Reassessing the goals in type 2 diabetes management: A time for change?

David Haslam

Type 2 diabetes is associated with a significant risk of micro- and macrovascular complications, with the risk of cardiovascular disease (CVD), in particular, two- to five-times higher for people with type 2 diabetes compared with healthy individuals. This article considers the steps that can be taken in primary care to minimise these risks, in particular by screening asymptomatic individuals for type 2 diabetes, establishing and maintaining both metabolic and CVD treatment targets, and implementing appropriate and intensive treatment early in the disease process. The article also considers whether incretin-based therapies, a relatively new treatment option for type 2 diabetes, have a role in the management of the condition early in the disease process.

Individuals with type 2 diabetes may remain asymptomatic for many years, resulting in delayed diagnosis and treatment. A report states that 2.1 million people of at least 17 years of age with a diagnosis of diabetes were registered at GP practices in England in 2008 (NHS Information Centre for Health and Social Care et al, 2008). The discrepancy between this figure and the estimated prevalence from modelling suggests that approximately 350 000 adults with diabetes were undiagnosed (NHS Information Centre for Health and Social Care et al, 2008).

The importance of effective screening

Earlier and more extensive screening is necessary to reduce the number of people with undiagnosed type 2 diabetes. The importance of such screening is apparent from a Canadian study in which 21–39% of individuals at the time of type 2 diabetes diagnosis already had some sight-threatening retinopathy (International Diabetes Federation Clinical Guidelines Taskforce, 2005).

Particular attention should be paid to screening individuals at a higher risk of type 2 diabetes, including obese people, those presenting with other metabolic syndrome criteria, a history of gestational diabetes or a strong family history of diabetes. As people with cardiovascular disease (CVD) often have undiagnosed type 2 diabetes or glucose intolerance (Norhammar et al, 2002; Matz et al, 2006), there is a clear rationale for incorporating CVD risk

Article points

1. Screening should identify individuals with type 2 diabetes early in the course of the condition so they can gain prompt access to lifestyle counselling, monitoring and treatment intervention.
2. Good type 2 diabetes management requires treatments that provide good glycaemic control with low rates of hypoglycaemia, but that can also improve cardiovascular risk factors and have the potential to preserve beta-cell function.
3. Early intensive multifactorial treatment intervention based on the individual's risk assessment is recommended, provided treatment goals can be achieved safely and responsibly.

Key words

- Incretin therapies
- Multifactorial treatment
- Oral antidiabetes drugs
- Type 2 diabetes

Author's details can be found at the end of this article.

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1. Management guidelines from NICE, the European Society of Cardiology/European Association for the Study of Diabetes (EASD), the American Diabetes Association (ADA)/EASD) and the Joint British Societies detail recommended goals for levels of HbA_{1c}, fasting and postprandial glucose, blood pressure and lipids.
2. Despite the many guidelines for the management of type 2 diabetes, target blood glucose and cardiovascular disease risk factor goals are currently poorly attained.

scores, such as the Systematic Coronary Risk Evaluation (SCORE) (Conroy et al, 2003), UK Prospective Diabetes Study (UKPDS) Risk Engine (Stevens et al, 2001), Framingham (Wilson et al, 1998), and QRISK-2 (Hippisley-Cox et al, 2008), into screening methodologies. The NHS "Health Check" programme – which assesses vascular risk in adults aged 40–74 years with no existing diagnosed vascular disease – is an important step in this direction (Department of Health, 2009). This programme should identify individuals with type 2 diabetes early in the course of the condition so they can gain prompt access to lifestyle counselling, monitoring and treatment intervention.

Ensuring individuals achieve treatment goals

Current type 2 diabetes management fails to reach treatment goals

Management guidelines from NICE (2009), the European Society of Cardiology/European Association for the Study of Diabetes (EASD) (Rydén et al, 2007), the American Diabetes Association (ADA)/EASD (Nathan et al, 2009) and the Joint British Societies (JBS-2) (British Cardiac Society et al, 2005) detail recommended goals for levels of HbA_{1c}, fasting and postprandial glucose, blood pressure and lipids (*Table 1*). While two of the guidelines also include BMI or weight (*Table 1*), abdominal obesity (as measured by waist circumference) is more accurate than BMI for predicting cardiometabolic risk (Balkau et al, 2007; Smith and Haslam, 2007). Of the recommended goals, HbA_{1c} is generally considered the standard measure for assessing blood glucose control.

