Insulin: standard therapy following oral hypoglycaemic failure in type 2 diabetes?

The cost burden of managing type 2 diabetes and its complications could overwhelm the NHS in the next 20 years. The available therapies should be used wisely to conserve resource and maintain health. This article outlines a strategy for use of the available treatments.

Type 2 diabetes and its management represent a significant challenge to our health service: 2.9 million people in the UK have been diagnosed with diabetes (Diabetes UK, 2012) and this is predicted to rise to 5 million by 2025. This is equivalent to 400 people being diagnosed every day (Diabetes UK, 2012).

Type 2 diabetes comes with significant mortality and morbidity and a detrimental impact on quality of life. A diagnosis of diabetes confers a threefold increased risk of cardiovascular disease in men and a fourfold increased risk in women, and a diagnosis at the age of 40 years is associated with a lifespan reduction of 7 years (Goodkin, 1975; Donnelly et al, 2000). Diabetes remains the most common cause of blindness in those of working age (Diabetes UK, 2012), is the single most common cause of end-stage renal failure (Diabetes UK, 2012), and is the most common cause of major lower limb amputation (Diabetes UK, 2012).

Once preventative strategies have failed the goals for diabetes treatments must be to reduce the burden of morbidity and premature mortality and to improve quality of life for those living with this condition. Treatments must also be cost effective such that widespread access to high quality therapies is assured within our ever more cash-constrained NHS.

For the purposes of this article it is assumed that the case for lipid and blood pressure-lowering therapies is already accepted in this context. Cost per quality-adjusted life year data showing that blood pressure-lowering therapy saves $790 for each person with one quality-adjusted life year gain and lipid-lowering therapy costs between $40 000 and 55 000 per quality-adjusted life year for those aged 40–75 years (CDC Diabetes Cost effectiveness Group, 2002). This article will therefore focus on the role of glycaemic control strategies in achieving these goals.

Glycaemic control as an appropriate goal

First we have to be realistic about what we can achieve with tight glycaemic control. In the UK Prospective Diabetes Study (UKPDS) trial, a policy of tight glycaemic control from diagnosis achieved a mean glycosylated haemoglobin (HbA_{1c}) of 7% (53 mmol/mol) over a period of 10 years against a mean HbA_{1c} of 7.9% (63 mmol/mol) in a conventional control group (UK Prospective Diabetes Study (UKPDS) Group, 1998a,b). At 10 years there was a 25% relative risk reduction in the predetermined microvascular events of retinopathy or renal failure which was highly significant (P=0.0099) and a reduction in the relative risk of myocardial infarction of 16% of borderline significance (P=0.052). This equates to a number needed to treat of 20 patients over 10 years with an intensive glucose control policy to prevent any diabetes-related end point, although a less impressive figure of 119 patients over 5 years to prevent one myocardial infarction (UK Prospective Diabetes Study (UKPDS) Group, 1998a,b).

Ten-year follow-up data confirm the long-lasting benefits of this early tight glycaemic control policy (Holman et al, 2008) with the relative risks of adverse outcomes maintained despite the fact that within 1 year of study end the HbA_{1c} in both intervention and non-intervention groups equalized. The 15% reduction in the relative risk of myocardial infarction in the insulin and sulphonylurea group was now statistically significant (Holman et al, 2008).

The data also indicate that while the relationship between vascular disease and HbA_{1c} appears to be linear (Stratton et al, 2000), that between HbA_{1c} and microvascular complications appears exponential, a fact that should be considered in relation to the timing and proposed benefits of therapy intensification.

Despite these data the benefits of tight glycaemic control have been thrown into some doubt by a succession of studies designed to define the cardiovascular benefits of glycaemic control. In the ADVANCE and ACCORD studies individuals with established type 2 diabetes and cardiovascular disease risk factors randomized to the intervention groups received intensive glucose control strategies designed to achieve an HbA_{1c} ≤6.5% or 6% respectively (Action to Control Cardiovascular Risk in Diabetes Study Group et al, 2008; ADVANCE Collaborative Group et al, 2008). In the VADT study poorly controlled military veterans in the intervention group were treated to achieve HbA_{1c} 1.5% lower than that of the standard control group (achieving mean HbA_{1c} 6.9% *vs* 8.4%) (Duckworth et al, 2009). In none of these studies did the

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glucose-lowering intervention lower the risk of major cardiovascular events or death and ACCORD, the study with the most stringent target for glycaemic control, was stopped early because of increased mortality.

