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)

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Glycemic management in type 2 diabetes mellitus has become increasingly complex and, to some extent, controversial, with a widening array of pharmacological agents now available (1–5), mounting concerns about their potential adverse effects and new uncertainties regarding the benefits of intensive glycemic control on macrovascular complications (6–9). Many clinicians are therefore perplexed as to the optimal strategies for their patients. As a consequence, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) convened a joint task force to examine the evidence and develop recommendations for antihyperglycemic therapy in nonpregnant adults with type 2 diabetes. Several guideline documents have been developed by members of these two organizations (10) and by other societies and federations (2,11–15). However, an update was deemed necessary because of contemporary information on the benefits/risks of glycemic control, recent evidence concerning efficacy and safety of several new drug classes (16,17), the withdrawal/restriction of others, and increasing calls for a move toward more patient-centered care (18,19).

This statement has been written incorporating the best available evidence and, where solid support does not exist, using the experience and insight of the writing group, incorporating an extensive

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

E de g a d hea h ca e ac

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 hospitalizations. 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.

Re a h f g ce c c c e

It is well established that the risk of microvascular and macrovascular complications is related to glycemia, as measured by HbA_{1c}; 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 glycemic targets. In the UK Prospective Diabetes Study (UKPDS) (30,31), patients with newly diagnosed type 2 diabetes were randomized to two treatment policies. In the standard group, lifestyle intervention was the mainstay with pharmacological therapy used only if hyperglycemia became severe. In the more intensive treatment arm, patients were randomly assigned to either a sulfonylurea or insulin, with a subset of overweight patients randomized to metformin. The overall HbA_{1c} achieved was 0.9% lower in the intensive policy group compared with the conventional policy arm (7.0% vs. 7.9%). 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 HbA_{1c} only 0.6% lower than the conventional policy group. The UKPDS 10-year follow-up demonstrated that the relative benefit of having been in the intensive management policy group was maintained over a decade, resulting in the emergence of statistically significant benefits on cardiovascular disease (CVD) 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 HbA_{1c} 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 Diamicron 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 HbA_{1c} <6.0% using complex combinations of oral agents and insulin. ADVANCE aimed for an HbA_{1c} ≤6.5% using a less intensive approach based on the sulfonylurea gliclazide. 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 HbA_{1c}, 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 HbA_{1c} 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).

O e e f he a h ge e f e 2 d abe e

Any rise in glycemia is the net result of glucose influx exceeding glucose outflow from the plasma compartment. In the fasting state, hyperglycemia 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 hyperglycemia.

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 glycemia, are profoundly compromised. This functional islet incompetence is the main quantitative determinant of hyperglycemia (37) and progresses over time. In addition, in type 2 diabetes, pancreatic α-cells hypersecrete 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 glycemia—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 insulinotropic peptide [GIP]) are also found in type 2 diabetes, but it remains unclear whether

Table 1—*Properties of currently available glucose-lowering agents that may guide treatment choice in individual patients with type 2 diabetes mellitus*

Class	Compound(s)	Cellular mechanism	Primary physiological action(s)	Advantages	Disadvantages	Cost
Biguanides	• Metformin	Activates AMP-kinase	• ↓ Hepatic glucose production	• Extensive experience • No weight gain • No hypoglycemia • Likely ↓ CVD events (UKPDS)	• Gastrointestinal side effects (diarrhea, abdominal cramping) • Lactic acidosis risk (rare) • Vitamin B_{12} deficiency • Multiple contraindications: CKD, acidosis, hypoxia, dehydration, etc.	Low
Sulfonylureas	2nd generation • Glyburide/ glibenclamide • Glipizide • Gliclazide[b] • Glimepiride	Closes K_{ATP} 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_{ATP} 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[c]	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[e]
α-Glucosidase inhibitors[a]	• Acarbose • Miglitol • Voglibose[b,d]	Inhibits intestinal α-glucosidase	• Slows intestinal carbohydrate digestion/absorption	• No hypoglycemia • ↓ Postprandial glucose excursions • ? ↓ CVD events (STOP-NIDDM) • Nonsystemic	• Generally modest HbA_{1c} efficacy • Gastrointestinal side effects (flatulence, diarrhea) • Frequent dosing schedule	Moderate
DPP-4 inhibitors	• Sitagliptin • Vildagliptin[a] • Saxagliptin • Linagliptin • Alogliptin[b,d]	Inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations	• ↑ Insulin secretion (glucose-dependent) • ↓ Glucagon secretion (glucose-dependent)	• No hypoglycemia • Well tolerated	• Generally modest HbA_{1c} efficacy • Urticaria/angioedema • ? Pancreatitis	High

