Management of Hyperglycemia 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)

SILVIO E. INZUCCHI, MD
RICHARD M. BERGENSTAL, MD
JOHN B. BUSE, MD, PHD
MICHAELA DIAMANT, MD, PhD
ELE FERRANNINI, MD

MICHAEL NAUCK, MD
ANNE L. PETERS, MD
APOSTOLOS TSAPAS, MD, PHD
RICHARD WENDER, MD
DAVID R. MATTHEWS, MD, DPHIL

G
trole in modifying the natural history of type 2 diabetes (4,6). The implementa-

These recommendations should be considered within the context of the needs, preferences, and tolerances of each patient; individualization of treatment is the corner-

 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-centered 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 organizing principle underlying health care 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 utilization 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 health care decisions may enhance adherence to therapy.

**BACKGROUND**

**Epidemiology and health care impact**

Both the prevalence and incidence of type 2 diabetes are increasing worldwide, particularly in developing countries, in conjunction with increased obesity rates and westernization of lifestyle. The attendant economic burden for health care 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 hospitalization. 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 glycemic control to outcomes**

It is well established that the risk of cardiovascular and macrovascular complications is related to glycaemia, as measured by HbA1c; this remains a major focus of therapy (29). Prospective randomized 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 randomized to either a sulfonylurea or insulin, with a subset of overweight patients randomized to metformin. The overall HbA1c achieved was 0.9% lower in the intensive policy group compared with the conventional policy arm (7.0% vs. 7.9%). Associated with this difference in glycemic control was a reduction in the risk of microvascular complications (retinopathy, nephropathy, neuropathy) with intensive therapy. A trend toward 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 HbA1c 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) end points 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 HbA1c levels between the groups converged soon after the randomized 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 DiaMictlon Modified-Release Controlled Evaluation (ADVANCE) (35), Veterans Affairs Diabetes Trial (VADT) (36)] reported the effects of two levels of glycemic control on cardiovascular end points in middle-aged and older individuals with well-established type 2 diabetes at high risk for cardiovascular events. ACCORD and VADT aimed for an HbA1c ≤6.0% using complex combinations of oral agents and insulin. ADVANCE aimed for an HbA1c ≤6.5% using a less intensive approach based on the sulfonylurea glimepiride. None of the trials demonstrated a statistically significant reduction in the primary combined cardiovascular end points. 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 hypoglycemia were threefold higher with intensive treatment. It remains unclear, however, if hypoglycemia 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 HbA1c, benefited from the more intensive strategies. Modest improvements in some microvascular end points in the studies were likewise demonstrated. Finally, a meta-analysis of cardiovascular outcomes in these trials suggested that every HbA1c reduction of ~1% may be associated with a 15% relative risk reduction in nonfatal 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 β-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 α-cells hypersекrete glucagon, further promoting hepatic glucose production (38). Importantly, islet dysfunction is not necessarily irreversible. Enhancing insulin action relieves β-cell secretory burden, and any intervention that improves glycaemia—from energy restriction to, most strikingly, bariatric surgery—can ameliorate β-cell dysfunction to an extent (39). More recently recognized abnormalities in the incretin system (represented by the gut hormones, glucagon-like peptide 1 [GLP-1], and glucose-dependent insulinoctropic 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 underutilization. Moreover, an increased delivery of fatty acids to the liver favors their oxidation, which contributes to increased gluconeogenesis, whereas the absolute overabundance of lipids promotes hepatosteatosis (41).

Antihyperglycemic 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.

