Management of type 2 diabetes: the current situation and key opportunities to improve care in the UK

Management of type 2 diabetes in the UK

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Abstract

In common with global trends, the number of individuals with Type 2 diabetes in the UK is rising, driven largely by obesity. The increasing prevalence of younger individuals with type 2 diabetes is of particular concern, due to the accelerated course of diabetes-related complications that is observed in this population. The importance of good glycaemic control in the prevention of microvascular complications of diabetes is widely accepted and there is a growing body of evidence to support a benefit in the reduction of cardiovascular events in the long-term. Despite the importance of maintaining a healthy weight for the prevention of type 2 diabetes; the results from trials of lifestyle intervention strategies to reduce body weight have been disappointing. New glucose-lowering agents offer some promise in this regard, offering an opportunity to combat the dual burden of hyperglycaemia and obesity simultaneously. The timing and appropriate choice of glucose lowering therapy has never been more complex owing to rising prevalence in the young, concomitant obesity in some 90% of adults with type 2 diabetes and an ever increasing range of therapeutic options. The present review evaluates performance measures specific to weight and glycaemic control in type 2 diabetes in the UK using data from the Quality and Outcomes Framework in England and Wales, and Scottish Diabetes Survey. Potential barriers to improvement in standards of care for people with type 2 diabetes are considered, including patient factors, clinical inertia and the difficulties in translating therapeutic guidelines into everyday clinical practice.

Introduction

The publication of the updated National Institute for Health and Care Excellence (NICE) guidance for the management of type 2 diabetes [1] is a timely prompt to review opportunities to improve diabetes care. These guidelines have incorporated some recent therapeutic advances and have focused mainly on glycaemic indicators with regard to drug choices. By contrast the American Diabetes Association (ADA) [2] and International Diabetes Federation (IDF) [3] guidelines emphasise other factors to be considered in the choice of diabetes medicines in order to improve care. Due to the complexities of the condition, the range of drug classes to be considered, and patient and prescriber treatment considerations, the realities of clinical practice are indeed complex.

Efforts to curb the inevitable rise in complications associated with diabetes have led to a systematic evaluation of quality of care in England and Wales. Since 2004, disease specific indicators for both processes of care and treatment targets have been assessed through the pay for performance, Quality and Outcomes Framework (QOF). This review aims to evaluate contemporary care in the UK based on performance measures for glycaemic control and body-mass index. Particular emphasis will be placed on guidance from NICE that is most relevant to UK practice, and on which the QOF measures are based. In addition, barriers to ‘gold standard” care, and opportunities to improve existing standards, will be considered from a UK perspective.

Importance of glycaemic control

There is established evidence confirming that improved blood glucose control results in substantial benefits in diabetes microvascular disease outcomes,[4-6] reducing

disability in diabetes mediated by end organ damage to the eyes, kidneys and nerves. Diabetes is also associated with significant premature mortality, and around half of individuals with type 2 diabetes will die prematurely as a result of cardiovascular disease (CVD) [7]. The evidence for a reduction in CVD with intensive glucose control is less convincing when compared with microvascular outcomes. However, long-term follow-up among individuals with both type 1 [8] and type 2 diabetes [9, 10] randomised to strict glycaemic control has suggested that cardiovascular events are reduced when compared with standard treatment arms.

The 10-year extension post intervention in The UK Prospective Diabetes Study (UKPDS) reported a significant 15% reduction in myocardial infarction (MI) and 13% reduction in all-cause mortality among patients with type 2 diabetes receiving intensive therapy (sulphonylurea-insulin) compared to controls [9]. In the cohort of overweight patients receiving metformin, intensive therapy was associated with even greater reductions in the risk of MI (33%) and death (27%) [11]. At the conclusion of the interventional study, conventional treatment and intensive therapy corresponded with HbA1c levels of 7.9% and 7.0%, respectively. Importantly, the outcome benefits described above produced a legacy effect after a further 10-year extension, where no significant differences in glycaemic control were observed between study groups.

In addition to glycaemic control, subsequent trials have evaluated other risk factors and shown that effective control of blood pressure and cholesterol in type 2 diabetes reduces rates of CVD and mortality [12, 13].

Importance of weight control

A recent report from Public Health England suggests that 90% of adults with type 2 diabetes are overweight or obese [14]. The relationship between BMI in type 2

diabetes and outcome has been extensively scrutinised. Reports of an obesity paradox in type 2 diabetes where raised BMI is associated with reduced mortality [15, 16] have been criticised for being underpowered or failing to adequately adjust for smoking history (associated with both reduced BMI and mortality). The obesity paradox was challenged by an analysis of pooled data from two large observational cohort studies including 11,427 patients with incident type 2 diabetes [17]. A direct linear relationship between mortality and BMI was observed among individuals who had never smoked and a J-shaped association among those with a history of smoking, where smoking attenuated the benefit of a low BMI. BMI data in this study were collected before, or shortly after, a diagnosis was made. A population-based cohort study in the UK supported the notion that both smoking and obesity contribute to the risk of all-cause mortality in type 2 diabetes. In this study a U-shaped curve associated with BMI and mortality was found; the hazard ratios for those with a BMI of 35-54 kg/m2 and 15-19 kg/m2 were 1.43 (1.28-1.59) and 1.38 (1.18-1.61), respectively (Figure 1) [18]. These data underscore the importance of maintaining a healthy body weight from the early stages of type 2 diabetes.

