UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
Trenton

NOVO NORDISK INC., *et al.*, *Plaintiffs*, v. XAVIER BECERRA, *et al.*, *Defendants.*	No. 3:23-cv-20814-ZNQ-JBD

DECLARATION OF DR. NATHAN LANEY

I, Dr. Nathan Laney, declare as follows pursuant to 28 U.S.C. § 1746

1. I am a resident of Florida. I am over the age of eighteen, and I am competent to provide this declaration.

2. I received an MD in 2003 from the University of Missouri-Kansas City School of Medicine and an MBA from Florida International University in 2022. I am board certified in endocrinology. I have been at Novo Nordisk, Inc. since 2015. I have worked as Regional Medical Liaison - Philadelphia; Regional Medical Scientist - South Atlantic; Scientific Director, Diabetes TA; and most recently as the Medical Director at Novo Nordisk Inc. Before that, I spent six years as a practicing endocrinologist at St. Luke's Endocrinology & Diabetes. In all of these roles, I have either worked directly with patients or with healthcare professionals on diabetes management options, including insulin selection and dosing, to improve outcomes for patients living with diabetes. In my role as Medical Director at Novo Nordisk Inc., I have been deeply

involved in the Company's response to CMS inquiries under the Inflation Reduction Act and other related medical policy discussions.

The Need for Insulin to Manage Diabetes

3. In healthy individuals, beta cells in the pancreas release the hormone insulin to help regulate glucose levels in the blood. At mealtimes, insulin output from the beta cells acutely increases to allow the body to use and/or store glucose released from the digestion of food. Most patients living with diabetes have either Type 1 diabetes (T1D), an autoimmune disease where beta cells have been destroyed by the body's own immune system yielding insufficient and/or total loss of insulin production by the pancreas, or Type 2 diabetes (T2D), where the body suffers from a combination of disorders involving glucose metabolism, including inadequate insulin secretion, insulin resistance, and metabolic syndrome.

4. There is no cure for diabetes. While medicines have improved treatment, if diabetes is not properly controlled, and often even if it is well treated, it can lead over time to complications including vision impairment (or even blindness), loss of kidney function, and nerve damage which can increase the risk of amputations. Diabetes is also associated with cardiovascular risks, including myocardial infarction, stroke, heart failure, and peripheral arterial disease.

5. Innovations resulting in the development of new products to assist in insulin therapy have provided patients with the necessary tools for managing this chronic disease. Important advances include the development of both prandial—or

mealtime—insulins (fast-acting insulins taken at mealtime to prevent excessive elevations in blood sugar levels after the meal) and basal insulins (slower, longer-acting insulins that control blood sugar levels between meals and when the patient is not eating).

Insulin Dosing

6. The cornerstone of diabetes management is ensuring that treatment approaches are tailored to individual patients.

7. Controlling insulin dosing is critical. "In people with type 1 diabetes, treatment with analog insulins is associated with less hypoglycemia and weight gain as well as lower [average blood sugar levels or] A1C compared with human insulins. More recently … insulin formulations with enhanced rapid-action profiles have been introduced … and faster-acting insulin aspart and insulin lispro-aabc may reduce prandial excursions better than [rapid acting analogues or] RAA." Nuha A. ElSayed et al., *Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023*, 43 Diabetes Care S140, S141 (2023) (endnotes omitted) (attached as Exhibit A). However, choosing between appropriate analogue prandial insulin products is just the starting point. Individual patients must have their insulin doses adjusted and tailored to their individual needs.

8. Because insulin dictates how much sugar cells absorb, too much insulin can cause hypoglycemia, or low blood sugar; too little insulin can cause hyperglycemia, or too high of blood sugar levels in the blood. Increased hypoglycemia increases risk

of complications, including decreased sensitivity to hypoglycemia over time which amounts to hypoglycemic unawareness. And, with more hypoglycemic events comes increased risk of impaired cognitive function, heart arrhythmias, and mortality. When increased hyperglycemia leads to overall poor control of diabetes, it can be associated with both microvascular and macrovascular complications. Microvascular complications refer to those conditions affecting organs supplied by smaller blood vessels, and include visual disturbances, or retinopathy; reduced kidney function, or nephropathy; and disorders of the nerves, or neuropathy. In fact, diabetes remains the leading cause of blindness and chronic kidney failure in the United States, and neuropathy significantly increases the risk of these patients to develop foot ulcers and infections that lead to amputations. Macrovascular complications refer to those conditions affecting organs supplied by larger blood vessels, and include conditions like myocardial infarctions, strokes, heart failure, and peripheral arterial disease.

9. Landmark clinical data in patients with both T1D and T2D have shown that targeting appropriate overall blood sugar control reduces the risk of developing microvascular and macrovascular complications. In terms of appropriate overall blood sugar control, the laboratory measurement historically used to assess overall control is the A1C, which reflects the average glucose levels over the past 3 months. Ideally, the goal is to achieve an A1C level that is below 7%, as this is the threshold lowering the rate of hyperglycemia related complications. *See* Nuha A. ElSayed et al., *Glycemic Targets: Standards of Care in Diabetes—2023*, 46 Diabetes Care S97 (2023) (attached as Exhibit

B). A1C is the sum of all glucose exposure, including fasting blood glucose ("FBG") and post prandial glucose ("PPG") levels—blood sugar levels after a meal. This is particularly important at lower A1C levels, where PPG is the predominant contributor to A1C targets. Therefore, while A1C is an important measure, other measurements, such as PPG levels, should also be considered when assessing a person's overall diabetes control. *See* Louis Monnier et al., *Contributions of Fasting and Postprandial Glucose to Hemoglobin A1c*, 12 Endocrine Prac. 42 (2006) (attached as Exhibit C).

10. Once patients are using insulin as part of their diabetes treatment, additional modalities can be implemented to monitor blood sugar control, including continuous glucose monitoring with a device that continuously measures interstitial glucose levels over the course of the day and/or home blood glucose monitoring with a device that measures capillary glucose levels at the time the capillary blood is obtained.

11. Insulin dosing is a complex process that requires the consideration of multiple factors on an individual basis. For patients with T1D and the subset of patients with T2D who require insulin, insulin coverage is necessary throughout the day. This 24-hour insulin coverage is provided through a basal insulin component and a mealtime insulin component, both of which are intended to maintain blood sugar levels in the desired target range. The basal insulin works in the background to keep blood sugar levels in the desired target range between meals and while the individual is not eating. The mealtime insulin works to keep blood sugar levels after meals, known as PPG, from rising too high.

12. Each patient will have individualized basal and mealtime insulin needs. For example, the basal insulin component can be achieved through once- or twice-daily injections with either the newer, long-acting basal insulin analogues or the older, longer-acting NPH regular insulin, or even through the continuous administration of a rapid acting insulin analogue via an insulin pump. The mealtime component preferably will be met by one of the newer, rapid acting or ultra-rapid acting insulin analogues. Selection and dosing of both the basal insulin and the mealtime insulin will be highly specific to individual patients.

13. Because the underlying disturbances in blood sugar metabolism carry significant differences between patients living with T1D and T2D, the initiation of insulin therapy is different.

14. Most individuals with T1D are treated with multiple daily injections of insulin, including a combination of both prandial insulin and basal insulin, or with continuous subcutaneous infusion of the newer rapid- or ultra-rapid-acting insulin analogues administered through an external insulin pump. For patients who are living with T1D, in particular, where their B-cells are producing very little to no insulin, insulin therapy is life sustaining. In general, a weight-based approach can be used to initiate insulin therapy, with typical total daily insulin requirements ranging between 0.4-1 unit/kg/day.

15. Patients living with T2D have several other medications available to control blood sugar levels initially in the disease process. Due to the progressive nature

of T2D, many individuals with T2D eventually require insulin therapy to overcome progressive declines in insulin production from the B-cells and control their blood sugar levels. These patients typically continue using their oral anti-diabetes medications and/or non-insulin injectable medications to control blood sugar levels, with the exception of classes known to non-discriminately stimulate insulin secretion like the sulfonylurea and glinide classes of diabetes medications. Unlike patients living with T1D, most individuals with T2D will initially add a basal insulin to their non-insulin medications, with use of mealtime insulin initiation reserved for those patients suffering from significant elevations in blood sugar levels (e.g., up into the 300 mg/dL range) or when additional control of blood sugar levels is necessary. The basal insulin dose for those patients is generally initiated using either the fixed starting dose outlined in the FDA-approved product label for the long-acting analogues, or a weight-based dose between 0.1-0.3 units/kg/day, and then titrated upwards until the desired fast blood sugar target is achieved. *See* ElSayed et al. (Exhibit A); Susan L. Samson et al., *American Association of Clinical Endocrinology Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm - 2023 Update*, 29 Endocrine Prac. 305 (2023) (attached as Exhibit D). When T2D patients need to advance their regimens to include mealtime insulin, the more conservative approach would be to start mealtime insulin at a fixed dose of 4-5 units prior to the largest meal or calculating the starting dose using either 10 percent of the basal insulin or a weight-based approach dose as the starting point.

16. For both T1D and T2D patients who require mealtime insulin, once the total daily insulin dose for a patient is calculated, generally half of the dose is given as the basal insulin component and the other half is split between other meals. The mealtime component is then further divided among the number of meals the individual consumes daily. *See* ElSayed et al. (Exhibit A); Samson et al. (Exhibit D). From this starting point, both T1D and T2D patients must account for *when* their mealtime insulin will start working after it is injected, as well as how to adjust their planned dose based on current blood sugar level, what they are eating, and their activity level—in order to avoid causing either high or low blood sugar levels after meals related to their mealtime insulin. This process is a balancing act between increasing the basal insulin dose to lower fasting blood sugar levels while simultaneously monitoring for when it is appropriate to add or adjust mealtime insulin. If the titration process is not handled with care, these patients are at risk for persistent episodes of high blood sugars levels after meals as well as low blood sugar levels when they are not eating.

17. The dosing regimen will differ across different mealtime insulin formulations, as different insulins are absorbed into the bloodstream at different rates and thus have different rates of onset. For instance, patients that use a short-acting human regular insulin as their mealtime insulin would have to inject their mealtime insulin dose 30 minutes before they even start eating their meal, while the same patient using a rapid acting analogue like NovoLog®, would only have to administer their mealtime dose 5-10 minutes before they start eating. Patients using an ultra-rapid

analogue like FIASP® would wait until they start eating or up to 20 minutes after they start eating before they must inject their mealtime insulin. For this reason, among others, the optimal time to administer prandial insulin varies based on the specific insulin product and the needs of the individual patient.

Insulin Administration

18. Taking insulin in pill form is not an option as, under current technology, the insulin in the pill would be broken down like a protein in food and would be ineffective. Insulin is therefore injected, either under the skin (subcutaneously) or intravenously, in order for it to enter the bloodstream and travel to the cells where it exerts its action to regulate blood sugar levels. The need for this type of administration makes insulin delivery devices critical to patient use.

19. Insulin products are generally available in (1) a vial, to be used with a syringe, (2) a pen injector or (3) a pump device.

20. The vial-and-syringe method, which requires the patient to draw up the appropriate amount of insulin through a syringe, can pose risks such as drawing the incorrect insulin dose, and can be particularly challenging for those with vision impairment or dexterity limitations.

21. Pen injectors and insulin pumps can mean more precise and flexible dosing, which can reduce the risk of hyperglycemia (too high blood sugar) and hypoglycemia (too low blood sugar). A pen injector enables the patient to dial in the correct dose, resulting in easier and more accurate administration and less pain on

injection—as well as more accurate dosing. Patients can also opt for an insulin pump—a small, computerized device that continuously delivers insulin as programmed.

22. Different injectors and pumps are used for different insulin products. For example, while NovoLog® products and FIASP® products are both available for pump use, the pumps used for the different products are not the same. FIASP® products cannot be used in certain pumps due to risks of occlusion (or blockage in pump tubing); those pumps are labeled only for use with NovoLog® products.

The NovoLog® Products

23. NovoLog® is Novo Nordisk Inc.'s ("Novo") rapid-acting mealtime insulin. It is indicated to improve glycemic control in adults and pediatric patients with diabetes mellitus. The NovoLog® family of products includes: NovoLog® 10 mL (100 units/mL, or "U100") vial; NovoLog® PenFill® 3 mL (U100) cartridges, for use with a reusable insulin pen; and NovoLog® FlexPen® 3 mL (U100), a single-patient-use prefilled insulin pen. Each of these products is a distinct product that is used for different purposes, but I refer to them together as the "NovoLog® products."

24. Patients administer NovoLog® products 5–10 minutes before a meal; the American Diabetes Association ("ADA") and the American Association of Clinical Endocrinology ("AACE") consider them to be "rapid-acting" insulin products.

The FIASP® Products

25. FIASP® is Novo's *ultra*-rapid-acting mealtime insulin. It is indicated to improve glycemic control in adults and pediatric patients with diabetes mellitus. The

FIASP® family of products includes: FIASP® 10 mL (U100) vial; FIASP® FlexTouch® 3 mL (U100), a single-patient-use prefilled insulin pen; FIASP® PenFill® 3 mL (U100) cartridges, for use with a reusable insulin pen; and FIASP® PumpCart®, a 1.6 mL (U100) cartridge for use with insulin pumps. Each of these products is a distinct product that is used for different purposes, but I refer to them together as the "FIASP® products."

26. In addition to different prescribing guidance from the ADA and the AACE for the FIASP® family of products versus the NovoLog® family of products, the FDA-approved prescribing information also differs, reflecting, among other things, these products' different onset of action and dosing regimens, and the differing clinical studies that supported FDA approval of the different products.

27. Onset of appearance for FIASP® products has consistently been shown to be twice as fast as that for NovoLog® products as a result of the faster onset of exposure and increased initial absorption rate seen with the FIASP® products.

28. The ADA and the AACE consider the FIASP® products to be "ultra-rapid-acting" insulin products. Patients administer at their first bite or within 20 minutes after starting a meal. This provides patients with more flexible options for dosing. They can use a FIASP® product right at the start of a meal, up to 20 minutes after starting the meal, or at an interim point, as they deem as optimal to account for factors affecting their dosing.

29. The ADA Standards of Care differentiate "rapid-acting" insulins from "ultra-rapid-acting insulins." ElSayed et al. (Exhibit A at S143). According to the AACE Consensus Statement published in 2023, "Rapid-acting insulin analogs are preferred over human insulin preparations (e.g., regular insulin) because of their comparatively earlier onset of action." Samson et al. (Exhibit D at 319).

The FIASP® and NovoLog® Products Differ in Clinically Meaningful Ways

30. The different products included in the NovoLog® family of products and the FIASP® family of products all contain the same active ingredient, insulin aspart. But that does not mean that all of the different products within each family qualify as a single product. There are meaningful differences between the products in terms of how they are prescribed, dosed, and used by patients. As described above, when a healthcare provider writes an insulin prescription they write it not just for the active ingredient, but for the dosage and delivery method appropriate for each individual patient based on their needs.

31. The goal of therapy is to provide an insulin regimen that mimics normal insulin secretion, which requires consideration of factors that would affect normal insulin secretion in the body—factors like the individual's current blood sugar level, the size and makeup of the meal, and even the body's current demand for sugar based on recent and/or future activity level.

32. Basal insulin and short-acting human insulin R help control blood sugar levels, but they are too slow to be responsive to mealtime insulin needs. Both the

NovoLog® products and the FIASP® products help lower mealtime blood sugar spikes—but they do so at different rates.

33. The FIASP® products are formulated with vitamin B3 (niacinamide) to increase the speed of initial absorption and an amino acid (L-arginine) to stabilize the formulation. As a result, and as reflected in pharmacokinetic and pharmacodynamic clinical studies, the insulin in the FIASP® products enters the bloodstream faster than that in the NovoLog® products, resulting in a faster onset of action. In fact, the onset for FIASP® products is approximately 2.5 minutes, more than twice as fast as NovoLog® products' onset at just over 5 minutes. The onset of the glucose-lowering effect (onset of action) is statistically significantly faster as a result of the faster onset of exposure and increased initial absorption rate seen with the FIASP® products.

34. Because the faster onset of FIASP® products allows for later dosing with respect to the meal, the dose timing is different between the NovoLog® products and the FIASP® products. That is why the FIASP® products can be dosed flexibly, between the start of a meal and up to 20 minutes later, as compared to the NovoLog® products, which are dosed 5-10 minutes *before* the start of a meal.

35. Being able to take a FIASP® product after starting a meal is very important. As described above, each mealtime insulin dose is driven by how much the person eats, what they eat, and when they eat it, *i.e.*, is subject to hunger, availability, and interruptions. The patient must tailor the dose for each meal, to account for the meal itself, as well as to make other adjustments, such as adjustments related to exercise. For

example, a patient planning to eat a meal heavy in carbohydrates will have a different insulin need from a patient eating a low-carbohydrate meal. But ultra-fast-acting insulins can be dosed based on food *actually consumed* instead of estimates of what might be consumed.

36. The ability to wait until after a meal has been decided upon, ordered, or even consumed, offers a considerable benefit to some patients. For pediatric and elderly patients, for example, there is a real concern that they will not eat as expected, which can require dose adjustments after a meal or result in hypoglycemia. In a survey of parents of pediatric patients with Type 1 diabetes, 81% indicated that, at least once a week, their children ate more or less food than anticipated after dosing mealtime insulin. *See* Wendy Lane et al., *Exploring the Burden of Mealtime Insulin Dosing in Adults and Children with Type 1 Diabetes*, 39 Clinical Diabetes J. 347 (2021) (attached as Exhibit E). And for all patients, there can be interruptions—a child may need something just as the person is sitting down to eat after dosing, or a waiter at a restaurant may inform the patient that their selection is not available after placing an order and administering an insulin dose accordingly.

37. A patient using a rapid-acting insulin must eat the planned amount once dosed, or they may experience hypoglycemia, with the side effects that ensue. Nocturnal hypoglycemia also can occur if a patient does not eat enough food after taking an insulin dose or taking more insulin that prescribed in the evening. In a survey of adults with

Type 1 diabetes, 58% of patients reported a need for additional food intake as a corrective action to prevent hypoglycemia at least once a week. *See id.* (Exhibit E).

38. The flexibility of ultra-rapid-acting insulin, however, allows a patient to ensure what they are eating—and that they are in fact consuming it—*before* dosing. That, in turn, enables a person to best match their insulin dose to their actual intake, minimizing the chance of taking too much or too little insulin (which can have adverse consequences and could lead to adverse events or serious adverse events). The improved flexibility in timing of mealtime and post-meal dosing can therefore improve therapeutic adherence which could lead to better glycemic control. *See id.* (Exhibit E). For a patient taking insulin on a daily basis, this flexibility is absolutely key to quality of life, controlling their diabetes, and avoiding daily highs and lows.

39. In addition to the added flexibility of ultra-rapid mealtime insulin for some patients, the differences in onset timing can result in lower PPG levels after a meal. In a survey of adults with Type 1 diabetes, 91% reported experiencing challenges with mealtime insulin dosing, including the need to inject more insulin after a meal because of eating more or different food than anticipated. *See id.* (Exhibit E).

40. High PPG levels have been linked to the development of vascular complications and other adverse effects. *See* Kenneth S. Hershon et al., *Importance of Postprandial Glucose in Relation to A1c and Cardiovascular Disease*, 37 Clinical Diabetes J. 250 (2019) (attached as Exhibit F).

41. Too little insulin, and for patients with Type 2 diabetes, the loss of early phase endogenous insulin secretion, contributes to elevated PPG levels after a meal, but with improved dosing flexibility and other clinical characteristics of a ultra rapid acting insulins, PPG levels can be better controlled. When administered at mealtime, FIASP® outperformed NovoLog® in terms of significantly reducing 1-hour PPG increments in both Type 1 and Type 2 diabetes patients in multiple clinical trials. *See* David Russell-Jones et al., *Fast-Acting Insulin Aspart Improves Glycemic Control in Basal-Bolus Treatment for Type 1 Diabetes: Results of a 26-Week Multicenter, Active-Controlled, Treat-to-Target, Randomized, Parallel-Group Trial (Onset 1)*, 40 Diabetes Care 943 (2017) (attached as Exhibit G); Keith Bowering et al., *Faster Aspart Versus Insulin Aspart as Part of a Basal-Bolus Regimen in Inadequately Controlled Type 2 Diabetes: The Onset 2 Trial*, 40 Diabetes Care 951 (2017) (attached as Exhibit H). This, in turn, can result in fewer instances of immediate post-prandial hypoglycemia, complications and long-term clinical impacts. A randomized, blinded clinical trial in adults with Type 2 diabetes found a lower relative risk of severe hypoglycemia for FIASP® compared to NovoLog®. *See* Wendy S. Lane et al., *A Randomized Trial Evaluating the Efficacy and Safety of Fast-Acting Insulin Aspart Compared With Insulin Aspart, Both in Combination With Insulin Degludec With or Without Metformin, in Adults With Type 2 Diabetes (ONSET 9)*, 43 Diabetes Care 1710 (2020) (attached as Exhibit I).

42. Thus, the ADA Standards of Care have recognized that ultra rapid-acting insulins like the FIASP® products may reduce prandial excursions better than rapid-

acting insulins like NovoLog®. In fact, there is a demonstrated statistically significant reduction in A1C in patients with T1D when FIASP® was dosed at mealtime versus NovoLog® dosed at mealtime. *See* Russell-Jones et al. (Exhibit G).

43. Because of these differences, it is medically critical to appropriately differentiate between the different NovoLog® products and the different FIASP® products to avoid inadvertent substitution and the potential for medication errors—particularly given the disparate injection timing of the different products.

44. For instance, if a patient administered a NovoLog product® after starting a meal, they would have a blood sugar spike; if a patient administered a FIASP® product several minutes before starting a meal, they would risk hypoglycemia. In addition, as with all drugs, users of a product within the NovoLog® family of products inadvertently administered a product within the FIASP family of products (or vice versa) without changing their dosing procedure accordingly, they may experience adverse events.

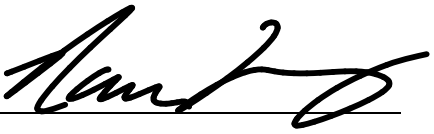
45. Confusion between a FIASP® product and a NovoLog® product when used in an insulin pump can result in occlusion (or blockage in pump tubing), which can result in nondelivery of needed insulin, which could lead to an individual with Type 1 diabetes to develop a life-threatening condition called diabetic ketoacidosis, or DKA. While DKA can develop following short periods of insulin nondelivery over the course of minutes to hours in patients with Type 1 diabetes, those living with Type 2 diabetes also could be at risk for developing an alternate condition called hyperosmolar

hyperglycemic state, though this would generally require much longer periods of insulin nondelivery over days rather than minutes or hours, as well as cessation of other diabetes medications used to control glucose levels.

46. A healthcare provider would not prescribe a NovoLog® product *and* a FIASP® product, nor would a healthcare provider transition patients between these products without significant discussion and training related to dosing regimens and delivery devices.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on this 07 day of December, 2023.

By: 

Declaration of Dr. Nathan Laney

Exhibit A

9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes—2023*

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Nuha A. ElSayed, Grazia Aleppo, Vanita R. Aroda, Raveendhara R. Bannuru, Florence M. Brown, Dennis Bruemmer, Billy S. Collins, Marisa E. Hilliard, Diana Isaacs, Eric L. Johnson, Scott Kahan, Kamlesh Khunti, Jose Leon, Sarah K. Lyons, Mary Lou Perry, Priya Prahalad, Richard E. Pratley, Jane Jeffrie Seley, Robert C. Stanton, and Robert A. Gabbay, on behalf of the American Diabetes Association

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 1 DIABETES

Recommendations

- **9.1** Most individuals with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. **A**
- **9.2** Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. **A**
- **9.3** Individuals with type 1 diabetes should receive education on how to match mealtime insulin doses to carbohydrate intake, fat and protein content, and anticipated physical activity. **B**

Insulin Therapy

Because the hallmark of type 1 diabetes is absent or near-absent β-cell function, insulin treatment is essential for individuals with type 1 diabetes. In addition to hyperglycemia, insulinopenia can contribute to other metabolic disturbances like hypertriglyceridemia and ketoacidosis as well as tissue catabolism that can be life threatening. Severe metabolic decompensation can be, and was, mostly prevented with once- or twice-daily injections for the six or seven decades after the discovery of insulin. However, over the past three decades, evidence has accumulated supporting more intensive insulin replacement, using multiple daily injections of insulin or continuous subcutaneous administration through an insulin pump, as providing the best combination of effectiveness and safety for people with type 1 diabetes. The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy with multiple daily injections or continuous subcutaneous insulin infusion (CSII) reduced A1C and was associated with improved long-term outcomes (1–3).

Disclosure information for each author is available at https://doi.org/10.2337/dc23-SDIS.

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The study was carried out with short-acting (regular) and intermediate-acting (NPH) human insulins. In this landmark trial, lower A1C with intensive control (7%) led to ~50% reductions in microvascular complications over 6 years of treatment. However, intensive therapy was associated with a higher rate of severe hypoglycemia than conventional treatment (62 compared with 19 episodes per 100 patient-years of therapy). Follow-up of subjects from the DCCT more than 10 years after the active treatment component of the study demonstrated fewer macrovascular as well as fewer microvascular complications in the group that received intensive treatment (2,4).

Insulin replacement regimens typically consist of basal insulin, mealtime insulin, and correction insulin (5). Basal insulin includes NPH insulin, long-acting insulin analogs, and continuous delivery of rapid-acting insulin via an insulin pump. Basal insulin analogs have longer duration of action with flatter, more constant plasma concentrations and activity profiles than NPH insulin; rapid-acting analogs (RAA) have a quicker onset and peak and shorter duration of action than regular human insulin. In people with type 1 diabetes, treatment with analog insulins is associated with less hypoglycemia and weight gain as well as lower A1C compared with human insulins (6–8). More recently, two injectable insulin formulations with enhanced rapid-action profiles have been introduced. Inhaled human insulin has a rapid peak and shortened duration of action compared with RAA and may cause less hypoglycemia and weight gain (9) (see also subsection ALTERNATIVE INSULIN ROUTES in PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES), and faster-acting insulin aspart and insulin lispro-aabc may reduce prandial excursions better than RAA (10–12). In addition, longer-acting basal analogs (U-300 glargine or degludec) may confer a lower hypoglycemia risk compared with U-100 glargine in individuals with type 1 diabetes (13,14). Despite the advantages of insulin analogs in individuals with type 1 diabetes, for some individuals the expense and/or intensity of treatment required for their use is prohibitive. There are multiple approaches to insulin treatment, and the central precept in the management of type 1 diabetes is that some form of insulin be given in a planned regimen tailored to the individual to keep them safe and out of diabetic ketoacidosis and to avoid significant hypoglycemia, with every effort made to reach the individual's glycemic targets.

Most studies comparing multiple daily injections with CSII have been relatively small and of short duration. However, a systematic review and meta-analysis concluded that CSII via pump therapy has modest advantages for lowering A1C (−0.30% [95% CI −0.58 to −0.02]) and for reducing severe hypoglycemia rates in children and adults (15). However, there is no consensus to guide the choice of injection or pump therapy in a given individual, and research to guide this decision-making is needed (16). The arrival of continuous glucose monitors (CGM) to clinical practice has proven beneficial in people using insulin therapy. Its use is now considered standard of care for most people with type 1 diabetes (5) (see Section 7, "Diabetes Technology"). Reduction of nocturnal hypoglycemia in individuals with type 1 diabetes using insulin pumps with CGM is improved by automatic suspension of insulin delivery at a preset glucose level (16–18). When choosing among insulin delivery systems, individual preferences, cost, insulin type and dosing regimen, and self-management capabilities should be considered (see Section 7, "Diabetes Technology").

The U.S. Food and Drug Administration (FDA) has now approved multiple hybrid closed-loop pump systems (also called automated insulin delivery [AID] systems). The safety and efficacy of hybrid closed-loop systems has been supported in the literature in adolescents and adults with type 1 diabetes (19,20), and evidence suggests that a closed-loop system is superior to sensor-augmented pump therapy for glycemic control and reduction of hypoglycemia over 3 months of comparison in children and adults with type 1 diabetes (21). In the International Diabetes Closed Loop (iDCL) trial, a 6-month trial in people with type 1 diabetes at least 14 years of age, the use of a closed-loop system was associated with a greater percentage of time spent in the target glycemic range, reduced mean glucose and A1C levels, and a lower percentage of time spent in hypoglycemia compared with use of a sensor-augmented pump (22).

Intensive insulin management using a version of CSII and continuous glucose monitoring should be considered in most individuals with type 1 diabetes. AID systems may be considered in individuals with type 1 diabetes who are capable of using the device safely (either by themselves or with a caregiver) in order to improve time in range and reduce A1C and hypoglycemia (22). See Section 7, "Diabetes Technology," for a full discussion of insulin delivery devices.

In general, individuals with type 1 diabetes require 50% of their daily insulin as basal and 50% as prandial, but this is dependent on a number of factors, including whether the individual consumes lower or higher carbohydrate meals. Total daily insulin requirements can be estimated based on weight, with typical doses ranging from 0.4 to 1.0 units/kg/day. Higher amounts are required during puberty, pregnancy, and medical illness. The *American Diabetes Association/JDRF Type 1 Diabetes Sourcebook* notes 0.5 units/kg/day as a typical starting dose in individuals with type 1 diabetes who are metabolically stable, with half administered as prandial insulin given to control blood glucose after meals and the other half as basal insulin to control glycemia in the periods between meal absorption (23); this guideline provides detailed information on intensification of therapy to meet individualized needs. In addition, the American Diabetes Association (ADA) position statement "Type 1 Diabetes Management Through the Life Span" provides a thorough overview of type 1 diabetes treatment (24).

Typical multidose regimens for individuals with type 1 diabetes combine premeal use of shorter-acting insulins with a longer-acting formulation. The long-acting basal dose is titrated to regulate overnight and fasting glucose. Postprandial glucose excursions are best controlled by a well-timed injection of prandial insulin. The optimal time to administer prandial insulin varies, based on the pharmacokinetics of the formulation (regular, RAA, inhaled), the premeal blood glucose level, and carbohydrate consumption. Recommendations for prandial insulin dose administration should therefore be individualized. Physiologic insulin secretion varies with glycemia, meal size, meal composition, and tissue demands for glucose. To approach this variability in people using insulin treatment, strategies have evolved to adjust prandial doses based on predicted needs. Thus, education on how to

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adjust prandial insulin to account for carbohydrate intake, premeal glucose levels, and anticipated activity can be effective and should be offered to most individuals (25,26). For individuals in whom carbohydrate counting is effective, estimates of the fat and protein content of meals can be incorporated into their prandial dosing for added benefit (27) (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes").

The 2021 ADA/European Association for the Study of Diabetes (EASD) consensus report on the management of type 1 diabetes in adults summarizes different insulin regimens and glucose monitoring strategies in individuals with type 1 diabetes (**Fig. 9.1** and **Table 9.1**) (5).

Insulin Injection Technique

Ensuring that individuals and/or caregivers understand correct insulin injection technique is important to optimize glucose control and insulin use safety. Thus, it is important that insulin be delivered into the proper tissue in the correct way. Recommendations have been published elsewhere outlining best practices for insulin injection (28). Proper insulin injection technique includes injecting into appropriate body areas, injection site rotation, appropriate care of injection sites to avoid infection or other complications, and avoidance of intramuscular (IM) insulin delivery.

Exogenously delivered insulin should be injected into subcutaneous tissue, not intramuscularly. Recommended sites for insulin injection include the abdomen, thigh, buttock, and upper arm. Insulin absorption from IM sites differs from that in subcutaneous sites and is also influenced by the activity of the muscle. Inadvertent IM injection can lead to unpredictable insulin absorption and variable effects on glucose and is associated with frequent and unexplained hypoglycemia. Risk for IM insulin delivery is increased in younger, leaner individuals when injecting into the limbs rather than truncal sites (abdomen and buttocks) and when using longer needles. Recent evidence supports the use of short needles (e.g., 4-mm pen needles) as effective and well tolerated when compared with longer needles, including a study performed in adults with obesity (29).

Injection site rotation is additionally necessary to avoid lipohypertrophy, an accumulation of subcutaneous fat in response to the adipogenic actions of insulin at a site of multiple injections. Lipohypertrophy appears as soft, smooth raised areas several centimeters in breadth and can contribute to erratic insulin absorption, increased glycemic variability, and unexplained hypoglycemic episodes. People treated with insulin and/or caregivers should receive education about proper injection site rotation and how to recognize and avoid areas of lipohypertrophy. As noted in **Table 4.1**, examination of insulin injection sites for the presence of lipohypertrophy, as well as assessment of injection device use and injection technique, are key components of a comprehensive diabetes medical evaluation and treatment plan. Proper insulin injection technique may lead to more effective use of this therapy and, as such, holds the potential for improved clinical outcomes.

Noninsulin Treatments for Type 1 Diabetes

Injectable and oral glucose-lowering drugs have been studied for their efficacy as adjuncts to insulin treatment of type 1 diabetes. Pramlintide is based on the naturally occurring β-cell peptide amylin and is approved for use in adults with type 1 diabetes. Clinical trials have demonstrated a modest reduction in A1C (0.3–0.4%) and modest weight loss (~1 kg) with pramlintide (30–33). Similarly, results have been reported for several agents currently approved only for the treatment of type 2 diabetes. The addition of metformin in adults with type 1 diabetes caused small reductions in body weight and lipid levels but did not improve A1C (34,35). The largest clinical trials of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in type 1 diabetes have been conducted with liraglutide 1.8 mg daily, showing modest A1C reductions (~0.4%), decreases in weight (~5 kg), and reductions in insulin doses (36,37). Similarly, sodium–glucose cotransporter 2 (SGLT2) inhibitors have been studied in clinical trials in people with type 1 diabetes, showing improvements in A1C, reduced body weight, and improved blood pressure (38–40); however, SGLT2 inhibitor use in type 1 diabetes is associated with an increased rate of diabetic ketoacidosis. The risks and benefits of adjunctive agents continue to be evaluated, with consensus statements providing guidance on patient selection and precautions (41).

SURGICAL TREATMENT FOR TYPE 1 DIABETES

Pancreas and Islet Transplantation

Successful pancreas and islet transplantation can normalize glucose levels and mitigate microvascular complications of type 1 diabetes. However, people receiving these treatments require lifelong immunosuppression to prevent graft rejection and/or recurrence of autoimmune islet destruction. Given the potential adverse effects of immunosuppressive therapy, pancreas transplantation should be reserved for people with type 1 diabetes undergoing simultaneous renal transplantation, following renal transplantation, or for those with recurrent ketoacidosis or severe hypoglycemia despite intensive glycemic management (42).

The 2021 ADA/EASD consensus report on the management of type 1 diabetes in adults offers a simplified overview of indications for β-cell replacement therapy in people with type 1 diabetes (**Fig. 9.2**) (5).

PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES

Recommendations

9.4a Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. **A**

9.4b In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk (**Fig. 9.3** and **Table 9.2**). **A**

9.4c Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy (**Fig. 9.3** and **Table 9.2**). **A**

9.4d Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering

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Representative relative attributes of insulin delivery approaches in people with type 1 diabetes[1]

Injected insulin regimens	Flexibility	Lower risk of hypoglycemia	Higher costs
MDI with LAA + RAA or URAA	+++	+++	+++
Less-preferred, alternative injected insulin regimens			
MDI with NPH + RAA or URAA	++	++	++
MDI with NPH + short-acting (regular) insulin	++	+	+
Two daily injections with NPH + short-acting (regular) insulin or premixed	+	+	+

Continuous insulin infusion regimens	Flexibility	Lower risk of hypoglycemia	Higher costs
Hybrid closed-loop technology	+++++	+++++	++++++
Insulin pump with threshold/ predictive low-glucose suspend	++++	++++	+++++
Insulin pump therapy without automation	+++	+++	++++

Figure 9.1—Choices of insulin regimens in people with type 1 diabetes. Continuous glucose monitoring improves outcomes with injected or infused insulin and is superior to blood glucose monitoring. Inhaled insulin may be used in place of injectable prandial insulin in the U.S. [1]The number of plus signs (+) is an estimate of relative association of the regimen with increased flexibility, lower risk of hypoglycemia, and higher costs between the considered regimens. LAA, long-acting insulin analog; MDI, multiple daily injections; RAA, rapid-acting insulin analog; URAA, ultra-rapid-acting insulin analog. Reprinted from Holt et al. (5).

treatment regimen should consider approaches that support weight management goals (**Fig. 9.3** and **Table 9.2**). **A**

9.5 Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits. **A**

9.6 Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure. **A**

9.7 The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. **E**

9.8 A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences (**Fig. 9.3** and **Table 9.2**). **E**

9.9 Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit (**Fig. 9.3**, **Table 9.2**, **Table 10.3*B***, and **Table 10.3*C***) is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors (**Fig. 9.3**) (see Section 10, "Cardiovascular Disease and Risk Management," for details on cardiovascular risk reduction recommendations). **A**

9.10 In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. **A**

9.11 If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. **A**

9.12 Recommendation for treatment intensification for individuals not meeting treatment goals should not be delayed. **A**

9.13 Medication regimen and medication-taking behavior should be reevaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate specific factors that impact choice of treatment (**Fig. 4.1** and **Table 9.2**). **E**

9.14 Clinicians should be aware of the potential for overbasalization with insulin therapy. Clinical signals that may prompt evaluation of overbasalization include basal dose more than ~0.5 units/kg/day, high bedtime–morning or postpreprandial glucose differential, hypoglycemia (aware or unaware), and high glycemic variability. Indication of overbasalization should prompt reevaluation to further individualize therapy. **E**

The ADA/EASD consensus report "Management of Hyperglycemia in Type 2 Diabetes, 2022" (43–45) recommends a holistic, multifactorial person-centered approach accounting for the lifelong nature of type 2 diabetes. Person-specific factors that affect choice of treatment include individualized glycemic and weight goals, impact on weight, hypoglycemia and cardiorenal protection (see Section 10, "Cardiovascular Disease and Risk Management," and Section 11 "Chronic Kidney Disease and Risk Management"), underlying physiologic factors, side effect profiles of medications, complexity of regimen, regimen choice to optimize medication use and reduce treatment discontinuation, and access, cost, and availability of medication. Lifestyle

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Table 9.1—Examples of subcutaneous insulin regimens

Regimen	Timing and distribution	Advantages	Disadvantages	Adjusting doses
Regimens that more closely mimic normal insulin secretion				
Insulin pump therapy (hybrid closed-loop, low-glucose suspend, CGM-augmented open-loop, BGM-augmented open-loop)	Basal delivery of URAA or RAA; generally 40–60% of TDD. Mealtime and correction: URAA or RAA by bolus based on ICR and/or ISF and target glucose, with pre-meal insulin ∼15 min before eating.	Can adjust basal rates for varying insulin sensitivity by time of day, for exercise and for sick days. Flexibility in meal timing and content. Pump can deliver insulin in increments of fractions of units. Potential for integration with CGM for low-glucose suspend or hybrid closed-loop. TIR % highest and TBR % lowest with: hybrid closed-loop > low-glucose suspend > CGM-augmented open-loop > BGM-augmented open-loop.	Most expensive regimen. Must continuously wear one or more devices. Risk of rapid development of ketosis or DKA with interruption of insulin delivery. Potential reactions to adhesives and site infections. Most technically complex approach (harder for people with lower numeracy or literacy skills).	Mealtime insulin: if carbohydrate counting is accurate, change ICR if glucose after meal consistently out of target. Correction insulin: adjust ISF and/or target glucose if correction does not consistently bring glucose into range. Basal rates: adjust based on overnight, fasting or daytime glucose outside of activity of URAA/RAA bolus.
MDI: LAA + flexible doses of URAA or RAA at meals	LAA once daily (insulin detemir or insulin glargine may require twice-daily dosing); generally 50% of TDD. Mealtime and correction: URAA or RAA based on ICR and/or ISF and target glucose.	Can use pens for all components. Flexibility in meal timing and content. Insulin analogs cause less hypoglycemia than human insulins.	At least four daily injections. Most costly insulins. Smallest increment of insulin is 1 unit (0.5 unit with some pens). LAAs may not cover strong dawn phenomenon (rise in glucose in early morning hours) as well as pump therapy.	Mealtime insulin: if carbohydrate counting is accurate, change ICR if glucose after meal consistently out of target. Correction insulin: adjust ISF and/or target glucose if correction does not consistently bring glucose into range. LAA: based on overnight or fasting glucose or daytime glucose outside of activity time course, or URAA or RAA injections.
MDI regimens with less flexibility				
Four injections daily with fixed doses of N and RAA	Pre-breakfast: RAA ∼20% of TDD. Pre-lunch: RAA ∼10% of TDD. Pre-dinner: RAA ∼10% of TDD. Bedtime: N ∼50% of TDD.	May be feasible if unable to carbohydrate count. All meals have RAA coverage. N is less expensive than LAAs.	Shorter duration RAA may lead to basal deficit during day; may need twice-daily N. Greater risk of nocturnal hypoglycemia with N. Requires relatively consistent mealtimes and carbohydrate intake.	Pre-breakfast RAA: based on BGM after breakfast or before lunch. Pre-lunch RAA: based on BGM after lunch or before dinner. Pre-dinner RAA: based on BGM after dinner or at bedtime. Evening N: based on fasting or overnight BGM.

Continued on p. S145

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Table 9.1—Continued

Regimen	Timing and distribution	Advantages	Disadvantages	Adjusting doses
Four injections daily with fixed doses of N and R	Pre-breakfast: R ∼20% of TDD. Pre-lunch: R ∼10% of TDD. Pre-dinner: R ∼10% of TDD. Bedtime: N ∼50% of TDD.	May be feasible if unable to carbohydrate count. R can be dosed based on ICR and correction. All meals have R coverage. Least expensive insulins.	Greater risk of nocturnal hypoglycemia with N. Greater risk of delayed post-meal hypoglycemia with R. Requires relatively consistent mealtimes and carbohydrate intake. R must be injected at least 30 min before meal for better effect.	Pre-breakfast R: based on BGM after breakfast or before lunch. Pre-lunch R: based on BGM after lunch or before dinner. Pre-dinner R: based on BGM after dinner or at bedtime. Evening N: based on fasting or overnight BGM.
Regimens with fewer daily injections				
Three injections daily: N+R or N+RAA	Pre-breakfast: ∼40% N + ∼15% R or RAA. Pre-dinner: ∼15% R or RAA. Bedtime: 30% N.	Morning insulins can be mixed in one syringe. May be appropriate for those who cannot take injection in middle of day. Morning N covers lunch to some extent. Same advantages of RAAs over R. Least (N+R) or less expensive insulins than MDI with analogs.	Greater risk of nocturnal hypoglycemia with N than LAAs. Greater risk of delayed post-meal hypoglycemia with R than RAAs. Requires relatively consistent mealtimes and carbohydrate intake. Coverage of post-lunch glucose often suboptimal. R must be injected at least 30 min before meal for better effect.	Morning N: based on pre-dinner BGM. Morning R: based on pre-lunch BGM. Morning RAA: based on post-breakfast or pre-lunch BGM. Pre-dinner R: based on bedtime BGM. Pre-dinner RAA: based on post-dinner or bedtime BGM. Evening N: based on fasting BGM.
Twice-daily “split-mixed”: N+R or N+RAA	Pre-breakfast: ∼40% N + ∼15% R or RAA. Pre-dinner: ∼30% N + ∼15% R or RAA.	Least number of injections for people with strong preference for this. Insulins can be mixed in one syringe. Least (N+R) or less (N+RAA) expensive insulins vs analogs. Eliminates need for doses during the day.	Risk of hypoglycemia in afternoon or middle of night from N. Fixed mealtimes and meal content. Coverage of post-lunch glucose often suboptimal. Difficult to reach targets for blood glucose without hypoglycemia.	Morning N: based on pre-dinner BGM. Morning R: based on pre-lunch BGM. Morning RAA: based on post-breakfast or pre-lunch BGM. Evening R: based on bedtime BGM. Evening RAA: based on post-dinner or bedtime BGM. Evening N: based on fasting BGM.

BGM, blood glucose monitoring; CGM, continuous glucose monitoring; ICR, insulin-to-carbohydrate ratio; ISF, insulin sensitivity factor; LAA, long-acting analog; MDI, multiple daily injections; N, NPH insulin; R, short-acting (regular) insulin; RAA, rapid-acting analog; TDD, total daily insulin dose; URAA, ultra-rapid-acting analog. Reprinted from Holt et al. (5).

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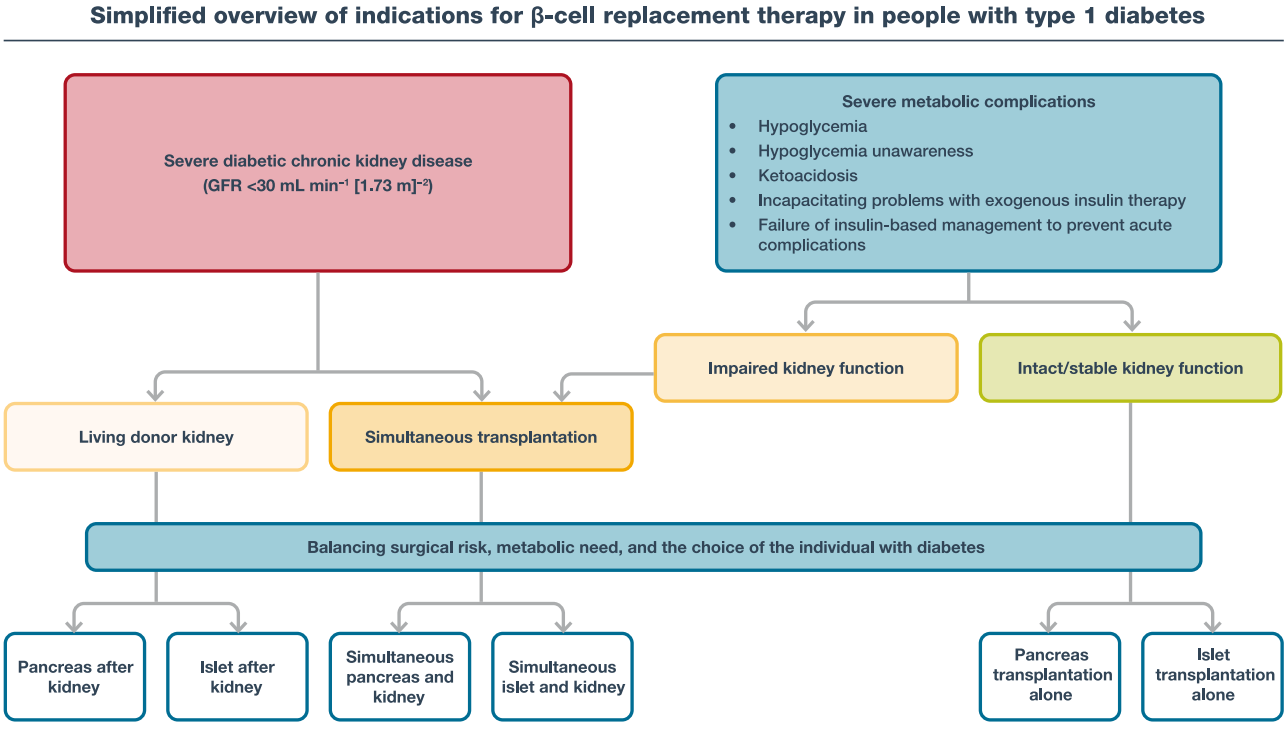

Figure 9.2—Simplified overview of indications for β-cell replacement therapy in people with type 1 diabetes. The two main forms of β-cell replacement therapy are whole-pancreas transplantation or islet cell transplantation. β-Cell replacement therapy can be combined with kidney transplantation if the individual has end-stage renal disease, which may be performed simultaneously or after kidney transplantation. All decisions about transplantation must balance the surgical risk, metabolic need, and the choice of the individual with diabetes. GFR, glomerular filtration rate. Reprinted from Holt et al. (5).

modifications and health behaviors that improve health (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes") should be emphasized along with any pharmacologic therapy. Section 13, "Older Adults," and Section 14, "Children and Adolescents," have recommendations specific for older adults and for children and adolescents with type 2 diabetes, respectively. Section 10, "Cardiovascular Disease and Risk Management," and Section 11, "Chronic Kidney Disease and Risk Management," have recommendations for the use of glucose-lowering drugs in the management of cardiovascular and renal disease, respectively.

Choice of Glucose-Lowering Therapy

Healthy lifestyle behaviors, diabetes self-management, education, and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. Pharmacotherapy should be started at the time type 2 diabetes is diagnosed unless there are contraindications. Pharmacologic approaches that provide the efficacy to achieve treatment goals should be considered, such as metformin or other agents, including combination therapy, that provide adequate efficacy to achieve and maintain treatment goals (45). In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and/or chronic kidney disease (CKD), the treatment regimen should include agents that reduce cardiorenal risk (see **Fig. 9.3**, **Table 9.2**, Section 10, "Cardiovascular Disease and Risk Management," and Section 11, "Chronic Kidney Disease and Risk Management"). Pharmacologic approaches that provide the efficacy to achieve treatment goals should be considered, specified as metformin or agent(s), including combination therapy, that provide adequate efficacy to achieve and maintain treatment goals (**Fig. 9.3** and **Table 9.2**). In general, higher-efficacy approaches have greater likelihood of achieving glycemic goals, with the following considered to have very high efficacy for glucose lowering: the GLP-1 RAs dulaglutide (high dose) and semaglutide, the gastric inhibitory peptide (GIP) and GLP-1 RA tirzepatide, insulin, combination oral therapy, and combination injectable therapy. Weight management is an impactful component of glucose-lowering management in type 2 diabetes (45,46). The glucose-lowering treatment regimen should consider approaches that support weight management goals, with very high efficacy for weight loss seen with semaglutide and tirzepatide (**Fig. 9.3** and **Table 9.2**) (45).

Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death (47). Metformin is available in an immediate-release form for twice-daily dosing or as an extended-release form that can be given once daily. Compared with sulfonylureas, metformin as first-line therapy has beneficial effects on A1C, weight, and cardiovascular mortality (48).

The principal side effects of metformin are gastrointestinal intolerance due to bloating, abdominal discomfort, and diarrhea; these can be mitigated by gradual dose titration. The drug is cleared by renal filtration, and very high circulating levels (e.g., as a result of overdose or acute renal failure) have been associated with lactic acidosis. However, the occurrence of this complication is now known to be very rare, and metformin may be

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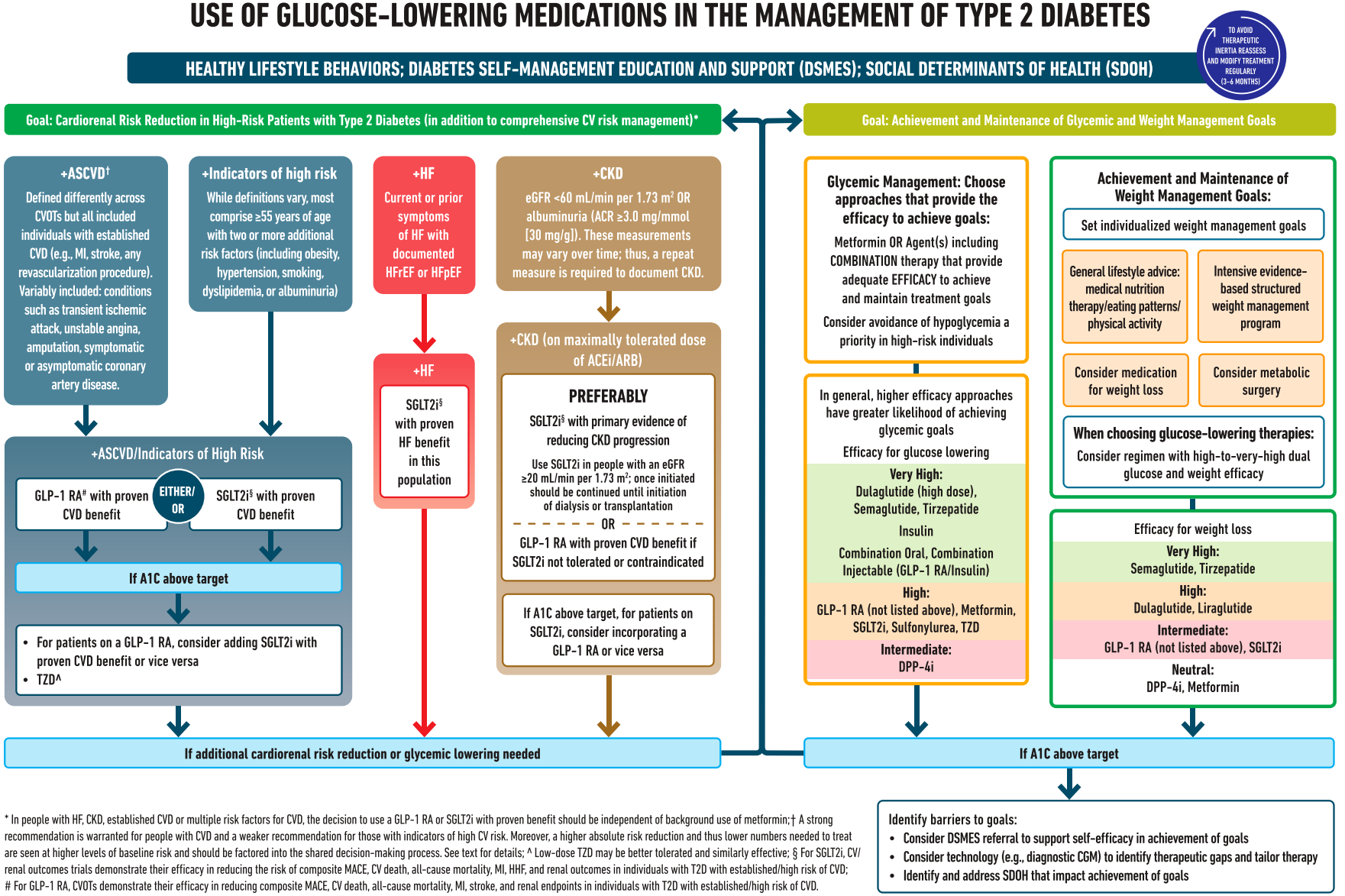
USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin;† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

Figure 9.3—Use of glucose-lowering medications in the management of type 2 diabetes. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TZD, thiazolidinedione. Adapted from Davies et al. (45).

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Table 9.2—Medications for lowering glucose, summary of characteristics

	Efficacy[1]	Hypoglycemia	Weight change[2]	CV effects		Renal effects		Oral/SQ	Cost	Clinical considerations
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*			
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	• Contraindicated with eGFR <30 mL/min per 1.73 m^2	Oral	Low	• GI side effects common; to mitigate GI side effects, consider slow dose titration, extended release formulations, and administration with food • Potential for vitamin B12 deficiency; monitor at regular intervals
SGLT2 inhibitors	Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	• See labels for renal dose considerations of individual agents • Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR	Oral	High	• DKA risk, rare in T2DM: discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentation (including euglycemic DKA); discontinue before scheduled surgery (e.g., 3–4 days), during critical illness, or during prolonged fasting to mitigate potential risk • Increased risk of genital mycotic infections • Necrotizing fasciitis of the perineum (Fournier gangrene), rare reports: institute prompt treatment if suspected • Attention to volume status, blood pressure; adjust other volume-contracting agents as applicable
GLP-1 RAs	High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ) Neutral: exenatide once weekly, lixisenatide	Neutral	Benefit for renal endpoints in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ)	• See labels for renal dose considerations of individual agents • No dose adjustment for dulaglutide, liraglutide, semaglutide • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ; oral (semaglutide)	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined (liraglutide, dulaglutide, exenatide extended release, semaglutide) • Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected
GIP and GLP-1 RA	Very high	No	Loss (very high)	Under investigation	Under investigation	Under investigation	• See label for renal dose considerations • No dose adjustment • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined • Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Neutral (potential risk, saxagliptin)	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin	Oral	High	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Joint pain • Bullous pemphigoid (postmarketing): discontinue if suspected
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	Oral	Low	• Congestive HF (pioglitazone, rosiglitazone) • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Weight gain: consider lower doses to mitigate weight gain and edema
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Neutral	• Glyburide: generally not recommended in chronic kidney disease • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	Oral	Low	• FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide); glimepiride shown to be CV safe (see text) • Use with caution in persons at risk for hypoglycemia
Insulin Human	High to very high	Yes	Gain	Neutral	Neutral	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	SQ; inhaled	Low (SQ)	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin Analogs								SQ	High	

CV, cardiovascular; CVOT, cardiovascular outcomes trial; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; GIP, gastric inhibitory polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; NASH, nonalcoholic steatohepatitis; MACE, major adverse cardiovascular events; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2DM, type 2 diabetes mellitus. *For agent-specific dosing recommendations, please refer to manufacturers' prescribing information. [1]Tsapas et al. (62). [2]Tsapas et al. (114). Reprinted from Davies et al. (45).

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safely used in people with reduced estimated glomerular filtration rates (eGFR); the FDA has revised the label for metformin to reflect its safety in people with eGFR ≥30 mL/min/1.73 m^2 (49). A randomized trial confirmed previous observations that metformin use is associated with vitamin B12 deficiency and worsening of symptoms of neuropathy (50). This is compatible with a report from the Diabetes Prevention Program Outcomes Study (DPPOS) suggesting periodic testing of vitamin B12 (51) (see Section 3, "Prevention or Delay of Type 2 Diabetes and Associated Comorbidities").

When A1C is ≥1.5% (12.5 mmol/mol) above the glycemic target (see Section 6, "Glycemic Targets," for appropriate targets), many individuals will require dual-combination therapy or a more potent glucose-lowering agent to achieve and maintain their target A1C level (45,52) (**Fig. 9.3** and **Table 9.2**). Insulin has the advantage of being effective where other agents are not and should be considered as part of any combination regimen when hyperglycemia is severe, especially if catabolic features (weight loss, hypertriglyceridemia, ketosis) are present. It is common practice to initiate insulin therapy for people who present with blood glucose levels ≥300 mg/dL (16.7 mmol/L) or A1C >10% (86 mmol/mol) or if the individual has symptoms of hyperglycemia (i.e., polyuria or polydipsia) or evidence of catabolism (weight loss) (**Fig. 9.4**). As glucose toxicity resolves, simplifying the regimen and/or changing to noninsulin agents is often possible. However, there is evidence that people with uncontrolled hyperglycemia associated with type 2 diabetes can also be effectively treated with a sulfonylurea (53).

