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POSITION STATEMENT

Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

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Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation
AGI	α-Glucosidase inhibitor
CAD	Coronary artery disease
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DPP-4	Dipeptidyl peptidase IV
GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon-like peptide 1
NPH	Neutral protamine Hagedorn
TZD	Thiazolidinedione
UKPDS	UK Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial

Introduction

Glycaemic management in type 2 diabetes mellitus has become increasingly complex and, to some extent, controversial, with a widening array of pharmacological agents now available [1–5], mounting concerns about their potential adverse effects and new uncertainties regarding the benefits of intensive glycaemic control on macrovascular complications [6–9]. Many clinicians are therefore perplexed as to the optimal strategies for their patients. As a consequence, the American Diabetes Association (ADA) and the European Association for

the Study of Diabetes (EASD) convened a joint task force to examine the evidence and develop recommendations for anti-hyperglycaemic therapy in non-pregnant adults with type 2 diabetes. Several guideline documents have been developed by members of these two organisations [10] and by other societies and federations [2, 11–15]. However, an update was deemed necessary because of contemporary information on the benefits/risks of glycaemic control, recent evidence concerning efficacy and safety of several new drug classes [16, 17], the withdrawal/restriction of others and increasing calls for a move towards more patient-centred care [18, 19].

This statement has been written incorporating the best available evidence and, where solid support does not exist, using the experience and insight of the writing group, incorporating an extensive review by additional experts (acknowledged below). The document refers to glycaemic control; yet this clearly needs to be pursued within a multifactorial risk reduction framework. This stems from the fact that patients with type 2 diabetes are at increased risk of cardiovascular morbidity and mortality; the aggressive management of cardiovascular risk factors (blood pressure and lipid therapy, antiplatelet treatment and smoking cessation) is likely to have even greater benefits.

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These recommendations should be considered within the context of the needs, preferences and tolerances of each patient; individualisation of treatment is the cornerstone of success. Our recommendations are less prescriptive than and not as algorithmic as prior guidelines. This follows from the general lack of comparative-effectiveness research in this area. Our intent is therefore to encourage an appreciation of the variable and progressive nature of type 2 diabetes, the specific role of each drug, the patient and disease factors that drive clinical decision-making [20–23] and the constraints imposed by age and co-morbidity [4, 6]. The implementation of these guidelines will require thoughtful clinicians to integrate current evidence with other constraints and imperatives in the context of patient-specific factors.

Patient-centered approach

Evidence-based advice depends on the existence of primary source evidence. This emerges only from clinical trial results in highly selected patients, using limited strategies. It does not address the range of choices available, or the order of use of additional therapies. Even if such evidence were available, the data would show median responses and not address the vital question of who responded to which therapy and why [24]. Patient-centred care is defined as an approach to 'providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions' [25]. This should be the organising principle underlying healthcare for individuals with any chronic disease, but given our uncertainties in terms of choice or sequence of therapy, it is particularly appropriate in type 2 diabetes. Ultimately, it is patients who make the final decisions regarding their lifestyle choices and, to some degree, the pharmaceutical interventions they use; their implementation occurs in the context of the patients' real lives and relies on the consumption of resources (both public and private).

Patient involvement in the medical decision-making constitutes one of the core principles of evidence-based medicine, which mandates the synthesis of best available evidence from the literature with the clinician's expertise and patient's own inclinations [26]. During the clinical encounter, the patient's preferred level of involvement should be gauged and therapeutic choices explored, potentially with the utilisation of decision aids [21]. In a shared decision-making approach, clinician and patient act as partners, mutually exchanging information and deliberating on options, in order to reach a consensus on the therapeutic course of action [27]. There is good evidence supporting the effectiveness of this approach [28]. Importantly, engaging patients in healthcare decisions may enhance adherence to therapy.

Background

Epidemiology and healthcare impact

Both the prevalence and incidence of type 2 diabetes are increasing worldwide, particularly in developing countries, in conjunction with increased obesity rates and westernisation of lifestyle. The attendant economic burden for healthcare systems is skyrocketing, owing to the costs associated with treatment and diabetes complications. Type 2 diabetes remains a leading cause of cardiovascular disorders, blindness, end-stage renal failure, amputations and hospitalisations. It is also associated with increased risk of cancer, serious psychiatric illness, cognitive decline, chronic liver disease, accelerated arthritis and other disabling or deadly conditions. Effective management strategies are of obvious importance.

Relationship of glycaemic control to outcomes

It is well established that the risk of microvascular and macrovascular complications is related to glycaemia, as measured by HbA_{1c}; this remains a major focus of therapy [29]. Prospective randomised trials have documented reduced rates of microvascular complications in type 2 diabetic patients treated to lower glycaemic targets. In the UK Prospective Diabetes Study (UKPDS) [30, 31], patients with newly diagnosed type 2 diabetes were randomised to two treatment policies. In the standard group, lifestyle intervention was the mainstay with pharmacological therapy used only if hyperglycaemia became severe. In the more intensive treatment arm, patients were randomly assigned to either a sulfonylurea or insulin, with a subset of overweight patients randomised to metformin. The overall HbA_{1c} achieved was 0.9% lower in the intensive policy group compared with the conventional policy arm (7.0 vs 7.9% [53 vs 63 mmol/mol]). Associated with this difference in glycaemic control was a reduction in the risk of microvascular complications (retinopathy, nephropathy, neuropathy) with intensive therapy. A trend towards reduced rates of myocardial infarction in this group did not reach statistical significance [30]. By contrast, substantially fewer metformin-treated patients experienced myocardial infarction, diabetes-related and all-cause mortality [32], despite a mean HbA_{1c} only 0.6% lower than the conventional policy group. The UKPDS 10-year follow-up demonstrated that the relative benefit of having been in the intensive management policy group was maintained over a decade, resulting in the emergence of statistically significant benefits on cardiovascular disease (CVD) endpoints and total mortality in those initially assigned to sulfonylurea/insulin, and persistence of CVD benefits with metformin [33], in spite of the fact that the mean HbA_{1c} levels between the groups converged soon after the randomised component of the trial had concluded.

In 2008, three shorter-term studies (Action to Control Cardiovascular Risk in Diabetes [ACCORD] [34], Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation [ADVANCE] [35], Veterans Affairs Diabetes Trial [VADT] [36]) reported the effects of two levels of glycaemic control on cardiovascular endpoints in middle-aged and older individuals with well-established type 2 diabetes at high risk for cardiovascular events. ACCORD and VADT aimed for an HbA_{1c} <6.0% (<42 mmol/mol) using complex combinations of oral agents and insulin. ADVANCE aimed for an HbA_{1c} ≤6.5% (≤48 mmol/mol) using a less intensive approach based on the sulfonylurea gliclazide. None of the trials demonstrated a statistically significant reduction in the primary combined cardiovascular endpoints. Indeed, in ACCORD, a 22% increase in total mortality with intensive therapy was observed, mainly driven by cardiovascular mortality. An explanation for this finding has remained elusive, although rates of hypoglycaemia were threefold higher with intensive treatment. It remains unclear, however, if hypoglycaemia was responsible for the adverse outcomes, or if other factors, such as more weight gain, or simply the greater complexity of therapy, contributed. There were suggestions in these trials that patients without overt CVD, with shorter duration of disease, and lower baseline HbA_{1c}, benefited from the more intensive strategies. Modest improvements in some microvascular endpoints in the studies were likewise demonstrated. Finally, a meta-analysis of cardiovascular outcomes in these trials suggested that every HbA_{1c} reduction of ~1% may be associated with a 15% relative risk reduction in non-fatal myocardial infarction, but without benefits on stroke or all-cause mortality [36].

Overview of the pathogenesis of type 2 diabetes

Any rise in glycaemia is the net result of glucose influx exceeding glucose outflow from the plasma compartment. In the fasting state, hyperglycaemia is directly related to increased hepatic glucose production. In the postprandial state, further glucose excursions result from the combination of insufficient suppression of this glucose output and defective insulin stimulation of glucose disposal in target tissues, mainly skeletal muscle. Once the renal tubular transport maximum for glucose is exceeded, glycosuria curbs, though does not prevent, further hyperglycaemia.

