Treatment of Type 2 Diabetes: From "Guidelines" to "Position Statements" and Back

Recommendations of the Israel National Diabetes Council

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Given the increased prevalence of type 2 diabetes worldwide, most patients are treated by their primary health care team (PHCT). PHCTs need guidance in choosing the best treatment regimen for patients, since the number of glucose-lowering agents (GLAs) is rapidly increasing, as is the amount of clinical data regarding these drugs. The American Diabetes Association/European Association for the Study of Diabetes Position Statement emphasizes the importance of personalized treatment and lists drug efficacy, risk of hypoglycemia, effect on weight, side effects, and cost as important parameters to consider when choosing GLAs. The suggested Israeli guidelines refocus earlier international recommendations from 2012 and 2015, based on emerging data from cardiovascular outcome trials as well as what we believe are important issues for patient care (i.e., durability, hypoglycemia risk, and weight gain).

We suggest prioritizing glucose-lowering agents (GLAs) according to their effects on the parameters listed above as well as adherence to therapy and cardiovascular (CV) safety. We suggest, in parts of the world where it is economically feasible, treatment with second-line therapy drugs that have a decreased side effect profile, do not cause hypoglycemia or weight gain, and have established CV safety. Using these presumably "safer" drugs allows us to strive for tighter glucose control. The three groups of GLAs that meet these criteria are dipeptidyl peptidase (DPP)-4 inhibitors, glucagon-like peptide 1 receptor agonists (GLP-1 RAs), and sodium–glucose cotransporter (SGLT) 2 inhibitors. For patients with an HbA_{1c} >7.5% at diagnosis, initial combination therapy should be considered, and for those with symptomatic hyperglycemia or HbA_{1c} >9%, initial (possibly short-term) insulin therapy should be considered. For most patients, we consider BMI the leading reference for choosing between the three groups: DPP-4 inhibitors or SGLT2 inhibitors for BMI <30 kg/m^2, GLP-1 RAs or SGLT2 inhibitors for BMI 30–35 kg/m^2, and GLP-1 RAs for BMI >35 kg/m^2. Often, combination of two GLAs is not enough to achieve target glucose control; the addition of a third GLA can be determined by different patient characteristics including age, renal function, presence of previous CV disease, etc.

The American Diabetes Association/European Association for the Study of Diabetes Position Statement: From Guidelines to Position Statement

Type 2 diabetes is a complex disease to treat, and there is no specific treatment algorithm that will be appropriate for all patients. Therefore, the best approach

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according to the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) Position Statement is for the clinician to individualize therapy by considering the available treatment options and then determine the optimal approach for the individual patient (1,2). Two major changes were included in the 2012 ADA/EASD Position Statement compared with the previous ADA/EASD guidelines (1,3). The first is setting the HbA_{1c} target as approaching near normoglycemia, with different degrees of stringency according to patient characteristics. The second is the listing of six (1) options of GLAs as second-line options of therapy. The ADA/EASD Position Statement leaves all possibilities open for the discretion of the treating physician. In this article, we will discuss this approach, as well as offer our alternative suggestions.

Medical Guidelines for the Treatment of Type 2 Diabetes

A medical guideline (also called a clinical guideline, clinical protocol, or clinical practice guideline) is defined as, "a document with the aim of *guiding decisions* and criteria regarding diagnosis, management, and treatment in specific areas of healthcare" (4) (italics added). However, clinical guidelines have certain limitations. Most importantly, clinical guidelines can never replace clinical judgment. By definition, they cannot "cover" all possible clinical situations and do not take into account interpatient variability in response to treatment, side effects, personal values, and preferences. International guidelines are even more limited by regional and racial differences (e.g., α-glucosidase inhibitors are not an option in the ADA/EASD guidelines [1–3], while they are commonly used in some parts of Asia). Importantly, differences in medical coverage, prices of drugs, and the income of patients may have great influence on GLA choices. Unlike in oncology, personalized medicine in diabetes treatment is based on phenotypic rather than genotypic expression (e.g., patient weight, age, fasting and postprandial glucose levels, etc.), on health care provider experience, and, often, on trial and error (5). Some of the most commonly used diabetes guidelines/Position Statements (3,6–8) include lists of treatment options, which allow the treating PHCT and patient to tailor treatment according to the drug properties, therapeutic target, and patient preferences but may leave some PHCTs without sufficient guidance.

