Achieving glycaemic control: Current and future management opportunities

Melanie Calvert, Aparna Shankar, Richard McManus, Nick Freemantle

Diabetes poses a serious clinical and financial challenge (Turner et al, 1999). The prevalence of diabetes is continuing to increase and estimates suggest that by the year 2036, there will be approximately 20 % more cases of type 2 diabetes in the UK than in 2000, with associated rapid increases in micro- and macrovascular complications and subsequent reduced quality of life (Bagust et al, 2002; Morgan et al, 2006). It has been estimated that by 2040–2050, health care expenditure for diabetes could increase to £2.2 billion. In the UK, most people with type 2 diabetes are managed entirely within primary care and increasing numbers of practices are developing management skills previously available only in secondary care (Khunti and Ganguli, 2000). Tight glycaemic control has been shown to reduce the risk of microvascular complications for people with type 2 diabetes, including renal failure and retinopathy. It also reduces the risk of macrovascular complications and appears potentially cost effective, but in practice, is often not achieved (UKPDS, 1998; Clarke et al, 2005; Dormandy et al, 2005). In this paper, we describe current practice, guidelines and potential barriers to optimal management of type 2 diabetes in primary care. We consider different approaches for improving care, including new therapies, guideline development and education.

Suboptimal glycaemic control is apparent in many people with type 2 diabetes, despite apparent intensification of therapy with both oral treatment and insulin (Hippisley-Cox and Pringle, 2004; de Lusignan et al, 2005; Fox et al, 2006; Calvert et al, 2007a; Calvert et al, 2007b). A large observational study using data from UK primary care in 2003 showed that 17.3% of people with type 2 diabetes controlled on diet alone and 38.4% of those on medication had an HbA_{1c} above 7.5% (Hippisley-Cox and Pringle, 2004). Our own work evaluating the period from 1999 to 2003 confirmed these findings, indicating that 40% of people on a single oral agent and 50% of people prescribed a second oral agent had an HbA_{1c} ≥7.5% (Calvert

Article points

1. Tight glycaemic control has been shown to reduce the risk of microvascular complications for people with type 2 diabetes, including renal failure and retinopathy.
2. It also reduces the risk of macrovascular complications and appears potentially cost effective, but in practice, is often not achieved.
3. In this article, we describe current practice, guidelines and potential barriers to optimal management of type 2 diabetes in primary care. Different approaches for improving care are considered.

Key words

- Glycaemic control
- Guidelines

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et al, 2007b). More recently, looking at 1995–2005, we found that 62% of people on multiple oral agents and 73% of those prescribed insulin or oral agents had an HbA_{1c} ≥7.5%, and that the median time to insulin intiation for individuals prescribed multiple oral agents was 7.7 years (95% CI: 7.4–8.5) (Calvert et al, 2007a).

Recent evidence suggests that the glycaemic monitoring and the proportion of people reaching target HbA_{1c} levels <7.5% and ≤10% have improved in the UK following the introduction of the Quality Outcomes Framework of the new General Medical Services contract, but improvements were occurring before the contract and it is unclear whether or not these trends in improvement will continue or the extent to which the contract is responsible for them (DoH, 2004; Campbell et al, 2005; Campbell et al, 2007; Gulliford et al, 2007; Tahrani et al, 2007). Despite improvements over time, it is clear that oral hypoglycaemic agents and insulins with proven clinical efficacy remain underutilised and that the transition between therapies is unduly slow (Calvert et al, 2007a). Even when used appropriately, the efficacy of available treatments diminishes over time due to the decline in beta-cell function, leaving a therapeutic gap for the development of new treatment options and ideally a cure (Turner et al, 1999).