Combination Therapy

Because type 2 diabetes is a progressive disease in many individuals, maintenance of glycemic targets often requires combination therapy. Traditional recommendations have been to use stepwise addition of medications to metformin to maintain A1C at target. The advantage of this is to provide a clear assessment of the positive and negative effects of new drugs and reduce potential side effects and expense (54). However, there are data to support initial combination therapy for more rapid attainment of glycemic goals (55,56) and later combination therapy for longer durability of glycemic effect (57). The VERIFY (Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes) trial demonstrated that initial combination therapy is superior to sequential addition of medications for extending primary and secondary failure (58). In the VERIFY trial, participants receiving the initial combination of metformin and the dipeptidyl peptidase 4 (DPP-4) inhibitor vildagliptin had a slower decline of glycemic control compared with metformin alone and with vildagliptin added sequentially to metformin. These results have not been generalized to oral agents other than vildagliptin, but they suggest that more intensive early treatment has some benefits and should be considered through a shared decision-making process, as appropriate. Initial combination therapy should be considered in people presenting with A1C levels 1.5–2.0% above target. Finally, incorporation of high-glycemic-efficacy therapies or therapies for cardiovascular/renal risk reduction (e.g., GLP-1 RAs, SGLT2 inhibitors) may allow for weaning of the current regimen, particularly of agents that may increase the risk of hypoglycemia. Thus, treatment intensification may not necessarily follow a pure sequential addition of therapy but instead reflect a tailoring of the regimen in alignment with person-centered treatment goals (**Fig. 9.3**).

Recommendations for treatment intensification for people not meeting treatment goals should not be delayed. Shared decision-making is important in discussions regarding treatment intensification. The choice of medication added to initial therapy is based on the clinical characteristics of the individual and their preferences. Important clinical characteristics include the presence of established ASCVD or indicators of high ASCVD risk, HF, CKD, obesity, nonalcoholic fatty liver disease or nonalcoholic steatohepatitis, and risk for specific adverse drug effects, as well as safety, tolerability, and cost. Results from comparative effectiveness meta-analyses suggest that each new class of noninsulin agents added to initial therapy with metformin generally lowers A1C approximately 0.7–1.0% (59,60) (**Fig. 9.3** and **Table 9.2**).

For people with type 2 diabetes and established ASCVD or indicators of high ASCVD risk, HF, or CKD, an SGLT2 inhibitor and/or GLP-1 RA with demonstrated CVD benefit (see **Table 9.2**, **Table 10.3*B***, **Table 10.3*C***, and Section 10, "Cardiovascular Disease and Risk Management") is recommended as part of the glucose-lowering regimen independent of A1C, independent of metformin use and in consideration of person-specific factors (**Fig. 9.3**). For people without established ASCVD, indicators of high ASCVD risk, HF, or CKD, medication choice is guided by efficacy in support of individualized glycemic and weight management goals, avoidance of side effects (particularly hypoglycemia and weight gain), cost/access, and individual preferences (61). A systematic review and network meta-analysis suggests greatest reductions in A1C level with insulin regimens and specific GLP-1 RAs added to metformin-based background therapy (62). In all cases, treatment regimens need to be continuously reviewed for efficacy, side effects, and burden (**Table 9.2**). In some instances, the individual will require medication reduction or discontinuation. Common reasons for this include ineffectiveness, intolerable side effects, expense, or a change in glycemic goals (e.g., in response to development of comorbidities or changes in treatment goals). Section 13, "Older Adults," has a full discussion of treatment considerations in older adults, in whom changes of glycemic goals and de-escalation of therapy are common.

The need for the greater potency of injectable medications is common, particularly in people with a longer duration of diabetes. The addition of basal insulin, either human NPH or one of the long-acting insulin analogs, to oral agent regimens is a well-established approach that is effective for many individuals. In addition, evidence supports the utility of GLP-1 RAs in people not at glycemic goal. While most GLP-1 RAs are injectable, an oral formulation of semaglutide is commercially available (63). In trials comparing the addition of an injectable GLP-1 RA or insulin in people needing further glucose lowering, glycemic efficacy of injectable GLP-1 RA was similar or greater than that of basal insulin (64–70). GLP-1 RAs in these trials had a lower risk of hypoglycemia and beneficial effects on body weight compared with insulin, albeit with greater gastrointestinal side effects. Thus, trial results support GLP-1 RAs as the preferred option for individuals requiring the potency of an injectable therapy for glucose control (**Fig. 9.4**). In individuals

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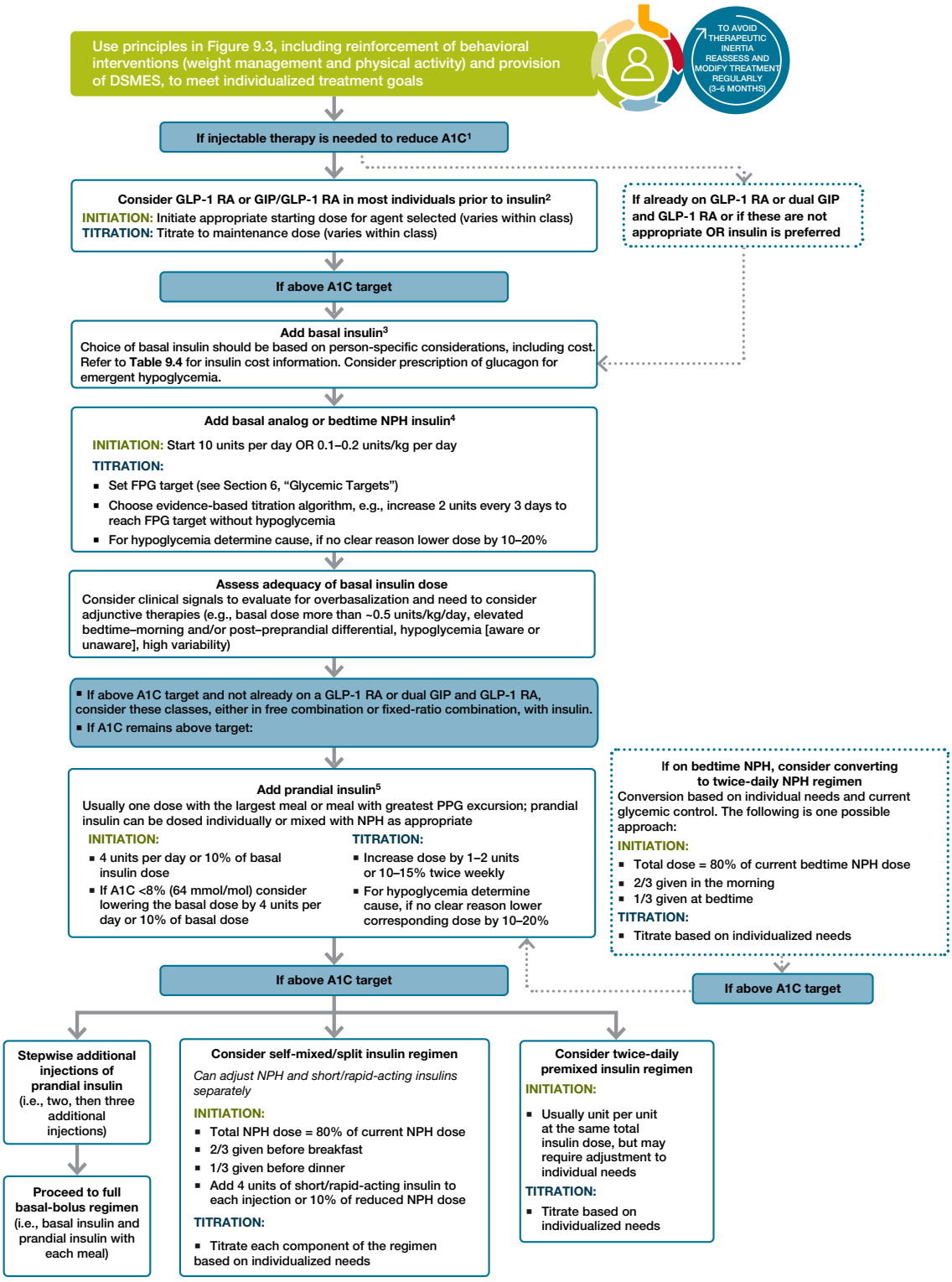

1. Consider insulin as the first injectable if evidence of ongoing catabolism, symptoms of hyperglycemia are present, when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (300 mg/dL [16.7 mmol/L]) are very high, or a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RA, consider individual preference, A1C lowering, weight-lowering effect, or fequency of injection. If CVD is present, consider GLP-1 RA with proven CVD benefit. Oral or injectable GLP-1 RA are appropriate.
3. For people on GLP-1 RA and basal insulin combination, consider use of a fixed-ratio combination product (IDegLira or iGlarLixi).
4. Consider switching from evening NPH to a basal analog if the individual develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with an A.M. dose of a long-acting basal insulin.
5. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin regimen to decrease the number of injections required.

Figure 9.4—Intensifying to injectable therapies in type 2 diabetes. DSMES, diabetes self-management education and support; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide 1 receptor agonist; max, maximum; PPG, postprandial glucose. Adapted from Davies et al. (43).

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who are intensified to insulin therapy, combination therapy with a GLP-1 RA has been shown to have greater efficacy and durability of glycemic treatment effect, as well as weight and hypoglycemia benefit, than treatment intensification with insulin alone (45). However, cost and tolerability issues are important considerations in GLP-1 RA use.

Costs for diabetes medications have increased dramatically over the past two decades, and an increasing proportion is now passed on to patients and their families (71). **Table 9.3** provides cost information for currently approved noninsulin therapies. Of note, prices listed are average wholesale prices (AWP) (72) and National Average Drug Acquisition Costs (NADAC) (73), separate measures to allow for a comparison of drug prices, but do not account for discounts, rebates, or other price adjustments often involved in prescription sales that affect the actual cost incurred by the patient. Medication costs can be a major source of stress for people with diabetes and contribute to worse medication-taking behavior (74); cost-reducing strategies may improve medication-taking behavior in some cases (75).

Cardiovascular Outcomes Trials

There are now multiple large randomized controlled trials reporting statistically significant reductions in cardiovascular events in adults with type 2 diabetes treated with an SGLT2 inhibitor or GLP-1 RA; see Section 10, "Cardiovascular Disease and Risk Management" for details. Participants enrolled in many of the cardiovascular outcomes trials had A1C ≥6.5%, with more than 70% taking metformin at baseline, with analyses indicating benefit with or without metformin (45). Thus, a practical extension of these results to clinical practice is to use these medications preferentially in people with type 2 diabetes and established ASCVD or indicators of high ASCVD risk. For these individuals, incorporating one of the SGLT2 inhibitors and/or GLP-1 RAs that have been demonstrated to have cardiovascular disease benefit is recommended (see **Fig. 9.3**, **Table 9.2**, and Section 10, "Cardiovascular Disease and Risk Management"). Emerging data suggest that use of both classes of drugs will provide additional cardiovascular and kidney outcomes benefit; thus, combination therapy with an SGLT2 inhibitor and a GLP-1 RA may be considered to provide the complementary outcomes benefits associated with these classes of medication (76). In cardiovascular outcomes trials, empagliflozin, canagliflozin, dapagliflozin, liraglutide, semaglutide, and dulaglutide all had beneficial effects on indices of CKD, while dedicated renal outcomes studies have demonstrated benefit of specific SGLT2 inhibitors. See Section 11, "Chronic Kidney Disease and Risk Management," for discussion of how CKD may impact treatment choices. Additional large randomized trials of other agents in these classes are ongoing.

Insulin Therapy

Many adults with type 2 diabetes eventually require and benefit from insulin therapy (**Fig. 9.4**). See the section INSULIN INJECTION TECHNIQUE, above, for guidance on how to administer insulin safely and effectively. The progressive nature of type 2 diabetes should be regularly and objectively explained to patients, and clinicians should avoid using insulin as a threat or describing it as a sign of personal failure or punishment. Rather, the utility and importance of insulin to maintain glycemic control once progression of the disease overcomes the effect of other agents should be emphasized. Educating and involving patients in insulin management is beneficial. For example, instruction of individuals with type 2 diabetes initiating insulin in self-titration of insulin doses based on glucose monitoring improves glycemic control (77). Comprehensive education regarding blood glucose monitoring, nutrition, and the avoidance and appropriate treatment of hypoglycemia are critically important in any individual using insulin.

Basal Insulin

Basal insulin alone is the most convenient initial insulin treatment and can be added to metformin and other noninsulin injectables. Starting doses can be estimated based on body weight (0.1–0.2 units/kg/day) and the degree of hyperglycemia, with individualized titration over days to weeks as needed. The principal action of basal insulin is to restrain hepatic glucose production and limit hyperglycemia overnight and between meals (78,79). Control of fasting glucose can be achieved with human NPH insulin or a long-acting insulin analog. In clinical trials, long-acting basal analogs (U-100 glargine or detemir) have been demonstrated to reduce the risk of symptomatic and nocturnal hypoglycemia compared with NPH insulin (80–85), although these advantages are modest and may not persist (86). Longer-acting basal analogs (U-300 glargine or degludec) may convey a lower hypoglycemia risk compared with U-100 glargine when used in combination with oral agents (87–93). Clinicians should be aware of the potential for overbasalization with insulin therapy. Clinical signals that may prompt evaluation of overbasalization include basal dose greater than ∼0.5 units/kg, high bedtime–morning or postprepandial glucose differential (e.g., bedtime–morning glucose differential ≥50 mg/dL), hypoglycemia (aware or unaware), and high variability. Indication of overbasalization should prompt reevaluation to further individualize therapy (94).

The cost of insulin has been rising steadily over the past two decades, at a pace severalfold that of other medical expenditures (95). This expense contributes significant burden to patients as insulin has become a growing "out-of-pocket" cost for people with diabetes, and direct patient costs contribute to decrease in medication-taking behavior (95). Therefore, consideration of cost is an important component of effective management. For many individuals with type 2 diabetes (e.g., individuals with relaxed A1C goals, low rates of hypoglycemia, and prominent insulin resistance, as well as those with cost concerns), human insulin (NPH and regular) may be the appropriate choice of therapy, and clinicians should be familiar with its use (96). Human regular insulin, NPH, and 70/30 NPH/regular products can be purchased for considerably less than the AWP and NADAC prices listed in **Table 9.4** at select pharmacies. Additionally, approval of follow-on biologics for insulin glargine, the first interchangeable insulin glargine product, and generic versions of analog insulins may expand cost-effective options.

Prandial Insulin

Many individuals with type 2 diabetes require doses of insulin before meals, in addition to basal insulin, to reach glycemic targets. If the individual is not already being treated with a GLP-1 RA, a GLP-1 RA (either in free combination or fixed-ratio combination) should be considered prior to prandial insulin to further

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Table 9.3—Median monthly (30-day) AWP and NADAC of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S.

Class	Compound(s)	Dosage strength/ product (if applicable)	Median AWP (min, max)†	Median NADAC (min, max)†	Maximum approved daily dose*
Biguanides	• Metformin	850 mg (IR)	$106 ($5, $189)	$2	2,550 mg
		1,000 mg (IR)	$87 ($3, $144)	$2	2,000 mg
		1,000 mg (ER)	$242 ($242, $7,214)	$32 ($32, $160)	2,000 mg
Sulfonylureas (2nd generation)	• Glimepiride	4 mg	$74 ($71, $198)	$3	8 mg
	• Glipizide	10 mg (IR)	$70 ($67, $91)	$6	40 mg
		10 mg (XL/ER)	$48 ($46, $48)	$11	20 mg
	• Glyburide	6 mg (micronized)	$52 ($48, $71)	$12	12 mg
		5 mg	$79 ($63, $93)	$9	20 mg
Thiazolidinedione	• Pioglitazone	45 mg	$345 ($7, $349)	$4	45 mg
α-Glucosidase inhibitors	• Acarbose	100 mg	$106 ($104, $106)	$29	300 mg
	• Miglitol	100 mg	$241 ($241, $346)	NA	300 mg
Meglitinides	• Nateglinide	120 mg	$155	$27	360 mg
	• Repaglinide	2 mg	$878 ($58, $897)	$31	16 mg
DPP-4 inhibitors	• Alogliptin	25 mg	$234	$154	25 mg
	• Saxagliptin	5 mg	$565	$452	5 mg
	• Linagliptin	5 mg	$606	$485	5 mg
	• Sitagliptin	100 mg	$626	$500	100 mg
SGLT2 inhibitors	• Ertugliflozin	15 mg	$390	$312	15 mg
	• Dapagliflozin	10 mg	$659	$527	10 mg
	• Canagliflozin	300 mg	$684	$548	300 mg
	• Empagliflozin	25 mg	$685	$547	25 mg
GLP-1 RAs	• Exenatide (extended release)	2 mg powder for suspension or pen	$936	$726	2 mg**
	• Exenatide	10 μg pen	$961	$770	20 μg
	• Dulaglutide	4.5 mg mL pen	$1,064	$852	4.5 mg**
	• Semaglutide	1 mg pen	$1,070	$858	2 mg**
		14 mg (tablet)	$1,070	$858	14 mg
	• Liraglutide	1.8 mg pen	$1,278	$1,022	1.8 mg
	• Lixisenatide	20 μg pen	$814	NA	20 μg
GLP-1/GIP dual agonist	• Tirzepatide	15 mg pen	$1,169	$935	15 mg**
Bile acid sequestrant	• Colesevelam	625 mg tabs	$711 ($674, $712)	$83	3.75 g
		3.75 g suspension	$674 ($673, $675)	$177	3.75 g
Dopamine-2 agonist	• Bromocriptine	0.8 mg	$1,118	$899	4.8 mg
Amylin mimetic	• Pramlintide	120 μg pen	$2,783	NA	120 μg/injection††

AWP, average wholesale price; DPP-4, dipeptidyl peptidase 4; ER and XL, extended release; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; IR, immediate release; max, maximum; min, minimum; NA, data not available; NADAC, National Average Drug Acquisition Cost; SGLT2, sodium-glucose cotransporter 2. †Calculated for 30-day supply (AWP [72] or NADAC [73] unit price × number of doses required to provide maximum approved daily dose × 30 days); median AWP or NADAC listed alone when only one product and/or price. *Utilized to calculate median AWP and NADAC (min, max); generic prices used, if available commercially. **Administered once weekly. ††AWP and NADAC calculated based on 120 μg three times daily.

address prandial control and to minimize the risks of hypoglycemia and weight gain associated with insulin therapy (45). For individuals who advance to prandial insulin, a prandial insulin dose of 4 units or 10% of the amount of basal insulin at the largest meal or the meal with the greatest postprandial excursion is a safe estimate for initiating therapy. The prandial insulin regimen can then be intensified based on individual needs (**Fig. 9.4**). Individuals with type 2 diabetes are generally more insulin resistant than those with type 1 diabetes, require higher daily doses (~1 unit/kg), and have lower rates of hypoglycemia (97). Titration can be based on home glucose monitoring or A1C. With significant additions to the prandial insulin dose, particularly with the evening meal, consideration should be given to decreasing basal insulin. Meta-analyses of trials comparing rapid-acting insulin analogs with human regular insulin in type 2 diabetes have not reported important differences in A1C or hypoglycemia (98,99).

Concentrated Insulins

Several concentrated insulin preparations are currently available. U-500 regular insulin is, by definition, five times more concentrated than U-100 regular insulin. U-500 regular insulin has distinct pharmacokinetics with delayed onset and longer duration of action, has characteristics more like an intermediate-acting (NPH) insulin, and can be used as two or three daily injections (100). U-300 glargine and U-200 degludec are three and two times as concentrated as their U-100

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Table 9.4—Median cost of insulin products in the U.S. calculated as AWP (72) and NADAC (73) per 1,000 units of specified dosage form/product

Insulins	Compounds	Dosage form/product	Median AWP (min, max)*	Median NADAC*
Rapid-acting	• Lispro follow-on product	U-100 vial	$118 ($118, $157)	$94
		U-100 prefilled pen	$151	$121
	• Lispro	U-100 vial	$99†	$79†
		U-100 cartridge	$408	$326
		U-100 prefilled pen	$127†	$102†
		U-200 prefilled pen	$424	$339
	• Lispro-aabc	U-100 vial	$330	$261
		U-100 prefilled pen	$424	$339
		U-200 prefilled pen	$424	NA
	• Glulisine	U-100 vial	$341	$272
		U-100 prefilled pen	$439	$351
	• Aspart	U-100 vial	$174†	$140†
		U-100 cartridge	$215†	$172†
		U-100 prefilled pen	$224†	$180†
	• Aspart (“faster acting product”)	U-100 vial	$347	$277
		U-100 cartridge	$430	$344
		U-100 prefilled pen	$447	$357
	• Inhaled insulin	Inhalation cartridges	$1,418	NA
Short-acting	• Human regular	U-100 vial	$165††	$132††
		U-100 prefilled pen	$208	$166
Intermediate-acting	• Human NPH	U-100 vial	$165††	$132††
		U-100 prefilled pen	$208	$168
Concentrated human regular insulin	• U-500 human regular insulin	U-500 vial	$178	$142
		U-500 prefilled pen	$230	$184
Long-acting	• Glargine follow-on products	U-100 prefilled pen	$261 ($118, $323)	$209 ($209, $258)
		U-100 vial	$118 ($118, $323)	$95
	• Glargine	U-100 vial; U-100 prefilled pen	$136†	$109†
		U-300 prefilled pen	$346	$277
	• Detemir	U-100 vial; U-100 prefilled pen	$370	$296
	• Degludec	U-100 vial; U-100 prefilled pen; U-200 prefilled pen	$407	$326
Premixed insulin products	• NPH/regular 70/30	U-100 vial	$165††	$133††
		U-100 prefilled pen	$208	$167
	• Lispro 50/50	U-100 vial	$342	$274
		U-100 prefilled pen	$424	$339
	• Lispro 75/25	U-100 vial	$342	$273
		U-100 prefilled pen	$127†	$103†
	• Aspart 70/30	U-100 vial	$180†	$146†
		U-100 prefilled pen	$224†	$178†
Premixed insulin/GLP-1 RA products	• Glargine/Lixisenatide	100/33 μg prefilled pen	$646	$517
	• Degludec/Liraglutide	100/3.6 μg prefilled pen	$944	$760

AWP, average wholesale price; GLP-1 RA, glucagon-like peptide 1 receptor agonist; NA, data not available; NADAC, National Average Drug Acquisition Cost. *AWP or NADAC calculated as in **Table 9.3**. †Generic prices used when available. ††AWP and NADAC data presented do not include vials of regular human insulin and NPH available at Walmart for approximately $25/vial; median listed alone when only one product and/or price.

formulations, respectively, and allow higher doses of basal insulin administration per volume used. U-300 glargine has a longer duration of action than U-100 glargine but modestly lower efficacy per unit administered (101,102). The FDA has also approved a concentrated formulation of rapid-acting insulin lispro, U-200 (200 units/mL), and insulin lispro-aabc (U-200). These concentrated preparations may be more convenient and comfortable for individuals to inject and may improve treatment plan engagement in those with insulin resistance who require large doses of insulin. While U-500 regular insulin is available in both prefilled pens and vials, other concentrated insulins are available only in prefilled pens to minimize the risk of dosing errors.

Alternative Insulin Routes

Insulins with different routes of administration (inhaled, bolus-only insulin delivery patch pump) are also available (45). Inhaled insulin is available as a rapid-acting insulin; studies in individuals with type 1 diabetes suggest rapid pharmacokinetics (8). Studies comparing inhaled insulin with injectable insulin have demonstrated its faster onset and shorter duration compared with rapid-acting insulin lispro as well as clinically meaningful A1C reductions and weight reductions compared with insulin aspart over 24 weeks (103–105). Use of inhaled insulin may result in a decline in lung function (reduced forced expiratory volume in 1 s [FEV_1]). Inhaled insulin is contraindicated in individuals with chronic lung disease, such as asthma and chronic obstructive pulmonary disease, and is not

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recommended in individuals who smoke or who recently stopped smoking. All individuals require spirometry (FEV_1) testing to identify potential lung disease prior to and after starting inhaled insulin therapy.

Combination Injectable Therapy

If basal insulin has been titrated to an acceptable fasting blood glucose level (or if the dose is >0.5 units/kg/day with indications of need for other therapy) and A1C remains above target, consider advancing to combination injectable therapy (**Fig. 9.4**). This approach can use a GLP-1 RA or dual GIP and GLP-1 RA added to basal insulin or multiple doses of insulin. The combination of basal insulin and GLP-1 RA has potent glucose-lowering actions and less weight gain and hypoglycemia compared with intensified insulin regimens (106–111). The DUAL VIII (Durability of Insulin Degludec Plus Liraglutide Versus Insulin Glargine U100 as Initial Injectable Therapy in Type 2 Diabetes) randomized controlled trial demonstrated greater durability of glycemic treatment effect with the combination GLP-1 RA–insulin therapy compared with addition of basal insulin alone (57). In select individuals, complex insulin regimens can also be simplified with combination GLP-1 RA–insulin therapy in type 2 diabetes (112). Two different once-daily, fixed dual combination products containing basal insulin plus a GLP-1 RA are available: insulin glargine plus lixisenatide (iGlarLixi) and insulin degludec plus liraglutide (IDegLira).

Intensification of insulin treatment can be done by adding doses of prandial insulin to basal insulin. Starting with a single prandial dose with the largest meal of the day is simple and effective, and it can be advanced to a regimen with multiple prandial doses if necessary (113). Alternatively, in an individual on basal insulin in whom additional prandial coverage is desired, the regimen can be converted to two doses of a premixed insulin. Each approach has advantages and disadvantages. For example, basal-prandial regimens offer greater flexibility for individuals who eat on irregular schedules. On the other hand, two doses of premixed insulin is a simple, convenient means of spreading insulin across the day. Moreover, human insulins, separately, self-mixed, or as premixed NPH/regular (70/30) formulations, are less costly alternatives to insulin analogs. **Figure 9.4** outlines these options as well as recommendations for further intensification, if needed, to achieve glycemic goals. When initiating combination injectable therapy, metformin therapy should be maintained, while sulfonylureas and DPP-4 inhibitors are typically weaned or discontinued. In individuals with suboptimal blood glucose control, especially those requiring large insulin doses, adjunctive use of a thiazolidinedione or an SGLT2 inhibitor may help to improve control and reduce the amount of insulin needed, though potential side effects should be considered. Once a basal-bolus insulin regimen is initiated, dose titration is important, with adjustments made in both mealtime and basal insulins based on the blood glucose levels and an understanding of the pharmacodynamic profile of each formulation (also known as pattern control or pattern management). As people with type 2 diabetes get older, it may become necessary to simplify complex insulin regimens because of a decline in self-management ability (see Section 13, "Older Adults").

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Declaration of Dr. Nathan Laney

Exhibit B

Diabetes Care Volume 46, Supplement 1, January 2023

6. Glycemic Targets: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

ASSESSMENT OF GLYCEMIC CONTROL

Glycemic control is assessed by the A1C measurement, continuous glucose monitoring (CGM) using time in range (TIR) and/or glucose management indicator (GMI), and blood glucose monitoring (BGM). A1C is the metric used to date in clinical trials demonstrating the benefits of improved glycemic control. Individual glucose monitoring (discussed in detail in Section 7, "Diabetes Technology") is a useful tool for diabetes self-management, which includes meals, physical activity, and medication adjustment, particularly in individuals taking insulin. CGM serves an increasingly important role in the management of the effectiveness and safety of treatment in many people with type 1 diabetes and in selected people with type 2 diabetes. Individuals on a variety of insulin treatment plans can benefit from CGM with improved glucose control, decreased hypoglycemia, and enhanced self-efficacy (Section 7, "Diabetes Technology") (1).

Glycemic Assessment

Recommendations

6.1 Assess glycemic status (A1C or other glycemic measurement such as time in range or glucose management indicator) *at least* two times a year in patients who are meeting treatment goals (and who have stable glycemic control). **E**

6.2 Assess glycemic status at least quarterly and as needed in patients whose therapy has recently changed and/or who are not meeting glycemic goals. **E**

A1C reflects average glycemia over approximately 3 months. The performance of the test is generally excellent for National Glycohemoglobin Standardization Program

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(NGSP)-certified assays (ngsp.org). The test is the primary tool for assessing glycemic control and has a strong predictive value for diabetes complications (2–4). Thus, A1C testing should be performed routinely in all people with diabetes at initial assessment and as part of continuing care. Measurement approximately every 3 months determines whether patients' glycemic targets have been reached and maintained. A 14-day CGM assessment of TIR and GMI can serve as a surrogate for A1C for use in clinical management (5–9). The frequency of A1C testing should depend on the clinical situation, the treatment plan, and the clinician's judgment. The use of point-of-care A1C testing or CGM-derived TIR and GMI may provide an opportunity for more timely treatment changes during encounters between patients and health care professionals. People with type 2 diabetes with stable glycemia well within target may do well with A1C testing or other glucose assessment only twice per year. Unstable or intensively managed patients or people not at goal with treatment adjustments may require testing more frequently (every 3 months with interim assessments as needed for safety) (10). CGM parameters can be tracked in the clinic or via telehealth to optimize diabetes management.

A1C Limitations

The A1C test is an indirect measure of average glycemia and, as such, is subject to limitations. As with any laboratory test, there is variability in the measurement of A1C. Although A1C variability is lower on an intraindividual basis than that of blood glucose measurements, clinicians should exercise judgment when using A1C as the sole basis for assessing glycemic control, particularly if the result is close to the threshold that might prompt a change in medication therapy. For example, conditions that affect red blood cell turnover (hemolytic and other anemias, glucose-6-phosphate dehydrogenase deficiency, recent blood transfusion, use of drugs that stimulate erythropoiesis, end-stage kidney disease, and pregnancy) may result in discrepancies between the A1C result and the patient's true mean glycemia (11). Hemoglobin variants must be considered, particularly when the A1C result does not correlate with the patient's CGM or BGM levels. However, most assays in use in the U.S. are accurate in individuals who are heterozygous for the most common variants (ngsp.org/interf.asp). Other measures of average glycemia such as fructosamine and 1,5-anhydroglucitol are available, but their translation into average glucose levels and their prognostic significance are not as clear as for A1C and CGM. Though some variability in the relationship between average glucose levels and A1C exists among different individuals, in general the association between mean glucose and A1C within an individual correlates over time (12).

A1C does not provide a measure of glycemic variability or hypoglycemia. For patients prone to glycemic variability, especially people with type 1 diabetes or type 2 diabetes with severe insulin deficiency, glycemic control is best evaluated by the combination of results from BGM/CGM and A1C. Discordant results between BGM/CGM and A1C can be the result of the conditions outlined above or glycemic variability, with BGM missing the extremes.

Correlation Between BGM and A1C

Table 6.1 shows the correlation between A1C levels and mean glucose levels based on the international A1C-Derived Average Glucose (ADAG) study, which assessed the correlation between A1C and frequent BGM and CGM in 507 adults (83% non-Hispanic White) with type 1, type 2, and no diabetes (13), and an empirical study of the average blood glucose levels at premeal, postmeal, and bedtime associated with specified A1C levels using data from the ADAG trial (14). The American Diabetes Association (ADA) and the American Association for Clinical Chemistry have determined that the correlation (r = 0.92) in the ADAG trial is strong enough to justify reporting both the A1C result and the estimated average glucose (eAG) result when a clinician orders the A1C test. Clinicians should note that the mean plasma glucose numbers in **Table 6.1** are based on ~2,700 readings per A1C measurement in the ADAG trial. In a report, mean glucose measured with CGM versus central laboratory–measured A1C in 387 participants in three randomized trials demonstrated that A1C may underestimate or overestimate mean glucose in individuals (12). Thus, as suggested, a patient's BGM or CGM profile has considerable potential for optimizing their glycemic management (13).

Table 6.1—Estimated average glucose (eAG)

A1C (%)	mg/dL*	mmol/L
5	97 (76–120)	5.4 (4.2–6.7)
6	126 (100–152)	7.0 (5.5–8.5)
7	154 (123–185)	8.6 (6.8–10.3)
8	183 (147–217)	10.2 (8.1–12.1)
9	212 (170–249)	11.8 (9.4–13.9)
10	240 (193–282)	13.4 (10.7–15.7)
11	269 (217–314)	14.9 (12.0–17.5)
12	298 (240–347)	16.5 (13.3–19.3)

Data in parentheses are 95% CI. A calculator for converting A1C results into eAG, in either mg/dL or mmol/L, is available at professional.diabetes.org/eAG. *These estimates are based on ADAG data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, or no diabetes. The correlation between A1C and average glucose was 0.92 (13,14). Adapted from Nathan et al. (13).

A1C Differences in Ethnic Populations and Children

In the ADAG study, there were no significant differences among racial and ethnic groups in the regression lines between A1C and mean glucose, although the study was underpowered to detect a difference and there was a trend toward a difference between the African and African American and the non-Hispanic White cohorts, with higher A1C values observed in the African and African American cohorts compared with non-Hispanic White cohorts for a given mean glucose. Other studies have also demonstrated higher A1C levels in African American participants than in White participants at a given mean glucose concentration (15,16). In contrast, a recent report in Afro-Caribbean individuals found lower A1C relative to glucose values (17). Taken together, A1C and glucose parameters are essential for the optimal assessment of glycemic status.

A1C assays are available that do not demonstrate a statistically significant difference in individuals with hemoglobin variants. Other assays have statistically significant interference, but the difference is not clinically significant. Use of an assay with such statistically significant interference may explain a report that

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Table 6.2—Standardized CGM metrics for clinical care

1. Number of days CGM device is worn (recommend 14 days)	
2. Percentage of time CGM device is active (recommend 70% of data from 14 days)	
3. Mean glucose	
4. Glucose management indicator	
5. Glycemic variability (%CV) target ≤36%*	
6. TAR: % of readings and time >250 mg/dL (>13.9 mmol/L)	Level 2 hyperglycemia
7. TAR: % of readings and time 181–250 mg/dL (10.1–13.9 mmol/L)	Level 1 hyperglycemia
8. TIR: % of readings and time 70–180 mg/dL (3.9–10.0 mmol/L)	In range
9. TBR: % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L)	Level 1 hypoglycemia
10. TBR: % of readings and time <54 mg/dL (<3.0 mmol/L)	Level 2 hypoglycemia

CGM, continuous glucose monitoring; CV, coefficient of variation; TAR, time above range; TBR, time below range; TIR, time in range. *Some studies suggest that lower %CV targets (<33%) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas. Adapted from Battelino et al. (35).

for any level of mean glycemia, African American individuals heterozygous for the common hemoglobin variant HbS had lower A1C by about 0.3 percentage points when compared with those without the trait (18,19). Another genetic variant, X-linked glucose-6-phosphate dehydrogenase G202A, carried by 11% of African American individuals, was associated with a decrease in A1C of about 0.8% in hemizygous men and 0.7% in homozygous women compared with those without the trait (20).

A small study comparing A1C to CGM data in children with type 1 diabetes found a highly statistically significant correlation between A1C and mean blood glucose, although the correlation (r = 0.7) was significantly lower than that in the ADAG trial (21). Whether there are clinically meaningful differences in how A1C relates to average glucose in children or in different ethnicities is an area for further study (15,22,23). Until further evidence is available, it seems prudent to establish A1C goals in these populations with consideration of individualized CGM, BGM, and A1C results. Limitations in perfect alignment between glycemic measurements do not interfere with the usefulness of BGM/CGM for insulin dose adjustments.

Glucose Assessment by Continuous Glucose Monitoring

Recommendations

6.3 Standardized, single-page glucose reports from continuous glucose monitoring (CGM) devices with visual cues, such as the ambulatory glucose profile, should be considered as a standard summary for all CGM devices. **E**

6.4 Time in range is associated with the risk of microvascular complications and can be used for assessment of glycemic control. Additionally, time below range and time above range are useful parameters for the evaluation of the treatment plan (**Table 6.2**). **C**

CGM is rapidly improving diabetes management. As stated in the recommendations, time in range (TIR) is a useful metric of glycemic control and glucose patterns, and it correlates well with A1C in most studies (24–29). New data support the premise that increased TIR correlates with the risk of complications. The studies supporting this assertion are reviewed in more detail in Section 7, "Diabetes Technology"; they include cross-sectional data and cohort studies (30–32) demonstrating TIR as an acceptable end point for clinical trials moving forward and that it can be used for assessment of glycemic control. Additionally, time below range (<70 and <54 mg/dL [3.9 and 3.0 mmol/L]) and time above range (>180 mg/dL [10.0 mmol/L]) are useful parameters for insulin dose adjustments and reevaluation of the treatment plan.

For many people with diabetes, glucose monitoring is key for achieving glycemic targets. Major clinical trials of insulin-treated patients have included BGM as part of multifactorial interventions to demonstrate the benefit of intensive glycemic control on diabetes complications (33). BGM is thus an integral component of effective therapy of patients taking insulin. In recent years, CGM has become a standard method for glucose monitoring for most adults with type 1 diabetes (34). Both approaches to glucose monitoring allow patients to evaluate individual responses to therapy and assess whether glycemic targets are being safely achieved. The international consensus on TIR provides guidance on standardized CGM metrics (**Table 6.2**) and considerations for clinical interpretation and care (35). To make these metrics more actionable, standardized reports with visual cues, such as the ambulatory glucose profile (**Fig 6.1**), are recommended (35) and may help the patient and the health care professional better interpret the data to guide treatment decisions (24,27). BGM and CGM can be useful to guide medical nutrition therapy and physical activity, prevent hypoglycemia, and aid medication management. While A1C is currently the primary measure to guide glucose management and a valuable risk marker for developing diabetes complications, the CGM metrics TIR (with time below range and time above range) and GMI provide the insights for a more personalized diabetes management plan. The incorporation of these metrics into clinical practice is in evolution, and remote access to these data can be critical for telehealth. A rapid optimization and harmonization of CGM terminology and remote access is occurring to meet patient and health care professional needs (36–38). The patient's specific needs and goals should dictate BGM frequency and timing and consideration of CGM use. Please refer to Section 7, "Diabetes Technology," for a more complete discussion of the use of BGM and CGM.

With the advent of new technology, CGM has evolved rapidly in both accuracy and affordability. As such, many patients have these data available to assist with self-management and their health care professionals' assessment of glycemic status. Reports can be generated from CGM that will allow the health care professional and person with diabetes to determine TIR, calculate GMI, and

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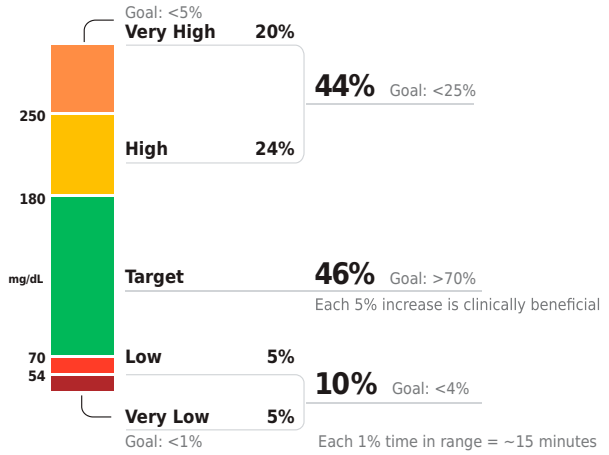
Diabetes Care Volume 46, Supplement 1, January 2023

AGP Report: Continuous Glucose Monitoring

Time in Ranges

Goals for Type 1 and Type 2 Diabetes



Test Patient DOB: Jan 1, 1970

14 Days: August 8–August 21, 2021

Time CGM Active: 100%

Glucose Metrics

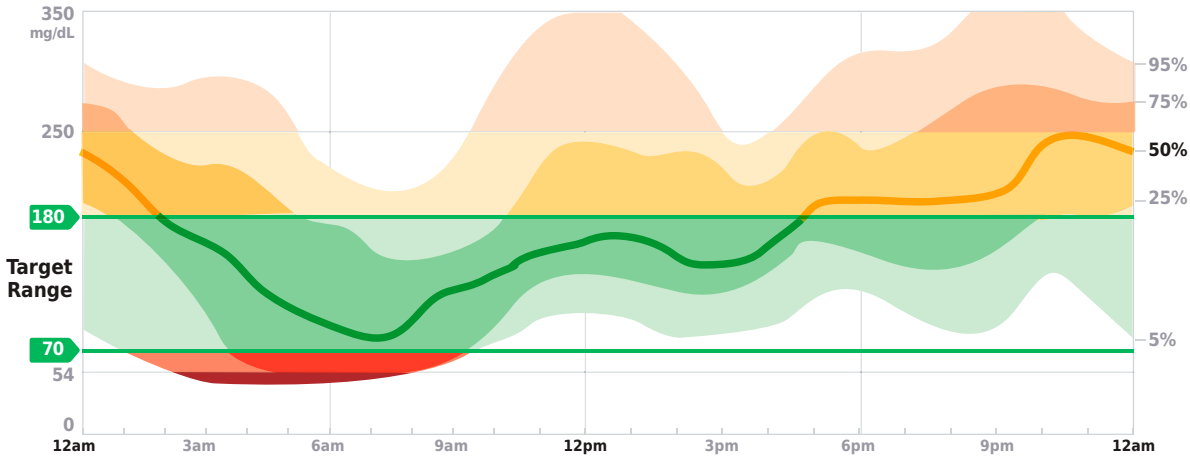
Average Glucose ..... **175 mg/dL**
Goal: <154 mg/dL

Glucose Management Indicator (GMI) **7.5%**
Goal: <7%

Glucose Variability **45.5%**
Defined as percent coefficient of variation
Goal: ≤36%

Ambulatory Glucose Profile (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if they occurred in a single day.



Daily Glucose Profiles

Each daily profile represents a midnight-to-midnight period.

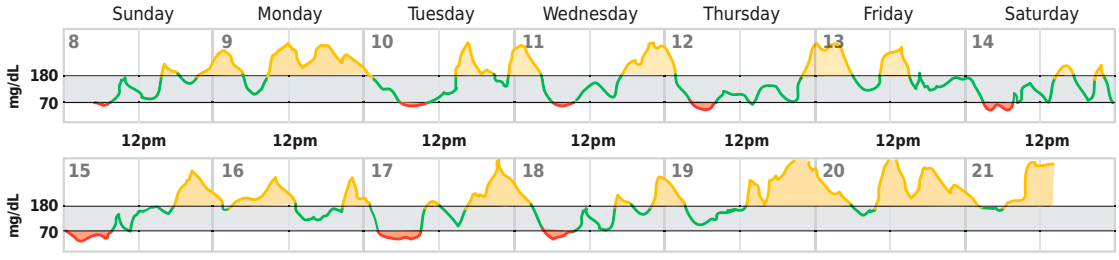


Figure 6.1—Key points included in standard ambulatory glucose profile (AGP) report. Reprinted from Holt et al. (34).

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assess hypoglycemia, hyperglycemia, and glycemic variability. As discussed in a recent consensus document, a report formatted as shown in **Fig. 6.1** can be generated (35). Published data from two retrospective studies suggest a strong correlation between TIR and A1C, with a goal of 70% TIR aligning with an A1C of ~7% (8,26). Note the goals of therapy next to each metric in **Fig. 6.1** (e.g., low, <4%; very low, <1%) as values to guide changes in therapy.

GLYCEMIC GOALS

For glycemic goals in older adults, please refer to Section 13, "Older Adults." For glycemic goals in children, please refer to Section 14, "Children and Adolescents." For glycemic goals during pregnancy, please refer to Section 15, "Management of Diabetes in Pregnancy." Overall, regardless of the population being served, it is critical for the glycemic targets to be woven into the overall person-centered strategy. For example, in a very young child, safety and simplicity may outweigh the need for glycemic stability in the short run. Simplification may decrease parental anxiety and build trust and confidence, which could support further strengthening of glycemic targets and self-efficacy. In healthy older adults, there is no empiric need to loosen control; however, less stringent A1C goals may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits (39,40).

However, the health care professional needs to work with an individual and should consider adjusting targets for simplifying the treatment plan if this change is needed to improve safety and medication-taking behavior. Setting goals by face-to-face or remote consultations has been shown to be more effective than usual care for glycemic control in type 2 diabetes for fasting plasma glucose and glycated hemoglobin (41).

Recommendations

6.5a An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate. **A**

6.5b If using ambulatory glucose profile/glucose management indicator to assess glycemia, a parallel goal for many nonpregnant adults is time in range of >70% with time below range <4% and time <54 mg/dL <1%. For those with frailty or at high risk of hypoglycemia, a target of >50% time in range with <1% time below range is recommended. (See **Fig. 6.1** and **Table 6.2**.) **B**

6.6 On the basis of health care professional judgment and patient preference, achievement of lower A1C levels than the goal of 7% may be acceptable and even beneficial if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. **B**

6.7 Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits. Health care professionals should consider deintensification of therapy if appropriate to reduce the risk of hypoglycemia in patients with inappropriate stringent A1C targets. **B**

6.8 Reassess glycemic targets based on the individualized criteria in **Fig. 6.2**. **E**

6.9 Setting a glycemic goal during consultations is likely to improve patient outcomes. **E**

A1C and Microvascular Complications

Hyperglycemia defines diabetes, and glycemic control is fundamental to diabetes management. The Diabetes Control and Complications Trial (DCCT) (33), a prospective randomized controlled trial of intensive (mean A1C about 7% [53 mmol/mol]) versus standard (mean A1C about 9% [75 mmol/mol]) glycemic control in people with type 1 diabetes, showed definitively that better glycemic control is associated with 50–76% reductions in rates of development and progression of microvascular (retinopathy, neuropathy, and diabetic kidney disease) complications. Follow-up of the DCCT cohorts in the Epidemiology of Diabetes Interventions and Complications (EDIC) study (42,43) demonstrated persistence of these microvascular benefits over two decades despite the fact that the glycemic separation between the treatment groups diminished and disappeared during follow-up.

The Kumamoto Study (44) and UK Prospective Diabetes Study (UKPDS) (45,46) confirmed that intensive glycemic control significantly decreased rates of microvascular complications in people with short-duration type 2 diabetes. Long-term follow-up of the UKPDS cohorts showed enduring effects of early glycemic control on most microvascular complications (47).

Therefore, achieving A1C targets of <7% (53 mmol/mol) has been shown to reduce microvascular complications of type 1 and type 2 diabetes when instituted early in the course of disease (2,48). Findings from the DCCT (33) and UKPDS (49) studies demonstrate a curvilinear relationship between A1C and microvascular complications. Such analyses suggest that, on a population level, the greatest number of complications will be averted by taking patients from very poor control to fair/good control. These analyses also suggest that further lowering of A1C from 7 to 6% (53 mmol/mol to 42 mmol/mol) is associated with further reduction in the risk of microvascular complications, although the absolute risk reductions become much smaller. The implication of these findings is that there is no need to deintensify therapy for an individual with an A1C between 6 and 7% in the setting of low hypoglycemia risk with a long life expectancy. There are now newer agents that do not cause hypoglycemia, making it possible to maintain glucose control without the risk of hypoglycemia (see Section 9, "Pharmacologic Approaches to Glycemic Treatment").

Given the substantially increased risk of hypoglycemia in type 1 diabetes and with polypharmacy in type 2 diabetes, the risks of lower glycemic targets may outweigh the potential benefits on microvascular complications. Three landmark trials (Action to Control Cardiovascular Risk in Diabetes [ACCORD], Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE], and Veterans Affairs Diabetes Trial [VADT]) were conducted to test the effects of near normalization of blood glucose on cardiovascular outcomes in individuals with long-standing type 2 diabetes and either known cardiovascular disease (CVD) or high cardiovascular

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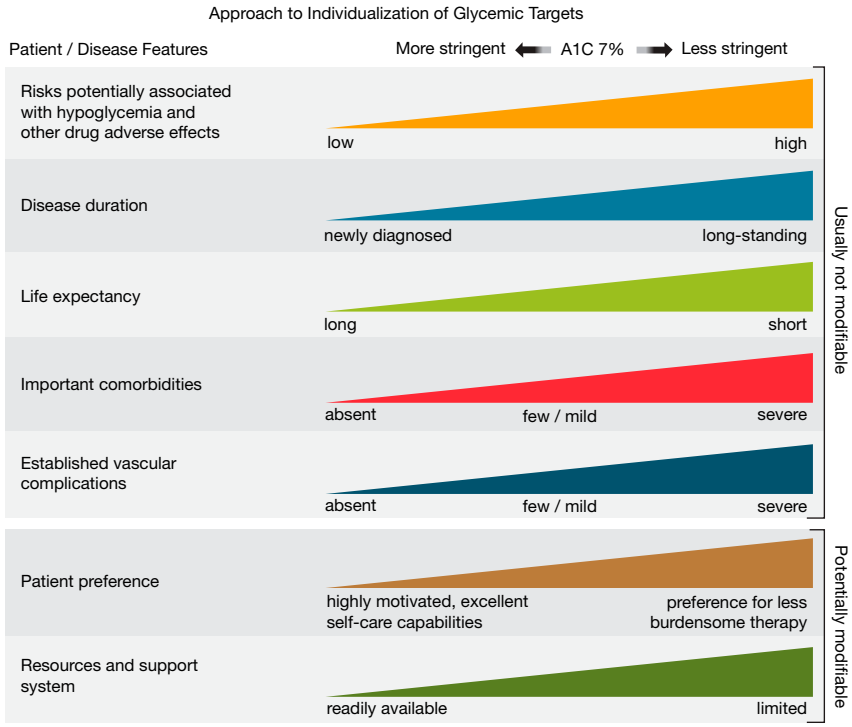

Figure 6.2—Patient and disease factors used to determine optimal glycemic targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. A1C 7% = 53 mmol/mol. Adapted with permission from Inzucchi et al. (71).

risk. These trials showed that lower A1C levels were associated with reduced onset or progression of some microvascular complications (50–52).

The concerning mortality findings in the ACCORD trial discussed below and the relatively intense efforts required to achieve near euglycemia should also be considered when setting glycemic targets for individuals with long-standing diabetes, such as those populations studied in ACCORD, ADVANCE, and VADT. Findings from these studies suggest caution is needed in treating diabetes to near-normal A1C goals in people with long-standing type 2 diabetes with or at significant risk of CVD.

These landmark studies need to be considered with an important caveat; glucagon-like peptide 1 (GLP-1) receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors were not approved at the time of these trials. As such, these agents with established cardiovascular and renal benefits appear to be safe and beneficial in this group of individuals at high risk for cardiorenal complications. Randomized clinical trials examining these agents for cardiovascular safety were not designed to test higher versus lower A1C; therefore, beyond post hoc analysis of these trials, we do not have evidence that it is the glucose lowering by these agents that confers the CVD and renal benefit (53). As such, based on clinician judgment and patient preferences, select patients, especially those with little comorbidity and a long life expectancy, may benefit from adopting more intensive glycemic targets if they can achieve them safely and without hypoglycemia or significant therapeutic burden.

A1C and Cardiovascular Disease Outcomes

Cardiovascular Disease and Type 1 Diabetes

CVD is a more common cause of death than microvascular complications in populations with diabetes. There is evidence for a cardiovascular benefit of intensive glycemic control after long-term follow-up of cohorts treated early in the course of type 1 diabetes. In the DCCT, there was a trend toward lower risk of CVD events with intensive control. In the 9-year post-DCCT follow-up of the EDIC cohort, participants previously randomized to the intensive arm had a significant 57% reduction in the risk of nonfatal myocardial infarction (MI), stroke, or cardiovascular death compared with those previously randomized to the standard arm (54). The benefit of intensive glycemic control in this cohort with type 1 diabetes has been shown to persist for several decades (55) and to be associated with a modest reduction in all-cause mortality (56).

Cardiovascular Disease and Type 2 Diabetes

In type 2 diabetes, there is evidence that more intensive treatment of glycemia in newly diagnosed patients may reduce long-term CVD rates. In addition, data from the Swedish National Diabetes Registry (56) and the Joint Asia Diabetes Evaluation (JADE) demonstrate greater proportions of people with diabetes being diagnosed at <40 years of age and a demonstrably increased burden of heart disease and years of life lost in people diagnosed at a younger age (57–60). Thus, to prevent both microvascular and macrovascular complications of diabetes, there is a major call to overcome therapeutic inertia and treat to target for an individual patient (60,61). During the UKPDS, there was a 16% reduction in CVD events (combined fatal or nonfatal MI and sudden death) in the intensive glycemic control arm that did not reach statistical significance (P = 0.052), and there was no suggestion of benefit on other CVD outcomes (e.g., stroke). Similar to the DCCT/EDIC, after 10 years of observational follow-up, those originally randomized to intensive glycemic control had significant long-term reductions in MI (15% with sulfonylurea or insulin as initial pharmacotherapy, 33% with metformin as initial pharmacotherapy) and in all-cause mortality (13% and 27%, respectively) (47).

ACCORD, ADVANCE, and VADT suggested no significant reduction in CVD outcomes with intensive glycemic control in participants followed for shorter durations (3.5–5.6 years) and who had more advanced type 2 diabetes and CVD risk than the UKPDS participants. All three trials were conducted in relatively older participants with a longer known duration of diabetes (mean duration 8–11 years) and either CVD or multiple cardiovascular risk factors. The target A1C among intensive-control participants was <6% (42 mmol/mol) in ACCORD, <6.5% (48 mmol/mol) in ADVANCE,

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and a 1.5% reduction in A1C compared with control participants in VADT, with achieved A1C of 6.4% vs. 7.5% (46 mmol/mol vs. 58 mmol/mol) in ACCORD, 6.5% vs. 7.3% (48 mmol/mol vs. 56 mmol/mol) in ADVANCE, and 6.9% vs. 8.4% (52 mmol/mol vs. 68 mmol/mol) in VADT. Details of these studies are reviewed extensively in the joint ADA position statement "Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials" (61).

The glycemic control comparison in ACCORD was halted early due to an increased mortality rate in the intensive compared with the standard treatment arm (1.41% vs. 1.14% per year; hazard ratio 1.22 [95% CI 1.01–1.46]), with a similar increase in cardiovascular deaths. Analysis of the ACCORD data did not identify a clear explanation for the excess mortality in the intensive treatment arm (62).

Longer-term follow-up has shown no evidence of cardiovascular benefit, or harm, in the ADVANCE trial (63). The end-stage renal disease rate was lower in the intensive treatment group over follow-up. However, 10-year follow-up of the VADT cohort (64) did demonstrate a reduction in the risk of cardiovascular events (52.7 [control group] vs. 44.1 [intervention group] events per 1,000 person-years) with no benefit in cardiovascular or overall mortality. Heterogeneity of mortality effects across studies was noted, which may reflect differences in glycemic targets, therapeutic approaches, and, importantly, population characteristics (65).

Mortality findings in ACCORD (62) and subgroup analyses of VADT (66) suggest that the potential risks of intensive glycemic control may outweigh its benefits in higher-risk individuals. In all three trials, severe hypoglycemia was significantly more likely in participants who were randomly assigned to the intensive glycemic control arm. Individuals with a long duration of diabetes, a known history of hypoglycemia, advanced atherosclerosis, or advanced age/frailty may benefit from less aggressive targets (67,68).

As discussed further below, severe hypoglycemia is a potent marker of high absolute risk of cardiovascular events and mortality (69). Therefore, health care professionals should be vigilant in preventing hypoglycemia and should not aggressively attempt to achieve near-normal A1C levels in people in whom such targets cannot be safely and reasonably achieved. As discussed in Section 9, "Pharmacologic Approaches to Glycemic Treatment," addition of specific SGLT2 inhibitors or GLP-1 receptor agonists that have demonstrated CVD benefit is recommended in patients with established CVD, chronic kidney disease, and heart failure. As outlined in more detail in Section 9, "Pharmacologic Approaches to Glycemic Treatment," and Section 10, "Cardiovascular Disease and Risk Management," the cardiovascular benefits of SGLT2 inhibitors or GLP-1 receptor agonists are not contingent upon A1C lowering; therefore, initiation can be considered in people with type 2 diabetes and CVD independent of the current A1C or A1C goal or metformin therapy. Based on these considerations, the following two strategies are offered (70):

1. If already on dual therapy or multiple glucose-lowering therapies and not on an SGLT2 inhibitor or GLP-1 receptor agonist, consider switching to one of these agents with proven cardiovascular benefit.
2. Introduce SGLT2 inhibitors or GLP-1 receptor agonists in people with CVD at A1C goal (independent of metformin) for cardiovascular benefit, independent of baseline A1C or individualized A1C target.

Setting and Modifying A1C Goals

Numerous factors must be considered when setting glycemic targets. The ADA proposes general targets appropriate for many people but emphasizes the importance of individualization based on key patient characteristics. Glycemic targets must be individualized in the context of shared decision-making to address individual needs and preferences and consider characteristics that influence risks and benefits of therapy; this approach may optimize engagement and self-efficacy.

The factors to consider in individualizing goals are depicted in **Fig. 6.2**. This figure is not designed to be applied rigidly but to be used as a broad construct to guide clinical decision-making (71) and engage people with type 1 and type 2 diabetes in shared decision-making. More aggressive targets may be recommended if they can be achieved safely and with an acceptable burden of therapy and if life expectancy is sufficient to reap the benefits of stringent targets. Less stringent targets (A1C up to 8% [64 mmol/mol]) may be recommended if the patient's life expectancy is such that the benefits of an intensive goal may not be realized, or if the risks and burdens outweigh the potential benefits. Severe or frequent hypoglycemia is an absolute indication for the modification of treatment plans, including setting higher glycemic goals.