Abnormal islet cell function is a key and requisite feature of type 2 diabetes. In early disease stages, insulin production is normal or increased in absolute terms, but disproportionately low for the degree of insulin sensitivity, which is typically reduced. However, insulin kinetics, such as the

ability of the pancreatic beta cell to release adequate hormone in phase with rising glycaemia, are profoundly compromised. This functional islet incompetence is the main quantitative determinant of hyperglycaemia [37] and progresses over time. In addition, in type 2 diabetes, pancreatic alpha cells hypersecrete glucagon, further promoting hepatic glucose production [38]. Importantly, islet dysfunction is not necessarily irreversible. Enhancing insulin action relieves beta cell secretory burden, and any intervention that improves glycaemia—from energy restriction to, most strikingly, bariatric surgery—can ameliorate beta cell dysfunction to an extent [39]. More recently recognised abnormalities in the incretin system (represented by the gut hormones, glucagon-like peptide 1 [GLP-1] and glucose-dependent insulinotropic peptide [GIP]) are also found in type 2 diabetes, but it remains unclear whether these constitute primary or secondary defects [40]. In most patients with type 2 diabetes, especially the obese, insulin resistance in target tissues (liver, muscle, adipose tissue, myocardium) is a prominent feature. This results in both glucose overproduction and underutilisation. Moreover, an increased delivery of fatty acids to the liver favours their oxidation, which contributes to increased gluconeogenesis, whereas the absolute overabundance of lipids promotes hepatosteatosis [41].

Anti-hyperglycaemic agents are directed at one or more of the pathophysiological defects of type 2 diabetes, or modify physiological processes relating to appetite or to nutrient absorption or excretion. Ultimately, type 2 diabetes is a disease that is heterogeneous in both pathogenesis and in clinical manifestation—a point to be considered when determining the optimal therapeutic strategy for individual patients.

Anti-hyperglycaemic therapy

Glycaemic targets

The ADA's 'Standards of Medical Care in Diabetes' recommends lowering HbA_{1c} to <7.0% (<53 mmol/mol) in most patients to reduce the incidence of microvascular disease [42]. This can be achieved with a mean plasma glucose of ~8.3–8.9 mmol/l (~150–160 mg/dl); ideally, fasting and pre-meal glucose should be maintained at <7.2 mmol/l (<130 mg/dl) and the postprandial glucose at <10 mmol/l (<180 mg/dl). More stringent HbA_{1c} targets (e.g. 6.0–6.5% [42–48 mmol/mol]) might be considered in selected patients (with short disease duration, long life expectancy, no significant CVD) if this can be achieved without significant hypoglycaemia or other adverse effects of treatment [20, 43]. Conversely, less stringent HbA_{1c} goals—e.g. 7.5–8.0% (58–64 mmol/mol) or even slightly higher—are appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, advanced complications, extensive comorbid conditions and those in whom the target is difficult to attain despite intensive self-management education, repeated counselling and effective doses of multiple glucose-lowering agents, including insulin [20, 44].

The accumulated results from the aforementioned type 2 diabetes cardiovascular trials suggest that not everyone benefits from aggressive glucose management. It follows that it is important to *individualise* treatment targets [5, 34–36]. The elements that may guide the clinician in choosing an HbA_{1c} target for a specific patient are shown in Fig. 1. As mentioned earlier, the desires and values of the patient should also be considered, since the achievement of any degree of glucose control requires active participation and commitment [19, 23, 45, 46]. Indeed, any target could reflect an agreement between patient and clinician. An important related concept is that the ease with which more intensive targets are reached influences treatment decisions; logically, lower targets are attractive if they can be achieved with less complex regimens and no or minimal adverse effects. Importantly, utilising the percentage of diabetic patients who are achieving an HbA_{1c} <7.0% (<53 mmol/mol) as a quality indicator, as promulgated by various healthcare organisations, is inconsistent with the emphasis on individualisation of treatment goals.

Therapeutic options

Lifestyle Interventions designed to impact an individual's physical activity levels and food intake are critical parts of type 2 diabetes management [47, 48]. All patients should receive standardised general diabetes education (individual or group, preferably using an approved curriculum), with a specific focus on dietary interventions and the importance of increasing physical activity. While encouraging therapeutic lifestyle change is important at diagnosis, periodic counselling should also be integrated into the treatment programme.

Weight reduction, achieved through dietary means alone or with adjunctive medical or surgical intervention, improves glycaemic control and other cardiovascular risk factors. Modest weight loss (5–10%) contributes meaningfully to achieving improved glucose control. Accordingly,

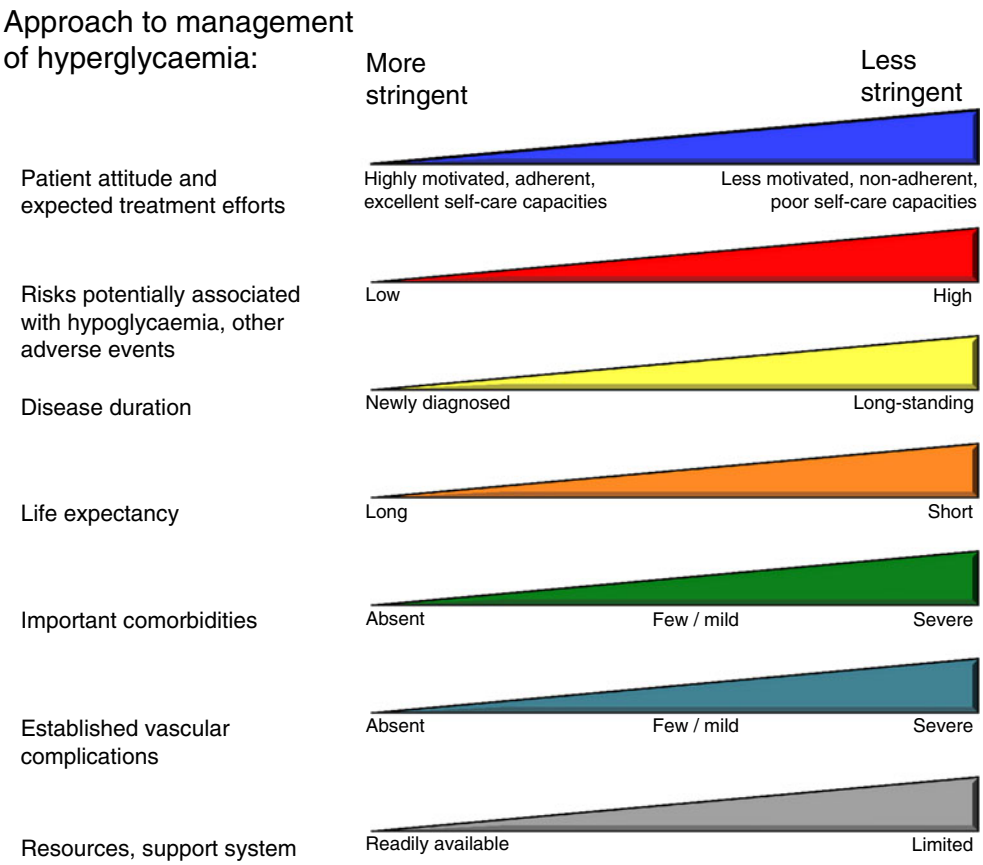

Fig. 1 Depiction of the elements of decision-making used to determine appropriate efforts to achieve glycaemic targets. Greater concerns about a particular domain are represented by increasing height of the ramp. Thus, characteristics/predicaments towards the left justify more stringent efforts to lower HbA_{1c}, whereas those towards the right are compatible with less stringent efforts. Where possible, such decisions should be made in conjunction with the patient, reflecting his or her preferences, needs and values. This 'scale' is not designed to be applied rigidly but to be used as a broad construct to help guide clinical decisions. Adapted with permission from Ismail-Beigi et al [20]

establishing a goal of weight reduction, or at least weight maintenance, is recommended.

