a benefit and actually start increasing risk? — i.e. what is the optimal range of values for HbA1c to achieve the lowest morbidity and mortality in type 2 diabetes?

A large retrospective cohort study based on UK GP prescribing data by Currie, et al,[8] identified a 'U-shaped' relationship between HbA1c levels and mortality in people with type 2 diabetes in whom oral hypoglycaemic drug treatment had been intensified. An HbA1c of about 7.5% (59mmol/mol) was associated with the lowest risk of all-cause mortality, with higher or lower levels associated with greater risk (see **Figure 3**). This relationship was apparent regardless of whether treatment was intensified with oral hypoglycaemic agents or with insulin. However, intensifying treatment with insulin-based therapy was associated with greater risk of all-cause mortality than intensifying treatment with oral hypoglycaemic drugs (HR 1.49, 95%CI 1.39 to 1.59, P<0.0001).[8] See MeReC Rapid Review No. 1017 for more details.

Keep it simple and safe whenever possible

Health professionals should continue to follow NICE guidance[4] and agree individual HbA1c targets with the patient, taking account of the patient's own preferences and the balance of likely benefits and burden of treatment. As we demonstrated in **Panels 1 and 2**, there are likely to be many competing priorities so a 'keep it simple and safe' approach seems appropriate for the initial management of blood glucose. If a patient's HbA1c can be reduced to about 7.5% (59mmol/mol) by diet, other lifestyle measures and/or treatment with metformin and/or a sulfonylurea, this would seem optimal based on current evidence.
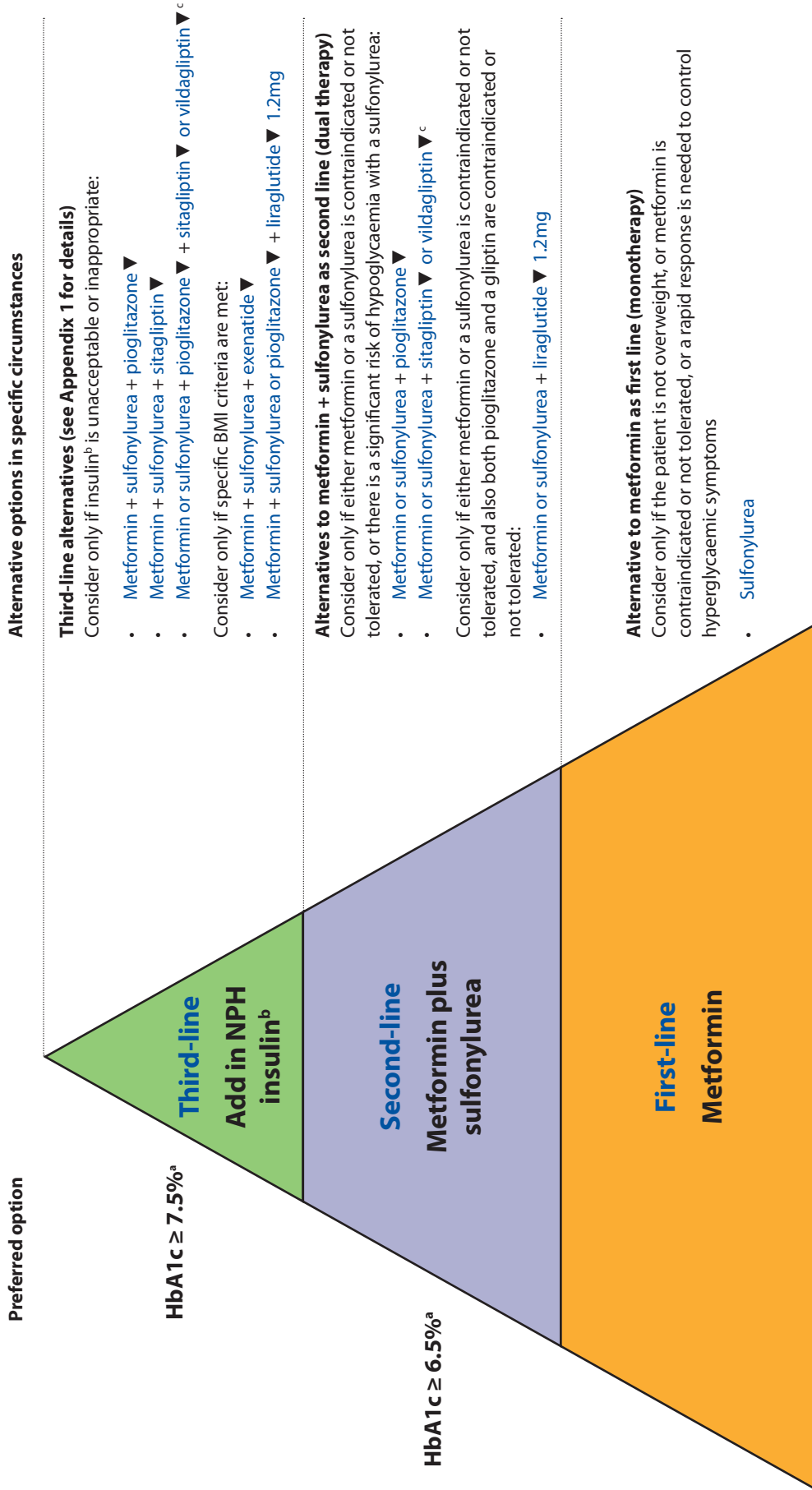
There are some data to suggest that there may be additional benefits of a lower HbA1c target in younger patients with earlier disease. The 10-year follow up of UKPDS,[23] a study performed in newly diagnosed patients, showed that the effect of intensified blood glucose control on cardiovascular disease was about twice that calculated by Yudkin and colleagues in patients with more advanced disease.[9] In a subgroup analysis of the CONTROL meta-analysis, there was a significant benefit in major cardiovascular events with more intensive control in patients with less than five years duration of diabetes, but not in patients with longer duration.[12] However, despite intensive treatment, UKPDS showed that HbA1c levels will increase over time as the disease progresses.[13]