Barriers to optimal glycaemic control

Barriers to successful management of diabetes occur at the patient, physician and systems level. The treatment regimen for people with diabetes is complex, typically requiring patients to make changes to lifestyle factors such as diet, exercise and weight, take multiple oral agents or insulin and self-monitor blood glucose. While the emphasis on behavioural factors means that people have a greater control over their condition than those with other chronic illnesses (Gatchel and Oordt, 2003), adherence to aspects of the self-care regimen is typically low (Nelson et al, 2007). Non-adherence may be associated with poor comprehension about the treatment regimen, low self-efficacy over making changes and a lack of belief in the benefits of medication (Peyrot et al, 2005a; Rubin, 2005). As diabetes progresses, many individuals are required to start or intensify insulin therapy. This transition is often met with reluctance (by psychological insulin resistance, for example) as patients may perceive this as indication of their personal failure to adequately manage their diabetes (Peyrot et al, 2005b). This, in turn, may reflect the ways in which physicians frame the need for intensification of treatment (Skinner, 2004).

Management in deprived areas and among ethnic minorities, who are often at a greater risk of developing diabetes, presents additional challenges reflected in worse control (Gulliford, 2007). Deprived areas often have less developed services and patients are likely to find lifestyle interventions such as dietary change harder to achieve (Hart, 1971). People from ethnic minority groups may find language barriers lead to poorer access to services and a poorer understanding of their condition (Hill, 2006; Healthcare Commission, 2007). Cultural factors have an impact on the way in which people view the causes, progression and management of their illness and may also limit the extent to which patients are able to make lifestyle changes and become active partners in care (Rhodes and Nocon, 2003; Bissell et al, 2004; Lawton et al, 2005; Stone et al, 2005; Lawton et al, 2006).

Physicians' hesitance in initiating or intensifying insulin treatment, perhaps due to concerns regarding weight gain and hypoglycaemic episodes resulting in a reduced quality of life, might explain the apparent clinical inertia observed in diabetes care (Brunton et al, 2006). Nurses have an important role to play, particularly in areas such as routine monitoring and transition to insulin, but may require further training and support (Greaves et al, 2003).

The ways in which healthcare professionals communicate with their patients also has important implications for patients' understanding of their condition and its management. A recent survey of

Page points

1. Knowledge of the complex mechanisms involved in glucose metabolism, combined with recent advances in genomics and proteomics, has led to new potential targets for the treatment of people with diabetes.
2. The thiazolidinediones were developed to provide alternative oral treatment for those people not controlled on more conventional agents.
3. In order to improve metabolic control and potentially reduce the number of nocturnal hypoglycaemic episodes, insulin analogues with prolonged duration of action have been developed.

over 68 000 people with diabetes found that less than half of them reported discussing ideas and goals for treatment or agreeing on a plan to manage their diabetes with their GP (Healthcare Commission, 2007).

At a systems level, the complex care required for the intensive management of type 2 diabetes, particularly with insulin, may not be available in all practices due to a lack of resources. Underfunding, poor access to specialist advice and secondary care, and a lack of organisational facilities such as linked computerised records act as barriers to practices providing high-quality diabetes care (Agarwal et al, 2002). In a recent survey of diabetes services in 152 PCTs in England, 12% were classified as 'weak', failing to provide sufficient services to help people manage their diabetes or providing no data on the same (Healthcare Commission, 2007).

Recent developments in treatment options

It was in the 1920s that Banting and Best first discovered insulin and its role in glucose homeostasis. More recently, researchers have identified that, in addition to insulin and glucagon, other hormones such as amylin, and gastrointestinal peptides such as glucagon-like peptide-1 and gastric inhibitory peptides play an important role in glucose homeostasis (Schmitz et al, 2004; Amori et al, 2007). Knowledge of the complex mechanisms involved in glucose metabolism, combined with recent advances in genomics and proteomics, has led to new potential targets for the treatment of people with diabetes.

