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Is the ADA/EASD algorithm for the management of type 2 diabetes (January 2009) based on evidence or opinion? A critical analysis

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Abstract

The ADA and the EASD recently published a consensus statement for the medical management of hyperglycaemia in patients with type 2 diabetes. The authors advocate initial treatment with metformin monotherapy and lifestyle modification, followed by addition of basal insulin or a sulfonylurea if glycaemic goals are not met (tier 1 recommendations). All other glucose-lowering therapies are relegated to a secondary (tier 2) status and only recommended for selected clinical settings. In our view, this algorithm does not offer physicians and patients the appropriate selection of options to individualise and optimise care with a view to sustained control of blood glucose and reduction both of diabetes complications and cardiovascular risk. This paper critically assesses the basis of the ADA/EASD algorithm and the resulting tiers of treatment options.

Keywords : ADA Consensus Statement ; Algorithm ; Cardiovascular risk ; EASD consensus statement ; Glucose-lowering therapy ; Hyperglycaemia ; Type 2 diabetes

Abbreviations

ADOPT	A Diabetes Outcome Progression Trial
CHF	Congestive heart failure
DIGAMI	Diabetes and Insulin-Glucose infusion in Acute Myocardial Infarction
DPP-IV	Dipeptidyl peptidase-4
GLP-1	Glucagon-like peptide-1
PROactive	PROspective pioglitAzone Clinical Trial In macroVascular Events
RECORD	Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes
UKPDS	UK Prospective Diabetes Study

Introduction

In August 2006, the ADA and the EASD published a joint consensus algorithm for the medical management of hyperglycaemia in type 2 diabetes [1]. Recently, an update introduced a two-tier categorisation of 'well validated' and 'less well validated' therapies [2].

Tier 1 treatments are initial metformin monotherapy and lifestyle modification, followed by addition of basal insulin or a sulfonylurea if glycaemic goals are not met. These interventions are considered to be: 'the best established and most effective and cost-effective therapeutic strategy for achieving the target glycaemic goals'. Although the authors, Nathan et al., endorse metformin plus insulin as a particularly effective combination, in practice most physicians and patients faced with these second-line options are likely to choose metformin plus a sulfonylurea. Recommended tier 2 approaches for second-line therapy comprise metformin plus either a thiazolidinedione (pioglitazone, since the authors advise against using rosiglitazone) or a glucagon-like peptide-1 (GLP-1) receptor agonist. The tier 2 treatments are recommended for consideration in selected clinical settings only.

The description of this publication as a consensus statement of the ADA and EASD is misleading, as it has not been formally endorsed by the two organisations. Indeed, the ADA states that 'consensus statements...are not official ADA recommendations', that they are 'produced under the auspices of the Association by invited experts' and that they are 'not subject to subsequent review or approval' [3]. In addition, the organisation has declared that the consensus statement represents the authors' views and not the official opinion of the association [2]. Nevertheless, the recommendations have been published under the auspices of the two societies and are likely to have considerable influence.

We are concerned that the authors of the consensus statement have not consistently employed an evidence-based approach; we also find many of their recommendations questionable. However, we acknowledge that some data were not available at the time of publication of the updated consensus statement. This paper critically assesses the basis of the purported consensus and the resulting tiers of treatment options.

Development process

Evidence-based guidelines have advanced medical practice and supported optimal prescribing for many diseases, and processes for their development are well established [4-6]. At the evidence collation stage, a systematic review of data is performed using a search strategy designed to identify all relevant data. The evidence base typically comprises a complex mix of data of variable quality and relevance, necessitating precise and explicit grading criteria [7]. A systematic review may be followed by a meta-analysis, i.e. a mathematical method of pooling the results of studies that meet predefined criteria. In the absence of a suitable body of evidence, expert/consensus opinion may be used. However, such opinion becomes less influential as the evidence grows. While gaps exist in the management of type 2 diabetes, the evidence base is sufficiently large to allow an evidence-based approach for many aspects. Current ADA standards of care in diabetes therefore classify expert consensus or clinical experience as the lowest forms of evidence [8]. Once collated, a working group discusses the data based on the evidence-based tables and draws conclusions. Guidelines are then developed and graded or weighted according to the strength of the supporting evidence. The draft guidelines should be subjected to peer (and sometimes public) review before being finalised.