Hypoglycaemic drugs — what are the options?

What does NICE recommend?

Metformin is the first-choice hypoglycaemic drug in type 2 diabetes, with a sulfonylurea as an alternative in certain circumstances.[4] See **Figure 4**. If blood glucose control is inadequate on monotherapy (HbA1c above 6.5% [48mmol/mol] **or other higher agreed level**), dual therapy with metformin and a sulfonylurea is the preferred second-line therapy. Their use is supported by long-term data from UKPDS,[23] and two large systematic reviews found that metformin and sulfonylureas achieve better or similar effects compared to the newer hypoglycaemic drugs.[27,28] If a person is still markedly hyperglycaemic on dual therapy (HbA1c above 7.5% [59mmol/mol] or other higher agreed level), the preferred third-line option is to add human NPH insulin to metformin and a sulfonylurea.[4]

Figure 4. Summary of NICE recommended treatment options for blood glucose lowering in type 2 diabetes[4,26]

Preferred option

Alternative options in specific circumstances

Third-line
Add in NPH insulin[b]

HbA1c ≥ 7.5%[a]

Third-line alternatives (see Appendix 1 for details)
Consider only if insulin[b] is unacceptable or inappropriate:

- Metformin + sulfonylurea + pioglitazone ▼
- Metformin + sulfonylurea + sitagliptin ▼
- Metformin or sulfonylurea + pioglitazone ▼ + sitagliptin ▼ or vildagliptin ▼ [c]

Consider only if specific BMI criteria are met:

- Metformin + sulfonylurea + exenatide ▼
- Metformin + sulfonylurea or pioglitazone ▼ + liraglutide ▼ 1.2mg

Second-line
Metformin plus sulfonylurea

HbA1c ≥ 6.5%[a]

Alternatives to metformin + sulfonylurea as second line (dual therapy)
Consider only if either metformin or a sulfonylurea is contraindicated or not tolerated, or there is a significant risk of hypoglycaemia with a sulfonylurea:

- Metformin or sulfonylurea + pioglitazone ▼
- Metformin or sulfonylurea + sitagliptin ▼ or vildagliptin ▼ [c]

Consider only if either metformin or a sulfonylurea is contraindicated or not tolerated, and also both pioglitazone and a gliptin are contraindicated or not tolerated:

- Metformin or sulfonylurea + liraglutide ▼ 1.2mg

First-line
Metformin

Alternative to metformin as first line (monotherapy)
Consider only if the patient is not overweight, or metformin is contraindicated or not tolerated, or a rapid response is needed to control hyperglycaemic symptoms

- Sulfonylurea

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[a] Or other higher agreed level.
[b] Long-acting insulin analogues (insulin detemir or insulin glargine) are alternatives to NPH insulin only in specific circumstances – see **Appendix 1**.
[c] Saxagliptin was not included in NICE clinical guideline 87.

