SUPPLEMENT REVIEW

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Options for Combination Therapy in Type 2 Diabetes: Comparison of the ADA/EASD Position Statement and AACE/ACE Algorithm

Timothy Bailey, MD

AMCR Institute, Escondido, Calif.

ABSTRACT

Treating patients with diabetes is one of the most challenging and important activities a physician (primary care physician or specialist) can undertake. A key to successful therapy for type 2 diabetes is the insight that this condition is progressive and that the need for additional agents over time is normative. The ability to individualize therapy by patient and medication characteristics comes from experience and knowledge of pertinent clinical studies. However, guidelines from expert bodies such as the American Diabetes Association/European Association for the Study of Diabetes and American Association of Clinical Endocrinologists/American College of Endocrinology can help clinicians of all levels of expertise to approach therapy choices more rationally. There is unity across these guidelines about the role and benefits of metformin as first-line pharmacological treatment, probability of good efficacy, low risk of hypoglycemia, modest weight loss, and overall long-term data. Unfortunately, this unity does not extend to recommendations for subsequent pharmacological agents and their use in combination to intensify treatment when insulin is not (yet) appropriate. Across both statements, some drug classes seem more prominent, and looking at their benefit—risk profile, it is clear why this is the case. The most profound recent change in diabetes therapy has been the introduction of incretin therapies. Incretin therapies minimize 2 important adverse effects seen with many other therapies: hypoglycemia and weight gain. These agents have increased the range of options available for early intensification of treatment of type 2 diabetes. In combination with more established therapies, there are more opportunities than ever to accommodate patient preferences while improving glycemic control and harnessing extraglycemic benefits of a second (or third) agent.
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The majority of type 2 diabetes (T2D) management is typically undertaken by primary care physicians (PCPs).[1] In everyday clinical practice, PCPs need to balance the relative merits of different drugs with differing mechanisms of actions and safety/tolerability profiles to prescribe the optimal therapy for individual patients. Fortunately, initiating therapy for newly diagnosed cases is comparatively straightforward, as there is agreement among leading guidelines in placing metformin monotherapy (in conjunction with lifestyle intervention) as the preferred first-line pharmacotherapy, providing it is not contraindicated.[2-6] Metformin has good efficacy and produces some weight loss with a low risk of hypoglycemia. Low cost also is another benefit. Metformin can cause transient gastrointestinal (GI) disturbances, but has an overall good long-term safety profile.[7]

Thereafter, clinical management of patients tends to become more challenging, because, due to the progressive nature of the disease, most patients will inevitably require

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Requests for reprints should be addressed to Timothy Bailey, MD, AMCR Institute, 700 West EI Norte Parkway, Suite 201, Escondido, CA 92026.

E-mail address: tbailey@amcrinstitute.com

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combination therapy in order to maintain glycemic control.[8] Apart from efficacy, additional agents can differ in risk of adverse effects, including hypoglycemia and weight gain, as well as cost. Prescribing a suitable combination regimen requires in-depth knowledge of numerous classes of medications and the prescribing information for individual drugs. It also requires appreciation of important differences among drugs within each class, many of which are relatively new and lack long-term data. Furthermore, this should be done while accounting for patient preferences and needs in order to provide individualized care.[4]

To assist physicians in selecting options for combination therapy, numerous expert guidelines, along with suggested treatment algorithms, have been produced.[2-5] Unfortunately, the unity in recommending metformin as first-line pharmacotherapy among leading guidelines does not extend to recommendations for subsequent pharmacological agents and their use in combination. This is mainly because comparative studies, which would provide an evidence base, are lacking. Although recent updates have brought some guidelines closer in agreement, substantive differences in content and approach remain. Consequently, the choice and timing of add-on therapies to metformin is not straightforward. There is agreement on minimizing risk and considering patient preferences, and American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) explicitly takes these factors into account when prioritizing different treatments in their algorithm. With this approach, patients can be offered a choice by considering the pros and cons of each option.

This review will compare the preferred noninsulin combination therapies presented by 2 widely used position or consensus statements: those from the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD)[4] and those from AACE/ACE.[2] The supporting rationales in these statements will be discussed, as they are key to understanding why specific drug classes and combinations are recommended when preferences are indicated. Insulin use will be discussed in 2 other articles in this supplement.[9,10]

ADA/EASD POSITION STATEMENTS AND AACE/ACE GUIDELINES: AN OVERVIEW

Both the newly updated (2013) AACE/ACE algorithm[2] and the ADA/EASD position statement (2012)[4] are very patient-focused. They both include multiple drug classes and emphasize the importance of minimizing risk of hypoglycemia and weight gain. Some drug classes are not included due to modest efficacy, limiting side effects, or infrequent use.

Both statements contain concise treatment summaries or algorithms to help guide selection of combination therapies (**Figures 1**, **2**).[2,4] In general, there are important commonalities in the processes, aims, and recommendations associated with these 2 resources. Both reflect the consensus opinions of their respective expert panels based upon their review of the medical literature and clinical expertise, and both statements acknowledge that the available literature on comparative effectiveness lags well behind the potential number of drug combinations that could be prescribed. Both statements strike a balance between relying upon evidence from randomized trials against using expert opinion when desired data are not available. Importantly, both statements stress the importance of tailoring therapy to individual patients.