Diabetes is a chronic disease that progresses over decades. Thus, a goal that might be appropriate for an individual early in the course of their diabetes may change over time. Newly diagnosed patients and/or those without comorbidities that limit life expectancy may benefit from intensive control proven to prevent microvascular complications. Both DCCT/EDIC and UKPDS demonstrated metabolic memory, or a legacy effect, in which a finite period of intensive control yielded benefits that extended for decades after that control ended. Thus, a finite period of intensive control to near-normal A1C may yield enduring benefits even if control is subsequently deintensified as patient characteristics change. Over time, comorbidities may emerge, decreasing life expectancy and thereby decreasing the potential to reap benefits from intensive control. Also, with longer disease duration, diabetes may become more difficult to control, with increasing risks and burdens of therapy. Thus, A1C targets should be reevaluated over time to balance the risks and benefits as patient factors change.

Recommended glycemic targets for many nonpregnant adults are shown in **Table 6.3**. The recommendations include blood glucose levels that appear to correlate with achievement of an A1C of <7% (53 mmol/mol). Pregnancy recommendations are discussed in more detail in Section 15, "Management of Diabetes in Pregnancy."

The issue of preprandial versus postprandial BGM targets is complex (72,73). Elevated postchallenge (2-h oral glucose tolerance test) glucose values have been associated with increased cardiovascular risk independent of fasting plasma glucose in some epidemiologic studies, whereas intervention trials have not

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Table 6.3—Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C	<7.0% (53 mmol/mol)*#
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individual patients. #CGM may be used to assess glycemic target as noted in Recommendation 6.5b and **Fig. 6.1**. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations (as per **Fig. 6.2**). †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in people with diabetes.

shown postprandial glucose to be a cardiovascular risk factor independent of A1C. In people with diabetes, surrogate measures of vascular pathology, such as endothelial dysfunction, are negatively affected by postprandial hyperglycemia. It is clear that postprandial hyperglycemia, like preprandial hyperglycemia, contributes to elevated A1C levels, with its relative contribution being greater at A1C levels that are closer to 7% (53 mmol/mol). However, outcome studies have shown A1C to be the primary predictor of complications, and landmark trials of glycemic control such as the DCCT and UKPDS relied overwhelmingly on preprandial BGM. Additionally, a randomized controlled trial in patients with known CVD found no CVD benefit of insulin treatment plans targeting postprandial glucose compared with those targeting preprandial glucose (73). Therefore, it is reasonable to check postprandial glucose in individuals who have premeal glucose values within target but A1C values above target. In addition, when intensifying insulin therapy, measuring postprandial plasma glucose 1–2 h after the start of a meal (using BGM or CGM) and using treatments aimed at reducing postprandial plasma glucose values to <180 mg/dL (10.0 mmol/L) may help to lower A1C.

An analysis of data from 470 participants in the ADAG study (237 with type 1 diabetes and 147 with type 2 diabetes) found that the glucose ranges highlighted in **Table 6.1** are adequate to meet targets and decrease hypoglycemia (14). These findings support that premeal glucose targets may be relaxed without undermining overall glycemic control as measured by A1C. These data prompted the revision in the ADA-recommended premeal glucose target to 80–130 mg/dL (4.4–7.2 mmol/L) but did not affect the definition of hypoglycemia.

HYPOGLYCEMIA

Recommendations

6.10 Occurrence and risk for hypoglycemia should be reviewed at every encounter and investigated as indicated. Awareness of hypoglycemia should be considered using validated tools. **C**

6.11 Glucose (approximately 15–20 g) is the preferred treatment for the conscious individual with blood glucose <70 mg/dL (3.9 mmol/L), although any form of carbohydrate that contains glucose may be used. Fifteen minutes after treatment, if blood glucose monitoring (BGM) shows continued hypoglycemia, the treatment should be repeated. Once the BGM or glucose pattern is trending up, the individual should consume a meal or snack to prevent recurrence of hypoglycemia. **B**

6.12 Glucagon should be prescribed for all individuals at increased risk of level 2 or 3 hypoglycemia, so that it is available should it be needed. Caregivers, school personnel, or family members providing support to these individuals should know where it is and when and how to administer it. Glucagon administration is not limited to health care professionals. **E**

6.13 Hypoglycemia unawareness or one or more episodes of level 3 hypoglycemia should trigger hypoglycemia avoidance education and reevaluation and adjustment of the treatment plan to decrease hypoglycemia. **E**

6.14 Insulin-treated patients with hypoglycemia unawareness, one level 3 hypoglycemic event, or a pattern of unexplained level 2 hypoglycemia should be advised to raise their glycemic targets to strictly avoid hypoglycemia for at least several weeks in order to partially reverse hypoglycemia unawareness and reduce risk of future episodes. **A**

6.15 Ongoing assessment of cognitive function is suggested with increased vigilance for hypoglycemia by the clinician, patient, and caregivers if impaired or declining cognition is found. **B**

Hypoglycemia is the major limiting factor in the glycemic management of type 1 and type 2 diabetes. Recommendations regarding the classification of hypoglycemia are outlined in **Table 6.4** (74–83). Level 1 hypoglycemia is defined as a measurable glucose concentration <70 mg/dL (3.9 mmol/L) but ≥54 mg/dL (3.0 mmol/L). A blood glucose concentration of 70 mg/dL (3.9 mmol/L) has been recognized as a threshold for neuroendocrine responses to falling glucose in people without diabetes. Because many people with diabetes demonstrate impaired counterregulatory responses to hypoglycemia and/or experience hypoglycemia unawareness, a measured glucose level <70 mg/dL (3.9 mmol/L) is considered clinically important (independent of the severity of acute hypoglycemic symptoms). Level 2 hypoglycemia (defined as a blood glucose concentration <54 mg/dL [3.0 mmol/L]) is the threshold at which neuroglycopenic symptoms begin to occur and requires immediate action to resolve the hypoglycemic event. If a patient has level 2 hypoglycemia without adrenergic or neuroglycopenic symptoms, they likely have hypoglycemia unawareness (discussed further below). This clinical scenario warrants investigation and review of the treatment plan (75,79). Use Clarke score, Gold score, or Pedersen-Bjergaard score to assess impaired awareness (76). Lastly, level 3 hypoglycemia is defined as a severe

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Table 6.4—Classification of hypoglycemia

	Glycemic criteria/description
Level 1	Glucose <70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L)
Level 2	Glucose <54 mg/dL (3.0 mmol/L)
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia

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event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery.

Symptoms of hypoglycemia include, but are not limited to, shakiness, irritability, confusion, tachycardia, and hunger. Hypoglycemia may be inconvenient or frightening to people with diabetes. Level 3 hypoglycemia may be recognized or unrecognized and can progress to loss of consciousness, seizure, coma, or death. Hypoglycemia is reversed by administration of rapid-acting glucose or glucagon. Hypoglycemia can cause acute harm to the person with diabetes or others, especially if it causes falls, motor vehicle accidents, or other injury. Recurrent level 2 hypoglycemia and/or level 3 hypoglycemia is an urgent medical issue and requires intervention with medical treatment plan adjustment, behavioral intervention, and, in some cases, use of technology to assist with hypoglycemia prevention and identification (76,79–82). A large cohort study suggested that among older adults with type 2 diabetes, a history of level 3 hypoglycemia was associated with greater risk of dementia (84). Conversely, in a substudy of the ACCORD trial, cognitive impairment at baseline or decline in cognitive function during the trial was significantly associated with subsequent episodes of level 3 hypoglycemia (85). Evidence from DCCT/EDIC, which involved adolescents and younger adults with type 1 diabetes, found no association between frequency of level 3 hypoglycemia and cognitive decline (86).

Studies of rates of level 3 hypoglycemia that rely on claims data for hospitalization, emergency department visits, and ambulance use substantially underestimate rates of level 3 hypoglycemia (87) yet reveal a high burden of hypoglycemia in adults over 60 years of age in the community (88). African American individuals are at substantially increased risk of level 3 hypoglycemia (88,89). In addition to age and race, other important risk factors found in a community-based epidemiologic cohort of older adults with type 2 diabetes include insulin use, poor or moderate versus good glycemic control, albuminuria, and poor cognitive function (88). Level 3 hypoglycemia was associated with mortality in participants in both the standard and the intensive glycemia arms of the ACCORD trial, but the relationships between hypoglycemia, achieved A1C, and treatment intensity were not straightforward. An association of level 3 hypoglycemia with mortality was also found in the ADVANCE trial (90). An association between self-reported level 3 hypoglycemia and 5-year mortality has also been reported in clinical practice (91). Glucose variability is also associated with an increased risk for hypoglycemia (92).

Young children with type 1 diabetes and the elderly, including those with type 1 and type 2 diabetes (84,93), are noted as particularly vulnerable to hypoglycemia because of their reduced ability to recognize hypoglycemic symptoms and effectively communicate their needs. Individualized glucose targets, patient education, nutrition intervention (e.g., bedtime snack to prevent overnight hypoglycemia when specifically needed to treat low blood glucose), physical activity management, medication adjustment, glucose monitoring, and routine clinical surveillance may improve patient outcomes (94). CGM with automated low glucose suspend and hybrid closed-loop systems have been shown to be effective in reducing hypoglycemia in type 1 diabetes (95). For people with type 1 diabetes with level 3 hypoglycemia and hypoglycemia unawareness that persists despite medical treatment, human islet transplantation may be an option, but the approach remains experimental (96,97).

In 2015, the ADA changed its preprandial glycemic target from 70–130 mg/dL (3.9–7.2 mmol/L) to 80–130 mg/dL (4.4–7.2 mmol/L). This change reflects the results of the ADAG study, which demonstrated that higher glycemic targets corresponded to A1C goals (14). An additional goal of raising the lower range of the glycemic target was to limit overtreatment and provide a safety margin in patients titrating glucose-lowering drugs such as insulin to glycemic targets.

Hypoglycemia Treatment

Health care professionals should continue to counsel patients to treat hypoglycemia with fast-acting carbohydrates at the hypoglycemia alert value of 70 mg/dL (3.9 mmol/L) or less. This should be reviewed at each patient visit. Hypoglycemia treatment requires ingestion of glucose- or carbohydrate-containing foods (98–100). The acute glycemic response correlates better with the glucose content of food than with the carbohydrate content of food. Pure glucose is the preferred treatment, but any form of carbohydrate that contains glucose will raise blood glucose. Added fat may retard and then prolong the acute glycemic response. In type 2 diabetes, ingested protein may increase insulin response without increasing plasma glucose concentrations (101). Therefore, carbohydrate sources high in protein should not be used to treat or prevent hypoglycemia. Ongoing insulin activity or insulin secretagogues may lead to recurrent hypoglycemia unless more food is ingested after recovery. Once the glucose returns to normal, the individual should be counseled to eat a meal or snack to prevent recurrent hypoglycemia.

Glucagon

The use of glucagon is indicated for the treatment of hypoglycemia in people unable or unwilling to consume carbohydrates by mouth. Those in close contact with, or having custodial care of, people with hypoglycemia-prone diabetes (family members, roommates, school personnel, childcare professionals, correctional institution staff, or coworkers) should be instructed on the use of glucagon, including where the glucagon product is kept and when and how to administer it. An individual does not need to be a health care professional to safely

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administer glucagon. In addition to traditional glucagon injection powder that requires reconstitution prior to injection, intranasal glucagon and ready-to-inject glucagon preparations for subcutaneous injection are available and may be beneficial in view of safety, efficacy, and ease of use. Care should be taken to ensure that glucagon products are not expired (102).

Hypoglycemia Prevention

Hypoglycemia prevention is a critical component of diabetes management. BGM and, for some individuals, CGM are essential tools to assess therapy and detect incipient hypoglycemia. People with diabetes should understand situations that increase their risk of hypoglycemia, such as when fasting for laboratory tests or procedures, when meals are delayed, during and after the consumption of alcohol, during and after intense physical activity, and during sleep. Hypoglycemia may increase the risk of harm to self or others, such as when driving. Teaching people with diabetes to balance insulin use and carbohydrate intake and physical activity are necessary, but these strategies are not always sufficient for prevention (77, 103–105). Formal training programs to increase awareness of hypoglycemia and to develop strategies to decrease hypoglycemia have been developed, including the Blood Glucose Awareness Training Program, Dose Adjusted for Normal Eating (DAFNE), and DAFNEplus. Conversely, some individuals with type 1 diabetes or type 2 diabetes and hypoglycemia who have a fear of hyperglycemia are resistant to relaxation of glycemic targets (74–83). Regardless of the factors contributing to hypoglycemia and hypoglycemia unawareness, this represents an urgent medical issue requiring intervention.

In type 1 diabetes and severely insulin-deficient type 2 diabetes, hypoglycemia unawareness (or hypoglycemia-associated autonomic failure) can severely compromise stringent diabetes control and quality of life. This syndrome is characterized by deficient counterregulatory hormone release, especially in older adults, and a diminished autonomic response, which are both risk factors for and caused by hypoglycemia. A corollary to this "vicious cycle" is that several weeks of avoidance of hypoglycemia has been demonstrated to improve counterregulation and hypoglycemia awareness in many people with diabetes (106). Hence, individuals with one or more episodes of clinically significant hypoglycemia may benefit from at least short-term relaxation of glycemic targets and availability of glucagon (107). Any person with recurrent hypoglycemia or hypoglycemia unawareness should have their glucose management treatment plan adjusted.

Use of CGM Technology in Hypoglycemia Prevention

With the advent of sensor-augmented CGM and CGM-assisted pump therapy, there has been a promise of alarm-based prevention of hypoglycemia (108,109). To date, there have been a number of randomized controlled trials in adults with type 1 diabetes and studies in adults and children with type 1 diabetes using real-time CGM (see Section 7, "Diabetes Technology"). These studies had differing A1C at entry and differing primary end points and thus must be interpreted carefully. Real-time CGM studies can be divided into studies with elevated A1C with the primary end point of A1C reduction and studies with A1C near target with the primary end point of reduction in hypoglycemia (98, 109–124). In people with type 1 and type 2 diabetes with A1C above target, CGM improved A1C between 0.3 and 0.6%. For studies targeting hypoglycemia, most studies demonstrated a significant reduction in time spent between 54 and 70 mg/dL. A report in people with type 1 diabetes over the age of 60 years revealed a small but statistically significant decrease in hypoglycemia (125). No study to date has reported a decrease in level 3 hypoglycemia. In a single study using intermittently scanned CGM, adults with type 1 diabetes with A1C near goal and impaired awareness of hypoglycemia demonstrated no change in A1C and decreased level 2 hypoglycemia (115). For people with type 2 diabetes, studies examining the impact of CGM on hypoglycemic events are limited; a recent meta-analysis does not reflect a significant impact on hypoglycemic events in type 2 diabetes (126), whereas improvements in A1C were observed in most studies (126–132). Overall, real-time CGM appears to be a useful tool for decreasing time spent in a hypoglycemic range in people with impaired awareness. For people with type 2 diabetes, other strategies to assist them with insulin dosing can improve A1C with minimal hypoglycemia (133,134).

INTERCURRENT ILLNESS

For further information on management of individuals with hyperglycemia in the hospital, see Section 16, "Diabetes Care in the Hospital."

Stressful events (e.g., illness, trauma, surgery) may worsen glycemic control and precipitate diabetic ketoacidosis or nonketotic hyperglycemic hyperosmolar state, life-threatening conditions that require immediate medical care to prevent complications and death. Any condition leading to deterioration in glycemic control necessitates more frequent monitoring of blood glucose; ketosis-prone patients also require urine or blood ketone monitoring. If accompanied by ketosis, vomiting, or alteration in the level of consciousness, marked hyperglycemia requires temporary adjustment of the treatment plan and immediate interaction with the diabetes care team. The patient treated with noninsulin therapies or medical nutrition therapy alone may require insulin. Adequate fluid and caloric intake must be ensured. Infection or dehydration are more likely to necessitate hospitalization of individuals with diabetes versus those without diabetes.

A clinician with expertise in diabetes management should treat the hospitalized patient. For further information on the management of diabetic ketoacidosis and the nonketotic hyperglycemic hyperosmolar state, please refer to the ADA consensus report "Hyperglycemic Crises in Adult Patients With Diabetes" (134).

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Declaration of Dr. Nathan Laney

Exhibit C

CONTRIBUTIONS OF FASTING AND POSTPRANDIAL GLUCOSE TO HEMOGLOBIN A1c*

Louis Monnier, MD,[1] and Claude Colette, PhD[2]

ABSTRACT

Objective: To define the respective contributions of fasting and postprandial plasma glucose to hemoglobin A1c (HbA1c) in patients with non-insulin-treated type 2 diabetes.

Methods: Previous studies of diurnal glycemic profiles are reviewed, and glucose values for predicting successful treatment of diabetes are suggested.

Results: By analyzing the results from prior studies of diurnal glycemic profiles, we found that the relative contribution of postprandial plasma glucose was high (70%) in patients with fairly good control of diabetes (HbA1c <7.3%) and decreased progressively (30%) with worsening diabetes (HbA1c >10.2%). In contrast, the contribution of fasting plasma glucose showed a gradual increase with increasing levels of HbA1c. By using the same model (the diurnal glycemic profile), we established that postmeal glycemia was a better predictor of good or satisfactory control of diabetes (HbA1c <7%) than was fasting glucose. The best cutoff values that ensured the optimal balance between high sensitivity and specificity were approximately 200 mg/dL at 11 AM and 160 mg/dL at 2 PM. The cut-point values for predicting treatment success (specificity ≥90%) were 162 mg/dL at 11 AM and 126 mg/dL at 2 PM.

Conclusion: Postprandial plasma glucose is the predominant contributor in patients with satisfactory to good control of diabetes, whereas the contribution of fasting plasma glucose increases with worsening diabetes. Postmeal thresholds for predicting good or satisfactory control of diabetes are dependent on the timing of the meals. **(Endocr Pract. 2006;12[Suppl 1]:42-46)**

Abbreviations:
AUC = area under the curve; **CGMS** = continuous glucose monitoring system; **FPF** = false-positive fraction; **HbA1c** = hemoglobin A1c; **PG** = plasma glucose; **ROC** = receiver operating characteristic

INTRODUCTION

Until recently, the exact contributions of fasting and postprandial glucose to the overall glycemic control of patients with type 2 diabetes remained largely undetermined (1). Because this issue had not been clearly resolved, both hemoglobin A1c (HbA1c) and fasting plasma glucose (PG) have been considered valid markers for overall glucose exposure and thus were routinely used to evaluate the control of diabetes (2). Recent studies, however, have suggested that a third component of the glucose triad—the postprandial glucose excursions—might have a role in the overall glycemic load and might also reflect glycemic control (3,4). A few years ago, in patients with non-insulin-treated type 2 diabetes, we found that postlunch and extended postlunch PG concentrations were better correlated with HbA1c than were fasting PG values (3). More recently, in the same type of patients, investigators reported that preprandial PG concentrations were more strongly related to HbA1c than were postprandial PG concentrations (5). The best correlation, however, was observed between HbA1c and mean daily glucose concentrations, a finding confirming that HbA1c is a function of both fasting and postprandial hyperglycemia (5,6). Despite published recommendations for achieving postprandial glucose levels of less than 180 mg/dL (7) or less than 140 mg/dL (8), two questions, at least, must be answered before postprandial glucose measurements become well recognized as indicators of diabetic control: (*1*) What are the respective contributions of fasting glucose and postprandial glucose increments to the overall glucose exposure as estimated from HbA1c (9-11)? and (*2*) Are we able to define precise timings and suitable

*This material was excerpted from the following publications: Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). *Diabetes Care*. 2003;26:881-885; and Monnier L, Colette C, Lapinski H. Global assessment for quality and safety of control in type 2 diabetic patients. *Eur J Clin Invest*. 2004;34:37-42.

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ranges for postprandial glucose values (12,13)? In the current review, we will attempt to provide appropriate responses to these two questions.

LESSONS FROM HUMAN PHYSIOLOGY: EXTENT OF POSTPRANDIAL STATES

The postprandial state, with respect to glucose, is defined as a 4-hour period that immediately follows ingestion of a meal (14). During this period, dietary carbohydrates (mainly starch and, to a lesser extent, oligosaccharides and disaccharides) are progressively hydrolyzed through several sequential enzymatic actions. The monosaccharides (primarily glucose units) that are released are absorbed by the intestine, enter the portal stream, and finally are delivered into the systemic circulation within a few minutes after eating. As a result, the PG concentration rapidly increases. Even though the glucose absorption decreases progressively with time, the overall period of absorption has approximately a 4-hour duration that corresponds to the postprandial state. The postabsorptive state consists of a 6-hour period that follows the postprandial period. During this interval, PG concentrations remain within a normal range in subjects without diabetes. The rate of removal of glucose from the circulation is compensated by the hepatic glucose output, which is mainly derived from the breakdown of the glycogen (glycogenolysis) stored during the preceding postprandial period.

The actual fasting state commences only at the end of the postabsorptive period (approximately 10 to 12 hours after the beginning of the last meal intake). During the fasting state, PG levels are maintained at a nearly normal steady state in subjects without diabetes. This stabilization is attributable to the progressive shift in glucose production from glycogenolysis to gluconeogenesis (glucose derived from lactate, alanine, and glycerol) as the duration of the fasting state is prolonged.

Therefore, in a nondiabetic person who consumes 3 meals per day at relatively fixed hours, the overall nyctohemeral period can be divided into 3 segments corresponding to fasting, postprandial, and postabsorptive states. The overall daily postprandial time (4 hours for each postmeal period) is equal to 12 hours and thus encompasses half a day: from 8 AM to 4 PM and from 7 PM (dinnertime) to 11 PM (Fig. 1) (15).

The actual fasting period is limited to only a brief time at the end of the night (from 5 AM to 8 AM). Furthermore, taking into account the overlap between the postprandial and postabsorptive periods, all the remaining segments of the day correspond to postabsorptive states: from 4 PM to 7 PM and from 11 PM to 5 AM (Fig. 1).

LESSONS FROM STUDIES OF PROLONGED GLYCEMIC PROFILES

Use of continuous glucose monitoring system (CGMS) is the best method for studying blood glucose patterns in real life over prolonged periods. Because the technology for the CGMS was not routinely available until recently (16,17), for many years we had used a 4-point diurnal glycemic profile as a surrogate (3). The rationale for this model is based on the determination of PG concentrations at 4 points: 8 AM (before breakfast), 11 AM (3 hours after breakfast), 2 PM (2 hours after lunch), and 5 PM (extended postlunch time). In these conditions, the prebreakfast PG value at 8 AM is considered to reflect an actual fasting state, the 2-hour postlunch value at 2 PM corresponds to a definite postprandial period, the 3-hour postbreakfast value is considered a compromise between a

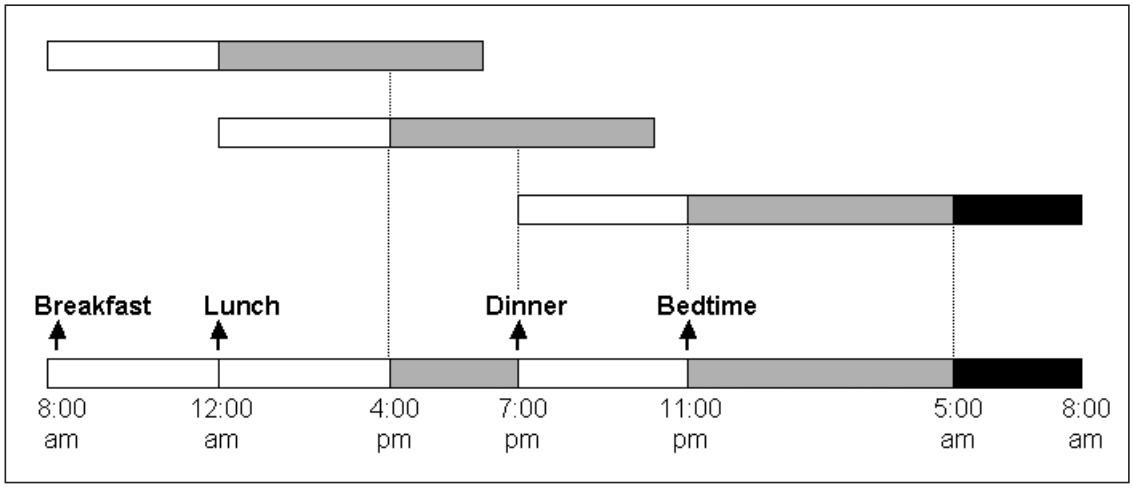

Fig. 1. Durations of postprandial (*white areas*), postabsorptive (*gray areas*), and fasting (*black area*) states. The postprandial and postabsorptive states last 4 and 6 hours, respectively; thus, the cumulative duration of postprandial states is approximately equal to 12 hours (a full half-day period) and the actual fasting state is limited to a 3-hour interval at the end of the night. Data from Monnier (15).

late postbreakfast and an early prelunch value, whereas the 5-hour postlunch value (extended postlunch time at 5 PM) is a marker of a postabsorptive period (14,15).

Contributions of Fasting and Postprandial Glucose to HbA1c in Patients With Type 2 Diabetes

We conducted a study in 290 patients with non-insulin-treated type 2 diabetes mellitus who were subclassified into 5 equal groups, stratified by quintiles of HbA1c. For that purpose, the 290 HbA1c values were ranked in increasing order, with random ranking when 2 or several HbA1c measurements were equal.

After an overnight fast, all patients were admitted at the outpatient clinic of the Department of Metabolism and were asked to eat a test breakfast at 8 AM and a test lunch at 12 AM. The energy and macronutrient contents of each test meal were standardized. As previously mentioned, 4 venous samples were collected for PG determinations at 8 AM, 11 AM, 2 PM, and 5 PM.

The diurnal PG response to meals was estimated as a whole by calculating the incremental area under the daytime PG curve from 8 AM to 5 PM. Two areas were calculated geometrically from the 4-point curve, the area below the baseline value being ignored. The first, the area under the curve (AUC) above fasting PG concentrations (AUC1), was calculated above a baseline level equal to the fasting PG value and was therefore considered a reflection of the postprandial glycemic responses to breakfast and lunch. The second area (AUC2) was calculated above a baseline level equal to 110 mg/dL (6.1 mmol/L), reflecting the increases in both fasting and postprandial PG. The baseline value of 110 mg/dL was chosen because this threshold has been defined as the upper limit of normal PG at fasting or preprandial times by the American Diabetes Association (18,19). Therefore, the difference (AUC2 − AUC1) can be considered an assessment of the increment in fasting PG values. As a result, the relative contributions of postprandial and fasting PG to the total PG increment were calculated, respectively, by using the following equations: (AUC1/AUC2) × 100 for the postprandial PG contribution and [(AUC2 − AUC1)/AUC2] × 100 for the fasting PG contribution.

As shown in Figure 2, the relative contribution of postprandial PG decreased gradually from the lowest to the highest quintile of HbA1c. In contrast, the relative contribution of fasting PG showed a gradual increase with increasing values of HbA1c.

For each relative postprandial or fasting PG contribution, analyzed individually, comparisons over quintiles of HbA1c showed significant differences first between the lowest quintile and all the following upper quintiles and second between the 2nd and the 5th quintile. Furthermore, significant differences were found in quintiles 1, 4, and 5 when relative postprandial and fasting PG contributions were compared within the same quintile. By using the MiniMed CGMS (Northridge, CA) (16) in a small subgroup of 38 patients investigated on an ambulatory basis

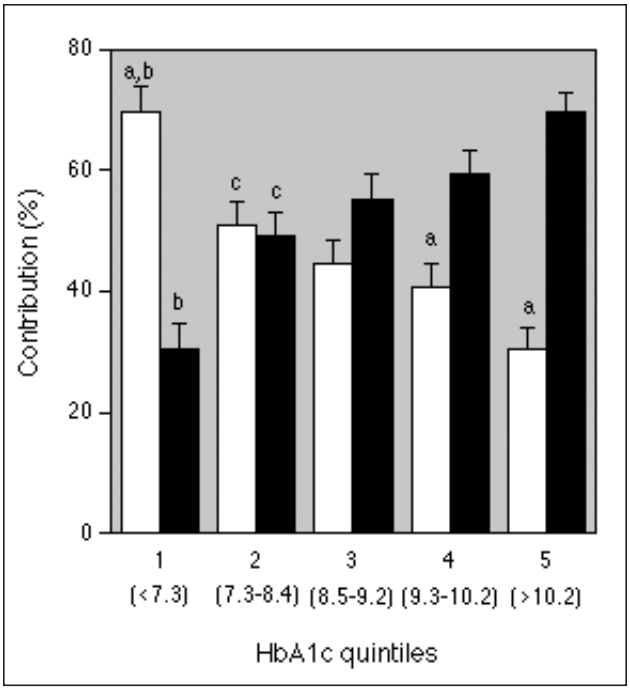

Fig. 2. Relative contributions (%) of postprandial (*white columns*) and fasting (*black columns*) hyperglycemia to the overall diurnal hyperglycemia. Variations are evident with quintiles of hemoglobin A1c (*HbA1c*) (11). Postprandial glucose makes the major contribution (70%) in the lowest quintile (HbA1c <7.3%). Fasting glucose is the main contributor in the 2 upper quintiles (HbA1c ≥9.3%). The contributions of postprandial and fasting glucose are approximately equivalent in patients with HbA1c ranging from 7.3% to 9.2%. Data from Monnier et al.

for 24 hours and by applying the aforementioned methods for the calculation of fasting and postprandial PG increments, we found that the relationship between the contribution of postprandial PG to the overall hyperglycemia and HbA1c was described by an exponential curve (Fig. 3) and that the contribution of postprandial PG became predominant (>50%) when HbA1c was <7.3% (unpublished data).

These results suggest that postprandial glycemic excursions have a major role in the metabolic dysequilibrium of patients who have mild or moderate hyperglycemia. On the contrary, fasting hyperglycemia appears as the main contributor to the overall diurnal hyperglycemia in patients with poorly controlled diabetes, and the role of postprandial glucose elevations decreases as the condition of patients with diabetes deteriorates toward poor diabetic control. This relationship was confirmed in the 38 patients investigated with the CGMS.

Thus, our results demonstrate a progressive shift in the respective contributions of fasting and postprandial hyperglycemia with progression from moderate to high hyperglycemia. The contribution of postprandial glucose excursions is predominant in patients with moderate diabetes (HbA1c <7.3%), whereas the contribution of fasting hyperglycemia increases with worsening diabetes. Such

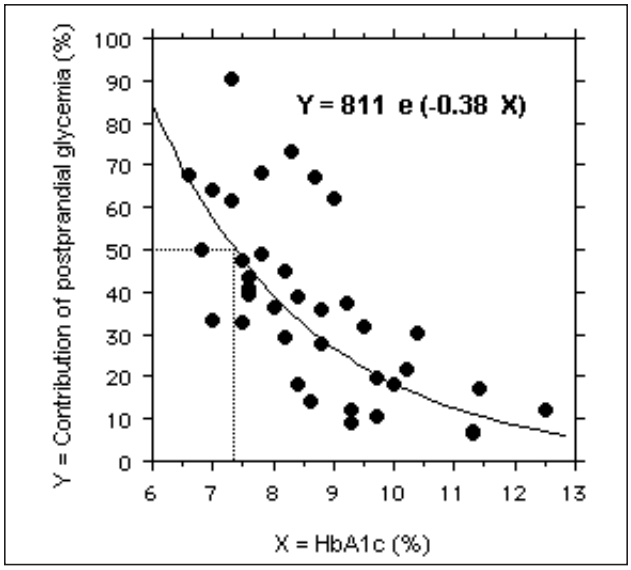

Fig. 3. Relationship between contributions of postprandial hyperglycemia to the overall hyperglycemia and hemoglobin A1c (*HbA1c*) in 38 patients with type 2 diabetes investigated with the continuous glucose monitoring system. (Some data points are superimposed on others.)

observations seem to conciliate the different results that have been reported in the literature because the shift in the respective contributions of fasting and postprandial hyperglycemia appears as a continuous spectrum from fairly to poorly controlled type 2 diabetes.

Prediction of Satisfactory Control of Diabetes by PG Values

By analyzing the 4-point diurnal glucose profiles in 480 patients with non-insulin-treated type 2 diabetes (13), we tested the performance of PG at each time point to detect a cutoff value that can define the quality of patients' control of diabetes as estimated from HbA1c levels. The tests were performed at a 7% threshold of HbA1c, a value less than this level being considered as a reference for good or satisfactory control of diabetes. Sensitivities and specificities for predicting the quality of control of diabetes were calculated at different levels of PG by using step-by-step increments (1 mmol/L for each step) of PG from a low (5 mmol/L or 90 mg/dL) to a high (13 mmol/L or 234 mg/dL) value. Sensitivity (true-positive fraction) was defined as the proportion of subjects predicted to have good or satisfactory glycemic control (HbA1c <7%) and who indeed had it. Specificity was defined as the proportion of subjects predicted not to have good or satisfactory glycemic control (HbA1c ≥7%) and who did not have it. We selected the optimal cutoff PG values by using a receiver operating characteristic (ROC) curve that we constructed by plotting sensitivity against the false-positive fraction (FPF) (1 − specificity) over the range of cut-point glucose values. The optimal cut points balancing between high sensitivity and specificity were selected at the shoulders of the ROC curves. In order to improve the clinical screening for patients with treatment success—that is, HbA1c <7%—we determined lower cutoff values characterized by specificities equal to or slightly greater than 90%—that is, FPF ≤0.10.

The results are summarized in Table 1. The cut points that were calculated from the shoulders of the ROC curves and that ensured the optimal balance between high sensitivity and high specificity were, respectively, 8 mmol/L (144 mg/dL) at 8 AM, 11 mmol/L (198 mg/dL) at 11 AM, 9 mmol/L (162 mg/dL) at 2 PM, and 7 mmol/L (126 mg/dL) at 5 PM. The best sensitivities and specificities were obtained at 11 AM, 2 PM, and 5 PM. The best cut points for predicting treatment success with a high specificity (≥90%)—that is, at a FPF threshold ≤0.10—were, respectively, 6 mmol/L (108 mg/dL) at 8 AM, 9 mmol/L (162 mg/dL) at 11 AM, 7 mmol/L (126 mg/dL) at 2 PM, and 6 mmol/L (108 mg/dL) at 5 PM.

From these results, it appears that setting peak postprandial glucose thresholds at 10 mmol/L (180 mg/dL), as suggested by the American Diabetes Association (7), could be adequate for the postbreakfast period because this value is between the two optimal PG cutoff values at 11

Table 1
Cutoff Values of Plasma Glucose for Predicting Patients With Hemoglobin Alc <7%

Time points	Optimal values (mg/dL) balancing between high sensitivity and specificity	Optimal values (mg/dL) based on specificity ≥90% for treatment success
8 AM	144	108
11 AM	198	162
2 PM	162	126
5 PM	126	108

Adapted from Monnier et al (13).

AM (162 and 198 mg/dL), but it is probably too high for the postlunch period at 2 PM, a time point at which the optimal cutoff values were 126 and 162 mg/dL, respectively (Table 1). Thus, these observations prompt the question of whether postmeal PG thresholds should be set at levels lower than 180 mg/dL. For example, other organizations have recommended that upper target limits for postmeal PG levels should be set at 140 mg/dL (8) or at 135 mg/dL (20). Such recommendations appear too stringent for postbreakfast periods but are certainly appropriate at postlunch times. Even though having worldwide uniformity for glycemic guidelines would be helpful, our results outline the difficulty with providing an average target for postprandial glucose. Despite the lack of available strong evidence-based data, it seems that achieving peak glucose levels of <180 mg/dL and <140 mg/dL during postbreakfast and postlunch periods, respectively, might be a reasonable goal.

CONCLUSION

The responses to the two questions that were raised at the beginning of this review are as follows: (*1*) Postprandial glucose makes the predominant contribution (70%) in patients with fairly good control of diabetes (HbA1c <7.3%), whereas fasting glucose is the main contributor in patients with poorly controlled diabetes. (*2*) Guidelines for establishing postmeal PG thresholds should recommend specific values for each meal. The first statement might have practical implications for implementing treatments in patients with type 2 diabetes, and the second one might be helpful for defining the objectives to facilitate achievement of optimal glycemic control.

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Declaration of Dr. Nathan Laney

Exhibit D

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AACE Consensus Statement

American Association of Clinical Endocrinology Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm — 2023 Update

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ABSTRACT

Objective: This consensus statement provides (1) visual guidance in concise graphic algorithms to assist with clinical decision-making of health care professionals in the management of persons with type 2 diabetes mellitus to improve patient care and (2) a summary of details to support the visual guidance found in each algorithm.
Methods: The American Association of Clinical Endocrinology (AACE) selected a task force of medical experts who updated the 2020 AACE Comprehensive Type 2 Diabetes Management Algorithm based on the 2022 AACE Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan and consensus of task force authors.
Results: This algorithm for management of persons with type 2 diabetes includes 11 distinct sections: (1) Principles for the Management of Type 2 Diabetes; (2) Complications-Centric Model for the Care of Persons with Overweight/Obesity; (3) Prediabetes Algorithm; (4) Atherosclerotic Cardiovascular Disease Risk Reduction Algorithm: Dyslipidemia; (5) Atherosclerotic Cardiovascular Disease Risk

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Disclaimer: This document represents the official position of the American Association of Clinical Endocrinology on the subject matter at the time of publication. Subject matter experts who participated on the task force used their judgment and experience supported by relevant scientific evidence as available. Every effort was made to achieve consensus among the task force members. Consensus statements are meant to provide guidance, but they are not to be considered prescriptive for any individual patient and cannot replace the judgment of a clinician. We encourage health care professionals to use this information in conjunction with their best clinical judgement. The presented guidance may not be appropriate in all situations. Any decision(s) by health care professionals to apply this guidance provided in this consensus statement must be made in consideration of local resources and individual patient circumstances.

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diabetes treatment
type 2 diabetes

Reduction Algorithm: Hypertension; (6) Complications-Centric Algorithm for Glycemic Control; (7) Glucose-Centric Algorithm for Glycemic Control; (8) Algorithm for Adding/Intensifying Insulin; (9) Profiles of Antihyperglycemic Medications; (10) Profiles of Weight-Loss Medications (new); and (11) Vaccine Recommendations for Persons with Diabetes Mellitus (new), which summarizes recommendations from the Advisory Committee on Immunization Practices of the U.S. Centers for Disease Control and Prevention.

Conclusions: Aligning with the 2022 AACE diabetes guideline update, this 2023 diabetes algorithm update emphasizes lifestyle modification and treatment of overweight/obesity as key pillars in the management of prediabetes and diabetes mellitus and highlights the importance of appropriate management of atherosclerotic risk factors of dyslipidemia and hypertension. One notable new theme is an emphasis on a complication-centric approach, beyond glucose levels, to frame decisions regarding first-line pharmacologic choices for the treatment of persons with diabetes. The algorithm also includes access/cost of medications as factors related to health equity to consider in clinical decision-making.

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Abbreviations

AACE, American Association of Endocrinology; ABCD, adiposity-based chronic disease; ABI, ankle-brachial index; ACE, American College of Endocrinology; ACEi, angiotensin-converting enzyme inhibitor; AGI, alpha-glucosidase inhibitor; AKI, acute kidney injury; apo B, apolipoprotein B; ARB, angiotensin II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; ATP, Adult Treatment Panel; A1C, hemoglobin A1C; BeAM, bedtime minus morning prebreakfast glucose; BG, blood glucose; BMI, body mass index; BP, blood pressure; BRC-QR, bromocriptine quick release; CAD, coronary artery disease; CCB, calcium channel blocker; CDC, U.S. Centers for Disease Control and Prevention; CGM, continuous glucose monitoring; CHF, congestive heart failure; CK, creatine kinase; CKD, chronic kidney disease; COLSVL, colesevelam; CoQ10, coenzyme q10; CPG, clinical practice guideline; CrCl, creatinine clearance; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DA, dopamine agonist; DASH, Dietary Approaches to Stop Hypertension; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; DM, diabetes mellitus; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; ER, extended release; FBG, fasting blood glucose; FDA, U.S. Food and Drug Administration; FPG, fasting plasma glucose; GERD, gastroesophageal reflux disease; GI, gastrointestinal; GIP/GLP-1 RA, glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist; GLN, glinide; GLP-1 RA, glucagon-like peptide-1 receptor agonist; GMI, glucose management indicator; GU, genitourinary; HCP, health care professional; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; HTN, hypertension; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IPE, icosapent ethyl; IV, intravenous; LADA, latent autoimmune diabetes in adults; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); LV, left ventricle; MACE, major adverse cardiovascular event; MEN2, multiple endocrine neoplasia type 2; MET, metformin; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; MTC, medullary thyroid carcinoma; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NCEP, National Cholesterol Education Program; NPH, neutral protamine Hagedorn; OA, osteoarthritis; OGTT, oral glucose tolerance test; OSA, obstructive sleep apnea; PCOS, polycystic ovary syndrome; PCSK9, proprotein convertase subtilisin/kexin type 9; PG, plasma glucose; PPG, postprandial glucose; PRAML, pramlintide; PVD, peripheral vascular disease; Rx, medical prescription; SAMS, statin-associated muscle symptoms; sCR, serum creatinine; SGLT2i, sodium glucose cotransporter 2 inhibitor; SU, sulfonylurea; TDD, total daily dose; TG, triglyceride; TIA, transient ischemic attack; TIR, time in range; TZD, thiazolidinedione; T1D, type 1 diabetes; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio; VLDL, very low-density lipoprotein

Introduction

The first iteration of the American Association of Clinical Endocrinology (AACE) algorithm for glycemic control was published in 2009 and expanded on the visual guidance provided by the American College of Endocrinology (ACE)/AACE Diabetes Road Maps to help clinicians navigate the expanded classes of approved antihyperglycemic agents.[1,2] At that time, thiazolidinediones (TZDs), alpha-glucosidase inhibitors, metformin, and sulfonylureas (SUs)/glinides were in use, with the addition of exenatide as well as dipeptidyl peptidase-4 inhibitors (DPP-4is). The next update was in 2013 with publication of the Comprehensive Type 2 Diabetes (T2D) Management Algorithm, which incorporated new sections on the management of overweight/obesity, dyslipidemia, and hypertension (HTN).[3] Revisions to this first iteration have been incorporated on a yearly basis through 2020,[4-8] and the task force is grateful for the contributions and framework provided by previous authors of the algorithm (see Acknowledgments). In 2022, the AACE published the Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan – 2022 Update,[9] which provided 170 revised or new graded recommendations accompanied by detailed, evidence-based rationales. This 2023 algorithm update builds on previous versions of the algorithm but with the incorporation of new management approaches that align with the 2022 AACE clinical practice guideline (CPG) on diabetes mellitus (DM). The algorithm is intended as a more concise document than the guideline, providing easily accessible, visual guidance for decision-making in the clinic setting. This summary is not intended to iterate all of the evidence base behind the algorithmic pathways, as this is detailed in the 2022 AACE DM CPG update.[9] Instead, the objective of this summary is to provide a written guide or "roadmap" through the graphic depictions of the algorithm contents.

The process for updating the algorithm involved multiple meetings of task force members/authors between January 2022 and November 2022. Smaller groups focused on specific algorithm subsections, which were then brought to the complete task force for discussion and peer review. It was intentional that a proportion of algorithm task force members overlapped with the diabetes CPG task force to ensure continuity and alignment with the 2022 published guideline recommendations. In this 2023 algorithm, there continues to be an emphasis on lifestyle modification and treatment of overweight/obesity as key pillars of the management of prediabetes and DM. In addition, the importance of appropriate management of the atherosclerotic risk factors of dyslipidemia and HTN is highlighted. One notable new theme is an obvious emphasis on a complication-centric approach, beyond glucose levels, to frame decisions regarding first-line pharmacologic choices for the treatment of persons with DM, as recommended in the 2022 AACE DM CPG update[9] and by other organizations.[10,11] However, the task force members/authors acknowledge that health care disparities and lack of access to newer medications remain a significant barrier for some persons with DM.

The algorithm is divided into discrete graphic sections that outline the principles for management of T2D (Algorithm Fig. 1) and guide management of adiposity-based chronic disease (ABCD) (Algorithm Fig. 2), prediabetes (Algorithm Fig. 3), and

atherosclerotic risk factors of dyslipidemia (Algorithm Fig. 4) and HTN (Algorithm Fig. 5). In addition, the algorithms for antihyperglycemic agents include both complication-centric (Algorithm Fig. 6) and glucose-centric (Algorithm Fig. 7) approaches, and there is direction for insulin initiation and titration (Algorithm Fig. 8). Convenient tables summarizing the benefits and risks of antihyperglycemic medications (updated) (Algorithm Fig. 9) and weight-loss pharmacotherapy (new) (Algorithm Fig. 10) are provided. A new table of immunization guidance is provided that summarizes recommendations from the Advisory Committee on Immunization Practices of the U.S. Centers for Disease Control and Prevention (CDC) (Algorithm Fig. 11).

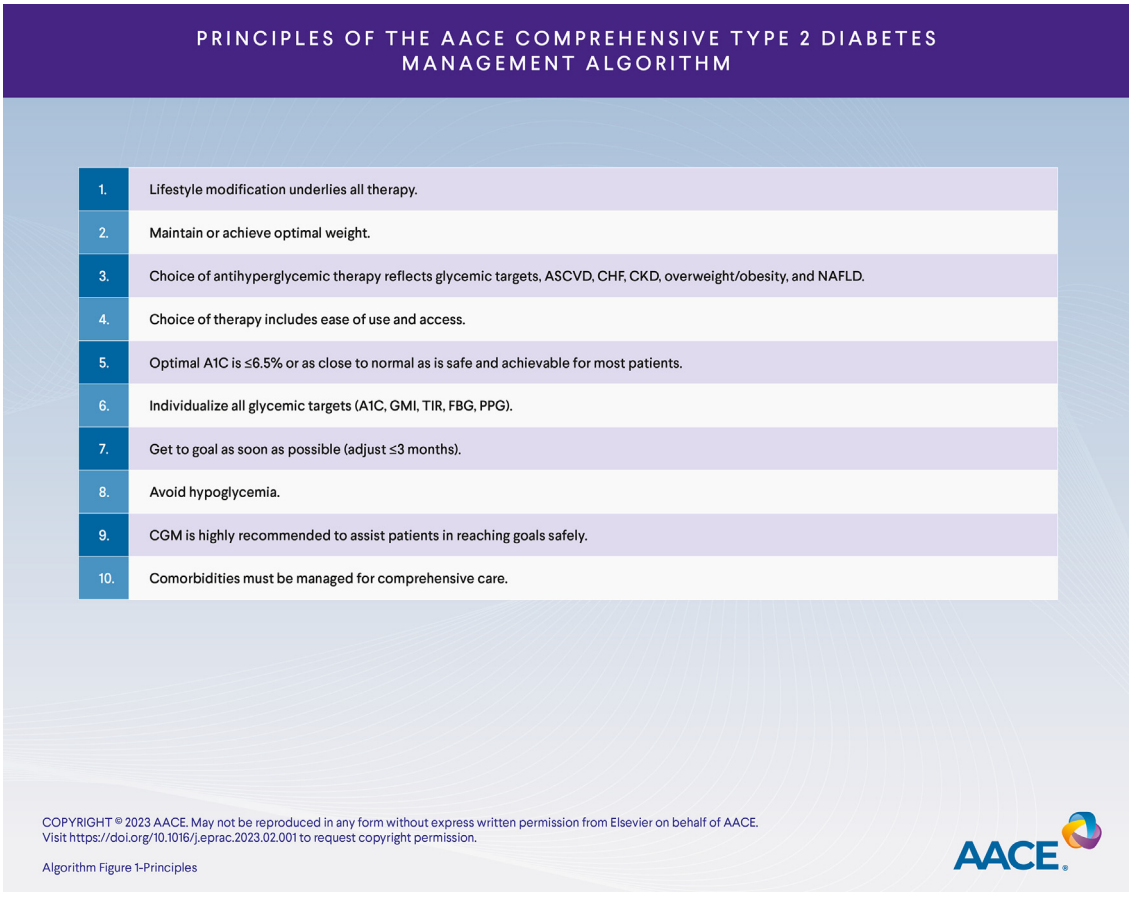
Principles of the AACE Comprehensive T2D Management Algorithm

Following are the principles of this algorithm for the management of T2D (Algorithm Fig. 1).

Lifestyle modification underlies all therapy. Lifestyle modification includes exercise, healthy dietary changes, smoking cessation, and reduced alcohol intake. Additional aspects of lifestyle modification include assessment and management of sleep disorders and depression. The Complications-Centric Model for the Care of Persons with Overweight/Obesity (Algorithm Fig. 2) emphasizes the underlying components of a comprehensive assessment for staging overweight/obesity in the context of ABCD and provides guidance on proposed interventions to improve the overall health of persons with overweight/obesity.

Maintain or achieve optimal weight. Excess weight results in insulin resistance and increases the risk for prediabetes and T2D, but also leads to multiple complications beyond dysglycemia that comprise ABCD and lead to excess morbidity and mortality. Lifestyle intervention to achieve weight loss is a key pillar of the comprehensive treatment of persons with prediabetes to decrease progression to T2D. Weight loss also improves many of the cardiometabolic and biomechanical components of ABCD, including increased glycemia, dyslipidemia, elevated blood pressure (BP), cardiovascular disease (CVD), nonalcoholic fatty liver disease (NAFLD), sleep apnea, and osteoarthritis, albeit with varied thresholds ranging from >5% to >15% of body weight.

Choice of antihyperglycemic therapy reflects glycemic targets, atherosclerotic cardiovascular disease (ASCVD), congestive heart failure (CHF), chronic kidney disease (CKD), overweight/obesity, and NAFLD. Although glycemic control has an essential role in the prevention and decreased progression of T2D complications, there is evidence for the positive impact of individual pharmacotherapies on outcomes of comorbidities beyond glycemic control. Clinicians should use the coexistence of these frequently associated conditions to select the antihyperglycemic therapy or therapies with the most potential for improved overall outcomes. The 2022 AACE CPG update on a DM comprehensive care plan[9] recommends that "if there is established or high risk for ASCVD, heart failure [HF], and/or CKD, clinicians should prescribe a glucagon-like peptide-1 receptor agonist (GLP-1 RA) or a sodium glucose cotransporter 2 inhibitor (SGLT2i) with proven efficacy for the specific condition(s)" independent of glycemic control.[9] Additional considerations could include the choice of a medication with potential benefit for stroke



Algorithm Fig. 1. Principles of the AACE Comprehensive Type 2 Diabetes Management Algorithm. *AACE* = American Association of Endocrinology.

or NAFLD (eg, pioglitazone). This important paradigm shift was the impetus for the updated Complications-Centric Algorithm for Glycemic Control (Algorithm Fig. 6). The Profiles of Antihyperglycemic Medications table (Algorithm Fig. 9) also summarizes key aspects of the benefits and risks of available pharmacotherapies from this perspective.

Choice of therapy includes ease of use and access. The armamentarium of antihyperglycemic agents has expanded over the past 2 decades beyond the insulin secretagogues (SUs/glinides), TZDs, and metformin. Large prospective clinical trials have confirmed the efficacy of new medical therapies for glycemic control but also revealed a positive impact on progression of ASCVD, CHF, and diabetic kidney disease (DKD) or CKD in those with DM. The evolution of basal and rapid-acting analog insulins has also led to improvements in predictability of glucose response with decreased hypoglycemia. Ideally, decision-making regarding prescription of antihyperglycemic agents and insulin analogs should be based on what is most likely to benefit the patient, balanced with the risks and potential side effects. However, barriers to access including availability, cost, insurance coverage, and formularies need to be considered, and this is acknowledged in the Glucose-Centric Algorithm for Glycemic Control (Algorithm Fig. 7) and the table outlining the Profiles of Weight-Loss Medications (Algorithm Fig. 10).

Optimal hemoglobin A1c (A1C) is ≤6.5% or as close to normal as is safe and achievable for most patients. For most patients, an A1C of ≤6.5% should be targeted.[9] Achieving this A1C goal may require targeting fasting plasma glucose (FPG) to <110 mg/dL and 2-hour postprandial glucose (PPG) to <140 mg/dL.[9] The impact of tight glycemic control for the prevention and/or decreased progression of microvascular and microangiopathic complications of T2D is well established.[12-14] Although there are epidemiologic data supporting an association of A1C and CVD/all-cause mortality on a continuum,[15] early clinical trial evidence did not directly support that there was mitigation of negative macrovascular disease outcomes with intensive glucose lowering and there was an association with negative CVD outcomes with hypoglycemic events.[16] Pharmacologic therapies that have a lower risk of hypoglycemia and have proven efficacy in cardiovascular outcomes trials (CVOTs), particularly GLP-1 RA and SGLT2i, may allow for stricter glycemic control. However, the key word is "safe" with consideration of patient-specific characteristics that would recommend a less stringent A1C target (eg, 7%-8%), including the following[9,13,14,17]:

- Limited life expectancy
- History of severe hypoglycemia
- Hypoglycemia unawareness
- Advanced renal disease
- Other severe comorbid conditions with a high risk for CVD events
- Long T2D disease duration with difficulty to attain an A1C goal
- Prohibitive cognitive and/or psychological status

Individualize all glycemic targets (A1C, glucose management indicator [GMI], time in range [TIR], fasting blood glucose [FBG], and PPG). A1C is a convenient measurement in the clinical setting that is widely used to assess glycemic control and should be measured every 3 months when not at goal and a minimum of twice per year in persons at goal. A1C also has limitations and can be imprecise in some populations, including people with altered red blood cell lifespan, hemoglobinopathies, CKD, and some racial backgrounds. In addition, other glucose parameters have been shown to correlate with outcomes, such as TIR, as generated by continuous glucose monitoring (CGM). It is recommended that TIR (glucose range 70-180 mg/dL) be >70%, combined with minimal time below range (4% for <70 mg/dL and <1% for <54 mg/dL).[18-20] CGM also can generate the GMI, which is of utility as a surrogate for an A1C.[21] When available, these alternative glucose parameters should be incorporated for monitoring and adjustment of therapy.

Get to goal as soon as possible (adjust ≤3 months). Therapeutic inertia—failure of clinicians to escalate therapy or initiate new therapies—is a major threat to achieving improved health outcomes in persons with overweight/obesity, prediabetes, and T2D.[22,23] Clinicians should continuously evaluate treatment goals at each visit, ideally ≤3 months, and consider making therapeutic changes to more rapidly achieve targets for glucose, lipids, and BP.

Avoid hypoglycemia. Hypoglycemia, defined as blood glucose (BG) <70 mg/dL, is associated with an increased risk for adverse outcomes including mortality.[14,16] Therefore, the optimal treatment for T2D should take into account the risk of hypoglycemia. Antihyperglycemic agents and A1C goals should be chosen to avoid hypoglycemia.[9] Agents such as DPP-4i, GLP-1 RA, and SGLT2i have a lower risk of hypoglycemia compared with that of insulin and SUs and are preferred to achieve optimal glycemic goals.

CGM is highly recommended to assist persons with diabetes in reaching goals safely. CGM has provided a major advance in the treatment of persons with all forms of DM. For those persons with T2D, and on basal insulin, clinical trials have shown that CGM is associated with increased TIR, improved A1C, and decreased hypoglycemia, including severe hypoglycemic events.[24-26] The 2021 AACE CPG: The Use of Advanced Technology in the Management of Persons With Diabetes Mellitus[20] discusses the different avenues for application of CGM including for all persons with DM on multiple-dose insulin (≥3 injections/day) or an insulin pump as well as those who have frequent or severe hypoglycemia, nocturnal hypoglycemia, or hypoglycemia unawareness.[20] Real-time CGM or intermittently scanned CGM including alarms or alerts is recommended, particularly for persons with hypoglycemia who would benefit from these warnings.[20] However, as an alternative, intermittently scanned CGM may also provide valuable information in persons who are newly diagnosed with T2D and/or at low risk for hypoglycemia. Diagnostic (professional use) CGM can be used for new T2D diagnosis and for those with hypoglycemia but without access to personal CGM and can be educational for the person with T2D (eg, effects on behaviors including diet and exercise) and also aid the clinician in investigating avenues to improve glycemic control with medical therapies.

Comorbidities must be managed for comprehensive care. Hypertension and dyslipidemia are comorbidities often associated with T2D that further increase the risk for complications including CVD, chronic kidney failure, and retinopathy. Improvements in glycemic control must be accompanied by treatment of concomitant dyslipidemia and HTN for optimized outcomes.