Obese people are seven times more likely to develop type 2 diabetes compared to those with a healthy BMI (20-25 kg/m^2), with a threefold increased risk among those who are overweight [19]. Beyond incident type 2 diabetes, obesity is associated with other cardiovascular risk factors, including hypertension and, importantly, resistant hypertension [20, 21]. Dietary interventions in the trial setting have yielded benefits in both the prevention of type 2 diabetes and improvement in glycaemic and blood pressure control among individuals with existing type 2 diabetes [22, 23]. Similarly, weight loss achieved through bariatric surgery has shown promise for patients with obesity and uncontrolled diabetes in terms of glycaemic control,[24] and metabolic changes observed postoperatively suggest there may be glycaemia benefits independent of weight loss per se [25].

The impact of lifestyle-mediated weight loss on cardiovascular outcomes in type 2 diabetes has also been investigated, most notably in the Look AHEAD study, which reported improved glycaemic control and CVD risk factor profile among participants randomised to intensive lifestyle intervention. This translated into clinically significant weight loss (8.6% of initial weight versus 0.7% among controls) at one year [26]. Despite sustained positive effects associated with intensive lifestyle intervention including the need for fewer glucose-lowering drugs and increased likelihood of achieving HbA1c levels <7% (53 mmol/mol) [27], the 10-year follow-up study showed no significant difference between groups for cardiovascular morbidity and mortality [28]. The spectrum of glucose lowering medications in type 2 diabetes includes those that promote weight gain (insulin, sulphonylureas and thiazolidinediones) and offer weight neutrality (metformin and dipeptidyl peptidase-4 inhibitors). The availability of novel agents associated with weight loss (glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter 2 inhibitors) offer promise for combatting obesity in type 2 diabetes as part of a multifactorial approach including good lifestyle.

Economic considerations

The burden of diabetes to the NHS is thought to represent around 5-10% of the overall budget and is projected to account for around 17% in 2035 [29-31], with current direct costs attributable to type 2 diabetes estimated at around £8.8bn [31]. A health economics assessment undertaken by the York Health Economics Consortium suggests that less than a quarter of this cost relates to the treatment and ongoing management of diabetes; the remainder is attributable to the treatment of complications of the disease [31]. Because the effects of hyperglycaemia are cumulative [4, 11], it seems intuitive that early implementation of evidence based guidance and greater achievement of glycaemic and weight targets would reduce the

incidence of complications or, at the very least delay their onset, resulting in cost savings for the health service. It is entirely paradoxical; therefore, to withhold best practice management early in the disease trajectory of type 2 diabetes in an effort to curb spending, as such practice is likely to increase the incidence of complications that account for a disproportionate share of overall healthcare costs. Early control of glycaemia in the decade following diagnosis, as observed in UKPDS, can mitigate risk of microvascular complications and has important legacy benefits for reduction of cardiovascular disease in the long-term [9].

Achievement of glycaemic (HbA1c) and BMI guideline targets on a population level

Glycaemic control

An estimated 3.5 million individuals in the United Kingdom have type 2 diabetes [32], a figure that is expected to rise to over 5.5 million by 2035 [31], driven by population growth, ageing and rising levels of obesity. In the past two decades in the UK, the proportion of younger adults below the age of 40 with newly diagnosed type 2 diabetes has doubled [33]. Rising prevalence of young-onset diabetes will have a negative impact on the incidence of diabetes related complications as they are likely to develop at an earlier stage of life [34, 35], with implications for the individual and the health care authority in which they reside. Among individuals with type 2 diabetes in youth, higher HbA1c is associated with greater risk of complications [36], reinforcing the importance of optimising glycaemic control early on in the natural history of disease.

The 2015 NICE guidance recommends an HbA1c target of 48 mmol/mol (6.5%) for individuals with type 2 diabetes managed by lifestyle and a single glucose-lowering

agent (Table 1) [1]. Additional or add-on therapy is advocated when HbA1c rises to 58 mmol/mol (7.5%) or higher with intensified monotherapy and reinforced lifestyle advice. At this junction, the target HbA1c is increased to 53 mmol/mol (7.0%). The UK National Diabetes Audit measures the effectiveness of diabetes care in England and Wales against NICE standards. In the most recent audit year (2014-2015), around 4700 primary care practices and 99 specialised services contributed data on 1.9 million individuals with diabetes [37]. Between 2009 and 2015, between 90 and 95% of patients with T2DM underwent HbA1c monitoring at 6 monthly intervals, of whom 65 to 67% achieved NICE treatment targets (applicable to that period) of ≤58 mmol/mol (7.5%) (Figure 2). Significantly, the lowest rates of achievement were among patients under 40 years and those aged 40 to 64 years, and appreciable geographical variation in achievement of treatment targets was observed.

