

Management strategies for diabetes

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Diabetes remains one of the biggest health challenges in the developed world, with a current prevalence of approximately 4% of the UK general population. In addition, there is an unprecedented rise in the incidence of type 2 diabetes in recent times [1], along with a much earlier age of onset. At the same time, the advent of newer drugs, especially those involving the incretin axis, makes choosing therapeutics a challenging task.

The overall management of diabetes has certainly come a long way. Compared to the early years of conservative approaches, treatment for diabetes has advanced considerably due to newer drugs and the emerging role of organ transplantation as a potential cure for the disease. Given the changing demographics of the current generation of patients, the concept of a 'standard' treatment strategy no longer holds.

In this chapter, we will discuss the various management strategies for diabetes, including nonpharmacological interventions such as dietary and lifestyle advice. Given the complexity of the disease, along with the choice of multiple treatment options, the majority of the discussion will focus on the management of type 2 diabetes. We have also compared the latest guidance from the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), and the National Institute of Clinical Excellence (NICE).

Glycemic goals of treatment

There is good evidence to support controlling hyperglycemia as a means of reducing long-term complications of diabetes. The most crucial studies providing this evidence are the Diabetes Control and Complications Trial (DCCT) [2] and the Stockholm Diabetes Intervention Study (SDID) [3] in type 1 diabetes, along with the UK Prospective Diabetes Study (UKPDS) [4,5] and Kumamoto Study [6] in type 2 diabetes.

The most recent ADA/EASD guidelines (published in April 2012) [7] recommend a 'general' glycemic goal of $<7\%$ glycated hemoglobin (HbA1c), with exceptions for certain individuals. The latest update from NICE, released in May 2009 [8], recommends an HbA1c $\geq 6.5\%$ as the threshold for initiating or up-titrating therapy in general, while $\geq 7.5\%$ remains the trigger for triple therapy. However both ADA/EASD and NICE guidance caution against adopting a blanket glycemic 'target' for all patient groups. Factors such as life expectancy and risk of hypoglycemia need to be taken into account for each individual before intensifying treatment.

While there is increasing evidence to support aggressive glycemic control at the point of diagnosis in order to improve metabolic memory and induce a state of 'remission' [9–14], there have been recent conflicting data questioning the safety and overall benefit of tighter glycemic control in terms of reducing cardiovascular events [15–17].

Given the current evidence, it is important to individualize such targets after a careful risk-benefit assessment. Along with glycemic targets, aiming for optimum blood pressure and lipid profile should also remain an integral part of diabetes management and reducing the risk of cardiovascular disease.

Importance of lifestyle issues and patient education

Diabetes is a lifelong condition that is essentially managed by the individual and/or a carer. An individual's lifestyle, especially with regard to physical activity and overall caloric intake, has an enormous impact on the course of diabetes. This is of particular relevance in the long-term management of type 2 diabetes due to the progressive nature of the disease. In addition, lifestyle issues are of greater importance due to the unprecedented rise in incidence of diabetes secondary to increasing

adiposity levels. Lifestyle advice given in the form of structured education enables self-management and should be at the heart of diabetes care. According to the National Service Framework (NSF) for diabetes, “people with diabetes need the knowledge, skills and motivation to assess their risks, to understand what they will gain from changing their behavior or lifestyle and to act on that understanding by engaging in appropriate behaviors” [18]. In addition, research has shown that patients who never received diabetes education showed a four-fold increased risk of major complications [19]. A Health Commission survey in 2007 suggested that only 11% of people with type 2 diabetes reported being offered structured education [20].

As change in lifestyle warrants a change in behavior, it is usually much more difficult to implement and, hence, can be perceived as a less effective method of managing diabetes. This is perhaps why physicians use pharmacological intervention at an early stage instead of emphasizing the importance of lifestyle change. Nevertheless, the role of lifestyle modification should not be undermined. Targeting the appropriate patient group with an individualized lifestyle plan devised by an expert should remain an integral part of diabetes management. Such advice may be offered one-to-one or in a group session, depending on local arrangements. In addition, the advice needs to be consistent and delivered by trained healthcare professionals with diabetes-related expertise. In the UK, NICE recommends offering structured education at the time of diagnosis, with annual reinforcement and review [8].