Continued on p. 1368

Table 1—*Continued*

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

[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).

legumes), low-fat dairy products, and fresh fish should be emphasized. High-energy foods, including those rich in saturated fats, and sweet desserts and snacks should be eaten less frequently and in lower amounts (50–52). Patients who eventually lose and keep weight off usually do so after numerous cycles of weight loss and relapse. The health care team should remain nonjudgmental but persistent, revisiting and encouraging therapeutic lifestyle changes frequently, if needed.

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

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

Oral agents and noninsulin injectables. Important properties of antihyperglycemic agents that play a role in the choice of drug(s) in individual patients are summarized in Table 1. Ultimately, the aims of controlling glycemia are to avoid acute osmotic symptoms of hyperglycemia, to avoid instability in blood glucose 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., HbA_{1c}) generally reflect changes in the probability of developing microvascular disease but not necessarily macrovascular complications. Particularly from a patient standpoint, stability of metabolic control over time may be another specific goal.

Metformin, a biguanide, remains the most widely used first-line type 2 diabetes drug; its mechanism of action predominately involves reducing hepatic glucose production (54,55). It is generally considered weight-neutral with chronic use and does not increase the risk of 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.

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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 (ε-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.

Initial and Subsequent Therapy

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, HbA_{1c} goals. Because of frequent gastrointestinal side effects, it should be started at a low dose with gradual titration. Patients with a high baseline HbA_{1c} (e.g., ≥9.0%) 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 HbA_{1c} (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 HbA_{1c} target over ~3 months, the next step would be to add a second oral agent, a GLP-1 receptor agonist, or basal insulin (5,10). Notably, the higher the HbA_{1c}, the more likely insulin will be required. On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of ~1% (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

long-term complications will likely reduce long-term expenses attributed to the disease.

Advancing to triple combination therapy. Some studies have shown advantages of adding a third 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 β-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 beginning injectable therapy, but, if the practitioner feels that such a transition is important, encouragement and education can usually overcome such reticence. Insulin is typically begun at a low dose (e.g., 0.1–0.2 U kg^{-1} day^{-1}), although larger amounts (0.3–0.4 U kg^{-1} day^{-1}) are reasonable in the more severely 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 uptitrate 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 neared, 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 HbA_{1c} remains above goal after 3–6 months of basal insulin titration (91). The same would apply if large drops in glucose occur during overnight hours or in between meals, as the basal insulin dose is increased. In this scenario, the basal insulin dose would obviously need to be simultaneously decreased as prandial insulin is initiated. Although basal insulin is titrated primarily against the fasting glucose, generally irrespective of the total dose, practitioners should be aware that the need for prandial insulin therapy will become likely the more the daily dose exceeds 0.5 U kg^{-1} day^{-1}, especially as it approaches 1 U kg^{-1} day^{-1}. The aim with mealtime insulin is to blunt postprandial glycemic excursions,