ANTIHYPERGLYCEMIC THERAPY

Glycemic targets
The ADA’s “Standards of Medical Care in Diabetes” recommends lowering HbA1c to <7.0% 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 premeal 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 HbA1c targets (e.g., 6.0–6.5%) might be considered in selected patients (with short disease duration, long life expectancy, no significant CVD) if this can be achieved without significant hypoglycemia or other adverse effects of treatment (20,43). Conversely, less stringent HbA1c goals—e.g., 7.5–8.0% or even slightly higher—are appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced complications, extensive comorbid conditions and those in whom the target is difficult to attain despite intensive self-management education, repeated counseling, 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 individualize treatment targets (5,34–36). The elements that may guide the clinician in choosing an HbA1c 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 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, utilizing the percentage of diabetic patients who are achieving an HbA1c <7.0% as a quality indicator, as promulgated by various health care organizations, is inconsistent with the emphasis on individualization 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 standardized 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 counseling should also be integrated into the treatment program.

Weight reduction, achieved through dietary means alone or with adjunctive medical or surgical intervention, improves glycemic control and other cardiovascular risk factors. Modest weight loss (5–10%) contributes meaningfully to achieving improved glucose control. Accordingly, establishing a goal of weight reduction, or at least weight maintenance, is recommended.

Dietary advice must be personalized (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 fiber (such as vegetables, fruits, whole grains, and
Table 1—Properties of currently available glucose-lowering agents that may guide treatment choice in individual patients with type 2 diabetes mellitus

<table>
<thead>
<tr>
<th>Class</th>
<th>Compound(s)</th>
<th>Cellular mechanism</th>
<th>Primary physiological action(s)</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
</table>
| Biguanides             | Metformin                                   | Activates AMP-kinase                                                             | ↓ Hepatic glucose production                                                                 | • Extensive experience  
  • No weight gain  
  • No hypoglycemia  
  • Likely ↓ CVD events (UKPDS) | • Gastrointestinal side effects (diarrhea, abdominal cramping)  
  • Lactic acidosis risk (rare)  
  • Vitamin B<sub>12</sub> deficiency  
  • Multiple contraindications: CKD, acidosis, hypoxia, dehydration, etc. | Low  |
| Sulfonylureas 2nd generation | Glyburide/glibenclamide  
  Glipizide  
  Gliclazide<sup>b</sup>  
  Glimepiride | Closes K<sub>ATP</sub> channels on β-cell plasma membranes | ↑ Insulin secretion                                                                 | • Extensive experience  
  • ↓ Microvascular risk (UKPDS) | • Hypoglycemia  
  • Weight gain  
  • ? Blunts myocardial ischemic preconditioning  
  • Low durability | Low  |
| Meglitinides (glinides) | Repaglinide  
  Nateglinide | Closes K<sub>ATP</sub> channels on β-cell plasma membranes | ↑ Insulin secretion                                                                 | • ↓ Postprandial glucose excursions  
  • Dosing flexibility | • Hypoglycemia  
  • Weight gain  
  • ? Blunts myocardial ischemic preconditioning  
  • Frequent dosing schedule | High  |
| Thiazolidinediones     | Pioglitazone  
  Rosiglitazone<sup>e</sup> | Activates the nuclear transcription factor PPAR-γ | ↑ Insulin sensitivity                                                                 | • No hypoglycemia  
  • Durability  
  • ↑ HDL-C  
  • ↓ Triglycerides (pioglitazone)  
  • ? ↓ CVD events (ProACTIVE, pioglitazone) | • Weight gain  
  • Edema/heart failure  
  • Bone fractures  
  • ↑ LDL-C (rosiglitazone)  
  • ? ↑ MI (meta-analyses, rosiglitazone)  
  • ? ↑ Bladder cancer (pioglitazone) | High<sup>e</sup>  |
| α-Glucosidase inhibitors<sup>a</sup> | Acarbose  
  Miglitol  
  Voglibose<sup>b,d</sup> | Inhibits intestinal α-glucosidase | Slows intestinal carbohydrate digestion/absorption | • No hypoglycemia  
  • ↓ Postprandial glucose excursions  
  • ? ↓ CVD events (STOP-NIDDM)  
  • Nonsystemic | • Generally modest HbA<sub>1c</sub> efficacy  
  • Gastrointestinal side effects (flatulence, diarrhea)  
  • Frequent dosing schedule | Moderate  |
| DPP-4 inhibitors       | Sitagliptin  
  Vildagliptin<sup>a</sup>  
  Saxagliptin  
  Linagliptin  
  Alogliptin<sup>b,d</sup> | Inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations | ↑ Insulin secretion (glucose-dependent)  
  ↓ Glucagon secretion (glucose-dependent) | • No hypoglycemia  
  • Well tolerated | • Generally modest HbA<sub>1c</sub> efficacy  
  • Urticaria/angioedema  
  • ? Pancreatitis | High  |