Lifestyle intervention also has a role in diabetes prevention, especially in high-risk groups. Also, those with impaired fasting glucose (IFG; fasting glucose of 6.0–6.9 mmol/L) or impaired glucose tolerance (IGT; fasting glucose of <7.0 mmol/L and 2 hour post-glucose readings between 7.8–11.1 mmol/L) are 5 to 15 times more likely to develop type 2 diabetes [21]. Obesity is the strongest risk factor for type 2 diabetes. The National Health and Nutrition Examination Survey III (1998–1994) data showed that the risk of diabetes is approximately 50% in patients with body mass index (BMI) of 30 kg/m² or more [22]. Targeted lifestyle intervention can delay or even prevent the incidence of type 2 diabetes in such individuals [23,24].

It is important that we continue to recognise lifestyle modification as a crucial part of preventing and managing diabetes, warranting active participation of both patients and health professionals.

What determines treatment choice?

Broadly speaking, the initial choice of treatment is guided by the type of diabetes. All individuals with suspected or proven type 1 diabetes should be commenced on insulin as first-line treatment.

In type 2 diabetes, treatment is not as straightforward. The initial treatment is guided by the HbA1c at diagnosis, the presence of osmotic symptoms, evidence of catabolic state (rapid unintentional weight loss), and the presence of any organ dysfunction that may preclude the use of a particular therapeutic agent. In addition, other attributes including age, body weight, convenience of administration, and impact on work-related issues (such as driving motor vehicles) also play a crucial role in determining the order of medications used. The efficacy and side effect profile of each drug in the individual patient is also taken into account.

In individuals with an initial HbA1c of $<10\%$ in the absence of osmotic symptoms, the general consensus is to start metformin, especially in those who are overweight. Despite an increasing number of options for addressing hyperglycemia, only metformin has been shown to improve prognosis as a primary endpoint in a randomized-controlled trial [25]. Sulfonylureas are an option in cases where metformin use is contraindicated or not tolerated. Sulfonylureas are also prescribed where rapid therapeutic response is desired, especially in the symptomatic group.

Initial treatment should be up-titrated at a rapid pace to aim for an agreed target HbA1c. Patients should be made aware of the progressive nature of the disease; after a successful initial response to oral therapy, patients fail to maintain target HbA1c levels ($<7\%$) at a rate of 5–10% per year. An analysis from the UKPDS study found that 50% of patients originally controlled with a single drug required the addition of a second drug after 3 years; after 9 years, 75% of patients needed multiple therapies to achieve the target HbA1c value [26].

Several agents can be considered as add-on therapy when metformin monotherapy fails, including sulfonylureas, thiazolidinediones (TZDs),

and alpha-glucosidase inhibitors. Oral agents as monotherapy (TZDs, metformin, repaglinide, alpha-glucosidase inhibitors and sulfonylureas) improve glycemic control to almost the same degree (eg, decrease in HbA1c of approximately 1%) [27]. When combining two antidiabetes drugs, a further 1% HbA1c reduction can be obtained. These agents are discussed in more detail in Chapter 4.

Individuals with markedly raised HbA1c at diagnosis ($>10\%$), with or without osmotic and catabolic symptoms, should be treated more aggressively, with early use of insulin to be considered. This issue is discussed further in Chapter 3.

Current guidelines for treatment

The emergence of new incretin-based drugs makes prescribing in diabetes more exciting but far from easy. Unfamiliarity with these new drugs and relatively higher prescription costs warrants judicious use at this stage.

Clinical guidelines help with this conundrum by bringing the best available evidence to the point of practice. However, guidelines often do not provide recommendations for all clinical scenarios. In this chapter we endeavor to cover the most up-to-date recommendations based on the clinical guidelines from the ADA, EASD, and NICE on the management of type 2 diabetes. By comparing available guidelines, we aim to provide a balanced viewpoint to aid appropriate and effective prescribing for clinicians.

ADA/EASD consensus statement

The latest ADA/EASD consensus statement is based on clinical trial evidence and the clinical judgement of ten named authors [7]. The general glycemic goal advised by the ADA/EASD consensus is a HbA1c level $<7\%$, with recommendations for individualized targets in some patients.