The recommendations of Nathan et al. [2] do not appear to meet many of these standards. For example, the strategies used to search for data systematically are not stated and there is no formal grading of evidence. The authors cite the use of 'clinical judgment, that is, our collective knowledge and clinical experience' as a principal secondary source of evidence. The panel comprised only seven physicians (five North American, two European). It is therefore questionable whether some recommendations can reflect the available evidence base, as outlined below in terms of the key attributes of glucose-lowering treatments.

Glucose-lowering effects

The selection of glycaemic targets and glucose-lowering treatments should be individualised on the basis of patient-specific factors (age, stage of diabetes, cardiovascular risk factors, weight, risk associated with hypoglycaemia etc.) and of effects on multiple pathophysiological aspects of type 2 diabetes [9].

According to Nathan et al., glucose-lowering efficacy is the principal factor by which drugs should be differentiated. Their algorithm states that 'The over-arching principle in selecting a particular intervention will be its ability to achieve and maintain glycaemic goals' [2]. They tabulate the reductions in HbA_{1c} expected with different classes used as monotherapy, but provide few supporting references. Sulfonylureas and metformin are each said to reduce HbA_{1c} by 1.0% to 2.0%, although the baseline levels, time-scale, patient populations, specific agent and dose are not defined. Thiazolidinediones are said to reduce HbA_{1c} by 0.5% to 1.4%, suggesting lower glucose-lowering efficacy, but this is not supported by evidence from large, randomised head-to-head trials, which found no significant differences vs sulfonylureas or metformin [10, 11] and better long-term efficacy for

thiazolidinediones [12]. A systematic evidence-based review also supports the view that these agents produce similar absolute reductions in HbA_{1c} [13]. We agree with Nathan et al. on the importance of maintaining long-term glycaemic control. In this context, the relegation of thiazolidinediones appears puzzling in light of evidence from A Diabetes Outcome Progression Trial (ADOPT), where rosiglitazone was significantly better than glibenclamide or metformin at maintaining glycaemic targets over 4 years [12].

Meta-analysis of randomised controlled trials indicates that GLP-1 receptor agonists (exenatide, liraglutide) also reduce HbA_{1c} by ~1% and are non-inferior to active comparators [14]. In a head-to-head study, liraglutide was more effective than exenatide, presumably due to its longer half-life [15]. On meta-analysis, the dipeptidyl peptidase-4 (DPP-IV) inhibitors (sitagliptin, vildagliptin) were slightly less effective than other oral glucose-lowering agents [14, 16], but were non-inferior to sulfonylureas over 52 weeks when added to metformin [17, 18].

In type 2 diabetes, insulin is commonly initiated as addon therapy either as a basal dose of a long-acting analogue (insulin glargine [A21Gly,B31Arg,B32Arg human insulin] or insulin detemir [B29Lys(e-tetradecanoyl),desB30 human insulin]) or prandially using biphasic (premixed) formulations, although the optimal approach and most efficient use of the different long-acting, intermediate-acting (e.g. NPH insulin), rapid-acting and biphasic formulations remains controversial [19]. Nathan et al. recommend the initiation of basal insulin, followed by intensification, if required. However, a recent meta-analysis suggests that greater reductions in HbA_{1c} can be achieved using biphasic or rapid-acting prandial formulations rather than a basal approach [20]. Although the recent 3-year results of the Treating To Target in Type 2 Diabetes study (4-T study) showed that basal (detemir-based) or prandial (insulin aspart [B28Asp human insulin]-based) insulin regimens provided better glycaemic control when added to oral therapy vs adding to a biphasic (aspart-based) regimen, total insulin dose was highest in the basal group (88 U), prandial insulin use was higher in the basal group (51 vs 28 U in the biphasic group) and most patients eventually received more complex insulin regimens irrespective of initial therapy [21]. Glargine appears to offer no benefit in terms of glycaemic control over NPH insulin, while detemir might be slightly less effective than NPH [22].

Clearly, basal insulin has the advantage of greater convenience. Moreover, detemir and glargine are associated with less overall hypoglycaemia than multiple daily injections of rapid-acting analogues and biphasic or NPH insulin [22-27]. However, a systematic review suggests that biphasic insulin is not associated with more nocturnal or more severe hypoglycaemia than basal insulin analogues [27]. In recent head-to-head studies, there was no difference in glycaemic control or hypoglycaemia with glargine vs detemir [28, 29].