*Continued on p. 5*
<table>
<thead>
<tr>
<th>Class</th>
<th>Compound(s)</th>
<th>Cellular mechanism</th>
<th>Primary physiological action(s)</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile acid sequestrants$^a$</td>
<td>Colesevelam</td>
<td>Binds bile acids in intestinal tract, increasing hepatic bile acid production; $^?$ activation of farnesoid X receptor (FXR) in liver</td>
<td>$\cdot$ Unknown</td>
<td>$\cdot$ No hypoglycemia</td>
<td>$\cdot$ Generally modest HbA$_{1c}$ efficacy $^b$ $\cdot$ Constipation $\cdot$ $^?$ Triglycerides $\cdot$ $^?$ May ↓ absorption of other medications</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$\cdot$ $^?$ ↓ Hepatic glucose production</td>
<td>$\cdot$ ↓ LDL-C</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$\cdot$ $^?$ ↓ Incretin levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine-2 agonists$^a$</td>
<td>Bromocriptine (quick-release)$^d$</td>
<td>Activates dopaminergic receptors</td>
<td>$\cdot$ Modulates hypothalamic regulation of metabolism</td>
<td>$\cdot$ No hypoglycemia</td>
<td>$\cdot$ Generally modest HbA$_{1c}$ efficacy $^b$ $\cdot$ Dizziness/syncope $\cdot$ Nausea $\cdot$ Fatigue $\cdot$ Rhinitis</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$\cdot$ ↑ Insulin sensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>Exenatide</td>
<td>Activates GLP-1 receptors</td>
<td>$\cdot$ ↑ Insulin secretion (glucose-dependent)</td>
<td>$\cdot$ No hypoglycemia</td>
<td>$\cdot$ Gastrointestinal side effects (nausea/vomiting) $\cdot$ $^?$ Acute pancreatitis $\cdot$ $^?$ C-cell hyperplasia/medullary thyroid tumors in animals $\cdot$ Injectable $\cdot$ Training requirements</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Exenatide extended release</td>
<td></td>
<td>$\cdot$ ↓ Glucagon secretion (glucose-dependent)</td>
<td>$\cdot$ Weight reduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liraglutide</td>
<td></td>
<td>$\cdot$ Slows gastric emptying</td>
<td>$\cdot$ Potential for improved $\beta$-cell mass/function</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$\cdot$ ↑ Satiety</td>
<td>$\cdot$ Cardiovascular protective actions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylin mimetics$^a$</td>
<td>Pramlintide$^d$</td>
<td>Activates amylin receptors</td>
<td>$\cdot$ ↓ Glucagon secretion</td>
<td>$\cdot$ No hypoglycemia</td>
<td>$\cdot$ Generally modest HbA$_{1c}$ efficacy $^b$ $\cdot$ Gastrointestinal side effects (nausea/vomiting) $\cdot$ Hypoglycemia unless insulin dose is simultaneously reduced $\cdot$ Injectable $\cdot$ Frequent dosing schedule</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$\cdot$ Slows gastric emptying</td>
<td>$\cdot$ Weight reduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$\cdot$ ↑ Satiety</td>
<td>$\cdot$ ↓ Postprandial glucose excursions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulins</td>
<td>Human NPH</td>
<td>Activates insulin receptors</td>
<td>$\cdot$ ↑ Glucose disposal</td>
<td>$\cdot$ Universally effective</td>
<td>$\cdot$ Hypoglycemia</td>
<td>Variable$^f$</td>
</tr>
<tr>
<td></td>
<td>Human Regular</td>
<td></td>
<td>$\cdot$ ↓ Hepatic glucose production</td>
<td>$\cdot$ Theoretically unlimited efficacy</td>
<td>$\cdot$ Weight gain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lispro</td>
<td></td>
<td>$\cdot$ ↓ Microvascular risk (UKPDS)</td>
<td>$\cdot$ Mitogenic effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aspart</td>
<td></td>
<td></td>
<td>$\cdot$ Injectable</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glulisine</td>
<td></td>
<td></td>
<td>$\cdot$ Training requirements</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glargine</td>
<td></td>
<td></td>
<td>$^*$ &quot;Stigma&quot; (for patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Detemir</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Premixed (several types)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$Limited use in the U.S./Europe. $^b$Not licensed in the U.S. $^c$Prescribing highly restricted in the U.S., 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 (analogs > human insulins) and dosage. CKD, chronic kidney disease; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; 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).
glycemic control (e.g., HbA1c) generally requires long-term, large-scale clinical trials — not available for most drugs. Effects on surrogate measures for metabolic control over time, and to prevent/delay the development of diabetes 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 glycemic control (e.g., HbA1c) 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 hypoglycemia. 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 β-cells, these drugs stimulate insulin release (56). While effective in controlling glucose levels, their use is associated with modest weight gain and risk of hypoglycemia. 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 hypoglycemia (58). They require more frequent dosing, however.