For Whom Are Guidelines for the Treatment of Patients With Type 2 Diabetes Written?

According to the International Diabetes Federation atlas (9), diabetes is on the rise, with >415 million patients affected worldwide as of 2015. Owing to these numbers, most patients with diabetes are and will in the foreseeable future be treated by their respective PHCTs. Early intervention trials (most prominently the UK Prospective Diabetes Study [UKPDS] follow-up study [10]), compared with later intervention 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] [11–13]), demonstrated the importance of early intervention in prevention of CV and microvascular complications—a phenomenon called "metabolic memory" (14). When one looks at referral patterns from family physicians to endocrinologists/diabetologists around the globe (15), it is clear that most patients with type 2 diabetes who are referred to specialists have long disease duration and often already suffer from diabetes complications. Thus, it is important to provide treatment guidelines for PHCTs who play a key role in both diabetes prevention and early treatment of diabetes so as to prevent diabetes micro- and macrovascular complications.

The Complexity of Treating Hyperglycemia in Patients With Type 2 Diabetes

Treating patients with type 2 diabetes has become a complex issue owing to at least three different components.

First, individualization of the stringency by which glycemic control targets are set (1,16–19) has left many open questions regarding the best glycemic target for a given patient (20–22). While the ADA/EASD Position Statement (1,2) supports a target HbA_{1c} of <7% for most patients, it recommends a more stringent target (HbA_{1c} 6.0–6.5%) for select patients, as long as it can be achieved without increased risk of hypoglycemia or other prominent side effects. However, what is the evidence that tighter control is beneficial? If tighter control can be achieved without increased risk, why should we limit it only to a selected population? Shouldn't the target for a specific patient be driven by the safety of the measures used to achieve this target? Should we maintain treatment once a patient has achieved or even exceeded his/her specific glycemic target? However, even if we use safer drugs, are the increased cost and the polypharmaceutical burden worth procuring lower targets? The suggested guidelines presented in this article stratify HbA_{1c} targets not only by patient characteristics but also by treatment regimen—the risk the treatment poses for hypoglycemia and the individual's risk for hypoglycemia (Fig. 1).

Second, the number of drugs and classes of GLAs are increasing rapidly, with multiple combinations of therapies available. The level of evidence required today for the introduction of new GLAs differs from what was required in the past (23), and no such information will be available for some of the older drug groups. However, the experience of health care providers as well as patient experience with the older GLAs should not be dismissed. How can we compare two totally different means of evidence collection?

Third, the amount of data available from clinical trials in general, and CV outcome trials in particular, is increasing rapidly. After the U.S. Food and Drug Administration 2008 guidance to the industry regarding the necessity to demonstrate CV safety of GLAs (24), the world of diabetes clinical research has changed (25). Recently, >150,000 patients with type 2 diabetes have taken part in CV outcome studies with GLAs, and the amount of data these trials provide, regarding both CV safety (26–29) and efficacy (30), as well as other outcomes (hospitalization for heart failure, renal outcomes, adverse events of special interest, etc.), is vast. How should these data affect our guidelines? How can we extrapolate data from very specific patient populations to the general population of people with type 2 diabetes?

Considering the fact that diabetes is only one of the countless medical conditions that PHCTs treat, it is challenging to keep up with this mountain of data. It is difficult for the PHCTs to sort the data by strength of evidence and to judge the data relevance with respect to individual