See NICE's algorithm on blood glucose lowering drugs and the NICE pathway on managing type 2 diabetes for all treatment options.
For more detail on the recommendations see clinical guideline 87[4] and technology appraisal 203.[26]

Table 2. Summary comparison of the newer hypoglycaemic drugs[a]

	Positives	Negatives
Glitazones pioglitazone▼ (*rosiglitazone withdrawn 2010*)	• Oral • Similar HbA1c reductions to metformin or sulfonylurea[3,31,32]	• No convincing evidence that patient-oriented outcomes (POOs) are positively influenced[31,32] • Safety concerns include heart failure[33] (particularly in combination with insulin),[34] fractures,[35] possible association with bladder cancer with pioglitazone,[36] ischaemic heart disease with rosiglitazone[33] • Weight gain[3] • Cost
Gliptins (DPP-4 inhibitors) saxagliptin▼ sitagliptin▼ vildagliptin▼	• Oral • Similar HbA1c reductions to glitazones[37] • No weight gain[37]	• No POO data[37] • No long term safety data[37] • Cost • Safety concerns include skin disorders, pancreatitis with sitagliptin and vildagliptin, hypersensitivity reactions and acute renal failure with sitagliptin, liver dysfunction with vildagliptin[a]
GLP-1 mimetics exenatide▼ liraglutide▼	• Similar HbA1c reductions to insulin[37] and some other comparators[26] • Weight loss[26,37]	• Parenteral • No POO data from RCTs[26,37,38] • No long term safety data[26,37] • Cost • Severe pancreatitis and renal failure with exenatide[39]
Insulin analogues insulin detemir insulin glargine	• Similar HbA1c reductions to insulin[37] • Less nocturnal hypoglycaemia than insulin[37]	• Parenteral • No POO data[37] • No long term safety data[37] • Cost (very high cost per QALY)[37] • Insulin glargine – possible association with cancer[40,41]

a See Summaries of Product Characteristics (SPCs) for full product information.

Newer hypoglycaemic drugs are effective at reducing HbA1c levels, but they all lack robust clinical outcome data

What is the role of the newer hypoglycaemic drugs?

Many new hypoglycaemic drugs have been introduced over recent years, all of which may have a role for certain individual patients with type 2 diabetes who require further blood glucose control. However, these are all usually third-line options.[4] See **Figure 4** for a summary of NICE's recommendations and **Appendix 1** for additional information.

Progression to triple hypoglycaemic therapy should not be automatic — clinicians and patients should discuss adherence with existing therapies and carefully weigh the potential benefits of a further reduction in HbA1c, against the risks of adding another drug. NICE has produced guidance on medicines adherence to enable patients to make informed choices by involving and supporting them in decisions about prescribed medicines.[29] Patients being considered for third-line therapy are already likely to be taking a statin, antihypertensives, and aspirin if appropriate, as well as first- and second-line hypoglycaemic agents. Clinicians need to consider the law of cumulative benefits (or diminishing returns)[30] and discuss with individual patients what additional improvement in outcomes might be gained from adding in a third hypoglycaemic drug in absolute terms, and how this may affect their quality of life.

How do the newer hypoglycaemic drugs compare?

Table 2 summarises the main pros and cons of the newer hypoglycaemic drugs. More detail on the evidence can be found in Parts 4b and 4c of the recently updated NPC e-learning workshop on type 2 diabetes.