The choice of treatment is based on effectiveness of individual therapies and basal level of glycemic control. In cases of high basal HbA1c (eg, HbA1c $>9\%$), a more aggressive approach using insulin alone or combination therapy is recommended. While metformin remains the ‘gold standard’ first-line agent, the ADA/EASD guidelines now recommend insulin for many patients at all stages of the disease, including

first-line (in the setting of marked uncontrolled hypoglycemia), and/or HbA1c >12%, or the presence of ketonuria or catabolic symptom) [7].

Thiazolidinediones

The ADA/EASD authors advise caution in using TZDs due to increased risks of fluid retention, heart failure, and incidence of fractures [7]. Currently in the US, TZDs are approved for use in combination with metformin, sulfonylureas, glinides, and insulin [28]. The FDA has substantially restricted the use of rosiglitazone by requiring a risk evaluation and mitigation strategy (REMS) due to an increased risk for cardiovascular ischemia [29].

Glucagon-like peptide-1 agonists

The glucagon-like peptide [GLP-1] agonists exenatide and liraglutide are approved for use in the US with sulfonylurea, metformin, and/or a TZD [28]. However, unlike the NICE guidance, the ADA/EASD does not suggest a restriction in use of GLP-1 agonists in individuals with a BMI >35 kg/m² [7].

Dipeptidyl peptidase-4 inhibitors

The ADA/EASD authors note that dipeptidyl peptidase-4 (DPP-4) inhibitors have ‘intermediate’ efficacy in combination with metformin. They can also be used in a triple combination with metformin plus a sulfonylurea, TZD, or insulin. These inhibitors are weight-neutral and have been found to be well tolerated [7].

Insulin

The updated ADA/EASD guidelines recommend starting most patients with basal insulin. Rapid insulin analog preparations should be used for patients who need prandial insulin therapy due to diminished insulin secretory capacity [7].

Initiating therapy

The ADA/EASD’s general recommendations are found in Figure 2.1. All patients should start by making lifestyle changes, such as healthy eating and increased exercise, and continue with these changes for the duration.

ADA/EASD general recommendations for antidiabetic therapy in type 2 diabetes						
Healthy eating, weight control, increased physical activity						
Initial drug monotherapy	Metformin					
Efficacy (↓ HbA1C)	High					
Hypoglycemia	Low risk					
Weight	Neutral/loss					
Side effects	GI/lactic acidosis					
If needed to reach individualized HbA1C target after ~3 months, proceed to two-drug combination (order not meant to denote any specific preference):						
Two-drug combinations*	Metformin + Sulfonyleurea**	Metformin + TZD	Metformin + DPP-4 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + Insulin (usually basal)	
Efficacy (↓ HbA1C)	High	High	Intermediate	High	Highest	
Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	High risk	
Weight	Gain	Gain	Neutral	Loss	Gain	
Major side effect(s)	Hypoglycemia	Edema, HF, FXs	Rare	GI	Hypoglycemia	
If needed to reach individualized HbA1C target after ~3 months, proceed to two-drug combination (order not meant to denote any specific preference):						
Three-drug combinations	Metformin + Sulfonyleurea† + TZD or DPP-4-i or GLP-1-RA or insulin†	Metformin + TZD + SU† or DPP-4-i or GLP-1-RA or insulin†	Metformin + DPP-4 inhibitor + SU† or TZD or insulin†	Metformin + GLP-1 receptor agonist + SU† or TZD or insulin†	Metformin + Insulin (usually basal) + TZD or DPP-4-i or GLP-1-RA	
If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3–6 months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents:						
More complex insulin strategies				Insulin (multiple daily doses)		

Figure 2.1 ADA/EASD general recommendations for antglycemic therapy in type 2 diabetes. Reinforce lifestyle interventions at every visit and check HbA1c every 3 months until <7%, and then every 6 months. The interventions should be changed if HbA1c is ≥7%. ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; DPP-4, dipeptidyl peptidase-4; FX, fracture; GLP-1-RA, glucagon-like peptide-1 receptor agonists; HbA1c, glycated hemoglobin; HF, heart failure; GI, gastrointestinal; SU, sulfonyleurea; TZD, thiazolidinedione. *Consider beginning at this stage in patients with very high HbA1c (eg, <9%). **Consider rapid-acting, non-sulfonyleurea secretagogues (meglitinides) in patients with irregular meal schedules or who develop late postprandial hypoglycemia on sulfonyleureas. †Usually a basal insulin (NPH, glargine, detemir) in combination with noninsulin agents. Adapted with permission from Inzucchi et al 2012 [7].