Complications-Centric Model for the Care of Persons with Overweight/Obesity (ABCD)

Lifestyle intervention is the essential foundation for the management of persons with prediabetes and T2D. Although the phrase lifestyle intervention is often thought of in relation to nutrition, weight loss, and exercise, a comprehensive plan also should include assessment, counseling, and intervention of sleep hygiene and sleep disorders, promotion of healthy habits beyond diet, including moderation of alcohol intake and cessation of smoking, and

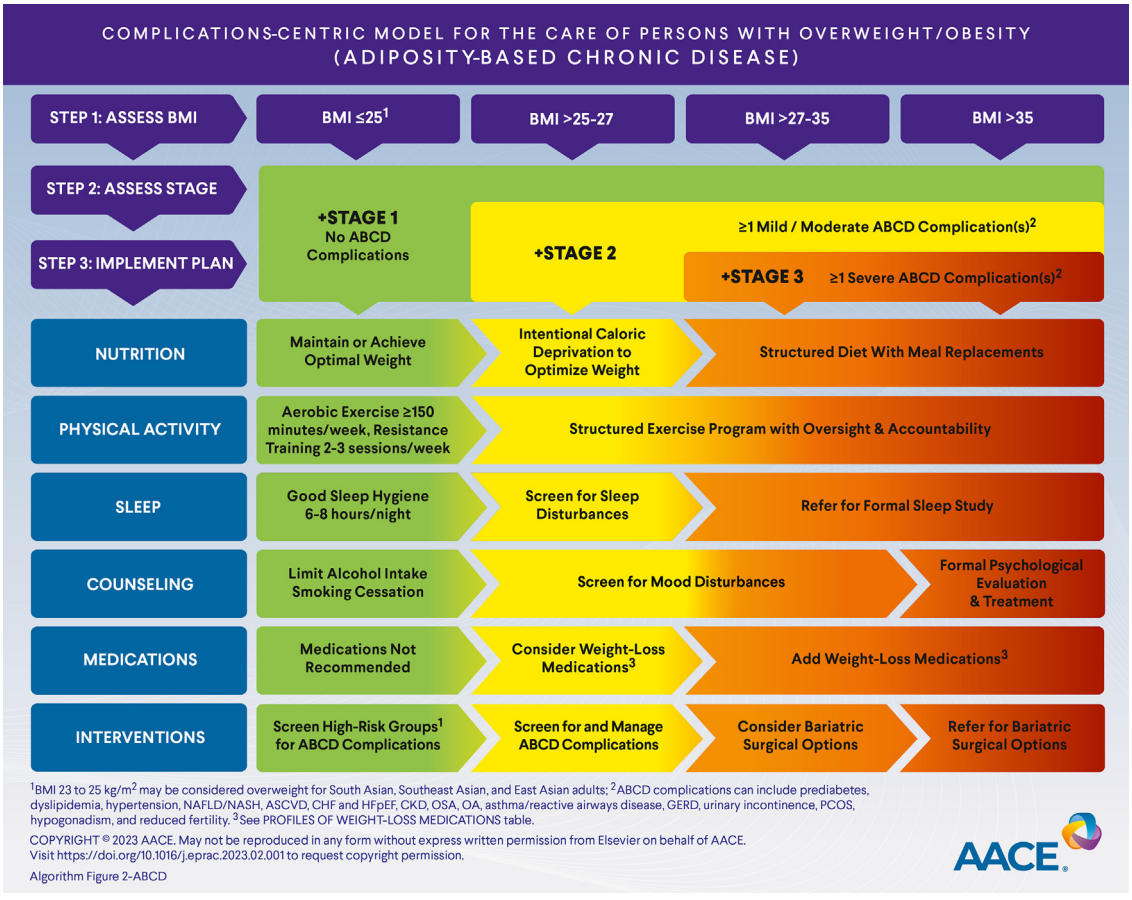
monitoring for mood disturbances that can impact success in incorporating durable change (Algorithm Fig. 2). In addition, with advances in weight management, clinicians must consider and incorporate pharmacologic and surgical interventions, including bariatric procedures, as indicated based on a patient-centered assessment.

In 2017, AACE published a position statement on the diagnostic term ABCD.[27] The objective of the document was to embrace the importance of viewing overweight/obesity as a chronic disease and to emphasize the importance of assessing persons with overweight/obesity for the existence of or risk for associated complications, beyond body mass index (BMI), including the following:

- Prediabetes
- Dyslipidemia
- HTN
- NAFLD
- ASCVD
- CHF with reduced ejection fraction
- Heart failure with preserved ejection fraction
- CKD
- Obstructive sleep apnea (OSA)
- Osteoarthritis
- Gastroesophageal reflux disease
- Urinary incontinence
- Hypogonadism
- Polycystic ovary syndrome
- Reduced fertility

Determination of the presence of ABCD complications allows for staging of persons with overweight/obesity, which can impact the approach to interventions.

- Step 1 is to calculate BMI with the understanding of the published thresholds of what is overweight ($\geq$25 kg/m^2) or obese ($\geq$30 kg/m^2), noting that lower thresholds for overweight/obesity may apply for South, East, and Southeast Asian persons ($\geq$23.5 kg/m^2 for overweight and $\geq$25 kg/m^2 for obese).
- Step 2 provides further classification of the stage of overweight/obesity by assessing for the presence of ABCD complications, as listed above. Previous AACE guidance documents have utilized stages 0, 1, and 2 for ABCD severity, but a recent AACE consensus statement centered on obesity stigma and weight bias[28] recommends a shift to stages 1, 2, and 3 to avoid inviting treatment inertia at stage 0, where primary prevention must still be in place. The revised staging also incorporates weight bias/stigma and mental health as key components of ABCD that should be addressed in addition to the cardiometabolic and biomechanical complications which can be improved by treatment of obesity. Patients may have an elevated BMI but lack physical complications (Stage 1). Alternatively, patients without a substantially elevated BMI may already have manifested components of ABCD, and action is required. Stage 2 obesity includes patients who have $\geq$1 mild-to-moderate obesity complications. The highest stage 3 includes patients with multiple and/or more severe complications and applies to patients already diagnosed with T2D as a severe ABCD complication. The combination of BMI with stage is helpful to inform the clinician of needed interventions.



Algorithm Fig. 2. Complications-Centric Model for the Care of Persons with Overweight/Obesity (Adiposity-Based Chronic Disease).

- Step 3 requires implementation of a comprehensive lifestyle modification plan for the patient that encompasses all aspects of the health of the patient and includes nutrition, physical activity, sleep, counseling, medications, and interventions.

Nutrition

For persons above optimal weight, caloric deprivation of 500 to 1000 kcal daily energy deficit in the context of a healthy diet should be initiated to promote weight loss. In the context of ABCD, a minimum threshold of >5% to ≥10% is needed to have a positive impact on glycemia, BP, and lipids. Weight loss of ≥15% may help to mitigate other ABCD complications such as OSA and nonalcoholic steatohepatitis. The selection of a diet should be personalized, but choices include Mediterranean, low-fat, low-carbohydrate, very low–carbohydrate, vegetarian, vegan, and Dietary Approaches to Stop Hypertension (DASH) diets. Structured diets with prepared meals or liquid meal replacements may increase adherence to the calorie limitations. Adherence also may be improved with weight-loss programs or apps that encourage external accountability.

Physical Activity

A plan for physical activity should take into account any physical limitations and disabilities, some of which may derive from overweight/obesity itself. Ideally, the amount of physical activity should progress to include moderate, aerobic exercise ≥150 minutes per week divided into 3 to 5 sessions, combined with 2 to 3 sessions of resistance training per week.

Sleep

Reduced sleep duration is associated with adverse outcomes, including obesity, T2D, HTN, CVD, and mortality. In adults >18 years of age, 6 to 8 hours of sleep per night is recommended. OSA is highly prevalent in persons with T2D and/or obesity. Clinicians should incorporate routine screening for sleep disorders either clinically, with questions about symptoms of OSA (eg, snoring, choking, daytime sleepiness, fatigue, and nonrestorative sleep), or using a formal screening tool, such as the STOP-Bang questionnaire.[29] Testing with home oximetry or a formal sleep study may be indicated. Persons who meet criteria for OSA should be referred for appropriate diagnostic studies and intervention, such as with prescription of a continuous positive airway pressure device.

Counseling

Depression and diabetes distress are prevalent in persons with T2D and can result in nonadherence to diet, exercise, and medication regimens. Potential formal screening tools include the WHO Wellbeing Index,[30] the Patient Health Questionaire-9,[31] or the Beck Depression Inventory III.[32] Appropriate referral for cognitive behavioral therapy or medical intervention should be considered when depression is present.

Medications

Weight-loss medications should be considered, in combination with a reduced-calorie diet, to achieve and sustain weight-loss goals in patients with BMI 27 kg/m^2 to 29.9 kg/m^2 with T2D or ≥1 ABCD complication and all persons with a BMI >30 kg/m^2. See also Profiles of Weight-Loss Medications (Algorithm Fig. 10). Caution is required for persons >65 years of age with T2D and ABCD; assessment of bone health and sarcopenia is important.

Interventions

Metabolic (bariatric) procedures are an effective option for persons with T2D and ABCD and should be considered in persons with a BMI of 30 kg/m^2 to 34.9 kg/m^2 with uncontrolled DM in spite of lifestyle and medical therapy and BMI >35 kg/m^2 and ≥1 ABCD complications, including prediabetes, that can be remedied with weight loss.

Prediabetes Algorithm

Prediabetes is a cardiometabolic state resulting from failure of the pancreas to compensate for insulin resistance most often caused by overweight/obesity. Prediabetes continues to be defined by the presence of impaired fasting glucose (IFG) (100-125 mg/dL) and/or impaired glucose tolerance (IGT) (140-199 mg/dL) at 2 hours of an oral glucose tolerance test (OGTT) with ingestion of 75 g of glucose.[9] A1C values of 5.7% to 6.4% may indicate chronic hyperglycemia and the existence of prediabetes, but an OGTT should be used to confirm diagnosis (Algorithm Fig. 3).[9] Metabolic syndrome using National Cholesterol Education Program Adult Treatment Panel III criteria is considered a prediabetes equivalent, so that persons diagnosed with metabolic syndrome are at high risk for developing DM.[33,34]

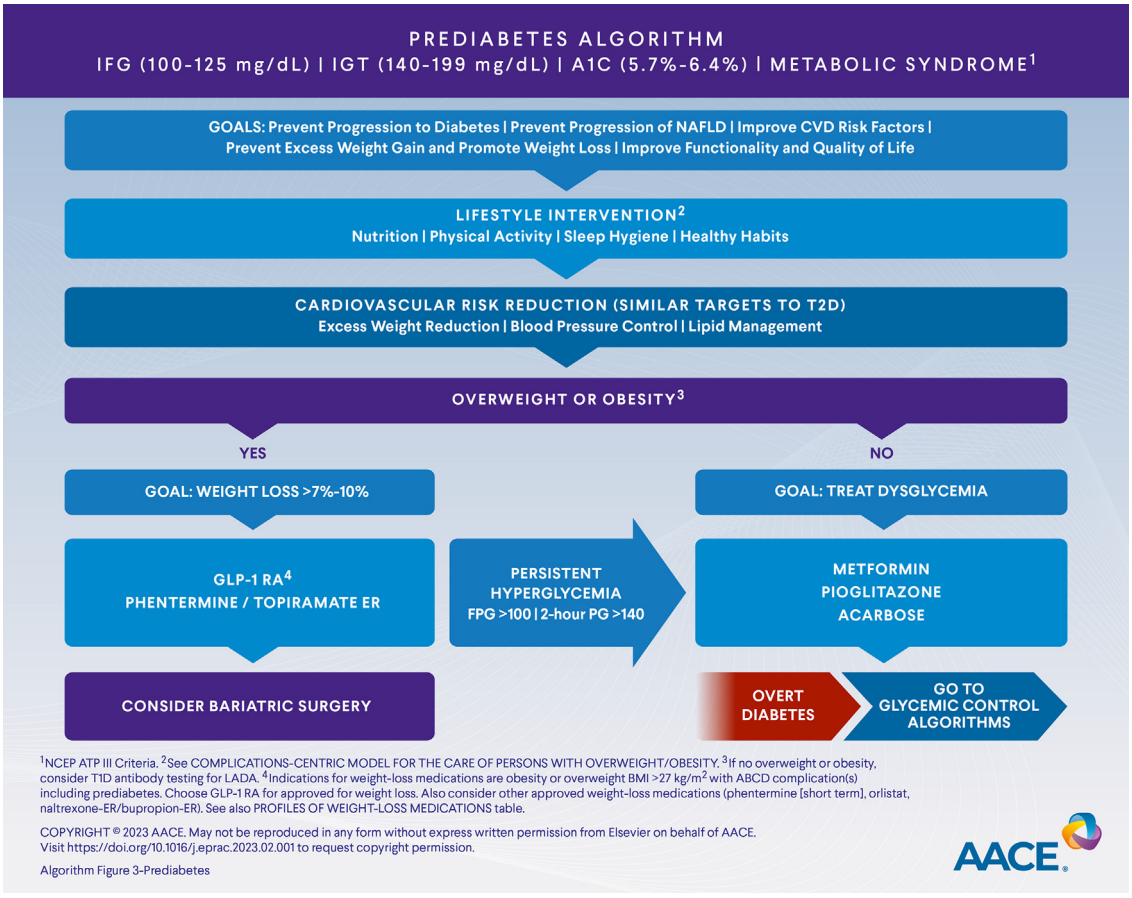
The prediabetes algorithm includes medical nutrition therapy (with reduction and modification of caloric intake to achieve weight loss in those who are overweight or obese), appropriately prescribed physical activity, avoidance of tobacco products, and adequate sleep quantity and quality. Additional topics commonly taught in DM self-management education and support programs outline principles of glycemia treatment options; BG monitoring; insulin dosage adjustments; acute complications of DM; and prevention, recognition, and treatment of hypoglycemia.

There are ample data that prediabetes confers an increased risk for progression to T2D and ASCVD.[35-37] Therefore, in addition to prevention of progression to overt T2D, other key goals in the treatment of prediabetes and metabolic syndrome should include weight loss and/or prevention of weight gain, mitigation of the CVD risk factors HTN and dyslipidemia, and prevention of progression of NAFLD.

Although ABCD is a risk factor for prediabetes and subsequent DM, these are distinct entities that can occur independently, so the presence of prediabetes should alert the clinician to assess for additional complications of ABCD to guide clinical decision-making and therapeutic choices (see section on Complications-Centric Model for the Care of Persons with Overweight/Obesity [Algorithm Fig. 2]). If overweight/obesity and/or ABCD is absent, the possibility of other etiologies of elevated glucose beyond insulin resistance should be considered, including the potential for latent autoimmune diabetes in adults, which would merit screening for type 1 diabetes antibodies.

Weight loss is highly effective in preventing the progression of prediabetes to T2D. Lifestyle intervention to promote weight loss is essential, but the addition of weight-loss pharmacotherapies or bariatric procedures may need to be considered depending on patient-specific characteristics, including stage of obesity (see section on Complications-Centric Model for the Care of Persons with Overweight/Obesity [Algorithm Fig. 2]). Data have shown that weight reduction of 7% to 10% in persons with overweight/obesity is an important threshold, as this degree of weight loss has been demonstrated to be highly effective in preventing progression to T2D.[38,39]

Lifestyle interventions that have been shown to reduce progression to T2D[38,40,41] and decrease the risk of CVD should be a part of the strategy for all individuals with prediabetes independent of



Algorithm Fig. 3. Prediabetes Algorithm.

weight status. This should involve a healthy meal plan, such as the Mediterranean[42,43] or DASH diet.[44,45] Other diets including low-fat, low-carbohydrate, vegetarian, and vegan diets can also be considered. Regular physical activity through a combination of aerobic and resistance exercises to achieve ≥150 minutes per week of moderately intense aerobic exercise over 3 to 5 sessions and resistance exercise consisting of single-set repetitions targeting the major muscle groups 2 to 3 times per week should be added.[46-50] Nonexercise active leisure activities should be encouraged to reduce sedentary behavior. Behavioral health should be incorporated for optimal outcomes.

Pharmacotherapy for weight loss should be considered when lifestyle measures alone are inadequate to achieve goal weight loss in those with ABCD. The U.S. Food and Drug Administration (FDA)–approved agents shown to have efficacy to achieve weight-loss goals that impact prediabetes include semaglutide 2.4 mg, liraglutide 3 mg, and phentermine/topiramate-extended release (ER).[39,51-54] Tirzepatide is a weekly dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA that has been shown to cause substantial weight loss in persons with overweight/obesity but has not received regulatory approval for this indication at this time.[55] Other weight-loss medications approved by the FDA (naltrexone-ER/bupropion-ER, short-term phentermine, or orlistat) could be considered if the above medications are not tolerated or are not accessible to the patient (see Algorithm Fig. 10, Profiles of Weight-Loss Medications).

A nonpharmacologic option for persons with a BMI >25 mg/kg^2 is hydrogel capsules, containing cellulose and citric acid, taken before meals, which achieved ≥5% weight loss in a majority of participants in placebo-controlled trials, including persons with prediabetes and T2D.[56] Additional devices that have regulatory approval by the FDA for the treatment of obesity, but not T2D, include intragastric balloons, transpyloric shuttle, and gastric aspiration.[57-59] Bariatric procedures are more effective than lifestyle interventions and medications in weight reduction and should be considered in those with prediabetes with a BMI >35 kg/m^2.[60]

For patients with prediabetes who do not meet the BMI criteria of overweight/obesity but who still require intervention for prediabetes after implementation of lifestyle modifications, pharmacologic agents with evidence of efficacy in preventing progression to T2D should be considered. Although there are currently no drugs approved by the FDA with an indication to prevent the progression of prediabetes to T2D, metformin, pioglitazone, and acarbose have evidence of efficacy in clinical trials.[38,61,62]

Despite the interventions discussed above, persons with prediabetes are at high risk to progress to T2D. Clinicians are directed to sections on the Complications-Centric Algorithm for Glycemic Control (Algorithm Fig. 6) and the Glucose-Centric Algorithm for Glycemic Control (Algorithm Fig. 7) for further guidance on antihyperglycemic pharmacotherapy.

ASCVD Risk Reduction Algorithm: Dyslipidemia

Treatment of dyslipidemia (Algorithm Fig. 4) is an essential component of DM and prediabetes management. The combined effects of insulin deficiency, insulin resistance, and hyperglycemia cause multiple disruptions in lipoprotein metabolism.[63-68] This leads to an especially atherogenic state characterized by increased levels of apolipoprotein B (apo B)–containing particles, including

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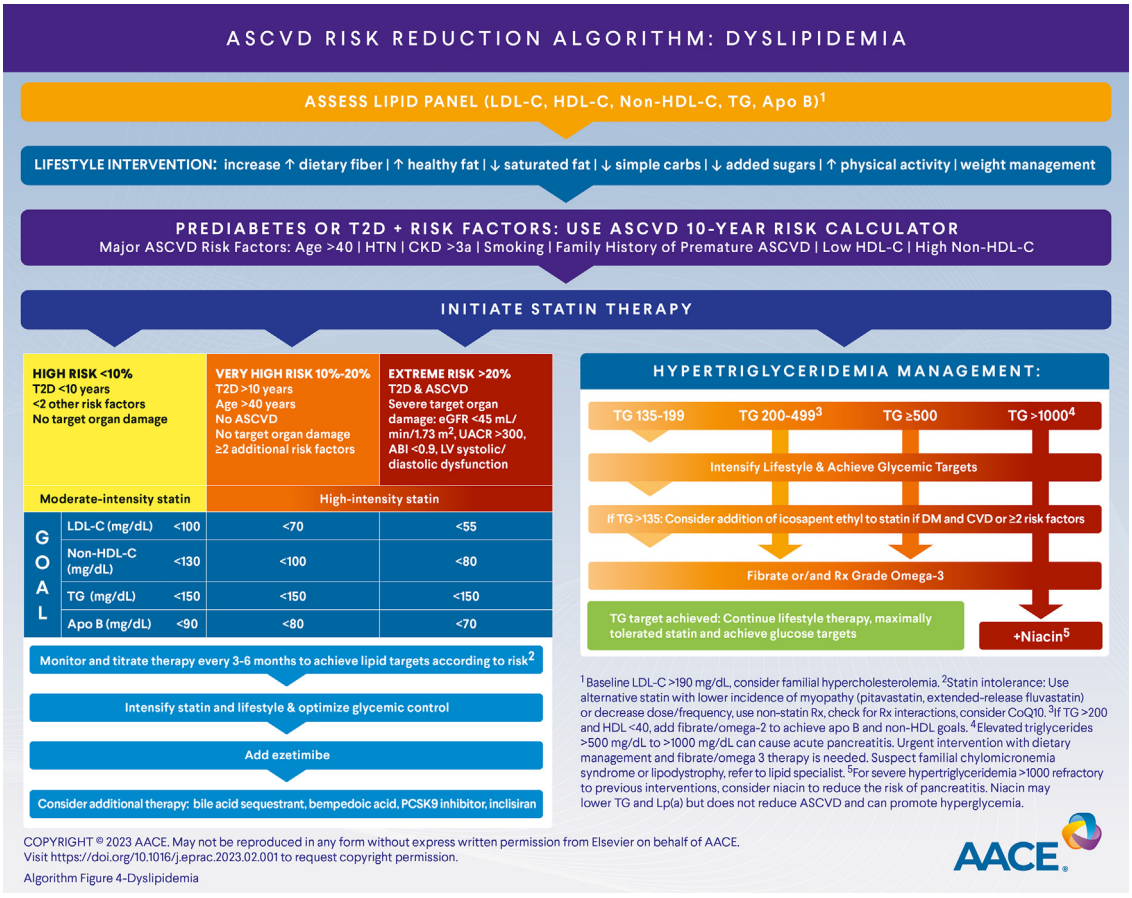


Algorithm Fig. 4. Atherosclerotic Cardiovascular Disease Risk Reduction Algorithm: Dyslipidemia.

triglyceride (TG)-rich very low-density lipoprotein (VLDL), intermediate-density lipoprotein, and remnant particles resulting in low levels of high-density lipoprotein-cholesterol (HDL-C) and increased levels of small, dense, low-density lipoprotein cholesterol (LDL-C).[69-71] Additional detailed guidance for management of dyslipidemia is available in the 2017 AACE Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease[72] and the 2020 Algorithm on the Management of Dyslipidemia and Prevention of Cardiovascular Disease.[73]

Step 1. Assess Lipid Panel at First Visit or at Diagnosis

All adult persons with prediabetes or T2D should be screened with a lipid panel at diagnosis and annually to assess ASCVD risk. The standard lipid panel includes total cholesterol, TG levels, HDL-C, and LDL-C. Fasting lipid panels are not necessary for therapeutic decisions, and nonfasting lipid panels may aid patient compliance with timely blood draws.[74]

Secondary causes of dyslipidemia should be excluded. There may be a contributing underlying medical condition or medication, and intervention—if medically appropriate—may improve or resolve the abnormalities. Evaluation should begin with a medical, family, and nutrition history. Review all medications, over-the-counter medications, and supplements. Laboratory testing for thyroid, renal, and liver function may expose secondary causes. Persons with baseline LDL-C >190 mg/dL should be investigated for familial hypercholesterolemia. With extremely high TG levels, a diagnosis of familial chylomicronemia syndrome is a possibility. With both disorders, referral to a lipid specialist for assessment and management is recommended.

Additional secondary causes of dyslipidemia include medical conditions such as overweight or obesity, hyperglycemia, hypothyroidism, pregnancy, stage ≥3 CKD (particularly with albuminuria), nephrotic syndrome, cholestatic disease, lipodystrophy, paraproteinemia (eg, dysgammaglobulinemia, multiple myeloma), and chronic inflammatory conditions (eg, rheumatoid arthritis, systemic lupus erythematosus).

Medications that can cause or exacerbate dyslipidemia include oral estrogens and progestins, anabolic steroids, selective estrogen receptor modulators, highly active antiretroviral therapy such as protease inhibitors for the treatment of HIV, immunosuppressive medications (eg, cyclosporine, mammalian target of rapamycin kinase inhibitor), glucocorticoids, retinoids, interferon, taxol derivatives, L-asparaginase, cyclophosphamide, atypical antipsychotic agents, beta-blockers, and thiazide diuretics. Although bile acid sequestrants can reduce cholesterol, these agents may also increase TG levels and should be used cautiously in patients with elevated TG levels. In addition, TG levels and LDL-C levels may change as glycemic control improves, so the impact of initiation of antihyperglycemic therapy must be taken into account when considering adding or titrating antilipid therapies.

Ancillary apo B measurement is recommended to assess for residual ASCVD risk from remnant and small dense lipoproteins not revealed with a standard lipid panel.[75-78] Apo B is superior for predication of ASCVD risk over LDL-C and is more accurate than non-HDL-C.[79,80] There are additional biomarkers, including high sensitivity C-reactive protein,[81] lipoprotein(a) (Lp[a]),[82] coronary artery calcium score,[83-86] and ankle-brachial index (ABI)[87] that are independently associated with increased risk of ASCVD events, and these may be helpful when the lipid management goal is unclear.[88]

When the decision to initiate or intensify treatment is uncertain, such as for a person with prediabetes and without previous CV events, a risk calculator can also be helpful to estimate 10-year risk for ASCVD (Table 1).

Step 2. Initiate Lifestyle Intervention

The most common secondary cause of dyslipidemia is a diet high in carbohydrates and/or simple sugars combined with a sedentary lifestyle. Excessive alcohol consumption also contributes to dyslipidemia, particularly hypertriglyceridemia; minimization of alcohol consumption should be encouraged. Persons with dyslipidemia should be provided with tools to promote weight loss with caloric deprivation if overweight/obese. Loss of body weight ≥5% improves TG levels and continued further decline in TG levels is noted even at >15% weight loss.[89] Counseling on lifestyle interventions is essential and should include advice on a healthful diet (whole-foods, plant-based, Mediterranean, and DASH diets); avoidance of processed foods, saturated fat, simple carbohydrates, white starches, and added sugars; and increased intake of dietary fiber (30-40 g per day) and lean proteins (eg, fish, lean meat, and skinless poultry).[73] Exercise regimens should include a minimum of 150 minutes per week of moderate-intensity activity divided into 3 to 5 sessions per week, along with ≥2 resistance training sessions per week.[73]

Step 3. Determine Patient-Specific Lipid Targets

Treatment targets are based on the duration of T2D and the presence of traditional ASCVD risk factors, including advancing age, HTN, CKD stage ≥3, smoking, family history of premature ASCVD in males <55 years of age and females <65 years of age, low HDL-C, or high non–HDL-C. Assessment of the patient's risk category helps to determine lipid treatment targets and direct appropriate lipid-lowering therapy. Patients with prediabetes or T2D can be classified to set goals of therapy as follows:

- High risk (<10% 10-year risk): T2D duration <10 years and <2 additional traditional ASCVD risk factors with no target organ damage
  - o Goal: LDL-C <100 mg/dL, apo B <90 mg/dL, and non–HDL-C <130 mg/dL
- Very high risk (10%-20% 10-year risk): T2D >10 years with ≥2 traditional ASCVD risk factors and no target organ damage
  - o Goal: LDL-C <70 mg/dL, apo B <80 mg/dL, and non–HDL-C <100 mg/dL
- Extreme risk (>20% 10-year risk): T2D or prediabetes plus established ASCVD or target organ damage (left ventricular [LV] systolic or diastolic dysfunction, estimated glomerular filtration rate [eGFR] <45 mL/min/1.73 m^2, or ABI <0.9)
  - o Goal: LDL-C <55 mg/dL, apo B <70 mg/dL, and non–HDL-C <90 mg/dL

Step 4. Initiate a Statin as First-Line Therapy

Unless contraindicated, a statin should be used as the first-line therapy for dyslipidemia in persons with T2D. High-risk patients (T2D with <10% 10-year risk) should be started on moderate-intensity statin therapy, which results in an LDL-C reduction in the range of 30% to 40% (Table 2). For patients with prediabetes, the benefits of statin therapy should be weighed in the context of their ASCVD risk score and the minor risk of progression to T2D with statin use.[90,91] For persons at very high risk (10%-20% 10-year risk) and extreme risk (>20% 10-year risk), high-intensity statin therapy, which lowers LDL-C by 50% to 60%, should be started regardless of baseline LDL-C level (Table 2).[9,92,93] Residual risk can persist even with maximally tolerated statin therapy in persons with multiple risk factors and persons with stable clinical ASCVD. Lipids should initially be monitored at 6- to 12-week intervals to determine if intensification of therapy is needed and then at less frequent intervals (eg, 6 months) once goals are attained.

Some patients may manifest statin intolerance. Statin-associated muscle symptoms (SAMS) are characterized by bilateral muscle symptoms—pain, weakness, cramping, and stiffness—associated with onset of statin use, but the causality is not always clear.[94,95] The incidence of statin intolerance is in the range of 5% to 20%, with lower rates in placebo-controlled trials; clinical trials with direct queries about muscle symptoms did not show a significant difference in the rates of muscle symptoms among statin and placebo groups.[94] SAMS may resolve with discontinuation and recur when rechallenged with the same or alternative statin. Management includes acknowledging the patient's symptoms and considering the addition of creatine kinase (CK). The FDA–accepted definition of statin-induced myopathy is pain or weakness accompanied by a CK level >10-fold higher than the upper limit of normal laboratory range, but this is rare (<0.1% over placebo). The risk of severe rhabdomyolysis with CK >40-fold, the upper limit of normal is approximately 1 to 4 in 10,000 per year.[94]

Risk factors for myopathy include age >65 years, female sex, low BMI, East Asian heritage, history of muscle symptoms, impaired renal and/or hepatic function, DM, HIV infection, concomitant medications (eg, fibrates, erythromycin, fluconazole), vitamin D deficiency, hypothyroidism, and acute infection.[73] Drug interactions should be considered, particularly for concomitant medications and statins that have high first-pass metabolism and are metabolized through CYP3A4 (eg, simvastatin, lovastatin). When symptoms resolve, and if myopathy was not severe, a rechallenge with a lower dose or less frequent dosing (1-3 times per

Table 1
ASCVD 10-year Risk Calculators

Reynolds CVD Risk Score	http://www.reynoldsriskscore.org/
Framingham CVD Risk Score	https://www.framinghamheartstudy.org/fhs-risk-functions/hard-coronary-heart-disease-10-year-risk/
American College of Cardiology/American Heart Association Pooled Cohort CVD Risk Calculator	http://www.cvriskcalculator.com/
Multi-Ethnic Study of Atherosclerosis (MESA) Risk Score	https://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx

Table 2
Intensity of Statin Therapy

	Low Intensity	Moderate Intensity	High Intensity
Simvastatin 10 mg	10 mg	20-40 mg	—
Pravastatin 10-20 mg	10-20 mg	40-80 mg	—
Lovastatin 20 mg	20 mg	40 mg	—
Fluvastatin 20-40 mg	20-40 mg	40 mg BID/80 mg XL	—
Pitavastatin 1 mg	1 mg	2-4 mg	—
Atorvastatin	—	10-20 mg	40-80 mg
Rosuvastatin	—	5-10 mg	20-40 mg

Modified from [9,92,93].

week), or use of a hydrophilic statin with less association with myopathy (eg, pitavastatin, fluvastatin) may allow continuation of statin therapy. Even though observational studies showed that normalization of 25-hydroxy-vitamin D_3 levels[96] may help with statin-induced myopathy, a secondary analysis of the VITamin D and OmegA-3 Trial (VITAL) showed that the frequency of statin-induced myopathy did not differ with vitamin D supplementation compared with placebo.[97] However, adding coenzyme Q10 supplementation can be considered.[96]

Step 5A. Intensify Therapy to Achieve Lipid Target

In persons with T2D, additional laboratory testing of lipid levels should be undertaken at frequent intervals (every 6-12 weeks) to direct titration of the statin or addition of an adjunct therapy in order to achieve lipid targets; less frequent testing intervals can be considered once lipid goals are consistently achieved. If lipid targets cannot be achieved with maximally tolerated statin therapy, then the addition of the cholesterol absorption inhibitor ezetimibe (10 mg/day) should be considered. If treatment goals are not met on a maximally tolerated statin combined with ezetimibe, additional therapy with a bile acid sequestrant (colesevelam, colestipol, cholestyramine) or bempedoic acid (adenosine triphosphate-citrate lyase inhibitor) is an option. In extreme risk patients with lipid values above targets on maximal high-intensity statin in combination with the above-mentioned add-on therapies, there may be a need for more aggressive therapy with a proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) or inclisiran (PCSK9 siRNA), with consideration of approved indications and access.

Step 5B. Hypertriglyceridemia Management

Management of hypertriglyceridemia also is important for optimal lipid levels with a goal of <150 mg/dL in persons with T2D. If needed, pioglitazone and/or insulin may improve both glycemic control and TG levels. In persons with fasting TG level of >200 mg/dL despite a maximally tolerated statin, optimal glucose control, tight adherence to a healthy diet (eg, avoidance of simple carbohydrates, fruit juices, and alcohol), fenofibrate, and/or high-dose prescription grade omega-3 fatty acid may help to achieve goals for TG levels and non–HDL-C. Over-the-counter fish oil supplements are not approved by the FDA for hypertriglyceridemia. In persons with a fasting TG level of >200 mg/dL despite a maximally tolerated statin, optimal glucose control, tight adherence to a healthy diet, fenofibrate, and/or high-dose prescription grade omega-3 fatty acid may help to achieve goals for TG levels and non–HDL-C. However, the CV risk reduction with addition of fibrates, on the background of an optimally dosed statin, for TG levels >200 to 500 mg/dL has not been definitively established. The incidence of CV events in T2D with TG levels >200 was not reduced by pemafibrate in the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) trial, despite lowering of TG, VLDL, remnant cholesterol, and Apo C-III levels.[98] However, subgroup analysis and meta-analyses of trials with fibrates have shown improved ASCVD outcomes in persons with elevated TG levels (>200 mg/dL) and/or HDL-C (<40 mg/dL).[9,72,99-101]

The Reduction of Cardiovascular Events with Icosapent Ethyl - Intervention Trial (REDUCE-IT) demonstrated that the addition of icosapent ethyl (IPE) to statin therapy positively reduced CVD events by 25% in T2D participants with TG levels >135 mg/dL and ASCVD or age >50 years and a second CV risk factor, although this effect was independent of TG level lowering.[102] Potential concerns about the magnitude of the beneficial effect of IPE with use of the mineral oil placebo in REDUCE-IT have been voiced, but overall, IPE should be considered if TG levels are >135 mg/dL in persons with T2D and with established ASCVD or ≥2 additional traditional CVD risk factors.

For severe hypertriglyceridemia (TG levels ≥1000 mg/dL), a very low-fat diet may be required in addition to a fibrate and/or prescription omega-3 fatty acid. For refractory cases, if the fasting TG level remains >1000 mg/dL, niacin may be needed to lower TG levels and reduce the risk of pancreatitis. Notably, niacin may lower TG levels and Lp(a) but does not reduce ASCVD and can worsen glycemia.

ASCVD Risk Reduction Algorithm: Hypertension

HTN is prevalent among persons with T2D and increases the risk of macrovascular and microvascular complications of DM.[103] The coexistence of prediabetes and HTN also increases the risk of CV events.[104] Data from the UK Prospective Diabetes Study (UKPDS) demonstrated that increased BP control in persons with T2D decreased the risk of death related to DM and micro- and macrovascular complications, which has been confirmed in subsequent clinical trials.[105,106]

AACE has set a systolic BP goal for the majority of patients with T2D as <130 mm Hg with a diastolic BP goal of <80 mm Hg (Algorithm Fig. 5).[9] A lower target can be considered for persons with micro- or macroalbuminuria, moderate/high risk for or with established ASCVD, peripheral vascular disease, or retinopathy. It is recognized that some persons with T2D may not tolerate a goal of <130/80 mm Hg, including those with autonomic neuropathy with orthostatic hypotension, acute coronary syndrome (acute myocardial infarction [MI] or unstable angina), frailty, or medication intolerance.

The accuracy of BP measurement in the clinical setting should be ensured using appropriately maintained and calibrated equipment, trained and proficient medical staff, and with the patient in the appropriate position (ie, sitting in a chair with feet on floor, arm supported at heart level) with a correctly sized cuff. Ideally, serial measurements should be taken and averaged.

Step 1. Initiate Lifestyle Interventions

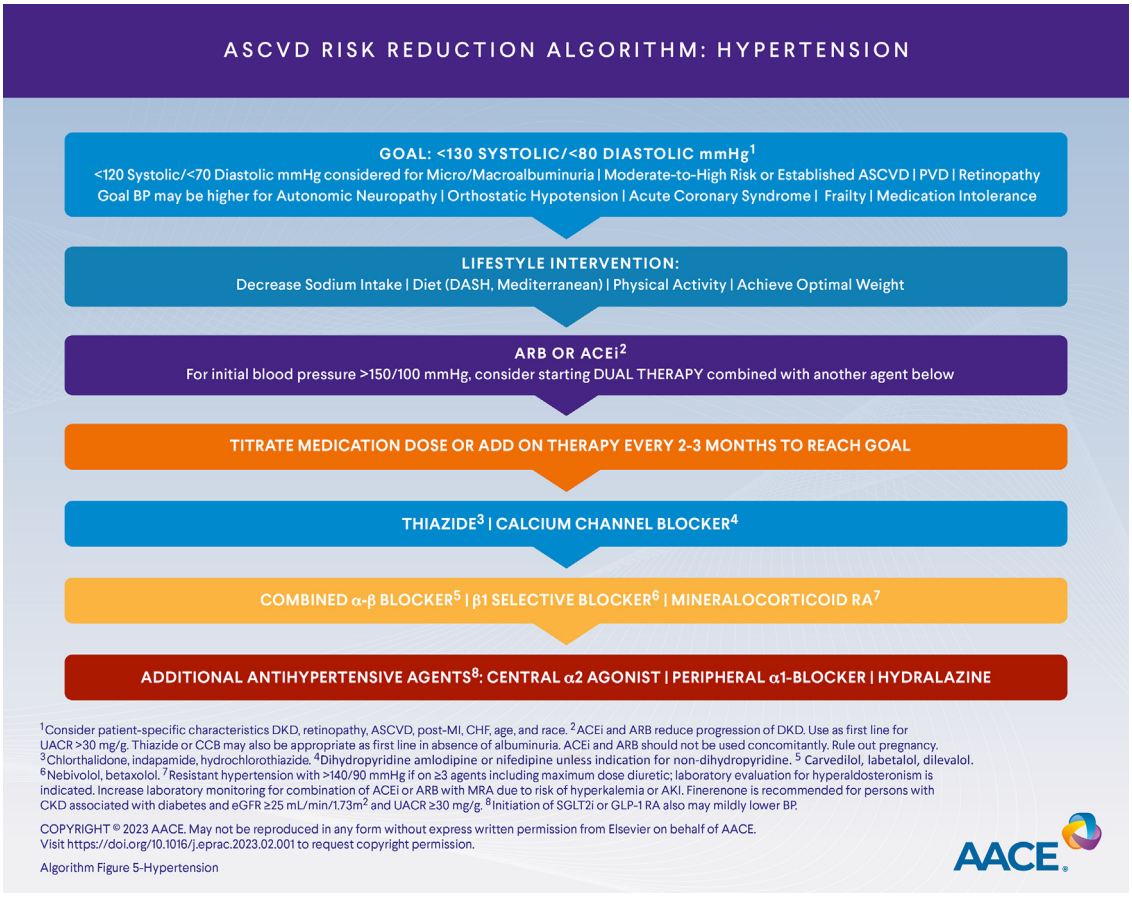
Weight loss of ≥5% lowers BP with the largest impact in persons who lose 10% to >15%.[89,107] Exercise several times per week is also an important component in the treatment of HTN, because there are reductions in both systolic and diastolic BP with endurance (aerobic) and dynamic resistance training.[108] Patients also should be counseled on limiting dietary sodium such as with the DASH diet.[109] Mediterranean diets also have been demonstrated to lower BP.[110]

Step 2. Start an Angiotensin-Converting Enzyme Inhibitor or Angiotensin II Receptor Blocker

Angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs) are considered first-line therapies for HTN in persons with T2D, particularly in those with DKD. Both agents are efficacious, but there is no additional benefit for coadministration of an ACEi and an ARB together, and combination may cause harm.[111-114] The dose should be titrated up on a regular basis (minimum every 2-3 months) to reach the BP goal. For those persons who manifest intolerance to an ACEi (eg, cough), an ARB can be substituted. If the initial BP is >150/100 mm Hg, dual therapy may need to be used at the outset (see Step 3. Add-on Therapy).

Step 3. Add-on Therapy

If the BP goal is not achieved with optimally titrated ACEi or ARB therapy alone, additional add-on therapy is needed. Other antihypertensive agents also have shown efficacy in slowing GFR decline



Algorithm Fig. 5. Atherosclerotic Cardiovascular Disease Risk Reduction Algorithm: Hypertension.

in persons with T2D and HTN, including diuretics and calcium channel blockers.[115] A thiazide diuretic (eg, hydrochlorothiazide, chlorthalidone, indapamide) is an effective second-line antihypertensive, and there are numerous combination pills with ACEi or ARBs with the potential to increase adherence. The dihydropyridine calcium channel blockers amlodipine or nifedipine also can be considered as add-on therapies.

Understanding that many persons with HTN can require multiple antihypertensive medications to achieve their goal BP, additional therapies can include β-blockade. Notably, β-blockers can be associated with weight gain, thought to be secondary to decreased energy expenditure.[116,117] This may be more pronounced with older agents such as atenolol or metoprolol, so the use of newer α-β blockade (carvedilol, labetalol, dilevalol) or β1-selective agents (nebivolol or betaxolol) may be more weight sparing. The central α2 agonist (clonidine) or a peripheral α1 RA (eg, doxazosin, prazosin, terazosin) may be needed for persons who are still hypertensive despite multiple therapies. Hydralazine also may be an effective adjunct therapy but requires multiple doses throughout the day.

Primary hyperaldosteronism is an underdiagnosed cause of endocrine HTN, and there should be a low threshold for screening.[118,119] For the purposes of this algorithm, patients should be screened if they have resistant HTN (>140/90 mm Hg) on ≥3 medications, including a maximum-dose diuretic. A mineralocorticoid receptor antagonist (MRA) (eg, eplerenone, spironolactone) is the rational choice for the medical management of primary hyperaldosteronism but also can be considered for resistant HTN in persons with T2D. More frequent laboratory monitoring of potassium levels and kidney function should be performed in persons on a combination of an ACEi or ARB with an MRA. There also are data supporting the benefits of the nonsteroidal MRA finerenone for progression of CKD and risk of HF, ASCVD events, and related mortality in persons with T2D and microalbuminuria (urine albumin-to-creatinine ratio ≥30 mg/g), macroalbuminuria, or more advanced CKD but with an eGFR >25 mL/min/1.73 m^2.[120-123] Although finerenone can modestly reduce systolic BP, its effects are independent of pretreatment BP levels, and regulatory approval is for risk reduction for eGFR decline, end-stage kidney disease, CV death, nonfatal MI, and hospitalization for HF in persons with CKD and T2D.[124]

For those persons initiated on GLP-1 RA or SGLT2i, there may be a mild reduction in BP when these agents are started.[125-128]

Complications-Centric Algorithm for Glycemic Control

Persons with T2D experience significant morbidity caused by ASCVD, which is the leading cause of mortality in T2D despite contemporary therapy with lipid-modifying, antiplatelet, and antihypertensive agents.[129] Therapeutic lifestyle changes remain a fundamental component of glycemic control and should include a healthy meal plan, regular physical activity, healthful behavior practices, and weight management. Importantly, some agents belonging to 2 of the newer classes of antihyperglycemic agents, GLP-1 RA and SGLT2i, have been demonstrated in large, international, multicenter randomized, controlled trials to reduce ASCVD risk in persons with T2D and established ASCVD as well as in those at high risk for ASCVD. The CVOTs demonstrate that each antihyperglycemic agent has distinct effects on various components of CV risk, with some showing reduction in CV death, improvement in CKD, reduction in hospitalization for HF, and/or reduced risk of

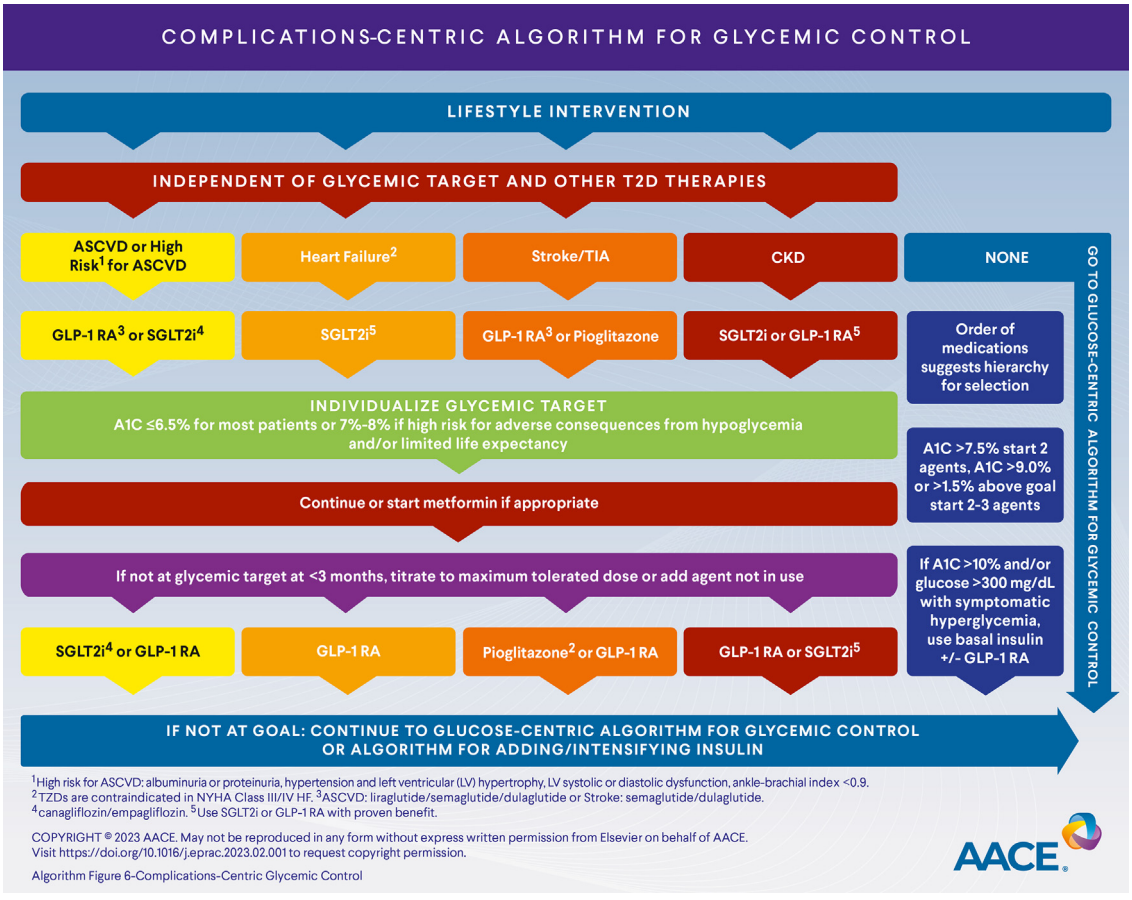
stroke. There is a need for a paradigm shift from an exclusively glucose-centric approach to add a complications-centric approach in the algorithm for glycemic control of persons with T2D (Algorithm Fig. 6).

Three of the GLP-1 RAs have been demonstrated to significantly lower the risk of major adverse cardiovascular events (MACEs) (the composite endpoint "3-point MACE" includes nonfatal MI, nonfatal stroke, and CV death), whereas SGLT2is lower the risk of hospitalization for HF, improve renal outcomes, and some reduce the risk of CV death and/or MACE. The definition of high risk was not consistent across all CVOTs, but generally included albuminuria or proteinuria, HTN and LV hypertrophy, LV systolic or diastolic dysfunction, and/or ABI <0.9. A 2021 meta-analysis of GLP-1 RA CVOTs found a 14% (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.80-0.93, $P < .001$) reduction in risk of MACEs in persons with or without established ASCVD, A1C, or background antihyperglycemic therapy.[130] Therefore, when persons with T2D have established ASCVD or are at high risk, a GLP-1 RA with proven CV benefit (eg, liraglutide, semaglutide, or dulaglutide) should be initiated as a first-line therapy independent of A1C goal or other antihyperglycemic treatments, including metformin.[9] As an alternative to GLP-1 RA, with consideration of comorbidities, potential side effects, and/or patient preference, clinicians may recommend initiating an SGLT2i with proven CV benefit to reduce the risk of MACE or CV death in persons with T2D and established ASCVD.[131,132] For persons with T2D and established ASCVD or at high risk for ASCVD, the use of an SGLT2i reduces the risk of hospitalization for HF regardless of background antihyperglycemic therapy, CV therapy, or A1C,[9] and in persons with HF and/or CKD, SGLT2i should be initiated as first-line therapy.

SGLT2is clearly have been shown to significantly and robustly reduce the risk of hospitalization for HF or CV death in persons with T2D with or without ASCVD and to improve HF-related symptoms in persons with established HF regardless of LV ejection fraction, background glucose-lowering therapies, or HF therapies.[9] A recent meta-analysis showed that use of an SGLT2i resulted in a 32% reduction in risk of hospitalization for HF (HR 0.68 [95% CI 0.61-0.76]) and a 15% reduction in CV death (HR 0.85 [95% CI 0.78-0.93]) compared with placebo.[133] SGLT2is should be recommended in persons with T2D and HF regardless of A1C goal or other antihyperglycemic treatments, including metformin.

Studies with DPP-4i have shown neutrality compared with placebo regarding MACEs but saxagliptin has been shown to increase the rate of HF hospitalizations.[134] There also was a trend for HF hospitalizations with alogliptin in post hoc analysis of the EXAMINE trial, so caution is advised with use of this agent for persons with New York Heart Association Class III or IV CHF.[135] TZDs can worsen fluid retention and should not be used in persons who have symptomatic HF, and initiation of pioglitazone is contraindicated in individuals with New York Heart Association Class III or Class IV CHF.[136] However, in patients with insulin resistance but without DM who experienced a stroke or transient ischemic attack, pioglitazone has been shown to reduce the risk of acute coronary syndromes.[137] Studies of acarbose on CVD have been limited to patients with impaired glucose tolerance, with 1 study reporting a nearly 50% reduction in MACEs[138] associated with decreased postprandial glucose, while another showed no effect,[139] albeit in patients with already established CVD.

The risk of stroke is markedly increased in DM, with a National Health and Nutrition Examination Survey study demonstrating an



Algorithm Fig. 6. Complications-Centric Algorithm for Glycemic Control.

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odds ratio of 28 (95% CI 19-41).[140] Across meta-analyses, GLP-1 RA appear to reduce risk of stroke by 15% to 17% in persons with T2D and prior ASCVD or at high risk for ASCVD.[9,130,141,142] The 3 GLP-1 RA agents approved by the FDA to reduce the risk of MACEs (including stroke) are dulaglutide (with or without established ASCVD), liraglutide, and subcutaneous semaglutide (in persons with established CVD).[143] In persons with T2D and ASCVD or those at high risk for ASCVD, use of GLP-1 RA with proven benefit is recommended to reduce stroke risk.[9] Pioglitazone, a TZD, appears to reduce the risk of recurrent stroke and should also be considered to reduce the risk of recurrent stroke in persons with insulin resistance, prediabetes, or T2D and a prior transient ischemic attack (TIA) or stroke.[9,144,145] With regard to stroke and SGLT2i, 2 meta-analyses have shown that there was a reduced HR of 0.5 for hemorrhagic stroke when pooling data from completed SGLT2i trials, while there was no significant impact on ischemic stroke.[146,147]

Nearly 50% of U.S. adults with kidney failure have DM.[148] The evidence for benefit of SGLT2is to reduce adverse renal outcomes is robust, with an approximately 38% reduction in composite outcomes, which varied across trials but included worsening of eGFR or creatinine, end-stage kidney disease with or without need for kidney replacement therapy or transplant, kidney death, or CV death.[133] Use of an SGLT2i with proven benefit is recommended as foundational therapy to reduce progression of DKD and CVD risk for persons with T2D and DKD with eGFR 25 mL/min/1.73 m^2 or 20 mL/min/1.73 m^2 if HF is also present.[9,149,150] Two prospective placebo-controlled trials have examined the impact of dapagliflozin (included participants with eGFR 25 to 70 mL/min/1.73^2 and 200-5000 mg urine albumin/g creatinine) and empagliflozin (included participants with eGFR 20 to <45 mL/min/1.73 m^2 or >45 mL/min/1.73 m^2 with >200 mg urine albumin/g creatinine) decline in eGFR and progression of CKD, with a majority of participants enrolled with known T2D.[151,152] Dapagliflozin slowed the rate of decline more in patients with T2D than in patients without T2D, while the impact on eGFR decline was similar for both groups with empagliflozin. GLP-1 RAs also are an option to reduce progression of albuminuria, eGFR decline, and ASCVD risk in persons with T2D and DKD with eGFR 15 mL/min/1.73 m^2.[9,153,154]

The A1C target should be individualized in persons with T2D and ASCVD or at high risk for ASCVD, with a target A1C of ≤6.5% in most nonpregnant adults if it can be achieved safely. Consideration of life expectancy, disease duration, presence or absence of micro- and macrovascular complications, CV disease risk factors, comorbid conditions, and risk of hypoglycemia as well as cognitive and psychological status must be considered.[9,16] Newer antihyperglycemic agents such as GLP-1 RA and SGLT2i are associated with a lower risk of hypoglycemia unless used with SUs, glinides, and/or insulin. Less stringent A1C goals (7%-8%) should be adopted in persons with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced renal disease, extensive comorbid conditions, or longstanding DM in whom the A1C goal has been difficult to attain despite intensive efforts as long as the person remains free of hyperglycemia-associated symptoms.[9,13,14,17]

If further lowering of the A1C is needed to achieve the individualized glycemic target(s) and renal function is GFR >30 mL/min/1.73 m^2, metformin should be considered if the patient is not already taking this agent. Each medication should be up-titrated to the maximally tolerated approved dose and additional antihyperglycemic agents should be added on to achieve glycemic targets. If the initial A1C is >7.5%, early combination therapy with 2 agents may be needed, and for those with an initial A1C of >9% or 1.5% above goal, then 2 or 3 antihyperglycemic agents should be initiated concomitantly. If there is symptomatic hyperglycemia, an A1C >10% and/or BG >300 mg/dL, suggestive of marked insulin deficiency, basal insulin should be initiated to reduce glucose as safely and promptly as possible. In this scenario, use of a combination basal insulin with a GLP-1 RA can also be considered, but with the understanding that GLP-1 RA will require a titration phase that could potentially delay glycemic control. Clinicians should refer to the Algorithm for Adding/Intensifying Insulin section (Algorithm Fig. 8) and the Profiles of Antihyperglycemic Medications table (Algorithm Fig. 9) for additional guidance.

If a person with T2D does not have established or high risk for ASCVD, HF, stroke/TIA, or CKD, then the clinician should refer to the Glucose-Centric Algorithm for Glycemic Control section (Algorithm Fig. 7) and the Profiles of Antihyperglycemic Medications table (Algorithm Fig. 9).

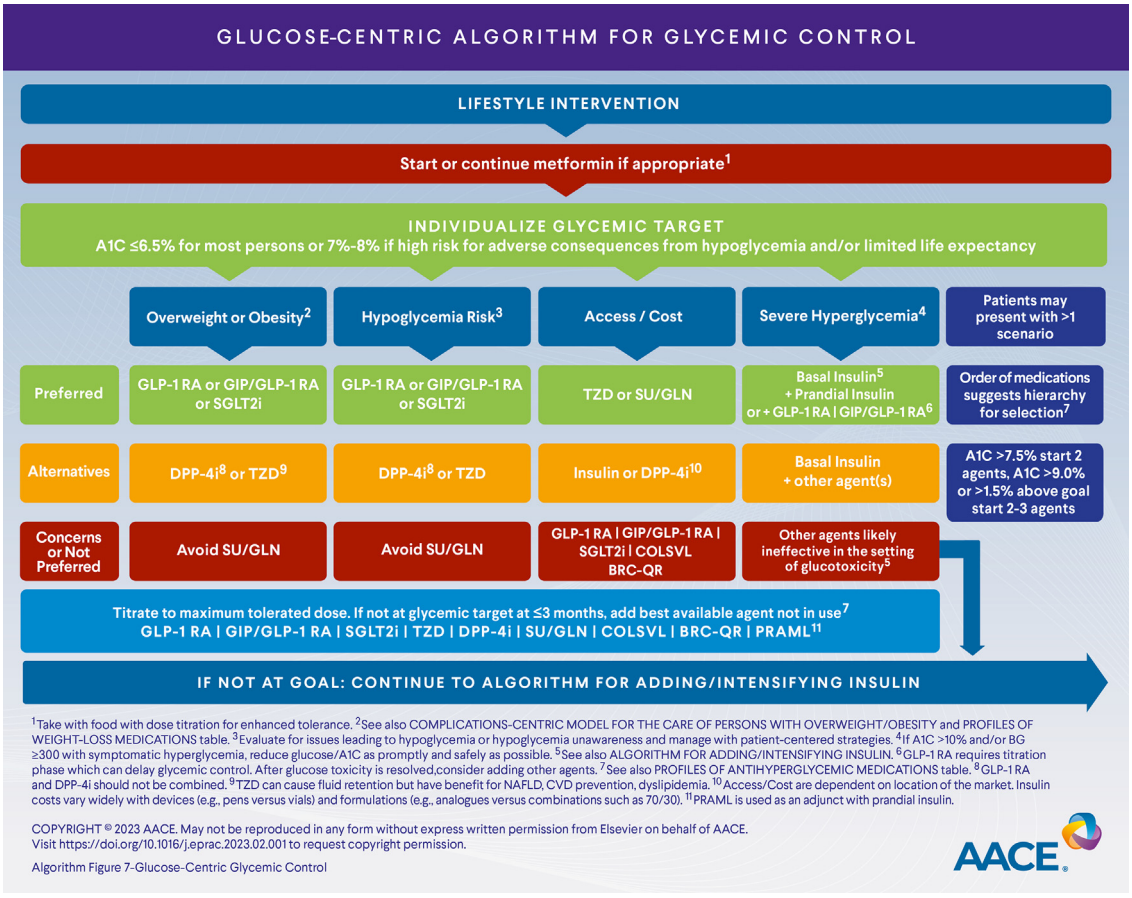
Glucose-Centric Algorithm for Glycemic Control

The Glucose-Centric Algorithm for Glycemic Control (Algorithm Fig. 7) is for determining initial and add-on therapies for persons with DM but without established or high risk for ASCVD, HF, stroke/TIA, or CKD. Metformin should be initiated if there is no contraindication (eg, GFR <30 mL/min/1.73 m^2). In order to maximize tolerability, metformin should be started at a low dose and titrated over the course of a few weeks to the maximally tolerated dose.[16] The newer antihyperglycemic agents such as GLP-1 RA and SGLT2i are associated with low risk of hypoglycemia unless combined with SUs, glinides, and/or insulin.