There were significant differences in the approaches used to achieve glycaemic control across these three studies and the VADT study population had significantly different baseline characteristics from the other two. One of the major differences between these studies and the UKPDS is that in UKPDS subjects were treated and followed from diagnosis rather than having treatment intensification many years after diagnosis following substantial periods of poor control. Hypoglycaemia induced by rapid tightening of control and drug regimens involving multiple agents are likely to have been key determinants of the unexpectedly poor outcomes.

Importantly none of the major studies has looked at those over the age of 70 years, meaning that the evidence base may not apply to 46% of those currently treated for type 2 diabetes. Is it then possible to pick through the data and the apparent contradictions and come up with sensible goals for intervention on glycaemic control such that we can better frame the debate on the optimal strategy with which to achieve this?

Some rudimentary conclusions for type 2 diabetes are laid out below which might influence interpretation of the National Institute for Health and Clinical Excellence (2009) guidance (*Figure 1*).

If the patient is under the age of 60 years at diagnosis of type 2 diabetes then aiming for HbA_{1c} < 53 mmol/mol (7%) from diagnosis, with a treatment strategy based on metformin first line augmented by sulphonylurea and/or insulin therapy as indicated, has long-lasting and worthwhile benefits in terms of reducing both microvascular and macrovascular complications, although the benefits on macrovascular disease are modest (UK Prospective Diabetes Study (UKPDS) Group, 1998a,b; Nathan et al, 2005; Holman et al, 2008; Diabetes UK, 2012).

Looking at the lifetime risks of microvascular complications, this approach seems reasonable in those up to 65 years of age (Vijan et al, 1997; Diabetes UK, 2012):

- Once advanced macrovascular or microvascular complications are established, while improvements in glycaemic control may be beneficial, aiming for really tight glycaemic control is unlikely to be so and targets should be individualized on this basis
- More complex treatment regimens targeting tight glycaemic control using multiple hypoglycaemic agents may increase mortality (Goodkin, 1975; Donnelly et al, 2000; Action to Control Cardiovascular Risk in Diabetes Study Group et al, 2008)
- If diabetes is diagnosed in someone aged >70 years the benefits of tight glycaemic control are limited
- The benefits of tighter glycaemic control must always be balanced against the risks of hypoglycaemia. In a treatment escalation strategy the threshold at which the next change is made must take this into account.

Which agents should be used?

Having decided on target glycaemic thresholds for intervention at different stages we are left with the dilemma as to which agents to choose and when. National Institute for Health and Clinical Excellence (2009) guidance suggests that the accepted norm would be to start with a trial of lifestyle change followed by metformin monotherapy, dual oral therapy with metformin and a sulphonylurea and then progression to isophane insulin in combination with oral therapy as beta cell failure progresses (Diabetes UK, 2012). A number of caveats allow for the use of alternative regimens in specific circumstances.

The contention of this article is that the assumed normal treatment progression outlined by the National Institute for Health and Clinical Excellence remains the only evidence-based treatment strategy in terms of hard clinical outcomes and should therefore remain the norm for the majority of patients unless there are specific individual patient factors dictating a different approach.

Metformin as initial therapy

The evidence supporting metformin as the initial treatment choice in type 2 diabetes is convincing and well accepted. In the UKPDS sub-study of 1704 individuals who exceeded 120% of their ideal body weight, the group assigned to a strategy based on metformin as initial therapy demonstrated reductions in diabetes-related deaths (32%), all-cause mortality (36%) and myocardial infarction (39%) by study end with respect to usual care, all of these effects being greater than those reductions based on sulphonylurea therapy as a first-line agent (UK Prospective Diabetes Study (UKPDS) Group, 1998a; Diabetes UK, 2012).

