

A comparison of US treatment guidelines for Type 2 diabetes mellitus: applications to the newly diagnosed patient



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Practice points

- Diagnostic criteria for diabetes include: fasting plasma glucose concentration of 126 mg/dl or greater, plasma glucose concentration of at least 200 mg/dl after 2 h of ingesting a 75-g oral glucose load, or symptoms of hyperglycemia and a random glucose concentration of at least 200 mg/dl, or hemoglobin A_{1c} (A1c) of 6.5% or higher. These criteria are consistent for both American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) guidelines.
- A1c goals for each guideline reviewed are as follows: the ADA <7% (but should be individualized), AACE <6.5% and American College of Physicians (ACP) <7%.
- Metformin remains a mainstay of initial treatment for Type 2 diabetes mellitus (T2DM) for all widely accepted recommendations, and provides safety and tolerability to the patient.
- ADA/European Association for the Study of Diabetes (EASD) supports a 'patient-centered' approach to therapeutic interventions and recommends all patients receive diabetes education as part of their therapeutic plan.
- In addition to blood glucose control, the ADA recommends focusing attention on cardiovascular disease (CVD) risk reduction: BP <140/80 mmHg (<130/80 mmHg for younger individuals with undue treatment burden), LDL goal <100 mg/dl (<70 mg/dl for individuals with CVD), aspirin therapy (10-year risk of CVD >10%), screening and treatment of microvascular disease (nephropathy, neuropathy and retinopathy), smoking cessation, lifestyle modifications, and updated immunizations (hepatitis B, pneumococcal and influenza).
- ADA/EASD recommends medical therapy options be chosen based on patient-specific factors including cost, adverse effect profile, administration, injection preference, blood glucose target (fasting plasma glucose or postprandial glucose) and efficacy. Metformin is considered first line due to its low cost, efficacy and lack of hypoglycemia.
- AACE treatment algorithm centers treatment decisions based on entry A1c, categorizing patients based on severity of disease at diagnosis and provides drug options for each category in a suggested hierarchy of use.
- AACE recommendations indicate that therapy should be escalated if the patient is not meeting glycemic targets within 3 months of drug initiation.
- AACE provides specific insulin-dosing recommendations for initiation and titration based on disease severity and type of insulin regimen started.
- ACP recommends oral pharmacologic therapy when lifestyle modifications, including diet, exercise and weight loss, have failed.
- ACP recommends a second agent to metformin when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia.

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SUMMARY: As diabetes is a common disease state that is often underdiagnosed and undermanaged, this article aims to provide a practical approach to understanding the details of widely accepted recommendations for diabetes in the USA. Three guidelines are reviewed highlighting screening, diagnosis and treatment algorithms, with a focus on practical application to a patient scenario. The guidelines reviewed are published by the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD), the American Association of Clinical Endocrinologists (AACE) and the American College of Physicians (ACP). By applying to the scenario of a newly diagnosed diabetic patient, this article aspires to highlight treatment differences between each expert recommendation, providing insight into evaluations made to determine the ideal initial treatment regimen.

KEYWORDS

- American Diabetes Association/European Association for the Study of Diabetes • American Association of Clinical Endocrinologists • American College of Physicians
- hemoglobin A_{1c} • glucose
- metformin • Type 2 diabetes mellitus

Diabetes mellitus is one of the most common disease states affecting the general population at an increasingly alarming rate. The WHO estimates that 347 million people worldwide have diabetes and projects that diabetes will be the seventh leading cause of death in 2030. Additionally, diabetes increases the risk of heart disease and stroke, and is recognized as the leading cause of kidney failure as well as a noted cause of blindness [9]. The American Diabetes Association (ADA) has estimated that for the USA in 2012, diabetes has resulted in US\$176 billion in direct medical costs and US\$69 billion in indirect medical costs, such as disability, work loss and premature mortality [10]. For these reasons there is a very large focus on accurate and timely diagnosis, as well as appropriate and aggressive treatments to reduce disease burden on the patients and health systems in general.

In the USA there are several widely accepted guiding documents to assist the practitioner in obtaining glycemic control focusing on hyperglycemia management, which can cause some confusion when deciding the optimal modality for the patient. This goal of this review is to briefly outline diagnostic criteria and differences in treatment pathways of Type 2 diabetes mellitus (T2DM) for three USA guidelines: the ADA, the American Academy of Clinical Endocrinologists (AACE) and the American College of Physicians (ACP). This article will focus on hyperglycemia management rather than dietary education and specific recommendations regarding microvascular complications.

Review of guidelines

• **American Diabetes Association**

The ADA annually publishes their Standards of Medical Care in Diabetes. The 2014 version upheld their diagnostic criteria for T2DM: A1c $\geq 6.5\%$, fasting plasma glucose (FPG) ≥ 126 mg/dl, 2-h plasma glucose ≥ 200 mg/dl after an oral glucose tolerance test (OGTT)

using a glucose load containing 75-g anhydrous glucose, or random plasma glucose ≥ 200 mg/dl with classic symptoms of hyperglycemia [1]. A diagnosis of diabetes in the absence of hyperglycemic symptoms requires a repeat failing test.