Although the newer hypoglycaemic drugs are effective at reducing HbA1c levels, they all lack robust clinical outcome data, particularly around their cardiovascular effects, and long term safety data in people with type 2 diabetes (see **Table 2**). Improvements in surrogate markers (e.g. HbA1c levels) do not automatically confer benefits on patient mortality or morbidity, as highlighted with the withdrawal of rosiglitazone due to increased cardiovascular risks.[42] There are currently no robust data from large RCTs on the effect of adding any of these third-line treatments on improving patient-oriented outcomes (POOs) — i.e. helping people to live longer and/or healthier lives. People with diabetes are already at an increased risk of cardiovascular disease, and the

Expensive insulin analogues are increasingly prescribed instead of human NPH insulin

aim of treatment is to reduce these risks, not simply improve surrogate markers. Except for the long-acting insulin analogues, all the newer drugs are 'Black Triangle' drugs under intensive surveillance by the MHRA, and any suspected adverse reactions should be reported via the Yellow Card Scheme.

What about long-acting insulin analogues?

As we have discussed, the preferred basal insulin in type 2 diabetes is human NPH insulin. Long-acting insulin analogues (insulin detemir, insulin glargine) are newer insulins that have been recommended by NICE in specific patient circumstances (see **Appendix 1**).[4] However, for most people with type 2 diabetes, long-acting insulin analogues offer no significant advantage over human NPH insulin and are much more expensive.[43] An association between higher doses of insulin glargine and cancer has been suggested in some studies, but current evidence is conflicting.[40,41] The results of further trials are expected in 2011/12. [Personal communication, Sanofi Aventis 2010]

Despite lack of evidence of benefit in POOs in type 2 diabetes, expensive insulin analogues are increasingly prescribed instead of human NPH insulin. In the majority of PCTs, more than 80% of all intermediate or long-acting insulin items (excluding biphasic insulins)

are long-acting insulin analogues and in many PCTs the proportion is more than 90%.[44] A NICE health economic analysis found that the incremental cost per QALY (compared with human NPH insulin), taking into account the reduced risk of hypoglycaemia, was greater than £100,000 in all modelling scenarios, and in some cases in excess of £400,000.[4] This is substantially greater than the £20,000 to £30,000 per QALY threshold usually considered in NICE's cost-effectiveness evaluations.

Quality, Innovation, Productivity and Prevention (QIPP)

Given the increasing prevalence and costs of managing people with type 2 diabetes, it is important to consider carefully the role of newer hypoglycaemic drugs. The NPC QIPP document includes recommendations to review, and where appropriate, revise prescribing of oral hypoglycaemic drugs, long-acting insulin analogues and blood glucose testing strips, to ensure prescribing is in line with NICE guidance.[45] See the NHS Diabetes report on self monitoring of blood glucose in non-insulin-treated type 2 diabetes for more information.[46] QIPP prescribing parameters are now available from the NHS Business Services Authority to support prescribers and organisations with local implementation.[44]

Appendix 1. Additional information on newer hypoglycaemic drugs[4,26]

Second-line therapy

• Only consider if HbA1c remains **above 6.5% (48mmol/mol) or other higher agreed level**.

• Pioglitazone, sitagliptin and vildagliptin should be continued only if the person has a beneficial metabolic response (a reduction in HbA1c of at least 0.5 percentage points [5.5mmol/mol] at six months).

• Liraglutide 1.2mg should be continued only if stricter conditions are achieved (a reduction of at least one percentage point [11mmol/mol] in HbA1c at six months).

Third-line therapy

• Only consider if HbA1c remains **above 7.5% (59 mmol/mol) or other higher agreed level**.

• Sitagliptin or pioglitazone are an option provided the person has a beneficial metabolic response (see above).

• Liraglutide or exenatide should be considered only if BMI ≥35 kg/m^2 in people of European descent and there are problems associated with high weight, or if BMI <35 kg/m^2 and insulin is unacceptable because of occupational implications or weight loss would benefit comorbidities.

• Liraglutide or exenatide should be continued only if stricter metabolic conditions are achieved (a reduction of at least one percentage point [11mmol/mol] in HbA1c and a weight loss of at least 3% of initial body weight at six months).

• Long-acting insulin analogues may be considered as an alternative to human NPH insulin if the patient needs assistance from a carer or health professional to inject insulin, and use of a long-acting insulin analogue would reduce the frequency of injections from twice to once daily, or the patient's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes, or the patient would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs, or the patient cannot use the device to inject NPH insulin.

