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The new NICE guidelines for type 2 diabetes – a critical analysis

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Abstract

"Common sense is not so common"
– Voltaire (1694–1778)

The latest NICE guidelines for the management of type 2 diabetes are now available for consultation. They contain sensible recommendations regarding lifestyle, patient education, monitoring and targets.

Unfortunately, the pharmacotherapy section shows a distinct failure of common sense. The recommendations include using the insulin secretagogue repaglinide as a first-line agent, where metformin is not tolerated or contraindicated, or second-line in combination with metformin. Pioglitazone is recommended as the principal second-line therapy with metformin. The advice on glucagon-like peptide-1 receptor agonist (GLP-1ra) usage and assessment of efficacy and failure to recommend long acting analogue insulins over isophane are also major concerns.

The recommendations appear to be based on meta-analyses and pharmacoeconomics, driven by an imperative on costs and failing to appreciate the "value" of the options under consideration. The cost to patients and the health service of the serious side-effects of these treatments is underestimated.

Given the emphasis in these guidelines on the importance of lifestyle changes, including weight loss, plus an over-riding need to avoid hypoglycaemia, these pharmacotherapeutic recommendations appear paradoxical in the extreme.

We believe that these recommendations, if enacted, will undermine seriously the reputation of NICE both nationally and internationally.

Abbreviations and acronyms

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADA	American Diabetes Association
BMI	Body mass index
DPP4	Diptidyl peptidase 4
EASD	European Association for the Study of Diabetes
GLP-1ra	Glucagon-like peptide-1 receptor agonist
GP	General practitioner
HbA1c	Glycated haemoglobin
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
SGLT2	Sodium glucose co-transporter 2
VADT	Veterans Administration Diabetes Trial
WHO	World Health Organisation

Introduction

The long awaited revision and updating of the NICE guidelines for type 2 diabetes has now been released for consultation.[1] The task was never going to be easy for the guideline development group, given the complexity and sheer volume of research data around a plethora of new and old therapies and the need to update advice on screening, patient education and monitoring. Drawing together and selecting the evidence and applying complex methods of analysis, each tailored to the technology under scrutiny, has clearly been a mammoth task.

Good in parts

Some parts of the report make good sense: namely lifestyle advice, patient education, monitoring and targets. These include supporting and defining "structured education", although "little robust evidence of the effectiveness of any particular educational approach for people with type 2 diabetes was found",[2,3] plus audit and customisation of the evidence-based programme to the needs of the person.

With dietary advice presently based on limited evidence, the recommendations make much of the importance of diet and exercise in supporting glycaemic control, but do not suggest changing current practice. There is a strong recommendation for longer-term trials to be undertaken to test the long-term efficacy and safety of low carbohydrate diets.

The guideline development group recognises the increasing cost pressures of blood glucose monitoring and the failure of well-

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designed trials[4] to show that feedback from this measurement improves overall glycaemic control. Monitoring may improve wellbeing for some patients, however, and is clearly useful as a safety measure when considering hypoglycaemia. They suggest that monitoring in type 2 diabetes patients is only necessary for those at risk from hypoglycaemia. There is economic sense in following this recommendation for an average commissioning group in the UK that spends £1.5m on glucose monitoring and £3.5m on drugs. Clearly, if enacted, any weaning off for many patients who have become psychologically dependent on the activity needs to be carried out with respect and sensitivity.

The guidelines development group is also pragmatic on the issue of targets, with a suggested HbA_{1c} target of 48 mmol/mol (6.5%), but with a more realistic target of 53 mmol/mol (7.0%) when drugs that can produce hypoglycaemia are introduced. Moreover, they agree that targets need to be customised to meet "the complexities of individual patient needs".[1] It seems perverse, however, to follow the recommendation of waiting until HbA_{1c} rises to >58mmol/mol (7.5%) before intensification (shades of the "waiting for failure" approach of traditional diabetes management?). Additionally, recommendations to customise and tailor treatment to individual needs and safety are welcome, but paradoxically do not seem to have been applied to the choice of pharmacotherapy!

On reviewing the evidence for intensification of glycaemic control, the guidelines development group describes clear evidence for reduced risk of microvascular complications and amputations (at least in recently diagnosed patients). The "jury is still out" regarding cardiovascular protection, however; in particular, there remain significant concerns regarding serious hypoglycaemia and its consequences, especially for older, longer-duration high-risk patients.