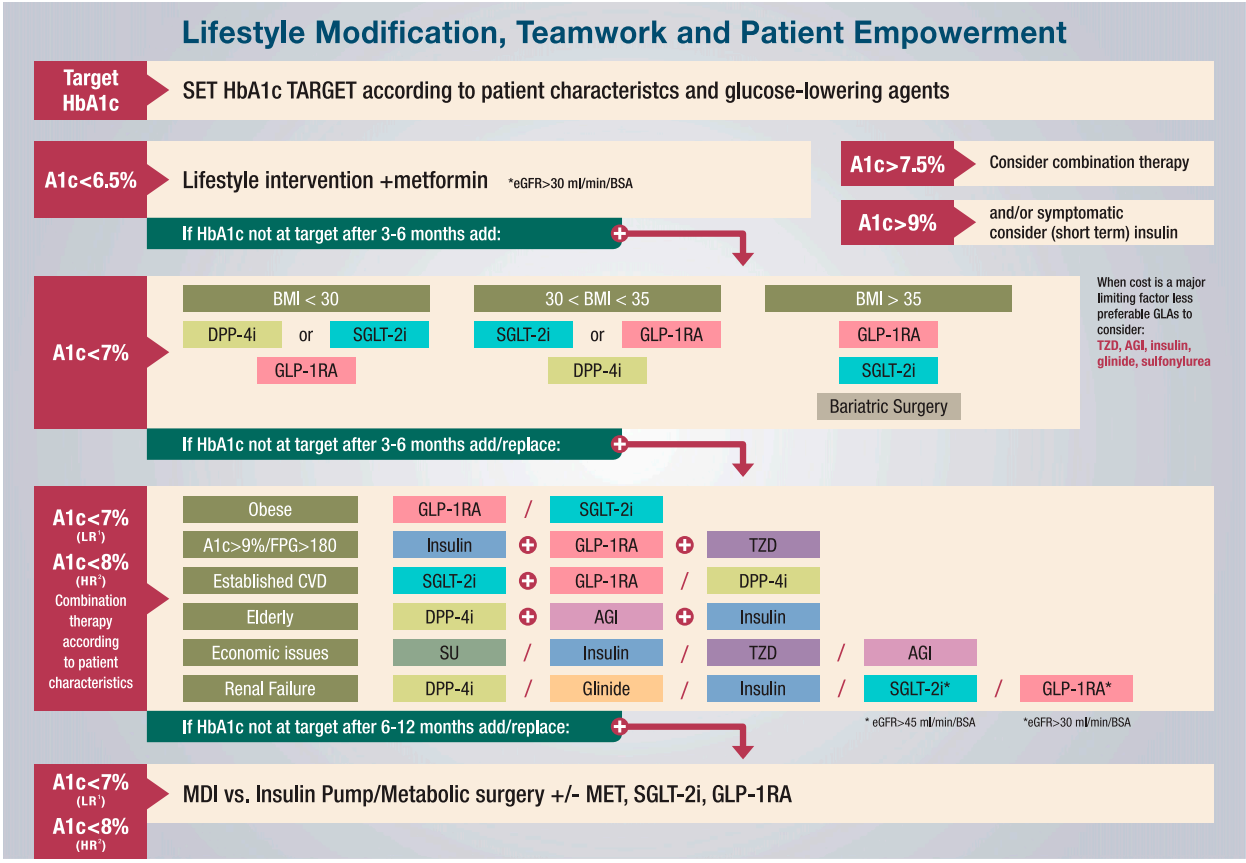

Figure 1—The Israel National Diabetes Council guidelines for the treatment of type 2 diabetes. AGI, alpha-glucosidase inhibitors; BSA, body surface area; CVD, CV disease; DPP-4i, DPP-4 inhibitors; eGFR, estimated glomerular filtration rate; FPG>180, fasting plasma glucose >180 mg/dL; HR^2, high risk of hypoglycemia; LR^1, low risk of hypoglycemia; MDI, multiple daily injections; MET, metformin; SGLT-2i, SGLT2 inhibitors; TZD, thiazalidinediones.

patient within the short time available for each patient in the primary care setting. PHCTs therefore are in need of expert guidance**!**