These benefits in mortality reduction have been replicated in a number of different studies in those with diabetes (CDC Diabetes Cost-effectiveness Group 2002; Johnson et al, 2002, 2005; Tzoulaki et al, 2009; Diabetes UK, 2012), diabetes and vascular disease (UK Prospective Diabetes Study (UKPDS) Group 1998a,b; Jørgensen et al, 2010; Roussel et al, 2010), and diabetes and heart failure (UK Prospective Diabetes Study (UKPDS) Group 1998a,b; Evans et al, 2010). Importantly these studies also confirmed that the com-

Figure 1. Suggested minor amendments to glycaemic targets in the National Institute for Health and Clinical Excellence (2009) guidance for type 2 diabetes.

1. If age <65 years at diagnosis then a glucose control strategy to achieve a target glycosylated haemoglobin (HbA_{1c}) <48 mmol/mol (6.5%) for monotherapy with metformin and <53 mmol/mol (7%) with dual oral therapy (sulphonylurea added to metformin in the majority of cases) optimizes benefits and risks
2. When stepping up glycaemic control with a third agent a target of 58 mmol/mol (7.5%) is reasonable
3. If diabetes is diagnosed in someone aged >70 years the benefits of tight glycaemic control are very limited. Given its safety and beneficial effects metformin monotherapy might still be considered at a similar stage as in younger individuals but less stringent targets should be applied before second- or third-line agents are used

bination of metformin with sulphonylureas was not harmful, putting to bed any concerns over a slightly anomalous result from the UKPDS data.

No other agent can lay claim to such benefits and as metformin also remains the cheapest treatment option the case is securely made.

Second-line agents: value added?

What then of the potential second-line agents? Here the waters are somewhat more murky and cost is very much part of the equation.

The average glucose-lowering efficacy is very similar across all the second-line agents and some individuals may respond more favourably to some agents than others, usually with very limited if any ability to identify in advance which agent will have the greatest effect. The goal then is to identify which agents have an added benefit.

Sulphonylureas

Sulphonylureas, most commonly gliclazide in the UK, are the recommended usual choice and the most commonly used agents. They come with a low price tag, well known side-effect profile, familiarity and robust clinical data as to their use from the UKPDS study (Holman et al, 2008; UK Prospective Diabetes Study (UKPDS) Group, 1998b). While the studies referenced in the previous section broadly confirm the superiority of metformin over sulphonylureas as monotherapy (although gliclazide performs better than other sulphonylureas; Holman et al, 2008; Jørgensen et al, 2010), the data from Saskatchewan suggest that provided an individual is on metformin, the addition of a sulphonylurea does not increase mortality (Stratton et al, 2000; Johnson et al, 2002, 2005).

The key here is being aware of the side-effect profile of sulphonylureas and choosing your glycaemic targets. The key concern is avoiding hypoglycaemia, the presence of which can predict a number of adverse outcomes (UK Hypoglycaemia Study Group, 2007; Action to Control Cardiovascular Risk in Diabetes Study Group et al, 2008; ADVANCE Collaborative Group et al, 2008; Dluhy and McMahon, 2008). From the data available, aiming for an HbA_{1c} of 7% with these agents when pursuing more stringent control, asking about hypoglycaemia and monitoring as clinically indicated seems a reasonable strategy for avoiding the pitfalls of these agents while pursuing the benefits of early good control.

Pioglitazone

Pioglitazone is now the only thiazolidenedione in the UK, following the withdrawal of rosiglitazone because of concerns over an increased risk of myocardial infarction. Pioglitazone appears to have a favourable risk profile in terms of ischaemic heart disease. The PROACTIVE study demonstrated a 16% relative risk reduction (2.1% absolute risk, number needed to treat 50) in the secondary end point of all-cause mortality, myocardial or stroke at 3 years (Dormandy et al, 2005; Duckworth et al, 2009). There was an increase in events coded as heart failure but no increased risk of death from heart failure, suggesting that these episodes were related to the well-known effect of thiazolidenediones on increasing fluid retention. These findings are supported by data from the general practice research database interrogated by Tzoulaki et al (2009) to look at outcomes related to the use of different oral treatments. They found that pioglitazone use (alone or in combination) was associated with a 31–39% reduction in all-cause mortality compared to metformin monotherapy and a non-significant increased risk of heart failure.

Pioglitazone has not become routinely used as second-line therapy, however, partly because of its price, but also because of its potential to exacerbate heart failure, its associated effects on weight gain and because of more recent concerns over its association with the development of bladder cancer and the increased risk of fractures of the distal radius seen in women. Now this medication is out of patent the price is likely to fall and it will be interesting to see how those drawing up guidance documents will interpret the risks and benefits.