Thus, basal insulin has potential advantages over biphasic or prandial insulin regimens in terms of less hypoglycaemia and less weight gain (see below). However, accumulating evidence indicates that control of postprandial hyperglycaemia is also important in achieving HbA_{1c} goals [30]. We suggest that, in some patients, the glycaemic benefits of biphasic or prandial insulin regimens outweigh the risk of hypoglycaemia and these regimens should be positioned as alternatives for initial insulin therapy according to an individualised approach.

Summary: glucose-lowering effects and a re-evaluation of the ADA/EASD algorithm

- In the short term (<1 year), the glucose-lowering efficacy of monotherapy with metformin, sulfonylureas or thiazolidinediones (and probably glinides and incretin-based therapies) is similar and may not be a compelling factor on which to base treatment choice. As such, other advantages/disadvantages of these agents (e.g. hypoglycaemia risk, weight gain) should be afforded greater importance within the limits of approved indications (Table 1) [31]
- More consideration should be given to long-term glucose control, including use of individual therapies or combinations with more sustained glucose-lowering effects
- Metformin and sulfonylureas, recommended by Nathan et al. as Tier 1 agents [2], are inexpensive and improve short-term glycaemic control, but sulfonylureas in particular are associated with progressive treatment failure and may not be the most appropriate choice over the long term
- The optimal approach to add-on (or indeed initial) insulin therapy remains unclear and should not be restricted solely to consideration of basal insulin therapy

Cardiovascular benefit-risk relationships

The effects of glucose-lowering treatments on cardiovascular outcomes are of central importance, as cardiovascular disease is the major cause of death in patients with diabetes. The consensus statement algorithm states: 'there are insufficient data to support one class (or combination) of glucose-lowering agents over another

with regard to their effects on complications' [2]. Certainly, few prospective studies have assessed cardiovascular outcomes during long-term treatment and the cardiovascular benefit-risk relationship of some agents and combinations remains controversial.

Metformin

In the UK Prospective Diabetes Study (UKPDS), 'intensive' treatment starting with metformin in overweight patients reduced the rate of all micro- and macrovascular complications vs less intensive diet-based treatment alone. This reduction was significantly greater than with sulfonylureas or insulin [32]. Metformin also conferred significant reductions in diabetes-related death, all-cause death, myocardial infarction and all macrovascular events combined vs conventional treatment. A significant benefit vs sulfonylureas or insulin was seen for all-cause death [33]. On 10-year post-interventional follow-up, the significant reductions in myocardial infarction, death and any diabetes-related endpoint persisted [33]. Observational analyses have also shown reduced rates of all-cause and cardiovascular mortality with metformin vs sulfonylurea monotherapy [34-36].

Therefore, there is some evidence for a significant beneficial effect of initial metformin monotherapy on cardiovascular outcomes. The UKPDS is often considered to be the most compelling evidence for a macrovascular benefit of any single glucose-lowering medication. However, the sample size was relatively small by current standards. As Nathan et al. note, these findings require confirmation [2].

Sulfonylureas

There are no prospective data clearly supporting an effect of sulfonylureas on macrovascular outcomes. In 1970, the University Group Diabetes Program (UGDP) Study reported a link between tolbutamide and increased cardiovascular risk [37]. In the UKPDS, 'intensive' therapy starting with sulfonylureas or insulin reduced microvascular complications (mostly retinopathy) vs diet alone over 11 years, but did not significantly reduce mortality or macrovascular complications (a 16% relative reduction in myocardial infarction had borderline statistical significance) [38]. Individually, neither chlorpropamide nor glibenclamide significantly reduced these endpoints. After 10 years of post-interventional, observational follow-up, significant reductions in myocardial infarction and death were observed in patients initially randomised to sulfonylureas or insulin vs conventional therapy, despite the convergence of glycaemic control and treatments [33]. However, this analysis did not differentiate the relative effect of sulfonylureas or insulin.

Recently, the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) trial showed that intensive therapy based on gliclazide significantly reduced the risk of a combined macrovascular/microvascular endpoint (driven mostly by reduced nephropathy) vs less intensive therapy, but had no significant effect on macrovascular events alone [39].

Observational analyses have shown higher rates of all-cause and cardiovascular mortality with sulfonylurea vs metformin monotherapy [34-37]. Sulfonylurea use was also associated with in-hospital mortality among patients undergoing coronary angioplasty [40].