The ADA/EASD Position Statement: Lifestyle Modification

Both the 2012 and 2015 ADA/EASD Position Statements (1,2) include a visual diagram stressing the importance of continued emphasis on lifestyle modification throughout the course of diabetes treatment, although lifestyle modification is not proven to improve CV outcomes (31). Previously, lifestyle modification was often thought of as a prerequisite "first step" in diabetes management in order to advance to the next step of medical intervention; the more modern integrative view is better represented in the ADA/EASD Position Statement by the surrounding of the entire graph with the light-blue box/line of lifestyle modification. Lifestyle modification is often essential to the success of glycemic control, even when the most powerful GLAs are used (32). A large proportion of weight gain attributed to the initiation of insulin therapy can be avoided with simple lifestyle reinforcement measurements. In consideration of lifestyle modification or any other long-term treatment of type 2 diabetes, the importance of teamwork and patient empowerment cannot be underestimated (18,19). Teamwork includes a multidisciplinary team of nurses, dietitians, social workers, medical psychologists, and the treating physician. At the same time, teamwork includes communication and shared responsibilities between the PHCT and the diabetologist/endocrinologist and timely referral of the more difficult-to-manage patients to specialists. Above all, teamwork refers to the involvement and empowerment of the patient and his or her immediate family and friends (18). In order to emphasize its importance, we added teamwork and patient empowerment to our suggested guidelines, alongside the recommendation for continued reinforcement of lifestyle modification (Fig. 1).

The ADA/EASD Position Statement Versus the Israeli Suggested Guidelines: Consideration for the Choice of GLAs

Although the place of metformin as first line in the treatment of type 2 diabetes is well established, it is important to note that the only CV outcome trial to support its beneficial CV effect was the UKPDS trial (10), where only 342 patients were included in the metformin arm and the number of coronary death events was 16 with metformin compared with 36 in the competing arm. This amount of data would not have been sufficient by today's standards. As more data become available from SGLT2 inhibitor, GLP-1 RA, and other CV outcome trials, we might need to make adjustments to the current guidelines.

With regard to metformin and the six options of second-line agents, the ADA/EASD Position Statement (2) lists five important parameters to consider when choosing a GLA: efficacy, risk of hypoglycemia, effect