In Scotland during the same time period, achievement of the NICE target ≤58 mmol/mol (7.5%) ranged from 60 to 64%. Between 13% and 15% of those with type 2 diabetes in Scotland had an HbA1c >75 mmol/mol (9.0%) [38]. This statistic is alarming given that UKPDS reported MI event rates of 20 per 1000 person years among participants with an HbA1c between 9.0 and 10.0% compared to 13 per 1000 person years among those with good glycaemic control (HbA1c 6.0-7.0%) [39]. In that study, for each 1% reduction in HbA1c events rates were reduced significantly for diabetes-related deaths (21%), myocardial infarction (14%) and microvascular complications (37%). It is also significant that no lower HbA1c threshold for risk was observed for any endpoint **(Figure 3)**.

International comparisons

UK data on achievement of HbA1c goals can be compared with the most recent reports based on the National Health and Nutrition Examination Survey in the US,

where, between 2007 and 2010, 52.2% and 79.1% of participants had an HbA1c <53 mmol/mol (7.0%) and <64 mmol/mol (8.0%), respectively [40]. Among patients in the Swedish National Diabetes Register with type 2 diabetes and no history of coronary heart disease, 78.4% achieved national guideline targets of an HbA1c <56 mmol/mol (7.3%) in 2008 [41]. Although not a directly comparable cohort, these European data would suggest that UK achievement of glycaemic goals are not among the best in Europe. The European Study on Cardiovascular Risk Prevention and Management in Usual Daily Practice (EURIKA) that collected data between 2009 and 2010 suggested wide variation in achievement of glycaemic goals across European countries. Among 2046 patients with type 2 diabetes, an HbA1c of <48 mmol/mol (6.5%) was achieved in 36.7%, and varied between 26.0% and 48.4% between the 12 countries that contributed patients, although numbers in each were small [42]. A report from the Guideline Adherence to Enhance Care (GUIDANCE) study conducted across 8 European countries in primary and specialist care found only 53.6% of participants had an HbA1c <53 mmol/mol (7.0%), again with a lack of between-country consistency in achievement of targets [43].

Weight (BMI) control

Body-mass index was also well recorded in both England and Wales, and Scotland. From 2009, a record of BMI was made in between 82.0 and 89.7% of individuals with type 2 diabetes in Scotland [38], and 83.1 to 90.9% in England and Wales [32]. The BMI data for Scotland in 2014 suggest that 87% of patients with type 2 diabetes were overweight or obese (BMI ≥25 kg/m^2), over half of patients satisfied BMI criteria for obesity (≥30 kg/m^2) and 26% of patients had severe obesity (BMI ≥35 kg/m^2). Similarly, in 2009-2010 in England and Wales, 90% of adults with type 2 diabetes aged 15-54 years were overweight or obese. Consistent with findings of inferior glycaemic control in younger people with type 2 diabetes in the National Diabetes

Audit, the proportion with overweight or obesity was greater among individuals aged 16-54 years than those 55 years or older (Figure 4) [44].

Barriers to optimal care and opportunities for improvement

The overall benefit of improved glycaemic control and weight reduction in type 2 diabetes has been demonstrated definitively [45-47], yet achievement of targets on a population level remains poor. Suboptimal treatment and control of type 2 diabetes is a multifactorial issue, and the success of any strategy to overcome it will be predicated on an understanding of the progressive natural history of the disease and the ability to overcome a number of practical barriers. The progressive nature of type 2 diabetes means an escalation of treatment is usual in order to improve glycaemic control and reduce complications [48]. A “one size fits all” approach is unlikely to be effective because disease progression results from a combination of impaired insulin sensitivity and beta-cell dysfunction that vary on an individual basis. Additionally there is a wide range in patient responses to the different drugs and drug classes used in diabetes [49]. The result of inadequate response to single therapy is often a complex prescribing pattern, which has implications for patients and physicians. The complexity of treatment regimen is inversely associated with adherence and [50, 51], in turn, poor adherence is associated with smaller reductions in HbA1c [52]. For physicians, interpreting and implementing clinical guidelines in the context of an individual patient can be a daunting prospect, further complicated by the wide range of treatment regimens now available.

Adherence issues

The World Health Organisation recognise patient non-adherence to therapies as one of the major barriers to improving health outcomes [53], and there are UK-based data

to support this view in type 2 diabetes. An analysis of primary care records, that were adjusted for confounding factors found that non-adherence to prescribed medications and clinic non-attendance were independent risk factors for death from any cause among individuals with type 2 diabetes [54]. Barriers to adherence can result from a multiplicity of factors including polypharmacy, complexity of medication regimens, tolerability of medications including side effects such as gastrointestinal disturbance, weight gain and hypoglycaemia, poor knowledge of disease and cognitive impairment among elderly patients. Modifications to reduce the frequency of administration or the number of therapies are likely to improve compliance, and the role of fixed-dose combinations or co-administered dual therapy with reduced pill burden is likely to expand in this regard [55]. Reasons for non-adherence may change during the course of disease, but adherence is most likely to decline in the first six months following initiation of therapy [56]. This finding has implications for starting de-novo drug treatment and escalating therapy. A report evaluating participants with type 2 diabetes newly started on a first antihyperglycaemic treatment suggests poor medication adherence was associated with elevated HbA1c and predicted delay to intensification of therapy [57]. Patients in the highest adherence quartile were significantly more likely to have their regimens intensified during at least three years of follow up than those in the lowest quartile for adherence (37.4% versus 26.7%).