Metformin therapy can be started at diagnosis or soon afterwards. If the target HbA1c is not reached after about 3 months, a sulfonylurea, a TZD, GLP-1 receptor antagonist, DPP-4 inhibitor, or basal insulin can be added to metformin. Three-drug combinations may also be considered. If the patient is taking insulin as part of a combination therapy regimen and their HbA1c levels have not lowered to target after 3–6 months, a more complex insulin strategy will need to be tried [7].

NICE recommendations

The latest NICE guidance (issued in May 2009) continues to recommend an HbA1c $\geq 6.5\%$ as the threshold for initiating or up titrating therapy, while HbA1c $\geq 7.5\%$ remains the trigger for triple therapy (Figure 2.2) [8].

NICE continues to recommend metformin as first-line treatment and sulfonylureas as second-line agents.

DPP-4 inhibitors

Compared to the ADA/EASD, NICE does offer more clarity in terms of role for DPP-4 inhibitors (eg, sitagliptin, vildagliptin) in the treatment algorithm. They are recommended instead of a sulfonylurea or metformin as second-line agents in those who are unable to take the combination due to intolerance or contraindication of use of either of the drugs. The guidelines emphasize the need to avoid sulfonylurea use in patients with increased risk of hypoglycemia.

Sitagliptin, the only DPP-4 inhibitor available at the time of publication of the NICE guideline, is also recommended as a third-line agent in combination with metformin and a sulfonylurea when insulin is unacceptable or inappropriate.

Thiazolidinediones

NICE recommends considering a TZD (eg, pioglitazone) as a second-line agent with either metformin or a sulfonylurea, similar to a DPP-4 inhibitors, or as third-line therapy in combination with metformin and a sulfonylurea with suboptimal control, where insulin is inappropriate [8]. NICE clearly recommends not continuing or commencing a TZD in people who have heart failure, or who are at higher risk of fracture [8].

The combination of insulin and pioglitazone continues to be recommended as an option in selected patients. The NICE guidelines suggest that TZD may be preferable to a DPP-4 inhibitor in case of marked insulin insensitivity, or if a DPP-4 inhibitor is contraindicated, or not preferred due to previous intolerance or poor response.

DPP-4 inhibitor and TZD should be continued only if there is evidence of a beneficial metabolic response (eg, a reduction of at least 0.5% HbA1c in 6 months).

Due to ongoing concerns of increased risk of cardiovascular disease associated with the use of rosiglitazone, the European Medicines Agency Committee for Medicinal Products for Humane Use (EMA CHMP) recommended the suspension of marketing of rosiglitazone across the UK from September 2010 [30].

GLP-1 mimetic

GLP-1 mimetic (exenatide) use is limited as a third-line treatment in individuals with a BMI ≥ 35 kg/m² in those of European descent (with appropriate adjustment for other ethnic groups), or a BMI < 35 kg/m² in patients for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. NICE recommends continuing GLP-1 mimetic therapy only if there is evidence of a beneficial metabolic response (eg, a HbA1c reduction of at least 1.0% and a weight loss of at least 3% of initial body weight after 6 months).

Long-acting human insulin analogs

Similar to the ADA/EASD guidance, NICE recommends insulin as a step-up option after triple therapy, or after dual therapy in case of suboptimal glycemic control.

A long-acting insulin analog (eg, insulin detemir, insulin glargine) is recommended over neutral protamine hagedorn insulin in people with significant hypoglycemia, device preference, or those who want to reduce the number of injections. Similarly, premixed preparations with short-acting insulin analogs are indicated when there is preference for injecting insulin immediately before a meal, or due to hypoglycemia or marked post-prandial hyperglycemia.