Thiazolidinediones (TZDs) are peroxisome proliferator–activated receptor γ agonists (59) that improve insulin sensitivity in skeletal muscle and reduce hepatic glucose production (54,55). They do not increase the risk of hypoglycemia 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). Recognized side effects of TZDs include weight gain, fluid retention leading to edema 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 4 (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 hypoglycemia by themselves.

Two agents that are used infrequently in the U.S. 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 U.S. as an antihyperglycemic 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 noninsulin pharmacological agents is said to be high for metformin, sulfonylureas, TZDs, and GLP-1 agonists (expected HbA1c 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 HbA1c, which is itself associated with greater treatment emergent glycemic 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 β-cell dysfunction that characterizes 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 glycemic profile as possible without unacceptable weight gain or hypoglycemia (73). As initial therapy, unless the patient is markedly hyperglycemic 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 (e-tetradecanoyl),desB30 human insulin]) formulations may be used. The latter two are associated with modestly less overnight hypoglycemia (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 analogs 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 analogs, 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 program 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 hypoglycemia, and “sick day” rules is imperative. Where available, certified diabetes educators can be invaluable in guiding the patient through this process.

**KEY POINTS**

- Glycemic targets and glucose-lowering therapies must be individualized.
- Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program.
- 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 minimize 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 Supplementary 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, HbA1c goals. Because of frequent gastrointestinal side effects, it should be started at a low dose with gradual titration. Patients with a high baseline HbA1c (e.g., ≥9.0%) 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 noninsulin agents or with insulin itself in this circumstance (78). If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations (e.g., >16.7–19.4 mmol/L [>300–350 mg/dL]) or HbA1c (e.g., ≥10.0–12.0%), insulin 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 stabilized, it may be possible to taper insulin partially or entirely, transferring to noninsulin antihyperglycemic 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 glycemic effects and side-effect profiles make them less attractive candidates. Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain and hypoglycemia should play a major role in drug selection (20,21). (See Supplementary Figs. for adaptations of Fig. 2 that address specific patient scenarios.)

**Advancing to dual combination therapy.** Figure 2 (and Supplementary Figs.) also depicts potential sequences of escalating glucose-lowering therapy beyond metformin. If monotherapy alone does not achieve/maintain an HbA1c target over ~2 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 HbA1c, the more likely insulin will be required. On average, any second agent is typically associated with an approximate further reduction in HbA1c of ~1% (70,79). If no clinically meaningful glycemic reduction (i.e., “nonresponder”) 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 (Table 1).