The ADA/EASD position statement notes that the panel's recommendations were predicated on effectiveness in lowering glucose levels, but pursued within a "multi-factorial risk-reduction framework." This includes accounting, when possible, for extraglycemic effects that may reduce long-term complications, safety profiles, tolerability, ease of use, and expense. The AACE/ACE algorithm also mentions the importance of accounting for total cost of therapy to the individual and society from treatment-related adverse events, complications such as hypoglycemia that may result in hospitalization, and additional blood glucose monitoring, in addition to the direct expense of individual medications, when making recommendations. The ADA/EASD position statement also includes an emphasis on factors such as patient adherence, age, weight, sex, race/ethnicity, and comorbidities when selecting a treatment. This again is aligned with the approach taken by the AACE/ACE. As an additional resource, the AACE/ACE algorithm provides a comprehensive table comparing 11 types of therapeutic agents against 6 broad categories of benefits and risks associated with those agents (ie, hypoglycemia, weight gain, renal or hepatic insufficiency, congestive heart failure and cardiovascular disease, GI symptoms, and effects on bone mineral density).

Despite broad similarities, the ADA/EASD and AACE algorithms are different in approach and format, which makes direct comparison challenging. This could at times create uncertainty among readers about the preferred combination regimen for individual patients. One of the most important differences between the AACE/ACE and former ADA/EASD statements was narrowed in that the newer ADA/EASD position statement now (like the AACE/ACE algorithm) differentiates aggressiveness of initial therapy according to baseline glycated hemoglobin (A1c). However, the points of inflection differ (ie, $<$7.5%, 7.6%-9.0%, $>$9.0% with AACE/ACE, and $<$9%, 9%-10%, and $>$10% with ADA/EASD).

Another difference is the approach to A1c targets. AACE/ACE recommends a primary goal of A1c 6.5%, allowing customization for comorbid conditions, duration of diabetes, history of hypoglycemia, hypoglycemia unawareness, limited life expectancy, and other patient factors. ADA/EASD recommends a target of $<$7.0% for most patients, but acknowledges that more stringent (ie, 6.0%-6.5%) A1c targets may be optimal for patients with short disease duration, long life expectancy, and absence of cardiovascular disease. Similarly, the merit of less stringent (ie, 7.5%-8.0%) A1c targets are discussed for patients who may have a short life expectancy, history of severe

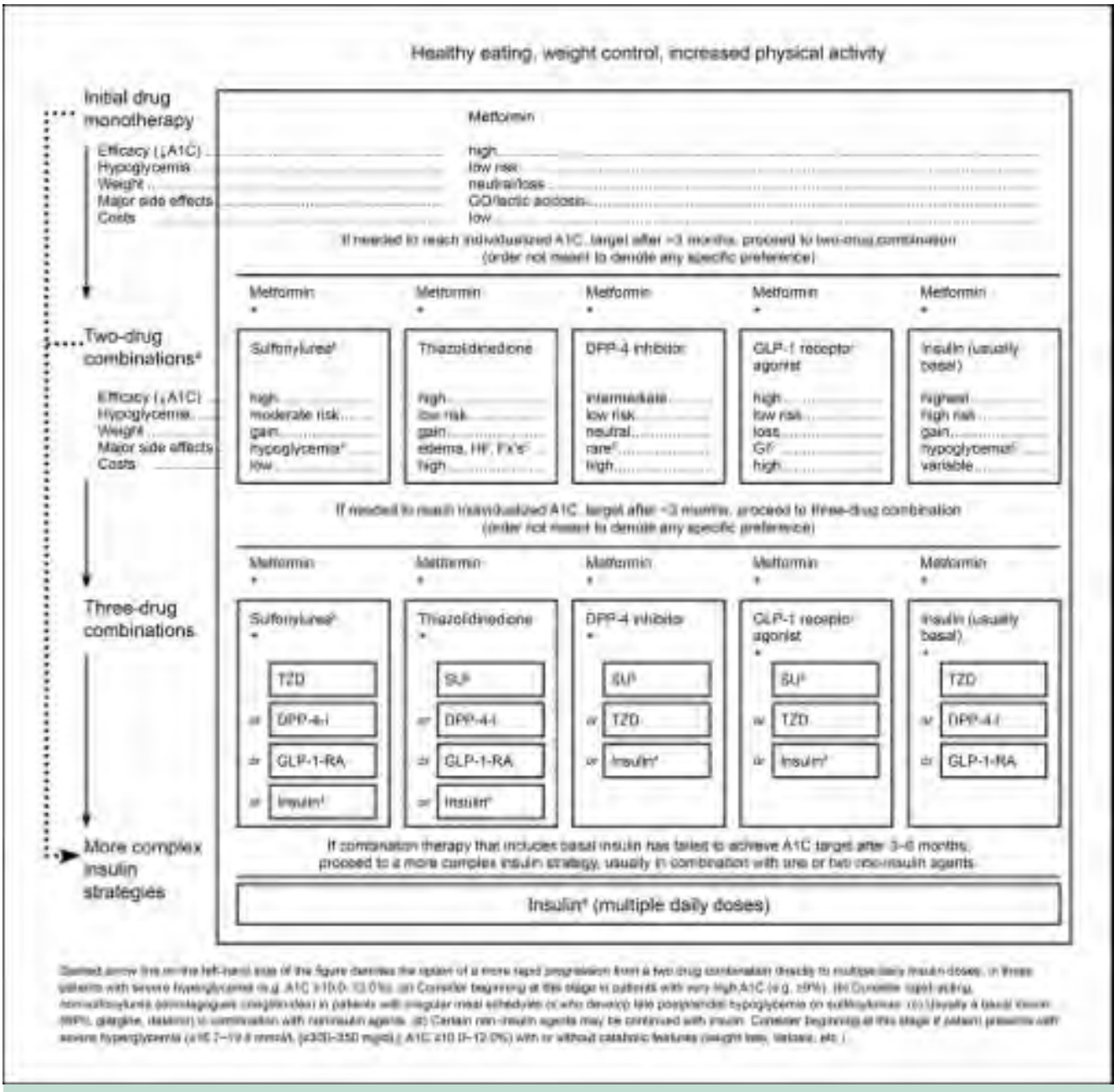

Figure 1 American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) general recommendations for antihyperglycemic therapy in type 2 diabetes (© ADA, and reproduced with permission from Inzucchi et al. *Diabetes Care*. 2012;35:1364-1379).[4] DPP-4i = dipeptidyl peptidase-4 inhibitor; FX = fracture; HF = heart failure; GI = gastrointestinal; GLP-1 = glucagon-like pepide-1; SU = sulfonylurea; TZD = thiazolidinedione.