Dipeptidyl peptidase-4 inhibitors

These have not yet been the subject of randomized controlled trials with cardiovascular or mortality end points but, as a result of new US Food and Drug Administration guidance, both saxagliptin and linagliptin have had to include cardiovascular safety data as part of their development programme and both appear to have potentially beneficial profiles on the basis of a systematic review of outcomes in phase 3 trials in the case of saxagliptin (Frederich et al, 2010), and a pre-specified meta-analysis of phase 3 trials in the case of linagliptin (Johansen et al, 2012). All four agents appear well tolerated, have few side effects and are weight neutral. Three of the agents can be used in patients with end-stage renal failure, although dose adjustments are required for vildagliptin and sitagliptin as they both exhibit partial renal excretion.

Insulin *vs* glucagon-like peptide-1 analogues as second- or third-line agents

Both insulins and glucagon-like peptide-1 (GLP-1) analogues may be considered in some situations as second-line agents (Inzucchi et al, 2012) despite their positioning by National Institute for Health and Clinical Excellence (2009). For the purposes of this article it is assumed that they are being considered, as per the National Institute for Health and Clinical Excellence guidance, when oral hypoglycaemic agents have failed to achieve or maintain the individualized glycaemic targets set for the individual with diabetes.

So which factors should we taken into consideration? Ultimately mortality, quality of life, safety, cost efficacy and the acceptability of the treatment to the patient are the primary end points on which we should focus.

Individual factors which are often considered separately but which significantly impact the outcomes above are weight gain and hypoglycaemia risk.

Insulin

Insulin is the third-line agent against which all others are judged, because it is the treatment modality with which we have the most experience and most hard end point data.

Insulin was the second- or third-line agent (depending on treatment arm) used to obtain tight glycaemic control in the UKPDS study and there are hard end point data on mortality and complication rate reduction from this study (UK Prospective Diabetes Study (UKPDS) Group 1998a,b; Stratton et al, 2000). Insulin was used alongside metformin and sulphonylureas to obtain tight glycaemic control in the Steno-2 study (Gaede et al, 2003) (NPH insulin once daily in combination with oral therapy in 45% of the treatment cohort) which achieved >50% reduction in cardiovascular and microvascular end points (number needed to treat = 5) over 7.8 years of follow up when an intensive multiple risk factor intervention approach was used. These benefits were still evident a further 5.5 years later (Gaede et al, 2008).

An intensive approach to glycaemic control did not enhance or diminish quality of life although the development of complications had an adverse impact (King et al, 2001).

Insulin therapy is safe and well tested over many years. The major safety concern with insulin therapy is the occurrence of hypoglycaemia (UK Hypoglycaemia Study Group, 2007). In type 2 diabetes the frequency of hypoglycaemic episodes described in those treated with insulin for <2 years was no different to that seen with sulphonylurea use and much less frequent than seen in type 1 diabetes (severe hypoglycaemia 0.1–0.2 episodes per person per year in type 2 diabetes *vs* 1.1–3.2 in type 1 diabetes). Hypoglycaemia risk is also dependent on the glycaemic target set and is thus modifiable if appropriate attention is paid such that insulin can be used safely in the vast majority of individuals (UK Hypoglycaemia Study Group, 2007).

Concerns regarding the likelihood of weight gain on initiation of insulin therapy are often cited when other options are chosen. However, it is important to understand and explain to patients the principal factors driving this. Weight gain is seen in association with therapies which improve glycaemic control by augmenting prevailing insulin concentrations. This effect is almost entirely caused by correction of metabolic inefficiencies of relative insulin deficiency and poor glycaemic control, and weight gain can be significantly ameliorated by using insulin in combination with metformin (Mäkimattila et al, 1999).

Weight gain on insulin initiation is reported to run at 2 kg for every 11 mmol/mol improvement in HbA_{1c} (Mäkimattila et al, 1999). However, this is by no means inevitable. The Northumbria diabetes team provide a pre-insulin assessment service and group insulin start service. The pre-insulin assessment service supports maximization of lifestyle and self-management strategies and its use has avoided the need for insulin in 64% of patients because they improved control and achieved targets (Oliver, 2009). This demonstrates the importance of paying due attention to lifestyle measures at this crucial point in decision making. The insulin start service contains a number of options to minimize weight gain on insulin initiation and on review of the efficacy of this approach over 2008–10 demonstrated a 1.7 kg weight gain for a 20 mmol/mol improvement in HbA_{1c}, with 33% of patients losing weight as well as improving control at 9 months (Forrest et al, 2012).