Dietary advice must be personalised [49]. Patients should be encouraged to eat healthy foods that are consistent with the prevailing population-wide dietary recommendations and with an individual's preferences and culture. Foods high in fibre (such as vegetables, fruits, wholegrains and legumes), low-fat dairy products and fresh fish should be emphasised. High-energy foods, including those rich in saturated fats, and sweet desserts and snacks should be eaten less frequently and in lower amounts [50–52]. Patients who eventually lose and keep weight off usually do so after numerous cycles of weight loss and relapse. The healthcare team should remain non-judgmental but persistent, re-visiting and encouraging therapeutic lifestyle changes frequently, if needed.

As much physical activity as possible should be promoted, ideally aiming for at least 150 min/week of moderate activity including aerobic, resistance and flexibility training [53]. In older individuals, or those with mobility challenges, so long as tolerated from a cardiovascular standpoint, any increase in activity level is advantageous.

At diagnosis, highly motivated patients with HbA_{1c} already near target (e.g. <7.5% [<58 mmol/mol]) could be given the opportunity to engage in lifestyle change for a period of 3–6 months before embarking on pharmacotherapy (usually metformin). Those with moderate hyperglycaemia or in whom lifestyle changes are anticipated to be unsuccessful should be promptly started on an anti-hyperglycaemic agent (also usually metformin) at diagnosis, which can later be modified or possibly discontinued if lifestyle changes are successful.

Oral agents and non-insulin injectables Important properties of anti-hyperglycaemic agents that play a role in the choice of drug(s) in individual patients are summarised in the text box 'Properties of currently available glucose-lowering agents that may guide treatment choice in individual patients with type 2 diabetes mellitus'. Ultimately, the aims of controlling glycaemia are to

avoid acute osmotic symptoms of hyperglycaemia, to avoid instability in blood glucose over time, and to prevent/delay the development of diabetic complications without adversely affecting quality of life. Information on whether specific agents have this ability is incomplete; an answer to these questions requires long-term, large-scale clinical trials—not available for most drugs. Effects on surrogate measures for glycaemic control (e.g. HbA_{1c}) generally reflect changes in the probability of developing microvascular disease but not necessarily macrovascular complications. Particularly from a patient standpoint, stability of metabolic control over time may be another specific goal.

Metformin, a biguanide, remains the most widely used first-line type 2 diabetes drug; its mechanism of action predominately involves reducing hepatic glucose production [54, 55]. It is generally considered weight-neutral with chronic use and does not increase the risk of hypoglycaemia. Metformin is associated with initial gastrointestinal side effects, and caution is advised to avoid its use in patients at risk for lactic acidosis (e.g. in advanced renal insufficiency, alcoholism), a rare complication of therapy. As noted earlier, there may be some cardiovascular benefits from this drug, but the clinical trial data are not robust.

The oldest oral agent class is the sulfonylurea insulin secretagogues. Through the closure of ATP-sensitive potassium channels on beta cells, these drugs stimulate insulin release [56]. While effective in controlling glucose levels, their use is associated with modest weight gain and risk of hypoglycaemia. In addition, studies have demonstrated a secondary failure rate that may exceed other drugs, ascribed to an exacerbation of islet dysfunction [57]. Shorter-acting secretagogues, the meglitinides (or glinides), stimulate insulin release through similar mechanisms but may be associated with less hypoglycaemia [58]. They require more frequent dosing, however.

Thiazolidinediones (TZDs) are peroxisome proliferator-activated receptor γ activators [59] that improve insulin sensitivity in skeletal muscle and reduce hepatic glucose production [54, 55]. They do not increase the risk of hypoglycaemia and may be more durable in their effectiveness than sulfonylureas and metformin [57]. Pioglitazone appeared to have a modest benefit on cardiovascular events as a secondary outcome in one large trial involving patients with overt macrovascular disease [60]. Another agent of this class, rosiglitazone, is no longer widely available owing to concerns of increased myocardial infarction risk [61]. Pioglitazone has recently been associated with a possible increased risk of bladder cancer [62]. Recognised side effects of TZDs include weight gain, fluid retention leading to oedema and/or heart failure in predisposed individuals and increased risk of bone fractures [57, 60].

Drugs focused on the incretin system have been introduced more recently [63]. The injectable GLP-1 receptor agonists mimic the effects of endogenous GLP-1, thereby stimulating pancreatic insulin secretion in a glucose-dependent fashion, suppressing pancreatic glucagon output, slowing gastric emptying and decreasing appetite. Their main advantage is weight loss, which is modest in most patients but can be significant in some. A limiting side effect is nausea and vomiting, particularly early in the course of treatment. Concerns regarding an increased risk of pancreatitis remain unresolved. The oral dipeptidyl peptidase IV (DPP-4) inhibitors enhance circulating concentrations of active GLP-1 and GIP [64]. Their major effect appears to be in the regulation of insulin and glucagon secretion; they are weight neutral. Typically, neither of the incretin-based classes cause hypoglycaemia by themselves.

Two agents that are used infrequently in the USA and Europe are the α-glucosidase inhibitors (AGIs), which retard gut carbohydrate absorption [65], and colesevelam, a bile acid sequestrant whose mechanism of glucose-lowering action remains poorly understood and whose major additional benefit is LDL-cholesterol reduction [66]. Both have gastrointestinal effects, mainly flatulence with AGIs and constipation with colesevelam. The dopamine agonist bromocriptine is only available in the USA as an anti-hyperglycaemic agent [67]. Its mechanism of action and precise role are unclear. The amylin agonist, pramlintide, is typically reserved for patients treated with intensive insulin therapy, usually in type 1 diabetes mellitus; it decreases postprandial glucose excursions by inhibiting glucagon secretion and slowing gastric emptying [68].

The glucose-lowering effectiveness of non-insulin pharmacological agents is said to be high for metformin, sulfonylureas, TZDs and GLP-1 agonists (expected HbA_{1c} reduction ~1.0–1.5%) [1, 69, 70], and generally lower for meglitinides, DPP-4 inhibitors, AGIs, colesevelam and bromocriptine (~0.5–1.0%). However, older drugs have typically been tested in clinical trial participants with higher baseline HbA_{1c}, which is itself associated with greater treatment emergent glycaemic reductions, irrespective of therapy type. In head-to-head studies, any differential effects on glucose control are small. So agent- and patient-specific properties, such as dosing frequency, side-effect profiles, cost and other benefits often guide their selection.

Insulin Due to the progressive beta cell dysfunction that characterises type 2 diabetes, insulin replacement therapy is frequently required [71]. Importantly, most patients maintain some endogenous insulin secretion even in late stages of disease. Accordingly, the more complex and intensive strategies of type 1 diabetes are not typically necessary [72].

Ideally, the principle of insulin use is the creation of as normal a glycaemic profile as possible without unacceptable weight gain or hypoglycaemia [73]. As initial therapy, unless the patient is markedly hyperglycaemic and/or symptomatic, a 'basal' insulin alone is typically added [74]. Basal insulin provides relatively uniform insulin coverage throughout the day and night, mainly to control blood glucose by suppressing hepatic glucose production in between meals and during sleep. Either intermediate-acting (neutral protamine Hagedorn [NPH]) or long-acting (insulin glargine [A21Gly,B31Arg, B32Arg human insulin] or insulin detemir [B29Lys(ε-tetradecanoyl),desB30 human insulin]) formulations may be used. The latter two are associated with modestly less overnight hypoglycaemia (insulin glargine, insulin detemir) than NPH and possibly slightly less weight gain (insulin detemir), but are more expensive [75, 76]. Of note, the dosing of these basal insulin analogues may differ, with most comparative trials showing a higher average unit requirement with insulin detemir [77].