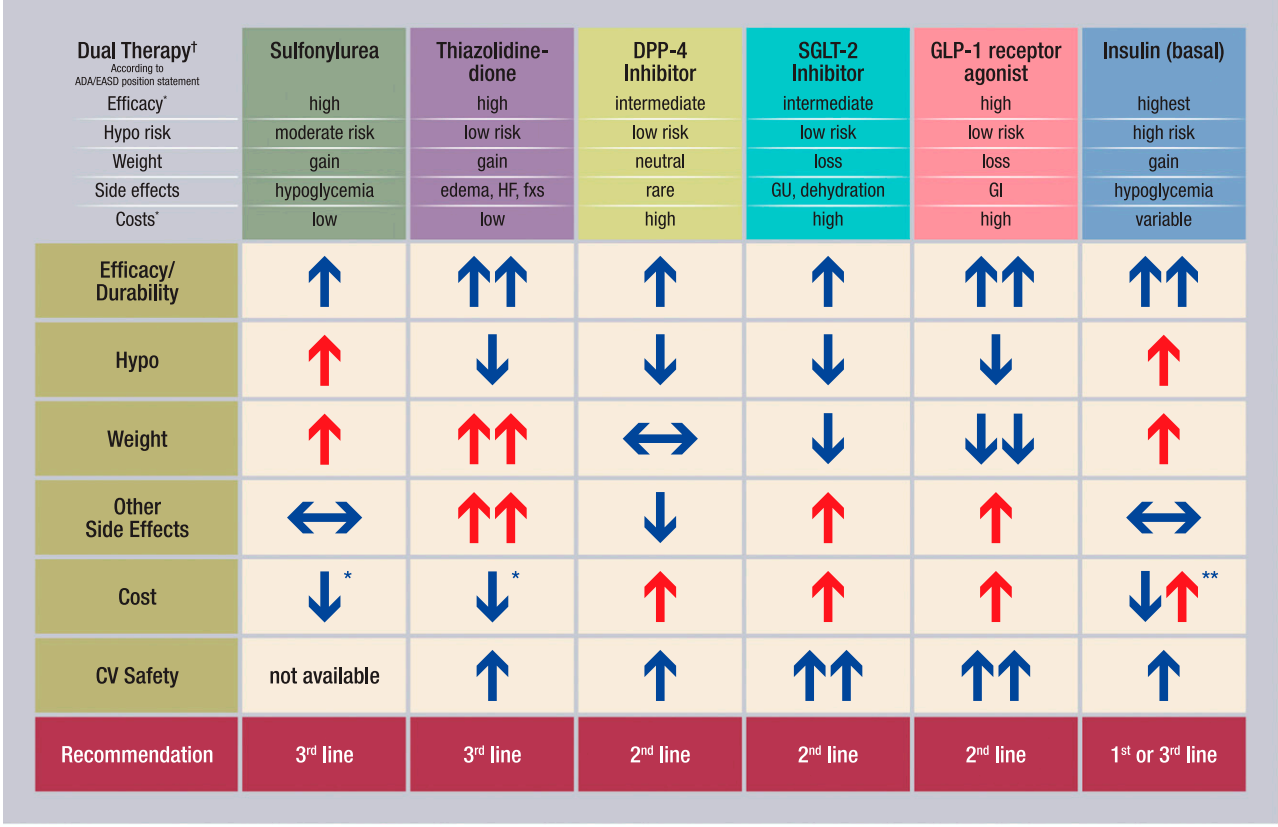

Figure 2—ADA/EASD Position Statement versus Israeli recommendations. *Low direct cost of medication but high cost for treatment of side effects including hypoglycemia, fractures, etc. **Cost is variable, with newer insulin analogues being more expensive. High cost for treatment of side effects including hypoglycemia. †According to ADA/EASD Position Statement. GI, gastrointestional; GU, genitourinary; Hypo, hypoglycemia; HF, heart failure; fxs, fractures.

on weight, side effects, and cost (Fig. 2). However, when one looks at the six groups of GLAs according to these parameters as well as CV safety, treatment durability, and compliance, it is striking how different the results are for the different groups of GLAs.

Efficacy and Durability

The ADA/EASD Position Statement (2) lists sulfonylureas (SUs), thiazolidinedione (TZDs), and GLP-1 RAs as having high efficacy; DPP-4 inhibitors and SGLT2 inhibitors as intermediate; and insulin as having the highest efficacy. In head-to-head trials comparing DPP-4 inhibitors (33) or SGLT2 inhibitors (34) with SUs, some show initial benefits with SUs; however, within a year, there is no difference in glycemic control between these groups of drugs. Direct comparison of GLP-1 RAs to basal and even short-acting insulin also did not yield significant differences in glycemic control (35). When discussing GLA efficacy, we cannot avoid referring to the issue of glycemic durability; SUs, specifically when compared with TZDs, have poor durability (36). We therefore think that while TZDs, GLP-1 RAs, and insulin might be more effective in achieving and maintaining glycemic control than the other GLAs, SUs, DPP-4 inhibitors, and SGLT2 inhibitors may be considered to have similar effects on blood glucose reduction (37), with limited information on durability available thus far. The ongoing Glycemia Reduction Approaches in Diabetes (GRADE) randomized control trial, which is testing glimepiride, sitagliptin, liraglutide, and insulin glargine as second-line therapy, will provide us with important data regarding the durability of these therapies (38).

Risk of Hypoglycemia

The ADA/EASD Position Statement lists SUs having as a moderate risk for hypoglycemia and insulin as high risk. When considering the relatively low rates of hypoglycemia in the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) study (39) despite excellent control, we might conclude that this difference no longer holds true when referring to the newer basal insulins. However, we should bear in mind that the ORIGIN population comprised recently diagnosed patients who used very low doses of insulin and who had residual β-cell function. This might be very different than treating a more advanced patient. Often hypoglycemia prevents patients from achieving better glycemic control, has a deleterious effect on quality of life, and is associated with a major economic burden including the need to self-monitor blood glucose levels and days lost at work (40). Since GLAs that carry a very low risk of hypoglycemia exist, shouldn't low risk of hypoglycemia be considered a requirement for drugs to qualify as a second-line (and not third-line) option?

Weight

The rate of obesity among patients with type 2 diabetes varies in different regions of the world (9); however, it is strongly associated with type 2 diabetes and is often referred to as "diabesity" (41). Increased weight is associated with

increased morbidity and mortality both in the general population and among patients with type 2 diabetes (42). However, insulin glargine and pioglitazone cause weight gain but have not been associated with increased mortality (39,43,44). Since certain classes of GLAs do not cause weight gain (DPP-4 inhibitors) and may even promote weight loss (metformin, GLP-1 RAs, SGLT2 inhibitors), the use of these GLAs over others that cause weight gain should be encouraged.