Despite the many guidelines for the management of type 2 diabetes, target blood glucose and CVD risk factor goals are currently poorly attained. The National Diabetes Audit analysis for general practice for 2007–2008 reported that 63% of people with diabetes in England reached HbA_{1c} levels of ≤7.5% (≤58 mmol/mol) (NHS Information Centre for Health and Social Care, 2009). The NICE cholesterol target (<5 mmol/L) and diastolic and systolic blood pressure targets (≤75 and ≤135 mmHg, respectively) were attained by 78 and 30% of people, respectively. Similarly, an evaluation of cholesterol goal achievement in UK clinical practice determined that most people (~73%) did not achieve the stringent JBS-2 cholesterol

Table 1. Recommended treatment targets for people with type 2 diabetes.

Organisation	HbA_{1c} (%) [mmol/mol]	FPG (mmol/L)	PPG (mmol/L)	LDL-cholesterol (mmol/L)	BP (mmHg)	BMI/weight
National Institute for Health and Clinical Excellence (NICE, 2009)	<6.5 [<48]	–	<8.5	–	<140/80 (<130/80 in high-risk people)	Weight loss 5–10%
European Society of Cardiology/European Association for the Study of Diabetes (Rydén et al, 2007)*	≤6.5 [≤48]	<6.0	<7.5	≤1.8	<130/80	<25 kg/m^2
American Diabetes Association/European Association for the Study of Diabetes (Nathan et al, 2009)	<7.0 [<53]	3.9–7.2	<10	–	–	–
Joint British Societies (British Cardiac Society et al, 2005)†	<6.5 [<48]	4.0–6.0	≤7.8	<2.0	<140/85 (<130/80 in high-risk people)	–

*These targets are for people with type 2 diabetes and coronary artery disease.
†Optimal rather than audit standard targets are listed.
BMI=body mass index; BP=blood pressure; FPG=fasting plasma glucose; LDL=low-density lipoprotein; PPG=postprandial glucose.

target (<4.0 mmol/L; British Cardiac Society et al, 2005), even with prescribed therapy (Rajagopalan et al, 2007).

Barriers to reaching treatment goals

A multitude of factors underlie the failure to reach treatment goals. Treatment goals may not be achieved because appropriate or intensified treatment is given too late in the disease process, resulting from delays in diagnosis and/or in the current stepwise treatment protocols. Patients' adherence to the treatment plan may also be poor, perhaps due to fears regarding hypoglycaemia and weight gain, but particularly with dosing regimens that are complex. A treatment adherence study of people with type 2 diabetes in Scotland, for example, demonstrated that only one in three people had adequate adherence (defined as ≥90%) when prescribed one tablet per day, and adherence decreased linearly with increases in the number of prescribed medications to be taken daily (Donnan et al, 2002).

Type 2 diabetes management may also be hindered by the failure of treatments to arrest the decline in beta-cell function and/or the tendency of some treatments to increase CVD risk factors, such as abdominal obesity. In the UKPDS 49, effective diabetes control progressively deteriorated over time (Turner et al, 1999). For people receiving insulin monotherapy, the proportion attaining the HbA_{1c} goal (<7.0% [<53 mmol/mol]) declined from 47% at 3 years to 37 and 28% at 6 and 9 years, respectively; corresponding values of 50, 34 and 24% were reported for people treated with a sulphonylurea.

Weight gain is associated with many commonly used type 2 diabetes treatments, such as insulin, sulphonylureas and meglitinides (Nathan et al, 2009). Weight gain is also apparent with thiazolidinedione treatment, however there is some evidence that although the overall fat mass is increased, a redistribution of fat from visceral to lower-risk subcutaneous areas occurs (Kushner and Sujak, 2009). This is exemplified by data from UKPDS 33, in which people receiving insulin or sulphonylureas had increased weight gains of 4.0 and 1.7–2.6 kg, respectively, compared with the conventional therapy group receiving dietary advice (UKPDS Group, 1998). In contrast, metformin is considered to be weight-neutral (Nathan et al, 2009).