Testing of asymptomatic patients for diabetes is recommended for those who are overweight or obese (BMI ≥ 25 kg/m²) and have at least one risk factor for diabetes: physical inactivity, first-degree relative with diabetes, high-risk race/ethnicity, women who delivered a baby weighing >9 lbs or were diagnosed with gestational diabetes mellitus (GDM), hypertension or on current anti-hypertensive therapy, high-density lipoprotein (HDL)-cholesterol <35 mg/dl or triglycerides (TGs) >250 mg/dl, women with polycystic ovary syndrome, A1c $\geq 5.7\%$, impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) on previous test, conditions associated with insulin resistance, or history of cardiovascular disease (CVD) [1]. For those individuals who are lower risk, testing for diabetes should begin at 45 years of age. Screening and diagnostic criteria for diabetes entail the same tests. If patients are considered to have prediabetes – A1c 5.7–6.4%, FPG 100–125 mg/dl, or 2-h plasma glucose of 140–199 mg/dl – screening for diabetes should be performed yearly. All others may be tested every 3 years due to the unlikelihood that individuals would develop significant complications of diabetes within 3 years, if the previous test yielded a false negative.

Once the diagnosis of diabetes is made, the ADA recommends the identification of patient-specific goals for diabetes management. Depending on the patient's duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular disease complications, history of hypoglycemia unawareness, and individual preferences, the ADA suggests variations of diabetes goals to best meet the individual's needs. These goals can vary from an A1c $<6.5\%$ for newly diagnosed

patients without CVD to <8% for patients with long-standing diabetes, elderly and at high risk for hypoglycemia. For individuals who are not identified as needing a higher A1c target, the ADA aims for an A1c <7.0%, preprandial glucose of 70–130 mg/dl and postprandial glucose <180 mg/dl [1].

The intent of treating diabetes is to prevent the undesirable microvascular complications of retinopathy, neuropathy and nephropathy. Patients with T2DM should be screened for diabetic retinopathy with a dilated and comprehensive eye examination shortly after diagnosis and annually thereafter [1]. In the event of one or two normal eye exams, patients may have less frequent eye exams (every 2–3 years). Patients with T2DM should also be screened for diabetic neuropathy following diabetes diagnosis and at least annually thereafter [1]. Simple clinical tests can be used in the diagnosis of diabetic neuropathy: pinprick sensation using a tuning fork, 10-g monofilament pressure sensation and ankle reflexes. The ADA suggests combining tests to increase sensitivity in detection [1]. To test for diabetic nephropathy, patients should also have a urinary albumin excretion measurement and serum creatinine measured annually. Previously the terms ‘microalbuminuria’ (30–299 mg/day) and ‘macroalbuminuria’ (≥300 mg/day) were used but are now referred to as ‘increased urinary albumin excretion’ (≥30 mcg/mg of creatinine). Treatment still remains as either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) [1].

Patients with diabetes are at risk for cardiovascular disease and the condition itself represents a 20% risk equivalent. To reduce the risk for CVD, the ADA recommends that patients with hypertension and diabetes be treated to a systolic blood pressure (SBP) <140 mmHg [1]. However, in younger individuals with undue treatment burden, lower SBP targets of <130 mmHg may be appropriate [1]. Diastolic blood pressure (DBP) should be targeted to <80 mmHg regardless of SBP goal determined [1]. The ADA encourages lifestyle modifications and pharmacological agents such as ACEIs/ARBs in hypertension management. The ADA also recommends that if antihypertensive therapy is needed, at least one medication should be dosed at bedtime [1].

Controlling lipid parameters is likewise essential in diabetes management. A fasting lipid panel obtained annually is recommended

in most adult patients with diabetes. The ADA recommends a low-density lipoprotein (LDL)-cholesterol goal <100 mg/dl for individuals without CVD, and in those with a history of CVD, an LDL goal <70 mg/dl using a high-dose statin is advised [1]. The ADA also recommends an HDL goal >50 mg/dl for women and >40 mg/dl for men, and TGs <150 mg/dl. Statin therapy is recommended regardless of baseline lipid panels in patients with a history of CVD or without CVD but who are >40 years of age and have at least one additional CVD risk factor – family history of CVD, hypertension, smoking, dyslipidemia or albuminuria [1].

Furthermore, aspirin therapy (75–162 mg/day) is to be considered for primary prevention in patients with 10-year risk of CVD >10%. The ADA discourages the use of aspirin for CVD prevention in patients with <5% CV risk, and for patients with CV risk between 5 and 10% clinical judgment is recommended [1]. In patients with history of CVD, aspirin therapy should be used for secondary prevention and clopidogrel used when a patient has an allergy to aspirin.

Additionally, for patients with diabetes ≥6 months of age, the ADA recommends annual influenza vaccination [1]. Moreover, the ADA recommends administration of pneumococcal vaccine for patients ≥2 years of age with diabetes, as well as a one-time revaccination for patients >64 years of age who were previously immunized when they were <65 years of age if the vaccine was administered >5 years ago [1]. The ADA further recommends consideration for repeat pneumococcal vaccination in patients with nephrotic syndrome, chronic renal disease and immunocompromised states [1]. The ADA also recommends hepatitis B vaccination in unvaccinated adults aged 19–59 years and consideration of revaccination in patients with diabetes ≥60 years of age [1].