Patient factors

Fear of weight gain or hypoglycaemia, whether real or perceived, can negatively influence adherence to medication [58, 59]. Furthermore, individuals who are obese have been shown to have significantly poorer adherence than their non-obese counterparts with type 2 diabetes [60]. Many glucose lowering treatments are known to drive weight gain and observational data from the UK suggest that weight gain

after initiating a new glucose-lowering therapy is associated with increasing primary care spending that results from both increased prescribing and contact with primary care physicians [61]. Such barriers may be overcome with the availability of glucose-lowering therapies that offer weight neutrality or reduction, and those with reduced incidence of hypoglycaemia, although the benefits of these agents for adherence will rely on patient awareness. Where agents can successfully combine efficacy in HbA1c reductions and weight loss, as has been demonstrated in real world data on SGLT2 inhibitors and GLP-1 receptor agonists [62, 63], patients may gain positive reinforcement to maintain good adherence and improve lifestyle choices to promote further weight loss.

Patient education

Patient education remains a foundation of existing type 2 diabetes programmes and is a widely recommended strategy to improve outcome [64]. While it is indisputable that patient knowledge is important for several aspects of care, there are few trial data to support the efficacy of this approach for improvement in glycaemic control. A meta-analysis of 18 randomised controlled trials evaluating the effect of educational interventions on body weight and glycaemic control in type 2 diabetes reported pooled reductions in HbA1c of 0.4%, compared with control arms [65]. A more recent study evaluating the effectiveness of a group-based self management (X-PERT) programme in the UK also demonstrated modest improvements in HbA1c (-0.6%) when compared to a control group with type 2 diabetes attending individual appointments [66]. Participation was also associated with improvement in BMI (-0.2kg/m^2 vs +0.4kg/m^2) and waist circumference at 14 months. Assessment of the diabetes education and self-management programme (DESMOND) in 731 individuals with newly diagnosed type 2 diabetes, at 207 general practices in the UK, failed to demonstrate any benefit in HbA1c control in comparison with controls at

three years [67]. Beyond the controlled trial setting, evidence is currently lacking to support long-term benefits of structured education.

In the same way that diabetes management is increasingly tailored to a specific patient profile, the solutions to poor adherence should also be personalised. The patient-healthcare provider relationship is central to the solution and should aim to build trust and a greater understanding of the disease and treatment options. The majority of diabetes is self-managed and patients must “buy in to” a strategy to prolong healthy life and reduce the risks of complications.

Clinical inertia

Clinical inertia has been defined as a failure to intensify treatment on a timely basis despite inadequate treatment response. It is a phenomenon common to several major chronic diseases including hypertension and dyslipidaemia, as well as diabetes. This difficulty in translating evidence based guidance on escalation of treatment into practice has been attributed to barriers at the healthcare system, healthcare provider and patient level [68, 69]. The magnitude of the problem is highlighted by the statistic that less than two thirds of patients in the UK are achieving even modest HbA1c targets of ≤58 mmol/mol (7.5%), as previously discussed. A study by Khunti et al using administrative care data on over 80,000 individuals with type 2 diabetes in UK primary care suggests there are significant delays in treatment intensification following sup-optimal HbA1c control [70]. The mean HbA1c level at which escalation of treatment occurred was 8.7, 9.1 and 9.7% among individuals taking one, two or three oral antihyperglycaemic medications, respectively. Furthermore the median time to starting a second-line treatment for those poorly controlled (HbA1c > 7%) on monotherapy was 2.9 years. A further UK-based study reported a mean gap of 7.7 years from initiation of a second or third line

oral antihyperglycaemic agent and insulin therapy, with a mean HbA1c of around 10% (86 mmol/mol) at the time of first insulin prescription [71]. Data from controlled trials indicating improvement in these outcomes translates into meaningful reductions in diabetes-related complications has been replicated in “real-world” data. A study involving over 100,000 patients registered at a general practice in the UK found the risk of cardiovascular events is increased when treatment escalation is delayed [72].

Given the wealth of available treatment algorithms for type 2 diabetes and the apparent lack of adherence to them in many cases, much of the emphasis has been placed on physician behaviour and education in efforts to overcome inertia and improve care [73-75]. This is, however, a simplistic view because physician inertia may also be influenced by patient-related and systematic factors [76-78]. For their part, health care professionals should aim to detect problems early, set realistic goals and promptly intervene [79]. These steps are reliant on a sound understanding of the available treatment options and their implementation will have significant overlap with systemic factors in the healthcare system in which they practice.