A serious failure of common sense?

On the major issue of guidance on drug treatment to control blood glucose, the consultation document demonstrates a failure of common sense and clinical judgement. In our opinion, the draft proposals are so out of kilter with current recommendations for "best practice" that, if enacted, they will reduce quality of care and patient safety and will set back modern diabetes management by decades. At best, it is our belief that most clinicians will ignore the recommendations or "pay lip service" to them, thus undermining the valuable role NICE can play in giving clear, credible, and cost effective advice. An additional concern would also be that of Commissioning bodies taking up the guidance or enforcing it without proper consultation with clinicians.

Direct insulin secretagogues

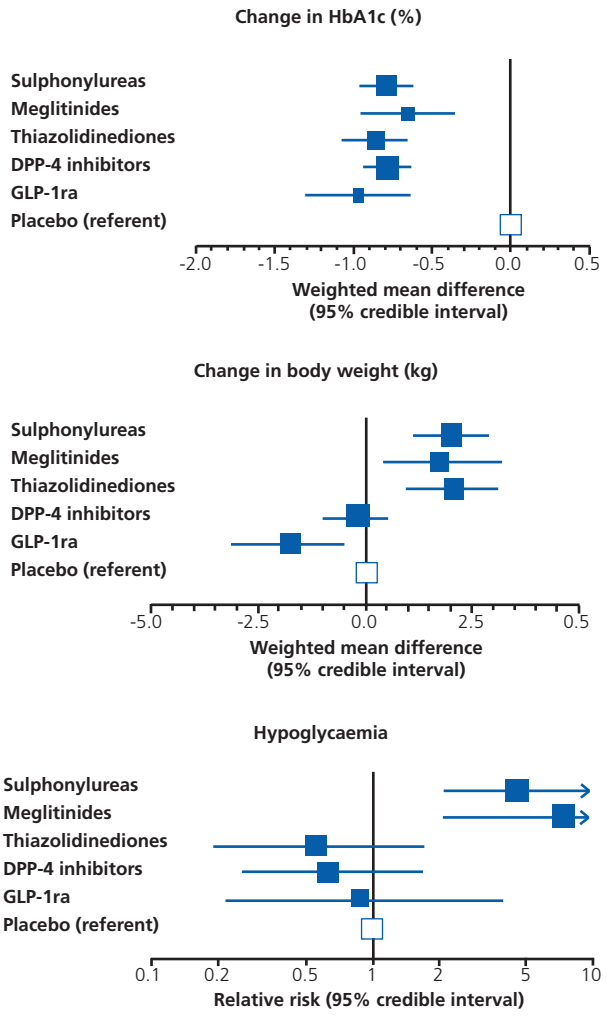
The guidelines development group appears to accept that sulphonylureas should no longer be the automatic second-line treatment following metformin, a practice that most clinicians have moved on from, which represents a clear recognition of the side-effects and potential dangers of these drugs. Sulphonylureas can cause significant weight gain and dramatically increase the risk of hypoglycaemia compared with other oral agents[5,6] and patients should monitor for this (although many do not). These drugs may still have some place in the drug armamentarium, but this should be at later stages of intensification and with careful selection and monitoring. The danger of hypoglycaemia associated with sulphonylureas is of particular concern for the elderly and/or people with renal impairment. In a recent audit, patients taking a sulphonylurea accounted for 33% of admissions for hypoglycaemia to an Accident and Emergency department among people with type 2 diabetes.[7] The frail elderly were at particularly high risk, for whom 1-year all-cause mortality was an alarming 28%.

The UK Hypoglycaemia Study Group highlighted the extent of the problem by evaluating prospectively the incidence of hypoglycaemia over 9–12 months in a study funded by the Department of Transport and conducted in six different regions of the UK.[8] They found that 40% of patients on sulphonylureas and 50% on insulin experienced symptomatic hypoglycaemia during this time. The risk of a severe hypoglycaemic episode (requiring 3rd party help) in type 2 diabetes patients over the first two years of treatment was essentially identical for those on a sulphonylurea versus insulin (7% in each group). In addition, all these patients underwent two separate episodes of continuous glucose monitoring each for 72 hours: 22% of patients on sulphonylureas and 20% of patients on insulin recorded glucose values below 2.2 mmol/L for more than 20 minutes – many were unaware of their hypoglycaemia and many were car drivers!