Thiazolidinediones

The thiazolidinediones (TZDs) were developed to provide alternative oral treatment for those people not controlled on more conventional agents. However, the utility of this class of medication has been reduced by concerns regarding adverse effects. The first agent in the class, troglitazone, was withdrawn following evidence of increased incidence of drug-induced hepatitis (BMJ, 2000). Rosiglitazone and pioglitazone were subsequently developed and may both be used to treat people with type 2 diabetes for whom monotherapy is insufficient and who cannot take metformin and a sulphonylurea in combination (NICE, 2008b). Although both TZDs represent the same class of drugs, they appear to have different effects on cardiovascular outcomes (Lincoff et al, 2007; Nissen and Wolski, 2007; Singh et al, 2007). Both rosiglitazone and pioglitazone have been shown to be associated with increased risk of heart failure and meta-analyses have shown that rosiglitazone is associated with an increased risk of myocardial infarction (Nissen and Wolski, 2007; Singh et al, 2007; Solomon and Winkelmayer, 2007). Pioglitazone, on the other hand, appears to be associated with a decrease in the composite outcome of death, myocardial infarction and stroke (hazard ratio: 0.82; 95% CI: 0.72–0.94; P=0.005), with a reduction in all components of the composite outcome (Lincoff et al, 2007).

Developments with insulin

The current standard for basal insulin is neutral protamine hagedorn (NPH) insulin. In order to improve metabolic control and potentially reduce the number of nocturnal hypoglycaemic episodes, insulin analogues with prolonged duration of action have been developed. Insulins glargine and detemir have both been licensed for use in people with type 1 and type 2 diabetes (Joint Formulary Committee, 2007). Insulin glargine has been appraised by NICE (NICE, 2002b), and a rapid update on newer agents such as sitagliptin, vildagliptin, exenatide, liraglutide, TZDs and insulin detemir is expected in February 2009 (NICE, 2008b). Insulin glargine is not recommended for routine use in people with type 2 diabetes. NICE guidance recommends that it should only be considered for those who require assistance from a carer or healthcare professional to administer their insulin injections, for those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemic episodes, or for those who would otherwise need twice-daily basal insulin injections in combination with oral antidiabetic drugs (NICE, 2008b).

Insulin detemir is accepted for restricted use within NHS Scotland. The Scottish Medicines Consortium suggested that its use should be 'targeted on patients attempting to achieve better hypoglycaemic control as there may be some benefit related to a reduced intra-individual variation in glycaemic profile for insulin detemir compared with established insulins' (Scottish Medicines Consortium, 2004). However, a recent Cochrane review of long-term trials comparing long-acting insulin analogues with NPH insulin showed similar effectiveness in metabolic control (Horvath et al, 2007). Although fewer individuals using the long-acting analogues experienced symptomatic overall or noctural

hypoglycaemic episodes. Furthermore, the cost-effectiveness of such agents is not yet proven.

Alternative insulin-delivery systems

Transdermal insulin

Microelectronics and ultrasound are currently being exploited by companies trying to deliver insulin transdermally. Preliminary results show some promise but no transdermal insulins are currently licensed for use (Phosphagenics, 2007).

Pfizer stops sales of inhaled insulin (Exubera)

On the 18th October 2007, Pfizer announced that it would no longer be making inhaled insulin available to patients because too few people were taking the therapy (Pfizer, 2007). It appears that the decision to withdraw inhaled insulin was purely commercial, as a result of poor sales. Why did Exubera fail? Dosage was based upon milligrams, rather than the more familiar units, and there were differences in the bioavailability of different doses. The device was quite bulky, around the size of an early mobile phone, which may have limited the extent to which people felt comfortable carrying it around. The increasing use of long-acting analogue insulins means that a person starting insulin could contrast three inhalation sessions with Exubera (involving perhaps two separate inhalation doses at each session), with a single injection of insulin taken in the evening in the privacy of their own home. Further, the potential benefit of avoiding injections was in part offset by the need for pulmonary testing at commencement of therapy, and not all practitioners may have easy access to appropriate testing facilities. NICE guidance recommended the limited use of inhaled insulin in people meeting specific criteria and that treatment should begin and be monitored at a specialist diabetes centre (NICE, 2006). This, combined with additional concerns about the long-term effects of inhalation on lung function, may have led to its limited use in the primary care setting.