Metformin plus sulfonylureas

Sulfonylureas are the only oral agents recommended by Nathan et al. for routine addition to metformin monotherapy [2]. No prospective studies have demonstrated a benefit of this combination on diabetes complications. Indeed, concerns about adverse cardiovascular effects of biguanide/sulfonylurea combination therapy were raised by the UGDP study [41]. Subsequently, in the UKPDS, the addition of metformin to sulfonylurea therapy was associated with an increased risk of diabetes-related and all-cause death, although this was not confirmed by an epidemiological analysis [32].

Observational studies have analysed cardiovascular outcomes for metformin/sulfonylurea combination therapy with conflicting results. Some found an increased risk of all-cause and cardiovascular mortality, while others found no association or reduced risk [42]. The difficulty of excluding bias from observational studies is well known and the potential for confounding should be considered. However, a meta-analysis showed an increased risk of the composite of cardiovascular hospitalisation or mortality with sulfonylureas plus metformin vs either metformin monotherapy, sulfonylurea monotherapy or diet [42].

Insulin

Intensive insulin therapy has been shown to protect against long-term macrovascular complications in type 1 diabetes [43] and against microvascular complications in type 1 and type 2 diabetes [38, 44, 45]. However, there is no clear evidence that insulin treatment as such reduces the risk of macrovascular outcomes in type 2 diabetes [46].

In the UKPDS, insulin had no significant effect on any macrovascular outcome [38] and its contribution to the delayed benefit of intensive therapy at follow-up was not investigated [33]. Observational studies have had conflicting results, including increased and decreased risk of cardiovascular events vs other therapies [47-50].

In the Diabetes and Insulin-Glucose infusion in Acute Myocardial Infarction (DIGAMI) study in type 2 diabetes, insulin infusion followed by insulin injections reduced long-term mortality rates by 28% relative to conventional routine glucose-lowering therapy [51]. This contrasted with DIGAMI-2, which reported no difference in total mortality rates and a trend towards more non-fatal recurrent myocardial infarction and stroke in patients receiving acute and chronic insulin therapy vs routine therapy (with or without acute insulin) [52]. A post-hoc analysis from DIGAMI-2 found that the risk of non-fatal myocardial infarction and stroke increased significantly in patients on insulin at discharge (vs no insulin), was unchanged with sulfonylureas and decreased with metformin [53]. The Hyperglycemia and its Effect after Acute Myocardial Infarction on Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus (HEART2D) Study failed to show any benefit of prandial vs basal insulin on cardiovascular outcomes following acute myocardial infarction [54].

Thiazolidinediones

The effect of thiazolidinediones on cardiovascular outcomes has received considerable attention in recent years and these agents are now perhaps the best studied in this respect.

Data from several sources suggest that cardiovascular risk is reduced with pioglitazone [55-58]. In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) trial, participants with type 2 diabetes and macrovascular disease were randomised to pioglitazone vs placebo, alongside guideline-driven therapy [55, 56]. The primary endpoint, a composite of coronary, cerebrovascular and peripheral macrovascular events, showed a trend towards benefit from pioglitazone. The main secondary endpoint (death, myocardial infarction or stroke) showed a significant effect favouring pioglitazone. In subgroup analyses, pioglitazone significantly reduced the risk of recurrent myocardial infarction and recurrent stroke [56]. In subsequent meta-analyses, pioglitazone was associated with reduced rates of all-cause death [57] and of the composite of death, myocardial infarction and stroke [58]. In a UK retrospective cohort study, pioglitazone was associated with a lower risk of all-cause mortality than metformin and a favourable risk profile vs rosiglitazone [36].

Nathan et al. [2] note well publicised meta-analysis data suggesting an increased risk of myocardial infarction with rosiglitazone [59, 60] and advise against its use [2]. However, additional meta-analyses have not all reached the same conclusion [61]. Recently, the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study, which looked at rosiglitazone added to metformin or a sulfonylurea vs metformin/sulfonylurea combination, was inconclusive on possible adverse effects on myocardial infarction, but suggested no impact on overall cardiovascular morbidity or mortality [62]. Large observational analyses have contributed additional real-world evidence with conflicting results [63, 64]. Thus, the cardiovascular benefit-risk profile of rosiglitazone remains controversial.