Given the above concerns, it seems most surprising that the insulin secretagogue, repaglinide, is recommended first-line for those who cannot tolerate metformin and as a possible second-line combination agent, on the basis of a complex network meta-analysis using results from a small number of clinical trials[9] and the health economic analysis. These trials need to be judged against the overwhelming evidence from and experience of clinicians and patients across the world who have researched and used these agents and judged them to have significant limitations, i.e. three-times daily dosing (likelihood of massive reduction in adherence rates), increased risk of hypoglycaemia and promote weight gain (like all drugs that secrete insulin in a non-glucose dependent fashion).[9] Indeed, a recent meta-analysis comparing a range of antidiabetes agents clearly shows that the risk of hypoglycaemia with repaglinide is at least as great as that with sulphonylureas, with similar weight gain (Figure 1).[10]

The WHO recognises that adherence rates for drugs for chronic diseases are only 50% after one year.[11] It is estimated that, in Europe, this costs 125 billion Euros and contributes to 200,000 deaths per annum.[12] Patients report poor tolerability (side-effects) as the single most common reason for non-adherence,[13] with hypoglycaemia and weight gain cited as being fundamental to this problem in type 2 diabetes.[14] In addition, advising a "best practice" target of 48 mmol/mol for HbA_{1c} and then admitting this should not be strived for (for good reason) in patients taking drugs which can cause hypoglycaemia is a clear admission that patients on the therapies recommended by NICE (repaglinide and sulphonylureas) will be disadvantaged compared with those taking alternatives which do not cause this problem!

Figure 1. Effects of insulin secretagogues, pioglitazone and incretin-based antidiabetic therapies on HbA_{1c}, body weight and the risk of hypoglycaemia from a meta-analysis of 27 randomised, controlled trials in patients with type 2 diabetes sub-optimally controlled by metformin.
Adapted from Phung *et al*.[10]



Pioglitazone

What possible sense is there in recommending pioglitazone as the principal second-line agent to metformin? The consultation document takes us into the paradoxical situation where diet and exercise with weight loss are recommended as fundamental to the management of type 2 diabetes, while simultaneously promoting two drugs that promote weight gain as alternatives to/combination partners for metformin. Indeed, this is a major problem of the thiazolidinedione class.[5] Additionally, we have the cardiovascular safety issue with rosiglitazone with its subsequent withdrawal from the European market, as well as class effects such as fluid retention, aggravated heart failure (due in part to sodium retention), fractures and even the arguable possibility of increased risk of bladder cancer. One can only conclude that the guidelines development group has not given enough weight to these potentially serious side effects and safety concerns (widely recognised by MHRA warnings, the summary of product characteristics for the agent and the cautions expressed in the ADA-EASD guidelines) because pioglitazone is now generic and cheap and scores highly on their economic modelling.

Incretin-based therapies

Whilst the consultation document recognises the value of GLP-1ra therapies, including the potential for significant weight loss, they still stand by the non-evidence-based recommendation of only using these injectables in people with BMI >35 kg/m^2. There is a "get-out" clause which allows clinicians to use them at a lower BMI where "weight loss would benefit other significant obesity-related comorbidities". And yet the value of introducing a GLP-1ra in the obese to try to produce weight loss early on in the treatment pathway is commented on and left to clinician's discretion. The advice to use the least expensive option at first appears sensible, but evidence is emerging that there are clinically important differences between the shorter and longer duration agents.[15,16] Customising GLP-1ra to patients' needs may be an important part of their effective and safe use in therapy. Advising the use of GLP-1ra (or DPP-4 inhibitors) with the lowest acquisition costs might also be problematic given the more limited licence, differences in recommendations in patients with renal impairment and the much smaller worldwide clinical experience when compared with more expensive agents from the same class.

In addition, the recommendation that GLP-1ra should be stopped unless both weight loss and HbA_{1c} criteria are met seems illogical. We know from experience that some patients will drop their HbA_{1c} dramatically with this therapy but will not lose 3% weight, while others may lose much weight but may have a smaller drop in their HbA_{1c}. Common sense supports reviewing the efficacy of these relatively expensive treatments, but with a balanced approach.[16]

We also take issue with the recommendation that GLP-1ra/insulin combinations can only be commenced within specialist care. This combination is much easier to use than insulin intensification regimes, which many GPs undertake frequently. This recommendation seems difficult to justify when the NHS is promoting more practice-based care for type 2 diabetes in the community.