Side Effects and Patient Adherence

Drugs with a low side effect profile and minimal need for daily glucose measurements may be associated with improved adherence compared with those associated with higher rates of side effects, specifically, weight gain and hypoglycemia (45). Some GLAs have a low side effect profile and subsequently high rates of patient adherence to therapy, most notably DPP-4 inhibitors (33), while others do not (e.g., TZDs, SUs, GLP-1 RAs, insulin). Side effects may also partly explain why patients have higher rates of drug discontinuation in "real-world" observational trials compared with clinical trials (46). Individual patient beliefs, preferences, and specific lifestyle circumstances (for example, fear of hypoglycemia, fear of injection, high-risk occupation [drivers], tolerability of gastrointestinal side effects, etc.) are always important considerations that cannot be incorporated into any suggested guidelines and need to be discussed on a one-to-one basis.

Cost

The cost of treating patients with diabetes around the world is a major consideration for patients, health care organizations, and governments (9). Cost might be the most prominent limiting factor in the use of newer, more expensive agents both at the patient level and at the national level. However, it is important to emphasize that a large part of the expense is incurred when treating diabetes complications (hypoglycemia, end-stage microvascular disease, CV disease, etc.) and not due to GLAs. Insulin and SUs, which are considered inexpensive drugs, have been shown to be the second and fourth leading cause of emergency room admissions due to drug side effects among patients >65 years old in the U.S. (47). The rehabilitation of a woman after a fracture of the hip associated with TZD use is another example of the great expense of "low-cost" GLAs. New drugs, although expensive, may reduce the frequency of blood glucose monitoring (48) and might have lower rates of side effects. The immediate, sometimes very high cost of newer GLAs must be weighed against potential downstream cost spent on treatment of side effects and complications. When cost is a major limiting factor, less preferable GLAs to be consider include pioglitazone, α-glucosidase inhibitors, insulin, and SUs.

CV Safety

The ADA/EASD Position Statement did not list this parameter as a consideration when choosing GLAs, although the approach of the U.S. Food and Drug Administration differs (1,2,24). The dispute over the necessity of CV outcome trials is ongoing (23,25), while the amount of data emanating from published trials is immense. Clinical trial data are available for the CV safety of insulin (39), pioglitazone (43,44), DPP-4 inhibitors (26–28), GLP-1 RAs (29), and SGLT2 inhibitors (30). The recent data regarding CV superiority of the SGLT2 inhibitor empagliflozin (30) and a recent press release regarding the Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial (CV safety of the GLP-1 RA liraglutide) (49) indicate the potential for further changes in our drug selection in the future. While many more data are being collected regarding the newer agents, it has become even harder to compare them with older agents, for which such data are not available.

Guideline Suggestion

The guideline suggestion (Fig. 1) presented here is an updated version of one that was previously published (50) and accepted by the Israel National Diabetes Council, a multidisciplinary team chosen to serve as an advisory board to the Israeli Ministry of Health. This suggestion should be considered within the context of the Israeli health care system, which includes universal health coverage as part of a statutory/obligatory health insurance system. All citizens can choose from among four competing nonprofit health plans, which are charged with providing a broad package of benefits stipulated by the government (51). The guideline suggestion presented here differs from the previous version as well as from the ADA/EASD and American Association of Clinical Endocrinologists/American College of Endocrinology guidelines in the following aspects.

We added emphasis on the importance of teamwork and patient empowerment in endorsing lifestyle modifications throughout the course of treatment—as a backbone for all other interventions.

The setting of an HbA_{1c} target is based not only on patient characteristics but also on the GLA used. When metformin and lifestyle intervention are the only treatments administered, we may strive to normalize blood glucose levels also in patients at high risk for hypoglycemia, without significant increased risk for side effects or cost. When suggested second-line agents that carry minimal risk of inducing hypoglycemia are used, we can aim to achieve tight glycemic control (HbA_{1c} <7%), even in a high-risk patient population, owing to proven microvascular benefit (12,13). However, at this treatment stage, the achievement of normoglycemia should be considered according to individual patient adherence and the cost of treatment. When the risk for side effects, most prominently hypoglycemia and weight gain, is increased by the GLAs used (recommended as third-line GLAs), an individualization of the HbA_{1c} target according to patient characteristics is recommended (<7% in patients at low risk for hypoglycemia vs. <8% in patients at high risk for hypoglycemia).