Incretin-based therapies

Glucagon-like peptide-1 infusion has been shown to confer beneficial cardiovascular effects (using 'soft' surrogate endpoints) in patients with or without diabetes [65]. Moreover, animal studies with GLP-1 agonists suggest the potential to reduce infarct size and improve survival after myocardial infarction [65-67]. However, no completed clinical studies have yet examined the effect of GLP-1 agonists or DPP-IV inhibitors on primary 'hard' cardiovascular endpoints.

Summary: cardiovascular benefit-risk relations and a re-evaluation of the ADA/EASD algorithm

• Due to the high risk of macrovascular events in type 2 diabetes and absence of any well-established macrovascular benefit for glucose-lowering as such, more consideration should be given to the macrovascular benefit-risk profiles of individual glucose-lowering therapies. At present, there is good evidence of benefit for metformin (as initial therapy) in primary prevention and for pioglitazone (as part of guideline-driven therapy) in secondary prevention
• Special emphasis on metformin/sulfonylurea as the combination of choice is questionable in the absence of any outcomes data and considering evidence of a potential adverse impact on outcomes
• While caution is appropriate, exclusion of rosiglitazone from the algorithm (based on a perceived increased risk of myocardial infarction from low-grade evidence) may be unfounded considering the lack of any adverse impact on overall cardiovascular morbidity and mortality rates in RECORD [62]

Other important pathophysiological and clinical effects

Nathan et al. acknowledge that drug effects on non-glycaemic cardiovascular risk factors may be important [2]. However, little explicit consideration of the evidence supporting the relative benefit of different agents is provided, and these properties do not appear to have influenced the recommendations. We argue that effects on the pathophysiological abnormalities in type 2 diabetes and in cardiovascular disease warrant greater consideration.

Beta cell protection

The importance of progressive beta cell failure in the pathophysiology of type 2 diabetes is well recognised [9, 68]. Sulfonylureas, in particular, are associated with rapid beta cell decline and treatment failure [9, 12, 32, 38]. Although metformin is associated with beta cell decline, studies suggest that it is not as marked as with sulfonylureas [9, 12, 32].

Accumulating data suggest that thiazolidinediones, GLP-1 agonists and DPP-IV inhibitors may help to maintain beta cell mass and function [9, 68]. For thiazolidinediones, this is consistent with: (1) the maintenance of durable glucose control seen in randomised controlled trials over several years [9, 12]; (2) the delay of treatment failure with rosiglitazone vs either metformin or glibenclamide in ADOPT [12]; and (3) the delayed progression to diabetes seen in prediabetic patients [69, 70].

Analyses of intensive insulin therapy vs oral agents (metformin, gliclazide) in patients with new-onset type 2 diabetes found that recovery and maintenance of beta cell function (HOMA-B) was more favourably affected with insulin [71, 72].

In clinical studies with adjunctive exenatide, short-term reductions in HbA_{1c} have been maintained for over 3 years during open-label extension [9, 15, 73]. Beta cell function was significantly improved with exenatide compared with insulin glargine over 1 year, but returned to pre-treatment values 4 weeks after treatment cessation [74]. Evidence from short-term clinical studies suggests that liraglutide and DPP-IV inhibitors may also benefit beta cell function [9, 15].

Anti-atherogenic effects

Atherogenic risk factors associated with type 2 diabetes include a characteristic dyslipidaemia profile, subclinical inflammation, hypertension and obesity [75]. Different glucose-lowering agents have very distinct patterns of effects on these factors, which may confer antiatherogenic benefits (Table 1). Metformin appears to improve the lipid profile, with decreases in triacylglycerol and LDL-cholesterol levels and (in some studies) increases in HDL-cholesterol [76]. Thiazolidinediones improve diabetic dyslipidaemia, with benefits for pioglitazone over sulfonylureas, metformin and rosiglitazone [77, 78]. A systematic review found that, while thiazolidinediones, sulfonylureas and metformin were equally effective at improving glycaemic control, only metformin improved LDL-cholesterol, only thiazolidinediones improved HDL-cholesterol, and both metformin and thiazolidinediones improved blood pressure [13]. Studies using surrogate clinical measures of atherosclerosis showed that pioglitazone significantly slowed progression of carotid intima-media thickness and prevented progression of coronary atherosclerosis vs glimepiride [79, 80]. Insulin may exert anti-inflammatory actions that could be anti-atherogenic/cardioprotective, although this remains controversial [81]. Insulin may also lower LDL-cholesterol and triacylglycerol levels [82, 83].