• American Association of Clinical Endocrinology

The AACE consensus statement and treatment algorithm for the management of hyperglycemia were most recently published in mid-2013 [2]. These updated guidelines do not specifically address diagnostic criteria for diabetes; however, an earlier publication, the AACE Diabetes Care Plan Guidelines [3], delineate the diagnostic criteria and subsequent management of diabetes mellitus. According to the AACE, and similar to the ADA Standards of Care, diagnosis of diabetes

can be made with the following: fasting plasma glucose concentration 126 mg/dl or greater (after a minimum of 8 h of fasting), or plasma glucose concentration of at least 200 mg/dl after 2 h of ingesting a 75-g oral glucose load after a fast of at least 8 h, or symptoms of uncontrolled hyperglycemia (e.g., polydipsia, polyphagia, polyuria) and a random glucose concentration of at least 200 mg/dl, or A1c of 6.5% or higher. In the absence of hyperglycemia symptoms listed above, the same test should be repeated on a different day to confirm diagnosis. Additionally, these recommendations address identification of pre-diabetes by the presence of impaired glucose tolerance (glucose value 140–199 mg/dl 2 h after a 75-g glucose load) and/or impaired fasting glucose (value of 100–125 mg/dl) and recognize that A1c levels between 5.5 and 6.4% should signal further testing and not be utilized to diagnose pre-diabetes.

Once diagnosis of diabetes is made, the AACE recommends targeting an A1c goal of <6.5%, fasting plasma glucose <110 mg/dl, and a 2-h postprandial glucose concentration of <140 mg/dl for healthy patients without significant comorbidities and at low risk of hypoglycemia [3]. However, per the most recent treatment algorithm, the AACE recognizes the need for individualized goals and recommends an A1c goal of above 6.5% for individuals with concurrent diseases or at high risk for hypoglycemia [2]. Additionally, the Care Plan guidelines recommend the following goals for prevention of cardiovascular disease risk reduction: blood pressure <130/80 mmHg, LDL \leq 70 mg/dl (highest risk patients) or \leq 100 mg/dl, non-HDL lipoprotein cholesterol <100 (highest risk) or <130 mg/dl, apolipoprotein B <80 mg/dl (highest risk) or <90 mg/dl, HDL-cholesterol >40 mg/dl in men and >50 mg/dl in women, and triglycerides (TG) <150 mg/dl. The AACE defines ‘highest risk patients’ as diabetic patients with the presence of existing/previous cardiovascular disease. Similar to the ADA guidelines for anticoagulant therapy with aspirin, the AACE recommends all patients receive anticoagulation therapy for secondary cardiovascular disease prevention but only patients of highest risk (10-year risk >10%) receive aspirin for primary prevention [3].

Further screening in the newly diagnosed T2DM patient includes screening for diabetic nephropathy and retinopathy at the time of diagnosis and annually thereafter, unless microvascular problems detected. Screening for nephropathy include assessment of serum creatinine to

estimate glomerular filtration rate (GFR) and urine albumin excretion. Screening for retinopathy includes an annual dilated eye examination. While there are treatments available for both of the aforementioned complications, optimal glucose, blood pressure and lipid control are recommended for progression of these complications [3].

• **American College of Physicians**

The American College of Physicians (ACP) developed practice guidelines in 2012 for the oral pharmacological treatment of T2DM by comparing the safety and efficacy of these available treatment options [4]. The ACP guidelines are based upon a systemic review by Bennett and colleagues [5] and an evidence report sponsored by the Agency for Healthcare Research and Quality (AHRQ) [4]. This guidance document is quite different from the ADA and AACE documents as it does not provide recommendations for initial diagnosis, non-medication management and long-term screening for diabetic complications. The ACP statement, congruent with the ADA guidelines, does recognize that an A1c goal of <7% should be sufficient for most patients [4].

The ACP guidelines aim to answer four key questions:

- For adult patients with T2DM, what is the comparative effectiveness of these treatment options for the intermediate outcomes of glycemic control (A1c), weight or lipids?
- For adult patients with T2DM, what is the comparative effectiveness of these treatment options for the long-term clinical outcomes of all-cause mortality, cardiovascular mortality, cardiovascular and cerebrovascular morbidity, retinopathy, nephropathy, and neuropathy?
- For adult patients with T2DM, what is the comparative safety of these treatment options for the following adverse events and side effects: hypoglycemia, liver injury, congestive heart failure, severe lactic acidosis, cancer, severe allergic reactions, hip and non-hip fractures, pancreatitis, cholecystitis, macular edema or decreased vision, and gastrointestinal side effects?
- For patients 65 years and older, do these treatment options differ in safety and efficacy in terms of mortality, hypoglycemia, and cardiovascular and cerebrovascular outcomes? [4].

Based upon the review of the evidence, the four questions were summarized as follows:

Question 1: medications reduced HbA_{1c} levels to similar degrees. Metformin was more effective when used as monotherapy and in combination therapy for reducing A1c levels, bodyweight and plasma lipid levels.

Question 2: due to low quality or insufficient evidence, no conclusion was drawn in the comparative effectiveness of the oral medications for long-term clinical outcomes.

Question 3: evidence showed that the risk of hypoglycemia with sulfonylureas exceeds metformin or thiazolidinediones. Metformin is associated with more gastrointestinal adverse effects. Thiazolidinediones are associated with an increased risk of heart failure.

Question 4: the current evidence was not sufficient to show a difference in safety or efficacy among treatment options for patients aged 65 years and older [4].