Moving from the top to the bottom of the figure, potential sequences of antihyperglycemic therapy. In most patients, begin with lifestyle changes; metformin monotherapy is added at, or soon after, diagnosis (unless there are explicit contraindications). If the A1c target is not achieved after 3 months, consider one of the 5 treatment options combined with metformin: a sulfonylurea, TZD, DPP-4 inhibitor, GLP-1 receptor agonist, or basal insulin. (The order in the chart is determined by historical introduction and route of administration and is not meant to denote any specific preference.) Choice is based on patient and drug characteristics, with the over-riding goal of improving glycemic control while minimizing side effects. Shared decision-making with the patient may help in the selection of therapeutic options. The figure displays drugs commonly used in both the US and Europe. Rapid-acting secretagogues (meglitinides) may be used in place of sulfonylureas. Other drugs not shown (a-glucosidase inhibitors, colesevelam, dopamine agonists, pramlintide) may be used where available.

[a]Consider beginning at this stage in patients with very high A1c (eg, >9%).

[b]Consider rapid-acting, nonsulfonylurea secretagogues (meglitinides) in patients with irregular meal schedules or who develop late postprandial hypoglycemia on sulfonylureas.

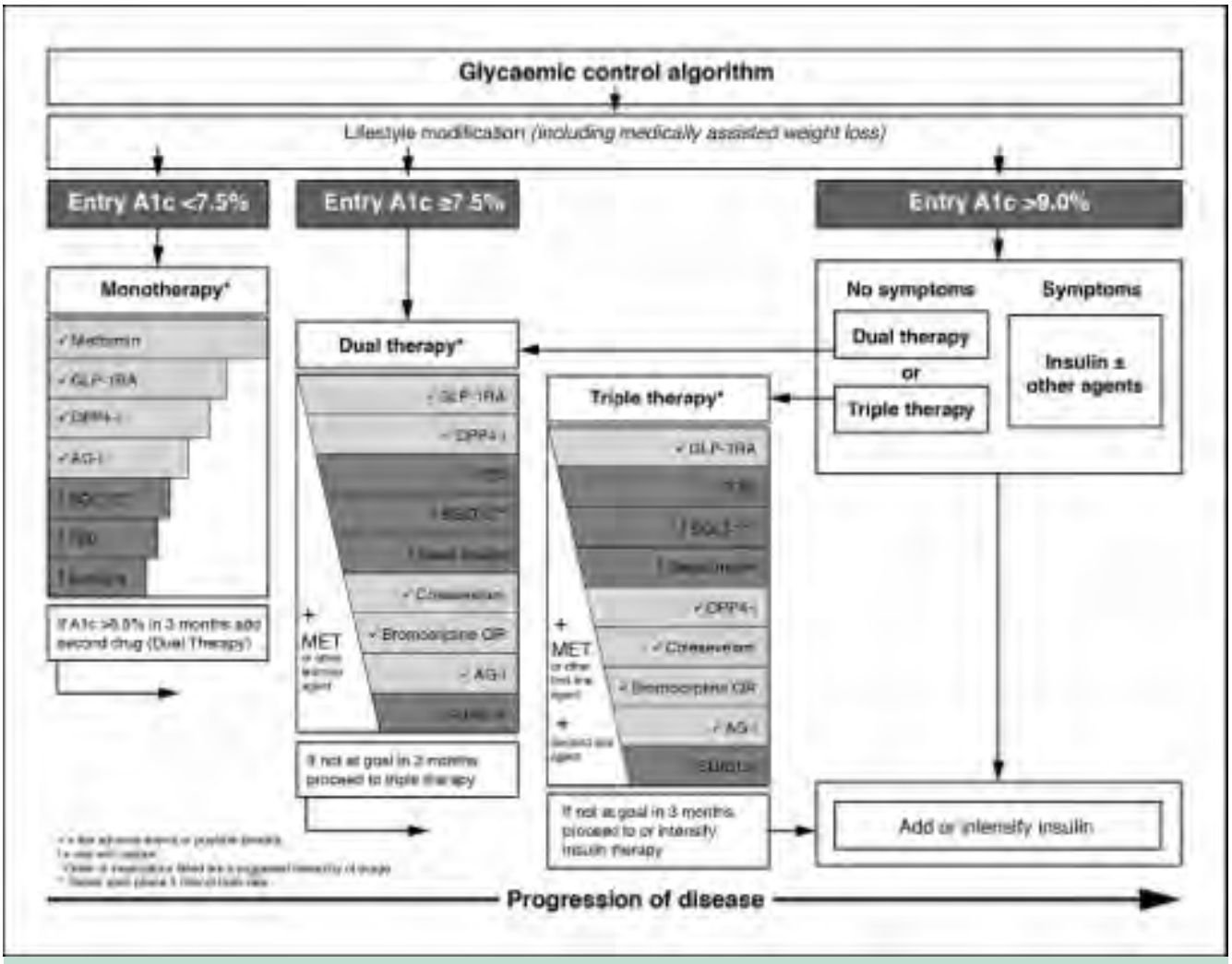

Figure 2 AACE/ACE treatment algorithm for the management of type 2 diabetes (© ACE, and reproduced with permission from Garber et al. *Endocr Pract* 2013;19:327-336).[2]