Although the majority of patients with type 2 diabetes requiring insulin therapy can be successfully treated with basal insulin alone, some, because of progressive diminution in their insulin secretory capacity, will require prandial insulin therapy with shorter-acting insulins. This is typically provided in the form of the rapid insulin analogues, insulin lispro (B28Lys,B29Pro human insulin), insulin aspart (B28Asp human insulin) or insulin glulisine (B3Lys, B29Glu human insulin), which may be dosed just before the meal. They result in better postprandial glucose control than the less costly human regular insulin, whose pharmacokinetic profile makes it less attractive in this setting.

Ideally, an insulin treatment programme should be designed specifically for an individual patient, to match the supply of insulin to his or her dietary/exercise habits and prevailing glucose trends, as revealed through self-monitoring. Anticipated glucose-lowering effects should be balanced with the convenience of the regimen, in the context of an individual's specific therapy goals (Fig. 1).

Proper patient education regarding glucose monitoring, insulin injection technique, insulin storage, recognition/treatment of hypoglycaemia, and 'sick day' rules is imperative. Where available, certified diabetes educators can be invaluable in guiding the patient through this process.

Key points

- Glycaemic targets and glucose-lowering therapies must be individualised
- Diet, exercise and education remain the foundation of any type 2 diabetes treatment programme
- Unless there are prevalent contraindications, metformin is the optimal first-line drug
- After metformin, there are limited data to guide us. Combination therapy with an additional 1–2 oral or injectable agents is reasonable, aiming to minimise side effects where possible
- Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control
- All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs and values
- Comprehensive cardiovascular risk reduction must be a major focus of therapy

Implementation strategies

Initial drug therapy It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent [42] (Fig. 2 and electronic supplementary material [ESM] Figs). It is initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. Because of frequent gastrointestinal side effects, it should be started at a low dose with gradual titration. Patients with a high baseline HbA_{1c} (e.g. ≥9.0% [≥75 mmol/mol]) have a low probability of achieving a near-normal target with monotherapy. It may therefore be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance [78]. If a patient presents with significant hyperglycaemic symptoms and/or has dramatically elevated plasma glucose concentrations (e.g. >16.7–19.4 mmol/l [>300–350 mg/dl]) or HbA_{1c} (e.g. ≥10.0–12.0% [86–108 mmol/mol]), insulin

Properties of currently available glucose-lowering agents that may guide treatment choice in individual patients with type 2 diabetes mellitus

Class	Compound(s)	Cellular mechanism	Primary physiological action(s)	Advantages	Disadvantages	Cost
Biguanides	• Metformin	Activates AMP-kinase	• ↓ Hepatic glucose production	• Extensive experience • No weight gain • No hypoglycaemia • Likely ↓ CVD events (UKPDS)	• Gastrointestinal side effects (diarrhoea, abdominal cramping) • Lactic acidosis risk (rare) • Vitamin B_{12} deficiency • Multiple contraindications: CKD, acidosis, hypoxia, dehydration, etc.	Low
Sulfonylureas	2nd generation • Glibenclamide/ glyburide • Glipizide • Gliclazide[b] • Glimepiride	Closes K_{ATP} channels on beta cell plasma membranes	• ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk (UKPDS)	• Hypoglycaemia • Weight gain • ? Blunts myocardial ischaemic preconditioning • Low durability	Low
Meglitinides (glinides)	• Repaglinide • Nateglinide	Closes K_{ATP} channels on beta cell plasma membranes	• ↑ Insulin secretion	• ↓ Postprandial glucose excursions • Dosing flexibility	• Hypoglycaemia • Weight gain • ? Blunts myocardial ischaemic preconditioning • Frequent dosing schedule	High
Thiazolidinediones	• Pioglitazone • Rosiglitazone[c]	Activates the nuclear transcription factor PPAR-γ	• ↑ Insulin sensitivity	• No hypoglycaemia • Durability • ↑ HDL-C • ↓ Triacylglycerols (pioglitazone) • ? ↓ CVD events (ProACTIVE, pioglitazone)	• Weight gain • Oedema / heart failure • Bone fractures • ↑ LDL-C (rosiglitazone) • ? ↑ MI (meta-analyses, rosiglitazone) • ? ↑ Bladder cancer (pioglitazone)	High[e]
α-Glucosidase inhibitors[a]	• Acarbose • Miglitol • Voglibose[b,d]	Inhibits intestinal α-glucosidase	• Slows intestinal carbohydrate digestion/absorption	• No hypoglycaemia • ↓ Postprandial glucose excursions • ? ↓ CVD events (STOP-NIDDM) • Non-systemic	• Generally modest HbA_{1c} efficacy • Gastrointestinal side effects (flatulence, diarrhoea) • Frequent dosing schedule	Moderate
DPP-4 inhibitors	• Sitagliptin • Vildagliptin[a] • Saxagliptin • Linagliptin • Alogliptin[b,d]	Inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations	• ↑ Insulin secretion (glucose-dependent) • ↓ Glucagon secretion (glucose-dependent)	• No hypoglycaemia • Well tolerated	• Generally modest HbA_{1c} efficacy • Urticaria/angio-oedema • ? Pancreatitis	High

Bile acid sequestrants[a]	• Colesevelam	Binds bile acids in intestinal tract, increasing hepatic bile acid production; ? activation of farnesoid X receptor (FXR) in liver	• Unknown • ? ↓ Hepatic glucose production • ? ↑ Incretin levels	• No hypoglycaemia • ↓ LDL-C	• Generally modest HbA_{1c} efficacy • Constipation • ↑ Triacylglycerols • May ↓ absorption of other medications	High
Dopamine-2 agonists[a]	• Bromocriptine (quick-release)[d]	Activates dopaminergic receptors	• Modulates hypothalamic regulation of metabolism • ↑ Insulin sensitivity	• No hypoglycaemia • ? ↓ CVD events (Cycloset Safety Trial)	• Generally modest HbA_{1c} efficacy • Dizziness/syncope • Nausea • Fatigue • Rhinitis	High
GLP-1 receptor agonists	• Exenatide • Exenatide extended release • Liraglutide	Activates GLP-1 receptors	• ↑ Insulin secretion (glucose-dependent) • ↓ Glucagon secretion (glucose-dependent) • Slows gastric emptying • ↑ Satiety	• No hypoglycaemia • Weight reduction • ? Potential for improved beta cell mass/function • ? Cardiovascular protective actions	• Gastrointestinal side effects (nausea/vomiting) • ? Acute pancreatitis • C cell hyperplasia/ medullary thyroid tumours in animals • Injectable • Training requirements	High
Amylin mimetics[a]	• Pramlintide[d]	Activates amylin receptors	• ↓ Glucagon secretion • Slows gastric emptying • ↑ Satiety	• ↓ Postprandial glucose excursions • Weight reduction	• Generally modest HbA_{1c} efficacy • Gastrointestinal side effects (nausea/vomiting) • Hypoglycaemia unless insulin dose is simultaneously reduced • Injectable • Frequent dosing schedule	High
Insulins	• Human NPH • Human Regular • Lispro • Aspart • Glulisine • Glargine • Detemir • Pre-mixed (several types)	Activates insulin receptors	• ↑ Glucose disposal • ↓ Hepatic glucose production	• Universally effective • Theoretically unlimited efficacy • ↓ Microvascular risk (UKPDS)	• Hypoglycaemia • Weight gain • ? Mitogenic effects • Injectable • Training requirements • 'Stigma' (for patients)	Variable[f]

[a] Limited use in the USA/Europe. [b] Not licensed in the USA. [c] Prescribing highly restricted in the USA; withdrawn in Europe. [d] Not licensed in Europe. [e] To be available as a generic product in 2012, with expected significant reductions in cost. [f] Depends on type (analogues> human insulins) and dosage. CKD, chronic kidney disease; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase IV; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; PPAR, peroxisome proliferator-activated receptor; ProACTIVE, Prospective Pioglitazone Clinical Trial in Macrovascular Events [60]; STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus [134]; UKPDS, UK Prospective Diabetes Study [29–33]