Targeting all risk factors and initiating early intensive therapy

Micro- and macrovascular disease

Several studies have demonstrated that intensively managing hyperglycaemia decreases diabetes-related microvascular disease. UKPDS 35, for example, showed that the risk of microvascular complications was reduced by 37% when HbA_{1c} was reduced by 1% (Stratton et al, 2000). However, both the incidence of, and mortality due to, macrovascular disease are more significant than those due to microvascular disease. In UKPDS 17, diabetic microvascular disease was experienced by 9% of people with type 2 diabetes, while 20% experienced macrovascular complications; additionally, a fatal outcome occurred 70 times more frequently with macrovascular disease compared with microvascular disease (Turner et al, 1996).

Current evidence suggests that macrovascular outcomes can be improved by managing all metabolic and CVD risk factors. In the Steno-2 study, which targeted several risk factors with intensive treatment (including lifestyle modification, CVD primary prevention with aspirin and maintenance of an HbA_{1c} level ≤6.5% [≤48 mmol/mol] using a stepped treatment algorithm) over an average of 7.8 years, the risk of both macro- and microvascular events was reduced by approximately 50% when hyperglycaemia, hypertension, dyslipidaemia and microalbuminuria were targeted in combination (Gaede et al, 2003). This CVD risk reduction is higher than that observed in most studies using single-factor intervention therapies. In addition, a decrease in the ratio of saturated and unsaturated fatty acids, and total fat intake in the daily diet of people, in the intensive treatment arm was significantly lower than those for the people in the standard treatment arm (Gaede et al, 2001).

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2. Type 2 diabetes management may also be hindered by the failure of treatments to arrest the decline in beta-cell function or the tendency of some treatments to increase cardiovascular disease (CVD) risk factors, such as abdominal obesity.
3. Several studies have demonstrated that intensively managing hyperglycaemia decreases diabetic microvascular disease.
4. Current evidence suggests that macrovascular outcomes can be improved by managing all metabolic and CVD risk factors.

Page points

1. The literature regarding the effects of intensive glycaemic control alone on macrovascular outcomes appears conflicting. However, it is possible that discrepancies arise in part because of differences in the timings of interventions relative to the disease process, with early intervention associated with more positive outcomes.
2. In the UK Prospective Diabetes Study, while there were no differences between groups for the risk of myocardial infarction at the end of the intervention period, participants were followed-up for a further 10 years after the cessation of randomised treatment, and a significant reduction in the risk of myocardial infarction was apparent in the group formerly assigned to intensive treatment.

In a 5.5-year follow-up to the Steno-2 study, the beneficial effects on CVD events were sustained, demonstrating the effectiveness of multifactorial treatment for people with type 2 diabetes (Gaede et al, 2008). The benefits of tailoring this multifaceted approach to the individual's needs with personalised education and surveillance were demonstrated in a 6-year Danish study in primary care, as metabolic and CVD risk factors (HbA_{1c}, fasting plasma glucose, systolic blood pressure and cholesterol levels) were reduced, compared with routine, non-individualised type 2 diabetes management (Olivarius et al, 2001).

The literature regarding the effects of intensive glycaemic control alone on macrovascular outcomes appears conflicting. However, it is possible that discrepancies arise in part because of differences in the timings of interventions relative to the disease process, with early intervention associated with more positive outcomes. For example, analyses of data from the General Practice Research Database (GPRD), involving more than 47 000 people over a 12-year period, revealed that the likelihood of both all-cause mortality and progression to first large-vessel event was reduced for those taking a combination of metformin with sulphonylurea compared with people whose regimens included insulin (Currie et al, 2010). Of relevance here is the fact that the group receiving metformin with sulphonylurea had a shorter duration of diabetes and fewer people with comorbidities at baseline compared with the group receiving insulin regimens. This interpretation of the GPRD data, with macrovascular benefits perhaps dependent on early intervention, resonates with findings from other studies (Holman et al, 2008; ACCORD [Action to Control Cardiovascular Risk in Diabetes] Study Group et al, 2011; ADVANCE [Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation] Collaborative Group et al, 2008; Reaven et al, 2009). In the UKPDS, people newly diagnosed with type 2 diabetes at baseline were randomly allocated to either intensive treatment (sulphonylurea or insulin or metformin) or conventional treatment (a change in diet) (Holman et al, 2008). While there were no differences between groups for the risk of myocardial infarction at the end of the intervention period, participants were followed-up for a further 10 years after the cessation of randomised treatment, and a significant reduction in the risk of myocardial infarction was apparent in the group formerly assigned to intensive treatment. Similarly, in a sub-study analysis of the VADT (Veteran's Affairs Diabetes Trial) data, participants with less advanced atherosclerosis had a greater improvement in CVD outcomes with intensive therapy compared with people with more advanced atherosclerosis (Reaven et al, 2009). In the ACCORD and ADVANCE studies, participants with diabetes and micro- or macrovascular disease achieved good glycaemic control without a reduction in cardiovascular risk (ACCORD Study Group et al, 2011; ADVANCE Collaborative Group et al, 2008).