A1c = glycated hemoglobin; AACE = American Association of Clinical Endocrinologists; ACE = American College of Endocrinology; AGI = alpha-glucosidase inhibitors; DPP-4i = dipeptidyl peptidase 4; GLN = L-glutamine; GLP-1RA = glucagon-like peptide-1 receptor agonist; SGLT-2 = sodium/glucose cotransporter 2; SU = sulfonylurea, TZD = thiazolidinediones; QR = quick release.

Within each category of A1c, there is a progression from monotherapy, to dual therapy, to triple therapy, to insulin therapy with or without additional agents. The order of presentation of regimens indicates general priorities that should be customized to the individual patient, with consideration of the contraindications and precautions, allergies, comorbid conditions, drug−drug interactions, and drug−laboratory interactions. Physicians must be thoroughly familiar with complete prescribing information before selection of therapy. In each case, response to therapy should be monitored closely (determination of A1c every 2 to 3 months), and titration of dosages or changes of regimen should be implemented in a timely manner.

hypoglycemia, advanced complications, and multiple comorbid conditions, for example.

A third important difference is how the 2 statements address choices of drugs for combination therapy. The ADA/EASD position statement lists options of commonly used regimens for monotherapy, dual therapy, and triple therapy, specifying that the order of presentation reflects historical introduction, but without indicating treatment preferences within each option. The ADA/EASD panel cites lack of sufficient primary data from long-term comparative efficacy trials as the reason for avoiding specific recommendations, thus moving away from the more prescriptive (algorithmic) approach to treatment selection used in a previous version of their consensus statement.[11]

The ADA/EASD position statement lists add-on therapies from left to right, with the older oral medications to the left and the newer injectable medications to the right, and includes the disclaimer that this order should not imply preference. In contrast, the AACE/ACE algorithm provides specific priorities for selection of agents both in monotherapy and in combination therapy. Both allow for individualized therapy. The ADA/EASD position statement

Table Comparison of the AACE/ACE Algorithm for 2009, and 2013, and ADA/EASD Position Statement. © 2012 Springer, and Adapted with Permission from Rodbard & Jellinger, *Diabetologia*. 2012;55:2850-2852[12]

	AACE/ACE (2009) [2013]	ADA/EASD (2012)
A1c target	6.5% (can be customized by risk)	<7% (lower risk patients 6.0—6.5%, higher risk 7.5—8%)
Therapy escalation interval	3 months	3-6 months
Agent-specific advice	Stronger	Lesser*
Priority for SU	Lower (risk of hypoglycemia, weight gain, lack of durability)	Listed first in Dual and Triple*
Priority for TZD	Lower (risk of weight gain, CHF, fractures) [Lower (risk of weight gain, fluid retention, CHF, bone loss)]	Listed second in Dual and Triple*
Priority for SGLT-2	Not listed [Lower (risk of GU infections)]	Not listed
Priority for incretin-based therapies	GLP-1 receptor agonist preferred to DPP-4 after metformin for [Mono,] Dual and Triple	GLP-1 receptor agonist listed fourth and DPP-4 listed third in Dual and Triple
Insulin analogs	Preferred	Mention of less hypoglycemia and better glucose excursions
Consider start with dual therapy	A1c 7.6—9%	A1c ≥9%
Consider start with insulin	A1c >9%	A1c ≥10%
Concern for medication cost	Lower	Higher
Concern for total cost of care†	High	Not clearly stated*

AACE = American Association of Clinical Endocrinologists; ACE = American College of Endocrinology; ADA = American Diabetes Association; CHF = coronary heart failure; EASD = European Association for the Study of Diabetes; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like pepide-1; SGLT-2 = sodium-glucose cotransporter 2; SU = sulfonylurea; TZD = thiazolidinedione.

*On-line supplement has guidance for patients with the following concerns: hypoglycemia, weight gain, cost of therapy.

†Cost of care includes cost of hospitalization due to hypoglycemia, other adverse events, additional blood glucose testing due to hypoglycemia, and medication costs.

provides 3 tables with adapted recommendations specifically to minimize hypoglycemia, weight gain, and cost; however, as these are located in the online supplementary material, many readers will not access them.

Both statements present important and useful information to assist physicians with clinical decision-making for individual patients. Despite the differences in format and approach, by reference to both the algorithm and supporting text, it is possible to gain greater understanding of when and why certain drugs may be preferred for certain patients, or particular drugs should be used (or avoided) in combination therapy (excluding insulin-based combinations) (**Table**).[12]

TRADITIONAL COMBINATION THERAPY OPTIONS

Metformin is now the cornerstone of combination therapy for T2D. Metformin was available in Europe for many years before US approval in 1995. In the US, approval of metformin was delayed because of safety concerns over conditions such as lactic acidosis, a very rare disorder that can occur due to metformin accumulation (for which there is a black box warning on the product insert). Metformin is contraindicated in patients with serum creatinine above the normal limit for their age. Metformin should be carefully titrated in individuals with modest decreases in glomerular filtration rate and in elderly (≥80 years) patients to establish the minimum dose, and renal function should be regularly monitored. Metformin should be avoided in individuals with clinical or laboratory evidence of hepatic impairment.[13]