Differences in guidelines

When comparing the three guidelines, it is evident that the ADA/European Association for the Study of Diabetes (EASD) and AACE give more guidance to therapy recommendations including add-on therapy and insulin usage than ACP provides. The ACP only provides recommendations on A1c goal and initial monotherapy. ADA/EASD and ACP both recommend an A1c goal of <7%. However, the AACE recommends a more stringent A1c goal of <6.5%. All three guidelines do agree that metformin is the initial agent of choice for monotherapy. AACE provides a broader selection of medications for dual therapy and bases the treatment selection on hypo/hyperglycemia and weight gain. Although the ADA/EASD guideline also evaluates adverse effects, it considers cost, efficacy and glucose readings for dual treatment recommendations. Both ADA/EASD and AACE recommend a third agent be added if goal A1c is not reached. The ADA/EASD and AACE do differ slightly on when to initially start insulin. The ADA/EASD suggests insulin be started in patients with an A1c greater than 10–12%. However, AACE recommends initiating insulin in symptomatic patients with an A1c greater than 9%. Please also refer to **Table 1** for a summary of these similarities and differences.

As one can imagine, each treatment guideline contains inherent differences in their proposed medication algorithms. Depending on the

practitioner involved in the management of the individual patient, there is certainly some room for discrepancy of treatment based on algorithm recommendations. Taken into account is provider experience with specific medical therapy options, personal preference and individual patient presentation. Below is a detail of each of the three guidelines recommendations. Please also refer to **Table 1** for a summary of these differences.

• American Diabetes Association

Upon diagnosis of diabetes, the ADA strongly encourages lifestyle modifications be initiated. This includes not only physical activity (moderate intensity of 150 min/week) and moderate weight loss of 7% bodyweight, but also medical nutrition therapy (MNT) including but not limited to reduction in calories and dietary fat intake. In 2012, the ADA and EASD published a position statement that provides a patient-centered approach to therapeutic interventions, which is referred to within the Standards of Care [6]. Patient-centered care is defined as an approach to “providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions” [7]. The ADA/EASD recommends each patient receive diabetes education regarding diet and exercise, as this is a cornerstone of therapy. When determining the intensity of diabetes treatment, patient attitude and availability of resources/support are taken into consideration along with the ADA’s patient-specific factors.

This position statement suggests that patients with an A1c <7.5% incorporate lifestyle modifications for 3–6 months before considering pharmacotherapy. Those with moderate glycaemic control would need pharmacotherapy (usually metformin) at diagnosis, along with lifestyle modifications. In the event lifestyle changes create a substantial improvement in glycaemic control, consideration may be given to customizing or discontinuing the anti-hyperglycaemic agent. Metformin remains the initial therapeutic agent of choice. Its low cost, efficacy and lack of hypoglycemia make it a prime choice for most individuals. The ADA/EASD do not promote a particular second-line agent; however, they recommend taking into consideration efficacy, adverse effect profile, cost, injection preference and glucose target (FPG or PPG). Each of these factors must also keep in mind the patient’s preferences. If

Table 1. Guideline chart comparison.

Recommendations	A1c goal	Initial monotherapy	Dual therapy	Treatment selection based on:	Triple therapy (add to metformin)	When to initiate insulin
ADA/EASD	<7.0% (individualized based on patient factors)	Metformin	<ul style="list-style-type: none"> • Other oral med: <ul style="list-style-type: none"> – SU – TZD – DPP-4i • GLP1-RA • Basal insulin 	<ul style="list-style-type: none"> • Efficacy • AE profile • Cost • Glucose issue (fasting or prandial) 	<ul style="list-style-type: none"> • Add any other agent from dual therapy class • Strongly consider insulin if A1c >8.5% 	<ul style="list-style-type: none"> • At diagnosis if A1c >10–12% • Possible second line option (basal only)
AACE	<6.5% (individualized based on patient factors)	Metformin	<ul style="list-style-type: none"> • GLP1-RA • DPP-4i • TZD • SGLT-2 • Basal insulin • Colesevelam • Bromocriptine • AG-I • Meglitinide/SU 	<ul style="list-style-type: none"> • Degree of hyperglycemia • Risk of hypoglycemia • Potential for weight gain 	<ul style="list-style-type: none"> • Add another agent not previously selected 	<ul style="list-style-type: none"> • Symptomatic patients with A1c >9% (insulin with or without other agents) • Possible second line option (basal only)
ACP	<7%	Metformin	No recommendations	No recommendations	No recommendations	No recommendations

AACE: American Association of Clinical Endocrinologists; ACP: American College of Physicians; ADA: American Diabetes Association; AE: Adverse effect; AG-I: Alpha glucosidase inhibitor; A1c: Hemoglobin A_{1c}; DPP-4i: Dipeptidyl-peptidase inhibitor; EASD: European Association for the Study of Diabetes; GLP1-RA: GLP-1 receptor agonist; SU: Sulfonylurea; TZD: Thiazolidinedione.

after 3 months the patient is not at goal A1c, a two-drug combination including initial therapy of metformin plus sulfonylurea (SU; meglitinides may be used in place of SU), thiazolidinedione (TZD), glucagon-like peptide 1 receptor agonist (GLP-1RA), dipeptidyl-peptidase IV inhibitor (DPP-IV inhibitors) or basal insulin is recommended [6]. If after another 3-month trial a patient is not at A1c goal, then a three-drug combination therapy is required, including the aforementioned therapies. The ADA/EASD recommends initiating a two-drug regimen in patients initially presenting with A1c ≥9% and starting basal insulin in individuals who present with A1c ≥10–12% [6]. When initiating insulin, 0.1–0.2 units/kg is the usual starting dose, and higher doses of 0.3–0.4 units/kg are used when a patient presents with severe hyperglycemia. If a patient fails to obtain goal A1c on combination therapy, which includes basal insulin, then a multiple-dose insulin regimen in combination with one or two non-insulin agents would be instituted [6].