Does inhaled insulin have a future?

Recently, Eli Lilly and Novo Nordisk have also shelved their inhaled insulin products but MannKind Corporation continues with its development programme (Reuters 2008a; Reuters 2008b; Reuters 2008c). Developing inhaled insulin technologies presents particular technological and regulatory challenges, as the efficacy and safety of the new route appropriately needs to be established, with injectable insulin the natural comparator. For market authorisation for Exubera, 11 randomised phase II and III trials assessing its efficacy in people with either type 1 or type 2 diabetes compared with specific marketed diabetes agents were conducted in more than 3200 individuals. The trials demonstrated similar decreases in HbA_{1c} in comparison to injectable short-acting human insulin when used in combination with intermediate- or long-acting insulin (Hollander et al, 2004; Quattrin et al, 2004; Skyler et al, 2005 Skyler et al, 2007) and significant efficacy with HbA_{1c} decreases of up to 1.9% with the addition of Exubera to one or two oral agents (Rosenstock et al, 2005; Barnett et al, 2006). It is likely that the regulatory hurdles faced by any future devices will remain high, albeit the concerns of authorities may be mediated by the continued absence of identified safety issues with Exubera (Barnett et al, 2007). The future of new devices will depend not only on proven efficacy and safety but also on cost-effectiveness, competitiveness with optimised injectable regimens, device size and convenience of inhalation. Exubera was used in a niche market: in people with 'needle phobia'. Whether or not inhaled insulin use will become more widespread remains to be seen (Mathieu and Gale, 2008).

Delivery systems for people with poor visual acuity and dexterity problems

Recent developments have also been made in injection devices aimed at the visually impaired and those lacking dexterity. For example, the Innolet® doser has a large dial, is prefilled and has an audible click to aid dosing (Novo Nordisk, 2007). It is currently accepted for restricted use within

Page points

1. Normal insulin secretion is augmented when glucose is taken orally over and above intravenous administration.
2. A recent meta-analysis showed that the injectable GLP-1 analogues, exenatide and liraglutide, resulted in modest reductions in HbA1c compared with placebo.
3. The oral antidiabetic agent sitagliptin was the first in the class of DPP-IV inhibitors and has been approved by the FDA for use alone or in combination with metformin or a TZD when glycaemic control is inadequate.
4. People with type 2 diabetes have a deficiency in amylin leading to inadequate glucagon suppression following meals, accelerated gastric emptying and increased postprandial glucose in the bloodstream

NHS Scotland for the treatment of diabetes in people for whom insulin detemir is an appropriate choice of insulin and who have poor visual acuity and dexterity problems (National Electronic Library for Medicines, 2008).

Incretin-based therapies

Normal insulin secretion is augmented when glucose is taken orally over and above intravenous administration (Kreymann et al, 1987). This 'incretin effect' is mediated via the gut hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which stimulate insulin secretion as a response to glucose elevation and offer a potential avenue for new therapy (Todd and Bloom, 2007).

Incretin mimetics: GLP-1 analogues

People with type 2 diabetes have a decreased secretion of GLP-1, which leads to impaired or absent incretin-mediated insulin secretion. A recent meta-analysis showed that the injectable GLP-1 analogues, exenatide and liraglutide, resulted in modest reductions in HbA_{1c} compared with placebo (weighted mean difference: -0.97%; 95% CI: -1.13% to -0.81%) with similar efficacy in terms of glycaemic control to other hypoglycaemic agents without associated weight increases (Amori et al, 2007). GLP-1 analogues resulted in weight loss (1.4kg and 4.8kg vs placebo and insulin, respectively), but were associated with increased risk of nausea and vomiting. Since GLP-1 analogues work by increasing insulin secretion only in the presence of elevated blood glucose, they cannot, due to their glucose-dependent action, lead to hypoglycaemia when administered on their own. The majority of trials that have assessed the efficacy and safety of incretin-based therapies have had a 30-week or shorter duration and, therefore, the long-term safety and efficacy of these therapies remains to be evaluated. A long-acting release of exenatide, to be injected once-weekly, is currently under development (Kim et al, 2007).