Metformin acts by suppressing excess hepatic glucose production, and is effective in lowering both fasting plasma glucose (FPG) and postprandial glucose (PPG).[2,7,11,14] It is administered 2 to 3 times daily, usually with meals, although an extended-release formulation taken once daily is available. As monotherapy, it has a very low risk of hypoglycemia and can produce modest weight loss.[2]

As mentioned previously, the ADA/EASD position statement lists metformin monotherapy as the first-line pharmacological treatment for T2D. This is mirrored by the AACE/ACE algorithm, although only for patients with lower baseline A1c levels (6.5%-7.5%). For patients with A1c 7.6%-9.0%, AACE/ACE recommends beginning with dual therapy, and for patients in very poor control (A1c >9.0%), recommends more complex regimens, depending on diabetes history and symptoms, with metformin still included as one of the agents. Recommendations from the 2 statements as to how and when other drugs should be combined are discussed in the following sections.

Sulfonylureas

Sulfonylureas (SUs) are one of 2 classes of insulin secretagogues. As the oldest of the oral antidiabetes therapies, they tend to be less expensive than newer therapies.[2,11,14] SUs decrease blood glucose levels by increasing insulin secretion from the pancreas.[8] These agents bind to receptors on the surface of the pancreatic β-cells, triggering closure of the voltage-dependent potassium adenosine triphosphate channels, thereby facilitating cell-membrane depolarization

and entry of calcium into the cell.[15] This series of molecular interactions results in insulin being secreted. However, it is important to note that this occurs independently of actual blood glucose concentration, and thus, risk of hypoglycemia is high.[12,16]

Depending on the specific agent, SUs are administered orally once or twice daily and are longer-acting than the other class of secretagogues, the glinides.[17] SUs lower A1c levels by up to 2.0%.[14,18] The major adverse effect of SUs is hypoglycemia, with the older, long-acting SUs (eg, chlorpropamide and glyburide) having a greater risk than second-generation SUs (eg, gliclazide, glimepiride and glipizide).[2,6] Elderly patients, in particular, are at greater risk of severe hypoglycemia.[19] In clinical trials, a weight gain of approximately 2-5 kg is common with SUs.[14,20] SUs are a preferred option for patients with elevated FPG. Unfortunately, they may have a short time to secondary failure in certain patients. This was demonstrated in the "A Diabetes Outcome Progression Trial" (ADOPT), in which the cumulative incidence of failure at 5 years (when used as monotherapy in T2D) was 34% for glyburide, versus 21% for metformin and 15% for rosiglitazone.[8]

The ADA/EASD position statement lists SUs as one of 5 drug options (in combination with metformin) for dual therapy, and lists SUs as an option in 4 different triple therapy combinations. The AACE/ACE algorithm lists SUs as an option for dual or triple therapy combination, but due to the short period during which they retain clinical efficacy in most patients, risk of hypoglycemia and associated weight gain, AACE/ACE suggests that other agents, such as incretin-based therapies, should be considered first.

Glinides

Glinides are insulin secretagogues having a faster onset but shorter duration of action (1-2 hours) than SUs.[2,11,14] These agents bind to a different site on the pancreatic β-cell receptor than SUs.[21] When taken at meals, SUs attenuate PPG levels with little effect on FPG levels.[14] Glinides are administered orally 3 times daily before meals. They decrease A1c levels by 0.5%-1.5%;[18,21] in combination with metformin, repaglinide may be more effective than nateglinide at decreasing A1c and FPG.[22] The degree of weight gain with glinides is similar to SUs, but hypoglycemia may be less frequent.[23,24] Because glinides are metabolized by the liver and cleared by the kidney, they should be used with caution in patients with hepatic impairment. Repaglinide requires no initial dose adjustment in patients with creatinine clearance 40-80 mL/min, but should be started at a lower dose and be carefully titrated in patients with severe renal impairment (creatinine clearance 20-40 mL/min).[25] Glinides are particularly useful for those patients requiring flexible mealtime glucose control.

Although the ADA/EASD position statement does not specifically include the glinides in their general recommendations, they are suggested as an alternative for SUs. In the AACE /ACE guidelines, glinides are prioritized equal to SUs when A1c is 6.5%-7.5% and when A1c >7.5% as a last option in dual or triple therapy combination.

Thiazolidinediones

Thiazolidinediones (TZDs) are peroxisome proliferator-activated receptor gamma agonists. Two TZDs were widely used until recently: rosiglitazone and pioglitazone. Only pioglitazone is now available in most countries (see below). TZDs address the problem of insulin resistance by increasing the sensitivity of muscle, adipose tissue, and liver to endogenous and exogenous insulin. This results in increased glucose uptake by these tissues, and increased suppression of hepatic glucose output, with a low risk of hypoglycemia. Thus, their mode of action is complementary to other diabetes therapies such as secretagogues. TZDs are administered orally, once or twice daily, depending on the dosage, with or without food. When used as monotherapy, TZDs decrease A1c levels by 0.5%-1.4%.[18] Adverse effects identified for TZDs include weight gain, fluid retention, and peripheral edema, and both have been linked to an increased risk of congestive heart failure; product inserts contain black box warnings.[2] Both TZDs also are associated with an increased incidence of bone fracture in men and women.[26,27]