Exenatide and liraglutide may also exert benefits beyond glucose control, such as reduced blood pressure and weight loss [15]. While exenatide had no short-term effect on plasma lipids, significant benefits were observed during 3 years of open-label treatment in responders [73]. DPP-IV inhibitors may affect postprandial lipaemia [84].

Therapeutic effects of glucose-lowering agents on inflammatory mediators, haemostasis markers and other factors such as the anti-inflammatory mediator adiponectin (which is increased by thiazolidinediones) may also have clinical relevance [85, 86].

Effects on body weight

Management of type 2 diabetes should not neglect effects on body weight. Weight gain is an important disadvantage of sulfonylurea and insulin therapy. In the UKPDS, absolute average weight gain was 6.5 kg in the insulin group over 10 years. Relative to dietary therapy, it was 4.0, 2.6 and 1.7 kg with insulin, chlorpropamide and glibenclamide, respectively [38]. Although all insulins increase body weight, prandial (and probably biphasic) regimens generally produce more weight gain than basal regimens [20]. Basal detemir, in particular, consistently shows less weight gain than other formulations, including NPH and glargine [22, 28, 29].

Pioglitazone and rosiglitazone also produce weight gain. In PROactive, the increase was 3.6 kg with pioglitazone over 3 years and in ADOPT it was 4.8 kg with rosiglitazone over 5 years [12, 55]. Despite this, thiazolidinediones ameliorate insulin resistance and the weight gain appears to correlate with improvements in HbA_{1c} [87, 88].

Exenatide, liraglutide and metformin reduce body weight in monotherapy and limit weight gain in combination with sulfonylureas, thiazolidinediones and/or insulin [15, 89]. DPP-IV inhibitors are essentially weight neutral [16].

Table 1 *Evidence-based clinical advantages and disadvantages of current glucose-lowering therapies in type 2 diabetes*

Intervention	Main advantages	Main disadvantages
Metformin	•Reduces macrovascular risk •Weight loss •Low risk of hypoglycaemia •Improved multiple cardiovascular risk factors/markers (lipids, CRP, PAI-1, thrombocyte hyperactivity) •Drug costs •FDCs available (with sulfonylureas, thiazolidinediones, DPP-IV inhibitors)	•Gastrointestinal side effects •Potential cardiovascular safety issues in combination with sulfonylureas •Lactic acidosis (rare in patients without contraindications)
Sulfonylureas	•Reduces microvascular risk (glibenclamide) •Reduces nephropathy (gliclazide) •Drug costs •FDCs available (with metformin, thiazolidinediones)	•Rapid secondary failure (vs metformin or thiazolidinediones) •Weight gain (varies between different agents) •Moderate risk of hypoglycaemia (varies between different agents) •Potential cardiovascular safety issues, especially in combination with metformin
Thiazolidinediones	•More sustained glucose control (vs metformin or sulfonylureas) •Reduced macrovascular risk (pioglitazone only) •Low risk of hypoglycaemia •Reduced atherosclerosis progression (coronary IVUS [pioglitazone only], CIMT) •Improved multiple cardiovascular risk factors/markers (lipids, blood pressure, CRP, adiponectin, PAI-1, MMP-9) •Reduced microalbuminuria •FDCs available (with metformin, glimepiride)	•Weight gain •Peripheral oedema •Uncertain macrovascular risk profile with rosiglitazone •Increased incidence of CHF (but no increased macrovascular/ mortality consequences) •Increased risk of distal fractures in women •Drug costs

Glinides	•Reduces postprandial blood glucose	•No outcomes data •Hypoglycaemia (possibly similar risk to sulfonylureas) •Weight gain •Long-term efficacy/safety data lacking (especially in combination with other oral agents) •Drug costs
α-Glucosidase inhibitors	•Weight neutral •Low risk of hypoglycaemia	•No robust cardiovascular outcomes data •Gastrointestinal side effects (leading to poor adherence)
	•Serious side effects extremely rare	•Glucose-lowering efficacy only modest
DPP-IV inhibitors	•Low risk of hypoglycaemia (except in combination with a sulfonylurea)	•No outcomes data •Limited long-term clinical experience at present
	•Weight-neutral	•Possible link to pancreatitis
	•FDCs available (with metformin)	•Drug costs
Insulin	•Glucose-lowering efficacy (potentially limitless with uptitration)	•Most effective insulin strategy remains undetermined •Moderate to high risk of hypoglycaemia
	•Reduces microvascular risk	•Weight gain •Frequent blood glucose monitoring •May involve frequent injections •Drug costs (esp. analogues)
GLP-1 receptor agonists	•Low risk of hypoglycaemia (except in combination with a sulfonylurea) •Weight loss	•No outcomes data •Gastrointestinal side effects
	•Lowers blood pressure	•Limited long-term clinical experience at present
	•Potential beta cell protective effect	•Antibody formation (exenatide only) •Possible interaction with other drugs due to delayed gastric emptying •Possible link to pancreatitis •Drug costs