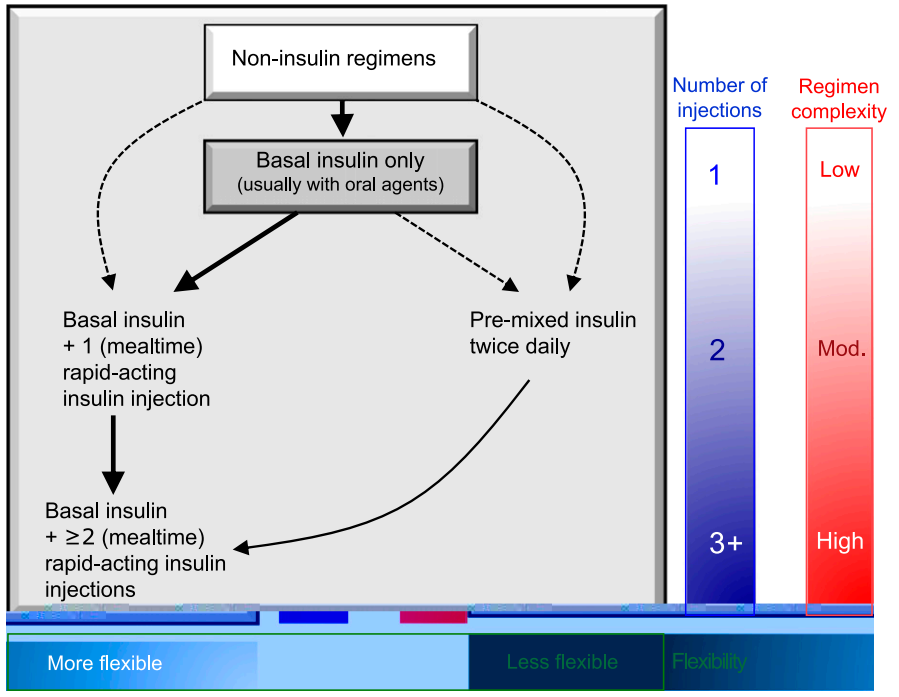

Figure 3—*Sequential insulin strategies in type 2 diabetes. Basal insulin alone is usually the optimal initial regimen, beginning at 0.1–0.2 units/kg body weight, depending on the degree of hyperglycemia. It is usually prescribed in conjunction with one to two noninsulin agents. In patients willing to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

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 HbA_{1c} to a larger degree, but often at the expense of slightly more hypoglycemia and weight gain (94). Disadvantages include the inability to titrate the shorter- from the longer-acting component of thes ttt5ibs1bryh6.1(y)5(o)-378.1(thes)-514-5.4(a)04-04TD0.5(d)-2d4(a)04-6(mo)-12n(d4(a)0o)-1at.l.6()-320.0132(a)0(a)

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.

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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 in its infancy. This is not surprising given the polygenic inheritance pattern of the disease. Indeed, while matching a drug's mechanism of action to the underlying causes of 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). While 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.

C b d e

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 proscriptive 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 hepatic disease, incretin-based drugs can be prescribed, except if there is a coexisting history of pancreatitis. Insulin has no restrictions for use in patients with liver impairment and is indeed the preferred choice in those with advanced disease.

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 emerging concern based mainly on the results of recent clinical trials and some cross-sectional evidence of increased risk of brain dysfunction in those with repeated episodes. In the ACCORD trial, the frequency of both minor and major hypoglycemia 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 dangerous in the elderly and occurs consistently more often as glycemic targets are lowered. Hypoglycemia may lead to dysrhythmias, but can also lead to accidents and falls (which are more likely to be dangerous in the elderly) (132), dizziness (leading to falls), confusion (so other therapies may not be taken or taken incorrectly), or infection (such as aspiration during sleep, leading to pneumonia). Hypoglycemia may be systematically underreported as a cause of death, so the true incidence may not be fully appreciated. Perhaps just as importantly, additional consequences of frequent hypoglycemia include work disability and erosion of the confidence of the patient (and that of family or caregivers) to live independently. Accordingly, in at-risk individuals, drug selection should favor agents that do not precipitate such events and, in general, blood glucose targets may need to be moderated.

FUTURE DIRECTIONS/ RESEARCH NEEDS

—For antihyperglycemic management of type 2 diabetes, the comparative evidence basis to date is relatively lean, especially beyond metformin monotherapy (70). There is a significant need for high-quality comparative-effectiveness research, not only regarding glycemic control, but also costs and those outcomes that matter most to patients—quality of life and the avoidance of morbid and life-limiting complications, especially CVD (19,23,70). Another issue about which more data are needed is the concept of durability of effectiveness (often ascribed to 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 effects. We need more clinical data on how phenotype and other patient/disease characteristics should drive drug choices. As new medications are introduced to the type 2 diabetes pharmacopeia, their benefit and safety should be demonstrated in studies versus best current treatment, substantial enough both in size and duration to provide meaningful data on meaningful outcomes. It is appreciated, however, that head-to-head comparisons of all combinations and permutations would be impossibly large (133). Informed judgment and the expertise of experienced clinicians will therefore always be necessary.

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