Incretin enhancers: Dipeptidyl peptidase 4 (DPP-IV) inhibitors

Dipeptidyl-peptidase-4 (DPP-IV) is an ubiquitous membrane-bound enzyme that is responsible for the rapid metabolism and inactivation of GLP-1, GIP and other peptides. DPP-IV inhibitors prevent GLP-1 and GIP degradation, thus increasing the number of circulating incretins (Todd and Bloom, 2007). The oral antidiabetic agent sitagliptin was the first in the class of DPP-IV inhibitors and has been approved by the FDA for use alone or in combination with metformin or a TZD when glycaemic control is inadequate (FDA, 2006); sitagliptin and vildagliptin have since been licensed for use in the UK.

Results of a recent meta-analysis showed that sitagliptin and vildagliptin have similar effects on glycaemic control as GLP-1 analogues (Amori et al, 2007). DPP-IV inhibitors appear to have a weight-neutral effect, but people receiving them appeared to have a slightly increased risk of infection, nasoparyngitis and headache. Several other DPP-IV inhibitors are currently under development (Bristol-Myers Squibb Press Release, 2008; Takeda Pharmaceutical Company Ltd, 2008).

While the results of DPP-IV inhibitors are encouraging, the enzymes have several other substrates, with the possibility of unknown side effects (Todd JF and Bloom, 2007), it is therefore crucial that these agents are highly specific. The long-term efficacy and safety of these inhibitors requires further evaluation.

Amylinomimetics

Amylin is a hormone that is co-secreted by pancreatic beta-cells at the same time as insulin. In people without diabetes, amylin plays a complementary role to insulin by moderating glucose appearance in the bloodstream by inhibiting postprandial glucose secretion, modulating appetite and slowing gastric emptying (Schmitz et al, 2004). People with type 2 diabetes have a deficiency in amylin leading to inadequate glucagon suppression following meals, accelerated gastric emptying and increased postprandial glucose in the bloodstream (Triplitt, 2007).

Amylin is relatively insoluble and, therefore, not readily injectable into the bloodstream; however, in 2005, the FDA licensed the use of a soluble amylin analogue: pramlintide (FDA, 2005). This therapy, which is injected separately from insulin, has been shown to lead to modest improvements in HbA_{1c} (-0.70 ± 0.11% vs -0.36 ± 0.08% for placebo, $P<0.05$) and weight loss in people with type 2 diabetes uncontrolled on basal insulin (Riddle et al, 2007).

Gene therapy and pancreatic beta-cell therapy

Enhanced beta-cell proliferation (either ex vivo or through regeneration of existing cells), islet

transplantation, directing the differentiation of stem cells into beta-cells and gene therapy, such as GLP-1 therapy, are all currently being explored with varying degrees of enthusiasm in the attempt to find a 'cure' for diabetes (Santana et al, 2006; Lee et al, 2007). However, currently, there appears greater activity in the development of new antidiabetic agents and little sustained attention to curative solutions, which many may find disappointing.

NICE guidance for people with type 2 diabetes

Glycaemic management

Glycaemic monitoring and targets for control were described in the NICE guidance on the management of people with type 2 diabetes (NICE, 2002a) and formed the basis of the structured framework for the care of people with diabetes in the Quality and Outcomes Framework (DoH, 2004). This guideline was updated in May 2008 (NICE, 2008a). The 2002 NICE guidance on the management of blood glucose for people with type 2 diabetes recommended that 'for each individual, a target HbA_{1c} (DCCT aligned) should be set between 6.5% and 7.5%, based on the risk of macro- and microvascular complications.' The ADA currently recommends a target HbA_{1c} of less than 7%, and the American Association of Clinical Endocrinologists suggests aiming for a value of 6.5% or lower (ADA, 2008; Nathan et al, 2006). The new NICE guidance for the management of type 2 diabetes also recommends this lower target. Due to the requirement for intensive monitoring, the likelihood for increased hypoglycaemic episodes and the use of expensive therapies, targets under 6.5% are not recommended in the 2008 update.