As a result of a meta-analysis,[28,29] indicating an increased risk of adverse cardiovascular outcomes with use of rosiglitazone, the European Medicines Agency implemented a suspension of the drug in Europe; simultaneously, the Food and Drug Administration announced restrictions to its use in the US.[30] By contrast, in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) Trial, the TZD pioglitazone was not associated with any increased incidence of overall adverse cardiovascular outcomes in a sample of patients with T2D and pre-existing cardiovascular disease, as assessed by a composite primary end point.[31,32] Furthermore, there was evidence of a decreased risk of certain individual cardiovascular outcomes (ie, all-cause mortality, myocardial infarction, stroke). However, for a number of reasons, including that these were secondary prespecified trial end points, and that the primary end point was not met, there has been great debate about the clinical significance of those findings.[33,34] Nevertheless, pioglitazone was well tolerated over the long term in that high-risk population of individuals with pre-existing cardiovascular disease.[35] Furthermore, in a meta-analysis of 19 trials, pioglitazone was associated with a significantly lower risk of death, myocardial infarction, or stroke.[36] However, pioglitazone also has been linked to an increased risk of hepatic effects and macular edema.

A significant point of controversy exists concerning the presence, clinical significance, and actual magnitude of what appears to be a small increase in risk of bladder cancer associated with pioglitazone use in various studies.[37-41] Pending availability of additional data, the European Medicines Agency issued a warning against using pioglitazone in patients with current (or history of) bladder cancer, or uninvestigated macroscopic hematuria.[42] Similarly, the Food

and Drug Administration also issued a safety warning.[43] It should be noted that this association between pioglitazone and bladder cancer has not been demonstrated in all populations studied.[44-47] Not surprisingly, conclusions about cancer risk also have been the subject of considerable debate, raising questions about trial design and interpretation of various data, as well as arguments for an overall positive risk−benefit ratio for pioglitazone.[32,35,38,45,48,49]

Concerns about side effects notwithstanding, the ADA/EASD position statement lists TZDs (with the caveat that rosiglitazone is not widely available) as one of 5 options for dual therapy, and in all 5 options for triple therapy. The AACE/ACE algorithm lists TZDs as an alternative monotherapy or dual therapy, and lists them as an option in triple therapy just after glucagon-like peptide-1 receptor agonists (GLP-1RAs), but with caution due to their potential adverse effects.

NEWER ANTIDIABETIC AGENTS: INCRETIN-BASED THERAPIES

The incretins are intestinal protein hormones that are secreted at low basal level in the fasting state, and stimulate insulin secretion in a glucose-dependent fashion following a meal.[50,51] Two key endogenous incretins have been identified: glucose-dependent insulin-releasing polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). In addition to stimulating insulin release, GLP-1 has the additional benefit of suppressing glucagon secretion.[52,53] Because these endogenous peptides are released in response to nutrient ingestion, stimulation of insulin release occurs in proportion to the actual glucose load ingested, thus, there is negligible risk of excess insulin being released and causing hypoglycemia.[18] This is in contrast to what occurs when secretagogues such as SUs or glinides are administered;[2,14] there is an inherent increased potential for hypoglycemia.[16,54,55] Due to the increased acceptance of the GLP-1RAs and dipeptidyl peptidase 4 (DPP-4) inhibitors in the newest versions of the ADA/EASD and AACE/ACE statements, particularly with GLP-1RAs being prioritized over DPP-4 inhibitors in the AACE/ACE guidelines, incretin-based therapies will be discussed in some detail here. Differences in their modes of action, efficacy, tolerability profiles, and extraglycemic effects are important to understand, as they may influence the choice for individual patients.

GLP-1 Receptor Agonists

As peptides, GLP-1RAs must be administered by injection to avoid degradation in the gut. There are 2 approved GLP-1RAs: exenatide (available as a twice-daily or a once-weekly subcutaneous injection) and liraglutide (available as a once-daily subcutaneous injection). The GLP-1RAs decrease A1c levels by 0.4%-1.6%.[50,56,57] The ADA/EASD position statement lists GLP-1RAs in one of 5 combinations for dual therapy and in 4 combinations for triple therapy.[4] GLP-1RAs are the top prioritized class after metformin for monotherapy, dual therapy, and triple therapy in the AACE algorithm. This prioritization before the DPP-4 inhibitors is likely because of greater glycemic control, the added benefit of weight reduction, and important extraglycemic effects such as reductions in plasma triglycerides, reduced hepatic fat, and decreased systolic and diastolic blood pressure. Prioritization over the glinides and SUs may be because of their safety profile. One development, subsequent to the earlier, 2009 AACE/ACE guidelines,[58] presumably key to their place in the updated algorithm, was the publication of head-to-head trials of GLP-1RAs versus DPP-4 inhibitors, as well as of the 2 GLP-1RAs versus each other. With respect to the former, in a 26-week randomized trial with a 26-week extension study, patients poorly controlled on metformin monotherapy were randomized to either once-daily liraglutide 1.2 mg or 1.8 mg, or once-daily sitagliptin 100 mg. Both the initial trial and extension study demonstrated a greater reduction in A1c using liraglutide (at either dose), compared with sitagliptin. In the initial trial, the reduction in A1c was 1.24% for liraglutide 1.2 mg, and 1.5% for liraglutide 1.8 mg, both $P < .0001$ versus −0.90% for sitagliptin.[59] In the extension trial, the reduction was 1.29% for liraglutide 1.2 mg, and 1.51% for liraglutide 1.8 mg, both $P = .0001$ versus −0.88% for sitagliptin.[60] In a 26-week extension study, patients treated with sitagliptin were randomized to receive liraglutide at either 1.2 or 1.8 mg, whereas liraglutide-treated patients continued with their previously assigned treatment.[61] Those who switched to liraglutide 1.2 mg decreased A1c by a further $0.2 \pm 0.1\%$ ($P = 0.006$), and those who switched to liraglutide 1.8 mg decreased by $0.5 \pm 0.1\%$ ($P = .0001$). Approximately half of patients in both dosing groups reached A1c <7.0%, compared with about 30% before switching in the original trial. Once-weekly exenatide (2 mg) was compared against once-daily sitagliptin (100 mg) in the "Diabetes therapy Utilization: Researching changes in A1c, weight, and other factors Through Intervention with exenatide ONce weekly" (DURATION)-2 trial. In that 26-week randomized, double-dummy, double-blind superiority trial, exenatide reduced A1c to a greater extent than sitagliptin (−1.5% vs −0.9%, respectively, $P < .0001$).[56] Weight loss also was greater for exenatide compared with sitagliptin (−2.3 kg vs −0.8 kg, respectively, $P = .0002$).