Some antihyperglycemic 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 hypoglycemia 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

---

**Figure 2**—Antihyperglycemic therapy in type 2 diabetes: general recommendations. Moving from the top to the bottom of the figure, potential sequences of antihyperglycemic therapy. In most patients, begin with lifestyle changes; metformin monotherapy is added at, or soon after, diagnosis (unless there are explicit contraindications). If the HbA1c 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 over-riding goal of improving glycemic control while minimizing 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 U.S. 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 HbA1c is very high (e.g., ≥9.0%). The therapeutic regimen should include some basal insulin before moving to more complex insulin strategies (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 hyperglycemia (e.g., HbA1c ≥10.0–12.0%). DPP-4-i, DPP-4 inhibitor; Fx’s, bone fractures; GI, gastrointestinal; GLP-1-RA, GLP-1 receptor agonist; HF, heart failure; SU, sulfonylurea. aConsider beginning at this stage in patients with very high HbA1c (e.g., ≥9%). bConsider rapid-acting, nonsulfonylurea secretagogues (meglitinides) in patients with irregular meal schedules or who develop late postprandial hypoglycemia on sulfonylureas. cSee Table 1 for additional potential adverse effects and risks, under “Disadvantages.” dUsually a basal insulin (NPH, glargine, detemir) in combination with noninsulin agents. eCertain noninsulin agents may be continued with insulin (see text). eRefer to Fig. 3 for details on regimens. eConsider beginning at this stage if patient presents with severe hyperglycemia (≥16.7–19.4 mmol/L [≥300–350 mg/dL]; HbA1c ≥10.0–12.0%) with or without catabolic features (weight loss, ketosis, etc.).
Advancing to triple combination therapy. Some studies have shown advantages of adding a third noninsulin agent to a two-drug combination that is not yet or no longer achieving the glycemic 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 B-cell loss, many patients, especially those with long-standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (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 hyperglycemia should specifically be avoided.

In using triple combinations the essential consideration is obviously to use agents with complementary mechanisms of action (Fig. 2 and Supplementary 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 begin 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 hyperglycemic. 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 titrate their own insulin dose based on several algorithms, each essentially involving the addition of a small dose increase if hyperglycemia persists (74,76,88). For example, the addition of 1–2 units (or, in those already on higher doses, increments of 5–10%) to the daily dose once or twice weekly if the fasting glucose levels are above the preagreed target is a reasonable approach (89). As the target is reached, dosage adjustments should be more modest and occur less frequently. Downward adjustment is advisable if any hypoglycemia 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 stabilized, 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 HbA1c 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 glycemic excursions.
Position Statement

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 premeal rapid-acting insulin analog 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 glycemic benefits of these more advanced regimens after basal insulin are generally modest in typical patients (92). So, again, individualization of therapy is key, incorporating the degree of hyperglycemia 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 optimize control.

A second, perhaps more convenient but less adaptable method involves “premixed” insulin, consisting of a fixed combination of an intermediate insulin with regular insulin or a rapid analog. Traditionally, this is administered twice daily, before morning and evening meals. In general, when compared with basal insulin alone, premixed regimens tend to lower HbA1c to a larger degree, but often at the expense of slightly more hyperglycemia 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 analog. 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 HbA1c.
2. All insulins are associated with some weight gain and some risk of hypoglycemia.
3. The larger the doses and the more aggressive the titration, the lower the HbA1c, but often with a greater likelihood of adverse effects.
4. Generally, long-acting insulin analogs reduce the incidence of overnight hypoglycemia, and rapid-acting insulin analogs reduce postprandial glucose excursions as compared with corresponding human insulins (NPH, Regular), but they generally do not result in clinically significantly lower HbA1c.