Translating guidelines into clinical practice

The introduction of incentivised payments in 2004 through QOF has arguably been the most significant systematic effort to drive standards in diabetes care in the UK. A systematic review of studies published between 1999 and 2006 found that the introduction of QOF incentives has led to significant improvements in both standards of care and major intermediary outcome measures including HbA1c [80]. These data are supported by a more recent study of routine administrative health data from practices in England which showed stepwise improvements in the proportion of patients achieving target HbA1c of ≤7.5% (59.1% in 2004-2005 versus 80.2% in 2007-2008 [81]. The QOF revision in 2011/2012 that raised the threshold at which

the HbA1c indicator was incentivised, from 53 mmol/L (7%) to 58 mmol/L (7.5%) may have served to increase clinical inertia around escalation of antihyperglycaemic therapy. Indeed, the proportion of patients achieving an HbA1c goal of <7.5% in England and Wales has never reached the levels of 2010/2011 since that year (Figure 2).

Despite the overall positive influence of QOF incentives on routine monitoring, and modest improvements in glycaemic control that have resulted, the trend for increased chronic disease management in primary care and away from disease specialists has placed pressure on providers in terms of length and frequency of appointments, and the levels of knowledge expected of them. Contemporary guidelines have done little to simplify the complexity and volume of research on glucose lowering agents [1, 2], such that they may be difficult to interpret for the specialist, let alone a primary health care provider who must be familiar with the management of several chronic diseases. The flow diagrams featured in recent NICE guidance are hard to follow and fail to provide clear recommendations for commonly encountered patient subgroups [82]. When simple and accessible, use of glucose algorithms at the point of care has been shown to improve physician behaviour as measured by frequency of intensification, with subsequent improvements in glycaemic control [83]. There are clear roles for treatment algorithms in diabetes, as these process of care interventions have also been shown to reduce clinical inertia in other areas of medicine [84]; however, they must be accessible to the primary care providers who undertake the lions share of diabetes management in the UK.

Timing and selection of add-on therapy

There exists near universal acceptance that metformin should remain the first-line therapy among individuals in whom lifestyle modification is insufficient to control

hyperglycaemia [1, 2, 64]. There is still a debate surrounding the selection of a second-line agent when metformin monotherapy fails to adequately control hyperglycaemia. It is here that the drive to individualise therapy is most relevant and the reason behind the complexity of many consensus guidelines. In the 2015 joint treatment guidelines from the European EASD and North American ADA, there are six drug classes to choose from when advancing to dual combination therapy, including sulfonylureas (SU), thiazolidinediones (TZD), dipeptidyl peptidase-4 (DPP-4) inhibitors, GLP-1 agonists, sodium-glucose cotransporter 2 (SGLT2) inhibitors and insulin. The EASD/ADA position statement acknowledges that initial combination therapy with metformin and a second-line agent may help patients to reach target HbA1c quicker than sequential therapy, particularly among individuals with very high baseline values [2], a position echoed by the American College of Endocrinologists for individuals with a baseline HbA1c >7.5% [85]. This recommendation is welcome for the reasons outlined above and contrasts slightly with those of the recent NICE document which provides a different message by its suggestion of waiting until HbA1c rises to >58 mmol/mol (7.5%) before escalation of therapy [1].

Sulfonylureas, with 60 years of clinical data, have been a mainstay of add-on therapy in type 2 diabetes and their combination with metformin has served as a control in several trials of newer agents. In a UK study using primary care data on over 25,000 individuals with type 2 diabetes, TZDs and DPP-4 inhibitors demonstrated near equivalent glucose lowering effects to SUs when combined with metformin [86]. There are some data to support greater HbA1c lowering with the combination of GLP-1 receptor agonists with metformin over combinations with a DPP-4 inhibitor [87], although other combinations with SUs and TZDs are broadly equivalent in their glucose lowering effects. The newest class of agent, SGLT2 inhibitors, have fewer data on comparative effectiveness but appear to offer similar efficacy to other agents, leading to HbA1c reductions ≈0.5 – 1.0% [88, 89]. Pooled data from regulatory

submissions and published trials suggest that SGLT2 inhibitors offer a magnitude of cardiovascular protection greater than might be expected by reductions in HbA1c alone [90, 91]. SGLT2 inhibitors work uniquely to lower the renal threshold for glucose, which is excreted at greater concentrations in the urine, leading to both lowering of blood glucose and reductions in weight owing to caloric loss. This class of antihyperglycaemics are likely to have the greatest role early in the disease course relative to other add-on therapies given that renal excretion of glucose with SGLT2 inhibitors will be attenuated with declining eGFR, which is progressive in type 2 diabetes [92, 93], and data to suggest they offer a longer duration of glucose lowering effect when compared to SUs [94], and on indirect comparison with the literature on DPP-4 inhibitors [95]. GLP-1 receptor agonists are the other class of glucose lowering drugs that promote weight loss, and there are early data to support reductions in cardiovascular events with these agents also [96]. They act on pancreatic islet cells to stimulate insulin secretion and inhibit glucagon secretion, while also delaying gastric emptying and promoting satiety, hence their propensity to promote weight loss. Real world data from the UK suggest that GLP-1 receptor agonists can offer greater reductions in HbA1c and improved weight control when compared to DPP-4 inhibitors [97], a finding that is supported by some trial evidence [98].