Given that T2D is a progressive disease, many individuals will require >1 antihyperglycemic medication to achieve their individualized A1C target over the course of the disease. Clinicians should consider multiple factors when selecting the second agent, including presence of overweight or obesity, hypoglycemia risk, access/cost, and presence of severe hyperglycemia. Patients often present with >1 of these factors, so using a patient-centered, shared decision-making approach is important. The order that medications are listed in the algorithm denotes the suggested preference hierarchy for selection. In those patients with overweight or obesity and the additional goal of weight loss, dual GIP/GLP-1 RA, GLP-1 RA, or SGLT2i class are preferred options. Persons with a history of hypoglycemia, at high risk of hypoglycemia. and/or at risk for severe complications from hypoglycemia should preferentially be initiated with an agent associated with low risk for hypoglycemia, including GLP-1 RA, SGLT2i, dual GIP/GLP-1 RA, TZD, or DPP-4i.

For many persons with T2D, access and cost are barriers to receiving newer antihyperglycemic agents. In this situation, a TZD, SU, or glinide would be the more economical choices. While TZDs are associated with low risk for hypoglycemia and have shown benefit for NAFLD, they also can increase weight, so patients must be counseled accordingly. Lastly, patients with symptomatic hyperglycemia and/or an A1C >10% suggestive of marked insulin deficiency should start basal insulin to improve glycemia as quickly as possible. Basal insulin can be initiated with or without initiation and titration of a GLP-1 RA if the patient is not already on this class of agents. Some patients with severe hyperglycemia may need simultaneous initiation of bolus insulin. Clinicians should refer to the Algorithm for Adding/Intensifying Insulin section (Algorithm Fig. 8) for more guidance about initiating or advancing insulin therapy.

In persons with newly diagnosed T2D who are drug naive, prospective studies support the initiation of combination therapy to achieve glycemic targets more quickly as compared with a stepwise approach.[155,156] For recently diagnosed individuals with



Algorithm Fig. 7. Glucose-Centric Algorithm for Glycemic Control.

T2D and an A1C ≥7.5%, early combination therapy may also be considered, usually with metformin combined with another agent that does not cause hypoglycemia, particularly a GLP-1 RA, SGLT2i, or DPP-4i.[9] Clinicians should be cognizant that combination of incretin-based therapies is not recommended (ie, DPP-4i with GLP-1 RA or dual GIP/GLP-1 RA). Antihyperglycemic medications should be titrated to the maximally tolerated dose to achieve the individualized A1C goal, and additional antihyperglycemic agents should be considered in a timely fashion to avoid therapeutic inertia. If the A1C is >9% or >1.5% above goal, ≥2 antihyperglycemic agents may need to be initiated at once.[9] Alternative agents and those associated with concerns regarding adverse effects or ineffectiveness are listed in the algorithm and the clinician is referred to the Profiles of Antihyperglycemic Medications table (Algorithm Fig. 9) for more details regarding the risks and benefits of each antihyperglycemic class.

Algorithm for Adding/Intensifying Insulin

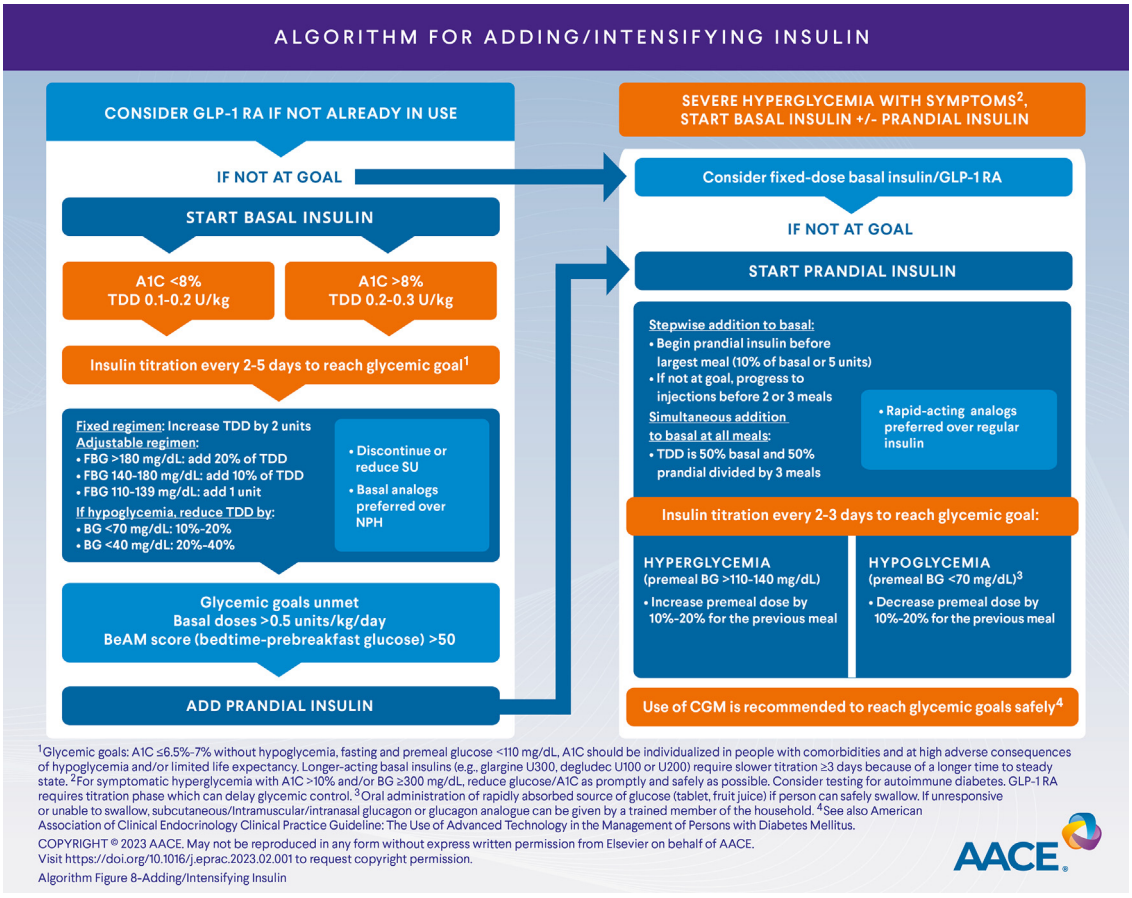
The overall goal of insulin therapy is to achieve glycemic control after failure of noninsulin antihyperglycemic agents. Glycemic targets should be individualized, although an A1C of 6.5% to 7% for persons on insulin is recommended for most patients (Algorithm Fig. 8). Although A1C is a key measure, insulin titration requires use of multiple glycemic parameters including FBG, premeal or 2-hour postprandial BG, and data from CGM, when available, including TIR, time below range, and GMI.[21] In general, targets for fasting and premeal glucose are <110 mg/dL without hypoglycemia and can be individualized based on a person's comorbidities and clinical status. The use of CGM is recommended for persons treated with insulin to optimize glycemic control while minimizing hypoglycemia.[20]

Symptomatic Hyperglycemia

Basal with or without prandial insulin treatment may be needed as initial therapy if the A1C is >10% and/or glucose values are >300 mg/dL, combined with catabolic symptoms, such as weight loss. If symptomatic hyperglycemia is present, a GLP-1 RA alone is not recommended as it requires titration and may delay glucose control. The goal of initial intensive insulin therapy for symptomatic hyperglycemia is to reduce glucose levels safely and promptly. After improved glycemic control is achieved with short-term insulin therapy, especially with a new diagnosis of DM,[157] a role for non-insulin antihyperglycemic agents could be considered.

Failure of Noninsulin Antihyperglycemic Treatments

For most persons who need intensification of glycemic control and who are already undergoing 3 to 4 oral therapies, a GLP-1 RA or GIP/GLP-1 RA should be the initial choice, if not already in use.[9] If glycemic targets are not achieved with these therapies, basal



Algorithm Fig. 8. Algorithm for Adding/Intensifying Insulin.

insulin should be added alone or as a basal insulin/GLP-1 RA combination injection. Stepwise addition of prandial insulin at 1 to 3 meals is recommended if additional glycemic control is required.

Basal Insulin Initiation

The dose of basal insulin can be based on A1C levels at the time of initiation. For an A1C <8%, basal insulin can be started at 0.1 to 0.2 U/kg/day and for an A1C >8%, 0.2 to 0.3 U/kg/day can be considered. Analog insulins, including detemir, glargine, or degludec are preferred over human insulins such as neutral protamine Hagedorn (NPH) to reduce hypoglycemia.[9,158] After basal insulin is initiated, discontinuation of SUs is recommended. Fixed-dose GLP-1 RA and basal insulin combinations also can provide improved glycemic control when basal insulin alone has not achieved targets.[159]

Basal Insulin Titration

Basal insulin should be titrated every 2 to 3 days to reach glycemic targets with a goal FBG of <110 mg/dL without hypoglycemia. Because of the longer half-life of insulin degludec, slower titration every 3 to 5 days is recommended. Persons taking insulin can be counseled on how to titrate insulin doses independently based on self-monitoring of blood glucose.[160,161] One approach to titration of basal insulin is to use the FBG and increase by 20% if >180 mg/dL, 10% if 140 to 180 mg/dL, and 1 unit if 110 to 139 mg/dL. Insulin doses should be reduced as follows for fasting hypoglycemia: FBG <70 mg/dL, decreased by 10% to 20%; FBG <40 mg/dL, decreased by 20% to 40%.

If the basal insulin dose is >0.5 units/kg/day or the bedtime minus morning prebreakfast glucose score is >50 mg/dL,[162] prandial insulin should be considered.

Initiation of Prandial Insulin

Rapid-acting insulin analogs are preferred over human insulin preparations (eg, regular insulin) because of their comparatively earlier onset of action. Prandial insulin can be initiated at the largest meal at 10% of the basal insulin dose or 5 units, with stepwise addition to other meals as additional glycemic control is needed.[163,164] Alternatively, prandial insulin can be started at all meals simultaneously at 50% of the total daily dose divided by the number of meals.[163,164]

Although less preferred, fixed-dose premixed insulins that combine a long-acting and short-acting insulin can also be considered for persons who may have concerns about multiple insulins and injections. Although premixed insulin requires fewer injections, it also has less flexibility for dosing adjustments and may increase hypoglycemia.[9,165] Nonetheless, premixed insulin may offer an alternative to achieve adequate glycemic control due to simplicity of the insulin regimen and increased adherence.

Prandial Insulin Titration

Goal premeal glucose targets are 110 to 140 mg/dL.[9] Prandial insulin should be titrated every 2 to 3 days, based on the premeal glucose of the meal until glycemic targets are met. One approach is to titrate prandial insulin as follows:

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- For pre-midday meal glucose >110 mg/dL, increase the morning meal dose by 10% to 20%
- For pre-evening glucose >140 mg/dL, increase the midday meal dose by 10% to 20%
- For bedtime glucose >140 mg/dL, increase the pre-evening meal dose by 10%
- Fixed-dose insulin can be titrated by 2 units every 2 to 3 days relying on the morning FBG because of the presence of basal insulin

Hypoglycemia

For premeal hypoglycemia (glucose <70 mg/dL), prandial insulin should be adjusted with the following approach:

- For pre-midday meal glucose <70 mg/dL, decrease AM meal dose by 10% to 20%
- For pre-evening meal glucose <70mg/dL, decrease pre-midday meal dose by 10% to 20%
- For bedtime glucose <70 mg/dL, decrease pre-evening meal dose by 10% to 20%

Persons with DM on insulin and their families/companions should be educated on the symptoms and treatment of hypoglycemia (<70 mg/dL) and severe hypoglycemia (<54 mg/dL). If a person can safely swallow, an oral source of glucose (eg, tablets, fruit juice) should be given.[166] For a person who is unresponsive or unable to take oral glucose, glucagon should be administered. There are multiple formulations of glucagon available. While older glucagon formulations require reconstitution before subcutaneous or intramuscular injection, soluble glucagon and a glucagon analog, dasiglucagon, are available that do not require reconstitution and are ready for immediate injection.[167,168] Intranasal glucagon also has been shown to be efficacious.[169-173]

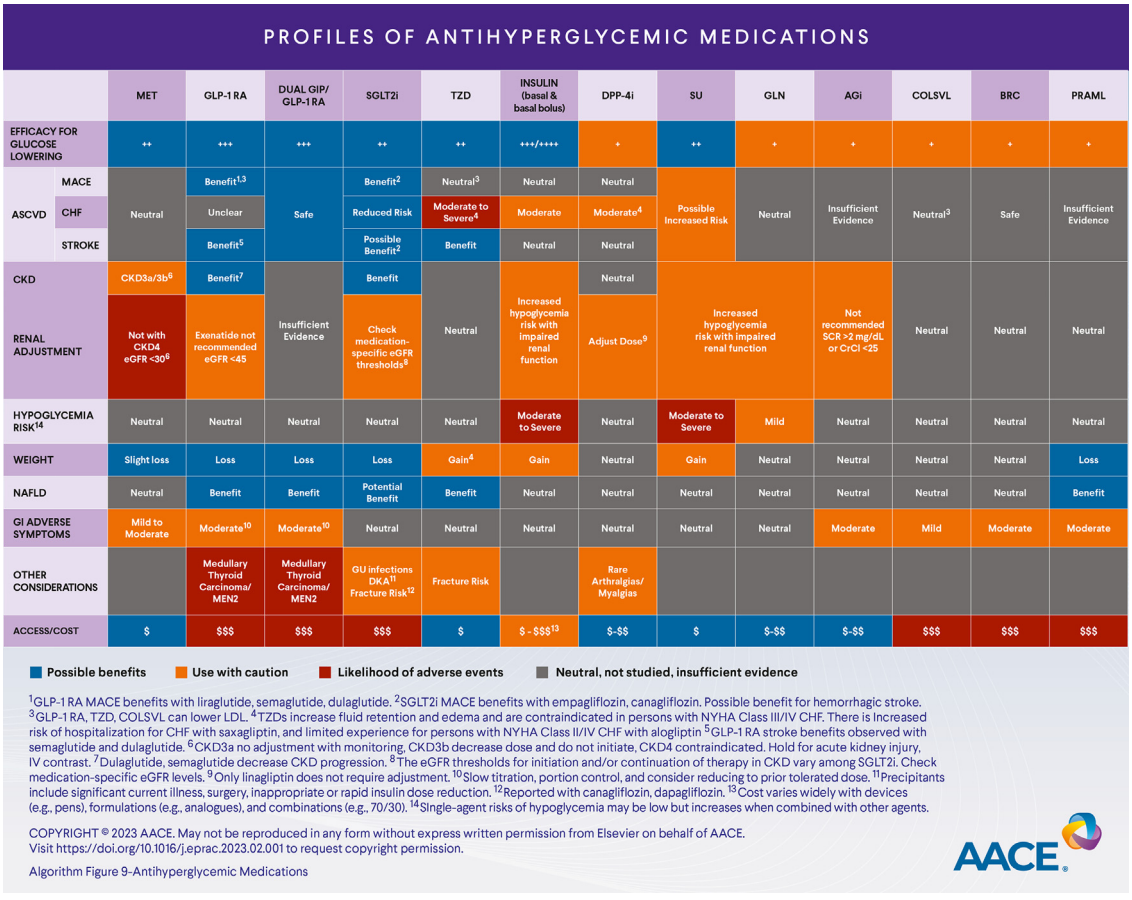
Profiles of Antihyperglycemic Medications

The table of Profiles of Antihyperglycemic Medications (Algorithm Fig. 9) provides a summary of clinically relevant information for approved medical therapies for the treatment of persons with T2D. Details regarding the mechanisms of action and evidence of benefits or harms are outside the scope of this algorithm; clinicians are encouraged to consult the 2022 AACE Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan[9] for more details.

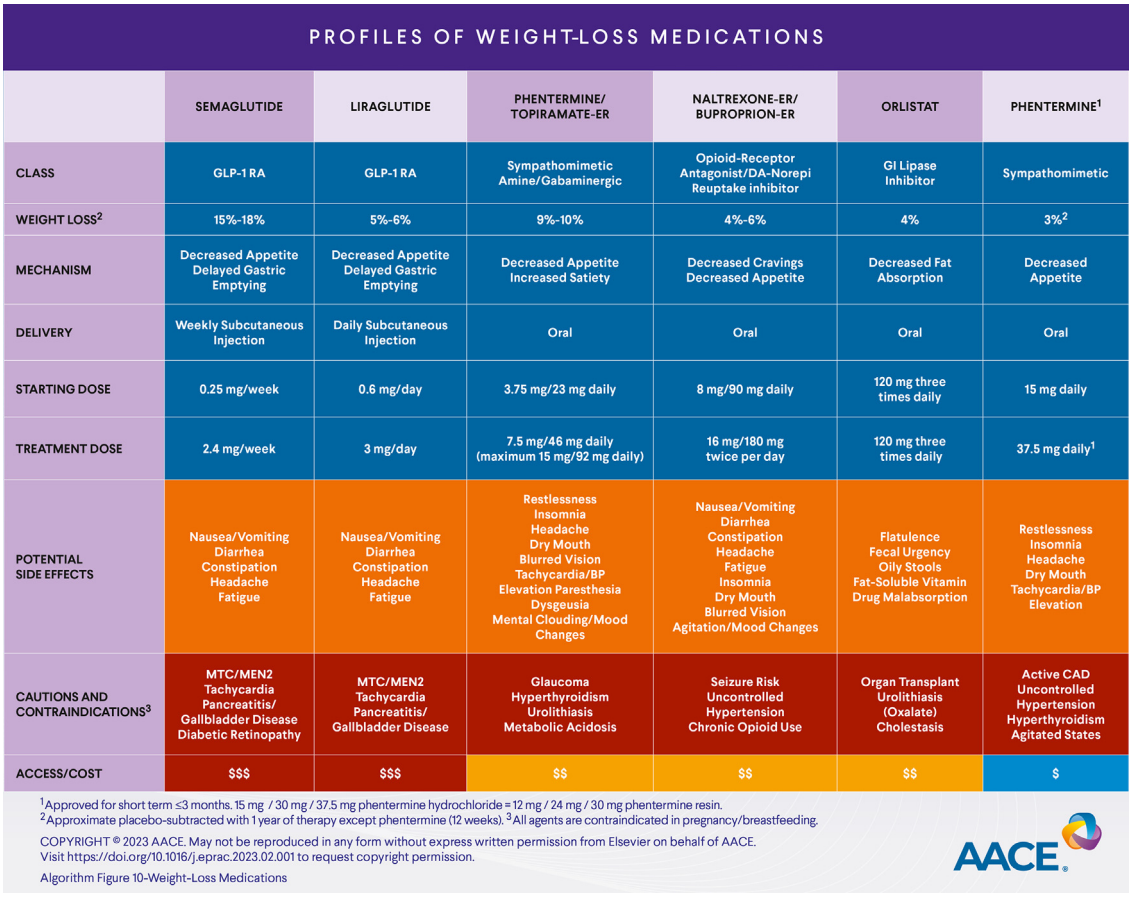
The organization of the pharmacologic agents (left to right) and the information selected for each medication (top to bottom) provide a framework for clinicians to select from the multiple available antihyperglycemic medications and to incorporate the highlighted benefits or cautions in discussions with patients. Medications on the left side of the table potentially have more positive indications to be considered first-line compared with agents on the right side of the table.

Profiles of Weight-Loss Medications

The table of Profiles of Weight-Loss Medications (Algorithm Fig. 10) summarizes weight-loss therapies currently approved by the FDA regarding approximate efficacy for weight loss, dosing and



Algorithm Fig. 9. Profiles of Antihyperglycemic Medications.



PROFILES OF WEIGHT-LOSS MEDICATIONS

	SEMAGLUTIDE	LIRAGLUTIDE	PHENTERMINE/ TOPIRAMATE-ER	NALTREXONE-ER/ BUPROPRION-ER	ORLISTAT	PHENTERMINE[1]
CLASS	GLP-1 RA	GLP-1 RA	Sympathomimetic Amine/Gabaminergic	Opioid-Receptor Antagonist/DA-Norepi Reuptake inhibitor	GI Lipase Inhibitor	Sympathomimetic
WEIGHT LOSS[2]	15%-18%	5%-6%	9%-10%	4%-6%	4%	3%[2]
MECHANISM	Decreased Appetite Delayed Gastric Emptying	Decreased Appetite Delayed Gastric Emptying	Decreased Appetite Increased Satiety	Decreased Cravings Decreased Appetite	Decreased Fat Absorption	Decreased Appetite
DELIVERY	Weekly Subcutaneous Injection	Daily Subcutaneous Injection	Oral	Oral	Oral	Oral
STARTING DOSE	0.25 mg/week	0.6 mg/day	3.75 mg/23 mg daily	8 mg/90 mg daily	120 mg three times daily	15 mg daily
TREATMENT DOSE	2.4 mg/week	3 mg/day	7.5 mg/46 mg daily (maximum 15 mg/92 mg daily)	16 mg/180 mg twice per day	120 mg three times daily	37.5 mg daily[1]
POTENTIAL SIDE EFFECTS	Nausea/Vomiting Diarrhea Constipation Headache Fatigue	Nausea/Vomiting Diarrhea Constipation Headache Fatigue	Restlessness Insomnia Headache Dry Mouth Blurred Vision Tachycardia/BP Elevation Paresthesia Dysgeusia Mental Clouding/Mood Changes	Nausea/Vomiting Diarrhea Constipation Headache Fatigue Insomnia Dry Mouth Blurred Vision Agitation/Mood Changes	Flatulence Fecal Urgency Oily Stools Fat-Soluble Vitamin Drug Malabsorption	Restlessness Insomnia Headache Dry Mouth Tachycardia/BP Elevation
CAUTIONS AND CONTRAINDICATIONS[3]	MTC/MEN2 Tachycardia Pancreatitis/ Gallbladder Disease Diabetic Retinopathy	MTC/MEN2 Tachycardia Pancreatitis/ Gallbladder Disease	Glaucoma Hyperthyroidism Urolithiasis Metabolic Acidosis	Seizure Risk Uncontrolled Hypertension Chronic Opioid Use	Organ Transplant Urolithiasis (Oxalate) Cholestasis	Active CAD Uncontrolled Hypertension Hyperthyroidism Agitated States
ACCESS/COST	$$$	$$$	$$	$$	$$	$

[1]Approved for short term ≤3 months. 15 mg / 30 mg / 37.5 mg phentermine hydrochloride = 12 mg / 24 mg / 30 mg phentermine resin.
[2]Approximate placebo-subtracted with 1 year of therapy except phentermine (12 weeks). [3]All agents are contraindicated in pregnancy/breastfeeding.

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Algorithm Figure 10-Weight-Loss Medications

Algorithm Fig. 10. Profiles of Weight-Loss Medications.

delivery, and potential side effects and contraindications. For a discussion of the evidence for use of these medications for persons with obesity, prediabetes, or T2D, the clinician should consult the 2022 AACE Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan.[9]

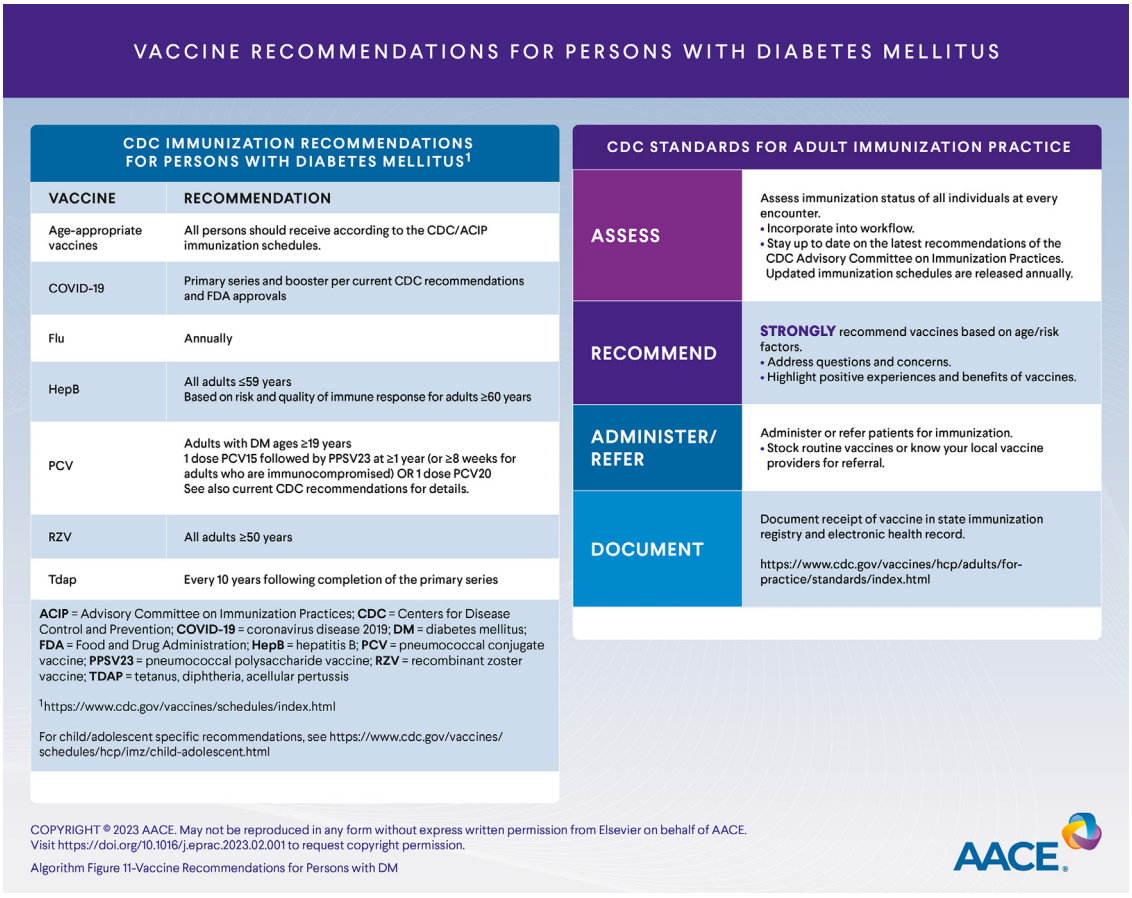
Vaccine Recommendations for Persons with Diabetes

Vaccine-preventable illnesses caused by bacteria and viruses result in significant morbidity and mortality, with worse outcomes among high-risk populations like persons with DM.[174-176] Vaccinations are effective in reducing the severity and associated morbidity and mortality related to these vaccine-preventable illnesses.[174,177] However, the rates of vaccination are suboptimal among patients with DM.[178]

The CDC Advisory Committee on Immunization Practices (ACIP) maintains a comprehensive and updated reference for age-appropriate vaccine recommendations (https://www.cdc.gov/vaccines/schedules/).[179] The AACE supports these recommendations from the CDC/ACIP (Algorithm Fig. 11). The key vaccines recommended for patients with DM also are detailed in the 2022 AACE DM CPG.[9]

Despite the evidence supporting effectiveness of vaccinations among patients with DM, most health care professionals (HCPs) do not routinely evaluate the vaccination status of their patients who rely on the HCP's recommendations to get vaccinated.[180] This results in missed opportunities to increase uptake of preventive vaccines. To address this gap in care, the CDC developed a set of steps that form a framework for implementing vaccinations in clinics called the Standards for Adult Immunization Practice (https://www.cdc.gov/vaccines/hcp/adults/for-practice/standards/index.html).[181] These steps, summarized below, recognize that many HCPs may not be vaccine providers but that they can still play a significant role in getting their patients vaccinated.

- Assess immunization status of all persons with DM at every encounter. This involves staying up to date with the latest vaccine recommendations, implementing protocols that facilitate review of patient immunization status by the care team, and sending reminders for vaccinations.[182]
- Strongly recommend vaccines to patients who are not fully vaccinated. Recommendation from the HCP is a strong predictor of vaccine acceptance by patients.[183] Address patient questions and concerns, explain benefits of vaccination, and highlight positive experiences with vaccinations.
- Administer the vaccines you stock and for those you do not stock, refer your patient to facilities that can provide these vaccines. Know the local resources where you can refer your patients for vaccination.
- Document vaccines administered in your office or by other vaccine providers in the electronic health record (EHR). Make sure the EHR communicates with your state's immunization information system in a bidirectional manner to consolidate vaccination records. Documentations will ensure patients get the vaccinations they need and will prevent unnecessary vaccinations.



Algorithm Fig. 11. Vaccine Recommendations for Persons with Diabetes Mellitus.

When incorporated into routine clinic visits, these steps will be effective in increasing vaccinations and providing protection for patients with DM. Having a properly trained staff and a culture of vaccine confidence in the entire clinical practice are important in ensuring that all health care team members are engaged in efforts to improve patient vaccinations. Other measures recommended to improve vaccination rates include making vaccinations more convenient, coadministration of compatible vaccines, and making use of vaccination champions in the clinical setting.[184]

Review Process

Drafts of this consensus statement were reviewed and approved by all task force members, the AACE CPG Oversight Committee, the AACE Board of Directors, and peer reviewers for *Endocrine Practice*.

Disclosures

The Task Force was empaneled in accordance with the AACE Conflict of Interest (COI) Policy and approved by the AACE COI Subcommittee, Clinical Practice Guidelines Oversight Committee, and AACE executive leadership. All members of the expert Task Force completed disclosures related to commercial and direct financial relationships within the preceding 12 months with companies that develop products connected with endocrine disorders. Categories for disclosure included employment, stock or other ownership, direct financial relationships (eg, speaker or consultant), research funding, authorship or panel involvement on a guideline or white paper related to an overlapping topic, or other situations related to a perceived COI. The AACE COI Subcommittee reviewed disclosures of potential authors against an AACE-approved list of affected companies related to the topic of this consensus statement and made recommendations regarding who could serve on the Task Force in the nonconflicted majority, those who could serve in the conflicted minority with management strategy, and those who were disqualified from serving on the Task Force. Members of this Task Force were reminded throughout development to update potential disclosures if any new relationships/potential COI arose during their appointments and to verify currency of disclosures. AACE made every effort to minimize the potential for COI that could influence guidance provided in this consensus statement.

S.L.S. is a member of the AACE Board of Directors and Executive Committee and has received research support to Mayo Clinic from Corcept, served on a steering committee, and been a national or overall principal investigator from Chiasma and Novartis, and is ABIM Chair, Longitudinal Knowledge Assessment Approval Committee for Endocrinology, Diabetes, and Metabolism. P.V. is a consultant for Takeda Pharmaceutical Company and has been a national or overall principal investigator for National Institutes of Health grant K23 DK 11324-01A1. L.B. is a consultant, with payment to Ochsner Health, for Corcept Therapeutics, Merck, Novo Nordisk, Salix Pharmaceuticals, and Sanofi. E.A.C. received research support to company from Abbott and AbbVie; is a consultant for Ascendis, Boehringer Ingelheim, and Novo Nordisk; is a speaker for Amryt, AstraZeneca, Bayer, Corcept, Eli Lilly, Boehringer Ingelheim, and Novo Nordisk; designed study protocol and is a national principal investigator for the GLITTER1 diabetes mellitus trial funded by Gan & Lee pharmaceuticals; is owner of Endocrinology Associates, Inc; and is part-owner of MediZen. R.J.G. is or has been a consultant for

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Algorithm Title Page

2023 AACE Type 2 Diabetes Algorithm Title Page. *AACE* = American Association of Endocrinology.

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COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

Abbreviations: AACE, American Association of Endocrinology; **ABCD**, adiposity-based chronic disease; **ABI**, ankle brachial index; **ACEi**, angiotensin-converting enzyme inhibitor; **AGI**, alpha-glucosidase inhibitor; **AKI**, acute kidney injury; **apo B**, apolipoprotein B; **ARB**, angiotensin II receptor blocker; **ASCVD**, atherosclerotic cardiovascular disease; **ATP**, Adult Treatment Panel; **A1C**, hemoglobin A1c; **BeAM**, bedtime minus a.m. pre-breakfast glucose; **BRC-QR**, bromocriptine quick release; **BG**, blood glucose; **BMI**, body mass index; **BP**, blood pressure; **CAD**, coronary artery disease; **CCB**, calcium channel blocker; **CDC**, Centers for Disease Control and Prevention; **CGM**, continuous glucose monitoring; **CHF**, congestive heart failure; **CKD**, chronic kidney disease; **COLSVL**, colesevelam; **CoQ10**, coenzyme q10; **COVID-19**, coronavirus disease 2019; **CrCl**, creatinine clearance; **CV**, cardiovascular; **CVD**, cardiovascular disease; **DA**, dopamine agonist; **DASH**, Dietary Approaches to Stop Hypertension; **DKA**, diabetic ketoacidosis; **DKD**, diabetic kidney disease; **DM**, diabetes mellitus; **DPP-4i**, dipeptidyl peptidase-4 inhibitor; **eGFR**, estimated glomerular filtration rate; **ER**, extended release; **FBG**, fasting blood glucose; **FDA**, US Food and Drug Administration; **FPG**, fasting plasma glucose; **GERD**, gastroesophageal reflux disease; **GI**, gastrointestinal; **GIP/GLP-1 RA**, glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist; **GLN**, glinide; **GLP-1 RA**, glucagon-like peptide-1 receptor agonist; **GMI**, glucose management indicator; **GU**, genitourinary; **HDL-C**, high-density lipoprotein cholesterol; **HF**, heart failure; **HFpEF**, heart failure with preserved ejection fraction; **HTN**, hypertension; **IFG**, impaired fasting glucose; **IGT**, impaired glucose tolerance; **LADA**, latent autoimmune diabetes in adults; **LDL-C**, low-density lipoprotein cholesterol; **Lp(a)**, lipoprotein(a); **LV**, left ventricle; **MACE**, major adverse cardiovascular events; **MEN2**, multiple endocrine neoplasia type 2; **MET**, metformin; **MI**, myocardial infarction; **MRA**, mineralocorticoid receptor antagonist; **MTC**, medullary thyroid carcinoma; **NAFLD**, nonalcoholic fatty liver disease; **NASH**, nonalcoholic steatohepatitis; **NCEP**, National Cholesterol Education Program; **NPH**, Neutral Protamine Hagedorn; **NYHA**, New York Heart Association; **OA**, osteoarthritis; **OSA**, obstructive sleep apnea; **PCOS**, polycystic ovary syndrome; **PCSK9**, proprotein convertase subtilisin/kexin type 9; **PG**, plasma glucose; **PPG**, postprandial glucose; **PRAML**, pramlintide; **PVD**, peripheral vascular disease; **RA**, receptor antagonist; **Rx**, medical prescription; **SCR**, serum creatinine; **SGLT2i**, sodium glucose cotransporter 2 inhibitor; **SU**, sulfonylurea; **TDD**, total daily dose; **TG**, triglycerides; **TIA**, transient ischemic attack; **TIR**, time in range; **TZD**, thiazolidinedione; **T1D**, type 1 diabetes; **T2D**, type 2 diabetes; **UACR**, urine albumin-to-creatinine ratio

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2023 AACE Type 2 Diabetes Algorithm Table of Contents. *AACE* = American Association of Endocrinology.

PRINCIPLES OF THE AACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

1. Lifestyle modification underlies all therapy.
2. Maintain or achieve optimal weight.
3. Choice of antihyperglycemic therapy reflects glycemic targets, ASCVD, CHF, CKD, overweight/obesity, and NAFLD.
4. Choice of therapy includes ease of use and access.
5. Optimal A1C is ≤6.5% or as close to normal as is safe and achievable for most patients.
6. Individualize all glycemic targets (A1C, GMI, TIR, FBG, PPG).
7. Get to goal as soon as possible (adjust ≤3 months).
8. Avoid hypoglycemia.
9. CGM is highly recommended to assist patients in reaching goals safely.
10. Comorbidities must be managed for comprehensive care.

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Algorithm Figure 1-Principles

[1]BMI 23 to 25 kg/m^2 may be considered overweight for South Asian, Southeast Asian, and East Asian adults; [2]ABCD complications can include prediabetes, dyslipidemia, hypertension, NAFLD/NASH, ASCVD, CHF and HFpEF, CKD, OSA, OA, asthma/reactive airways disease, GERD, urinary incontinence, PCOS, hypogonadism, and reduced fertility. [3]See PROFILES OF WEIGHT-LOSS MEDICATIONS table.

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Algorithm Figure 2-ABCD

[1]NCEP ATP III Criteria. [2]See COMPLICATIONS-CENTRIC MODEL FOR THE CARE OF PERSONS WITH OVERWEIGHT/OBESITY. [3]If no overweight or obesity, consider T1D antibody testing for LADA. [4]Indications for weight-loss medications are obesity or overweight BMI >27 kg/m^2 with ABCD complication(s) including prediabetes. Choose GLP-1 RA for approved for weight loss. Also consider other approved weight-loss medications (phentermine [short term], orlistat, naltrexone-ER/bupropion-ER). See also PROFILES OF WEIGHT-LOSS MEDICATIONS table.

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Algorithm Figure 3-Prediabetes

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Algorithm Figure 4-Dyslipidemia

[1]Consider patient-specific characteristics DKD, retinopathy, ASCVD, post-MI, CHF, age, and race. [2]ACEi and ARB reduce progression of DKD. Use as first line for UACR >30 mg/g. Thiazide or CCB may also be appropriate as first line in absence of albuminuria. ACEi and ARB should not be used concomitantly. Rule out pregnancy. [3]Chlorthalidone, indapamide, hydrochlorothiazide. [4]Dihydropyridine amlodipine or nifedipine unless indication for non-dihydropyridine. [5] Carvedilol, labetalol, dilevalol. [6]Nebivolol, betaxolol. [7] Resistant hypertension with >140/90 mmHg if on ≥3 agents including maximum dose diuretic; laboratory evaluation for hyperaldosteronism is indicated. Increase laboratory monitoring for combination of ACEi or ARB with MRA due to risk of hyperkalemia or AKI. Finerenone is recommended for persons with CKD associated with diabetes and eGFR ≥25 mL/min/1.73m^2 and UACR ≥30 mg/g. [8] Initiation of SGLT2i or GLP-1RA also may mildly lower BP.

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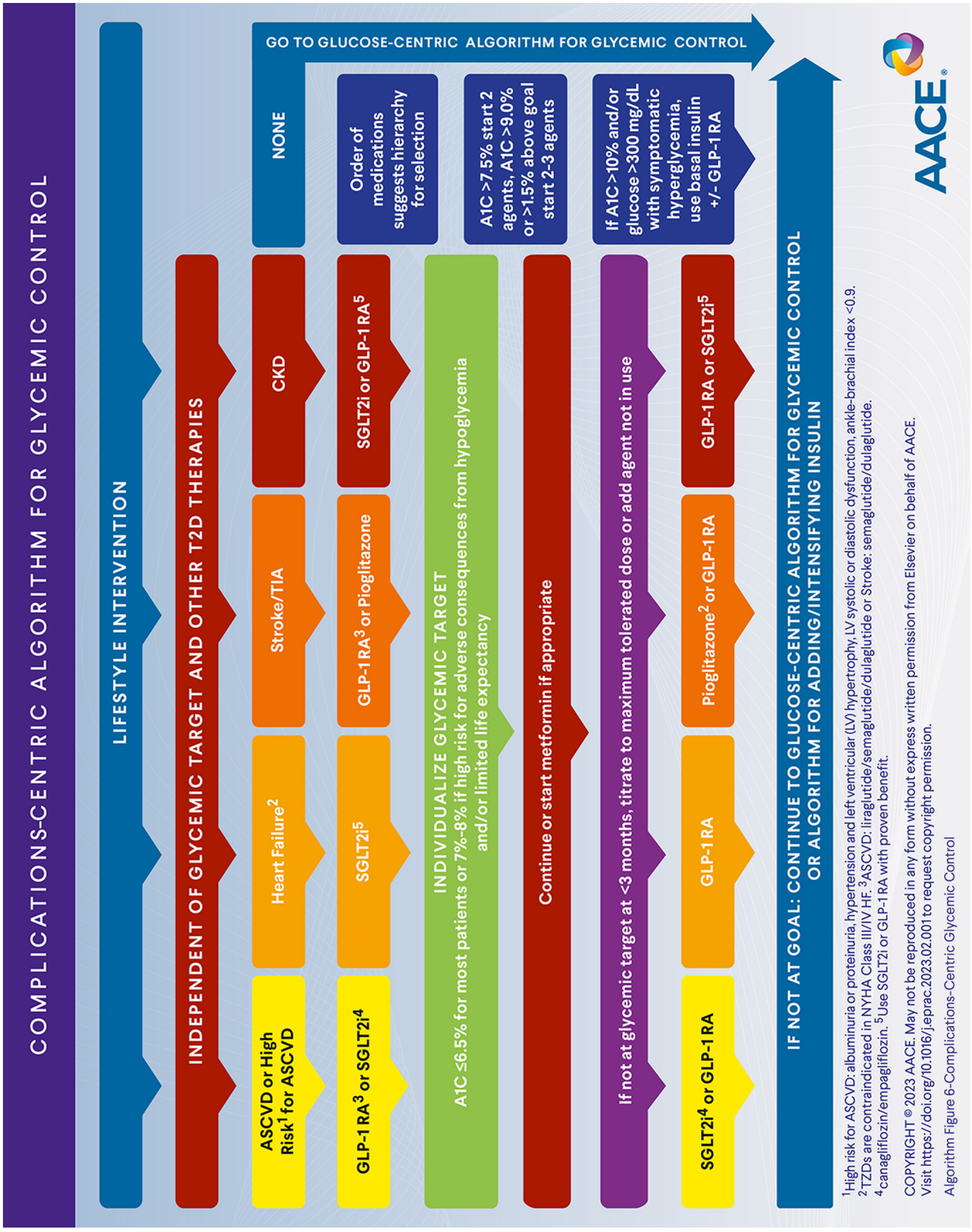
Algorithm Figure 5-Hypertension



[1]High risk for ASCVD: albuminuria or proteinuria, hypertension and left ventricular (LV) hypertrophy, LV systolic or diastolic dysfunction, ankle-brachial index <0.9.
[2]TZDs are contraindicated in NYHA Class III/IV HF. [3]ASCVD: liraglutide/semaglutide/dulaglutide or Stroke: semaglutide/dulaglutide.
[4]canagliflozin/empagliflozin. [5]Use SGLT2i or GLP-1 RA with proven benefit.

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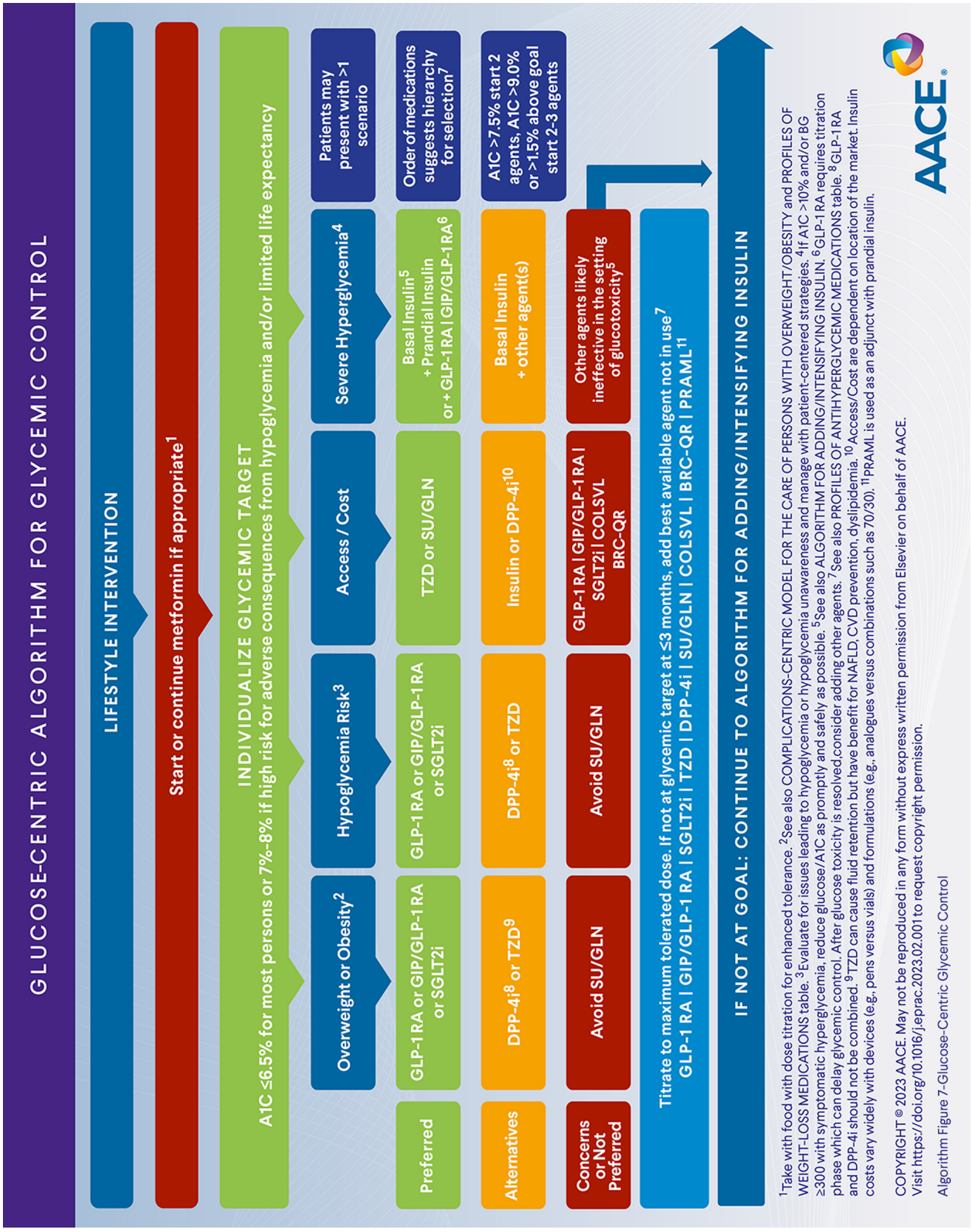
Algorithm Figure 6-Complications-Centric Glycemic Control



[1]Take with food with dose titration for enhanced tolerance. [2]See also COMPLICATIONS-CENTRIC MODEL FOR THE CARE OF PERSONS WITH OVERWEIGHT/OBESITY and PROFILES OF WEIGHT-LOSS MEDICATIONS table. [3]Evaluate for issues leading to hypoglycemia or hypoglycemia unawareness and manage with patient-centered strategies. [4]If A1C >10% and/or BG ≥300 with symptomatic hyperglycemia, reduce glucose/A1C as promptly and safely as possible. [5]See also ALGORITHM FOR ADDING/INTENSIFYING INSULIN. [6]GLP-1 RA requires titration phase which can delay glycemic control. After glucose toxicity is resolved,consider adding other agents. [7]See also PROFILES OF ANTIHYPERGLYCEMIC MEDICATIONS table. [8]GLP-1 RA and DPP-4i should not be combined. [9]TZD can cause fluid retention but have benefit for NAFLD.CVD prevention, dyslipidemia. [10]Access/Cost are dependent on location of the market. Insulin costs vary widely with devices (e.g., pens versus vials) and formulations (e.g., analogues versus combinations such as 70/30). [11]PRAML is used as an adjunct with prandial insulin.

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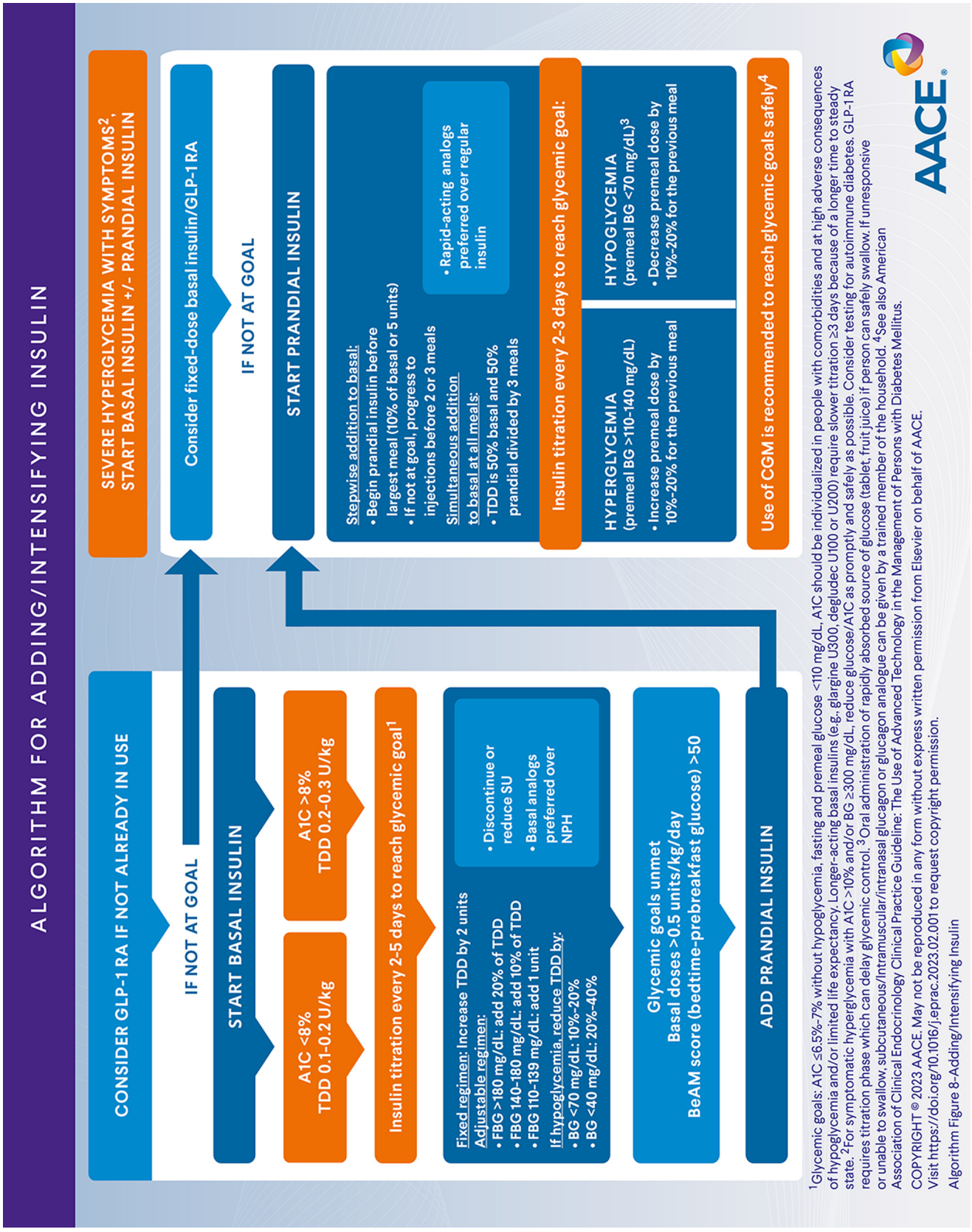
Algorithm Figure 7–Glucose-Centric Glycemic Control



[1]Glycemic goals: A1C ≤6.5%-7% without hypoglycemia, fasting and premeal glucose <110 mg/dL. A1C should be individualized in people with comorbidities and at high adverse consequences of hypoglycemia and/or limited life expectancy. Longer-acting basal insulins (e.g., glargine U300, degludec U100 or U200) require slower titration ≥3 days because of a longer time to steady state. [2]For symptomatic hyperglycemia with A1C >10% and/or BG ≥300 mg/dL, reduce glucose/A1C as promptly and safely as possible. Consider testing for autoimmune diabetes. GLP-1 RA requires titration phase which can delay glycemic control. [3]Oral administration of rapidly absorbed source of glucose (tablet, fruit juice) if person can safely swallow. If unresponsive or unable to swallow, subcutaneous/intramuscular/intranasal glucagon or glucagon analogue can be given by a trained member of the household. [4]See also American Association of Clinical Endocrinology Clinical Practice Guideline: The Use of Advanced Technology in the Management of Persons with Diabetes Mellitus.

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Algorithm Figure 8-Adding/Intensifying Insulin

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PROFILES OF ANTIHYPERGLYCEMIC MEDICATIONS

	MET	GLP-1 RA	DUAL GIP/ GLP-1 RA	SGLT2i	TZD	INSULIN (basal & basal bolus)	DPP-4i	SU	GLN	AGi	COLSVL	BRC	PRAML
EFFICACY FOR GLUCOSE LOWERING	++	+++	+++	++	++	+++/++++	+	++	+	+	+	+	+
ASCVD – MACE	Neutral	Benefit[1,3]	Safe	Benefit[2]	Neutral[3]	Neutral	Neutral	Possible Increased Risk	Neutral	Insufficient Evidence	Neutral[3]	Safe	Insufficient Evidence
ASCVD – CHF		Unclear		Reduced Risk	Moderate to Severe[4]	Moderate	Moderate[4]						
ASCVD – STROKE		Benefit[5]		Possible Benefit[2]	Benefit	Neutral	Neutral						
CKD	CKD3a/3b[6]	Benefit[7]	Insufficient Evidence	Benefit	Neutral	Increased hypoglycemia risk with impaired renal function	Neutral	Increased hypoglycemia risk with impaired renal function		Not recommended SCR >2 mg/dL or CrCl <25	Neutral	Neutral	Neutral
RENAL ADJUSTMENT	Not with CKD4 eGFR <30[6]	Exenatide not recommended eGFR <45		Check medication-specific eGFR thresholds[8]			Adjust Dose[9]						
HYPOGLYCEMIA RISK[14]	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate to Severe	Neutral	Moderate to Severe	Mild	Neutral	Neutral	Neutral	Neutral
WEIGHT	Slight loss	Loss	Loss	Loss	Gain[4]	Gain	Neutral	Gain	Neutral	Neutral	Neutral	Neutral	Loss
NAFLD	Neutral	Benefit	Benefit	Potential Benefit	Benefit	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Benefit
GI ADVERSE SYMPTOMS	Mild to Moderate	Moderate[10]	Moderate[10]	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate	Mild	Moderate	Moderate
OTHER CONSIDERATIONS		Medullary Thyroid Carcinoma/ MEN2	Medullary Thyroid Carcinoma/ MEN2	GU infections DKA[11] Fracture Risk[12]	Fracture Risk		Rare Arthralgias/ Myalgias						
ACCESS/COST	$	$$$	$$$	$$$	$	$ - $$$[13]	$-$$	$	$-$$	$-$$	$$$	$$$	$$$

■ Possible benefits ■ Use with caution ■ Likelihood of adverse events ■ Neutral, not studied, insufficient evidence

[1]GLP-1 RA MACE benefits with liraglutide, semaglutide, dulaglutide. [2]SGLT2i MACE benefits with empagliflozin, canagliflozin. Possible benefit for hemorrhagic stroke. [3]GLP-1 RA, TZD, COLSVL can lower LDL. [4]TZDs increase fluid retention and edema and are contraindicated in persons with NYHA Class III/IV CHF. There is Increased risk of hospitalization for CHF with saxagliptin, and limited experience for persons with NYHA Class II/IV CHF with alogliptin [5]GLP-1 RA stroke benefits observed with semaglutide and dulaglutide. [6]CKD3a no adjustment with monitoring, CKD3b decrease dose and do not initiate, CKD4 contraindicated. Hold for acute kidney injury, IV contrast. [7]Dulaglutide, semaglutide decrease CKD progression. [8]The eGFR thresholds for initiation and/or continuation of therapy in CKD vary among SGLT2i. Check medication-specific eGFR levels. [9]Only linagliptin does not require adjustment. [10]Slow titration, portion control, and consider reducing to prior tolerated dose. [11]Precipitants include significant current illness, surgery, inappropriate or rapid insulin dose reduction. [12]Reported with canagliflozin, dapagliflozin. [13]Cost varies widely with devices (e.g., pens), formulations (e.g., analogues), and combinations (e.g., 70/30). [14]SIngle-agent risks of hypoglycemia may be low but increases when combined with other agents.

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Algorithm Figure 9-Antihyperglycemic Medications

PROFILES OF WEIGHT-LOSS MEDICATIONS

	SEMAGLUTIDE	LIRAGLUTIDE	PHENTERMINE/ TOPIRAMATE-ER	NALTREXONE-ER/ BUPROPRION-ER	ORLISTAT	PHENTERMINE[1]
CLASS	GLP-1 RA	GLP-1 RA	Sympathomimetic Amine/Gabaminergic	Opioid-Receptor Antagonist/DA-Norepi Reuptake inhibitor	GI Lipase Inhibitor	Sympathomimetic
WEIGHT LOSS[2]	15%-18%	5%-6%	9%-10%	4%-6%	4%	3%[2]
MECHANISM	Decreased Appetite Delayed Gastric Emptying	Decreased Appetite Delayed Gastric Emptying	Decreased Appetite Increased Satiety	Decreased Cravings Decreased Appetite	Decreased Fat Absorption	Decreased Appetite
DELIVERY	Weekly Subcutaneous Injection	Daily Subcutaneous Injection	Oral	Oral	Oral	Oral
STARTING DOSE	0.25 mg/week	0.6 mg/day	3.75 mg/23 mg daily	8 mg/90 mg daily	120 mg three times daily	15 mg daily
TREATMENT DOSE	2.4 mg/week	3 mg/day	7.5 mg/46 mg daily (maximum 15 mg/92 mg daily)	16 mg/180 mg twice per day	120 mg three times daily	37.5 mg daily[1]
POTENTIAL SIDE EFFECTS	Nausea/Vomiting Diarrhea Constipation Headache Fatigue	Nausea/Vomiting Diarrhea Constipation Headache Fatigue	Restlessness Insomnia Headache Dry Mouth Blurred Vision Tachycardia/BP Elevation Paresthesia Dysgeusia Mental Clouding/Mood Changes	Nausea/Vomiting Diarrhea Constipation Headache Fatigue Insomnia Dry Mouth Blurred Vision Agitation/Mood Changes	Flatulence Fecal Urgency Oily Stools Fat-Soluble Vitamin Drug Malabsorption	Restlessness Insomnia Headache Dry Mouth Tachycardia/BP Elevation
CAUTIONS AND CONTRAINDICATIONS[3]	MTC/MEN2 Tachycardia Pancreatitis/ Gallbladder Disease Diabetic Retinopathy	MTC/MEN2 Tachycardia Pancreatitis/ Gallbladder Disease	Glaucoma Hyperthyroidism Urolithiasis Metabolic Acidosis	Seizure Risk Uncontrolled Hypertension Chronic Opioid Use	Organ Transplant Urolithiasis (Oxalate) Cholestasis	Active CAD Uncontrolled Hypertension Hyperthyroidism Agitated States
ACCESS/COST	$$$	$$$	$$	$$	$$	$

[1]Approved for short term ≤3 months. 15 mg / 30 mg / 37.5 mg phentermine hydrochloride = 12 mg / 24 mg / 30 mg phentermine resin.
[2]Approximate placebo-subtracted with 1 year of therapy except phentermine (12 weeks). [3] All agents are contraindicated in pregnancy/breastfeeding.