Hypoglycaemia

The GPRD study also showed increased all-cause mortality and progression to a first large-vessel disease event at high HbA_{1c} levels compared with HbA_{1c} levels of approximately 7.5% (58 mmol/mol), and an increased risk of all-cause mortality at low HbA_{1c} levels compared with levels of approximately 7.5% (58 mmol/mol) (Currie et al, 2010). The authors suggest that one explanation for the increased risk of all-cause mortality at lower HbA_{1c} levels may be the increased risk of hypoglycaemia associated with intensive glycaemic control, potentiating glucose variability and contributing to oxidative stress and vascular inflammation.

If hypoglycaemia is responsible for increased mortality risk it could be postulated that intensive glycaemic control should be implemented with antidiabetes agents associated with a particularly low risk of hypoglycaemia. However, the authors of a recent 5-year follow-up of the ACCORD trial concluded that although the intensively treated group experienced an

increased rate of overall mortality compared with the less intensively treated group, severe hypoglycaemia was not implicated (ACCORD Study Group et al, 2011).

Cost considerations

As health costs increase significantly with the prevalence of long-term diabetes complications (Clarke et al, 2003), one might expect that improved type 2 diabetes management early in the disease process would yield some cost benefits. ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care) will soon provide further data regarding the benefit and costs of intensive multifactorial treatment early in the disease process (Sandbaek et al, 2008).

Implementing good management strategies for type 2 diabetes in primary care

QOF

In the UK, QOF provides treatment indicators for use in primary care. The lowest HbA_{1c} levels for QOF indicators were tightened from ≤7.5 to ≤7.0% (≤58 to ≤53 mmol/mol) in 2009. Although there is clinical research evidence indicative of significant benefits with tight glycaemic control early in the disease process (Holman et al, 2008), setting indicators in this manner was not without problems.

By rewarding physicians to attain HbA_{1c} levels of ≤7.0% (≤53 mmol/mol), there was a natural temptation to drive the levels of people at 7.1% (54 mmol/mol) down further by intensifying treatment, even if their diabetes was well controlled. In addition, those people with HbA_{1c} levels of ≥10% (≥86 mmol/mol) may have been neglected because, for example, people who improve from 12 to 10% had a negative impact on incentive payments despite a marked improvement in glycaemic control. Debate over the QOF indicators has resulted in a change in the lowest HbA_{1c} levels back to ≥7.5% (≥58 mmol/mol) (NHS Employers, 2011).

Another limitation of the QOF indicators is the lack of incentives for screening obese or high-risk people, which is necessary for early treatment intervention. To achieve sufficient numbers of people with HbA_{1c} levels ≤7.0%, those with manageable levels should be treated earlier.

Hypoglycaemia

A key consideration in the safe delivery of intensive type 2 diabetes treatment remains the risk of hypoglycaemia. In the ACCORD and VADT trials, hypoglycaemia was significantly more common in the intensive therapy group compared with the standard therapy group (ACCORD Study Group et al, 2008; Duckworth et al, 2009).

There is an inherent risk of hypoglycaemia with therapies that increase insulin concentrations in the blood independently of blood glucose levels (such as insulin secretagogues and insulins). Over the first 10 years of the UKPDS, 36.5% of people treated with insulin reported hypoglycaemia, with 1.8% experiencing severe hypoglycaemic episodes (UKPDS Group, 1998). Other UK community-based studies have observed higher incidences of severe hypoglycaemic events (2–15%) in people treated with insulin (Leese et al, 2003; Henderson et al, 2003; Donnelly et al, 2005). In addition, in a study of people with type 2 diabetes treated with sulphonylureas or insulin for <2 years, there were no significant differences between the two treatments in the proportion of people experiencing mild (39 versus 51%) or severe hypoglycaemia (7% in both cases) (UK Hypoglycaemia Study Group, 2007).