The 2 GLP-1RAs (exenatide and liraglutide) also have been compared against each other in the Liraglutide Effect and Action in Diabetes (LEAD)-6[62,63] and DURATION-6[64] trials. In LEAD-6, patients poorly controlled on maximally tolerated doses of metformin or SU (or both) were randomized to either once-daily liraglutide 1.8 mg or twice-daily exenatide 10 μg, for 26 weeks. Liraglutide decreased A1c significantly more than exenatide (−1.12% vs −0.79%, respectively, $P < .0001$). Both drugs were well tolerated and associated with similar weight reduction (−3.24 kg for liraglutide vs −2.87 kg for exenatide).[62] In the 14-week extension study, patients who switched from exenatide to liraglutide were observed to have significant further improvements in A1c (−0.32%, $P < .001$) and weight

(−0.9 kg, $P < .001$).[63] In the DURATION-6 trial, once-daily liraglutide 1.8 mg was compared with once-weekly exenatide 2 mg, for 26 weeks.[64] Reductions in A1c were 1.48% for liraglutide versus 1.28% for exenatide, and more subjects taking liraglutide achieved A1c <7.0% (60.2% vs 52.3%, $P = .008$, for liraglutide and exenatide, respectively). Weight loss also was greater in the liraglutide group (−3.58 kg vs −2.68 kg, for liraglutide vs exenatide, respectively; treatment difference −0.90; 95% confidence interval, −0.40 to −1.41).

Given the promising results from GLP-1RAs, drug development efforts also have focused on modifying formulations to have an extended duration of action, with the goal of decreasing the frequency of dosing, as with the once-weekly formulation of exenatide. Another of these GLP1-RAs is albiglutide. In the Harmony-7 trial, albiglutide (50 mg) given once weekly was compared with liraglutide (1.8 mg) given once daily.[65] Both formulations led to significant decreases ($P < .001$) in A1c from baseline at Week 32 (−0.99% for liraglutide and −0.78% for albiglutide), with a greater decrease in weight in the liraglutide group (−2.19 kg vs −0.64 kg). During the initial titration period, incidence of GI events was higher in the liraglutide group, but declined to a plateau similar to albiglutide from Week 12 to end of study.

The most common side effects of GLP-1RAs are mild and transient nausea and vomiting in some patients; these tend to be less persistent in patients using liraglutide compared with exenatide twice daily,[62,66] and very rarely lead to discontinuation of therapy. Due to the glucose-dependent action of these agents, risk of hypoglycemia is minimal in the absence of co-treatment with SUs or insulin.[66,67]

GLP-1RAs have been linked to a possible increased risk of pancreatitis as a result of a small number of patients developing pancreatitis, either during clinical development or in postmarketing reports. At the time of publication of a 2010 review, there were reports of 8 patients developing acute pancreatitis while taking exenatide during clinical development; 36 cases were identified during postmarketing reports.[68] By comparison, 4 patients taking liraglutide developed acute (n = 3) or chronic (n = 1) pancreatitis during clinical trials.[68] Thirteen cases are now mentioned in the Victoza US label.[69] A direct causal relationship has not been established for GLP-1RAs. Patients with T2D are already at increased risk of acute pancreatitis,[70] and many risk factors and predisposing causes for pancreatitis exist.[70] Nevertheless, it is recommended that patients be monitored closely for risk factors and symptoms of acute pancreatitis.[18] GLP-1RAs should not be used in patients with coexisting pancreatitis; they should be discontinued if pancreatitis is suspected.

Preclinical testing of both liraglutide and exenatide in rodents also has been associated with development of C-cell hyperplasia and tumors in the thyroid gland, resulting in black box warnings on the product label for liraglutide and exenatide once weekly.[69,71] The clinical relevance of this laboratory finding is unclear. For example, human C-cells have barely detectable levels of GLP-1 receptors compared with the high levels on rodent C-cells.[72,73] Also, analysis of calcitonin in subjects during liraglutide phase 3 trials did not reveal a relationship between liraglutide therapy and plasma calcitonin.[74] Overall, the considerable differences between the biology of the GLP-1 system in rodents and people indicate that any risk of development of medullary thyroid cancer in people is very low.[70]

DPP-4 Inhibitors

DPP-4 inhibitors are orally administered low-molecular-weight drugs that inhibit the degradation of endogenous GLP-1 and GIP, thereby indirectly increasing circulating levels of these hormones and stimulating insulin secretion.[18] Four products are currently marketed in the US or Europe, or both: sitagliptin, saxagliptin, linagliptin, and vildagliptin (vildagliptin is not approved in the US). All 4 formulations also are available in combination with metformin, and sitagliptin is available in combination with simvastatin. A fifth product, alogliptin, is currently available only in Japan. DPP-4 inhibitors have been shown to decrease A1c levels by 0.6%-0.8%,[18] and are administered orally once or twice daily with or without food. They mainly affect PPG excursions, but also have been shown to decrease FPG levels and are generally considered to be weight-neutral.[18,50,51] Unlike GLP-1RAs, which can be administered in supraphysiological doses, the efficacy of DPP-4 inhibitors is limited by endogenous GLP-1 secretion.