Comparative effectiveness data from the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) that is expected to report in 2020 will provide much needed long-term data on available medications when added on to metformin [99]. The study will randomise 5000 participants to combination therapy with metformin and one of four agents: glimepiride, sitagliptin, liraglutide or insulin glargine; unfortunately the trial does not include an SGLT2 inhibitor arm. The primary endpoint has been confirmed as the time to failure of glycaemic control that is defined as an HbA1c of 7.0% or higher. Although secondary outcomes with

respect to hypoglycaemic episodes, weight, microvascular disease and cardiovascular risk factors will be monitored, the trial is primarily designed to address which agent provides the best long-term control of blood glucose.

Conclusions

Good glycaemic control is the cornerstone of any strategy to reduce the risk of diabetes-related complications, yet achievement of evidence based guideline targets in the UK is modest at best. While incentivised payments in primary practice have driven standards of care with respect to identifying poor HbA1c control in type 2 diabetes, this modifiable risk is not being addressed in a timely fashion. The reasons for this are complex and multifactorial, involving healthcare system, physician and patient factors. Efforts to address suboptimal care in the UK should involve an emphasis shift from the management of complications to their prevention, a move that will have enormous health and economic implications for the better. Key opportunities lie in the appropriate selection of therapies for the majority of people with type 2 diabetes who are overweight or obese, optimising the timing of add-on therapies and finally, addressing issues of patient adherence.

Conflict of Interest

SB has attended advisory panels for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Janssen, Eli Lilly & Co, Merck Sharp & Dohme, Novo Nordisk, Omnia-Med, and Sanofi; and is a board member for Glycosmedia. MF has received financial support for research, speaker meetings and consultancy from pharmaceutical companies Merck Sharpe and Dohme, Merck, AstraZeneca, Pfizer, Sanofi, Novo Nordisk, Eli Lilly, and Boehringer Ingelheim. DRJ has received research funding or advisory board or lecture fee honoraria from Novo Nordisk. KK is a

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Table 1. Summary of NICE and EASD guidelines for glycaemic (HbA1c) control in type 2 diabetes [2, 64, 82, 100]

Guideline	Cohort	HbA1c target mmol (%)
NICE CG 87 (2009)[100]	T2DM general target	48 mmol/mol (6.5%)
NICE NG 28 (2015)[1] †	T2DM managed by lifestyle and diet +/- single drug	48 mmol/mol (6.5%)
	T2DM, if HbA1c level not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher	53 mmol/mol (7.0%)*
	T2DM, on a drug associated with hypoglycaemia	53 mmol/mol (7.0%)
EASD / ADA position statement 2012 (update 2015)[2, 64]	T2DM general target	<53 mmol/mol (7.0%)
	Selected patients with short disease duration, long life expectancy, no CV risk factors	42-48 mmol/mol (6.0-6.5%)
	Selected patients with severe hypoglycaemia, limited life expectancy, advanced complications, extensive comorbidity	58-64 mmol/mol (7.5-8.0%)

* Intensify drug treatment
† Consider relaxing all above, on case-by-case basis, for older and frail patients with multiple comorbidities.

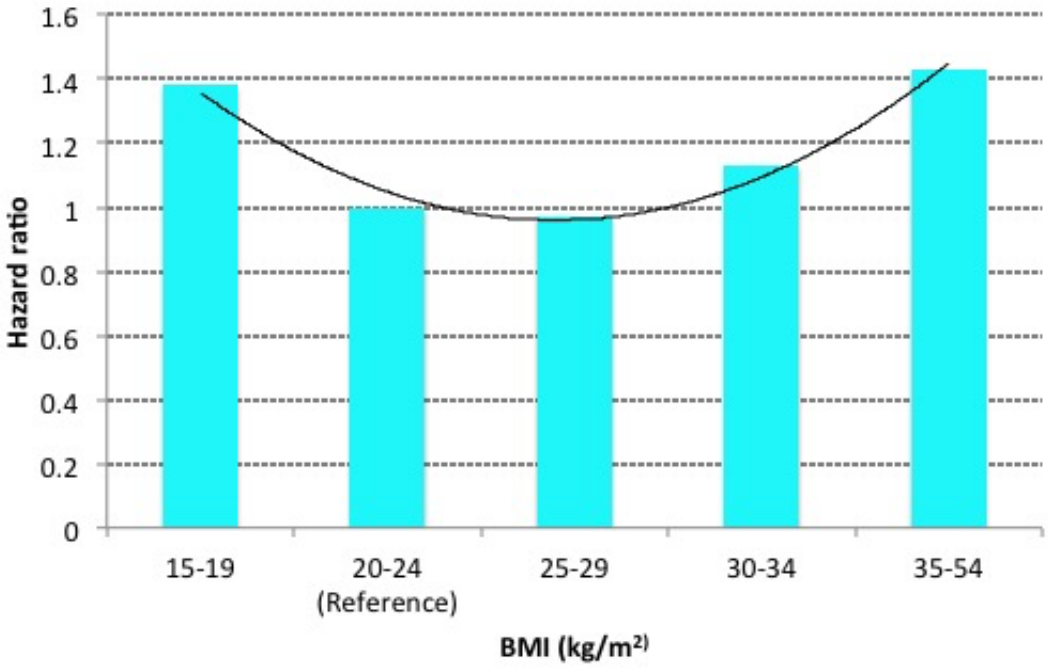

Figure 1. The association of BMI and all-cause mortality in type 2 diabetes

Adjusted for age, gender, smoking status and duration of diabetes
Adapted from Mulnier et al[18]