References

1. NHS Information Centre. Prescribing for Diabetes in England: 2004/05 to 2009/10. July 2010
2. Currie CJ, et al. Dispensing patterns and financial costs of glucose-lowering therapies in the UK from 2000 to 2008. Diabetic Medicine 2010;27:744–52
3. NICE. Type 2 diabetes. Full guideline 66. May 2008
4. NICE. The management of type 2 diabetes. Clinical guideline 87. May 2009
5. Clinical Knowledge Summaries. Diabetes type 2. Last revised July 2010
6. The Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose and risk of cause-specific death. N Engl J Med 2011;364:829–41
7. BHF. British Heart Foundation statistics. Mortality from diabetes. January 2009
8. Currie CJ, et al. Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study. Lancet 2010;375:481–89
9. Yudkin JS, et al. Intensified glucose lowering in type 2 diabetes: time for a reappraisal. Diabetologia 2010;53:2079–85
10. CTT Collaboration. Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008;371:117–25
11. Law MR, et al. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338:b1665
12. CONTROL writing group. Intensive glucose control and macrovascular outcomes in type 2 diabetes Diabetologia 2009;52:2288–98
13. UKPDS Group. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–53
14. UKPDS Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854–65
15. UKPDS Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;31:703–13
16. ACCORD Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–59
17. Montori VM, Fernández-Balsells M. Glycaemic control in type 2 diabetes: time for an evidence-based about-face? Ann Intern Med 2009;150:803–08
18. Lehman R, Krumholz HM. Tight control of blood glucose in long standing type 2 diabetes. BMJ 2009;338:b800
19. Yudkin JS, et al. Intensified glucose control in type 2 diabetes — whose agenda? Lancet 2011;377:1220–02
20. NICE. NM14 NICE QOF Advisory Committee recommendations. August 2010
21. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–72
22. VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–39
23. Holman R, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–89
24. NPC. Using evidence to guide practice — Supplement. MeReC Briefing 30, September 2005
25. Ismail-Beigi F, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010;376:419–30
26. NICE. Technology appraisal 203. Liraglutide for the treatment of type 2 diabetes mellitus. October 2010
27. Bolen S, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med 2007;147:386–99
28. Selvin E, et al. Cardiovascular outcomes in trials of oral diabetes medications. A systematic review. Arch Intern Med 2008;169:2070–80
29. NICE. Medicines adherence. Clinical guideline 76. January 2009
30. Timbie JW, et al. Variation in the net benefit of aggressive cardiovascular risk factor control across the US population of patients with diabetes mellitus. Arch Intern Med 2010;170:1037–44
31. Richter B, et al. Pioglitazone for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD006060. DOI: 10.1002/14651858.CD006060. pub2
32. Richter B, et al. Rosiglitazone for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD006063. DOI: 10.1002/14651858.CD006063. pub2
33. MHRA. Glitazones for diabetes. December 2007
34. MHRA/CSM. Insulin combined with pioglitazone: risk of cardiac failure. Drug Safety Update 2011;4(6):A2
35. MHRA/CSM. Rosiglitazone and pioglitazone: cardiovascular safety and fracture risk. Drug Safety Update 2007;1(3):10
36. European Medicines Agency. Press release: Update on ongoing European review of pioglitazone–containing medicines. 9th June 2011.
37. NICE. Type 2 diabetes. Short clinical guideline 87. May 2009
38. NPC. MeReC Rapid Review No. 2171. Limited observational evidence for CV risk reduction with exenatide ▼. December 2010
39. MHRA/CHM. Exenatide (Byetta ▼): risk of severe pancreatitis and renal failure. Drug Safety Update 2009;2(8):6
40. MHRA/CHM. Insulin glargine (Lantus): studies of possible cancer link. Drug Safety Update 2009;3(2):3–4
41. Mannucci E, et al. Doses of insulin and its analogues and cancer occurrence in insulin-treated type 2 diabetic patients. Diabetes Care 2010;33:1997–2003
42. Drug and Therapeutics Bulletin. Playing the numbers game. DTB 2011;49(1):1
43. Drug and Therapeutics Bulletin. Which insulin, regimen and device in type 2 diabetes? DTB 2010;48(12):134–38
44. NHS Business Services Authority. QIPP prescribing comparators. QIPP charts and data. Quarter to December 2010
45. NPC. Key therapeutic topics 2010/11 – Medicines management options for local implementation. First update February 2011
46. NHS Diabetes working group. Self monitoring of blood glucose in non-insulin-treated type 2 diabetes. March 2010