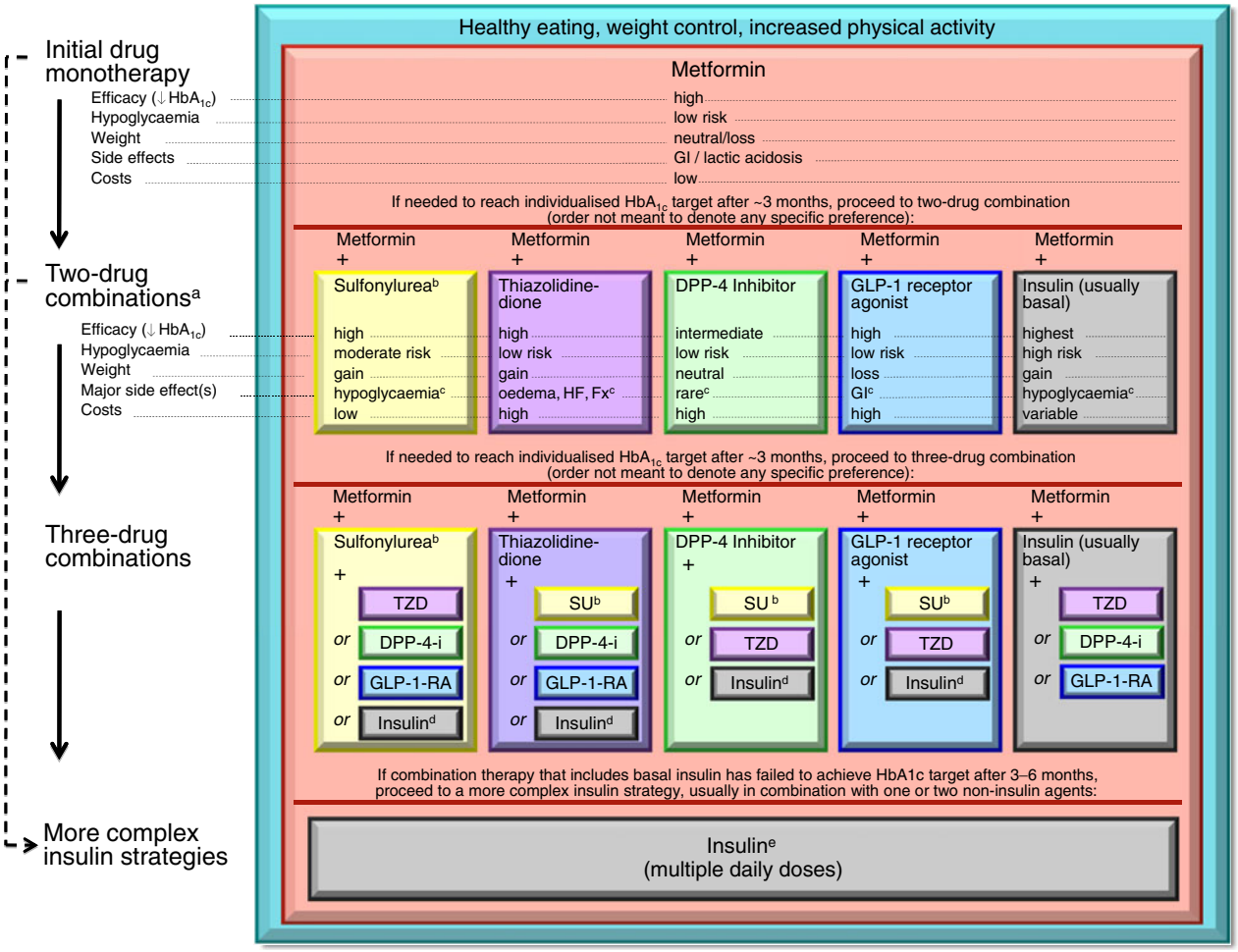

Fig. 2 Anti-hyperglycaemic therapy in type 2 diabetes: general recommendations. Moving from the top to the bottom of the figure, potential sequences of anti-hyperglycaemic therapy. In most patients, begin with lifestyle changes; metformin monotherapy is added at, or soon after, diagnosis (unless there are explicit contraindications). If the HbA_{1c} target is not achieved after ~3 months, consider one of the five treatment options combined with metformin: a sulfonylurea, TZD, DPP-4 inhibitor, GLP-1 receptor agonist or basal insulin. (The order in the chart is determined by historical introduction and route of administration and is not meant to denote any specific preference.) Choice is based on patient and drug characteristics, with the overriding goal of improving glycaemic control while minimising side effects. Shared decision-making with the patient may help in the selection of therapeutic options. The figure displays drugs commonly used both in the USA and/or Europe. Rapid-acting secretagogues (meglitinides) may be used in place of sulfonylureas. Other drugs not shown (α-glucosidase inhibitors, colesevelam, dopamine agonists, pramlintide) may be used where available in selected patients but have modest efficacy and/or limiting side effects. In patients intolerant of, or with contraindications for, metformin, select initial drug from other classes depicted, and proceed accordingly. In this circumstance, while published trials are generally lacking, it is reasonable to consider three-drug combinations other than metformin. Insulin is likely to be more effective than most other agents as a third-line therapy, especially when HbA_{1c} is very high (e.g. ≥9.0% [≥75 mmol/mol]). The therapeutic regimen should include some basal insulin before moving to more complex insulin strategies (see Fig. 3). Dashed arrow line on the left-hand side of the figure denotes the option of a more rapid progression from a two-drug combination directly to multiple daily insulin doses, in those patients with severe hyperglycaemia (e.g. HbA_{1c} ≥10.0–12.0% [≥86–108 mmol/mol]). [a]Consider beginning at this stage in patients with very high HbA_{1c} (e.g. ≥9% [≥75 mmol/mol]). [b]Consider rapid-acting, non-sulfonylurea secretagogues (meglitinides) in patients with irregular meal schedules or who develop late postprandial hypoglycemia on sulfonylureas. [c]See Text box 'Properties of currently available glucose-lowering agents that may guide treatment choice in individual patients with type 2 diabetes mellitus' for additional potential adverse effects and risks, under 'Disadvantages'. [d]Usually a basal insulin (NPH, glargine, detemir) in combination with non-insulin agents. [e]Certain non-insulin agents may be continued with insulin (see text). Refer to Fig. 3 for details on regimens. Consider beginning at this stage if patient presents with severe hyperglycemia (≥16.7–19.4 mmol/l [≥300–350 mg/dl]; HbA_{1c} ≥10.0–12.0% [≥86–108 mmol/mol]) with or without catabolic features (weight loss, ketosis, etc). DPP-4-i, DPP-4 inhibitor; Fx, bone fracture; GI, gastrointestinal; GLP-1-RA, GLP-1 receptor agonist; HF, heart failure; SU, sulfonylurea

therapy should be strongly considered from the outset. Such treatment is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency. Importantly, unless there is evidence of type 1 diabetes, once symptoms are relieved, glucotoxicity resolved, and the metabolic state

stabilised, it may be possible to taper insulin partially or entirely, transferring to non-insulin anti-hyperglycaemic agents, perhaps in combination.

If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a DPP-4 inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 receptor agonist might be useful. Where available, less commonly used drugs (AGIs, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycaemic effects and side-effect profiles make them less attractive candidates. Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain and hypoglycaemia should play a major role in drug selection [20, 21]. (See ESM Figs for adaptations of Fig. 2 that address specific patient scenarios.)