NICE guideline on type 2 diabetes

Blood glucose-lowering therapy

HbA1c $\geq 6.5\%^*$ after trial of lifestyle interventions

Metformin[†]

Consider sulfonylurea[§] here if:

- patient is not overweight (tailor the assessment of body weight-associated risk according to ethnic group[§]), or
- metformin is not tolerated or is contraindicated, or
- a rapid therapeutic response is required because of hyperglycemic symptoms

HbA1c $\geq 6.5\%^*$

HbA1c $< 6.5\%^*$

Monitor for deterioration

Consider a rapid-acting insulin secretagogue for people with erratic lifestyles

Consider substituting a DPP-4 inhibitor^{§§} or a thiazolidinedione^{¶¶} for the sulfonylurea if there is a significant risk of hypoglycemia (or its consequences) or a sulfonylurea is contraindicated or not tolerated

Metformin + sulfonylurea[§]

HbA1c $\geq 7.5\%^*$

HbA1c $< 7.5\%^*$

Monitor for deterioration

Consider adding sitagliptin or a thiazolidinedione^{¶¶} instead of insulin if insulin is unacceptable (because of employment, social, recreational or other personal issues, or obesity)

Consider adding exenatide^{**} to metformin and a sulfonylurea if:

- BMI ≥ 35 kg/m² in people of European descent^{††} and there are problems associated with high weight, or
- BMI < 35 kg/m² and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities

Add insulin^{†,‡}, particularly if the person is markedly hyperglycemic

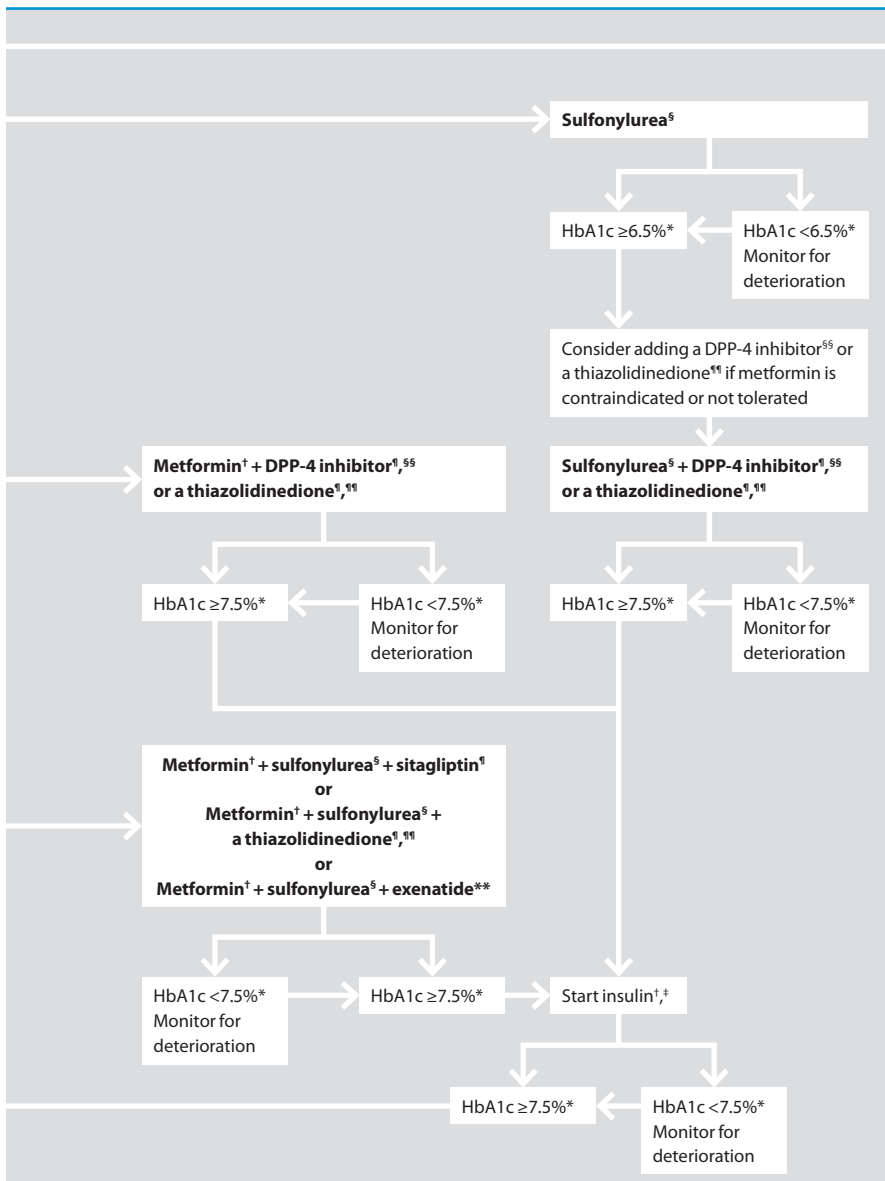
Insulin + metformin + sulfonylurea[§]