In general, the choice of diabetes medication regimen is based on patient-specific factors including cost, adverse effect profile, administration and efficacy. Alpha glucosidase inhibitors, pramlintide, dopamine antagonists and colesevelam may be used when available; however, limited efficacy and adverse effects create a barrier to their clinical use. Similar to AACE guidelines, an A1c <6.5–7% may be considered for patients with longer life expectancy.

• American Association of Clinical Endocrinology

As previously mentioned, the AACE consensus statement and treatment algorithm [2] were updated in mid-2013 from the 2009 consensus statement. The basic premise of the recently published AACE treatment algorithm centers treatment decisions based on entry A1c, categorizing patients based on severity of disease at diagnosis, either <7.5%, ≥7.5% or >9.0%, and provides drug options for each category in a suggested hierarchy of use. AACE strongly suggests that pharmacotherapy be selected based on patient specifics including: glycemic goals, patient limitations and side effects such as weight gain, risk of hypoglycemia and cardiovascular risk. For all categories it is recommended to escalate therapy (e.g., monotherapy to dual therapy) if the patient is not meeting glycemic targets within 3 months of drug initiation [2].

To expand further on the treatment algorithm, for individuals with A1c <7.5% at diagnosis monotherapy is likely sufficient and should be considered with metformin as most patients can achieve glycemic targets with lifestyle modifications and metformin. However, AACE recommends consideration of other drug classes as well, based on tolerability, such as: GLP-1 RAs, DPP-IV inhibitors or alpha-glucosidase inhibitors (AGIs), as they have fewer incidences of adverse events with possible benefit compared with other antidiabetic agents. Other drugs

such as sodium glucose transporter-2 (SGLT-2) inhibitors, TZDs, sulfonylureas or meglitinides can be considered as well, but may carry greater risk of adverse effects compared with the higher recommended agents. If A1c is not below 6.5% after 3 months of monotherapy, a second agent is recommended to be added in a complimentary fashion.

For the patients with an initial A1c $\geq 7.5\%$, the AACE algorithm recommends starting with dual therapy to include metformin plus a second agent in the following hierarchical order: GLP-1 RAs, DPP-IV inhibitors, TZDs, SGLT-2 inhibitors, basal insulin, colesevelam, bromocriptine, AGIs, and sulfonylureas or meglitinides. If glycemic control is not achieved in 3 months, then a third-line agent should be added.

In the case of a patient presenting with an A1c $>9.0\%$ at baseline, the clinician must consider the presence or absence of symptoms of hyperglycemia to determine treatment options. If no symptoms of hyperglycemia are present, then the clinician may consider either dual or triple therapy as previously outlined; however, if symptoms exist at baseline, the AACE recommends insulin with or without other agents. It should be noted in this scenario (baseline A1c $>9.0\%$ with symptoms present), the type of insulin (basal, bolus, mixed) is not distinguished. For each patient scenario, the AACE is consistent with their recommendation for treatment escalation after 3 months if A1c goals are not met [2].

A new addition to the AACE recommendations, which has not been provided in previous editions, is specific guidance on initiation and intensification of insulin therapy, which is broken down into two separate pathways. With respect to starting basal insulin, the AACE provides different dose recommendations based on A1c severity. For patients with an A1c $<8\%$, a total daily dose of 0.1–0.2 units/kg is recommended, while for those with A1c $>8\%$, a dose of 0.2–0.3 units/kg/day is recommended. For both dosing strategies, insulin titration is recommended every 2–3 days based either on fasting blood glucoses (i.e., if fasting glucose is between 140–180 mg/dl, add 2 units) or a fixed regimen (i.e., increase total daily dose by 2 units) to target glycemic control, as the initial dose recommendation is seldom sufficient to achieve control. The AACE recommends dose adjustments occur at regular and short intervals to achieve glucose targets. Subsequent

escalation to more intensive interventions is recommended if glycemic control is not obtained. No specific time frame is given in this case compared with the oral regimen algorithms, although one must suspect it to be similar. For patients already on basal insulin therapy, the AACE also provides direction for intensification of existing basal insulin therapy to include either addition of an in cretin mimetic, such as a GLP-1 RA or a DPP-4 inhibitor, or the addition of prandial insulin to target total daily dose of 0.3–0.5 units/kg. The algorithm recommends a 1:1 ratio of basal to prandial insulin, placing preference on insulin analogs rather than NPH, regular or pre-mixed insulin preparations, which could either increase risk of hypoglycemia or reduce flexibility of specific dose adjustments based on glycemic patterns. Dose-adjustment recommendations are also provided for the basal plus prandial insulin regimens but provide more specific suggestions for cases of hyper- or hypo-glycemia (i.e., fasting AM hypoglycemia or night-time hypoglycemia) [2].