For most patients, we recommend lifestyle intervention and metformin as first-line therapy unless they are unable to tolerate it; then a DPP-4 inhibitor or SGLT2 inhibitor may be a good alternative. The suggested guidelines state two exceptions where additional therapy should be initiated at the outset: the need for combination therapy or the need for insulin therapy. The American Association of Clinical Endocrinologists/American College of Endocrinology guidelines (6) suggest that combination therapy be initiated when HbA_{1c} is >7.5%. We would like to suggest that the actual HbA_{1c} is not the only value of importance; rather, the difference in HbA_{1c} from the patient's individual target should be considered. Since most oral antidiabetes drugs only reduce HbA_{1c} by <1%, when HbA_{1c} is significantly elevated above goal, only combination therapy or use of injectable agents (insulin and/or GLP-1 RAs) can reduce HbA_{1c} to target.

The second exception mentioned in our suggested guidelines is the need to consider immediate, sometimes short-term,

insulin treatment for patients with HbA_{1c} >9% or in a symptomatic patient. Current evidence reinforces the importance and safety of early short-term insulin therapy and the ability of such treatment to decrease glucotoxicity and lipotoxicity and to preserve β-cell function (39,52).

One of the most important aspects of all guidelines, well represented in the ADA/EASD Position Statement, is the setting of timelines for when to progress from one step to the next (53). It has previously been shown that depending on HbA_{1c}, the addition of another GLA takes an average of 5–19 months (54). We support the ADA/EASD Position Statement, which specifically proposes that if a patient has not achieved his or her glycemic target within 3–6 months, treatment should be changed or intensified.

In a setting where cost of GLAs is not a key limiting factor, we recommend as second-line therapy agents that do not cause hypoglycemia, weight gain, or significant side effects that might adversely affect drug adherence. Since there are many options for the treatment of diabetes and since the risk of hypoglycemia and weight gain is an important hurdle in achieving glycemic control in patients with type 2 diabetes, as is also stated in the ADA/EASD Position Statement (2), we consider these two requirements to be a prerequisite for qualification as a recommended second-line treatment option. Additionally, all second-line recommended treatments are newer agents that have been studied in large clinical trials, including CV outcome trials. The amount of safety data that are and will be available for these agents is reassuring. However, data regarding the durability of these drugs are still limited (55,56). When cost is a major limiting factor, less preferable GLAs to be considered include pioglitazone, α-glucosidase inhibitors, insulin, and SUs.

Besides HbA_{1c}, as explained above, we choose to use BMI as the basis for recommending a preferred second-line treatment for a specific patient. BMI might be the strongest phenotype to follow when considering treatment for patients with diabetes (57). For patients with BMI <30 kg/m^2, we consider DPP-4 inhibitors and SGLT2 inhibitors as equally preferable second-line treatment options. Both classes of drugs are easy to administer and well tolerated, with increased adherence to therapy, and to date have been known to be safe. GLP-1 RAs, although a good option especially for patients with increased BMI, are injectable agents with more gastrointestional side effects, therefore limiting patient adherence (46).

For patients with BMI 30–35 kg/m^2, we consider SGLT2 inhibitors and GLP-1 RAs as equally good options, and while compliance might be better with SGLT2 inhibitors, weight loss may be greater with GLP-1 RAs. DPP-4 inhibitors might not be preferred in this group of patients owing to the agents' weight neutrality. However, due to their good safety record and limited side effect profile, which greatly enhance compliance, DPP-4 inhibitors remain a reasonable option, especially in selected patients such as the elderly and those with renal failure (58,59).