It is important to appreciate that severe hypoglycaemic events may be more common than is recognised by primary care clinicians as there is no obligation for severe hypoglycaemic events requiring assistance from a paramedic to be reported to primary care (Leese et al, 2003). The choice of antidiabetes agent can do much to mitigate the risk of hypoglycaemia, while also achieving good glycaemic control.

Management strategies

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Page points

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Page points

1. The recent development of incretin-based therapies – namely the dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists – offer newer options for the management of type 2 diabetes.
2. DPP-4 inhibitors are orally administered agents that block the inactivation of GLP-1 and gastric inhibitory peptide, incretin hormones that are secreted from the gastrointestinal tract.
3. There are two injectable GLP-1 receptor agonists available in the UK – exenatide, administered twice-daily and liraglutide, administered once-daily.

also improve CVD risk factors and have the potential to preserve beta-cell function.

Currently, when lifestyle and dietary advice are no longer sufficient to maintain glycaemic control, metformin is the most commonly recommended first-line pharmacological intervention (Nathan et al, 2009; NICE, 2009; Rodbard et al, 2009). Other well-established agents commonly recommended for use early in the disease process include sulphonylureas and thiazolidinediones. The recent development of incretin-based therapies – namely the dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists – offer newer options for the management of type 2 diabetes.

Incretin-based therapies: approved uses and efficacy

DPP-4 inhibitors are orally administered agents that block the inactivation of GLP-1 and gastric inhibitory peptide, incretin hormones that are secreted from the gastrointestinal tract (Drucker and Nauck, 2006). DPP-4 inhibitors approved for use in the UK comprise sitagliptin, vildagliptin and saxagliptin. There are variations in the licenced indications of these drugs, which are listed in full in the relevant summary of product characteristics (Electronic Medicines Compendium [EMC] 2011a; b; c) and national guidance on their use is available from NICE (2009) and SIGN (2010).

These agents offer clinically important improvements in glycaemic control, generally in the range 0.5–1.1%, as monotherapy and in combination with a range of other oral antidiabetes drugs (Ahrén, 2008; Nathan et al, 2009). DPP-4 inhibitors are normally considered to be weight neutral (Ahrén, 2008; Nathan et al, 2009), although a mean weight loss of 0.96 kg has been reported with sitagliptin in a head-to-head study with liraglutide (Pratley et al, 2010).

Improved beta-cell function, assessed using the homeostasis assessment model of beta-cell function (HOMA-B) and proinsulin:insulin ratio, has been demonstrated in clinical trials with DPP-4 inhibitors (Pratley et al, 2008; Riche et al, 2009; DeFronzo et al, 2009). The limited data available also suggest that DPP-4 inhibitors may mediate reductions in blood pressure (Bosi et al, 2007; Pratley et al, 2010).

There are two injectable GLP-1 receptor agonists available in the UK – exenatide, administered twice-daily and liraglutide, administered once-daily. These agents stimulate glucose-dependent endogenous insulin secretion, decrease glucagon secretion and inhibit gastric emptying (Drucker and Nauck, 2006). There are variations in the specific licenced indications for exenatide and liraglutide in people with type 2 diabetes and full details can be found in the respective summary of product characteristics (EMC 2010; 2011d). National guidance on their use is available from NICE (2009; 2010) and SIGN (2010).

GLP-1 receptor agonists have demonstrated improvements in glycaemic control. Exenatide 10 µg reduced HbA_{1c} levels by 0.78–1.5% over 26–30 weeks, and 30–40% of people reached HbA_{1c} levels of ≤7.0% (≤53 mmol/mol) (Buse et al, 2004; DeFronzo et al, 2005; Kendall et al, 2005; Drucker et al, 2008; Buse et al, 2009). In those completing up to 3 years of treatment, glycaemic control was sustained and approximately half achieved HbA_{1c} levels ≤7.0% (≤53 mmol/mol) (Buse et al, 2007; Klonoff et al, 2008).