Adapted and modified from the evidence-based guideline of the German Diabetes Association [31] CIMT, carotid intima-media thickness; CRP, C-reactive protein; FDC, fixed-dose combination; IVUS, intravascular ultrasound; MMP-9, matrix metalloproteinase-9; PAI-1, plasminogen activator inhibitor-1

Consideration of adverse effects

Fluid retention and congestive heart failure

The potential for fluid retention and exacerbation of congestive heart failure (CHF) with thiazolidinediones is well recognised [90]. However, this does not appear to increase cardiovascular mortality rates and appropriate treatment of oedema will prevent CHF [90]. In PROactive, pioglitazone recipients experienced more serious heart failure events than participants on placebo, but without increased heart failure mortality rates [90]. Among patients with serious heart failure events, pioglitazone significantly lowered the risk of the main secondary endpoint vs placebo, with a trend towards lower risk for the primary endpoint and all-cause mortality [90]. A meta-analysis of controlled studies concluded that metformin is the only glucose-lowering agent not associated with measurable harm in patients with diabetes and heart failure, although randomised trials are lacking and warnings concerning lactic acidosis remain [91].

Bone fracture risk

Pioglitazone and rosiglitazone are associated with double the risk of fractures vs other oral agents [92]. Rates are two to three fractures per 100 patient-years, with most occurring in the distal long bones and related to trauma. This risk should be a particular consideration in postmenopausal women.

Gastrointestinal side effects

One of the few limitations of metformin is intolerance to its gastrointestinal side effects in a moderate proportion of patients [31]. This is also the main adverse event associated with exenatide [31].

Acute pancreatitis

Post-marketing cases of acute pancreatitis (including haemorrhagic/necrotising pancreatitis) have been reported with incretin-based therapies, including exenatide and sitagliptin [93, 94]. In clinical trials, however, the incidence was 1.79/1,000 person-years for exenatide (seven cases), 2.72 with placebo and 1.35 for comparators [95]. Recently, data from a large US health insurance database suggested annual acute pancreatitis rates of 0.13% among exenatide users and 0.12% among sitagliptin users [96]. This was comparable with the risk from metformin and glibenclamide, making evidence of an association between acute pancreatitis and incretin-based therapies weak at best [96].

Cancer

Malignancy is an emerging potential safety issue with some glucose-lowering therapies. Observational studies suggest that insulin or insulin secretagogues may be associated with increased risk of pancreatic cancer, whereas metformin may be associated with reduced cancer risk [97-99]. In a recent retrospective cohort study in general practice, patients on insulin or insulin secretagogues were more likely to develop solid cancers vs those on metformin, most of this excess risk being abolished by combination with metformin [99].

Hypoglycaemia

Latrogenic hypoglycaemia represents a barrier to intensive glucose control, and is a particular issue with insulin and (to some extent) sulfonylureas. Most guidelines recommend HbA_{1c} targets below 7.0% or 6.5% [2, 8, 31, 100], but without reference to specific antidiabetic treatments, diabetes duration or pre-existing cardiovascular disease. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, intensive control was associated with increased all-cause and cardiovascular mortality vs conventional therapy [100]. After 3.5 years, HbA_{1c} was 6.4% with intensive treatment and 7.5% with conventional treatment, and severe hypoglycaemic event rates were 10.5% and 3.5%, respectively. Although the cause of the increased mortality remains unclear, hypoglycaemia represents the most plausible explanation. Recently, alarming results from the statistically powerful UK General Practice Research Database have been published [101]. Among 48,000 patients with type 2 diabetes, the decile with the lowest HbA_{1c} (median 6.4%) had a significantly higher mortality rate (HR 1.52, 95% CI 1.32-1.76) vs the lowest-risk reference decile (median HbA_{1c} 7.5%), and the rate was higher than all other deciles apart from the highest HbA_{1c} (median 10.5%). Major cardiovascular events were also more frequent in this low HbA_{1c} group than any other decile. Within the lowest decile, insulin-treated patients had a greater mortality risk vs the reference decile (HR 1.79, 95% CI 1.45-2.22) than those not treated with insulin (HR 1.30, 95% CI 1.07-1.58), adding support to the hypothesis that premature death might relate to hypoglycaemia. Future controlled intervention studies are needed to clarify whether intensification of glucose control with insulin therapy alone further heightens mortality risk. Accordingly, diabetes guidelines might need revision to define a minimum HbA_{1c} value, especially for patients with long-standing diabetes or established cardiovascular disease.