The recently published AACE guidelines provide a useful tool in their treatment algorithms with respect to initial drug selection as well as escalation of therapy to include insulin initiation and dose adjustments. Compared to the previous publication in 2009, the 2013 consensus statement is clearer in treatment recommendations, providing a hierarchy of medications for each treatment strategy. Unique to the AACE consensus statements, although not specifically addressed in this manuscript, are treatment recommendations for prediabetes and obesity, which are designed to focus on the prevention of diabetes as well as, in the case of the obesity recommendations, an adjunct to the treatment of the obese diabetic patient. Although the AACE is not as widely followed by primary care providers in the USA, it has the potential to be highly instrumental in delivering more appropriate and aggressive early treatment of T2DM, provided wide dissemination and education to non-endocrinologists is accomplished

• American College of Physicians

Compared with the ADA and AACE guidelines, the ACP does not provide very specific treatment pathways, leaving much to the decision of the practitioner taking into account clinical presentation of the patient.

Based upon the review of evidence, the ACP developed three recommendations for oral agents in the treatment of T2DM:

Recommendation 1: the ACP recommends that clinicians add oral pharmacologic therapy in patients diagnosed with T2DM when lifestyle modifications, including diet, exercise and weight loss have failed to adequately improve hyperglycemia.

Recommendation 2: the ACP recommends that clinicians prescribe monotherapy with metformin for initial pharmacologic therapy to treat most patients with T2DM.

Recommendation 3: the ACP recommends that clinicians add a second agent to metformin to treat patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia [4].

Beyond these three recommendations, there is little to guide the practitioner in the way of intensification of therapy when the patient is not meeting glycemic goals. Additionally, the ACP recommendations do not provide a timeline of treatment intensification for the patient failing to meet goals. The ACP recommendations do provide appendices regarding price, adverse events and evidence for long-term outcomes for each oral anti hyperglycemic agent. However, the lack of specific recommendations limits the clinical utility of these guidelines.

Patient case

The application of each individual consensus statement, ADA, AACE and ACP, to a patient case will highlight the potentially different treatment modality options laid forth by each guideline. The patient is as follows:

The patient is a 42-year-old Hispanic male presenting to his primary care physician's office for a routine annual examination as required by his employer. He has been a long-distance commercial truck driver for the past 15 years, and prior to that he worked as a truck driver for a local agency. He currently has no specific complaints to his physician; however, he has noted increased thirst and urination for the past 3–4 weeks, which he attributed to recent long hauls requiring significant caffeine intake (coffee and sodas). His past medical history is significant only for hypertension (diagnosed in early 2013) and is currently taking hydrochlorothiazide 25 mg once daily. He reports only occasional alcohol use but does not smoke or use tobacco products.

- PMH: hypertension (2013)
- Medications:
 - Hydrochlorothiazide 25 mg, 1 tablet once daily
- Vitals: weight 228 lbs; height 5'9"; BP 148/81 mmHg; heart rate: 73; BMI: 33.7 kg/m²
- Family history: mother age 64 years (T2DM × 15 years; HTN × 3 years); father age 68 years (MI age: 44 years; HLD × 28 years)
- Typical diet:
 - Breakfast: skips other than coffee (4–8 cups during the day, adds sugar)
 - Lunch: drive through food (generally burgers and fries), coke
 - Dinner: diner food if able (patty melts, fries), sweet tea
- Labs (fasting):
 - Na: 144 mEq/l
 - K: 3.7 mEq/l
 - Cl: 102 mmol/l
 - CO₂: 23 mmol/l
 - BUN: 18 mg/dl
 - SCr: 1.0 mg/dl
 - Glu: 213 mg/dl
 - AST/ALT: 32/34 IU/l
 - Lipids: TC 215 mg/dl; TG 243 mg/dl; HDL 31 mg/dl; LDL 124 mg/dl
 - HbA1c: 8.5%
 - UA: unremarkable

• American Diabetes Association

According to the ADA's diagnostic criteria, this patient has diabetes: FPG ≥126 mg/dl, classic symptoms of hyperglycemia (polyuria, polydipsia), and A1c ≥6.5%. Now that a diagnosis has been made, the patient should receive diabetes education and immediately be incorporated into his diabetes management team. He and his provider should address possible lifestyle modifications that would enhance his therapeutic treatment plan. Considering that the patient is younger in age, lacks CVD history, and is at moderate risk for hypoglycemia, an A1C goal <7% would be appropriate. Since his A1c is of

moderate control, between 7.5 and 9%, the ADA recommends metformin therapy be initiated along with lifestyle changes, assuming no contraindications (for this patient, there are none). When addressing the option of metformin initiation, the patient and provider will assess the medication's cost (low cost), efficacy (1–2% A1c lowering), side effects (gastrointestinal discomfort, diarrhea) and administration schedule (twice to thrice daily, oral medication). If the patient agrees to metformin therapy and lifestyle modifications of 150 min per week of moderate-intensity exercise and decrease in saturated fats, as well as aiming for 7% weight loss, the patient will have 3 months to optimize his diabetes regimen. To improve likelihood of success with lifestyle modifications, the patient being the center of his care, will need to actively participate in how he can implement these changes. For example, the patient agrees to walk for 10 min every time he stops to get gas for his truck, and he agrees to choose healthier options from fast food restaurants.