For patients with BMI >35 kg/m^2, GLP-1 RAs constitute our second-line drug of choice. GLP-1 RAs have the greatest potential for weight loss (60); however, the typical reduction in body weight is relatively small, and it is not clear whether this reduction has an effect on long-term outcomes. SGLT2 inhibitors are an acceptable option, and they cause similar (albeit a little less) weight loss; however, as opposed to GLP-1 RAs, they do not have an effect on the hunger-satiety mechanism. For achievement of long-term sustainable results that lead to changes in life expectancy, many of these patients will eventually need to undergo bariatric surgery (61). The option of bariatric surgery should be discussed with possible candidates in the early stages of their disease—before they develop micro- and macrovascular complications. Preoperative treatment with GLP-1 RAs or SGLT2 inhibitors to improve both glycemic control and weight might be beneficial.

Often, two GLAs are not enough to reach a patient's specific glycemic target, at which point a third GLA or switching to a more potent GLA may be considered. Primary care physicians will sometimes consider referring patients reaching third-line therapy to a diabetes specialist. This depends to an extent on the resources available in the primary health care setting versus the multidisciplinary diabetes clinic.

For third-line therapy, we also suggest treatment with a GLA that best suits the patient's medical condition and personal preference. Some options for possible combinations are provided in this guideline suggestion according to specific patient characteristics (age, BMI, history of CV disease, etc.) (Fig. 1); however, there are many possibilities. It should be noted that since at this stage, some combinations of therapy include drugs that may induce hypoglycemia and weight gain, consideration should be given to the possibility of less stringent HbA_{1c} targets for some of these patient populations.

Finally, fourth-line therapy should be managed in a specialty multidisciplinary setting and include a combination of short- and long-acting insulin therapy, as well as GLP-1 RAs, oral therapy, and even consideration of metabolic surgery. At this point in treatment, we must carefully weigh the potential benefit of any treatment against potential harm and adjust the glycemic target accordingly.

Alternating between different members of the same class of GLAs has not yet been studied and therefore cannot be recommended. While some head-to-head studies between different GLP-1 RAs exist (62), the data regarding such a comparison for DPP-4 inhibitors are limited (63). It is therefore preferable to improve glycemic control by adding or switching to a different class of GLAs.

When can we declare a certain GLA as ineffective and stop treatment? With most classes of GLAs, a drug can be considered ineffective if no improvement in glycemic control (in most cases, HbA_{1c} reduction of >0.5%) occurs within 3–6 months after exclusion of technical and adherence issues. However, with GLP-1 RAs, and possibly also with SGLT2 inhibitors, all metabolic effects should be considered (weight, blood pressure) before treatment is discontinued.

In conclusion, we present here a suggestion to modify existing guidelines for the treatment of hyperglycemia in patients with type 2 diabetes. We hope this option will provide PHCTs around the globe with a more coherent, easy-to-follow guide to aid in our task of providing the best possible treatment to all patients with type 2 diabetes.

Duality of Interest. O.M. has served on the advisory board for Novo Nordisk, Eli Lilly, Sanofi, Merck Sharp & Dohme (MSD), Boehringer Ingelheim (BI), Janssen, Novartis, and AstraZeneca; has received grants (paid to institution) as a study physician by AstraZeneca and Bristol-Myers Squibb; has received research grant

support through Hadassah Hebrew University Hospital from Novo Nordisk; and has served on the speakers' bureau for AstraZeneca and Bristol-Myers Squibb, Novo Nordisk, Eli Lilly, Sanofi, Novartis, MSD, and BI. I.R. has served on the advisory board for AstraZeneca/Bristol-Myers Squibb, Eli Lilly, MSD, Novo Nordisk, Sanofi, Orgenesis, SmartZyme Innovation, Labstyle Innovations, and BI; has served as a consultant for AstraZeneca/Bristol-Myers Squibb, Insuline Medical, Gili Medical, Kamada, FuturRx, Nephrogenex, and Diabetes Medical Center (Tel Aviv, Israel); has served on the speakers' bureau for AstraZeneca/Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, MSD, Novartis Pharma AG, Novo Nordisk, Sanofi, Teva, and BI; and is a stockholder/shareholder in Insuline Medical, Labstyle Innovations, SmartZyme Innovation, Orgenesis, and Glucome. No other potential conflicts of interest relevant to this article were reported.

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