Insulin

The consultation document recognises throughout that hypoglycaemia, including serious hypoglycaemia, may accompany intensification of insulin. Nevertheless, the document recommends isophane insulin initially, with a switch to basal analogues only after suffering hypoglycaemia on isophane. This goes against all Hippocratic principles of avoiding harm and doing one's best for the individual patient and it is extremely difficult to understand the rationale for this beyond cost. And yet, we are encouraged to discuss options with patients and to fully brief

them on the choice and side effects of all treatments. Clearly, NICE accepts that the longer-acting insulins cause less hypoglycaemia as they recommend their use in type 1 diabetes for this reason. So why the continued discrimination against type 2 patients? Why do these patients have to prove they need the newer insulins by first suffering hypoglycaemia? Many studies, such as ACCORD and VADT, suggest that hypoglycaemia in vulnerable groups may contribute to mortality and significant morbidity.[17,18]

Most clinicians in the UK use long-acting analogues out of concern for patient safety and despite the previous guidance. It is a missed opportunity for NICE to truly recognise the severity and frequency of hypoglycaemia in type 2 diabetes and to recommend those treatments that minimise hypoglycaemia, particularly when these agents will soon come off patent.

Sequence selection

At present, major controversies in type 2 diabetes relate to the order and combination in which the different classes of oral and injectable antidiabetes agents are introduced. Not surprisingly, given all the caveats around these drugs, the flow diagrams are complex and confusing, and lack the simplicity of the recent ADA-EASD guidelines.[19] There is also little attempt to place the newest agents, the SGLT2-inhibitors, into these diagrams despite the fact that they have already had single technology appraisals by NICE and are already widely used. The same could be said about incretin-based therapies in general.

Conclusion

This consultation document contains some valuable recommendations in areas of diabetes care, but there seem to have been serious failures of common sense in the key area of which drugs and combinations to use in type 2 diabetes patients after or instead of metformin.

The complex network meta-analyses used are only fit for purpose when sensible clinical judgement provides the context for their use, and takes into account the very good reasons why most clinicians have abandoned the use of repaglinide and why many are fearful or extremely cautious regarding the use of pioglitazone. The consultation document demonstrates a clear disregard for the evidence, from both scientific studies and peer usage, and would have benefitted from the addition of some common sense to guide it towards appropriate recommendations. This also applies to the recommendations surrounding the use of injectables, including insulin.

It is our firmly-held view that these recommendations need re-evaluation. The guidelines development group may need strengthening with clinicians prepared to be advocates for patient safety and ready to apply common sense and practical judgement. Alternatively, the simplest and possibly best way forward would be for NICE to adopt and recommend the excellent ADA-EASD guideline[19] for the management of glycaemia.

We believe that adoption of the recommendations from the NICE Advisory Group for the management of glycaemia will seriously undermine the reputation of NICE both nationally and internationally.

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Dr W Hanif: University Hospital Birmingham, UK. Duality of interests: Chair, South Asian Health Foundation; research and travel grants and consultancy fees from Novo Nordisk, Sanofi, AstraZeneca, Merck and Boehringer Ingelheim Allianz

D Hicks: Nurse Consultant, Diabetes for Barnet, Enfield and Haringey Mental Health Trust; Co-chair of Training Research and Education for Nurses on Diabetes (TREND). Duality of interests: Worked with Novo Nordisk, Lilly, AstraZeneca, MSD, Abbott, Janssen, Roche and BD on advisory boards and provided presentations at conferences sponsored by the pharmaceutical industry.

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Professor SC Bain: Professor of Medicine (Diabetes), Swansea, UK. Duality of interests: Abbott, AstraZeneca/BMS, Boehringer Ingelheim, Eli Lily, GSK, MSD, Janssen, Novartis, Novo Nordisk, Sanofi, Takeda, Servier, Roche, Pfizer.