Not only will glucose control be crucial to reduce risk for microvascular complications, but he will need a statin medication to better control cholesterol (goal LDL <100 mg/dl, HDL >40 mg/dl, and TGs <150 mg/dl) as he is greater than 40 years of age with additional risk factors. The ADA also recommends a SBP <140 mmHg, with consideration of <130 mmHg in younger patients. Considering this patient, a SBP goal <130 mmHg may be an option once SBP <140 mmHg and DBP <80 mmHg is achieved, and the patient is assessed for anti-hypertensive tolerability and treatment burden. For this patient, who is already on a thiazide diuretic, an ACE inhibitor or ARB would be recommended for nephroprotection. Considering the cost and similar efficacy of these two classes, ACEIs would likely be the preferred treatment class. The ADA recommends aspirin therapy for patients with a risk score >10% and consideration in those with a score of 5–10%. For this patient, whose Framingham risk score is 5%, aspirin therapy for primary prevention is not warranted at this time [8].

Once the patient is equipped with diabetes education, metformin, ACE inhibitor and statin therapy, he would have 3 months to optimize this regimen. In the meantime, he would need a dilated and comprehensive eye exam from an ophthalmologist or optometrist and evaluation for diabetic neuropathy. Especially considering

this patient's truck driving career, assessment of any signs or symptoms of neuropathy would be crucial so that treatment options may be identified if needed. The patient would also need a urinary albumin excretion measurement and serum creatinine test either at diagnosis or follow-up appointment to assess for nephropathy. During follow-up diabetes appointments, his self-monitored blood glucose (SMBG) values will be assessed to determine if an additional anti-diabetes agent is needed. Taking into account his job, he would not be a candidate for insulin therapy. However, any of the second-tier medications could be considered for add-on therapy (SU, TZD, DPP-IV inhibitor or GLP-1RA). Each of these agents varies in cost, adverse effect profile, efficacy and administration schedule. Based on the ADA/EASD 'patient-centered care' approach, each of these options' pros and cons would be discussed with the patient for the next best therapeutic choice. Continued monitoring of blood pressure and lipids would be needed to ensure these goals are met. For a more detailed assessment of which additional anti-diabetes agent to use for two-drug combination, assessment of the patient's SMBG values would provide a stronger picture as to when his blood glucose values are elevated (postprandial or fasting) and provide an additional factor to take into consideration for choosing therapy.

• American Association of Clinical Endocrinologists

Similar to the diagnostic criteria laid forth by the ADA guidelines, this patient meets diagnostic criteria for T2DM based on the AACE guidelines as well. Based on his reference A1c, the AACE treatment algorithm recommends initiation with dual therapy to effectively and efficiently treat hyperglycemia. As the patient is overweight and has stable renal function, this patient would likely benefit from metformin as the backbone of his antidiabetic regimen, and one could expect a 1–2% A1c reduction once doses are maximized. Per the algorithm, the second option could be a variety of agents including: GLP-1 RAs, DPP-IV inhibitors and TZDs, among others, in a hierarchical order as previously described, but also patient preference and anticipated compliance must be taken into account.

GLP-1 RAs, although effective at A1c reduction (~0.5–1.0%) and are ranked highest on the list of second line agents, might receive resistance

from patients as they are currently available only as injections; however, the weight loss associated with these agents would be beneficial in this patient. DPP-IV inhibitors may be the better option for an incretin mimetic as they are oral agents that can be taken without relation to meals, which might improve compliance. Additionally, they also do not confer significant change in weight and the potential A1c reduction achieved, approximately 0.5–0.8%, would be sufficient in addition to maximized metformin to achieve adequate glycemic control. TZDs, although they provide adequately effective A1c reduction of 0.5–1.4%, could also be an option, although are associated with weight gain and may not be the best option in a patient such as this with a BMI >33 kg/m². SGLT-2 inhibitors, the most recently approved class of antidiabetic agents, have not been given enough time on the market as of yet to be widely recommended, although they provide 0.4–0.9% A1c reduction. Basal insulin is recognized as an option as the second part of the therapeutic plan; however, in the case of this patient who is employed as a commercial truck driver, the addition of insulin therapy may preclude his employment as a truck driver in certain states. Colesevelam is the next option in the hierarchy but would not be ideal in this patient as his baseline triglycerides are elevated, and the presence of a bile acid sequestrant would further raise triglycerides. Bromocriptine and AGIs, which are next on the list, confer a fair amount of GI side effects, nausea with bromocriptine and flatulence with AGIs, and are not ideal for a patient that spends a significant amount of time in his truck. Last, sulfonylureas/meglitinides are on the list of secondary options but also have a higher risk of hypoglycemia and weight gain compared with the aforementioned agents.

Thus, the ideal option, according to the AACE recommendations in addition to patient characteristics, efficacy and side effect profile, would be metformin combined with a DPP-4 inhibitor. In the USA there are combination products of these agents, such as sitagliptin + metformin and alogliptin + metformin, which are both approved by the US FDA and could facilitate patient compliance.

Comparable to the ADA recommendations, other therapeutic options to consider for this patient would be addition of a statin to target elevated LDL and addition of an ACE inhibitor to address elevated blood pressure and prevent

nephropathy. As this patient has a 10-year risk of CVD of approximately 5%, he likely does not require aspirin for primary prevention.