Summary: other pathophysiological and clinical effects and a re-evaluation of the ADA/EASD Algorithm
• In the absence of primary endpoint outcomes data, consideration of the impact of individual glucose-lowering drugs on cardiovascular risk factors/markers and measures of atherosclerosis progression is warranted
• As the progressive decline in beta cell function is a key factor limiting long-term glycaemic control, more consideration should be given to drugs with beta cell-preserving properties (preferably alongside clinical evidence for durable glycaemic control)
• The complex benefit-safety profiles of individual glucose-lowering agents highlight the need for individualised therapy in the pathophysiologically complex and heterogeneous type 2 diabetes population

Conclusions—implications for treatment guidelines

The algorithm published by Nathan et al. [2] under the auspices of the ADA and EASD has provoked debate on the optimal management of hyperglycaemia in type 2 diabetes [9, 102]. This paper is not designed to propose a specific treatment algorithm, but rather to point out important deficiencies in the algorithm of Nathan et al. and to argue for a re-evaluation of its recommendations. We believe that inconsistencies in the application of

accepted evidence-based procedures have resulted in a skewed ranking of agents. In our opinion, the recommended two-tier approach is not evidence based and does not offer the best quality of treatment on the basis of our understanding of the multifactorial pathophysiology of type 2 diabetes or the need for individualised therapy. Methodologically, the ADA-EASD algorithm seems to be based more on an outdated expert opinion model than on the evidence-based approach that represents the current standard for guideline development.

In our opinion, these recommendations do not take full account of the evidence on the appropriate priorities for treatment (in particular, the potential impact on clinically important endpoints such as macrovascular events) or on the benefits of all available classes of glucose-lowering agents. In favouring initial use of metformin monotherapy followed by sulfonylurea, an approach known to fail, this algorithm does not offer physicians and patients the appropriate selection of options to individualise and optimise care with a view to sustained control of blood glucose and reduction of diabetes complications.

Duality of interest

G. Schernthaner has received lecture fees from AstraZeneca/BMS, Eli Lilly, GSK, Merck, NovoNordisk, sanofi-aventis, Servier and Takeda. A. H. Barnett has received lecture fees from AstraZeneca/BMS, Eli Lilly, MSD, Novartis, NovoNordisk, sanofi-aventis and Servier. D. J. Betteridge has received lecture fees and honoraria for advisory boards from AstraZeneca, Eli Lilly, GSK Merck, NovoNordisk, Pfizer, Boehringer Ingelheim and Takeda, B. Charbonnel has received lecture fees from AstraZeneca/BMS, Boehringer Ingelheim, GSK, Merck, NovoNordisk, Roche, sanofi-aventis and Takeda. M. Hanefeld has received lecture from BACER-AG, sanofi-aventis, GlaxoSmithKline, Novartis, Takeda and MSD, M. T. Malecki has received lecture fees from Berlin-Chemie, Bioton, Eli Lilly, NovoNordisk, Roche and Servier, and grant support from Eli Lilly. R. Nesto has received lecture fees from GSK and sanofi-aventis. A. Scheen has received lecture fees from AstraZeneca/BMS, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, NovoNordisk, sanofi-aventis and Takeda. J. Seufert has received lecture fees from AstraZeneca/BMS, Bayer, Berlin Chemie, Eli Lilly, GlaxoSmithKline, Lifescan, Merck Sharp & Dohme, Novartis, NovoNordisk, Pfizer, sanofi-aventis and Takeda. R. DeFronzo has received lecture fees from Amylin, BMS, Eli Lilly, ISIS, Merck, Novartis and Takeda, The remaining authors declare that there is no duality of interest associated with this manuscript.

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