Professor AH Barnett: Emeritus Professor of Medicine, University of Birmingham and Consultant Physician, Heart of England NHS Foundation Trust, Birmingham, UK. Duality of interests: honoraria and lecture fees from AstraZeneca, MSD, Boehringer Ingelheim, Takeda, Novartis, Janssen, Eli Lilly, Sanofi, Novo Nordisk

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References

1. NICE. Type 2 diabetes: guideline consultation 2015. https://www.nice.org.uk/guidance/gid-cgwave0612/resources/type-2-diabetes-guideline-consultation2 (Accessed January 2015)
2. Khunti, K, Gray LJ, Skinner T, *et al*. Effectiveness of a diabetes education and self-management programme (DESMOND) for people with newly diagnosed type 2 diabetes mellitus: three year follow-up of a cluster randomised controlled trial in primary care. *BMJ* 2012;**344**:e2333. http://dx.doi.org/10.1136/bmj.e2333
3. Deakin TA, Cade JE, Wiliams R, Greenwood DC. Structured patient education: the Diabetes X-PERT Programme makes a difference. *Diabet Med* 2006 23;**9**:944-54. http://dx.doi.org/10.1111/j.1464-5491.2006.01906.x
4. Farmer A, Wade A, Goyder E, *et al*. Impact of self-monitoring of blood glucose in the management of patients with non-insulin treated diabetes: open parallel group randomised trial. *BMJ* 2007;**225**:132. http://dx.doi.org/10.1136/bmj.39247.447431.BE
5. Viberti G, Kahan SE, Greene DA, *et al*. A diabetes outcome progression trial (ADOPT): an international multicentre study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. *Diabetes Care* 2002;**25**:1737-43. http://dx.doi.org/10.2337/diacare.25.10.1737
6. Leese GP, Wang J, Broomhall J, *et al*. for the DARTS/MEMO Collaboration. Frequency of severe hypoglycaemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. *Diabetes Care* 2003;**26**:1176-80. http://dx.doi.org/10.2337/diacare.26.4.1176
7. Rajendran R, Hodgkinson D, Rayman G. Patients with diabetes requiring emergency department care for hypoglycaemia: characteristics and long-

term outcomes determined from multiple data sources. *Postgrad Med J* 2015 (in press). http://dx.doi.org/10.1136/postgradmedj-2014-132926
8. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia* 2007;**50**;1140-7. http://dx.doi.org/10.1007/s00125-007-0599-y
9. Shah ZH, Saleem KO. A comparative study of repanglinide and glibenclamide in type 2 diabetic patients. *Pakistan J Med Health Sci* 2011;**5**:476-9.
10. Phung OJ, Scholle JM, Talwar M, Coleman CL. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycaemic control, weight gain, and hypoglycaemia in type 2 diabetes. *JAMA* 2010;**303**:1410-18. http://dx.doi.org/10.1001/jama.2010.405
11. World Health Organisation. Adherence to long term therapies. Evidence for action. Switzerland, 2003.
12. Just what the doctor ordered: a EU response to medication non-adherence. Tuesday 28 September 2010, Bibliotheque Solvay, Brussels.
13. Grant RW, Devita NG, Singer DE, Meigs JB. Polypharmacy and medication adherence in patients with type 2 diabetes. *Diabetes Care* 2003;**26**:1408-12. http://dx.doi.org/10.2337/diacare.26.5.1408
14 Khunti K, Davies M. Glycaemic goals in patients with type 2 diabetes: current status, challenges and recent advances. *Diabetes Obes Metab* 2010;**12**:474-84. http://dx.doi.org/10.1111/j.1463-1326.2009.01186.x
15. Robinson LE, Holt TA, Rees K, *et al*. Effects of GLP-1 agonists on heart rate, blood pressure and body weight: Systematic review and meta-analysis. *BMJ Open* 2013;**3**:pii:e001986. http://dx.doi.org/10.1136/ bmjopen-2012-001986
16. Thong KY, Gupta PS, Cull ML, *et al*. GLP-1 receptor agonists in type 2 diabetes – NICE guidelines versus clinical practice. *Br J Diabetes Vasc Dis* 2014;**14**:52-9. http://dx.doi.org/10.15277/bjdvd.2014.015
17. Gerstein HC, Miller ME, Genuth S, *et al*. Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med* 2011;**364**: 818-28. http://dx.doi.org/10/1056/NEJMoa1006524
18. Skyler JS, Bergenstal R, Bonow RO, *et al*. Intensive glycaemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Diabetes Care* 2009;**32**:187-92. http://dx.doi.org/10.2337/dc08-9026
19. Inzucchi SE, Berganstal RM, Buse JB, *et al*. Management of hyperglycemia in type 2 diabetes, 2015: A patient-centered approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015;**38**:140-9. http://dx.doi.org/10.2337/dc14-2441