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 HbA1c reduction or prevention of hypoglycemia or weight gain after insulin is started, especially after the dose is titrated and stabilized. When basal insulin is used, continuing the secretagogue may minimize initial deterioration of glycemic control. However, secretagogues should be avoided once prandial insulin regimens are employed. TZDs should be reduced in dose (or stopped) to avoid edema 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 HbA1c and minimizing the required insulin dose (96). Data concerning the glycemic 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 hypoglycemia; for example, unsteadiness may result in falls and fractures (101), and a tenuous cardiac status may deteriorate into catastrophic events. It follows that glycemic 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 HbA1c of <7.5–8.0% 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-hyperglycemic agent should focus on drug safety, especially protecting against hypoglycemia, heart failure, renal dysfunction, bone fractures, and drug-drug interactions. Strategies specifically minimizing 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 glycemic targets (e.g., an HbA1c <6.5–7.0%) 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, glycemic 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 favored 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 antihyperglycemic 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 hyperglycemia, often responsive to oral agents, eventually develop more severe hyperglycemia 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 recognized (greater insulin resistance in Latinos (107), more β-cell dysfunction in East Asians (108)), using this information to craft optimal therapeutic strategies is not in 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 hyperglycemia 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). There are no prominent sex differences in the response to various antihyperglycemic 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 hypoglycemia may exacerbate myocardial ischemia 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 glycemic targets, patients should be educated to minimize risk. Because of possible effects on potassium channels in the heart, certain sulfonylureas have been proposed to aggravate myocardial ischemia through effects on ischemic 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 aging 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 hospitalizations, 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 hypoglycemia, which is multifactorial. Insulin and, to some degree, the incretin hormones are eliminated more slowly, as are antihyperglycemic drugs with renal excretion. Thus, dose reduction may be necessary, contraindications need to be observed, and consequences (hypoglycemia, fluid retention, etc.) require careful evaluation.

Current U.S. 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 U.K., the National Institute for Health and Clinical Excellence (NICE) guidelines are less prescriptive and more evidence-based than those in the U.S., 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 hypoglycemia 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. Glyburide (known as glibenclamide in Europe), 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
hypoglycemia. In patients with mild he-
patic 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 im-
pairment and is indeed the preferred choice
in those with advanced disease.

**Hypoglycemia.** Hypoglycemia 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 emerg-
ning 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 fre-
quency of both minor and major hyper-
glycemia was high in intensively managed
patients—threefold that associated with
conventional therapy (129). It remains
unknown whether hypoglycemia was
the cause of the increased mortality in the
intensive group (130,131). Clearly,
however, hypoglycemia is more danger-
ous in the elderly and occurs consistently
more often as glycemic targets are low-
ered. Hypoglycemia may lead to dys-
rhythrias, but can also lead to accidents
and falls (which are more likely to be dan-
gerous in the elderly) (132), dizziness
(leading to falls), confusion (so other ther-
apiest may not be taken or taken incor-
crrectly), or infection (such as aspiration
during sleep, leading to pneumonia). Hy-
poglycemia may be systematically under-
reported as a cause of death, so the true
incidence may not be fully appreciated.
Perhaps just as importantly, additional con-
sequences of frequent hypoglycemia in-
clude work disability and erosion of the
confidence of the patient (and that of family
or caregivers) to live independently. Accord-
ingly, in at-risk individuals, drug selection
should favor agents that do not precipitate
such events and, in general, blood glucose
targets may need to be moderated.

**FUTURE DIRECTIONS/RESEARCH NEEDS**—For antihyper-
glycemic management of type 2 diabetes,
the comparative evidence basis to date is
relatively lean, especially beyond metfor-
min monotherapy (70). There is a significant
need for high-quality comparative-
effectiveness research, not only regarding
glycemic control, but also costs and those
outcomes that matter most to patients—
quality of life and the avoidance of morbidity
and life-limiting complications, especially
coronary artery disease (CVD) (19,23,70).
Another issue about which more data are needed is the concept of du-
ability of effectiveness (often ascribed to
β-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 ef-
fects. We need more clinical data on how
phenotype and other patient/disease char-
acteristics should drive drug choices. As
new medications are introduced to the
type 2 diabetes pharmacopeia, their benefit
and safety should be demonstrated in stud-
ies versus best current treatment, substan-
tial enough both in size and duration to
provide meaningful data on meaningful
outcomes. It is appreciated, however, that
head-to-head comparisons of all combina-
tions and permutations would be impossi-
ibly large (133). Informed judgment and the
expertise of experienced clinicians will
therefore always be necessary.