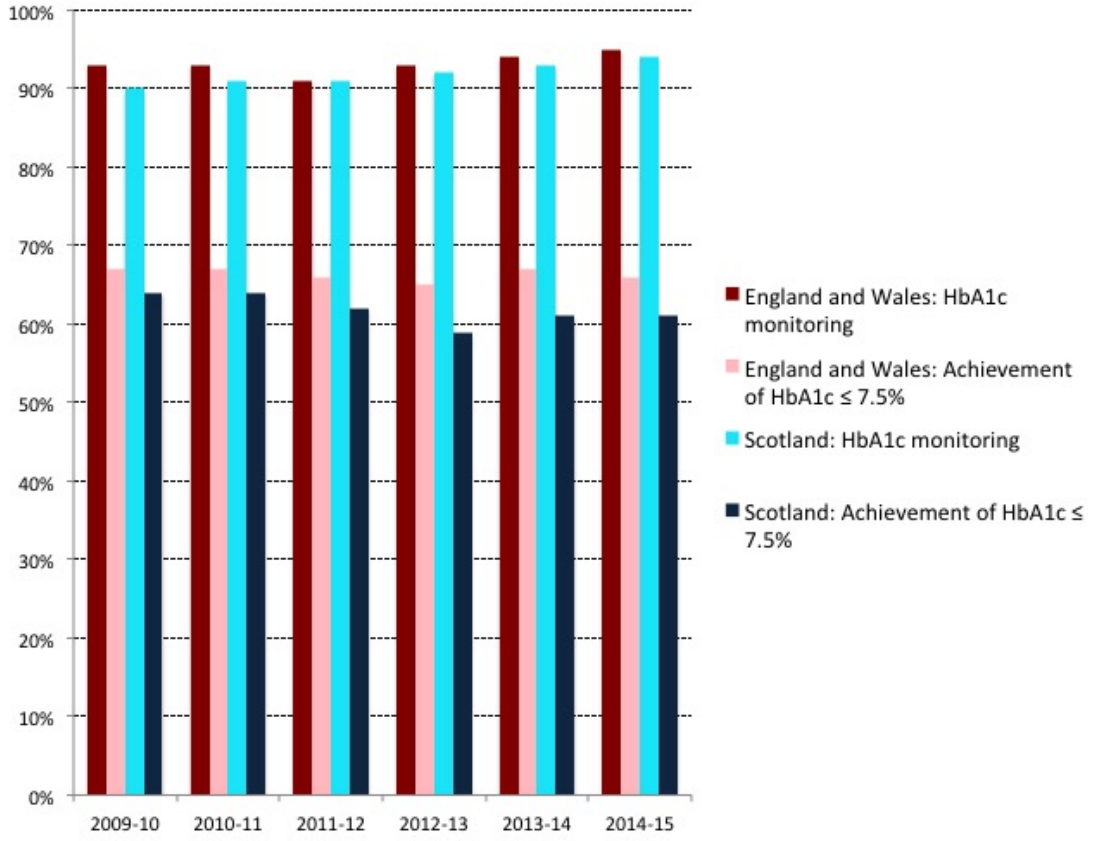

Figure 2. Percentage achievement of NICE recommended HbA1c monitoring and treatment targets (≤58 mmol/mol) among individuals with type 2 diabetes in England, Wales and Scotland[1, 37, 38]