The guideline also notes the difficulty in setting targets for commencing or intensifying treatment, as this needs to consider a variety of factors including current treatment, stage of illness, effects on quality of life and resource implications (NICE, 2008a). The Action to Control Cardiovascular Risk In Diabetes (ACCORD) trial examined the effect of lowering glucose to near normal levels ($HbA_{1c} \leq 6.0\%$). Median HbA1c was 6.4% in the intensive therapy group, compared to 7.5% in the standard treatment group after 1 year. However, intensive treatment was associated with a relative increase in mortality of 22%, as result of which patients in this arm were switched to standard therapy 18 months early in February 2008 (The Action to Control Cardiovascular Risk In Diabetes Study Group, 2008).

Education

Structured education for individuals diagnosed with diabetes is a key priority in the new NICE guidelines for diabetes (NICE, 2008a). People with diabetes need continued support and education that not only works at improving knowledge about diabetes but also supports them in acquiring and maintaining self-management skills (Day, 2000; Skinner, 2004). The use of a variety of strategies to provide information, ranging from the didactic to more interactive techniques that adapt to patients' preferred style of learning, can help in improving knowledge and self-management practices (NICE, 2002a).

Expert patient-led education programmes and programmes tailored to the needs of specific communities have been shown to be useful (O'hare et al, 2004; Deakin et al, 2006). The delivery of education through more easily accessible and potentially cost-effective media, such as the telephone and web-based services, are currently being explored (Kamel Boulos et al, 2006; Dale et al, 2007). Professionals need to communicate medical information in a way that is comprehensible to the patient and take into account a person's beliefs and values when setting treatment goals (Wolpert and Anderson, 2001; Skinner, 2004). Further efforts need to be made to provide up-to-date information and training to healthcare professionals in primary care so as to ensure high-quality care (Pierce et al, 2000; Agarwal et al, 2002).

Pharmacological therapy

Treatment to control blood glucose typically comprises a step-wise approach, including dietary advice with the addition of oral hypoglycaemic agents or insulin depending on subsequent glycaemic control measured by HbA_{1c} (*Figure 1*; NICE, 2007a;). The recommendations for the use of metformin and sulphonylureas remain largely unchanged in the new guidance. The addition of a TZD to metformin and sulphonylurea is now recommended for people with poor glucose control ($HbA_{1c} \geq 7.5\%$ or agreed individual target) where insulin is either contraindicated or is likely to be poorly tolerated. Triple therapy was not recommended in the 2002 guideline and this new recommendation is due to be updated in 2009.

Page points

1. The ADA currently recommends a target HbA1c of less than 7%, and the American Association of Clinical Endocrinologists suggests aiming for a value of 6.5% or lower.
2. People with diabetes need continued support and education that not only works at improving knowledge about diabetes but also supports them in acquiring and maintaining self-management skills.
3. Expert patient-led education programmes and programmes tailored to the needs of specific communities have been shown to be useful.