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Algorithm Figure 10-Weight-Loss Medications

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VACCINE RECOMMENDATIONS FOR PERSONS WITH DIABETES MELLITUS

CDC IMMUNIZATION RECOMMENDATIONS FOR PERSONS WITH DIABETES MELLITUS[1]

VACCINE	RECOMMENDATION
Age-appropriate vaccines	All persons should receive according to the CDC/ACIP immunization schedules.
COVID-19	Primary series and booster per current CDC recommendations and FDA approvals
Flu	Annually
HepB	All adults ≤59 years Based on risk and quality of immune response for adults ≥60 years
PCV	Adults with DM ages ≥19 years 1 dose PCV15 followed by PPSV23 at ≥1 year (or ≥8 weeks for adults who are immunocompromised) OR 1 dose PCV20 See also current CDC recommendations for details.
RZV	All adults ≥50 years
Tdap	Every 10 years following completion of the primary series

ACIP = Advisory Committee on Immunization Practices; **CDC** = Centers for Disease Control and Prevention; **COVID-19** = coronavirus disease 2019; **DM** = diabetes mellitus; **FDA** = Food and Drug Administration; **HepB** = hepatitis B; **PCV** = pneumococcal conjugate vaccine; **PPSV23** = pneumococcal polysaccharide vaccine; **RZV** = recombinant zoster vaccine; **TDAP** = tetanus, diphtheria, acellular pertussis

[1]https://www.cdc.gov/vaccines/schedules/index.html

For child/adolescent specific recommendations, see https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html

CDC STANDARDS FOR ADULT IMMUNIZATION PRACTICE

ASSESS	Assess immunization status of all individuals at every encounter. • Incorporate into workflow. • Stay up to date on the latest recommendations of the CDC Advisory Committee on Immunization Practices. Updated immunization schedules are released annually.
RECOMMEND	**STRONGLY** recommend vaccines based on age/risk factors. • Address questions and concerns. • Highlight positive experiences and benefits of vaccines.
ADMINISTER/ REFER	Administer or refer patients for immunization. • Stock routine vaccines or know your local vaccine providers for referral.
DOCUMENT	Document receipt of vaccine in state immunization registry and electronic health record. https://www.cdc.gov/vaccines/hcp/adults/for-practice/standards/index.html

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Algorithm Figure 11-Vaccine Recommendations for Persons with DM

Bayer, Boehringer Ingelheim, Eli Lilly and Company, Novo Nordisk, Pfizer, Sanofi, and Weight Watchers; has received research support to Emory University for investigator-initiated studies and been a national or overall principal investigator for Dexcom, Eli Lilly and Company, and Novo Nordisk; and has been partially supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health under Award Numbers P30DK111024-04S, 1K23DK123384. I.B.H. is on the advisory boards of Abbott, Bigfoot, GWave, and Roche; received research support from Beta Bionics, Insulet, and Medtronic Diabetes Care; participated in development of a consensus report on the Management of Type 1 Diabetes in Adults for the American Diabetes Association and European Association for the Study of Diabetes and an Endocrine Society guideline on inpatient diabetes management. S.D.I. is a member of the AACE Board of Directors and Executive Committee and is a consultant (without pay) for Myovant Sciences, Madrigal Pharmaceuticals, Siemens, and Novo Nordisk. K.E.I. is a member of the AACE Board of Directors and has received research support from Novo Nordisk and is on the board of the Nevada Clinical Endocrinologists Association. C.C.L. receives research support to Jaeb Coordinating Center and the University of Colorado for investigator-initiated studies from Dexcom, Inc, is treasurer of the American College of Diabetology, secretary of the Clinical Diabetes and Endocrine Institute, and chair of the Advisory Committee for the FDA on Endocrinologic and Metabolic Drugs, whose views are not represented herein. G.E.U. has received research support and been a national or overall principal investigator for AstraZeneca, Dexcom, and Novo Nordisk; serves as president, Medicine & Science, for the American Diabetes Association; and participated in development of the Endocrine Society guideline on hospital diabetes and Society of Critical Care guideline on ICU diabetes. W.M.V. and C.L.T. have no conflicts of interest to disclose.

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Panel Composition

The Task Force was empaneled in accordance with the AACE Conflict of Interest and Diversity, Equity, and Inclusion policies. This consensus statement was developed by a group of credentialed medical professionals in the field of endocrinology. Participants on this task force included current AACE members in good standing.

Updating Policy

AACE reviews and updates or retires its guidance documents every 3 to 5 years or after significant scientific developments or change in public policy as determined by AACE executive leadership, the AACE Clinical Practice Guidelines Oversight Committee, and relevant AACE disease state network(s).

Document Expiration Date: June 2026

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Erratum

In the May 2023 issue of *Endocrine Practice*, the paper by Samson et al (Samson SL, Vellanki P, Blonde L, et al. American Association of Clinical Endocrinology Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm — 2023 Update. Endocr Pract. 2023;29(5):305–340) contained inaccurate affiliation information for Dr Kenneth Izuora. Dr Izuora's correct title is Professor and not Associate Professor as originally published. The corrected affiliation info is as follows:

Professor, Department of Internal Medicine, Endocrinology, Kirk Kerkorian School of Medicine, University of Nevada Las Vegas, Las Vegas, Nevada

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Declaration of Dr. Nathan Laney

Exhibit E

FEATURE ARTICLE

Exploring the Burden of Mealtime Insulin Dosing in Adults and Children With Type 1 Diabetes

Wendy Lane,[1] Emma Lambert,[2] Jesso George,[3] Naveen Rathor,[3] and Nandu Thalange[4]

Timely and accurate mealtime insulin dosing can be an ongoing challenge for people with type 1 diabetes. This multinational, online study aimed to explore attitudes and behaviors around mealtime insulin dosing and the impact of mealtime dose timing, particularly with regard to premeal dosing (15–20 minutes before a meal). Although the majority of surveyed participants (96%) recognized the importance of accurate mealtime bolus insulin dosing, only a small proportion (35%) reported being "very confident" in accurate bolus insulin estimation. Given the choice, the majority of participants would prefer to administer insulin immediately before or after a meal, as this timing would improve their quality of life.

KEY POINTS

- Although the majority of surveyed participants (96%) recognized the importance of accurate mealtime bolus insulin dosing, only a small proportion (35%) reported being "very confident" in accurate bolus insulin estimation.
- Most responding adults with type 1 diabetes (91%) and parents of children with type 1 diabetes (97%) experienced challenge(s) related to premeal insulin dosing.
- Most responding adults with type 1 diabetes (91%) and parents of children with type 1 diabetes (92%) reported worrying about postmeal glucose levels at least occasionally.
- A high proportion of responding adults with type 1 diabetes (67%) and parents of children with type 1 diabetes (72%) said that having the freedom to administer mealtime insulin immediately before or after the start of a meal rather than 15–20 minutes before the meal would have a positive impact on their lives.

A large proportion of people with type 1 diabetes, both adults and children, do not achieve guideline-recommended A1C targets (1,2). Contributing to overall glycemic burden is postprandial glucose (PPG), which, together with fasting plasma glucose, is a target measure that is incorporated into guideline recommendations (3). Elevated PPG levels have been shown to be associated with a significant increase in health care resource utilization, including clinic visits, calls, emails to health care providers, and hospitalizations among adults with diabetes who use a multiple daily injection insulin (MDI) regimen (4). However, managing PPG remains one of the most challenging aspects of diabetes care.

PPG control is multifactorial; contributors include timing, quantity, and composition of the meal and asynchrony between postmeal glucose absorption and maximal exogenous insulin effect, which often lags behind glucose absorption by up to 2 hours. Patient-related causes greatly contribute to suboptimal PPG control and include reduced or skipped mealtime insulin doses and inaccurate estimation of carbohydrate intake (5).

Optimal timing of mealtime insulin dosing is a key factor in controlling PPG levels (6,7). In this article, for clarity, we refer to the administration of insulin 15–20 minutes before a meal as a "premeal bolus." When insulin is administered immediately before a meal (usually

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regarded as 0–2 minutes before the meal), we refer to this as a "mealtime bolus." Administration of insulin after the start of a meal is referred to as a "postmeal bolus."

Multiple studies and clinical practice guidelines have suggested that the optimal time to administer a rapid-acting insulin analog is 15–20 minutes before the start of a meal (6,8). This recommendation follows observations in general practice and studies evaluating the effect on PPG excursions of dose timing of rapid-acting insulin relative to meals in people with type 1 diabetes (Supplementary Table S1) (7,9–13). Premeal bolusing of rapid-acting insulin analogs 15 minutes before mealtime resulted in lower PPG excursions and more time spent in the euglycemic range (3.5–10.0 mmol/L) without increased risk of hypoglycemia (7).

Despite these results and clinical recommendations, real-world studies have demonstrated poor adherence to the recommended injection-to-meal interval, and postmeal bolus dosing is commonly observed (5,14,15). Synchronizing the administration of insulin with its anticipated effect on glucose absorption poses a significant challenge for many people with diabetes, especially children or anyone who struggles to adhere to lifestyle routines. Some of the challenges associated with mealtime insulin dosing include injection pain, embarrassment, and interference with daily activities (5,16).

Quantitative data from studies investigating the challenges of mealtime insulin dosing are scarce. Here, we explore attitudes and behaviors around mealtime insulin dosing and the impact of mealtime dose timing, particularly with regard to premeal dosing, in both adults and children with type 1 diabetes, as well as physicians who treat people with type 1 diabetes.

Research Design and Methods

Study Design and Recruitment

An online closed survey was conducted between 25 November 2019 and 6 February 2020 with adults with type 1 diabetes, parents of children with type 1 diabetes, and physicians who treat people with type 1 diabetes from across the United States, Canada, the United Kingdom, Japan, Spain, and France. Adults with type 1 diabetes and parents of children with type 1 diabetes were recruited online via social networks (e.g., Facebook, Twitter, Instagram, and Snapchat) as well as custom ad networks (Google). Participants were also invited through direct advertising on specific health sites or sourced through collaboration with charities and support groups. Physicians were recruited online from Sermo and its panel partners. Incentives were offered for participation in the form of reward points for participants and money for physicians (see Supplementary Materials). Online pilot interviews were conducted with a small sample of people with type 1 diabetes to ensure that the language, flow, and clarity of the survey was appropriate. An invitation link to the main survey was sent to participants via e-mail. Each participant was assigned a unique survey ID based on their IP address and machine ID. Once accessed, participants could not access the survey again. All participants provided informed consent and chose to take part in the survey, during which no personal identifying information was collected.

The survey was conducted by Ipsos Healthcare in compliance with Market Research Society, European Society for Opinion and Marketing Research, European Pharmaceutical Market Research Association, and British Healthcare Business Intelligence Association guidelines. All data collection/abstraction was conducted according to the Health Insurance Portability and Accountability Act and institutional review board policies and procedures.

Study Participants

Adults (age ≥18 years) and parents of children (age ≤15 years) who had had type 1 diabetes for ≥6 months and were administering insulin with meals (excluding fast-acting insulin aspart) were eligible to take the survey. Physicians were eligible if they fulfilled the following criteria: practicing for 3–40 years, treating at least 15 (United States) or 10 (other countries) people with type 1 diabetes (endocrinologists) or at least 5 people with type 1 diabetes (general practitioners/primary care physicians) in a typical month, responsible for starting or managing treatment for type 1 diabetes and for the prescription of mealtime insulin, and prescribing at least one mealtime insulin that required dosing at least 15–20 minutes before a meal.

Outcomes and Analysis

The survey set out to determine the challenges associated with administration of insulin with meals and to assess the extent to which premeal administration affects daily routines and the emotional well-being of people with type 1 diabetes and their carers. The survey also explored the extent to which physicians believe that premeal insulin dosing presents a challenge to people with type 1 diabetes. The main survey questions used are

provided in the Supplementary Materials. For this survey, premeal insulin administration refers to the administration of insulin 15–20 minutes before a meal.

Results are presented using descriptive statistics; no formal statistical analyses were conducted. Incomplete questionnaires were excluded from the analysis. The analysis provided weighted data, assuming equal sizes for each country, to give an overall indication of results across participating countries. Data analysis was conducted using SPSS statistical software (IBM).

Data Availability

The datasets generated and/or analyzed during this study are available from the corresponding author on reasonable request.

Results

Participants

A flow diagram for study participants is shown in Supplementary Figure S1. Of the 2,711 participants included in the study, 1,401 were adults with type 1 diabetes, and 350 were parents of children (≤15 years old) with type 1 diabetes. The remaining 960 participants were physicians who treated people with type 1 diabetes according to the criteria outlined above.

In adults included in the survey (46% of whom were male), the mean age at baseline was 43 ± 14 years and mean duration of diabetes was 19 ± 15 years. In children (64% of whom were male), the mean age at baseline was 10 ± 4 years, and the mean duration of diabetes was 4 ± 3 years. In both groups, >70% of people were administered insulin using an MDI regimen (pen or syringe), while ∼30% used an insulin pump (continuous subcutaneous insulin infusion). Insulin aspart and insulin lispro were the short-acting insulin analogs most commonly used (in 47 and 32% of adults, and in 38 and 35% of children, respectively), and 73% of adults and 91% of children used continuous glucose monitoring (CGM).

Of the participating physicians, 30.5% (n = 293) were general practitioners or primary care physicians, 39.3% (n = 377) were endocrinologists, 1.6% (n = 15) were pediatric endocrinologists, 23.2% (n = 223) were diabetologists, and 5.5% (n = 53) were pediatricians. Overall, 85.3% of interviewed physicians both initiate and manage insulin therapy for people with type 1 diabetes in their clinics, whereas 14.7% of them help manage their patients' diabetes but do not initiate treatment. Across specialties, the mean number of years in practice was 18.8 years (range 3–40). Of their patients, 72.5% were using MDI (pen or syringe), 26.4% used an insulin pump, and 2.6% used an inhaler; 49.4% of their patients were using CGM. Although survey participants did not have experience administering ultra-fast-acting insulin, 50.8% of participating physicians did have experience prescribing one of these agents, specifically fast-acting insulin aspart.

Attitudes Toward Mealtime Insulin Dosing

The majority of adults with type 1 diabetes (96%, n = 1349) and parents of children with type 1 diabetes (94%, n = 30) surveyed believed it is important (either very or fairly important) to take mealtime insulin accurately (Figure 1*A*). When asked about the level of confidence in accurately estimating the required amount of insulin needed for a meal, only 35% (n = 488) of adults and 47% (n = 164) of parents of children felt very confident, whereas 13% (n = 188) of adults and 10% (n = 35) of parents did not feel very confident or confident at all (Figure 1*B*). Of the surveyed physicians, only 16% (n = 115) felt that their patients were very confident in accurately estimating the amount of insulin required at mealtimes (Figure 1*B*).

Challenges With Mealtime Insulin Dosing

Based on a provided list of challenges associated with mealtime insulin dosing, 91% of adults and 97% of parents of children with type 1 diabetes reportedly experienced at least one of the listed challenges. Accordingly, almost all interviewed physicians (99.6%) believed that their patients faced challenges with mealtime insulin dosing. An overview of these challenges is presented in Supplementary Figures S2 and S3.

Overall, the main challenges reported for adults and children with type 1 diabetes included the need to inject more insulin after a meal because of eating more or different food than anticipated and not knowing how much insulin to take to cover a given amount of carbohydrate (Supplementary Figure S2). Similarly, according to physicians, the main challenge for people with type 1 diabetes regarding mealtime insulin dosing was knowing what and how much food is needed (Supplementary Figure S3). The individual frequencies for respondents who ate more or less than anticipated after mealtime insulin dosing are presented in Figure 2*A* and *B*, respectively. Overall, 70% of adults and 81% of parents of children stated that, at least once a week, they ate more or less food than anticipated after dosing mealtime insulin. Furthermore, at least once a week,

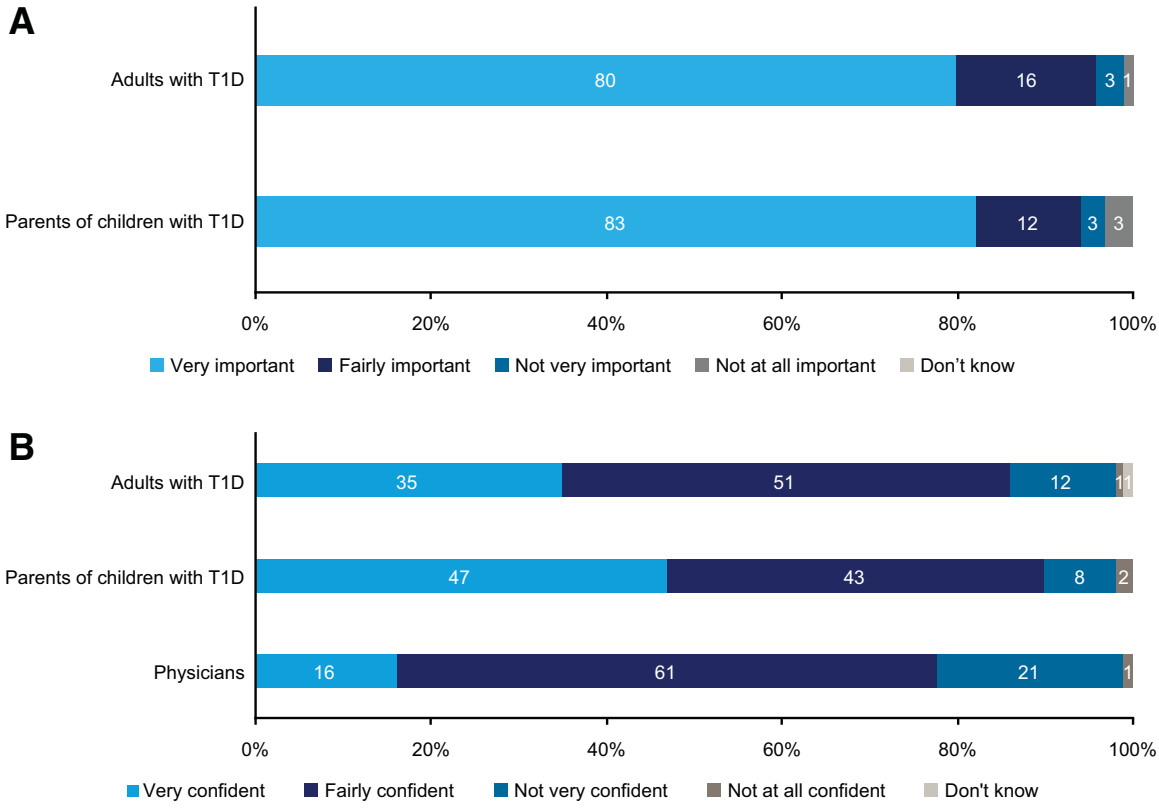


FIGURE 1 Attitudes toward mealtime insulin dosing. *A*) Importance of taking mealtime insulin accurately, as reported by adults and parents of children with type 1 diabetes. *B*) Confidence in estimating the amount of mealtime insulin accurately, as reported by adults with type 1 diabetes, parents of children with type 1 diabetes, and physicians assessing their patients with type 1 diabetes. Corresponding survey questions (A1 and A2 on the patient/parent survey and A1 on the physician survey) are included in the Supplementary Materials. T1D, type 1 diabetes.

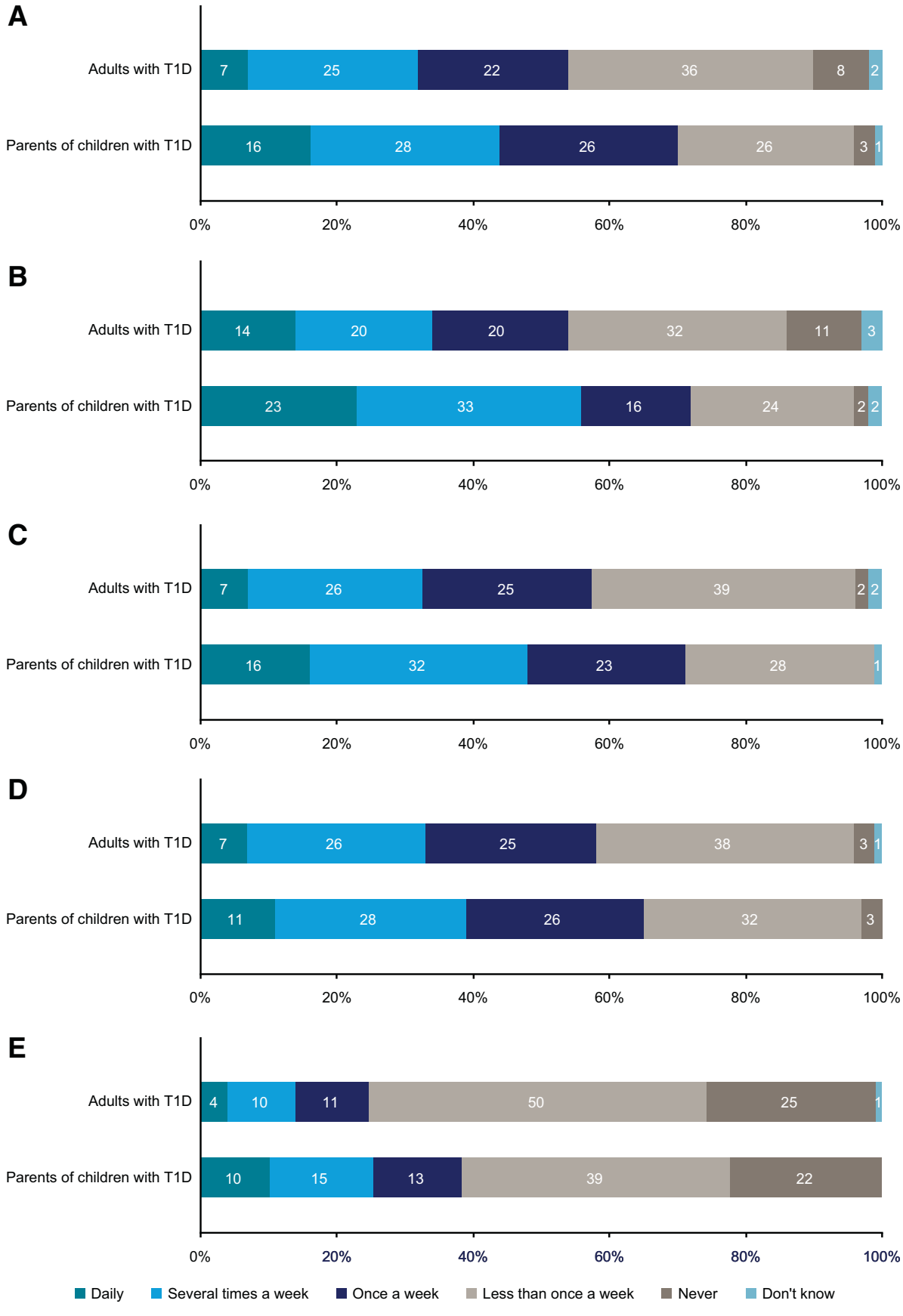
58% (n = 720) of adults and 70% (n = 241) of children needed additional food intake as a corrective action to prevent hypoglycemia as a result of eating a meal that had fewer grams of carbohydrates than anticipated (Figure 2*C*). Similarly, corrective insulin after consuming more food than was anticipated was reportedly needed at least once a week by 57% (n = 719) of adults and 65% (n = 219) of children (Figure 2*D*).

Of those surveyed, 25% (n = 348) of adults and 38% (n = 135) of children completely forgot to take their mealtime insulin at least once a week (Figure *2E*). Of the participating physicians, 21% (n = 200) stated that they always discussed mealtime insulin dosing, whereas 68% (n = 650) of physicians reported sometimes and 11% (n = 104) reported hardly ever having this discussion with their patients.

Impact of Premeal Insulin Administration

Overall, 82% of surveyed adults felt that having to administer insulin 15–20 minutes before their meals negatively affected their lifestyle greatly or to some extent. Similarly, 93% of parents felt that this practice had a negative impact to a great or to some extent on their child's day-to-day life. Accordingly, 19% (n = 264) of surveyed adults and 44% (n = 153) of parents chose not to eat out at least once a week because they were unsure about how much bolus insulin might be needed for the meal. The extent of the impact of premeal dosing on life in general, mood, social life, feeling of independence, work, and personal relationships is shown in Figure 3. The majority of physicians (91%, n = 876) agreed that the need for premeal dosing is an extra burden for their patients.

Most adults with type 1 diabetes (91%, n = 1,258) and parents of children with type 1 diabetes (92%, n = 321) worry about PPG levels after a meal to some extent (15 and 21% always, 28 and 31% often, and 48 and 40% occasionally, respectively). Few adults (8%, n = 119) or parents of children (8%, n = 27) reported never worrying about PPG levels.


A
Adults with T1D
7
25
22
36
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2
Parents of children with T1D
16
28
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0%
20%
40%
60%
80%
100%
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Adults with T1D
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0%
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80%
100%
E
Adults with T1D
4
10
11
50
25
1
Parents of children with T1D
10
15
13
39
22
0%
20%
40%
60%
80%
100%
Daily
Several times a week
Once a week
Less than once a week
Never
Don't know

FIGURE 2 Challenges with mealtime insulin dosing as reported by adults and parents of children with type 1 diabetes. *A*) Frequency of eating more than anticipated after dosing insulin according to their physician's guidance. *B*) Frequency of eating less than anticipated after dosing insulin according to their physician's guidance. *C*) Frequency of needing to consume extra food because a meal contained less carbohydrate content than anticipated. *D*) Frequency of needing to take extra insulin to correct additional food intake. *E*) Frequency of completely forgetting to take mealtime insulin. "At least once a week" was calculated by summing the responses for "daily," "several times a week," and "once a week." Corresponding survey questions (A5–A8 and A10 on the patient/parent survey) are included in the Supplementary Materials. T1D, type 1 diabetes.

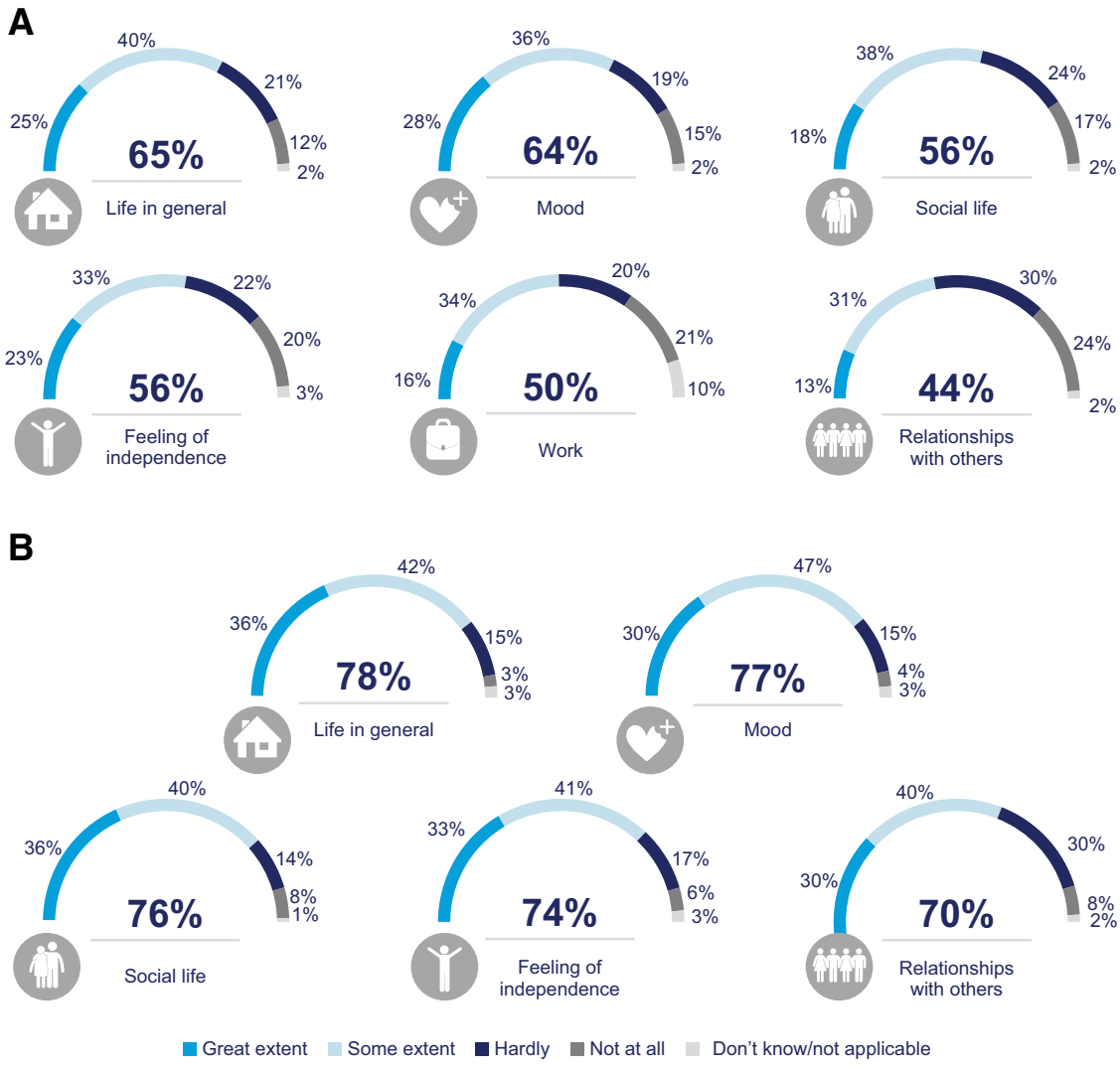

FIGURE 3 The extent of negative impact of premeal insulin dosing on day-to-day life in adults with type 1 diabetes (*A*) and parents of children with type 1 diabetes (*B*). The corresponding survey question (A14 on the patient/parent survey) is included in the Supplementary Materials.

The key emotions associated with mealtime dosing, reported both by adults and parents of children with type 1 diabetes, included acceptance (28 and 31%, respectively), ability to cope (30 and 26%), and being in control (26 and 25%). A feeling of inconvenience was also reported by many adults (34%). Of the interviewed physicians, 85% (n = 819) believed premeal dosing negatively affects the emotional well-being of patients.

Insulin Dosing Preferences

When asked what they would prefer, 73% (n = 1,023) of adults and 67% (n = 231) of parents of children with type 1 diabetes indicated that they would choose bolus

insulin administration either immediately before or after a meal (Figure 4). Furthermore, 55% (n = 772) of adults and 65% (n = 227) of parents of children with type 1 diabetes at least once a week resorted to post-meal insulin administration when they knew exactly what had been eaten.

A large proportion of adults (67%, n = 939) and parents of children (72%, n = 252) with type 1 diabetes claimed that having the freedom to administer insulin at mealtime either immediately before or after the start of a meal would have a positive impact (very positive or fairly positive) on their lives. Likewise, the majority of physicians believed that their patients' quality of life would improve (to a great or some extent) if mealtime insulin administration was feasible immediately before a meal (92% of physicians) or immediately after the start of a meal (89% of physicians).

Discussion

Here, we present the findings of a multinational survey conducted with >1,700 people with type 1 diabetes and >900 physicians with experience treating people with type 1 diabetes to assess perceptions, challenges, and impact of and behaviors associated with mealtime insulin dosing. To our knowledge, this is the first detailed study on understanding the burden associated with pre-meal administration of insulin (15–20 minutes before eating). The insights generated may be useful to clinicians for guiding bolus insulin management and decision-making.

Although nearly all surveyed participants (96%) recognized the importance of accurate mealtime bolus insulin dosing, only a small proportion (35%) reported being "very confident" in accurate bolus insulin estimation.

Moreover, one in four adults with type 1 diabetes and approximately one in three parents of children with type 1 diabetes acknowledged completely forgetting to administer prandial insulin at least once a week. This finding might be driven, in part, by a lack of confidence in accurate mealtime dosing, as reported by both people with type 1 diabetes and physicians in the survey.

Although not all were explored in this survey, it is well recognized that there are multiple barriers to treatment adherence and optimization and that treatment inertia exists (17). Barriers include patient factors (e.g., forgetting to take medications or fear of injections), medication factors (e.g., burdensome regimens and side effects), and system factors (e.g., inadequate follow-up, communication, and support) (17). Importantly, ~70% of surveyed physicians acknowledged only sometimes discussing challenges around mealtime dosing requirements when their patients raised the issue, clearly indicating the need for improved patient-doctor communication on this basic precept of diabetes management.

Not surprisingly, adjusting insulin dose to meals, or vice versa, was a key challenge reported by people with type 1 diabetes and their treating physicians. Accordingly, the need for additional food intake or additional insulin was reported frequently as necessary corrective actions occurring on at least a weekly basis. Parents of children with type 1 diabetes were more likely than adults with diabetes to report these challenges, as it is more difficult to predict the amount of food a child will eat. Consequently, at least half of surveyed participants resorted to postmeal insulin administration at least once a week.

It follows that the majority of surveyed people with type 1 diabetes and physicians felt that the need for premeal

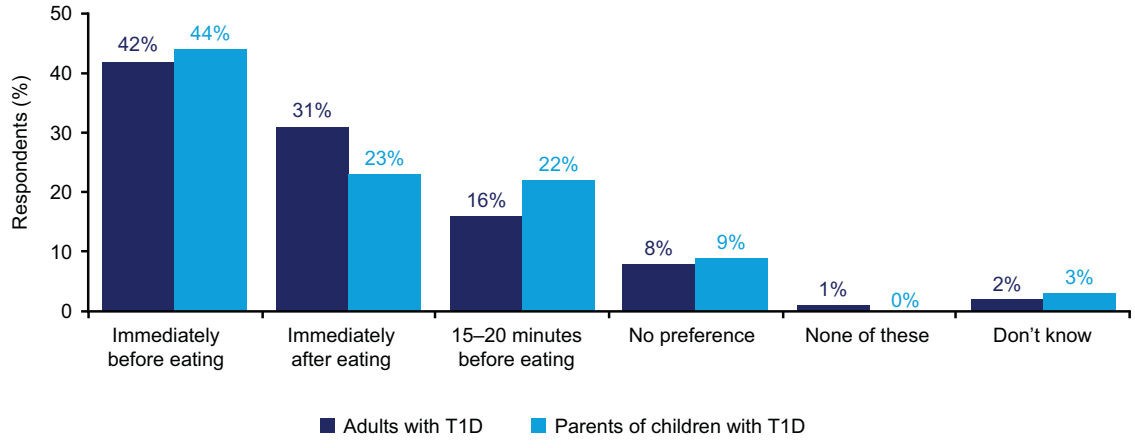

FIGURE 4 Preferred time for taking mealtime insulin given a choice, as reported by adults and parents of children with type 1 diabetes. The corresponding survey question (A18 on the patient/parent survey) is included in the Supplementary Materials. T1D, type 1 diabetes.

insulin administration has a negative impact on lifestyle and that an option to administer mealtime insulin immediately before or immediately after a meal would improve quality of life. This finding highlights the need for better education of people with type 1 diabetes around the correct adjustment of bolus insulin doses before meals. Additional food intake or insulin dosing should not be required as a postmeal corrective action.

Rapid-acting insulin analogs (i.e., insulin lispro, insulin glulisine, and insulin aspart) are generally recommended for use before a meal (18–20), and clinical guidelines recommend premeal insulin administration (21,22). When initially introduced, however, this first generation of mealtime insulin was also approved for postmeal administration, but this practice is now generally recognized as suboptimal, as it can result in higher A1C levels (compared with premeal administration of bolus insulin), postprandial hyper- and hypoglycemia, and ensuing complications (6,15). The importance of PPG is now widely accepted and is reflected in new guidelines (3,23,24).

This PPG emphasis was shown in our surveyed population, in which >90% of adults and parents of children with type 1 diabetes reported worrying about PPG levels to some degree, and ~70% indicated that they would prefer to administer insulin either at mealtimes or postmeal. Overall, there is an unmet need for safe and effective mealtime insulin alternatives that provide people with type 1 diabetes with the desired flexibility to dose closer to their meals. This need, at least in part, might be addressed by the advent of ultra-fast-acting insulins (25–28).

Fast-acting insulin aspart, one of the first ultra-fast-acting insulin analogs, approved in 2017 (29), has a quicker onset and offset of action and a greater early glucose-lowering effect than insulin aspart (25,30). Mealtime administration (specifically defined here as 0–2 minutes before a meal) of fast-acting insulin aspart showed noninferiority in A1C reduction and improved PPG control compared with insulin aspart in both adults with type 1 or type 2 diabetes (with or without an insulin pump) and children with type 1 diabetes (25,29,31). In a phase 3 treat-to-target trial in adults with type 1 diabetes, subjects randomized to postmeal faster aspart (20 minutes after the start of a meal) for all meals maintained A1C noninferior to that obtained with mealtime insulin aspart (31).

Improvements in PPG control have also been shown with the mealtime administration of ultra-rapid lispro (URLi), indicated for the treatment of type 1 or type 2 diabetes (32–34) and inhaled Technosphere insulin (35) in adults with type 1 diabetes (26–28). In a phase 3 treat-to-target trial in adults with type 1 diabetes, both mealtime and postmeal URLi demonstrated noninferiority to insulin lispro for change in A1C, and mealtime URLi was superior to insulin lispro in reducing PPG excursions (26).

The improved time-action profile, more rapid onset of action, and demonstrated efficacy of ultra-fast-acting compared with rapid-acting insulin analogs might indeed help to alleviate the need for corrective actions after meals and facilitate more flexible insulin dosing around meals while mitigating concerns about PPG excursions. At the time of writing, fast-acting insulin aspart and Technosphere insulin are available in several markets, and URLi was approved in the United States, the European Union, and Japan (32–34).

Patients on intensive insulin regimens should assess glucose levels regularly by either self-monitoring of blood glucose or CGM (36). The fact that 73% of adults and 91% of parents of children with type 1 diabetes in our survey were using CGM is reassuring, as close glucose monitoring is needed to monitor and optimize the use of ultra-fast-acting insulin.

Recent advances in the technology used to manage diabetes have led to the introduction of devices that can both monitor glucose and deliver insulin, some automatically (3), and even provide dosing reminders. Such tools will inevitably reduce the number of missed bolus doses in people with diabetes. “Smart” insulin pens can be programmed to calculate insulin doses to assist patients in real time and provide downloadable data reports allowing treating physicians to retrospectively review doses and make adjustments as needed (37). Sensor-augmented pumps, now approved by the U.S. Food and Drug Administration, are designed to suspend insulin dosing when they either detect low glucose or predict a fall in glucose within the next 30 minutes (3). Automated insulin delivery systems that include an insulin pump, a continuous glucose sensor, and an algorithm that determines insulin delivery, can regulate insulin dosing based on sensor-derived glucose levels. Users of these first-generation “hybrid closed-loop” systems must enter information about meals and deliver bolus insulin doses for meals and snacks. Numerous studies using a variety of systems with different algorithms, pumps, and sensors have been carried out to date in adults and children (3).

The limitations of our study, common to studies with online research designs, include the potential of inaccurate recall, false reporting, and restricted generalizability. Because of the modes of recruitment, our sample does not include people who have no access to a device connected to the Internet or who are inactive on social media platforms, those who are institutionalized, or those with the most severe comorbidities and disabilities. The former exclusion may lead to bias toward individuals with higher socioeconomic status. Nevertheless, the survey included a large number of participants from several countries to help increase the generalizability of its findings. It is also worth noting that the sample was limited to treating physicians and, as such, did not consider the views of other health care professionals involved in the care of people with type 1 diabetes. The survey did not exhaustively cover all potential challenges associated with mealtime dosing, as the impact on postprandial hypoglycemia was not explored. Although not a study limitation per se, it is acknowledged that this survey focused only on type 1 diabetes and that these findings may also be relevant to people with type 2 diabetes receiving insulin with an MDI regimen. Finally, our results might underestimate real-world dosing expectations given the potential of responder embarrassment regarding actual dosing habits.

The increasing availability and use of ultra-fast-acting insulins and their potential for greater flexibility in the timing of insulin administration will warrant further real-world studies to monitor people's attitudes toward the timing of insulin dosing and its potential impact on quality of life.

In summary, this study provides real-world insight into the challenges and behaviors associated with premeal insulin dosing in people with type 1 diabetes. The importance of injection timing is not always discussed by physicians, even though it is critical to achieving PPG control. Although the importance of accurate and timely dosing was recognized, premeal insulin administration poses a clear challenge to people with type 1 diabetes. Given the choice, participants said they would prefer mealtime or even postmeal administration as being clearly advantageous and beneficial to quality of life. Given the high proportion of people with type 1 diabetes with missed insulin boluses, more convenient timing may also aid therapeutic adherence. The advent of ultra-rapid insulin analogs now presents a possible solution to some of these issues. Physicians should aim to explore the issues around administration of insulin with meals and address their patients' needs through support, education, and, where clinically appropriate, consideration of ultra-rapid insulin therapy.

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DUALITY OF INTEREST

W.L. has served on advisory boards and received research grant support from Novo Nordisk and has received honoraria for serving on speakers' bureaus for Dexcom, Insulet, Novo Nordisk, and Xeris. E.L. is an employee of Ipsos MORI, which was commissioned to conduct this research. J.G. and N.R. are employees of Novo Nordisk. N.T. has received fees for speaking and consulting from Novo Nordisk A/S. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

All authors contributed to data interpretation, reviewed and contributed to the content of the manuscript, and approved the manuscript for publication. E.L. was part of the team who collected and analyzed the data. W.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

PRIOR PRESENTATION

Parts of this article were presented in abstract form at the virtual 56th Annual Meeting of the European Association for the Study of Diabetes, 21–25 September 2020.

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Declaration of Dr. Nathan Laney

Exhibit F

Importance of Postprandial Glucose in Relation to A1C and Cardiovascular Disease

Kenneth S. Hershon,[1] Barbara R. Hirsch,[1] and Ola Odugbesan[2]

IN BRIEF This article reviews the evidence regarding the impact of postprandial glucose (PPG) on overall A1C and its relation to cardiovascular disease (CVD). To date, four randomized, controlled trials have evaluated the impact of PPG reduction on CVD; however, only one of these successfully demonstrated a positive effect. Despite this, epidemiological evidence does indicate a cardiovascular benefit of PPG reduction, and agents that can be used to manage PPG in people with type 2 diabetes are also discussed.

In people without diabetes, ingestion of food results in a transient increase in plasma glucose, which elicits a postprandial increase in the secretion of insulin from pancreatic β-cells and suppression of glucagon secretion from α-cells. In people with type 2 diabetes, however, this normal response to blood glucose spikes is dampened, primarily due to reduced insulin production resulting from β-cell dysfunction and loss combined with insulin resistance, leading to hyperglycemia (1). Hyperglycemia is associated with increased risk of microvascular complications such as retinopathy, neuropathy, and nephropathy, as well as macrovascular complications, including increased risk of myocardial infarction (MI), cardiovascular disease (CVD), and stroke (2).

The achievement of glycemic control is the key principle in diabetes management. A1C provides a good indication of overall glycemic control during the previous 2–3 months and remains the gold standard for assessing glycemic control in patients with diabetes (3,4). As a result, treatment guidelines for diabetes have historically focused on reducing A1C to specified targets.

KEY POINTS

- Postprandial glucose (PPG) is a significant contributor to A1C that is often overlooked.
- Long-term goals cannot be achieved by targeting only fasting plasma glucose levels.
- PPG is an independent risk factor for cardiovascular disease.
- PPG should be measured after breakfast because post-breakfast excursions tend to be larger and more consistent, with lower day-to-day variation.

For example, the American Diabetes Association (ADA) recommends A1C targets ranging from <6.5% to <8.0% depending on factors such as patients' health, comorbid conditions, and duration of diabetes (5). The International Diabetes Federation (IDF), the American Association of Clinical Endocrinologists (AACE), and the American College of Endocrinology recommend a target of <6.5% where possible, with individualization of goals depending on patients' needs (6,7).

It is now well established that A1C levels are the result of a combination

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of both fasting plasma glucose (FPG) and postprandial glucose (PPG) levels (8,9), with the relative importance of each depending on factors such as the degree of glycemic control (9). Treatment may also influence this FPG-PPG relationship. For example, basal insulin primarily reduces FPG. Therefore, after its initiation in patients treated with oral antidiabetic drugs (OADs) with uncontrolled hyperglycemia, it is PPG that accounts for the majority (approximately two-thirds) of residual hyperglycemia (10). It has become increasingly apparent that long-term A1C target levels cannot be achieved by treating only FPG; rather, PPG must also be targeted by therapeutic strategies (11). Consequently, most treatment guidelines now include specific PPG targets alongside A1C and FPG targets. The ADA/European Association for the Study of Diabetes guidelines recommend targets of A1C <7.0%, FPG 80–130 mg/dL, and PPG <180 mg/dL (5); the IDF recommends targets of A1C <7.0%, FPG 115 mg/dL, and PPG <160 mg/dL (6); and AACE recommends targets of A1C <7.0%, FPG 110 mg/dL, and PPG ≤140 mg/dL (7). However, current strategies and therapies (i.e., metformin, sulfonylureas, thiazolidinediones, and basal insulins) are mainly effective in controlling FPG; the importance of PPG, particularly in maintaining long-term glycemic control, has been given less attention (12).

Studies have shown that, in addition to its contribution to overall A1C, PPG is an independent risk factor for CVD, with a demonstrated linear relationship of PPG and risk of cardiovascular (CV) death (13). Although a significant number of publications support PPG being an independent risk factor for CVD and death, data have varied (14–22). Furthermore, a prospective study was conducted in subjects with previously undiagnosed diabetes who had demonstrated no fasting hyperglycemia, in which subjects underwent oral glucose tolerance testing. This study concluded that, of those with isolated post-challenge hyperglycemia, women but not men showed a significantly increased risk of fatal CVD and heart disease compared to those without diabetes (23).

In this article, we review the evidence regarding the impact of PPG on overall A1C and its relationship to CVD in an attempt to help reach a consensus on the importance of controlling PPG in people with type 2 diabetes.

Impact of PPG on A1C

It is clear that A1C, as an index of overall glycemic control, is significantly affected by both FPG and PPG, although the data concerning the relative importance of each to A1C levels was initially varied. Monnier and Colette (9) investigated the relative contributions to A1C of FPG and PPG depending on the A1C level in an attempt to conciliate these different results. The group determined that the relative contributions changed, depending on whether patients' diabetes was well controlled or not, with PPG excursions predominating at lower A1C levels, and FPG predominating at higher A1C levels. They calculated that the relative contribution of PPG is 70% in patients with A1C <7.3%, reducing to 30% in patients with A1C >10.2% (Figure 1) (9).

A later analysis of data from six studies of treatment intensification with insulin or additional OADs supported these findings, determining that, where A1C is >7.0% despite OAD therapy, FPG dominates glucose exposure, contributing an average of 76–80% to hyperglycemia (10). The study also suggested that the type of antihyperglycemic treatment used may be more significant than the A1C level alone. Despite similar A1C levels, basal insulin reduced the FPG contribution to 32–41%, whereas alternative intensification regimens (i.e., insulin lispro, premixed insulin, or additional OADs) reduced the FPG contribution to 64–71% (10).

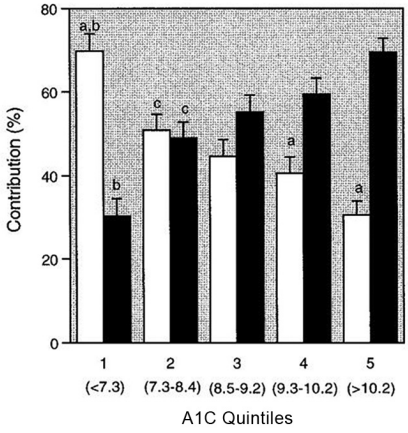

FIGURE 1. Relative contributions of postprandial (□) and fasting (■) hyperglycemia (%) to the overall diurnal hyperglycemia over quintiles of A1C. [a]Significant difference between FPG and PPG (paired *t* test). [b]Significantly different from all other quintiles (analysis of variance [ANOVA]). [c]Significantly different from quintile 5 (ANOVA). Reprinted with permission from ref. 8.

In a recent meta-analysis of 14 studies in patients with type 1 or type 2 diabetes, stronger correlations were found between PPG and A1C than between FPG and A1C (24). Furthermore, decreases in PPG resulted in greater A1C reductions than FPG reductions (24).

It has also been reported that, in type 2 diabetes, elevated PPG is one of the earliest abnormalities of glucose homeostasis, often arising before elevated FPG. This is distinctly exaggerated in patients with elevated FPG (25,26). Regardless of the exact contributions of each, the evidence clearly suggests that PPG and FPG are both significant contributors to A1C; therefore, both should be considered during treatment.

Impact of PPG on CVD

In addition to an increase in risk of microvascular complications, diabetes is associated with an overall two- to fourfold increased risk of developing CVD (1). Indeed, CVD is by far the

single largest cause of mortality in patients with type 2 diabetes, accounting for up to 75–80% of deaths (2,27). Traditional risk factors for diabetes such as hypertension, obesity, and atherogenic dyslipidemia do not fully account for the increased risk of CVD associated with diabetes (2). Increased A1C levels are well known to be associated with increased CVD risk, implying the contribution of PPG to A1C is a significant factor in this increased risk (2). In addition, most epidemiological studies agree that PPG is a significant independent risk factor for CVD and MI, regardless of whether a person has diabetes (28,29).

Studies have also shown that, in addition to CV events, PPG is a predictor of CV-related and all-cause mortality, whereas it appears that FPG is not (30). In the Honolulu Heart Program conducted in Japanese-American men aged 45–68 years, there was an increased risk of coronary heart disease (CHD) in patients with abnormal oral glucose tolerance test results (14). Similar results were seen in the Baltimore Longitudinal Study of Aging, which concluded that, regardless of FPG and A1C, a higher 2-hour PPG level was associated with increased risks of CVD, CVD mortality, and all-cause mortality (16). The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study analyzed data from 10 prospective European cohort studies that included 15,388 men and 7,126 women aged 30–89 years. The authors concluded that 2-hour PPG values were a better predictor than FPG of death from all causes and CVD, with the largest number of excess deaths being observed in patients showing impaired glucose tolerance (IGT) after a 2-hour oral glucose test but normal FPG levels (17). Additional analysis showed that mortality associated with FPG concentration was largely dependent on 2-hour PPG levels. In this study, ~33% of men and ~44% of women who had diabetes according to the 2-hour PPG values were not identified as having diabetes according to their FPG levels, highlighting the diagnostic value of PPG measurement (17).

It is important to stress that the Honolulu Heart Program, the Baltimore Longitudinal Study of Aging, and DECODE were noninterventional studies that looked at subjects who did not have diagnosed diabetes. It is therefore unclear whether they can inform us on how to better treat those with diagnosed diabetes.

A post hoc analysis determined that a prandial strategy targeting PPG with three premeal doses of insulin lispro daily may be associated with lower risk of subsequent CV events than a basal strategy of twice-daily NPH or once-daily insulin glargine 100 units/mL in older patients (19). A caveat of this study, which should be considered, is that the magnitude of the differences in PPG levels between the two treatment regimens was smaller than expected, and the trial was eventually stopped due to lack of efficacy (18).

A number of other studies support the findings from these studies that PPG levels are linked to CVD. In a 14-year follow-up of patients with type 2 diabetes managed in routine clinical practice, PPG and A1C, but not FPG, were found to have similar predictive power for CV events and all-cause mortality (20), whereas a review of a large number of epidemiological studies concluded that PPG is, in fact, a more powerful risk factor than either A1C or FPG (31). In the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM), patients with IGT were randomized to receive either placebo or acarbose, an α-glucosidase inhibitor (AGI) that lowers PPG. In addition to a 25% relative risk reduction in the development of type 2 diabetes and a 34% risk reduction for hypertension, patients treated with acarbose had a 49% risk reduction of developing CV events (32). Additionally, in a substudy of STOP-NIDDM, patients treated with acarbose showed a reduced incidence of silent MIs compared to those receiving placebo (33). The Acarbose Cardiovascular Evaluation trial, conducted in Chinese patients with IGT and CHD, showed no significant difference between acarbose and placebo for incidence of primary five-point composite outcome (CV death, nonfatal MI, nonfatal stoke, hospital admission for unstable angina, and hospital admission for heart failure) or any secondary CV outcomes (34). However, patients treated with acarbose did have a reduced incidence of diabetes.

A number of studies have given indications as to the underlying mechanisms for the association between PPG levels and CV risk. For example, a study of patients without diabetes showed that higher 1-hour PPG levels were significantly associated with increased arterial stiffness as determined by cardio-ankle vascular index values, a measure of the stiffness of the aorta, femoral artery, and tibial artery (35). Furthermore, in the Risk Factors in Impaired Glucose Tolerance for Atherosclerosis and Diabetes study, there was a closer correlation between PPG and carotid intima-media thickness than FPG in patients with IGT (36).

Hypertriglyceridemia is also a risk factor for CVD and is amplified in the postprandial state, rising concomitantly with postprandial hyperglycemia. Despite this, evidence suggests a direct atherogenic role for postprandial hyperglycemia independent of that of lipids (29). Postprandial hypertriglyceridemia has been shown to be associated with increased carotid intima-media thickness in patients with diabetes, meaning that it may be an independent risk factor for early atherosclerosis in these patients (37). Furthermore, the progression of atherosclerosis has also been shown to be slowed and even reversed by therapies that reduce PPG (38).

PPG has been shown to stimulate oxidative stress, which has been implicated as the underlying cause of

both macrovascular and microvascular complications in type 2 diabetes (39–42). Indeed, epidemiological and other studies have demonstrated a strong association between PPG and CV risk through oxidative stress, carotid intima-media thickness, and endothelial dysfunction (16,17). Glucose fluctuations have been shown to have a linear correlation with increased production of free radicals, and PPG induces overproduction of superoxide, which reacts with nitrous oxide to create derivatives that lead to endothelial damage (43). In the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research study, treatment of patients with IGT with the angiotensin II receptor antagonist valsartan (which reduces blood pressure) did not affect CV outcomes. It should be noted, however, that the patients in this trial were not hypertensive, and valsartan was not used for blood pressure control (21). Thus, the observed effects of PPG on CV outcomes may not be explained by increased blood pressure associated with hyperglycemia.

In summary, in addition to its significant contribution to A1C, the literature strongly indicates that PPG is an independent risk factor for CVD. It remains unclear, however, whether the most important aspect of PPG is how frequently it is above the optimal range or whether it is its maximal values. Regardless of this, the impact of PPG on CVD implies that reducing PPG in patients with diabetes may be of significant benefit to their long-term prognosis and quality of life, even though demonstration of this benefit in randomized controlled trials has been elusive.

Monitoring PPG

Although widely used and recommended for monitoring glycemic control, the cost of A1C testing is high, which means its availability is very limited in resource-poor settings (24). Given that studies indicate that PPG and A1C have similar predictive power for CV outcomes, regular monitoring of PPG with plasma glucose testing, which is considerably less costly and easier to perform, may represent a viable and practical alternative that enables the improvement of overall glycemic control and reduced the risk of CV complications.

Data from an observational study of people with type 2 diabetes suggest that PPG readings preferably should be obtained after breakfast rather than after lunch or dinner because post-breakfast excursions tend to be larger and more consistent, with lower day-to-day variation (44). Furthermore, the median time to peak concentration in this study was ~90 minutes, indicating that this is the time after the start of the meal that the reading should be taken (44). Postprandial self-monitoring of blood glucose (pp-SMBG) has been shown to be associated with improvements in glycemia, lipids, and weight, as well as exercise and dietary habits in subjects who have already reached their A1C goals; this provides a rationale for implementation of pp-SMBG when possible (45).

Diabetes organizations are increasingly recognizing that continuous glucose monitoring (CGM) may be an appropriate and useful diabetes management tool, especially in patients on insulin therapy. CGM technology is advancing rapidly; for example, the FreeStyle Libre and FreeStyle Libre Pro "flash" CGM systems do not require fingerstick calibration. While the Freestyle Libre system is intended to be used by patients for diabetes self-management, the FreeStyle Libre Pro is the first flash CGM system available for professional use in clinical practice. In a significant improvement over previous systems, the sensor is factory calibrated and can be continuously worn for up to 14 days, requiring no calibration via SMBG during that time period. Another system, the Dexcom G5, still requires calibration using SMBG; however, it has been granted a nonadjunctive indication by the U.S. Food and Drug Administration (FDA), meaning its readings alone can be used to modify therapy (46). More recently, the FDA approved the Dexcom G6 system, which does not require fingerstick calibration. Similarly, the FreeStyle Libre device does not require fingerstick SMBG calibration.

Reducing PPG

The most important and effective first step in diabetes management is to encourage patients to make lifestyle modifications, including increasing exercise and improving diet. However, diabetes is a progressive disease, and all patients will eventually require pharmacological treatment to maintain glycemic control. In general, treatment strategies to reduce A1C have focused on controlling FPG; however, as discussed, PPG is an important contributor to A1C. Controlling PPG is therefore a major unmet need, particularly in patients with longer durations of type 2 diabetes (12).

A number of treatment options are available to target PPG, including AGIs, amylin analogs, glinides, dopamine agonists, glucagon-like peptide 1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium–glucose cotransporter 2 (SGLT2) inhibitors, and rapid-acting insulins (Table 1) (3,47–62). Treatment guidelines provide algorithms for the intensification of therapy, including many of these agents, and recommend that specific strategies and choices should be based on patient- and disease-specific factors (5–7).