Mean reductions in HbA_{1c} levels for liraglutide 1.2 and 1.8 mg after 26 weeks in combination therapy ranged from 1.0–1.5% for both doses, allowing 35–58% of people receiving 1.2 mg and 42–55% receiving 1.8 mg to achieve HbA_{1c} levels of <7.0% (<53 mmol/mol) Marre et al, 2009; Nauck et al, 2009; Zinman et al, 2009; Russell-Jones et al, 2009; Buse et al, 2009; Pratley et al, 2010).

In addition to their antihyperglycaemic effects, GLP-1 receptor agonists provide other benefits for the management of people with type 2 diabetes. Weight loss has been demonstrated with both exenatide and liraglutide. Progressive weight reductions were associated with exenatide treatment, with a mean loss of 1.6–3.6 kg in 26- to 30-week studies (Buse et al, 2004; DeFronzo

et al, 2005; Kendall et al, 2005; Drucker et al, 2008; Buse et al, 2009) and, among completers, 5.3 kg after a 3-year treatment period (Klonoff et al, 2008). In combination with metformin, liraglutide treatment was associated with clinically meaningful weight loss after 26 weeks (1.2 mg: 2.6–2.9 kg; 1.8 mg: 2.8–3.4 kg) (Nauck et al, 2009; Pratley et al, 2010). As expected, in combinations including oral agents associated with weight gain (sulphonylureas or thiazolidinediones), weight benefits were more variable (Buse et al, 2009; Marre et al, 2009; Russell-Jones et al, 2009; Zinman et al, 2009).

GLP-1 receptor agonists also have the potential to maintain or improve beta-cell function. HOMA-B and proinsulin:insulin ratios indicate improvements in beta-cell function after exenatide treatment (Buse et al, 2004; DeFronzo et al, 2005; Buse et al, 2007). Improvements in first- and second-phase insulin secretion have been observed with liraglutide treatment, in addition to improvements in arginine-stimulated insulin secretion during hyperglycaemia (Vilsbøll et al, 2008).

Beneficial effects on blood pressure have also been reported with GLP-1 receptor agonists (Buse et al, 2009; Pratley et al, 2010).

Safety of incretin-based therapies

Incretin-based therapies are generally well tolerated and rates of hypoglycaemia are low, although rates may increase in combination with sulphonylureas (Ahrén, 2008; Buse et al, 2009).

Increased rates of infections with sitagliptin have been noted as being of possible concern (Richter et al, 2008; Nathan et al, 2009), but an association with sitagliptin or other DPP-4 inhibitors has not been established.

Concerns have also been raised over a potential relationship between incretin-based therapies and acute pancreatitis (US Food and Drug Administration, 2009a; b). In light of the uncertainty regarding such a relationship, the discontinuation of exenatide and liraglutide is recommended if pancreatitis is suspected (EMC, 2010; 2011d). The most common adverse event with GLP-1 receptor agonists is nausea, although this is generally transient (DeFronzo et al, 2005; Buse et al, 2009).

Given the data for both glycaemic and extraglycaemic benefits, the low rates of hypoglycaemia and good general tolerability, the author suggests that it may be appropriate to consider using incretin therapies earlier in the treatment pathway for selected people with type 2 diabetes.

Conclusion

Traditional blood glucose-lowering therapies for type 2 diabetes often result in inadequate management, providing insufficient glycaemic control over time and being limited by side-effects, such as weight gain and an increased risk of hypoglycaemia. In addition, improvements in beta-cell function are, at best, modest. A number of practical changes in type 2 diabetes management are thus required, particularly in primary care, where most of the early treatment decisions are made. Effective screening to facilitate early diagnosis of type 2 diabetes is critical, and should be followed by a complete metabolic and CVD risk assessment. Early intensive multifactorial treatment intervention based on the individual's risk assessment is recommended, provided treatment goals can be achieved safely and responsibly. The effects of blood glucose-lowering drugs on all risk factors and on beta-cell function should also be considered when making these treatment decisions. ■

"Early intensive multifactorial treatment intervention based on the individual's risk assessment is recommended, provided treatment goals can be achieved safely and responsibly."

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Conflicts of interest
Professor David Haslam receives occasional honoraria for speaking or consultancy from GlaxoSmithKline, Merck Sharp & Dohme, Bristol-Myers Squibb, Novo Nordisk and sanofi-aventis, and has participated in advisory board meetings for them.

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