With respect to adverse effects, the safety profile of DPP-4 inhibitors has been extensively studied, and so far remains good.[67,75-78] The most common adverse effects are upper respiratory infections and headache; however, as with GLP-1RAs, rare cases of pancreatitis and rare allergic reactions have been reported for sitagliptin, saxagliptin, and linagliptin. Dosages for all DPP-4 inhibitors (except linagliptin, which need not be adjusted as it is not cleared by renal mechanisms) must be reduced in patients with renal impairment. Sitagliptin is eliminated mainly via renal excretion, and dose should be reduced by half when creatinine clearance is ≥30−<50 mL/min, and by half again when creatinine clearance is <30 mL/min.[79,80] Saxagliptin also is eliminated via the liver, but it is recommended that the dose be reduced by half when creatinine clearance is <50 mL/min.[79,81] A recent long-term (52 weeks) study suggested that vildagliptin was well tolerated in patients with mild to moderate renal impairment,[82] although it has been suggested that dose should be reduced by half with any degree of renal impairment.[79]

The ADA/EASD position statement now lists DPP-4 inhibitors as one of 5 options for dual therapy and includes them in 4 different options for triple therapy combination, but without indicating any preference.[4] The AACE/ACE algorithm prioritizes incretin-based therapies over older agents such as SUs and glinides.[2] In addition, DPP-4 inhibitors are identified in the AACE/ACE guidelines as an alternative to metformin for monotherapy for those

patients who cannot tolerate the former. With respect to combination therapy, DPP-4 inhibitors are prioritized after the GLP-1 receptor agonists, but before older therapies such as SUs or glinides, due to a lower risk of hypoglycemia compared with those agents.

Other Agents

A variety of other agents are available for treating diabetes, although for most, their (comparatively) lower efficacy and side effects limit widespread use. These include the alpha-glucosidase inhibitors (AGIs): pramlintide, colesevelam, and bromocriptine. These agents are not directly included in the ADA/EASD algorithm, which only lists drugs that are commonly used in the US or Europe, but several are mentioned briefly in the accompanying text. These include AGIs, which delay absorption of carbohydrates from the gut, and colesevelam, a bile acid sequestrant whose primary advantage is lowering of low-density lipoprotein cholesterol. Both are associated with GI side effects. The AACE/ACE algorithm includes AGI therapies (as well as sodium/glucose cotransporter 2 inhibitors) as alternatives in monotherapy, dual therapy, and triple therapy.

PRACTICAL TIPS AND CLINICAL EXPERIENCE

Treating patients with diabetes is one of the most challenging and important activities a physician (PCP or specialist) can undertake. The ability to individualize therapy by patient and medication characteristics comes from experience and knowledge of pertinent clinical studies. Both of these guidelines help clinicians of all levels of expertise approach therapy choices more rationally.

The most profound recent change in diabetes therapy has been the introduction of incretin therapies. The different classes of incretin therapies (GLP1-RAs and DPP-4 inhibitors) minimize 2 important adverse effects seen with many other therapies: hypoglycemia and weight gain. In practice, adding injectable therapy is easier and more preferred than it had formerly been, as has been shown in at least one clinical trial with GLP-1RAs.[60] It also is important to correct any misconception that DPP-4 inhibitors are simply orally administered GLP1-RAs, when in fact, GLP1-RAs have a very different mechanism of action, are not limited in their efficacy by levels of endogenous GLP-1, and have important extraglycemic effects. Despite these benefits, the cost of newer therapies is a practical barrier for many patients.

A key to successful therapy for T2D is the insight that this condition is progressive and that the need for additional agents over time is normative. Presenting this to patients with diabetes can both reduce their guilt (ie, from recurrent hyperglycemia) and make them more open to initiating additional therapies. Although not specifically addressed in either statement, the availability of combined medications (eg, metformin + sitagliptin in a single tablet) can make therapy easier and less expensive.

CONCLUSIONS

The new AACE/ACE algorithm, in conjunction with the recent ADA/EASD position statement, both highlight the importance of individualizing therapy based on patient preferences, schedules, concomitant illness, hypoglycemic awareness, and safety profile of glucose-lowering agents. Intensifying treatment when insulin is not (yet) appropriate may seem complex because of the wide variety of treatment options, now including classes of drugs such as incretin-based therapies, and different approaches advocated by AACE/ACE and ADA/EASD. Nevertheless, across both statements, some drug classes seem more prominent, and it is clear why this is the case, looking at their profile of benefits to risk. There is unity across guidelines about the role and benefits of metformin as first-line pharmacological treatment, probability of good efficacy, low risk of hypoglycemia, modest weight loss, and overall long-term data. Despite risk of hypoglycemia and weight gain, SUs remain a common choice in both statements, although the 2 different classes of incretin-based therapies have begun to gain prominence due to their efficacy, low risk of hypoglycemia weight benefits, and, for GLP-1RAs, other important extraglycemic effects. These agents have increased the range of options available for early intensification of treatment of T2D. In combination with more established therapies, there are more opportunities than ever to accommodate patient preferences while improving glycemic control and harnessing extraglycemic benefits of a second (or third) agent.

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