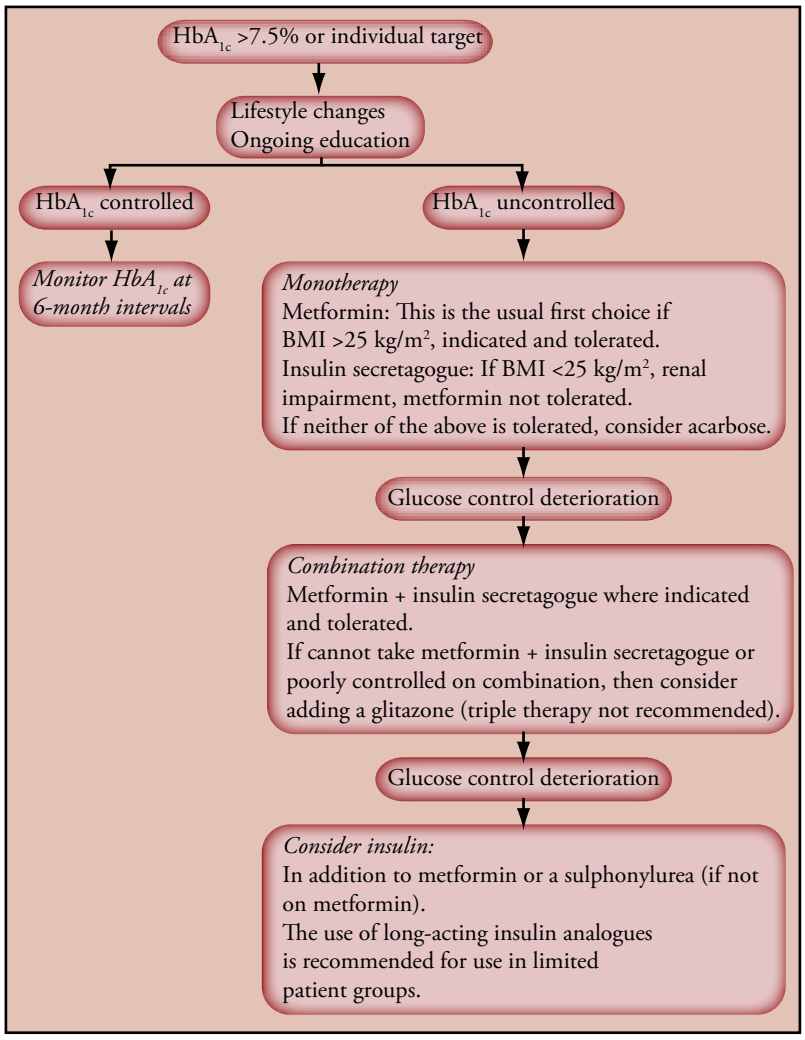

Figure 1. Step-wise approach in treatment to control blood glucose.

Individuals prescribed a TZD also need to be made aware of the risk of developing an oedema and prescription is not recommended for those with heart failure.

The guideline also suggests considering combined pioglitazone–insulin therapy in people who previously showed improved control in response to TZDs or to improve control in poorly controlled individuals who are already on high-dose insulin therapy. The routine use of exenatide (GLP-1 mimetic) is not recommended in people with type 2 diabetes, although this too is due to be further reviewed in 2009. Use of exenatide is only recommended in the case of people with a BMI over 35kg/m^2 with specific associated psychological, physical or biochemical problems, poor control on metformin and a sulphonylurea, and where medications such as insulin injections or TZDs would otherwise be initiated.

Summary

Despite improvements in glycaemic control and monitoring over time in the UK, many people with type 2 diabetes do not meet treatment targets and appear to have slow transitions between therapies. While it may be unrealistic for some individuals to meet targets, more intensive treatment of more individuals would help to avoid micro- and macrovascular complications that can have devastating effects. The increasing prevalence of type 2 diabetes and the aging population is likely to compound these problems. Promising developments in therapy continue to be made; however, the recent case of rosiglitazone highlights the need for caution in the use of surrogate measures as a basis for drug approval (Solomon and Winkelmayer, 2007). Policy makers and healthcare professionals need to ensure that available treatments are safe and efficacious with respect to important clinical outcomes, and are used by patients in an optimal and efficient way. ■

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'Policy makers and healthcare professionals need to ensure that available treatments are safe and efficacious with respect to important clinical outcomes, and are used by patients in an optimal and efficient way.'