**Acknowledgments**—This position statement
was written by joint request of the ADA and
the EASD Executive Committees, which have
approved the final document. The process in-
volved wide literature review, three face-to-face
meetings of the Writing Group, several tele-
conferences, and multiple revisions via e-mail
communications.

We gratefully acknowledge the following experts who provided critical review of a
draft of this statement: James Best, Melbourne
Medical School, The University of Melbourne,
Melbourne, Australia; Henk Bilo, Isala Clinics,
Zwolle, the Netherlands; John Boltri, Wayne State
University School of Medicine, Detroit,
MI; Thomas Buchanan, Keck School of
Medicine, University of Southern California,
Los Angeles, CA; Robert Ratner, MedStar Health Research
Institute/Georgetown University School of
Medicine, Washington, DC; Julio Rosenstock,
Dallas Diabetes and Endocrine Center at Medi-
cal City, Dallas, TX; Guntram Schernthaner,
Rudolfstiftung Hospital, Vienna, Austria; Robert
Sherwin, Yale University School of Medicine,
New Haven, CT; Jay Skylar, Miller School of
Medicine, University of Miami, Miami, FL;
Geralyn Spollett, Yale University School of
Nursing, New Haven, CT; Ellie Strock,
International Diabetes Center, Minneapolis, MN;
Agnathoses Tsatsoulis, University of Ioannina,
Ioannina, Greece; Andrew Wolf, University of
Virginia School of Medicine, Charlottesville,
VA; Bernard Zimman, Mount Sinai Hospital/
University of Toronto, Toronto, ON, Canada.
The American Association of Diabetes Edu-
cators, American College of Physicians, and
The Endocrine Society, and several other or-
ganizations who wished to remain anonym-
ous nominated reviewers who provided
input on the final draft. Such feedback does
not constitute endorsement by these groups
or these individuals. The final draft was also
er reviewed and approved by the Professional
Practice Committee of the ADA and the Panel for
Overseeing Guidelines and Statements of the
EASD. We are indebted to Dr. Sue Kirkman of
the ADA for her guidance and support during
this process. We also thank Carol Hill and Mary
Merkin for providing administrative assistance.

**Funding**—The three face-to-face meetings and the
travel of some of the writing group were sup-
ported by the EASD and ADA. D.R. Matthews
acknowledges support from the National In-
itute for Health Research.

**Duality of interest**—During the past 12 months, the following relationships with companies whose products
or services directly relate to the subject matter in
this document are declared:

**R.M. Bergenstal:** membership of scientific
advisory boards and consultation for or clinical
research support with Abbott Diabetes Care,
Amylin, Bayer, Becton Dickinson, Boehringer
Ingelheim, Calibra, DexCom, Eli Lilly, Halozyme,
Hemsley Trust, Hygeia, Johnson & Johnson,
Medtronic, NIH, Novo Nordisk, Roche, Sanofi,
and Takeda (all under contracts with his
employer). Inherited stock in Merck (held
by family)

**J.B. Buse:** research and consulting with
Amylin Pharmaceuticals, Inc.; AstraZeneca,
Biodel Inc.; Boehringer Ingelheim; Bristol-
Myers Squibb Company; Darts Pharmaceuticals,
Inc.; Eli Lilly and Company; F. Hoffmann-La
Roche Ltd; Halozyme Therapeutics; Johnson
& Johnson; Medtronic MiniMed; Merck &
Co., Inc.; Novo Nordisk; Pfizer Inc.; Sanofi,
and TransPharma Medical Ltd (all under contracts with his
employer)