Insulin Therapy

In patients treated with basal insulin who are not achieving glycemic targets, preprandial rapid-acting insulin analogs or premixed insulin formulations consisting of intermediate and rapid-acting insulin are often initiated (63). Rapid-acting insulins are a well-established and effective treatment for patients requiring prandial control. However, adverse effects associated with rapid-acting insulin

TABLE 1. FDA-Approved Pharmacological Interventions That Target Postprandial Hyperglycemia*

Agent	Mode of Action	A1C Reduction, %	PPG Reduction, mmol/L (mg/dL)	CV Benefit
AGIs				
Acarbose	Inhibits carbohydrate digestion, delaying absorption	0.4–0.8	4.0 (72)	
Miglitol	Inhibits carbohydrate digestion, delaying absorption; enhances GLP-1 activity	0.2–0.8	1.5–3.5 (27–63)	
Amylin analogs				
Pramlintide	Slows gastric emptying; suppresses glucagon activity; increases satiety	0.6	2.0 (36)	
Glinides				
Repaglinide	Stimulates insulin release	0.6–1.5	2.6 (47)	
Nateglinide	Stimulates insulin release	0.5–0.8	2.6 (47)	
Insulin				
Rapid-acting		1.5–2.5		
SGLT2 inhibitors				
Canagliflozin	Inhibition of glucose reuptake in the kidney; short-term inhibition of intestinal SLGT1 at higher doses	0.8–1.0	2.4–3.3 (43–59)	✓
Dapagliflozin	Inhibition of glucose reuptake in the kidney	0.6–1.0	3.6–3.8 (65–68)	
Empagliflozin	Inhibition of glucose reuptake in the kidney	0.7–0.8	2.0–2.6 (36–47)	
Incretin-based agents				
GLP-1 receptor agonists				
Exenatide	Enhances insulin secretion; inhibits glucagon release after eating; delays gastric emptying; promotes satiety Short-acting: predominant effect on PPG Long-acting: predominant effect on FPG	0.5–1.0†	3.6 (65)	
Liraglutide	Enhances insulin secretion; inhibits glucagon release after eating Predominant effect on FPG	1.0–1.5†	1.7–2.7 (31–49)	✓
Lixisenatide	Enhances insulin secretion; inhibits glucagon release after eating; delays gastric emptying; promotes satiety Predominant effect on PPG	0.5–0.9	3.1–5.9 (56–106)	
DPP-4 inhibitors				
Sitagliptin	Inhibits DPP-4, increasing levels of GLP-1	0.6–0.8	2.8 (50)	
Saxagliptin	Inhibits DPP-4, increasing levels of GLP-1	0.6–0.8	2.8 (50)	
Combination agents				
iDegLira	Complementary action of basal insulin on FPG and GLP-1 receptor agonist on PPG	0.8–1.9	Not reported	
iGlarLixi	Complementary action of basal insulin on FPG and GLP-1 receptor agonist on PPG	1.1–1.6	4.7–5.7 (85–103)	

*Adapted from refs. 3, 96, and 97, with additional data from refs. 47–62. *Used as monotherapy or in combination with other antidiabetic agents. †Assuming starting value ≥8%.*

analogs, including weight gain and increased risk of hypoglycemia, mean that patients and health care providers are often reluctant to initiate their use. In addition, data from population-based studies suggest that this approach may not be optimal, in terms of both long-term glycemic control and CV outcomes (12).

AGIs

AGIs significantly reduce PPG-dependent insulinotropic polypeptide (gastric inhibitory polypeptide) secretion and are effective at reducing PPG by altering the intestinal absorption of carbohydrates (64,65). In general, AGIs have modest A1C-lowering effects and a low risk of hypoglycemia and require frequent dosing (7,66), and the action of AGIs means that undigested carbohydrates reach the colon, resulting in flatulence and diarrhea (67). Although this effect may lessen over time, gastrointestinal side effects make AGIs difficult to tolerate for many patients, and this has limited their use (7).

Amylin Analogs

Amylin analogs target PPG by suppressing post-meal glucagon activity, slowing gastric emptying, and increasing satiety. This significantly reduces PPG and improves glycemic control when added to insulin and has a beneficial effect on weight (68). They are generally used as a supplement to basal insulin therapy in patients who are not meeting glycemic targets (69). The major disadvantages of amylin analogs are the need for multiple daily injections due to their short duration of action and increased risk of nausea. There is also in an increased risk of hypoglycemia, although this is lower than with rapid-acting insulins (12).

Glinides

Glinides are short-acting insulinotropic agents that rapidly increase insulin secretion and reduce PPG (70). Glinides are associated with an increased risk of hypoglycemia, although this is lower than that of sulfonylureas. They are also associated with weight gain, require frequent dosing, and have only modest A1C-lowering effects (7,66).

SGLT2 Inhibitors

SGLT2 inhibitors lower plasma glucose by inhibition of glucose reuptake in the kidney and so reduce both FPG and PPG (71). Canagliflozin 300 mg (maximum recommended dose) was shown to have provided greater reductions in PPG and insulin excursions, possibly related to a combination of renal SGLT2 inhibition and delayed absorption of ingested glucose due to intestinal SGLT1 inhibition (49). This insulin-independent mechanism of action means that they are not associated with weight gain, have a low risk of hypoglycemia, and can be used at any stage of type 2 diabetes. They have similar A1C-lowering efficacy to other OADs (7,66). Patients with type 2 diabetes and high risk for CV events who were treated with empagliflozin have been shown to have lower rates of a composite outcome of death from CV causes, nonfatal MI, or nonfatal stroke, as well as death from any cause, compared to placebo (71), and this was also seen in the canagliflozin CANVAS research program (72).

A disadvantage of SGLT2 inhibitors is that they result in elevated excretion of glucose in the urine, which is associated with urinary tract and genital infections in patients (particularly women) (73). Additionally, canagliflozin carries a black-box warning for lower-limb amputation, with an approximately twofold increased risk observed in patients with type 2 diabetes either with established CVD or at risk of CVD (74). However, it should be considered that the absolute risk remains low.

DPP-4 Inhibitors

DPP-4 inhibitors (i.e., sitagliptin, vildagliptin, saxagliptin, and linagliptin) are incretin-based therapies that provide another way of targeting PPG. They are associated with weight loss and lower risk of hypoglycemia than rapid-acting insulin. DPP-4 inhibitors prevent DPP-4 from degrading native incretins such as GLP-1, which in turn activate the GLP-1 receptor. This results in DPP-4 inhibitors and GLP-1 receptor agonists having similar effects resulting from activation of the GLP-1 receptor; however, GLP-1 receptor agonists have been shown to provide superior glycemic control compared to DPP-4 inhibitors (3,75), effectively stimulating glucose-dependent insulin secretion and suppressing postprandial glucagon levels, and thereby reducing PPG (76).

Unlike rapid-acting insulin, DPP-4 inhibitors have a neutral effect on hypoglycemia and weight. Some may carry a risk of congestive heart failure; however, this is uncertain due to short follow-ups and low-quality evidence of studies (77). Recent analysis has suggested that only saxagliptin in the SAVOR-TIMI 53 trial resulted in increased hospitalization for heart failure (78,79).

GLP-1 Receptor Agonists

GLP-1 receptor agonists are also an incretin-based therapy, meaning they have similar effects to DPP-4 inhibitors, resulting from activation of the GLP-1 receptor (3). As with DPP-4 inhibitors, this activation results in stimulation of insulin secretion and suppression of glucagon secretion from the pancreas in a glucose-dependent manner (11,80,81). They are also associated with a lower risk of hypoglycemia than rapid-acting insulins.

Because their mechanism of action differs from that of DPP-4 inhibitors, GLP-1 receptor agonists are associated with weight loss, whereas DPP-4 inhibitors are weight neutral; however, both classes are superior to rapid-acting insulins, which are associated with weight gain. The mechanism by which GLP-1 receptor agonists promote weight loss is multifactorial and involves both the brain and the gastrointestinal tract. They slow gastric emptying and increase satiety to varying degrees, resulting in reduced food intake and associated weight loss (11,82,83).

Evidence suggests that GLP-1 receptor agonists result in better glycemic control and greater weight loss than DPP-4 inhibitors (75). A study has shown that GLP-1 receptors are required to be present in the central nervous system, while another study showed that a small peptide GLP-1 receptor agonist can penetrate the brain, subsequently activating certain neurons to stimulate weight loss (84,85).

Short-acting GLP-1 receptor agonists such as lixisenatide and exenatide have a predominant effect on PPG and are associated with a greater effect on gastric emptying. Longer-acting GLP-1 receptor agonists such as liraglutide, exenatide long-acting release, albiglutide, and dulaglutide have more of an effect on FPG and a lesser effect on gastric emptying. It seems that continuous stimulation of the GLP-1 receptor can attenuate this effect of gastric emptying via tachyphylaxis (5,86).

Overall, GLP-1 receptor agonists are associated with a lower incidence of hypoglycemia compared to insulin (87). Trials investigating the CV safety of GLP-1 receptor agonists show comparable (88,89) or reduced (90,91) CV outcomes compared to placebo in patients with diabetes. A meta-analysis of these four trials suggested a class effect of GLP-1 receptor agonists for improving CV outcomes. This analysis suggested that treatment with a GLP-1 receptor agonist results in a significant (10%) reduction in relative risk for three major adverse cardiac events (CV mortality, nonfatal MI, and nonfatal stroke). Furthermore, there were relative risk reductions of 13% for CV mortality and 12% for all-cause mortality. There was no identified impact of GLP-1 receptor agonist therapy on fatal and nonfatal MI, fatal and nonfatal stroke, hospital admission for unstable angina, or hospital admission for heart failure (92).

It should be noted that it is unlikely that these improved CV outcomes can be attributed solely to reduced PPG. The meta-analysis included studies of longer-acting GLP-1 receptor agonists; although these do have a modest impact on PPG, it is likely a result of reduced basal glycemia. They have little to no sustained impact on the rate of gastric emptying, which is the factor most important for reduced PPG excursions seen with short-acting GLP-1 receptor agonists (85,93). The authors of the meta-analysis speculated that the CV effects may be related to antiatherogenic mechanisms, which affect common CV risk factors such as blood pressure, anti-inflammatory pathways, cardiac output, ischemic conditioning, and endothelial function (92).

Another meta-analysis, which included a greater number of studies and compared GLP-1 receptor agonist treatment to placebo or any other non–GLP-1 receptor agonist drugs, showed similar results. Patients with type 2 diabetes treated with a GLP-1 receptor agonist had lower all-cause mortality, CV mortality, and MI rates, whereas no significant differences were seen for stroke or heart failure (94).

Given their complementary modes of action, the combination of a GLP-1 receptor agonist and basal insulin is potentially an attractive option to manage both PPG and FPG. Titratable fixed-ratio combinations of basal insulin glargine and the GLP-1 receptor agonist lixisenatide (iGlarLixi), and of insulin degludec and liraglutide (iDegLira), were approved by the FDA in 2016 and are now on the market. In clinical trials, once-daily injections of these formulations have been shown to result in greater A1C reduction than basal insulin or a GLP-1 receptor agonist alone. These trials have also shown weight gain associated with basal insulin therapy to be mitigated, hypoglycemia to be reduced, and gastrointestinal adverse effects to be reduced compared to GLP-1 receptor agonists alone (60–62,95).

Conclusion

Studies have consistently demonstrated that PPG is a significant contributor to A1C and is also an independent risk factor for CVD. Long-term epidemiological studies and meta-analyses show that PPG, far more than FPG, is a predictor of CV risk. PPG is especially important to patients with diabetes who have achieved their FPG goal but whose A1C remains high. In patients with an A1C of ≥10.2%, PPG only contributes up to ~30% of 24-hour A1C; however, in patients closer to goal (A1C ≤7.3%), PPG contributes ~70% of 24-hour A1C (8). Therefore, patients who have achieved FPG goals but still have elevated A1C should consider PPG-targeting therapeutics.

Despite this association, studies have not consistently shown improved CV outcomes in patients taking PPG-lowering therapy. Although it is possible that PPG is merely a marker or surrogate for CV risk, it may be that the designs of studies conducted to date have been insufficient to fully answer this question (93). Overall, the data suggest that reducing PPG excursions may be protective against CVD. A range of available treatments can be used to target PPG, including rapid-acting insulin analogs, GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT2 inhibitors.

Control of PPG should be considered equally as important as FPG control in people with type 2 diabetes. However, despite the increasing apparent importance of PPG, it is commonly ignored by primary care providers (PCPs) in lieu of FPG control. Often, PCPs have been trained to address FPG first and therefore believe that management of PPG is of lesser importance. Many PCPs have also acquired a familiarity and comfort with the use of basal insulin. However, basal insulin is effective only up to a tipping point of ~0.5 units/kg; thereafter, further titration will likely result in hypoglycemia and weight gain.

Many patients are able to achieve an FPG target while their A1C remains high. At this point, agents targeting PPG are essential. However, these often require an additional injection, the use of carbohydrate counting, titration, or other nuances for which PCPs often have not been trained and would therefore be likely to refer such patients to an endocrinologist. Newer agents such as GLP-1 receptor agonists or fixed-ratio combinations may be added to basal insulin and can mitigate some of the issues of weight gain while not increasing the risk of hypoglycemia. However, there may be additional side effects with these agents, including increased gastrointestinal adverse effects, that will need to be managed.

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Author Contributions

All authors contributed equally to the idea and development of the manuscript. K.S.H. is the guarantor of this work and, as such, had full access to all the materials in the study and takes responsibility for the integrity of the materials and the accuracy of the dissemination of the materials.

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Declaration of Dr. Nathan Laney

Exhibit G

Diabetes Care Volume 40, July 2017

Fast-Acting Insulin Aspart Improves Glycemic Control in Basal-Bolus Treatment for Type 1 Diabetes: Results of a 26-Week Multicenter, Active-Controlled, Treat-to-Target, Randomized, Parallel-Group Trial (onset 1)

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OBJECTIVE

This multicenter, treat-to-target, phase 3 trial evaluated the efficacy and safety of fast-acting insulin aspart (faster aspart) versus conventional insulin aspart (IAsp) in adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS

The primary end point was change from baseline in HbA_{1c} after 26 weeks. After an 8-week run-in, subjects were randomized (1:1:1) to double-blind mealtime faster aspart (n = 381), IAsp (n = 380), or open-label postmeal faster aspart (n = 382)—each with insulin detemir.

RESULTS

HbA_{1c} was reduced in both treatment groups, and noninferiority to IAsp was confirmed for both mealtime and postmeal faster aspart (estimated treatment difference [ETD] faster aspart–IAsp, mealtime, –0.15% [95% CI –0.23; –0.07], and postmeal, 0.04% [–0.04; 0.12]); mealtime faster aspart statistically significantly reduced HbA_{1c} versus IAsp (P = 0.0003). Postprandial plasma glucose (PPG) increments were statistically significantly lower with mealtime faster aspart at 1 h (ETD –1.18 mmol/L [95% CI –1.65; –0.71], –21.21 mg/dL [–29.65; –12.77]; P < 0.0001) and 2 h (–0.67 mmol/L [–1.29; –0.04], –12.01 mg/dL [–23.33; –0.70]; P = 0.0375) after the meal test; superiority to IAsp for the 2-h PPG increment was confirmed. The overall rate of severe or blood glucose–confirmed (plasma glucose <3.1 mmol/L [56 mg/dL]) hypoglycemic episodes and safety profiles were similar between treatments.

CONCLUSIONS

Faster aspart effectively improved HbA_{1c}, and noninferiority to IAsp was confirmed, with superior PPG control for mealtime faster aspart versus IAsp. Subjects randomized to postmeal faster aspart for all meals maintained HbA_{1c} noninferior to that obtained with mealtime IAsp.

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Postprandial glycemic control is an essential component for meeting HbA_{1c} target levels of 6.5–7% (48–53 mmol/mol) (1–3). Such targets are recommended by several guidelines to reduce the incidence and slow the progression of diabetes-related complications (4–6). Yet, limiting postprandial plasma glucose (PPG) excursions is one of the most challenging aspects in achieving adequate glycemic control (7).

Basal-bolus insulin therapy in type 1 diabetes aims to replace physiologic insulin secretion. Rapid-acting insulin analogs, insulins aspart, glulisine, and lispro, were developed to control PPG excursions more effectively than regular human insulin (RHI), primarily by offering a faster onset and shorter duration of action (8–10).

Innovative modifications of insulin formulations and delivery methods that offer ultrafast insulin time-action profiles (11–18) aim to further improve PPG control by accelerating insulin absorption and appearance in the bloodstream. Fast-acting insulin aspart (faster aspart; an ultrafast mealtime insulin) is conventional insulin aspart (IAsp; NovoRapid/NovoLog) in a new formulation; nonclinical data demonstrate that addition of niacinamide promotes the formation of insulin aspart monomers after subcutaneous injection, facilitating a more rapid rate of insulin aspart absorption across the endothelium into the blood (19). In adults with type 1 diabetes, subcutaneous injection of faster aspart was associated with twice-as-fast onset of appearance in the bloodstream (4 vs. 9 min), twofold higher insulin concentration, and 74% greater insulin action in the first 30 min compared with IAsp (20). Furthermore, in the recently completed phase 3 clinical trials, faster aspart improved 1-h PPG control versus IAsp when administered as part of a basal-bolus regimen (21) and demonstrated superior glycemic control versus basal-only therapy (22) in subjects with type 2 diabetes.

A large proportion (81.4%) of people with diabetes would like their insulin regimen to fit with their daily life changes (23), and the option to take their insulin dose after a meal when necessary may address this need.

The objective of this double-blind trial was to confirm the efficacy of faster aspart in terms of glycemic control compared with mealtime IAsp after 26 weeks of randomized treatment. An open-label postmeal faster aspart dosing arm was also compared with IAsp to evaluate whether postmeal administration could prove effective in achieving glycemic control and thereby offer a clinically acceptable treatment option.

RESEARCH DESIGN AND METHODS

Trial Design

This 26-week (plus additional 26 weeks) multicenter, active-controlled, randomized, parallel-group trial compared double-blind mealtime faster aspart with mealtime IAsp in adults with type 1 diabetes. A 26-week open-label treatment group with postmeal faster aspart provided a second comparison with IAsp (Supplementary Fig. 1). The additional 26-week treatment period was included to document long-term safety (not reported here). Faster aspart and IAsp were delivered in a basal-bolus regimen with once- or twice-daily insulin detemir (Levemir).

The trial was conducted in accordance with the Declaration of Helsinki (24) and International Conference on Harmonization of Good Clinical Practice (25) and is registered with ClinicalTrials.gov (reg. no. NCT01831765).

Subjects

Adults (≥18 years old) with type 1 diabetes (diagnosed clinically) were eligible for inclusion if treated with basal-bolus insulin for ≥12 months prior to screening and if treated with any regimen of insulin detemir or glargine for ≥4 months prior to screening, with an HbA_{1c} of 7.0–9.5% (53–80 mmol/mol) and BMI of ≤35.0 kg/m^2. Exclusion criteria included any use of an antidiabetes drug other than insulin within 3 months prior to screening, an anticipated change in concomitant medications known to interfere significantly with glucose metabolism, cardiovascular (CV) disease within 6 months prior to screening, recurrent severe hypoglycemia (>1 event during the past 12 months), hypoglycemic unawareness as judged by the investigator, or hospitalization for diabetic ketoacidosis within 6 months prior to screening. Full criteria are listed in Supplementary Data.

Interventions

Basal Titration During the Trial

After an initial 2-week screening period, an 8-week run-in allowed for the optimization of basal insulin detemir (100 units/mL; 3.0-mL FlexPen). At the start of the run-in period, subjects switched unit for unit from their previous basal insulin (if required). The same once- or twice-daily dosing frequency that was used prior to screening was maintained initially, but subjects were permitted to switch dosing frequency during the run-in period if required.

During run-in, insulin detemir was titrated using a weekly treat-to-target approach, with a prebreakfast self-monitored plasma glucose (SMPG) target of 4.0–5.0 mmol/L (71−90 mg/dL) (Supplementary Tables 1 and 2). Subjects on a twice-daily regimen used a predinner SMPG target of 4.0–6.0 mmol/L (71−108 mg/dL) (Supplementary Table 2). After run-in, basal adjustments were only performed when required as judged by the investigator; changing the dose frequency after randomization was a withdrawal reason, according to the protocol.

Bolus Doses During the Trial

At the start of the 8-week run-in, all subjects commenced mealtime IAsp (all bolus insulins supplied at 100 units/mL; 3.0-mL PDS290 Pen injector). After run-in, subjects (with HbA_{1c} ≤9.5% [80 mmol/mol]) were randomized 1:1:1 to receive double-blind mealtime faster aspart, IAsp, or open-label postmeal faster aspart while continuing with insulin detemir. Mealtime bolus insulins were injected 0–2 min before a meal; postmeal faster aspart was injected at a fixed time of 20 min after the start of the meal. Randomization was stratified by the method used by the subject for adjusting bolus insulin (carbohydrate counting [flexible dosing] or dosing algorithm), current basal treatment regimen (once or twice daily), and continuous glucose monitoring and frequently sampled meal test subgroup participation.

At the beginning of the run-in period, subjects commenced mealtime IAsp (requiring subjects on other bolus insulins to switch unit for unit) and adjusted insulin doses as they had done before the trial. No titration of bolus insulin dose was performed by the investigator during run-in unless adjustments were necessary for safety reasons. At the randomization visit, subjects commenced the bolus regimen to which they had been randomized. It was the investigator's responsibility to ensure adequate

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education of each subject following the principles of flexible bolus dosing based on carbohydrate content (recommending additional local training, if required); subjects deemed proficient in carbohydrate counting were to continue using this method for bolus adjustments during the treatment period. All other subjects used a predefined bolus-dosing algorithm (Supplementary Table 3).

Meal carbohydrate content and preprandial plasma glucose (PG) values were used to determine bolus insulin doses for subjects following the principles of flexible dosing. Adjustments were made several times daily by the subject in accordance with the insulin-to-carbohydrate ratio and the PG correction (sensitivity) factor. A weekly review of the ratio and correction factor was performed by the investigator, based on individual subject SMPG values. The target preprandial PG range was 4.0–6.0 mmol/L (71−108 mg/dL); in case of hypoglycemic episodes, the dose could be reduced at the investigator's discretion.

Bolus titration (for subjects using the algorithm) was to the next preprandial target of 4.0–6.0 mmol/L (71–108 mg/dL) for both breakfast and lunch doses and to the same target at bedtime for the dinner dose. Adjustments were made twice weekly: once by the investigator and once by the subject (Supplementary Table 3).

SMPG

At the run-in visit, subjects were supplied with a blood glucose (BG) meter, factory calibrated to display PG values, and instructed to record the date, time, and value of all SMPG measurements from 7-9-7-point profiles (pre- and postmeal, bedtime, and once at 4:00 A.M.) on three consecutive days before the scheduled clinic visits at weeks 0, 12, and 26; 4-point profiles (preprandial and at bedtime) were recorded daily for titration purposes.

Standardized Meal Test

Subjects completing the run-in period had their 1- to 4-h PPG levels assessed after a bolus dose of IAsp (0.1 units/kg, calculated by the investigator) administered 0–2 min before a standardized mixed liquid meal test (80 g carbohydrate [Ensure] consumed within 12 min). Subjects attended the meal visit with a fasting PG (FPG) level within 4.0–8.8 mmol/L (71–160 mg/dL) for the test to be performed. Blood samples were drawn just before the meal and after 1, 2, 3, and 4 h. The meal test was repeated at week 26, with subjects administering the bolus dose (0.1 units/kg body weight, chosen as an approximation of a clinically relevant bolus dose needed for the given size of a standardized meal for subjects with type 1 diabetes) either 0–2 min before (mealtime faster aspart and IAsp) or 20 min after (postmeal faster aspart) the meal test.

Assessments

Primary End Point

The primary end point was change from baseline in HbA_{1c} after 26 weeks of treatment.

Secondary End Points

Confirmatory secondary end points included the following: change from baseline after 26 weeks of treatment in 2-h PPG increments (meal test) and body weight, and number of treatment-emergent severe or BG-confirmed hypoglycemic episodes. Hypoglycemic episodes were categorized as treatment emergent if the onset occurred on the first day of exposure to and no later than 1 day after the last day of randomized treatment. Severe hypoglycemia was defined according to the American Diabetes Association classification (26) and BG-confirmed hypoglycemia by a PG value <3.1 mmol/L (56 mg/dL; Novo Nordisk A/S definition) with/without symptoms consistent with hypoglycemia (Supplementary Table 4).

Supportive secondary end points included the following: HbA_{1c} responders (subjects achieving HbA_{1c} <7% [53 mmol/mol] or ≤6.5% [47.8 mmol/mol]); change from baseline in PPG and PPG increments (meal test); change from baseline in mean SMPG 7-9-7-point profile and mean 2-h PPG and mean 2-h PPG increments (7-9-7-point profile); PPG responders (subjects achieving overall mean 2-h PPG ≤7.8 mmol/L [140 mg/dL] in SMPG); change from baseline in 1,5-anhydroglucitol (1,5-AG) (a marker for postprandial hyperglycemia), FPG, and body weight; and total (basal + bolus) insulin doses. Analyses of laboratory efficacy parameters (HbA_{1c}, PG during the meal test, FPG, and 1,5-AG) were carried out by central laboratory (Supplementary Table 4).

Supportive secondary safety end points included the following: the numbers of treatment-emergent adverse events (TEAEs), hypoglycemic episodes, and injection-site and allergic reactions (Supplementary Table 4). All presented adverse events (except CV events) are TEAEs (i.e., with onset up to 7 days after the last day of treatment, excluding any events during run-in). Information on CV events and deaths occurring after randomization was sent for evaluation by an external event adjudication committee. Additional safety assessments, including physical examination, vital signs, fundoscopy, and electrocardiograms, were recorded at screening, baseline, and week 26. Laboratory parameters were recorded at various time points throughout the 26-week trial. Subject follow-up occurred at 7 and 30 days after the end of treatment.

Statistical Methods

All statistical analyses were based on the full analysis set (all randomized subjects) and prespecified. Safety end points were summarized using the safety analysis set (subjects receiving ≥1 dose of investigational products). Statistical analysis of the primary and secondary confirmatory hypotheses followed a stepwise hierarchical procedure (Supplementary Fig. 2). Noninferiority (primary end point) was confirmed if the upper boundary of the two-sided 95% CI was ≤0.4%. For analyses of noninferiority, one-sided *P* values are presented, and for all other analyses, two-sided *P* values for treatment differences are presented.

Change from baseline in HbA_{1c} after 26 weeks of treatment was analyzed using a mixed-effect model for repeated measurements where all changes in HbA_{1c} from baseline at trial visits were included in the analysis. Change from baseline in PPG and PPG increments (meal test) was analyzed separately using an ANOVA model. Responder end points (for HbA_{1c} and PPG) were analyzed separately based on a logistic regression model. Change from baseline in mean 7-9-7-point profiles; mean PPG; mean PPG increments (7-9-7-point profiles); 1,5-AG; FPG; and body weight were analyzed using a mixed-effect model for repeated measurements similar to the model used for the primary end point.

The number of treatment-emergent severe or BG-confirmed hypoglycemic episodes was analyzed using a negative binomial regression model.

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The sample-size calculation and additional details on the statistical methods for the primary and secondary end points are in Supplementary Data.

RESULTS

Trial Subjects

In total, 1,143 subjects were randomized to mealtime faster aspart (n = 381), IAsp (n = 380), or postmeal faster aspart (n = 382). All 1,143 randomized subjects were exposed to randomized trial product (Supplementary Fig. 3), and 92.9% of subjects completed the trial. Baseline characteristics were similar between the three groups (Table 1).

Hierarchical Testing Procedure

Steps 1–3 (which are described in more detail below) were confirmed. As step 4 could not be confirmed, the hierarchical statistical testing procedure was stopped (Supplementary Table 5).

Efficacy

Change in HbA_{1c}

Noninferiority of faster aspart, both mealtime and postmeal dosing, to mealtime IAsp in terms of change from baseline in HbA_{1c} was confirmed (estimated treatment difference [ETD] mealtime −0.15% [95% CI −0.23; −0.07], −1.62 mmol/mol [−2.50; −0.73]); postmeal 0.04% [−0.04; 0.12], 0.47 mmol/mol [−0.41; 1.36]; $P < 0.0001$ for noninferiority) (Fig. 1, steps 1 and 3). The reduction in HbA_{1c} was statistically significantly greater for mealtime faster aspart than for IAsp (P = 0.0003); however, superiority could not be considered confirmed, as this was not part of the hierarchical testing procedure (Supplementary Fig. 2).

Results for subjects who achieved the HbA_{1c} targets of <7.0% (53.0 mmol/mol) and ≤6.5% (47.8 mmol/mol) after 26 weeks' treatment are summarized in Supplementary Table 6. The odds of achieving HbA_{1c} <7.0% (53.0 mmol/mol) were statistically significantly higher with mealtime faster aspart compared with IAsp (estimated odds ratio 1.47 [95% CI 1.02; 2.13]; P = 0.0405) and not statistically significantly different between postmeal faster aspart and IAsp (0.73 [0.49; 1.07]) (Supplementary Table 6).

Meal Test

The estimated change from baseline in the 2-h PPG increment (meal test) was

Table 1—Baseline characteristics

Parameter	Faster aspart mealtime (n = 381)	Faster aspart postmeal (n = 382)	IAsp mealtime (n = 380)	Total (N = 1,143)
Age, years	46.1 (13.8)	43.5 (13.7)	43.7 (14.0)	44.4 (13.9)
Sex, n (%)				
Male	215 (56)	219 (57)	238 (63)	672 (59)
Female	166 (44)	163 (43)	142 (38)	471 (41)
Race, n (%)				
White	363 (95)	355 (93)	348 (92)	1,066 (93)
Black or African American	5 (1)	12 (3)	9 (2)	26 (2)
Asian	5 (1)	2 (1)	7 (2)	14 (1)
Native Hawaiian or other Pacific Islander	0 (0)	1 (0)	2 (1)	3 (0)
American Indian or Alaska Native	1 (0)	0 (0)	0 (0)	1 (0)
Other	0 (0)	3 (1)	3 (1)	6 (1)
NA	7 (2)	9 (2)	11 (3)	27 (2)
BMI, kg/m^2	26.4 (3.8)	26.9 (4.1)	26.7 (3.7)	26.7 (3.9)
Duration of diabetes, years	20.9 (12.9)	19.5 (12.1)	19.3 (11.8)	19.9 (12.3)
HbA_{1c}				
%	7.6 (0.7)	7.6 (0.7)	7.6 (0.7)	7.6 (0.7)
mmol/mol	59.7	59.9	59.3	59.7
FPG				
mmol/L	8.4 (3.1)	8.1 (3.2)	7.9 (2.8)	8.1 (3.0)
mg/dL	151.4	145.6	141.8	146.2
Antidiabetes treatment at screening, n (%)				
Basal	381 (100.0)	381 (99.7)	380 (100.0)	1,142 (99.9)
Glargine	269 (70.6)	259 (67.8)	277 (72.9)	805 (70.4)
Detemir	111 (29.1)	118 (30.9)	101 (26.6)	330 (28.9)
NPH insulin	0 (0.0)	4 (1.0)	1 (0.3)	5 (0.4)
Detemir + glargine	1 (0.3)	0 (0.0)	1 (0.3)	2 (0.2)
Bolus	381 (100.0)	382 (100.0)	379 (99.7)	1,142 (99.9)
Aspart	185 (48.6)	195 (51.0)	172 (45.3)	552 (48.3)
Lispro	159 (41.7)	157 (41.1)	166 (43.7)	482 (42.2)
Glulisine	27 (7.1)	22 (5.8)	30 (7.9)	79 (6.9)
RHI	9 (2.4)	8 (2.1)	10 (2.6)	27 (2.4)
RHI + aspart	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Glulisine + lispro	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Premix	0 (0.0)	1 (0.3)	1 (0.3)	2 (0.2)
NPH/human insulin	0 (0.0)	1 (0.3)	1 (0.3)	2 (0.2)

Data for baseline characteristics are arithmetic means (SD) unless otherwise stated. The conversion factor between mmol/L and mg/dL is 18. Detemir, insulin detemir; NA, not applicable (subjects from Belgium did not provide information and were classed as not applicable); NPH, neutral protamine Hagedorn.

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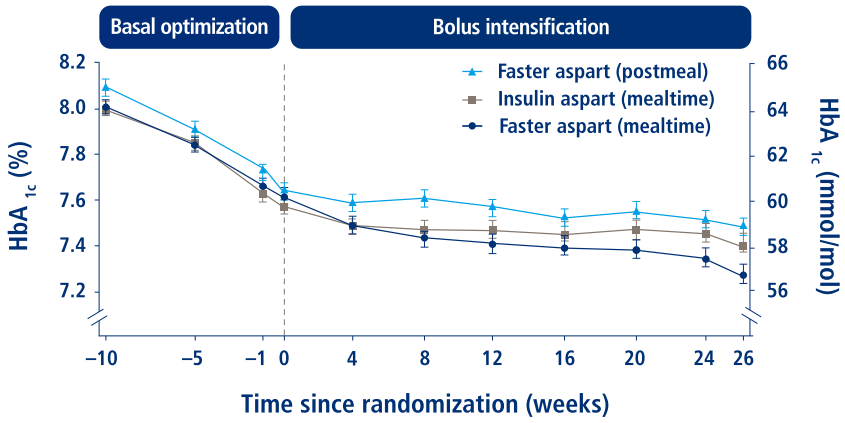

Figure 1—Mean HbA_{1c} over time. During run-in, observed mean HbA_{1c} was reduced from 8.1% (64.9 mmol/mol) to 7.6% (59.9 mmol/mol) for subjects subsequently randomized to receive postmeal faster aspart (n = 382), from 8.0% (64.0 mmol/mol) to 7.6% (59.7 mmol/mol) for subjects subsequently randomized to receive mealtime IAsp (n = 380), and from 8.0% (64.0 mmol/mol) to 7.6% (59.3 mmol/mol) for subjects subsequently randomized to receive mealtime faster aspart (n = 381). During the 26-week treatment period, the observed mean HbA_{1c} decreased to 7.5% (58.6 mmol/mol) with postmeal faster aspart, 7.4% (57.6 mmol/mol) with mealtime IAsp, and 7.3% (56.4 mmol/mol) with mealtime faster aspart. Error bars: ±SEM.

–0.3 mmol/L (–5.2 mg/dL) with mealtime faster aspart and 0.4 mmol/L (6.8 mg/dL) with IAsp (ETD mealtime faster aspart–IAsp –0.67 mmol/L [95% CI –1.29; –0.04], –12.01 mg/dL [–23.33; –0.70]; P = 0.0375), and superiority of mealtime faster aspart versus IAsp was confirmed for this end point (Fig. 2*A*, step 2, and Supplementary Fig. 2). The estimated change from baseline in 1-h PPG increment was –0.8 mmol/L (–15.1 mg/dL) for mealtime faster aspart and 0.3 mmol/L (6.1 mg/dL) for IAsp (ETD mealtime faster aspart–IAsp –1.18 mmol/L [95% CI –1.65; –0.71], –21.21 mg/dL [–29.65; –12.77]; $P <$ 0.0001) (Fig. 2*A*). There was no statistical difference in ETD for change from baseline in 3-h or 4-h PPG increments (Fig. 2*A*).

The estimated change from baseline in 1-h PPG increment (meal test) was 1.3 mmol/L (22.9 mg/dL) with postmeal faster aspart (ETD postmeal faster aspart–IAsp 0.93 mmol/L [95% CI 0.46; 1.40], 16.75 mg/dL [8.26; 25.24]; P = 0.0001) (Fig. 2*B*), but by 2 h, PPG increments for postmeal faster aspart versus mealtime IAsp were not statistically significantly different (ETD 0.30 mmol/L [95% CI –0.34; 0.93], 5.32 mg/dL [–6.05; 16.68]) (Fig. 2*B*).

The difference in mean 1- and 2-h PPG change from baseline between mealtime faster aspart and IAsp (after the meal test) was statistically significant in favor of mealtime faster aspart (ETD mealtime faster aspart–IAsp, 1 h, –1.41 mmol/L [95% CI –2.00; –0.82], –25.44 mg/dL [–36.12; –14.76], $P <$ 0.0001; 2 h, –0.93 mmol/L [–1.62; –0.23], –16.73 mg/dL [–29.26; –4.20], P = 0.0089). The difference in mean PPG change from baseline after 1 h between postmeal faster aspart and IAsp was statistically significant in favor of IAsp (ETD postmeal faster aspart–IAsp 0.69 mmol/L [95% CI 0.09; 1.28], 12.38 mg/dL [1.65; 23.11], P = 0.0238), while after 2 h there was no statistically significant difference between treatments (Supplementary Table 6).

SMPG

After 26 weeks, the mean of the 7-9-7-point profile was reduced in the two faster aspart treatment groups, with no statistically significant treatment differences versus IAsp (Supplementary Table 6). Reductions in 2-h PPG and 2-h PPG increments from baseline (7-9-7-point profiles) were observed at all main meals; however, there were no statistically significant treatment differences between faster aspart (mealtime or postmeal) and IAsp (Supplementary Table 6).

The proportions of subjects achieving the 2-h PPG target ≤7.8 mmol/L (140 mg/dL; 7-9-7-point profiles) by week 26 were 42.7% with mealtime faster aspart, 39.6% with postmeal faster aspart, and 38.6% with IAsp. The odds of achieving the target PPG level was not statistically significantly different between faster aspart (mealtime or postmeal) and IAsp (Supplementary Table 6).

Other Secondary Efficacy End Points

Treatment with mealtime faster aspart for 26 weeks resulted in a statistically significantly greater increase from baseline in 1,5-AG compared with IAsp (ETD 0.50 μg/mL [95% CI 0.24; 0.76]; P = 0.0001), whereas increases in 1,5-AG from baseline were not statistically significantly different between postmeal faster aspart and IAsp (Supplementary Table 6).

In both faster aspart treatment groups, mean FPG showed an increase from baseline until week 12 and thereafter a decrease until week 26, with no statistically significant differences versus IAsp (Supplementary Table 6). The mean body weight increase from baseline in all three treatment groups was <1 kg over the 26-week treatment period; there was no statistically significant difference between faster aspart (mealtime or postmeal) and IAsp in terms of body weight increase (ETD faster aspart–mealtime IAsp, mealtime, 0.12 kg [95% CI –0.30; 0.55]; postmeal, 0.16 kg [–0.27; 0.58]).

Insulin Dosing

During the trial, mean and median daily bolus insulin doses increased in all three treatment groups. By week 26, the doses were comparable between faster aspart (mealtime or postmeal) and IAsp (median total insulin dose [units/kg]: mealtime faster aspart, 0.801; postmeal faster aspart, 0.842; mealtime IAsp, 0.833), and the basal/bolus ratio was ~50/50 throughout the trial (Supplementary Table 7).

Safety

The overall rate of treatment-emergent severe or BG-confirmed hypoglycemic episodes, as well as the event rate of treatment-emergent severe hypoglycemic episodes, was comparable between faster aspart (mealtime or postmeal) and IAsp (Table 2). There were no statistically significant differences in the number of treatment-emergent severe or BG-confirmed hypoglycemic episodes between faster aspart (mealtime or postmeal) and IAsp, and superiority could not be confirmed (rate ratio faster aspart/IAsp, mealtime, 1.01 [95% CI 0.88; 1.15]; postmeal, 0.92 [0.81; 1.06]) (step 4).

The distribution of hypoglycemic episodes at 1 and 2 h after meals (Table 2) revealed that the rate of severe or BG-confirmed hypoglycemic episodes

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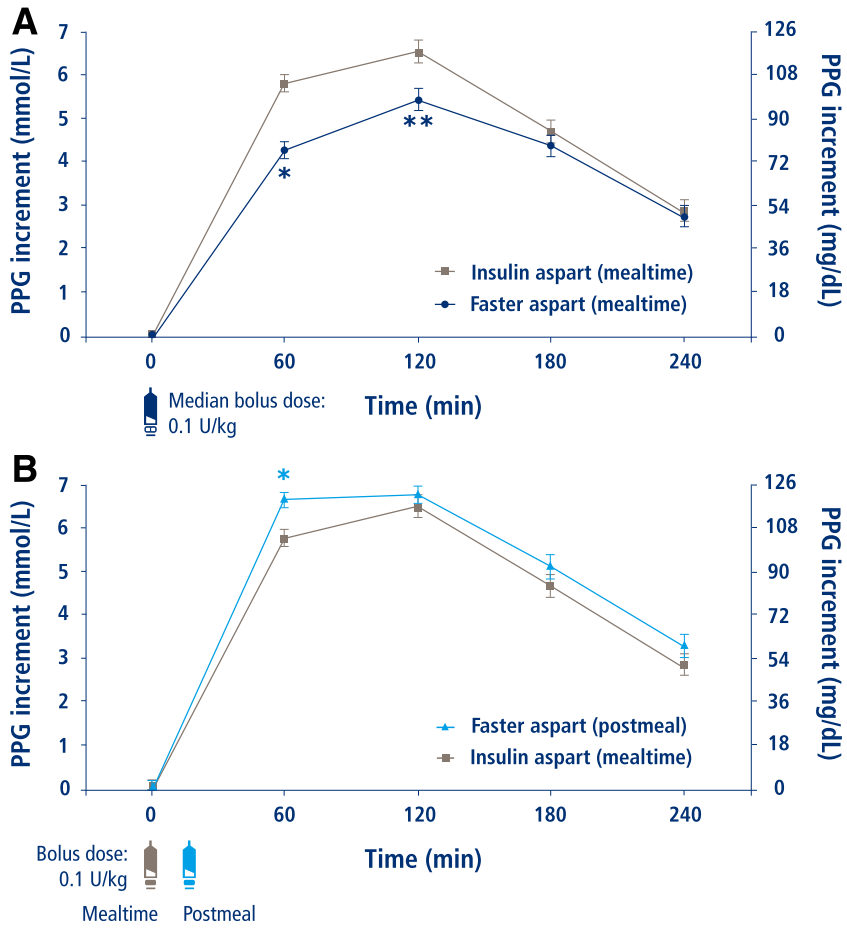

Figure 2—*A*: PPG increment at week 26 for mealtime faster aspart versus IAsp. Observed data. One-hour and 2-h PPG increments statistically significantly in favor of mealtime faster aspart: **P* < 0.0001 and ***P* = 0.0375, respectively. *B*: PPG increment at week 26 for postmeal faster aspart versus IAsp. Observed data. Mealtime IAsp dosed 0 to 2 min before meal; postmeal faster aspart dosed 20 min after meal. Change in 1-h PPG increment significantly in favor of IAsp: **P* = 0.0001. Error bars: ±SEM. The conversion factor between mmol/L and mg/dL is 18.

during the first hour after the start of a main meal was statistically significantly higher for mealtime faster aspart than for IAsp (rate ratio faster aspart/IAsp 1.48 [95% CI 1.11; 1.96]; $P < 0.0073$); however, the observed number of hypoglycemic episodes reported with mealtime faster aspart during the first hour after a meal (events per patient-year of exposure: 1.476) constituted a small fraction (~1 of 40) of all severe or BG-confirmed hypoglycemic episodes reported for mealtime faster aspart (Table 2).

The proportion of subjects reporting TEAEs and the rate of TEAEs were comparable between faster aspart (mealtime or postmeal) and IAsp. All injection-site reactions (22 events reported in 19 subjects) were nonserious and of mild or moderate severity. A total of 123 allergic reactions were reported by 107 (9.4%) subjects and evenly distributed across all three treatment groups; all were of mild or moderate severity (further details on TEAEs may be found in Supplementary Table 8).

Five subjects experienced six CV adverse events (one with mealtime faster aspart, three with postmeal faster aspart, and one with IAsp) that were positively adjudicated (of 10 that qualified for adjudication) by the event adjudication committee (Supplementary Table 9). During the trial, there were two deaths, both judged unlikely to be related to trial product (see Supplementary Data).

There were no clinically relevant differences from baseline to week 26 between faster aspart (mealtime or postmeal) and IAsp in physical examinations, vital signs, fundoscopy, electrocardiogram, or other laboratory assessments.

CONCLUSIONS

The current trial confirmed that, in subjects with type 1 diabetes on a basal-bolus regimen, both mealtime and

Table 2—Treatment-emergent hypoglycemic events

	Faster aspart mealtime			Faster aspart postmeal			IAsp mealtime			
	N (%)	E	R	*N* (%)	E	R	*N* (%)	E	R	Rate ratio (95% CI)
Treatment-emergent hypoglycemia										
Severe	26 (6.7)	46	0.25	30 (8.0)	47	0.26	32 (8.4)	51	0.27	
Severe or BG confirmed	358 (92.7)	10,993	58.99	358 (95.0)	9,961	54.43	370 (97.4)	11,078	58.65	
Meal-related severe or BG confirmed										
Within 1 h after a meal	131 (33.9)	275	1.476	85 (22.5)	131	0.716	108 (28.4)	182	0.964	
Within 2 h after a meal	258 (66.8)	1,391	7.464	231 (61.3)	969	5.295	251 (66.1)	1,108	5.866	
Severe or BG confirmed										
Faster aspart (mealtime)/IAsp*										1.01 (0.88; 1.15)
Faster aspart (postmeal)/IAsp										0.92 (0.81; 1.06)

Safety analysis set. Severe hypoglycemia was defined according to the American Diabetes Association classification (26). BG-confirmed hypoglycemia was defined as an episode with a PG value <3.1 mmol/L (56 mg/dL) with or without symptoms consistent with hypoglycemia (Novo Nordisk A/S definition). E, number of events; *N* (%), number (percentage) of subjects; R, event rate per patient-year of exposure. *Confirmatory analysis (step 4) not statistically significant.

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postmeal faster aspart are noninferior to mealtime IAsp regarding HbA_{1c} change from baseline. Switching to mealtime or postmeal faster aspart was effective in improving glycemic control: the reduction in HbA_{1c} with mealtime faster aspart was moderately, yet statistically significantly, greater than with IAsp. After 26 weeks of treatment, subjects receiving mealtime faster aspart were almost 1.5 times as likely to achieve the HbA_{1c} target of <7.0% (53 mmol/mol) than those receiving IAsp.

Mealtime faster aspart was effective in controlling PPG excursions, and superiority versus IAsp in 2-h PPG increments (meal test) was confirmed. A statistically significant difference was demonstrated for the 1-h PPG increment (meal test) in favor of mealtime faster aspart; mean 7-9-7-point SMPG profiles and associated 2-h PPG and 2-h PPG increments showed modest trends toward improvement in PPG. Treatment with mealtime faster aspart for 26 weeks resulted in a statistically significantly greater increase from baseline in 1,5-AG compared with IAsp. This finding indicates that there were fewer recent hyperglycemic excursions, signifying that although the difference between mealtime faster aspart and IAsp was small, PPG control was improved. These results suggest that faster aspart, which has an improved action profile (20), produces the same glycemic improvements over IAsp in type 1 diabetes (0.15% statistically significantly lower HbA_{1c} and 0.7–1.2 mmol/L lower PPG increments) as reported previously with IAsp versus RHI (0.15% statistically significantly lower HbA_{1c} [27] and 1.1–1.3 mmol/L lower PPG increments [28,29]).

In certain situations, postmeal dosing of insulin may offer increased flexibility compared with mealtime dosing—for instance, when an individual is unable to predict the exact timing or carbohydrate content of a meal in advance (e.g., on social occasions), when experiencing lack of appetite or nausea (e.g., the very elderly or frail), when appetite is unpredictable (e.g., children), if an injection is forgotten, or if an individual is anxious about severe hypoglycemia (30,31). Subjects randomized to dosing faster aspart postmeal for all meals maintained overall glycemic control noninferior to that obtained with mealtime IAsp, indicating that flexibility in timing of dose with faster aspart does not lead to worsening of glycemic control.

Treatment with faster aspart was well tolerated by the subjects in this trial, and no safety concerns were raised. Overall, there were no clinically relevant differences in the TEAE profiles across all three treatment groups (Supplementary Table 8). No statistically significant difference was seen in overall rate of severe or BG-confirmed hypoglycemic episodes between faster aspart (mealtime or postmeal) and IAsp. The timing of hypoglycemia in relation to a meal usually reflects the time-action profile of the administered insulin formulation. Thus, as expected, there was a higher rate of hypoglycemia in the first hour after a meal in the mealtime faster aspart arm than in the IAsp arm. This observation is consistent with the differing clinical pharmacology profiles of faster aspart and IAsp (20). Similar observations were reported when IAsp was compared with RHI in previous trials (28). Despite the higher rate of severe or BG-confirmed hypoglycemic episodes in the first hour (representing <3% of the overall episodes reported in this treatment group), there was no overall increase in severe or BG-confirmed hypoglycemia in the mealtime faster aspart arm compared with the IAsp arm.

The strengths of this trial include the number of subjects, the double blinding of subjects enrolled in the mealtime groups, and the additional 26-week period to document long-term safety and compare efficacy (which includes follow-up of subjects achieving target HbA_{1c} levels). Additionally, basal insulin dose was optimized on an individual basis prior to randomization with limited adjustments during the trial, thus allowing a clearer evaluation of the effect of the different bolus regimens. The bolus insulin dose of 0.1 units/kg used in this standardized meal test was in line with the median breakfast bolus dose measured at the end of the 26-week treatment period in each of the treatment groups. However, the meal test protocol was a potential limitation of the trial, as all subjects received the same 0.1 units/kg body weight bolus, and no adjustment was made for individual insulin-to-carbohydrate ratios: for all subjects, therefore, the insulin dose was an approximation of their usual dose.

Together with the results of previous studies (32,33,34), this trial has demonstrated that faster aspart given at mealtimes is noninferior to IAsp in terms of HbA_{1c} reduction while offering superior control of PPG excursions, without increased risk of overall hypoglycemia. Additionally, faster aspart offers the option of dosing up to 20 min postmeal while retaining overall glycemic control and without increased rates of overall hypoglycemia. This is an incremental step in more closely replicating the physiologic response of endogenous insulin release after a meal.

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Declaration of Dr. Nathan Laney

Exhibit H

Diabetes Care Volume 40, July 2017

Faster Aspart Versus Insulin Aspart as Part of a Basal-Bolus Regimen in Inadequately Controlled Type 2 Diabetes: The onset 2 Trial

Diabetes Care 2017;40:951–957 | https://doi.org/10.2337/dc16-1770

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EMERGING TECHNOLOGIES AND THERAPEUTICS

OBJECTIVE

This multicenter, double-blind, treat-to-target, phase 3 trial evaluated the efficacy and safety of fast-acting insulin aspart (faster aspart) versus insulin aspart (IAsp) in adults with type 2 diabetes receiving basal insulin and oral antidiabetic agents.

RESEARCH DESIGN AND METHODS

The primary end point was HbA_{1c} change from baseline after 26 weeks' treatment. After an 8-week run-in to optimize basal insulin, subjects were randomized (1:1) to mealtime faster aspart ($n = 345$) or IAsp ($n = 344$), titrated using a simple daily patient-driven algorithm, plus insulin glargine U100 and metformin.

RESULTS

HbA_{1c} change was –1.38% (faster aspart) and –1.36% (IAsp); mean HbA_{1c} was 6.6% for both groups. Faster aspart demonstrated noninferiority versus IAsp in reducing HbA_{1c} (estimated treatment difference [ETD] [95% CI] –0.02% [–0.15; 0.10]). Both treatments improved postprandial plasma glucose (PPG) control; the PPG increment (liquid meal test) was statistically significant in favor of faster aspart after 1 h (ETD [95% CI] −0.59 mmol/L [−1.09; −0.09]; −10.63 mg/dL [−19.56; −1.69]; $P = 0.0198$), but not after 2–4 h. Change from baseline in fasting plasma glucose, body weight, and overall severe/blood glucose–confirmed hypoglycemia rates (rate ratio [RR] [95% CI] 1.09 [0.88; 1.36]) were similar between treatments. Postmeal hypoglycemia (0−2 h) rates were 2.27 (faster aspart) and 1.49 (IAsp) per patient-year of exposure (RR [95% CI] 1.60 [1.13; 2.27]).

CONCLUSIONS

Faster aspart and IAsp were confirmed noninferior in a basal-bolus regimen regarding change from baseline in HbA_{1c}. Faster aspart improved 1-h PPG with no differences in 2−4-h PPG versus IAsp. Overall hypoglycemia rates were similar except for an increase in 0−2-h postmeal hypoglycemia with faster aspart.

Basal insulins are one of the recommended steps in type 2 diabetes treatment intensification when oral antidiabetic drugs (OADs) no longer provide sufficient glycemic control (1). As β-cell function decreases further, maintaining target HbA_{1c} levels becomes challenging, even when target fasting plasma glucose (FPG) levels have been achieved (2), and further therapeutic intensification may be required (3). The aim of

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such intensification is to prevent excessive postprandial plasma glucose (PPG) excursions, which contribute to overall hyperglycemia. Several studies have documented that in type 2 diabetes, the relative contribution of PPG to excess hyperglycemia increases as HbA_{1c} levels approach target (4,5).

Options for therapy intensification in type 2 diabetes include glucagon-like peptide-1 (GLP-1) receptor agonists or the addition of mealtime insulin as part of a basal-bolus regimen (1). Reduction of PPG excursions with the addition of bolus insulin has been clearly demonstrated in type 2 diabetes (6). First-generation rapid-acting insulin analogs represented a major step forward in reducing PPG excursions versus regular human insulin (RHI). However, there remains an unmet need for insulin analogs with an even faster onset of action than rapid-acting insulin analogs, which could potentially achieve better PPG control (7,8).

Fast-acting insulin aspart (faster aspart) is a new formulation of conventional insulin aspart (IAsp). Nonclinical data illustrate that the addition of niacinamide promotes the formation of insulin aspart monomers after subcutaneous (s.c.) injection, facilitating a more rapid rate of insulin aspart absorption across the endothelium into the blood (9). In adults with type 1 diabetes, s.c. injection of faster aspart was associated with twice as fast onset of appearance in the bloodstream (4 vs. 9 min), twofold higher insulin concentration, and 74% greater insulin action in the first 30 min versus IAsp (10). As part of a basal-bolus regimen in type 1 diabetes, mealtime faster aspart effectively improved HbA_{1c} (estimated treatment difference [ETD] [95% CI] –0.15% [–0.23; –0.07]), and noninferiority to IAsp was confirmed, with statistically superior 2-h PPG control versus IAsp (ETD [95% CI] −0.67 mmol/L [−1.29; −0.04]; –12.01 mg/dL [–23.33; –0.70]) (11). Statistically superior glycemic control versus basal-only therapy was observed in subjects with type 2 diabetes, where HbA_{1c} was reduced from 7.9% (63.2 mmol/mol) to 6.8% (50.7 mmol/mol) in the basal-bolus arm and from 7.9% (63.1 mmol/mol) to 7.7% (60.7 mmol/mol) in the basal arm (ETD [95% CI] –0.94% [–1.17; –0.72]; –10.29 mmol/mol [–12.75; –7.82]; $P < 0.0001$) (12).

The objective of this trial was to confirm the efficacy of mealtime faster aspart versus mealtime IAsp (NovoRapid/NovoLog), as part of a basal-bolus regimen in subjects with type 2 diabetes inadequately controlled with basal insulin and OADs.

RESEARCH DESIGN AND METHODS

Trial Design

This was a 26-week, multicenter, double-blind, active-controlled, treat-to-target randomized trial in subjects with type 2 diabetes comparing mealtime faster aspart with IAsp, both in combination with insulin glargine U100 (Lantus) and metformin. Subject follow-up occurred at 7 and 30 days after the end of trial (EOT). The trial was conducted in accordance with the Declaration of Helsinki (13) and the International Conference on Harmonization Good Clinical Practice (14).

Subjects

Subjects (≥18 years of age) with a BMI ≤40 kg/m^2 were eligible for inclusion if diagnosed with type 2 diabetes and treated with basal insulin for ≥6 months (current once-daily treatment with NPH insulin, insulin detemir, or insulin glargine U100 for ≥3 months) before screening. Eligible subjects had also been treated with metformin (stable dose ≥1,000 mg) alone or with a sulfonylurea, glinide, dipeptidyl peptidase 4 inhibitor, and/or an α-glucosidase inhibitor for ≥3 months before screening. Subjects receiving metformin monotherapy before enrollment were required to have an HbA_{1c} of 7.0–9.5% (53–80 mmol/mol) at screening or 7.0–9.0% (53–75 mmol/mol) if receiving OADs + metformin. Exclusion criteria specified no bolus insulin use, except short-term use because of intermittent illness (≤14 days' consecutive treatment), and no GLP-1 agonists and/or thiazolidinediones (all ≤3 months before screening); concomitant medications known to interfere significantly with glucose metabolism; cardiovascular (CV) disease ≤6 months before screening; recurrent severe hypoglycemia (>1 severe hypoglycemic event during the past 12 months), hypoglycemic unawareness as judged by the investigator, or hospitalization for diabetic ketoacidosis ≤6 months before screening. All inclusion/exclusion criteria are listed in the Supplementary Data.

Interventions

Basal Titration During the Trial

After an initial 2-week screening period, current OADs (except metformin) were discontinued, and subjects entered the 8-week run-in period, during which basal insulin glargine U100 (100 units/mL; administered s.c. once daily at approximately the same time in the evening using a 3.0 mL SoloStar pen injector) was optimized. Subjects were switched unit-for-unit from their previous basal insulin to once-daily insulin glargine U100. During run-in, basal insulin was titrated using a weekly treat-to-target approach, with a prebreakfast self-monitored plasma glucose (SMPG) target of 4.0−5.0 mmol/L (71−90 mg/dL) (Supplementary Table 1). After run-in, basal adjustments were performed when required as judged by the investigator, but basal dose frequency could not be changed.