Advancing to dual combination therapy Figure 2 (and ESM Figs) also depicts potential sequences of escalating glucose-lowering therapy beyond metformin. If monotherapy alone does not achieve/maintain an HbA_{1c} target over ~3 months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin [5, 10]. Notably, the higher the HbA_{1c}, the more likely insulin will be required. On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of ~1% (11 mmol/mol) [70, 79]. If no clinically meaningful glycaemic reduction (i.e. 'non-responder') is demonstrated, then, adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted. With a distinct paucity of long-term comparative-effectiveness trials available, uniform recommendations on the best agent to be combined with metformin cannot be made [80]. Thus, advantages and disadvantages of specific drugs for each patient should be considered (Text box 'Properties of currently available glucose-lowering agents that may guide treatment choice in individual patients with type 2 diabetes mellitus').

Some anti-hyperglycaemic medications lead to weight gain. This may be associated with worsening markers of insulin resistance and cardiovascular risk. One exception may be TZDs [57]; weight gain associated with this class occurs in association with decreased insulin resistance. Although there is no uniform evidence that increases in weight in the range observed with certain therapies translate into a substantially increased cardiovascular risk, it remains important to avoid unnecessary weight gain by optimal medication selection and dose titration.

For all medications, consideration should also be given to overall tolerability. Even occasional hypoglycaemia may be devastating, if severe, or merely irritating, if mild [81]. Gastrointestinal side effects may be tolerated by some, but not others. Fluid retention may pose a clinical or merely an aesthetic problem [82]. The risk of bone fractures may be a specific concern in postmenopausal women [57].

It must be acknowledged that costs are a critical issue driving the selection of glucose-lowering agents in many environments. For resource-limited settings, less expensive agents should be chosen. However, due consideration should be also given to side effects and any necessary monitoring, with their own cost implications. Moreover, prevention of morbid long-term complications will likely reduce long-term expenses attributed to the disease.

Advancing to triple combination therapy Some studies have shown advantages of adding a third non-insulin agent to a two-drug combination that is not yet or no longer achieving the glycaemic target [83–86]. Not surprisingly, however, at this juncture, the most robust response will usually be with insulin. Indeed, since diabetes is associated with progressive beta cell loss, many patients, especially those with long-standing disease, will eventually need to be transitioned to insulin, which should be favoured in circumstances where the degree of hyperglycaemia (e.g. ≥8.5%) makes it unlikely that another drug will be of sufficient benefit [87]. If triple combination therapy exclusive of insulin is tried, the patient should be monitored closely, with the approach promptly reconsidered if it proves to be unsuccessful. Many months of uncontrolled hyperglycaemia should specifically be avoided.

In using triple combinations the essential consideration is obviously to use agents with complementary mechanisms of action (see Fig. 2 and ESM Figs). Increasing the number of drugs heightens the potential for side effects and drug–drug interactions, raises costs and negatively impacts patient adherence. The rationale, benefits and side effects of each new medication should be discussed with the patient. The clinical characteristics of patients more or less likely to respond to specific combinations are, unfortunately, not well defined.

Transitions to and titrations of insulin Most patients express reluctance to beginning injectable therapy, but, if the practitioner feels that such a transition is important, encouragement and education can usually overcome such reticence. Insulin is typically begun at a low dose (e.g. 0.1–0.2 U kg^{-1} day^{-1}), although larger amounts (0.3–0.4 U kg^{-1} day^{-1}) are reasonable in the more severely hyperglycaemic. The most convenient strategy is with a single injection of a basal insulin, with the timing of administration dependent on the patient's schedule and overall glucose profile (Fig. 3).

Although extensive dosing instructions for insulin are beyond the scope of this statement, most patients can be taught to uptitrate their own insulin dose based on several algorithms, each essentially involving the addition of a small dose increase if hyperglycaemia persists [74, 76, 88]. For example, the addition of 1–2 units (or, in those already

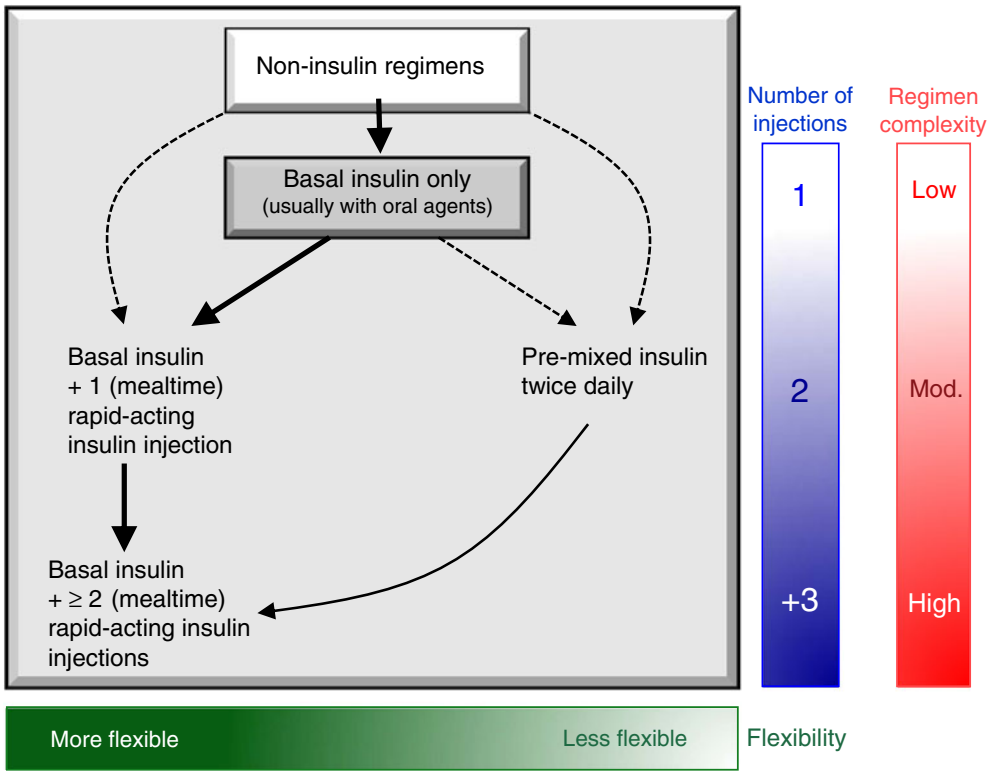

Fig. 3 Sequential insulin strategies in type 2 diabetes. Basal insulin alone is usually the optimal initial regimen, beginning at 0.1-0.2 U/kg body weight, depending on the degree of hyperglycaemia. It is usually prescribed in conjunction with one to two non-insulin agents. In patients willing to take more than one injection and who have higher HbA_{1c} levels (≥9.0% [≥75 mmol/mol]), twice daily pre-mixed insulin or a more advanced basal plus mealtime insulin regimen could also be considered (curved dashed arrow lines). When basal insulin has been titrated to an acceptable fasting glucose but HbA_{1c} remains above target, consider proceeding to basal plus mealtime insulin, consisting of one to three injections of rapid-acting analogues (see text for details). A less studied alternative—progression from basal insulin to a twice daily pre-mixed insulin—could be also considered (straight dashed arrow line); if this is unsuccessful, move to basal plus mealtime insulin. The figure describes the number of injections required at each stage, together with the relative complexity and flexibility. Once a strategy is initiated, titration of the insulin dose is important, with dose adjustments made based on the prevailing glucose levels as reported by the patient. Non-insulin agents may be continued, although insulin secretagogues (sulfonylureas, meglitinides) are typically stopped once more complex regimens beyond basal insulin are utilised. Comprehensive education regarding self-monitoring of blood glucose, diet, exercise and the avoidance of, and response to, hypoglycaemia are critical in any patient on insulin therapy. Mod., moderate

on higher doses, increments of 5–10%) to the daily dose once or twice weekly if the fasting glucose levels are above the pre-agreed target is a reasonable approach [89]. As the target is neared, dosage adjustments should be more modest and occur less frequently. Downward adjustment is advisable if any hypoglycaemia occurs. During self-titration, frequent contact (telephone, e-mail) with the clinician may be necessary. Practitioners themselves can, of course, also titrate basal insulin, but this would involve more intensive contact with the patient than typically available in routine clinical practice. Daily self-monitoring of blood glucose is of obvious importance during this phase. After the insulin dose is stabilised, the frequency of monitoring should be reviewed [90].