*Data provided for type 1 and type 2 diabetes combined

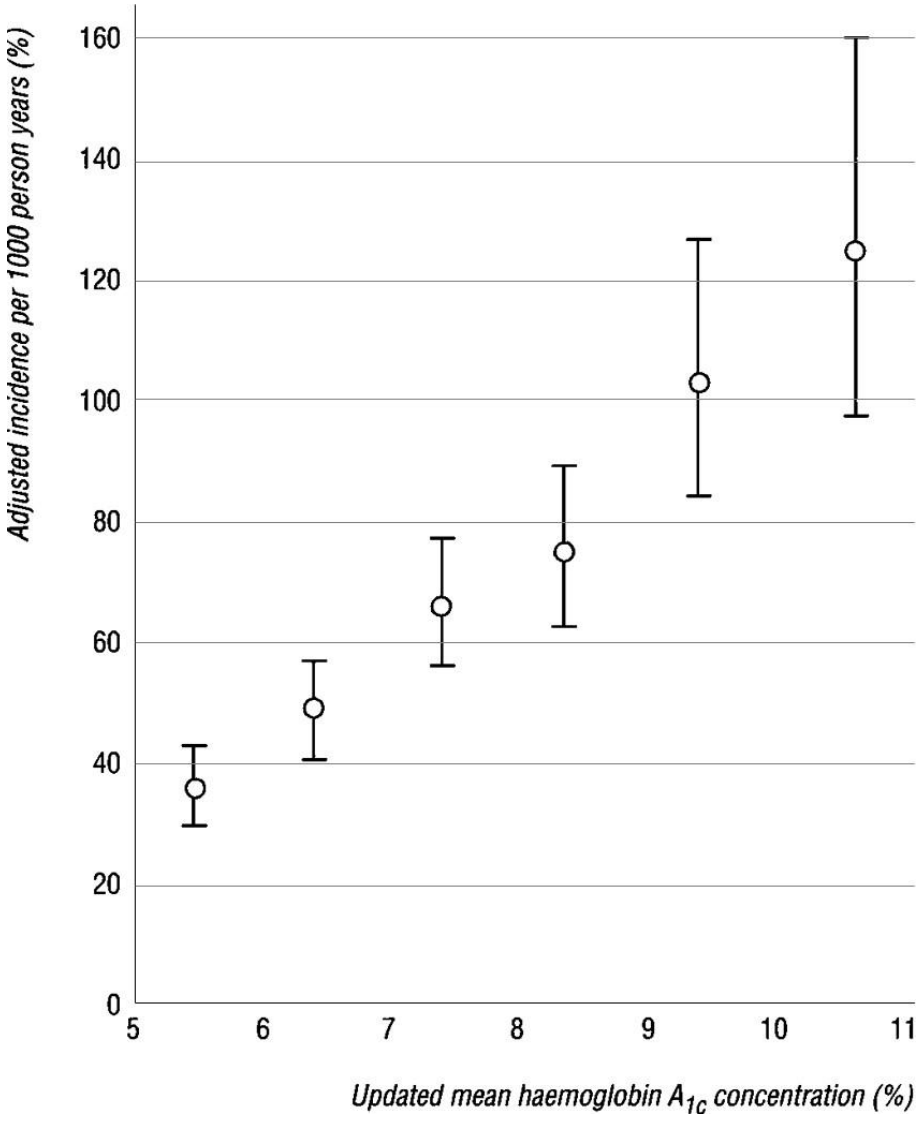

Figure 3. Endpoint related to diabetes: adjusted incidence rate and 95% confidence intervals for any endpoint related to diabetes by category of HbA1c*

*Endpoint includes myocardial infarction, sudden death, angina, stroke, renal failure, lower extremity amputation or death from peripheral vascular disease, death from hyperglycaemia or hypoglycaemia, heart failure, vitreous haemorrhage, retinal photocoagulation, and cataract extraction
Taken from Stratton et al, UKPDS 35[39]

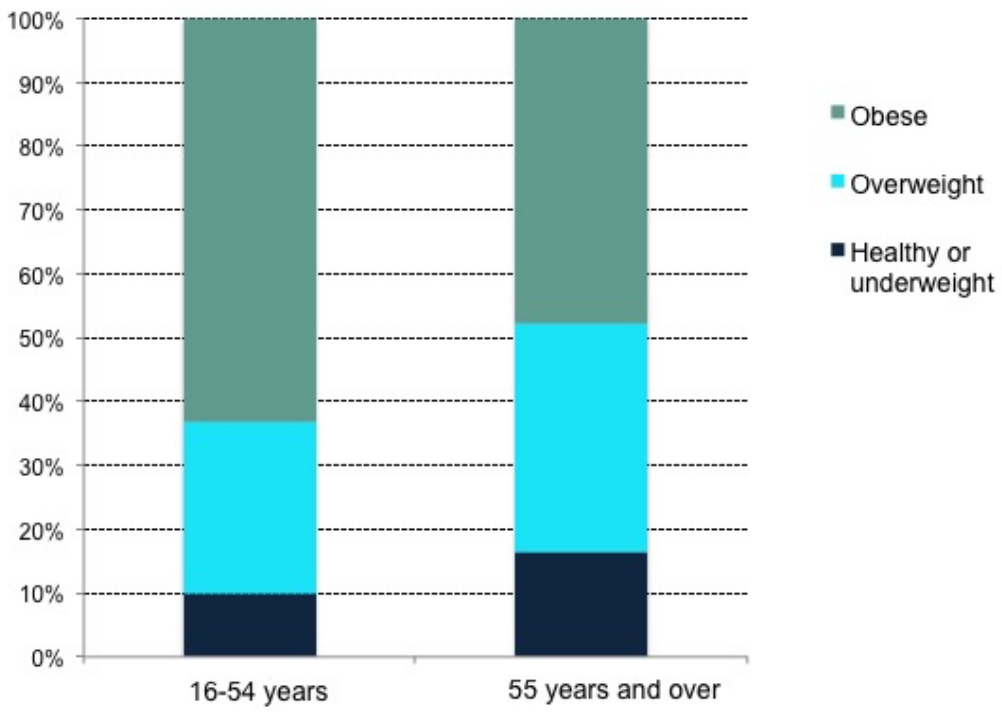

Figure 4. Weight status among adults with type 2 diabetes in England and Wales

Extrapolated from data provided by the National Diabetes Audit 2009-2010[44]

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