Bolus Doses During the Trial

After the run-in, subjects with HbA_{1c} 7.0−9.5% (53−80 mmol/mol) were randomized 1:1 to receive mealtime faster aspart (100 units/mL) or IAsp (100 units/mL), both with basal insulin glargine U100 and metformin (stratified according to continuous glucose monitoring [CGM] subgroup participation). Faster aspart or IAsp was administered s.c. 0–2 min before each main meal using a 3.0 mL PDS290 prefilled pen injector. The timing of bolus insulin administration was in line with the IAsp label, which recommends administration immediately before a meal (15). The double-blind treatment period (bolus insulin titration) was 26 weeks. After randomization, bolus insulin dose adjustments were performed daily by the subject and reviewed weekly by the investigator. Bolus dose adjustments were made by subjects based on SMPG values from the previous day, according to the titration guideline (Supplementary Table 1). Subjects commenced 4 units of mealtime insulin at each meal, which was titrated by 1-unit increases or decreases to achieve the next premeal or bedtime target of 4.0–6.0 mmol/L (70–108 mg/dL). Additional bolus dosing was allowed at the investigator's discretion.

SMPG

Subjects were supplied with a blood glucose (BG) meter (factory calibrated to display plasma glucose [PG] values) and instructed to record the date, time, and value of all SMPG measurements for 7-9-7-point profiles (preprandial, postmeal, bedtime, and once at 4 A.M.) on three consecutive days before the scheduled clinic visits at weeks 0, 12, and 26; 4-point

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profiles (preprandial and bedtime) were recorded daily for titration purposes.

Standardized Meal Test

PPG levels from 1 to 4 h were assessed in subjects completing the run-in period via a standardized liquid meal test containing ~80 g carbohydrate, consumed as quickly as possible and ≤12 min. To participate in the meal test, subjects had to be fasting with FPG levels within 4.0–8.8 mmol/L (72−160 mg/dL; SMPG measured before meal test). Blood samples were taken just before the meal and after 1, 2, 3, and 4 h. The same meal test was repeated at week 26, with the addition of the randomized treatment, a bolus insulin dose. The bolus insulin dose at the second meal test was calculated by dividing the carbohydrate content of the standardized liquid meal by the subject-specific insulin-to-carbohydrate ratio. This ratio was calculated using the "500 rule," whereby 500 was divided by the total daily insulin dose to determine the grams of carbohydrate covered by each unit of insulin (16).

Assessments

All end points reported were prespecified and are summarized in Supplementary Table 2.

Primary End Point

The primary end point was change from baseline in HbA_{1c} after 26 weeks' treatment.

Secondary End Points

Confirmatory secondary end points included change from baseline in 2-h PPG increment (meal test) after 26 weeks' treatment, number of treatment-emergent severe or BG-confirmed hypoglycemic episodes from baseline to week 26, and change from baseline to week 26 in body weight. Hypoglycemic episodes were categorized as treatment emergent if the onset of the episode occurred on the first day of exposure to, and no later than 1 day after the last day of, randomized treatment. Severe hypoglycemia was defined according to the American Diabetes Association (ADA) classification as an event requiring assistance of another person to actively administer carbohydrates or glucagon or take other corrective actions. PG concentrations may not be available during an event, but neurological recovery after the return of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration (17). BG-confirmed hypoglycemia was defined by a PG value <3.1 mmol/L (56 mg/dL; Novo Nordisk definition) with or without symptoms consistent with hypoglycemia.

Supportive secondary efficacy end points included HbA_{1c} responders (subjects achieving HbA_{1c} <7.0% [53.0 mmol/mol] or ≤ 6.5% [47.5 mmol/mol], as well as the proportions who achieved these targets without severe hypoglycemia); change from baseline in PPG from the meal test (at 1, 2, 3, and 4 h separately) and PPG increment from the meal test (at 1, 3, and 4 h separately), both after 26 weeks' randomized treatment; change from baseline in mean SMPG profile and mean PPG increments (7-9-7-point profile); PPG responders (subjects achieving an overall mean 2-h PPG ≤7.8 mmol/L [140 mg/dL] and the same targets without severe hypoglycemia, derived from the 7-9-7-point SMPG profile); change from baseline to week 26 in 1,5-anhydroglucitol (1,5-AG), a marker for postprandial hyperglycemia; change from baseline to week 26 in FPG; and daily insulin dose (basal, bolus, and total).

Supportive secondary safety end points included the numbers of treatment-emergent adverse events (TEAEs), hypoglycemic episodes at 1, 2, 4, and 6 h postmeal, daytime (0600−2359 h) and nocturnal (0001−0559 h) hypoglycemic episodes, allergic reactions, and injection-site reactions. An adverse event was defined as treatment emergent if onset occurred on or after the first day of exposure to treatment and no later than 7 days after the last day of treatment. CV events and deaths occurring after randomization were sent for evaluation by an external, independent, clinical safety event adjudication committee. Additional safety assessments, physical examination, vital signs, fundoscopy, electrocardiograms, and laboratory parameters were recorded at baseline and week 26.

Statistical Methods

Efficacy analysis was based on the full analysis set, following the intention-to-treat principle. Confirmatory end points were tested using a hierarchical (fixed-sequence) procedure (Supplementary Fig. 1). The primary end point was analyzed using a mixed-effect model for repeated measurements, where all calculated changes in HbA_{1c} from baseline at trial visits were included in the analysis. This model included treatment, region, and CGM strata as fixed effects; subject as a random effect; HbA_{1c} at baseline as a covariate; and interactions between all fixed effects and visit and between the covariate and visit. Noninferiority was confirmed if the upper boundary of the two-sided 95% CI was ≤0.4%. PPG and PPG increments (meal test) were based on an ANOVA model. Target end points were analyzed separately based on a logistic regression model. Body weight, FPG, 1,5-AG, and PPG increment (SMPG) were analyzed using a mixed-effect model for repeated measurements similar to the model used for the primary end point. For the primary analysis, the one-sided *P* value for noninferiority is presented; for the remaining analyses, the two-sided *P* value for treatment difference is presented. Additional details on the sample size, power determination, statistical methods for the secondary efficacy end points, and stepwise hierarchical test (Supplementary Fig. 1) are in the Supplementary Data.

Safety end points were summarized using the safety analysis set and analyzed using the full analysis set. Hypoglycemic episodes were summarized by severity, using Novo Nordisk and ADA hypoglycemia definitions, and by category and total number of events in relation to the time since the start of a meal (Supplementary Data).

RESULTS

Trial Subjects

The trial randomized 689 subjects to receive faster aspart (*n* = 345) or IAsp (*n* = 344). Overall, 682 subjects were exposed to randomized treatment (*n* = 341 in each group) (Supplementary Fig. 2), and 606 (88%; *n* = 301, faster aspart; *n* = 305, IAsp) completed the trial. Baseline characteristics were similar between groups (Table 1).

Hierarchical Testing Procedure

Step 1 was confirmed. Because step 2 was not confirmed, the stepwise testing procedure was stopped (Supplementary Table 3).

Efficacy

Change in HbA_{1c}

Mean HbA_{1c} in subjects subsequently randomized to the faster aspart and IAsp groups were, respectively, 8.2% and 8.1% (65.6 mmol/mol and 65.2 mmol/mol) before the 8-week run-in period and

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Table 1—Baseline characteristics at randomization

Parameter	Faster aspart *n* = 345	IAsp *n* = 344	Total *N* = 689
Age, years	59.6 (9.3)	59.4 (9.6)	59.5 (9.4)
Gender, *n* (%)			
Male	163 (47)	173 (50)	336 (49)
Female	182 (53)	171 (50)	353 (51)
Race, *n* (%)			
White	277 (80)	281 (82)	558 (81)
Asian	40 (12)	42 (12)	82 (12)
Black or African American	22 (6)	18 (5)	40 (6)
American Indian or Alaska Native	3 (1)	0 (0)	3 (0)
Native Hawaiian or other Pacific Islander	2 (1)	0 (0)	2 (0)
Other	1 (0)	3 (1)	4 (1)
Body weight			
kg	89.0 (16.9)	88.3 (16.7)	88.7 (16.8)
lb	196.3 (37.3)	194.7 (36.9)	195.5 (37.1)
BMI, kg/m^2	31.5 (4.7)	31.0 (4.5)	31.2 (4.6)
Duration of diabetes, years	13.2 (6.7)	12.3 (6.3)	12.7 (6.5)
HbA_{1c}			
%	8.0 (0.7)	7.9 (0.7)	7.9 (0.7)
mmol/mol	63.5 (7.5)	62.7 (7.7)	63.1 (7.6)
FPG			
mmol/L	6.8 (1.8)	6.8 (2.0)	6.8 (1.9)
mg/dL	121.7 (32.7)	122.7 (35.1)	122.2 (33.9)
Antidiabetic treatment at screening, *n* (%)			
Basal + OAD	345 (100.0)	344 (100.0)	689 (100.0)
Basal OD + 1 OAD	187 (54.2)	184 (53.5)	371 (53.8)
Basal OD + 2 OADs	149 (43.2)	152 (44.2)	301 (43.7)
Basal OD + >2 OADs	9 (2.6)	8 (2.3)	17 (2.5)

Values for baseline characteristics are arithmetic means (SD), unless stated otherwise. The conversion factor between mmol/L and mg/dL is 18. OD, once daily.

8.0% and 7.9% (63.5 mmol/mol and 62.7 mmol/mol) at baseline. By EOT, mean HbA_{1c} had decreased to 6.6% (49 mmol/mol) in both groups (Fig. 1). The estimated mean change in HbA_{1c} from baseline to EOT was –1.38% (–15.1 mmol/mol) for faster aspart and –1.36% (–14.9 mmol/mol) for IAsp. The ETD was –0.02% (95% CI –0.15; 0.10) (–0.24 mmol/mol [–1.60; 1.11]), confirming noninferiority of faster aspart to IAsp ($P < 0.0001$; hierarchical testing step 1) (Supplementary Fig. 1). By week 26, 74.8% of subjects in the faster aspart group and 75.9% in the IAsp group had achieved HbA_{1c} <7.0% (53 mmol/mol), and 71.9% and 72.7%, respectively, achieved this target without severe hypoglycemia (Supplementary Fig. 3*A* and Supplementary Table 4). By week 26, 54.5% and 56.4% of subjects had achieved HbA_{1c} ≤6.5% (47.5 mmol/mol), and 52.2% and 53.5% had achieved this target without severe hypoglycemia in the faster aspart and IAsp groups, respectively (Supplementary Fig. 3*B* and Supplementary Table 4).

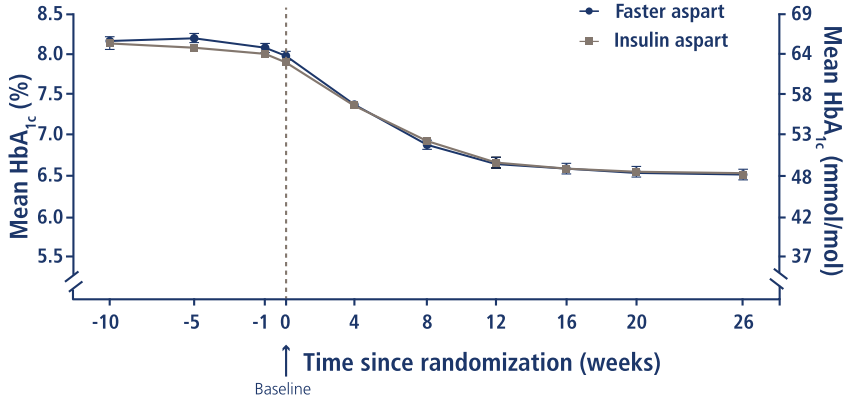

Figure 1—Mean HbA_{1c} over time. Error bars: ± SEM.

Meal Test

Estimated change from baseline in 2-h PPG increment was –3.2 mmol/L (–58.3 mg/dL) with faster aspart versus –2.9 mmol/L (–51.8 mg/dL) for IAsp. The ETD was –0.36 mmol/L (95% CI –0.81; 0.08) (−6.57 mg/dL [−14.54; 1.41]) (Fig. 2), which did not reach statistical significance. The estimated change from baseline in 1-h PPG increment was −2.1 mmol/L (−38.5 mg/dL) for faster aspart and −1.6 mmol/L (−27.9 mg/dL) for IAsp. The ETD was −0.59 mmol/L (95% CI −1.09; −0.09) (−10.63 mg/dL [−19.56; −1.69]), which was statistically significantly in favor of faster aspart ($P = 0.0198$) (Fig. 2 and Supplementary Table 4).

Statistical superiority of treatment with faster aspart versus IAsp could not be confirmed for change from baseline in 2-h PPG increment (Supplementary Fig. 1). There were no statistical differences between groups for change from baseline in 3-h or 4-h PPG increments or in PPG at any time point (Supplementary Table 4).

SMPG

Mean 9-point SMPG values (observed data) were reduced after the addition of bolus insulin doses (Supplementary Fig. 4). The observed mean of the 7-9-7-point profile was ~9.0 mmol/L (162.1 mg/dL) in both groups at baseline compared with ~6.9 mmol/L (124.4 mg/dL) by EOT (Supplementary Table 4). The change from baseline in 2-h PPG increment (7-9-7-point profile) was numerically greater with faster aspart versus IAsp at all meals, but this difference only reached statistical significance after lunch (–1.2 mmol/L [–21.4 mg/dL] vs. –0.8 mmol/L [–15.0 mg/dL]; ETD [95% CI] –0.35 mmol/L [–0.65; –0.05]; 6.36 mg/dL [–11.81; –0.92]; $P = 0.0219$) (Supplementary Table 4).

Overall, 71.2% and 67.2% of subjects achieved the 2-h PPG target of ≤7.8 mmol/L (140 mg/dL) at week 26 (7-9-7-point SMPG profile) in the faster aspart and IAsp groups, respectively (Supplementary Fig. 3*C* and Supplementary Table 4), with 69.4% and 64.5% of subjects, respectively, achieving the target without experiencing severe

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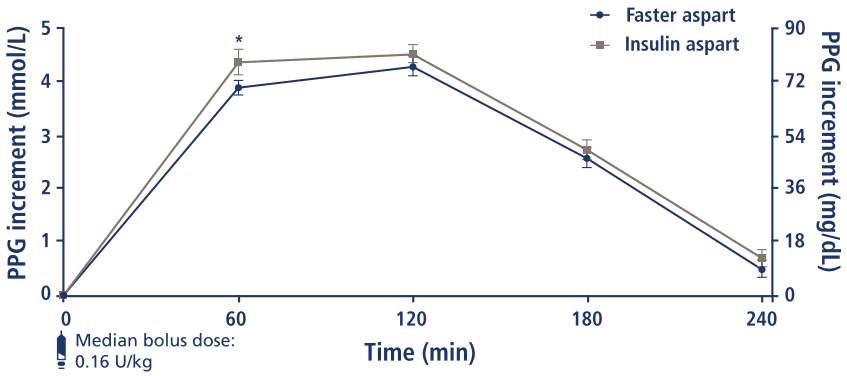

Figure 2—PPG increment (meal test) at week 26. *Change in 1-h PPG increment statistically significant in favor of faster aspart: ETD (95% CI): −0.59 (−1.09; −0.09) mmol/L; −10.63 (−19.56; −1.69) mg/dL; $P = 0.0198$. Observed data. Error bars: ± SEM. The conversion factor between mmol/L and mg/dL is 18.

hypoglycemia (Supplementary Fig. 3*C* and Supplementary Table 4).

Other Secondary Efficacy End Points

At EOT, increases in mean 1,5-AG levels were observed in both groups (to 12.8 μg/mL in faster aspart and 13.2 μg/mL in IAsp), with no difference in change from baseline between groups (Supplementary Table 4).

FPG remained similar from baseline to EOT in both groups (Supplementary Table 4). Body weight increased by ∼2.7 kg in both groups (ETD [95% CI] 0.00 kg [–0.60; 0.61]; 0.01 lb [–1.33; 1.35]).

Insulin Dosing

The total daily insulin dose increased during the treatment period for both groups due to the bolus intensification. Median total daily insulin dose increased from 0.56 units/kg to 1.02 units/kg in the faster aspart group and from 0.51 units/kg to 1.02 units/kg in the IAsp group (Supplementary Table 5). Observed insulin doses were similar between the faster aspart and IAsp groups. For both groups, the proportion of bolus daily insulin relative to total daily insulin was 56% after 26 weeks' treatment (Supplementary Table 5).

Safety (TEAEs)

The difference in overall rate of severe or BG-confirmed hypoglycemia was not statistically significant between treatment groups (treatment rate ratio [RR] 1.09 [95% CI 0.88; 1.36]) (Table 2). The number of severe or BG-confirmed hypoglycemic episodes per subject increased at a similar rate in both groups (Supplementary Fig. 5). The observed rates of severe hypoglycemic episodes were low in both groups (0.17 and 0.11 episodes per patient-year of exposure for, respectively, faster aspart and IAsp) (Table 2). The proportion of subjects who experienced severe hypoglycemia was 3.2% (faster aspart) and 3.8% (IAsp). The relative difference in the observed rates of severe hypoglycemic episodes between groups was not statistically significant.

For the interval 0−2 h after meals, a statistically significantly higher rate of meal-related hypoglycemia was reported for faster aspart (estimated RR 1.60 [95% CI 1.13; 2.27]; $P = 0.0082$), but there was no statistically significant difference between treatment groups for any other time frame or for daytime or nocturnal episodes of hypoglycemia (Table 2). The proportion of subjects reporting TEAEs and the rate of TEAEs was similar between groups (Supplementary Table 6). The most frequently reported TEAEs (≥1% of subjects; by preferred terms) across the treatment groups were nasopharyngitis and upper respiratory and urinary tract infections. Most events were nonserious and mild or moderate in severity. In total, 58 allergic reactions in 51 (7.5%) subjects were reported and evenly distributed across groups; most were nonserious. The event rate for injection-site reactions was low in this trial and similar between groups. All injection-site reactions were nonserious and did not recur, with the exception of two events of injection-site hematoma reported for one subject in the IAsp group.

The event adjudication committee positively adjudicated 12 adverse events as CV events (Supplementary Table 7). Six of these events were identified as major adverse CV events: two in the faster aspart group and four in the IAsp group. In the subjects with positively adjudicated CV events, most recovered/resolved and were judged by the investigator as unlikely to be related to trial products.

Table 2—Treatment-emergent hypoglycemic events

Treatment-emergent hypoglycemia	Faster aspart			IAsp			Treatment RR (faster aspart-to-IAsp)
	n (%)	E	R	*n* (%)	E	R	Estimate (95% CI)
Severe	11 (3.2)	27	0.17	13 (3.8)	17	0.11	1.25 (0.44; 3.55)
Severe or BG confirmed	262 (76.8)	2,857	17.9	250 (73.3)	2,692	16.6	1.09 (0.88; 1.36)
Meal-related severe or BG-confirmed hypoglycemia							
Within 1 h	45 (13.2)	78	0.49	39 (11.4)	62	0.38	1.29 (0.78; 2.15)
Within 2 h	112 (32.8)	362	2.27	96 (28.2)	241	1.49	1.60 (1.13; 2.27)*
Within 4 h	208 (61.0)	1,248	7.81	179 (52.5)	1,092	6.73	1.18 (0.91; 1.53)
Within 6 h	238 (69.8)	2,036	12.74	217 (63.6)	1,987	12.25	1.07 (0.84; 1.36)
Daytime and nocturnal severe or BG-confirmed hypoglycemia							
Daytime	257 (75.4)	2,572	16.09	245 (71.8)	2,475	15.25	1.07 (0.86; 1.33)
Nocturnal	104 (30.5)	285	1.78	84 (24.6)	217	1.34	1.38 (0.96; 2.00)

Severe hypoglycemia was defined according to the ADA classification (17). BG-confirmed hypoglycemia was defined as an episode with a PG value <3.1 mmol/L (56 mg/dL), with or without symptoms consistent with hypoglycemia (Novo Nordisk definition). E, number of events; R, event rate per patient-year of exposure. *$P = 0.0082$.

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There were no clinically relevant differences from baseline to EOT or between treatment groups in physical examinations, vital signs, fundoscopy, electrocardiograms, or laboratory assessments.

CONCLUSIONS

In this trial, treatment intensification with mealtime faster aspart or IAsp improved glycemic control in subjects with type 2 diabetes inadequately controlled on basal insulin and OADs, with faster aspart confirmed as noninferior to IAsp for HbA_{1c} change over 26 weeks. In both treatment groups, HbA_{1c} decreased during the first 16 weeks of treatment, stabilizing at ~6.6% thereafter until EOT, demonstrating that subjects were able to maintain tight glycemic control, as recommended by current guidelines (1), which is predicted to reduce the risk of long-term diabetes-associated complications (18–20). These results were achieved with a simple daily patient-driven algorithm that titrated mealtime insulin by 1-unit increases or decreases, as necessary, to achieve the next premeal or bedtime target of 4.0–6.0 mmol/L (70–108 mg/dL). The improvement in HbA_{1c} (~6.6%) over time was reflected in the high proportion of subjects who met the target HbA_{1c} level (<7.0% [53 mmol/mol]), including those without severe hypoglycemia, which is generally recommended by the European Association for the Study of Diabetes and ADA for type 2 diabetes (1). The degree of improvement in HbA_{1c} from baseline with the addition of prandial bolus insulin is notable and demonstrates the contribution of excessive PPG excursions to overall glycemic control. The final HbA_{1c} achieved in this trial (through a simple self-titration algorithm) is one of the lowest attained in a large randomized trial of basal-bolus insulin in type 2 diabetes (21).

Mealtime faster aspart and IAsp were effective in controlling PPG (assessed by both the meal test and SMPG) and improved levels of 1,5-AG, a marker for postprandial hyperglycemia (22,23). In studies of basal-bolus therapy in type 2 diabetes, changes in HbA_{1c} are often small and nonsignificant (~0.09%) (21). Given the heterogeneity of type 2 diabetes, both in regard to insulin resistance and residual β-cell function (24), that similar overall glycemic control was achieved with both faster aspart and IAsp is unsurprising. This similar control occurred despite a statistically significant improvement in the 1-h PPG increment (meal test) and a lower lunchtime 2-h PPG increment (7-9-7-point SMPG profile) with faster aspart. Here we report a 0.59 mmol/L (10.63 mg/dL) lower increment (meal test) in 1-h PPG with faster aspart versus IAsp. A previous meta-analysis of randomized clinical trials in type 1 and type 2 diabetes comparing IAsp and RHI reported a significant difference in PPG improvement between regimens in favor of IAsp, with overall estimates of –0.47 mmol/L (90-min PPG value); analysis of average change in PPG increment gave similar results (25). Faster aspart demonstrated statistically superior 2-h PPG control versus IAsp when used as part of a basal-bolus regimen in type 1 diabetes (11). Conceivably, in day-to-day clinical practice, people with type 2 diabetes who have marked reductions in endogenous insulin secretion might be the ones to most benefit from a faster-acting mealtime insulin.

After 26-weeks' treatment, 56% of the total insulin dose was provided by mealtime insulin in both groups. Use of CGM has previously shown that existing approaches for calculating basal-bolus doses may overestimate total insulin dose required and underestimate mealtime insulin requirements (26). Recommending a regimen in which the basal dose comprises <50% of the overall insulin dose is preferable for achieving optimal glycemic control in basal-bolus treatment (27). The results from the current trial broadly support this ratio.

Body weight gain was ~2.7 kg over 26 weeks for both treatment groups, which is typical of the weight gain associated with intensive insulin regimens (28).

The overall safety profiles for faster aspart and IAsp were similar and as expected for IAsp. Many people with diabetes fear hypoglycemia; however, although a high proportion of subjects achieved HbA_{1c} <7%, hypoglycemia rates were comparable with those previously reported (21), and no statistically significant differences were observed between the two treatments. The timing of hypoglycemia is usually indicative of the time-action profile of the administered insulin. The higher rate of overall hypoglycemic episodes within the first 2 h after a meal for faster aspart versus IAsp (absolute difference of ~0.8 events per patient-year of exposure) is consistent with the clinical pharmacology profiles of faster aspart and IAsp, wherein a greater early glucose-lowering effect with faster aspart was demonstrated versus IAsp (10). Similar observations were made previously when IAsp was compared with RHI (29). There were no statistically significant differences in hypoglycemic episodes between faster aspart and IAsp within 1, 4, and 6 h of a meal.

Strengths of the current trial include the double-blind design, use of a standardized meal test at baseline and after 26 weeks, and the relatively high (88%) completer rate. A limitation was the need for subjects to perform frequent finger-prick tests to record SMPG values, which, in the real-world setting, many patients may be unwilling to do. Advances in needle-free technology to measure glucose may, however, improve the practicality of intensive insulin self-management regimens in everyday life. Other limitations are the inclusion of subjects with relatively good glycemic control, who are not usually representative of subjects encountered in clinical practice, initiation of three bolus doses simultaneously, and the liquid meal test, which standardizes macronutrient composition between subjects but is not fully representative of a real-life setting. However, a treat-to-target trial of well-controlled subjects with type 2 diabetes showed that ~75% of subjects initiated with one bolus injection eventually required a full basal-bolus regimen (30), so it is of value to assess faster aspart in the same regimen.

In adults with type 2 diabetes inadequately controlled on basal insulin and OADs, insulin intensification with faster aspart or IAsp improved overall glycemic and PPG control, with statistically significantly improved 1-h PPG control with faster aspart. Overall hypoglycemia (severe or BG confirmed) rates were similar between treatment groups, with an increase in hypoglycemia rates during the 0−2 h postmeal interval with faster aspart. Thus, faster aspart and IAsp are both effective, well-tolerated treatment options for patients requiring mealtime insulin.

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Author Contributions. K.B. was the principal investigator of this study. K.B., C.C., J.H., M.R., M.S., R.S., D.-M.B., R.B.B., and B.W.B. were involved in the preparation, editing, and approval of the manuscript in collaboration with Novo Nordisk. D.-M.B. was the responsible medical officer. R.B.B. was the responsible statistician. K.B. is the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Declaration of Dr. Nathan Laney

Exhibit I

A Randomized Trial Evaluating the Efficacy and Safety of Fast-Acting Insulin Aspart Compared With Insulin Aspart, Both in Combination With Insulin Degludec With or Without Metformin, in Adults With Type 2 Diabetes (ONSET 9)

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OBJECTIVE

To evaluate the efficacy and safety of fast-acting insulin aspart (faster aspart) compared with insulin aspart (IAsp), both with insulin degludec with or without metformin, in adults with type 2 diabetes not optimally controlled with a basal-bolus regimen.

RESEARCH DESIGN AND METHODS

This multicenter, double-blind, treat-to-target trial randomized participants to faster aspart ($n = 546$) or IAsp ($n = 545$). All available information, regardless of treatment discontinuation or use of ancillary treatment, was used for evaluation of effect.

RESULTS

Noninferiority for the change from baseline in HbA_{1c} 16 weeks after randomization (primary end point) was confirmed for faster aspart versus IAsp (estimated treatment difference [ETD] −0.04% [95% CI −0.11; 0.03]; −0.39 mmol/mol [−1.15; 0.37]; $P < 0.001$). Faster aspart was superior to IAsp for change from baseline in 1-h postprandial glucose (PPG) increment using a meal test (ETD −0.40 mmol/L [−0.66; −0.14]; −7.23 mg/dL [−11.92; −2.55]; $P = 0.001$ for superiority). Change from baseline in self-measured 1-h PPG increment for the mean over all meals favored faster aspart (ETD −0.25 mmol/L [−0.42; −0.09]); −4.58 mg/dL [−7.59; −1.57]; $P = 0.003$). The overall rate of treatment-emergent severe or blood glucose (BG)–confirmed hypoglycemia was statistically significantly lower for faster aspart versus IAsp (estimated treatment ratio 0.81 [95% CI 0.68; 0.97]).

CONCLUSIONS

In combination with insulin degludec, faster aspart provided effective overall glycemic control, superior PPG control, and a lower rate of severe or BG-confirmed hypoglycemia versus IAsp in adults with type 2 diabetes not optimally controlled with a basal-bolus regimen.

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The progressive deterioration of β-cell function in type 2 diabetes requires the intensification of treatment over time (1). There are a number of antihyperglycemic therapies available for treating type 2 diabetes, and current guidelines recommend a stepwise approach to treatment intensification taking into account patient factors and preferences (2). For many people with long-standing type 2 diabetes, control of fasting hyperglycemia on regimens that include basal insulin is necessary but often insufficient to achieve and maintain HbA_{1c} goals (3). Options for treatment intensification targeting postprandial glucose (PPG) include the addition of a glucagon-like peptide 1 receptor agonist, a sodium–glucose cotransporter 2 inhibitor, a dipeptidyl peptidase 4 inhibitor, a rapid-acting insulin analog (RAIA), or a premix insulin (2).

Studies indicate that targeting PPG excursions is important for achieving overall glycemic control and reducing the risk of the macrovascular and microvascular complications of diabetes (4). Postprandial hyperglycemia has been shown to be associated with adverse outcomes even in the absence of fasting hyperglycemia, including elevated intraocular pressure and cognitive dysfunction (5,6). Although further evidence is needed to fully demonstrate the benefits of lowering PPG on hard end points, careful consideration should be given to the treatment options available to physicians to limit PPG excursions in people with type 2 diabetes.

RAIAs aim to mimic the physiological action of endogenous insulin secreted in response to meals to reduce PPG excursions. However, current RAIAs have a delayed onset and a longer duration of action compared with endogenous insulin in individuals without diabetes and there is an unmet need for mealtime insulins that more closely mimic physiological prandial insulin secretion.

Fast-acting insulin aspart (faster aspart) is a novel formulation of insulin aspart (IAsp) containing the excipients niacinamide and L-arginine. In people with type 2 diabetes, faster aspart is associated with an ~9 min earlier onset of action and an ~150% greater glucose-lowering effect during the first 30 min after dosing compared with IAsp (7). In the ONSET 2 trial, faster aspart was confirmed to be noninferior to IAsp in terms of change from baseline in HbA_{1c} after 26 weeks of treatment in bolus-naive adults with type 2 diabetes treated with basal insulin and oral antidiabetes agents (OADs). Moreover, faster aspart improved 1-h PPG after a meal test, with no differences in overall hypoglycemia rates compared with IAsp (8).

The aim of the ONSET 9 trial was to confirm the effect in terms of glycemic control of treatment with faster aspart compared with IAsp, both in combination with insulin degludec with or without metformin, in adults with type 2 diabetes not optimally controlled with a basal-bolus regimen. The trial also aimed to test superiority in terms of PPG regulation while evaluating the safety profile of both treatments. This was the first trial with faster aspart to recruit only participants with long-standing (≥10 years) type 2 diabetes treated with intensive (basal-bolus) insulin therapy for ≥1 year. The trial was designed to quantify a population average effect for participants with type 2 diabetes irrespective of adherence to randomized treatment and use of ancillary treatment. The primary objective was to estimate the effect based on difference in HbA_{1c} from baseline to 16 weeks under these circumstances.

RESEARCH DESIGN AND METHODS

Trial Design

In this phase 3b, multicenter, active-controlled, treat-to-target, randomized, parallel-group trial (ClinicalTrials.gov: NCT03268005), faster aspart was compared with IAsp, both in combination with insulin degludec with or without metformin, in adults with type 2 diabetes not optimally controlled with basal-bolus treatment (Supplementary Fig. 1). The trial consisted of a 12-week run-in period, a 16-week treatment period, and a 30-day follow-up period. At the start of the treatment period, participants were randomized 1:1 to double-blind treatment with either faster aspart or IAsp delivered in a basal-bolus regimen with once-daily insulin degludec with or without metformin. The trial included 165 sites across 17 countries (Supplementary Data). The trial was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice.

Study Population

Adults (≥18 years old) were eligible for inclusion if they were diagnosed with type 2 diabetes for ≥10 years and had been treated with a basal-bolus insulin regimen for ≥1 year before screening (defined as basal insulin once or twice daily and bolus insulin analog taken with meals at least three times daily) with or without OADs. Participants were required to have an HbA_{1c} of 7.0–10.0% (53–86 mmol/mol) at screening and an HbA_{1c} ≤9.0% (75 mmol/mol) at randomization.

Key exclusion criteria were as follows: treatment with injectable glucagon-like peptide 1 receptor agonists within a period of 90 days before screening; any anticipated initiation or change in concomitant medications (for >14 consecutive days) known to affect weight or glucose metabolism; myocardial infarction, stroke, or hospitalization for unstable angina and/or transient ischemic attack within 180 days before screening; heart failure of New York Heart Association class IV; or planned coronary, carotid, or peripheral artery revascularization known on day of screening. Additional exclusion criteria included any known or suspected hypersensitivity to trial products or related products and being pregnant, planning to become pregnant, or breastfeeding (see Supplementary Appendix for full list of inclusion and exclusion criteria).

Treatment Interventions

Basal Insulin Dosing

After a 2-week screening period, a 12-week run-in allowed for basal insulin titration. Participants switched from their previous basal insulin to insulin degludec once daily (100 units/mL at any time of the day, preferably at the same time every day, using a 3-mL pen injector) with dose optimization based on protocol-specified guidelines. Basal insulin dose was titrated weekly by the investigator to a prebreakfast target of 4.0–5.0 mmol/L (71–90 mg/dL) (Supplementary Table 1). An increase in dose was based on the mean of three prebreakfast self-measured blood glucose (SMBG) values measured on the last 2 days prior to and on the day of contact, while a decrease was based on the lowest of three prebreakfast SMBG values measured on the last 2 days prior to and on the day of contact. During the treatment period, basal insulin adjustments were not performed by the investigators unless for safety reasons.

Bolus Insulin Dosing

During the run-in period, participants continued their pretrial bolus insulin

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analog. The dose was not adjusted unless considered necessary for safety reasons by the investigator. During the 16-week treatment period, eligible participants with HbA_{1c} ≤9.0% (75 mmol/mol) were randomized 1:1 to receive double-blinded faster aspart or IAsp (both 100 units/mL, administered 0–2 min before each main meal using a 3-mL pen injector). Bolus insulin was titrated twice weekly in a treat-to-target approach to achieve a glycemic target of preprandial and bedtime blood glucose (BG) between 4.0 and 6.0 mmol/L (71 and 108 mg/dL). Participants titrated bolus insulin using a predefined bolus-dosing algorithm (Supplementary Table 2).

Other Diabetes Treatment

All OADs, except for metformin, were stopped at the start of the run-in period. The dose and dosing frequency of metformin were not changed during the trial unless for safety reasons. Initiation of any other diabetes treatment was not allowed during the screening, run-in, or treatment period.

SMBG Measurements

Participants were supplied with a BG meter (MyGlucoHealth [Entra Health] and FreeStyle [Abbott]) calibrated to display plasma-equivalent glucose values and instructed to record the date, time, and value of all SMBG measurements for 7-9-7 point profiles (preprandial, postprandial, bedtime, and once at 4:00 A.M.) on three consecutive days before the scheduled clinic visits at weeks 0, 8, and 16; four-point profiles (preprandial and bedtime) were recorded daily for titration purposes.

Meal Test Protocol

Participants were required to undergo a meal test with a fasting SMBG (adjusted to plasma glucose) of 4.0–8.8 mmol/L (71–160 mg/dL). The meal test was rescheduled if the participant's SMBG was outside of this range. Before randomization at week 0 (baseline), a bolus dose of the participant's pretrial insulin analog was administered followed by a mixed liquid-meal test (Ensure, Fortisip, or NutriDrink; all contained 78 g carbohydrate that needed to be consumed within 12 min). The bolus dose was calculated by dividing the digestible carbohydrate content of the liquid meal by an insulin:carbohydrate ratio. The insulin:carbohydrate ratio was calculated using the "500 rule," whereby 500 was divided by the participant's total daily dose (taken from the day before) of both basal and bolus insulin. Blood samples were taken 2 min before the meal and after 30 min and 1, 2, 3, and 4 h (0 h defined as start time of meal consumption). The meal test was repeated at week 16 with the participant's randomized trial product using the same bolus dose calculated at the baseline meal test. During the meal test, glucose rescue medication could be used if the participant experienced hypoglycemia (SMBG ≤3.9 mmol/L [70 mg/dL]).

Assessments

Primary End Point

The primary end point was change from baseline in HbA_{1c} 16 weeks after randomization.

Secondary End Points

Confirmatory secondary end points were change from baseline in 1-h PPG increment (meal test) and change from baseline in 1,5-anhydroglucitol 16 weeks after randomization. 1,5-anhydroglucitol was used as a surrogate marker for measuring PPG excursions (9).

Key supportive secondary efficacy end points included change from baseline 16 weeks after randomization in the following: fasting plasma glucose (FPG), PPG and PPG increment (meal test), PPG and PPG increment (7-9-7 point SMBG profile), mean of the 7-9-7 point SMBG profile, and the percentage of participants achieving HbA_{1c} <7.0% (53 mmol/L) and PPG ≤7.8 mmol/L (140 mg/dL) targets with and without severe hypoglycemia at 16 weeks.

Key supportive secondary safety end points included number of treatment-emergent adverse events, number of treatment-emergent hypoglycemic episodes, and change from baseline in body weight 16 weeks after randomization (end points are summarized in Supplementary Table 3).

Adverse events were defined as treatment emergent if the onset of the event occurred on or after the 1st day of exposure to randomized treatment and no later than 7 days after last day of treatment. Hypoglycemic episodes were defined as treatment emergent if the onset of the episode occurred on or after the 1st day of treatment administration after randomization and no later than 1 day after the last day of treatment. Severe hypoglycemia was defined according to the American Diabetes Association classification (10), and BG-confirmed hypoglycemia was defined as a plasma glucose value <3.1 mmol/L (56 mg/dL) with or without symptoms consistent with hypoglycemia.

Statistical Methods

All statistical analyses were prespecified. Efficacy end points were summarized and analyzed using the full analysis set, and results are presented based on data from all randomized participants for the entire trial period, which include data collected after participants prematurely discontinued treatment or initiated ancillary treatment. Safety end points (and insulin dose) were summarized using the safety analysis set (participants receiving one or more doses of IAsp or faster aspart) and are presented as either treatment emergent or based on data collected up to 7 days after the last dose of randomized treatment or the day before initiation of ancillary treatment.

Statistical analysis of the primary and secondary confirmatory end points followed a stepwise hierarchical procedure in order to control type 1 error (Supplementary Table 4). Noninferiority (primary end point) was confirmed if the upper boundary of the two-sided 95% CI was ≤0.4%. One-sided *P* values are presented for noninferiority analysis and for the other confirmatory analyses, with two-sided *P* values for treatment differences presented for all other analyses. Supportive analyses were not corrected for multiplicity.

Change from baseline in HbA_{1c} 16 weeks after randomization was analyzed using an ANOVA model after multiple imputation, where participants with missing data at scheduled visits had their HbA_{1c} values imputed using available information from the treatment arm to which the participant had been randomized. The model included treatment, region, and metformin use at baseline as factors and baseline HbA_{1c} as a covariate. A similar statistical model was used to analyze change from baseline to 16 weeks in PPG and PPG increments (meal test), 1,5-anhydroglucitol, FPG, PPG and PPG increment (7-9-7 point SMBG profile), mean of the 7-9-7 point SMBG profile, and body weight. For change from baseline in PPG and PPG increments (meal test), participants with missing data had their PPG values at week 16 imputed based on information from the IAsp arm.

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HbA_{1c} and PPG responder end points were analyzed using a logistic regression model. The number of treatment-emergent severe or BG-confirmed hypoglycemic episodes was analyzed using a negative binomial regression model.

Further details on the statistical methods for the primary and secondary end points and the sample-size calculation are provided in Supplementary Data.

Data and Resource Availability

The data sets generated during the current study are available from the corresponding author on reasonable request.

RESULTS

Trial Participants

Participants (n = 1,091) were randomized to faster aspart (n = 546) or IAsp (n = 545), and 99.6% (n = 544) and 99.8% (n = 544) of participants, respectively, were exposed to randomized trial product. A total of 1,062 participants (97.3%) completed the trial, while 1,053 participants (96.5%) completed the 16-week treatment period without premature discontinuation of randomized treatment (Supplementary Fig. 2). Premature discontinuation of randomized treatment occurred in 23 participants in the faster aspart arm and 15 in the IAsp arms (Supplementary Fig. 2). The number of participants who withdrew from the trial was distributed similarly across treatment arms (Supplementary Fig. 2). Baseline characteristics were similar between treatment arms (Table 1). There were no marked differences in antihyperglycemic treatment at screening between treatment arms.

Efficacy

HbA_{1c}

During the run-in period, observed mean HbA_{1c} was reduced from 8.25% (66.69 mmol/mol) to 7.15% (54.64 mmol/mol) for participants subsequently randomized to faster aspart and from 8.28% (67.01 mmol/mol) to 7.05% (53.54 mmol/mol) for those randomized to IAsp (Fig. 1). At the end of the 16-week treatment period, observed mean HbA_{1c} was 7.00% (52.96 mmol/mol) and 6.96% (52.59 mmol/mol) in the faster aspart and IAsp arms, respectively. Noninferiority of faster aspart to IAsp in change from baseline in HbA_{1c} after 16 weeks was confirmed (estimated treatment difference [ETD] −0.04% [95% CI −0.11; 0.03]; −0.39 mmol/mol [−1.15; 0.37]; $P < 0.001$ for noninferiority [0.4% margin]). Superiority of faster aspart versus IAsp regarding change from baseline in HbA_{1c} could not be confirmed (hierarchical testing was stopped after step 3 [Supplementary Table 4]).

At 16 weeks, the proportion of subjects achieving HbA_{1c} <7.0% (53 mmol/mol) was 49.6% in the faster aspart group and 51.7% in the IAsp group. The odds of achieving HbA_{1c} <7.0% (53 mmol/mol) were not statistically significantly different between faster aspart and IAsp (Supplementary Table 5).

Meal Test

PPG increment profiles at baseline and week 16 are shown in Fig. 2. The observed change from baseline in 1-h PPG increment after 16 weeks was −0.43 mmol/L (−7.72 mg/dL) in the faster aspart arm and 0.08 mmol/L (1.52 mg/dL) in the IAsp arm. Superiority of faster aspart to IAsp in terms of change from baseline in 1-h PPG increment was confirmed (ETD −0.40 mmol/L [95% CI −0.66; −0.14]; −7.23 mg/dL [−11.92; −2.55]; P = 0.001 for superiority) (Fig. 2). There were no statistically significant differences between treatment arms for change from baseline in 30-min or 2-, 3-, or 4-h PPG increment (Supplementary Table 5). Change from baseline in PPG favored faster aspart at 1 h and 2 h with ETDs of −0.47 mmol/L (95% CI −0.81; −0.13) (−8.47 mg/dL [−14.68; −2.27]) (P = 0.007) and −0.39 mmol/L (−0.78; −0.002) (−7.02 mg/dL [−14.00; −0.04]) (P = 0.049), respectively. There was no statistically significant difference between treatment arms for change from baseline in 30-min or 3- or 4-h PPG (Supplementary Table 5).

SMBG

Observed mean 7-9-7 point SMBG profiles at baseline and 16 weeks after randomization were similar between treatment arms (Supplementary Fig. 4). There was no statistically significant difference in the change from baseline in mean of the 7-9-7 point SMBG profile between faster aspart and IAsp (Supplementary Table 4). The observed change from baseline in the 1-h PPG increment mean over all main meals was −0.48 mmol/L (−8.66 mg/dL) with faster aspart and −0.23 mmol/L (−4.14 mg/dL) with IAsp, with a statistically significant ETD in favor of faster aspart (ETD −0.25 mmol/L [95% CI −0.42; −0.09]; −4.58 mg/dL [−7.59; −1.57]; P = 0.003). There were also significant treatment differences in 1-h PPG increment after lunch (−0.32 mmol/L [−0.57; −0.07]; −5.73 mg/dL [−10.19; −1.27]; P = 0.012) and the main evening meal (−0.27 mmol/L [−0.51; −0.03]; −4.80 mg/dL [−9.14; −0.47]; P = 0.030). There was no statistically significant difference between treatments after breakfast. Change from baseline in 1-h PPG for each individual meal or for the mean over all meals was not statistically significantly different for faster aspart versus IAsp (Supplementary Table 5).

The proportion of subjects achieving PPG ≤7.8 mmol/L (140 mg/dL) (based on SMBG values) 16 weeks after randomization was 34.1% in the faster aspart group and 35.2% in the IAsp group. The odds of achieving PPG ≤7.8 mmol/L (140 mg/dL) were not statistically significantly different between treatments (Supplementary Table 5).

1,5-anhydroglucitol

The observed mean change from baseline in 1,5-anhydroglucitol at 16 weeks was 1.38 μg/mL in the faster aspart arm and 0.89 μg/mL in the IAsp arm (Supplementary Fig. 5). The change from baseline in 1,5-anhydroglucitol 16 weeks after randomization was statistically significantly greater with faster aspart compared with IAsp (ETD 0.50 μg/mL [95% CI 0.11; 0.89]).

FPG and Insulin Dose

There was no statistically significant difference in change from baseline in FPG between treatment arms (Supplementary Table 5).

During the run-in period, the mean daily basal insulin dose increased from 41.35 units to 64.47 units with faster aspart and from 40.83 units to 64.81 units with IAsp. During the treatment period, the mean daily bolus insulin dose increased over time with both faster aspart and IAsp. Observed mean total daily insulin doses at week 16 were similar between treatments arms (118.52 units [1.23 units/kg] for faster aspart and 115.63 units [1.19 units/kg] for IAsp) (Supplementary Table 6). The basal and bolus splits at baseline and week 16 were similar in both treatment arms (baseline 62% and 38% and week 16 54% and 46%, respectively).

Safety

Treatment-emergent hypoglycemia rates are presented in Table 2. The overall rate of severe or BG-confirmed hypoglycemic

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Table 1—Baseline characteristics

Parameter	FA (n = 546)	IAsp (n = 545)	Total (n = 1,091)
Age, years	62.6 (8.6)	62.1 (8.8)	62.3 (8.7)
Sex, n (% male)	265 (48.5)	289 (53.0)	554 (50.8)
Body weight, kg	94.36 (19.96)	95.06 (21.46)	94.71 (20.72)
Body weight, lb	208.02 (44.01)	209.56 (47.32)	208.79 (45.68)
BMI, kg/m^2	33.43 (6.10)	33.25 (6.52)	33.34 (6.31)
Duration of diabetes, years	19.4 (7.0)	19.4 (7.5)	19.4 (7.3)
HbA_{1c}, %	7.15 (0.77)	7.05 (0.70)	7.10 (0.74)
HbA_{1c}, mmol/mol	54.64 (8.39)	53.54 (7.66)	54.09 (8.05)
FPG, mmol/L	6.52 (1.87)	6.38 (1.82)	6.45 (1.84)
FPG, mg/dL	117.51 (33.62)	114.89 (32.73)	116.20 (33.19)
Metformin use at baseline, n (% yes)	322 (59.0)	329 (60.4)	651 (59.7)

Data are means (SD) unless otherwise stated. Baseline is at randomization. FA, fast-acting insulin aspart.

episodes was statistically significantly lower for faster aspart versus IAsp (estimated treatment ratio 0.81 [95% CI 0.68; 0.97]; P = 0.019). Both daytime and nocturnal rates were lower for faster aspart versus IAsp (0.83 [0.70; 0.99], P = 0.038, and 0.66 [0.49; 0.88], P = 0.004, respectively). There was no statistically significant difference in the rate of severe or BG-confirmed hypoglycemic episodes observed within 1 or 2 h after the start of the meal (1.16 [0.78; 1.71] and 0.97 [0.71; 1.32], respectively). However, a significant difference favoring faster aspart was observed within 4 h after the start of the meal (0.78 [0.63; 0.98]; P = 0.030).

After the 16-week treatment period, the observed change from baseline in body weight was 1.19 kg and 1.12 kg with faster aspart and IAsp, respectively. There was no statistically significant difference in change from baseline between treatment arms.

No clinically relevant differences were observed in the treatment-emergent adverse event profiles (including injection site and allergic reactions) for faster aspart and IAsp during the 16-week treatment period (Supplementary Table 7). Wrong product administered (mainly a mix-up between basal and bolus insulin or vice versa) was reported more often with faster aspart (4.8% of participants) than with IAsp (2.2% of participants) (Supplementary Table 8). No clinically significant differences were seen with regard to vital signs, BMI, physical examination, safety laboratory assessments (biochemistry and hematology), electrocardiogram, and eye examination.

CONCLUSIONS

In this trial, intensified insulin titration with faster aspart or IAsp, both in combination with insulin degludec with or without metformin, improved glycemic control in patients with long-standing type 2 diabetes not optimally controlled on a basal-bolus regimen, and faster aspart was confirmed to be noninferior to IAsp in terms of the change from baseline in HbA_{1c} following 16 weeks of randomized treatment. Switching patients to, and optimization of, insulin degludec during the 12-week run-in period resulted in a considerable and sustained improvement in HbA_{1c} (~1.0%) in both treatment arms. Compared with the IAsp treatment arm, PPG regulation 1 h after a meal was significantly improved in the faster aspart treatment arm, demonstrated by the difference in change from baseline in 1-h PPG increment 16 weeks after randomization using either a meal test or SMBG measurement profiles and supported by a significantly greater increase in 1,5-anhydroglucitol with faster aspart. Together, these findings are encouraging given that patients with advanced type 2 diabetes (~19 years in the reported study population) treated with a basal-bolus regimen represent a difficult patient population to manage, with PPG control being particularly challenging.

The glycemic findings of ONSET 9 generally align with previous studies comparing the efficacy and safety of faster aspart in patients with type 2 diabetes. In ONSET 2, after a 12-week run-in period to optimize basal insulin glargine, faster aspart was found to be noninferior to IAsp in terms of change from baseline in HbA_{1c} after a 26-week treatment period; however, the reduction in HbA_{1c} (1.4%) by end of trial was numerically greater compared with that reported here (8). This difference is likely to reflect the difference in study population, as well as the basal insulin analog (glargine versus degludec) and run-in period duration; in ONSET 2, patients were bolus insulin naive prior to commencing the study and thus would have been more likely to experience a greater change in glycemic control with the addition of bolus insulin, while in our bolus-experienced population most of the change in HbA_{1c} occurred during the run-in period when switching basal insulin to insulin degludec.

Compared with IAsp, faster aspart has been shown to improve PPG control 1 h after a meal test in bolus-naive patients treated with basal insulin and OADs (8). In the current trial, changing the insulin in bolus-experienced patients to faster aspart significantly reduced 1-h PPG increments compared with IAsp, indicating

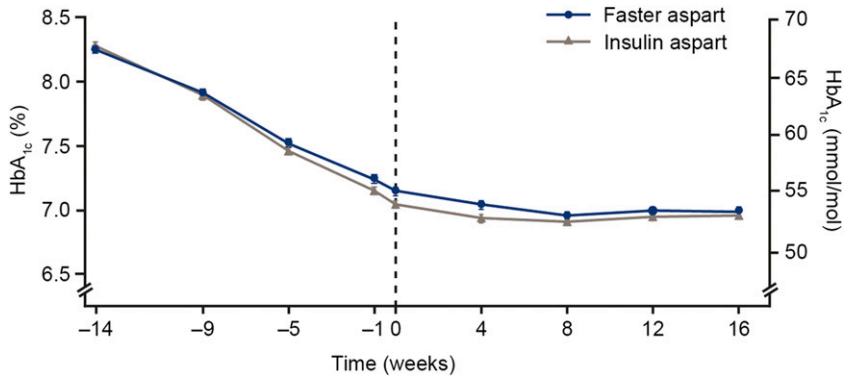

Figure 1—Mean HbA_{1c} over time. Error bars: ±SE (mean). All available information regardless of treatment discontinuation or use of ancillary treatment was used. ETD after 16 weeks for the change in HbA_{1c} from baseline was −0.04% (95% CI −0.11; 0.03); −0.39 mmol/mol (−1.15; 0.37). Noninferiority confirmed at 0.4% level (P value from the one-sided test for noninferiority evaluated at the 2.5% level: $P < 0.001$).

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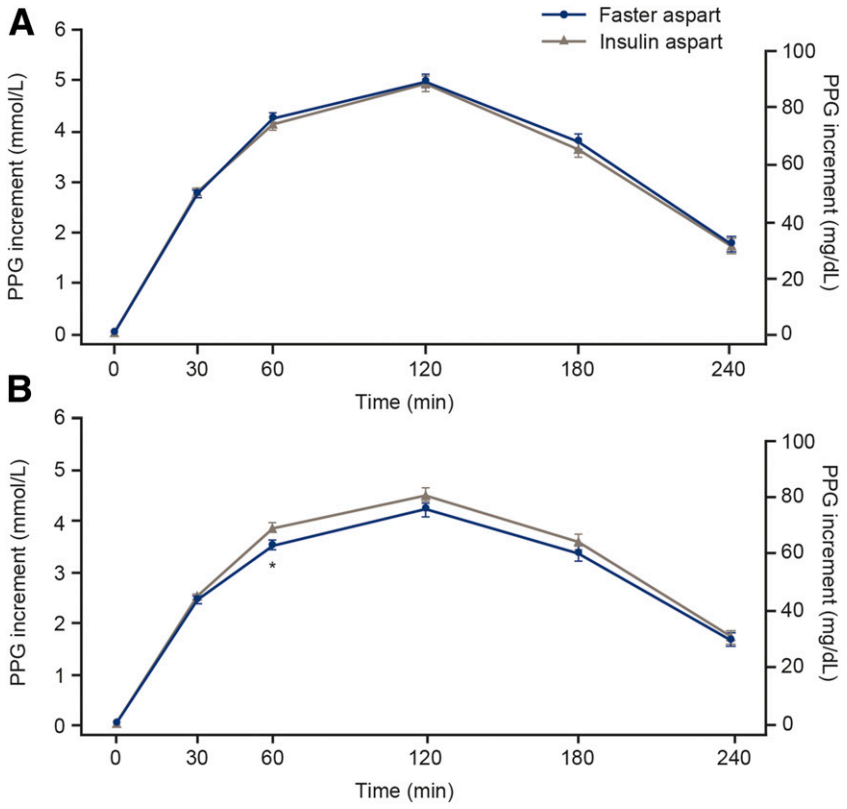

Figure 2—PPG increment after a meal test at baseline (*A*) and week 16 (*B*). Error bars: ±SE (mean). All available information regardless of treatment discontinuation or use of ancillary treatment was used. *ETD was −0.40 mmol/L (95% CI −0.66; −0.14); −7.23 mg/dL (−11.92; −2.55), and superiority was confirmed ($P = 0.001$).

that improvement in mealtime glucose control can be achieved in this clinically challenging population.

Hypoglycemia often impedes the achievement of optimal glycemic control in patients with type 2 diabetes treated with insulin. However, noninferior HbA_{1c} reduction and an improvement in PPG control were achieved alongside a significantly lower rate of overall, daytime, and nocturnal hypoglycemia with faster aspart versus IAsp. This aligns with a recent post hoc analysis of two large trials in adults with type 1 diabetes, which reported a lower rate of nocturnal hypoglycemia with faster aspart versus insulin aspart treatment (11).

These findings demonstrate that these next-generation insulins, faster aspart and insulin degludec, can provide important clinical value in tailoring of complex basal-bolus regimens to limit the incidence of hypoglycemia for patients with advanced type 2 diabetes.

Collectively, strengths of this trial include the positive efficacy and safety findings in a difficult-to-treat population of people with a mean diabetes duration of >19 years, along with a relatively high trial completion rate (>95%). The study also employed a double-blind design and used a meal test, which, although not fully representative of a real-life setting, standardized macronutrient composition between participants, to measure PPG control at baseline and 16 weeks. A limitation of the trial was the need for participants to perform frequent capillary BG monitoring for dose titration, which, in the real-world setting, many patients may be unwilling to do.

In conclusion, with use of a treat-to-target approach, intensive insulin titration with faster aspart provided effective overall glycemic control, superior PPG control, and a lower rate of severe or BG-confirmed hypoglycemia versus IAsp, both in combination with insulin degludec with or without metformin, in adults with advanced type 2 diabetes not optimally controlled with a basal-bolus regimen.

Table 2—Treatment-emergent hypoglycemic episodes

	FA				IAsp			
Hypoglycemia	*n*	%	E	R	*n*	%	E	R
Severe	16	2.9	18	0.11	10	1.8	14	0.08
Severe or BG confirmed								
Overall	367	67.5	2,227	13.40	391	71.9	2,749	16.52
Daytime	354	65.1	2,032	12.23	382	70.2	2,454	14.75
Nocturnal	116	21.3	195	1.17	136	25.0	295	1.77
Total	495	91.0	9,033	54.37	500	91.9	10,006	60.14
Meal-related severe or BG confirmed								
Within 1 h after a meal	57	10.5	74	0.45	55	10.1	65	0.39
Within 2 h after a meal	116	21.3	235	1.41	122	22.4	247	1.48
Within 4 h after a meal	232	42.6	768	4.62	269	49.4	974	5.85

Hypoglycemic episodes were defined as treatment emergent if the onset of the episode occurred on or after the 1st day of exposure to randomized treatment and no later than 1 day after the last day of exposure to randomized treatment. Severe hypoglycemia was defined according to the American Diabetes Association classification (10), and BG-confirmed hypoglycemia was defined as an episode with a plasma glucose value <3.1 mmol/L (<56 mg/dL) with or without symptoms consistent with hypoglycemia. Nocturnal was defined as occurring in the period between 00:01 and 05:59 h (both included). Episodes with missing time stamps were considered daytime episodes. Total episodes included episodes where subjects were able to self-treat and that were not BG confirmed as well as episodes where subjects were able to self-treat but could not be classified due to missing data. %, percentage of participants; E, number of events; FA, fast-acting insulin aspart; *n*, number of participants; R, event rate per patient-year of exposure.

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Author Contributions. W.S.L. and E.Fr. were the principal investigators of this clinical trial. E.Fa. and N.R. were the medical specialists for the trial and had the medical responsibility on a clinical trial level. M.I.S.K. was the responsible statistician. All authors had access to the study data, take responsibility for the accuracy of the analysis, contributed to data interpretation, reviewed and contributed to the content of the manuscript, and had authority in the decision to submit the manuscript. W.S.L. and E.Fr. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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