Consideration should be given to the addition of prandial or mealtime insulin coverage when significant postprandial glucose excursions (e.g. to >10.0 mmol/l [>180 mg/dl]) occur. This is suggested when the fasting glucose is at target but the HbA_{1c} remains above goal after 3–6 months of basal insulin titration [91]. The same would apply if large drops in glucose occur during overnight hours or in between meals, as the basal insulin dose is increased. In this scenario, the basal insulin dose would obviously need to be simultaneously decreased as prandial insulin is initiated. Although basal insulin is titrated primarily against the fasting glucose, generally irrespective of the total dose, practitioners should be aware that the need for prandial insulin therapy will become likely the more the daily dose exceeds 0.5 U kg^{-1} day^{-1}, especially as it approaches 1 U kg^{-1} day^{-1}. The aim with mealtime insulin is to blunt postprandial glycaemic excursions, which can be extreme in some individuals, resulting in poor control during the day. Such coverage may be provided by one of two methods.

The most precise and flexible prandial coverage is possible with ‘basal-bolus’ therapy, involving the addition of pre-meal rapid-acting insulin analogue to ongoing basal insulin. One

graduated approach is to add prandial insulin before the meal responsible for the largest glucose excursion—typically that with the greatest carbohydrate content, often, but not always, the evening meal [92]. Subsequently, a second injection can be administered before the meal with the next largest excursion (often breakfast). Ultimately, a third injection may be added before the smallest meal (often lunch) [93]. The actual glycaemic benefits of these more advanced regimens after basal insulin are generally modest in typical patients [92]. So, again, individualisation of therapy is key, incorporating the degree of hyperglycaemia needing to be addressed and the overall capacities of the patient. Importantly, data trends from self-monitoring may be particularly helpful in titrating insulins and their doses within these more advanced regimens to optimise control.

A second, perhaps more convenient but less adaptable method involves 'pre-mixed' insulin, consisting of a fixed combination of an intermediate insulin with regular insulin or a rapid analogue. Traditionally, this is administered twice daily, before morning and evening meals. In general, when compared with basal insulin alone, pre-mixed regimens tend to lower HbA_{1c} to a larger degree, but often at the expense of slightly more hypoglycaemia and weight gain [94]. Disadvantages include the inability to titrate the shorter- from the longer-acting component of these formulations. Therefore, this strategy is somewhat inflexible but may be appropriate for certain patients who eat regularly and may be in need of a simplified approach beyond basal insulin [92, 93]. (An older and less commonly used variation of this two-injection strategy is known as 'split-mixed', involving a fixed amount of intermediate insulin mixed by the patient with a variable amount of regular insulin or a rapid analogue. This allows for greater flexibility in dosing.)

The key messages from dozens of comparative insulin trials in type 2 diabetes include the following:

1. Any insulin will lower glucose and HbA_{1c}.
2. All insulins are associated with some weight gain and some risk of hypoglycaemia.
3. The larger the doses and the more aggressive the titration, the lower the HbA_{1c}, but often with a greater likelihood of adverse effects.
4. Generally, long-acting insulin analogues reduce the incidence of overnight hypoglycaemia, and rapid-acting insulin analogues reduce postprandial glucose excursions as compared with corresponding human insulins (NPH, Regular), but they generally do not result in clinically significantly lower HbA_{1c}.

Metformin is often continued when basal insulin is added, with studies demonstrating less weight gain when the two are used together [95]. Insulin secretagogues do not seem to provide for additional HbA_{1c} reduction or prevention of hypoglycaemia or weight gain after insulin is started, especially after the dose is titrated and stabilised. When basal insulin is used, continuing the secretagogue may minimise initial deterioration of glycaemic control. However, secretagogues should be avoided once prandial insulin regimens are employed. TZDs should be reduced in dose (or stopped) to avoid oedema and excessive weight gain, although in certain individuals with large insulin requirements from severe insulin resistance, these insulin sensitizers may be very helpful in lowering HbA_{1c} and minimising the required insulin dose [96]. Data concerning the glycaemic benefits of incretin-based therapy combined with basal insulin are accumulating; combination with GLP-1 receptor agonists may be helpful in some patients [97, 98]. Once again, the costs of these more elaborate combined regimens must be carefully considered.

Other considerations

Age

Older adults (>65–70 years) often have a higher atherosclerotic disease burden, reduced renal function, and more comorbidities [99, 100]. Many are at risk for adverse events from polypharmacy and may be both socially and economically disadvantaged. Life expectancy is reduced, especially in the presence of long-term complications. They are also more likely to be compromised by hypoglycaemia; for example, unsteadiness may result in falls and fractures [101], and a tenuous cardiac status may deteriorate into catastrophic events. It follows that glycaemic targets for elderly with long-standing or more complicated disease should be less ambitious than for the younger, healthier individuals [20]. If lower targets cannot be achieved with simple interventions, an HbA_{1c} of <7.5–8.0% (<58–64 mmol/mol) may be acceptable, transitioning upward as age increases and capacity for self-care, cognitive, psychological and economic status, and support systems decline.

While lifestyle modification can be successfully implemented across all age groups, in the aged, the choice of anti-hyperglycaemic agent should focus on drug safety, especially protecting against hypoglycaemia, heart failure, renal dysfunction, bone fractures and drug–drug interactions. Strategies specifically minimising the risk of low blood glucose may be preferred.

In contrast, healthier patients with long life expectancy accrue risk for vascular complications over time. Therefore, lower glycaemic targets (e.g. an HbA_{1c} <6.5–7.0% [48–53 mmol/mol]) and tighter control of body weight, blood pressure and circulating lipids should be achieved to prevent or delay such complications. This usually requires combination

therapy, the early institution of which may have the best chance of modifying the disease process and preserving quality of life.

Weight

The majority of individuals with type 2 diabetes are overweight or obese (~80%) [102]. In these, intensive lifestyle intervention can improve fitness, glycaemic control, and cardiovascular risk factors for relatively small changes in body weight [103]. Although insulin resistance is thought of as the predominate driver of diabetes in obese patients, they actually have a similar degree of islet dysfunction to leaner patients [37]. Perhaps as a result, the obese may be more likely to require combination drug therapy [20, 104]. While common practice has favoured metformin in heavier patients, because of weight loss/weight neutrality, this drug is as efficacious in lean individuals [75]. TZDs, on the other hand, appear to be more effective in those with higher BMIs, although their associated weight gain makes them, paradoxically, a less attractive option here. GLP-1 receptor agonists are associated with weight reduction [38], which in some patients may be substantial.

Bariatric surgery is an increasingly popular option in severe obesity. Type 2 diabetes frequently resolves rapidly after these procedures. The majority of patients are able to stop some, or even all, of their anti-hyperglycaemic medications, although the durability of this effect is not known [105].

In lean patients, consideration should be given to the possibility of latent autoimmune diabetes in adults (LADA), a slowly progressive form of type 1 diabetes. These individuals, while presenting with mild hyperglycaemia, often responsive to oral agents, eventually develop more severe hyperglycaemia and require intensive insulin regimens [106]. Measuring titres of islet-associated autoantibodies (e.g. anti-GAD) may aid their identification, encouraging a more rapid transition to insulin therapy.

Sex/racial/ethnic/genetic differences

While certain racial/ethnic features that increase the risk of diabetes are well recognised (greater insulin resistance in Latinos [107], more beta cell dysfunction in East Asians [108]), using this information to craft optimal therapeutic strategies is in its infancy. This is not surprising given the polygenic inheritance pattern of the disease. Indeed, while matching a drug's mechanism of action to the underlying causes of hyperglycaemia in a specific patient seems logical, there are few data that compare strategies based on this approach [109]. There are few exceptions, mainly involving diabetes monogenic variants often confused with type 2 diabetes, such as maturity-onset diabetes of the young (MODY), several forms of which respond preferentially to sulfonylureas [110]. While there are no prominent sex differences in the response to various anti-hyperglycaemic drugs, certain side effects (e.g. bone loss with TZDs) may be of greater concern in women.