**M. Diamant:** member of advisory boards of
Abbott Diabetes Care, Eli Lilly, Merck Sharp &
Dohme (MSD), Novo Nordisk, Poxel Pharma.
Consultancy for: Astra-BMS, Sanofi. Speaker
engagements: Eli Lilly, MSD, Novo Nordisk.
Through Dr. Diamant, the VU University receives research grants from Amylin/Eli Lilly, MSE, Novo Nordisk, Sanofi (all under contracts with the Institutional Research Foundation).

E. Ferrannini: membership on scientific advisory boards or speaking engagements for: Merck Sharp & Dohme, Boehringer Ingelheim, GlaxoSmithKline, BMS/AstraZeneca, Eli Lilly & Co., Novartis, Sanofi. Research grant support from: Eli Lilly & Co. and Boehringer Ingelheim.

S.E. Inzucchi: advisor/consultant to: Merck, Takeda, Boehringer Ingelheim. Research funding or supplies to Yale University: Eli Lilly & Co. and Boehringer Ingelheim. Participation in medical educational projects, for which unrestricted funding from Amylin, Eli Lilly, Boehringer Ingelheim, Merck, Novo Nordisk, and Takeda was received by Yale University.

D.R. Matthews: has received advisory board consulting fees or honoraria from Novo Nordisk, GlaxoSmithKline, Novartis, Eli Lilly, Johnson & Johnson, and Servier. He has research support from Johnson & Johnson and Merck Sharp & Dohme. He has lectured for Novo Nordisk, Servier, and Novartis.

M. Nauck: has received research grants (to his institution) from AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., Merck Sharp & Dohme, Novartis Pharma, GlaxoSmithKline, Novo Nordisk, Roche, and Tolerx. He has received consulting and travel fees or honoraria for speaking from AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Bristol-Myers Squibb, Diartis, Eli Lilly & Co., F. Hoffmann-La Roche Ltd., Intarcia Therapeutics, Merck Sharp & Dohme, Novo Nordisk, Sanofi-Aventis Pharma, and Versartis.

A.L. Peters: has received lecturing fees and/or for ad hoc consulting from Amylin, Lilly, Novo Nordisk, Sanofi, Takeda, Boehringer Ingelheim.

A. Tsapas: has received travel grant, educational grant, research grant and lecture fees from Merck Serono, Novo Nordisk, and Novartis, respectively.

R. Wender: declares he has no duty of interest.

Contribution statement
All the named writing group authors contributed substantially to the document including each writing part of the text. They were at the face-to-face meetings and teleconferences. All authors supplied detailed input and approved the final version. S.E. Inzucchi and D.R. Matthews directed, chaired, and coordinated the input with multiple e-mail exchanges between all participants.

References
Position Statement

principles for applying the Users’ Guides to patient care. JAMA 2000;284:1290–1296
42. Lee SJ, Eng C. Goals of glycemic control in frail older patients with diabetes. JAMA 2011;305:1350–1351
44. May C, Montori VM, Mair FS. We need minimally disruptive medicine. BMJ 2009;339:b2803
73. Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of Type 1 and Type 2 diabetes. Diabetologia 2002;45:937–948
76. Riddle MC. The Treat-to-Target Trial and related studies. Endocr Pract 2006;12(Suppl. 1):71–79
90. Garber AJ. The importance of titrating starting insulin regimens in patients with type 2 diabetes. Diabetes Obes Metab 2009;11(Suppl. 5):10–13
93. Raccah D. Options for the intensification of insulin therapy when basal insulin is not enough in type 2 diabetes mellitus. Diabetes Obes Metab 2008;10(Suppl. 2):76–82
Position Statement


123. Rodbard D. The combinatorics of medications related to an increased risk of falls and fall-related morbidity in the elderly. Ann Pharmacother 2010;44:712–717