• American College of Physicians

The ACP guidelines do not address diagnosis of T2DM. After using other guidelines to diagnose this patient, ACP guidelines would recommend that the patient be started on oral metformin after the failure of lifestyle modifications including dietary changes, exercise and weight loss. ACP does not provide specific recommendations on diet, exercise, weight loss amount or dosing of metformin. Due to the patient's current labs, occupation and the perceived difficulty of lifestyle changes, we would recommend starting pharmacotherapy. The ACP does not address other lipid or aspirin management.

While this case represents a newly diagnosed patient with DM, there are a plethora of other combinations of patient presentation, as many factors can change from patient to patient as well as within the same patient him/herself. For example, diet, exercise, employment and social history, among many others, can change from visit to visit and certainly from patient to patient. The potential for wide inter-patient variability highlights the conceivable difficulty in the total management of the diabetic patient, as well as the implicit need for patient-specific goals and a well-informed provider.

Conclusion

As is evident by the above discussion, there are many ways to approach the treatment of hyperglycemia in T2DM by applying different specific US-based guideline recommendations, focusing on drug therapy management. The goal of this article was to clarify these recommendations and present them in such a way as to not only highlight the differences, but to apply them to a single patient scenario. Effective treatment of T2DM will be an ongoing struggle for many practitioners and patients for many years to come and is not exclusive to medication management, but encompasses many aspects of care not discussed in this article. With the assistance of well-developed and researched treatment algorithms, hopefully the struggle will not be as significant as it once was.

Future perspective

Management of a newly diagnosed patient with T2DM poses multiple questions for a provider.

We as practitioners have learned throughout our schooling to practice evidence-based medicine and to apply guideline recommendations when possible. The use of guidelines for the hyperglycemic management of patients is a typical starting point. From there we must take into account the whole picture of the patient and provide individualized patient-centered care. Guidelines may differ in their recommendations, and practitioners vary in their approach for treating patients with T2DM. However, a similarity in each of these approaches is the commitment to meet the same end goal: reducing morbidity and mortality while meeting patient-specific needs. It is unlikely there will only be one US diabetes guideline for management of T2DM

in the foreseeable future. Understanding what the recommendations are and applying them to practice experience will ultimately yield positive outcomes and provide multiple options in the treatment arsenal for our patients.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

• of interest; •• of considerable interest

- 1 American Diabetes Association. Standards of medical care in diabetes – 2014. *Diabetes Care* 37, s14–s79 (2014).
- This annual guideline by the American Diabetes Association (ADA) provides a global overview of Type 2 diabetes, diagnostic criteria, monitoring, treatment, and prevention of microvascular and macrovascular disease. These standards of care highlight the progressive changes and evidence behind continuous updates in ADA guidelines for Type 2 diabetes.
- 2 Garber AJ, Abrahamson MJ, Barzilay JI *et al.* AACE comprehensive diabetes management algorithm 2013 consensus statement. *Endocr. Pract.* 19(Suppl. 2), 1–48 (2013).
- The detailed 2013 American Association of Clinical Endocrinologists (AACE) consensus statement provides very specific recommendations in text and graphic format, with the goal of simplifying treatment decisions with an aggressive therapeutic approach.
- 3 Handelsman Y, Mechanick JI, Blonde L *et al.* AACE Task Force for developing diabetes comprehensive care plan. *Endocr. Pract.* 17(Suppl. 2), 1–53 (2011).
- These are the 2011 American Association of Clinical Endocrinologists clinical practice guidelines for developing diabetes comprehensive care plans that incorporate not only glycemic control, but also tools for minimizing microvascular and macrovascular complications. A major focus is making recommendations that have an impact on cardiovascular disease, mortality and quality of life for the patient.
- 4 Qaseem A, Humphrey L, Sweet D *et al.* Oral pharmacologic treatment of Type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. *Ann. Intern. Med.* 156, 218–231 (2012).
- Practice guidelines developed in 2012 by the American College of Physicians for the oral pharmacological treatment of Type 2 diabetes.
- 5 Bennett WL, Maruthur NM, Singh S *et al.* Comparative effectiveness and safety of medications for Type 2 diabetes: an update including new drugs and 2-drug combinations. *Ann. Intern. Med.* 154, 602–613 (2011).
- American College of Physicians guidelines are based upon this systematic review and a report sponsored by the Agency for Healthcare Research and Quality.
- 6 Inzucchi SE, Bergenstal RM, Buse JM *et al.* Management of hyperglycemia in Type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 55, 1577–1596 (2012).
- This position statement paper by the ADA and European Association for the Study of Diabetes focuses on the progressive approach to medical therapy management in patients with Type 2 diabetes. This paper also addresses the various factors taken into consideration when determining HbA_{1c} goals for patients, and it places focused attention on ‘patient-centered’ approaches to management of Type 2 diabetes.
- 7 Institute of Medicine. *Crossing the Quality Chasm: A New Health System for the 21st Century*. The National Academies Press, Washington, DC, USA (2001).
- 8 Wilson PW, D’Agostino RB, Levy D *et al.* Prediction of coronary heart disease using risk factor categories. *Circulation* 97(18), 1837–1847 (1998).
- 9 World Health Organization. Diabetes. Fact sheet number 312. October 2013. www.who.int/mediacentre/factsheets/fs312/en/
- 10 American Diabetes Association. Statistics about diabetes. *Data from ‘Economic Costs of Diabetes in the U.S. in 2012.’* VA, USA American Diabetes Association. www.diabetes.org/diabetes-basics/statistics/?loc=db-slabnav