Comorbidities

Coronary artery disease Given the frequency with which type 2 diabetic patients develop atherosclerosis, optimal management strategies for those with or at high risk for coronary artery disease (CAD) are important. Since hypoglycaemia may exacerbate myocardial ischaemia and may cause dysrhythmias [111], it follows that medications that predispose patients to this adverse effect should be avoided, if possible. If they are required, however, to achieve glycaemic targets, patients should be educated to minimise risk. Because of possible effects on potassium channels in the heart, certain sulfonylureas have been proposed to aggravate myocardial ischaemia through effects on ischaemic preconditioning [112], but the actual clinical relevance of this remains unproven. Metformin may have some cardiovascular benefits and would appear to be a useful drug in the setting of CAD, barring prevalent contraindications [32]. In a single study, pioglitazone was shown to reduce modestly major adverse cardiovascular events in patients with established macrovascular disease. It may therefore also be considered, unless heart failure is present [60]. In very preliminary reports, therapy with GLP-1 receptor agonists and DPP-4 inhibitors has been associated with improvement in either cardiovascular risk or risk factors, but there are no long-term data regarding clinical outcomes [113]. There are very limited data suggesting that AGIs [114] and bromocriptine [115] may reduce cardiovascular events.

Heart failure With an ageing population and recent decreases in mortality after myocardial infarction, the diabetic patient with progressive heart failure is an increasingly common scenario [116]. This population presents unique challenges given their polypharmacy, frequent hospitalisations, and contraindications to various agents. TZDs should be avoided [117, 118]. Metformin, previously contraindicated in heart failure, can now be used if the ventricular dysfunction is not severe, if patient's cardiovascular status is stable and if renal function is normal [119]. As mentioned, cardiovascular effects of incretin-based therapies, including those on ventricular function, are currently under investigation [120].

Chronic kidney disease Kidney disease is highly prevalent in type 2 diabetes, and moderate to severe renal functional impairment (eGFR <60 ml/min) occurs in approximately 20–30% of patients [121, 122]. The individual with progressive renal dysfunction is at increased risk for hypoglycaemia, which is multifactorial. Insulin and, to some degree, the incretin hormones are eliminated more slowly, as are anti-hyperglycaemic drugs with renal excretion. Thus, dose

reduction may be necessary, contraindications need to be observed and consequences (hypoglycaemia, fluid retention, etc.) require careful evaluation.

Current US prescribing guidelines warn against the use of metformin in patients with a serum creatinine ≥133 mmol/l (≥1.5 mg/dl) in men or 124 mmol/l (≥1.4 mg/dl) in women. Metformin is eliminated renally, and cases of lactic acidosis have been described in patients with renal failure [123]. There is an ongoing debate, however, as to whether these thresholds are too restrictive and that those with mild–moderate renal impairment would gain more benefit than harm from using metformin [124, 125]. In the UK, the National Institute for Health and Clinical Excellence (NICE) guidelines are less proscriptive and more evidence-based than those in the USA, generally allowing use down to a GFR of 30 ml/min, with dose reduction advised at 45 ml/min [14]. Given the current widespread reporting of estimated GFR, these guidelines appear very reasonable.

Most insulin secretagogues undergo significant renal clearance (exceptions include repaglinide and nateglinide) and the risk of hypoglycaemia is therefore higher in patients with chronic kidney disease (CKD). For most of these agents, extreme caution is imperative at more severe degrees of renal dysfunction. Glibenclamide (known as glyburide in the USA and Canada), which has a prolonged duration of action and active metabolites, should be specifically avoided in this group. Pioglitazone is not eliminated renally, and therefore there are no restrictions for use in CKD. Fluid retention may be a concern, however. Among the DPP-4 inhibitors, sitagliptin, vildagliptin and saxagliptin share prominent renal elimination. In the face of advanced CKD, dose reduction is necessary. One exception is linagliptin, which is predominantly eliminated enterohepatically. For the GLP-1 receptor agonists exenatide is contraindicated in stage 4–5 CKD (GFR<30 ml/min) as it is renally eliminated; the safety of liraglutide is not established in CKD though pharmacokinetic studies suggest that drug levels are unaffected as it does not require renal function for clearance.

More severe renal functional impairment is associated with slower elimination of all insulins. Thus doses need to be titrated carefully, with some awareness for the potential for more prolonged activity profiles.

Liver dysfunction Individuals with type 2 diabetes frequently have hepatosteatosis as well as other types of liver disease [126]. There is preliminary evidence that patients with fatty liver may benefit from treatment with pioglitazone [45, 127, 128]. It should not be used in an individual with active liver disease or an alanine transaminase level above 2.5 times the upper limit of normal. In those with steatosis but milder liver test abnormalities, this insulin sensitizer may be advantageous. Sulfonylureas can rarely cause abnormalities in liver tests but are not specifically contraindicated; meglitinides can also be used. If hepatic disease is severe, secretagogues should be avoided because of the increased risk of hypoglycaemia. In patients with mild hepatic disease, incretin-based drugs can be prescribed, except if there is a coexisting history of pancreatitis. Insulin has no restrictions for use in patients with liver impairment and is indeed the preferred choice in those with advanced disease.

Hypoglycaemia

Hypoglycaemia in type 2 diabetes was long thought to be a trivial issue, as it occurs less commonly than in type 1 diabetes. However, there is emerging concern based mainly on the results of recent clinical trials and some cross-sectional evidence of increased risk of brain dysfunction in those with repeated episodes. In the ACCORD trial, the frequency of both minor and major hypoglycaemia was high in intensively managed patients—threefold that associated with conventional therapy [129]. It remains unknown whether hypoglycaemia was the cause of the increased mortality in the intensive group [130, 131]. Clearly, however, hypoglycaemia is more dangerous in the elderly and occurs consistently more often as glycaemic targets are lowered. Hypoglycaemia may lead to dysrhythmias, but can also lead to accidents and falls (which are more likely to be dangerous in the elderly) [132], dizziness (leading to falls), confusion (so other therapies may not be taken or taken incorrectly) or infection (such as aspiration during sleep, leading to pneumonia). Hypoglycaemia may be systematically under-reported as a cause of death, so the true incidence may not be fully appreciated. Perhaps just as importantly, additional consequences of frequent hypoglycaemia include work disability and erosion of the confidence of the patient (and that of family or caregivers) to live independently. Accordingly, in at-risk individuals, drug selection should favour agents that do not precipitate such events and, in general, blood glucose targets may need to be moderated.

Future directions/research needs

For anti-hyperglycaemic management of type 2 diabetes, the comparative evidence basis to date is relatively lean, especially beyond metformin monotherapy [70]. There is a significant need for high-quality comparative-effectiveness research, not only regarding glycaemic control, but also costs and those outcomes that matter most to patients—quality of life and the avoidance of morbid and life-limiting complications, especially CVD [19, 23, 70]. Another issue about which more data are needed is the concept of durability of effectiveness (often ascribed to beta cell preservation), which would serve to stabilize metabolic control and decrease the future treatment burden for patients.

Pharmacogenetics may very well inform treatment decisions in the future, guiding the clinician to recommend a therapy for an individual patient based on predictors of response and susceptibility to adverse effects. We need more clinical data on how phenotype and other patient/disease characteristics should drive drug choices. As new medications are introduced to the type 2 diabetes pharmacopoeia, their benefit and safety should be demonstrated in studies versus best current treatment, substantial enough both in size and duration to provide meaningful data on meaningful outcomes. It is appreciated, however, that head-to-head comparisons of all combinations and permutations would be impossibly large [133]. Informed judgment and the expertise of experienced clinicians will therefore always be necessary.

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