Acknowledging the potential for weight gain while then taking direct measures to counter it through ongoing education appears to be an effective strategy and one which, if more widespread in use, might lead to less trepidation around insulin initiation (Forrest et al, 2012).

Finally, insulin therapy is certainly cheaper than GLP-1 analogues. Insulin dose has to exceed 195 units a day of the cheapest basal insulin or 80 units a day of long-acting analogue insulin (using pricing in the British National Formulary; Joint Formulary Committee, 2013) before costs exceed those of the current cheapest GLP-1 analogue.

GLP-1 analogues

There are no long-term data on mortality for the GLP-1 analogues currently on the market and most studies looking at quality of life data are based on various modelling algorithms and come up with variable results.

Studies of both liraglutide and exenatide use appear to show improved outcomes in some aspects of patient satisfaction in comparison to sitagliptin, glimepiride and insulin glargine (Bode et al, 2010; Best et al, 2011; Davies et al, 2011). Both agents appear safe and initial concerns about the possible increased risk of pancreatitis appear now allayed. Despite an increase in medullary thyroid cancer in mice exposed to high concentrations of liraglutide, no such effect has been demonstrated in humans.

Prospective cardiovascular outcome trials for both liraglutide and exenatide are in progress. Current data on cardiovascular safety are gleaned from pooled analyses of patient level data from phase II and III clinical trials (Marso et al, 2011; Ratner et al, 2011) which are favourable for both agents with relative risks less than one for major cardiovascular events in comparison to all other glucose-lowering therapies assessed

Cost efficacy calculations for the use of liraglutide and exenatide have been performed in a number of modelling studies (Mittendorf et al, 2009; Valentine et al, 2011; Gaebler et al, 2012), which have used various approaches

to assess outcomes over a range of 10–40 years. None of these models really mirrored current clinical practice in the UK so their utility is limited but when exenatide therapy is compared to therapy with insulin glargine to maintain glycaemic control over a 10-year period the cost per quality-adjusted life year is €13 746 and the cost per incremental life year gained €238 201 (Mittendorf et al, 2009). The modelling was very sensitive to changes in assumptions for utility values related to weight change and glucose monitoring and we should not assume that because the final figure arrived at sits comfortably within perceived acceptability of costs in other analyses by the National Institute for Health and Clinical Excellence that these figures will actually be delivered in clinical practice. There is ultimately little to separate cost-efficacy of liraglutide and exenatide in direct comparisons (Valentine et al, 2011) and caution is needed when making judgements as to cost utility of these agents.

Conclusions

Current National Institute for Health and Clinical Excellence guidance offers a sensible approach to the escalation of therapies in type 2 diabetes and suggests that insulin should be considered the standard option when therapy is escalated as a result of the failure of oral therapy. Failure of oral therapy should be defined on the basis of individualized targets for each patient and the presence or absence of complications, the age of the patient and the risks of hypoglycaemia should play a significant part in this judgement. Given the current costs of GLP-1 analogue therapy, limited hard outcome data and the current financial climate within the NHS the use of these agents should be limited to those in whom clear benefit is derived. **BJHM**

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KEY POINTS

- Every day 400 people in the UK are diagnosed with diabetes and the costs of managing the condition continue to rise.
- Good glycaemic control is important in the prevention of microvascular end points and has a significant effect on macrovascular end points, but targets for glycaemic control need to be tailored for individuals, taking into account their age and the presence or absence of complications.
- Current National Institute for Health and Clinical Excellence guidance provides a sensible framework for guiding therapy and exceptions to this guidance should have a clear rationale and be justified.
- Glucagon-like peptide-1 analogues are a new and effective treatment for type 2 diabetes and offer the distinct potential advantage of weight loss but they are costly in comparison to insulin and their use should be reserved for those who will have a clear clinical benefit and cost efficacy should be considered when choosing such therapies.

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