Increase insulin dose and intensify regimen over time

Consider pioglitazone with insulin if:

- a thiazolidinedione has previously had a marked glucose-lowering effect, or
- blood glucose control is inadequate with high-dose insulin

Figure 2.2 NICE guideline on type 2 diabetes. *Or individually agreed target. [†]With active dose titration. [‡]See the NICE clinical guideline on obesity (www.nice.org.uk/CG43). [§]Offer once-daily sulfonylurea if adherence is a problem. ^{§§}Only continue DPP-4 inhibitor or thiazolidinedione if reduction in HbA1c of at least 0.5% points in 6 months. ^{¶¶}Only continue exenatide if reduction in HbA1c of at least 1% point and weight loss of at least 3% of initial body weight at 6 months.



^{††}With adjustment for other ethnic groups. ^{**}Continue with metformin and sulfonyleurea (and acarbose, if used), but only continue other drugs that are licensed for use with insulin. Review the use of sulfonyleurea if hypoglycemia occurs. ^{§§}DPP-4 inhibitor refers to sitagliptin or vildagliptin. ^{¶¶}Thiazolidinedione refers to pioglitazone. NICE, National Institute for Health and Clinical Excellence. Reproduced with permission from NICE 2009 [8].

Somewhat contrary to current practice, NICE guidelines suggest using human insulin preparations as a general rule, rather than as an exception. However, this is justified on grounds of cost-effectiveness.

Comparison summary

For comparison of the recommendations of NICE and the ADA/EASD, see Figure 2.3 [7,8].

Iatrogenic hypoglycemia has been addressed by both groups. The newer agents, especially those working through the incretin axis, are less likely to cause hypoglycemia. Both groups also sound caution against the indiscriminate use of newer agents. This is particularly relevant for incretin-based therapies due to the lack of long-term safety data. In addition, NICE guidance does provide clear treatment targets: if these are not met during the specified period, the add-on therapeutic agent should be discontinued. Though this may be crucial to avoid indiscriminate use of new incretin-based agents, it may not reflect real-life clinical practice. Therefore, as also endorsed by NICE, the ultimate decision regarding individual glycemic targets and methods of achieving them should be made by an active partnership between the clinician and the patient and not by blanket guidelines.

Therapeutics, however, comprise only a small part of the management of diabetes. Day-to-day clinical practice with meaningful outcomes in patients' lives is what really underpins high-quality care. Due to various

Comparisons of the recommendations of NICE and ADA/EASD		
	NICE	ADA/EASD
Date of publication	May 2009	April 2012
Threshold for action (HbA1c values)	>6.5%	>7%
Metformin	First line	First line
Sulfonylureas	First line/second line	Second line/third line
Thiazolidinediones	Pioglitazone/rosiglitazone	Pioglitazone
GLP-1 receptor agonists	BMI restriction	–
DPP-4 inhibitors	Second line/third line	Second line/third line

Figure 2.3 Comparisons of the recommendations of NICE and ADA/EASD. ADA, American Diabetes Association; BMI, body mass index; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; EASD; European Association for the Study of Diabetes; HbA1c; glycated hemoglobin; NICE, National Institute of Clinical Excellence.

factors, including treatment inertia, there are wide gaps between recommendations and clinical practice. Also, with the current move towards a 'pay for performance' culture in health care and a focus on predetermined 'outcome' targets [31], patient-centered care appears to be under threat. This is likely to be detrimental for patients with chronic disease such as diabetes where care plans have to be individually tailored.

While the ADA/EASD consensus group may allow flexibility in treatment strategy by suggesting a two-tier approach, NICE guidance is based on up-to-date evidence and aids in translating recommendations into real-world clinical practice. It also helps the individual physician to tailor treatment based on patients' needs, rather than purely upon predetermined outcome targets.

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